mathematics

MDPI

Article

A Network-Level Stochastic Model for Pacemaker GABAergic Neurons in Substantia Nigra Pars Reticulata

Karine Guimarães * and Aline Duarte

Instituto de Matemática e Estatística, Universidade de São Paulo, São Paulo 05508-220, Brazil; alineduarte@usp.br
* Correspondence: kguimaraes@usp.br

Abstract: In this paper we present computational simulations of a mathematical model describing the time evolution of membrane potentials in a GABAergic neural network. This model, with stochastic and evolutionary characteristics, is an application of the version introduced previously where the authors present the continuous time version of a new class of stochastic models for biological neural networks. The goal is to computationally simulate the model (with the interaction conditions of a GABAergic network) and make biological inferences. More specifically, the computational simulations of the model that describe spiking neurons with electrophysiological characteristics of a brain region called substantia nigra pars reticulata, emphasize changes in desynchronized firing activity and how changes in individual activity propagate through the network.

Keywords: stochastic model; computational model; GABAergic neurons; substantia nigra pars reticulata

MSC: 92-10

1. Introduction

To understand how neural systems work it is necessary to combine experimental studies of the animal and human nervous systems with numerical simulations of large-scale brain models. Large-scale simulations of activity and theoretical investigations of neuronal dynamics require models of neurons that are mathematically treatable, biologically relevant, and computationally fast.

The electrical behavior of neurons has been studied for more than six decades and there are many detailed models built from experimental data. Although models describing small areas of the cell membrane and considering stochastic dynamics of ion channels present behavior compatible with those found in biological neurons, until recently it was believed that the behavior of these models would converge to a deterministic average behavior when considering a large number of ion channels present in a neuron [1,2]. Thus, to the detriment of stochastic models, deterministic models have always been considered paradigms to describe the behavior of biological neurons.

However, it is known that the intrinsic electrical activity of many neurons is not deterministic. Membrane voltage depends on the probability of opening and closing of the ion channels [3]. Experiments on isolated cortical neurons—at rest in the absence of excitatory stimulation—repeatedly subjected to an electrical stimulus, showed that the reliability of the spiking instant depends on probabilistic properties of the applied signal, in disagreement with deterministic predictions [4]. In [5], the authors compared a stochastic model of the axonal membrane with its deterministic version, based on the mechanism of potentiation of the effects of fluctuations in a small number of ion channels. In this case, it was verified that the stochastic model is able to reproduce the precision and reliability properties of neurons in situations where the deterministic model fails. Together, these results suggest that action potential emission or propagation can randomly fail at several points, indicating a stochastic aspect in neuronal spiking.

check for updates

Citation: Guimarães, K.; Duarte, A. A Network-Level Stochastic Model for Pacemaker GABAergic Neurons in Substantia Nigra Pars Reticulata. *Mathematics* **2023**, *11*, 3778. https://doi.org/10.3390/math11173778

Academic Editors: Chi Chung Alan Fung and Wen-Hao Zhang

Received: 14 July 2023
Revised: 24 August 2023
Accepted: 29 August 2023
Published: 3 September 2023

In this paper, we present a numerical study of a mathematical model describing the continuous time evolution of membrane potentials in a GABAergic neural network in the absence of external excitatory stimuli. This model stands out for being a new class of inherently stochastic models for biological neural networks, where the activity of each neuron is represented by a point process. More specifically, it is an application of the version presented in [6] where the authors describe the continuous time version of the model introduced in [7]. It is the first time that this mathematical model is simulated under the interaction conditions described above.

The computational simulations of the model provide numerical results describing the spiking times of a system of neurons. The network architecture represents biological characteristics of a rat brain region called substantia nigra pars reticulata (SNr), which is the primary source of output from the sensorimotor basal ganglia. Experimental data already published in the scientific literature will be used as a guide to adjust the properties of computational architecture.

The mean goal of this work is to provide evidence on the efficiency of the model introduced by [6] in reproducing spiking times of a system of neurons under biological conditions.

Substantia Nigra Pars Reticulata

Substantia nigra (SN) is a subcortical region part of a major output nucleus of the basal ganglia. SN mainly consists of the primarily dopaminergic substantia nigra pars compacta (SNc) and the GABAergic substantia nigra pars reticulata [8–10].

SNr plays an important role in the physiology of the basal ganglia contributing to the regulation of motor and cognitive functions. The importance of this regulation can be seen in diseases such as Parkinson's disease, Huntington's chorea, Tourette syndrome, obsessive–compulsive disorder, and schizophrenia [11–15].

The SNr is essentially composed of projection neurons. The vast majority of SNr cells synthesize and release the neurotransmitter γ-aminobutryic acid (GABA), whose function is to inhibit and disinhibit neurons in their main target nuclei—i.e., to the striatum or to the output structures of the basal ganglia: the thalamus and brain stem [16–18].

These neurons receive excitatory glutamatergic inputs from the subthalamic, pedunculopontine nuclei and the prefrontal cortex [19]. However, the indirect glutamatergic input seems to have an insignificant role in the regulation of SNr neurons [20]. The majority of afferents to the SNr are from direct pathways that exert GABA-mediated inhibitory effects, arising from the globus pallidus and the striatum in conjunction with a lesser extent local axon collaterals from other SNr neurons [21,22].

A striking neurophysiological characteristic of SNr GABAergic neurons is that they are tonically active and fire sustained, spontaneous high frequency and short-duration spikes. Neurons capable of periodic spiking in the absence of synaptic input are referred to as autonomous spiking pacemakers [23]. The ability of sustaining a high-frequency of spikes comes from a combination of multiple ion channels, including a stronger transient voltage-gated sodium current with a faster activation and a faster recovery from inactivation. It also expresses a robust Kv3-like potassium current that activates rapidly and inactivates slowly, besides a tonically active transient receptor potential, calcium channels, and calcium-activated potassium channels [24–26].

SNr neurons are synaptically coupled by local axon collaterals microcircuits that can instead supply such feedback within the SN, providing a local signal processing. Besides, these synapses are constantly active, once they fire spontaneously, which results in a local asynchronous network [27–29].

Under basal conditions, inhibitory synapses from striatal neurons to SNr GABAergic neurons do not result in the inhibition of these neurons. However, when behaviorally necessary, activation of GABAergic striatal neurons that give rise to the direct pathway inhibits SNr tonic activity, inducing a pause of neuronal spikes and consequently of the system [30].

Post-stimulus time histogram—an average over trials with different initial conditions and different outcomes—of experimental measurements are used in [29] to show that the spiking rate changes after synaptic inhibition of an oscillating SNr neuron. In particular, the histogram shows that synaptic inhibition using photostimulation of the direct pathway synapses results in a rapid dip in the firing rate, followed by a rise above the baseline rate and an oscillation, before damping back to the baseline firing rate. These measurements were done on isolated neurons. Thus, from these observations, two questions arise: What happens at the network level? May these observations suggest a synchronization after pausing?

2. Mathematical Formulation

From a mathematical point of view, the model is a system of point processes. The SNr has ∼26,300 neurons in a rat [31]; therefore, we used this number as the system size.

Informally, N is a countable set that represents the 26,300 GABAergic neurons of the SNr and to each $i \in$ N the membrane potential is a stochastic process whose state at time t ≥ 0 is denoted by (V_i(t)). Each neuron i spikes at a rate $\phi(V_i(t))$ and its membrane potential is reset to resting potential when a spike occurs. Neurons interact through synapses, thus, each i $\in$ N is associated with a set V_i of presynaptic neurons. Whenever a neuron spikes the membrane potential of all its postsynaptic neurons receive an increment called synaptic weight.

Model Definition

Let $(V(t))_{t\geq 0}$ be a Markov process with

$$V(t) = (V_1(t), \ldots, V_i(t)) \in \mathbb{R}_+^N,$$

whose infinitesimal generator is given by

$$\mathcal{L}f(v) = \sum_{i\in N} \phi(v_i)[f(\Delta_i(v)) - f(v)] - \tau_M \sum_{i\in N} \frac{\partial f}{\partial v_i}(v) v_i, \tag{1}$$

where, for all $i \in I$, $\Delta_i : \mathbb{R}_+^N \to \mathbb{R}_+^N$ is defined by

$$(\Delta_i(v))_j = \begin{cases} v_j + w_{i\to j}, & \text{if } j \neq i, \\ v_{rest}, & \text{if } j = i, \end{cases} \tag{2}$$

$\tau_M \geq 0$, $\phi : \mathbb{R} \to \mathbb{R}_+$, $v_{rest} \in \mathbb{R}$ e $W = (w_{i\to j})_{i,j\in I} \in \mathbb{R}_+$, with $w_{i\to i} = 0$.

In (1), τ_M models the potential lost to the extracellular medium, which occurs due to the existence of leakage channels in the membrane cell of each neuron and ϕ(v) the probability of a neuron firing as a function of the membrane potential. Here we consider ϕ as the sigmoid activation function because they are biologically more plausible. Since biological neurons work in a binary form (activating vs. not activating), the sigmoid function is a good way to model this behavior, since it assumes values between 0 (non-activation) and 1 (activation). Furthermore, the ϕ function modulates the intrinsic activity of the network, that is, the probability of each neuron firing spontaneously and independently of external stimuli. The ϕ function is described by the logistic sigmoidal function

$$\phi(v_i) = \frac{\alpha}{1 + \beta \exp(-\gamma v_i)}, \tag{3}$$

where the constants $\alpha = 1$, $\beta = 1$ and $\gamma =$ Here, γ controls the slope of ϕ and β its translation.

The effect of the spiking of each neuron is described by the application Δ_i and the family of synaptic weights W. Specifically, $w_{i\to j}$ corresponds to the value added to the membrane potential of the neuron j whereas the neuron i spikes. Since we consider GABAergic neurons, this contribution is inhibitory, that is $w_{i\to j} < 0$, $\forall i \neq j$. Furthermore,

Δ_i describes the effect on the neuron's membrane potential at the times of its own firing, which is immediately reset to the resting value v_{rest}.

Between consecutive spikes of the network, the time evolution of the membrane potential of each neuron can be described by the following ordinary differential equation

$$\frac{dV_i}{dt} = -\tau_M V_i(t). \quad (4)$$

3. Results

For this study, we use the method of Gillespie [32] in order to simulate the behavior of SNr fast-spiking (FS) neurons. Since these neurons have pacemaker activity, the network architecture does not include excitatory input. As stated earlier, in SNr there are a total of N = 26,300 inhibitory neurons synaptically coupled by collateral axon microcircuits that provide feedback within SNr, providing local signal processing. Once these synapses are constantly active as they fire spontaneously, the effect is an asynchronous local network [29]. The results of the experiments in silico were plotted on graphs that represent the action potential of neurons in time. To understand the functioning of a complex neural network, it is necessary to do it from the sum of the parts: it starts by understanding the individual neuron and then the communication effect of one cell with others. In this way, we initially simulate an individual neuron with the neurophysiological characteristics described above. Table A1, in Appendix A, presents a complete description of all parameter values.

3.1. Baseline Case

The first simulation checks if the model works with the conditions that we established for the network architecture. Here, we verify if the model can reproduce a spontaneous spike. Figure 1 represents the firing times of one GABAergic pacemaker neuron (Neuron 1) which spikes regardless of any excitatory stimulus during 6000 milliseconds. The simulation time is chosen arbitrarily.

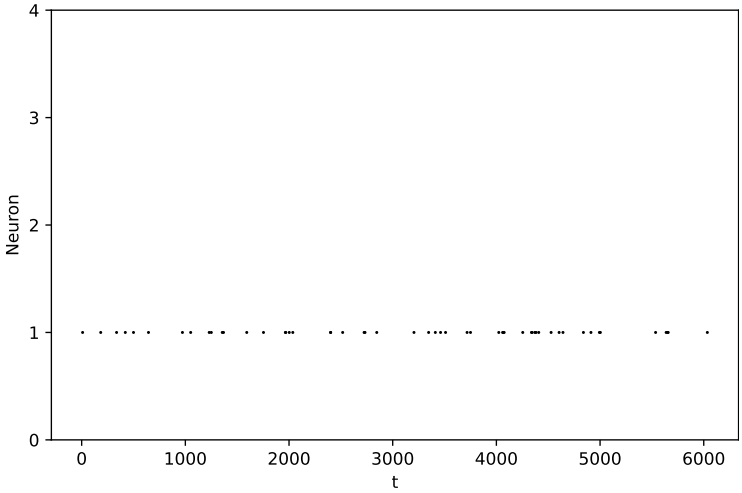


Figure 1. Spiking times of one GABAergic pacemaker neuron (Neuron 1) represented by black dots in a time interval of 6000 ms, with $V_1(0)$ chosen uniformly in $[-1, 0]$, $v_{rest} = -30$ and $\tau_M = 0.020$.

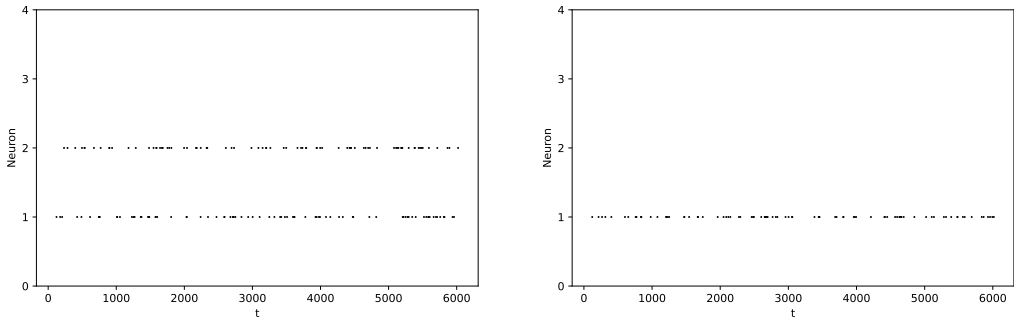
In Figure 2 a second GABAergic neuron is added. Here, it is important to point out that a geometric hypothesis of the model is that the neuron has only one compartment, that is, the dendrites, soma, and axon are condensed. Thus, the continuous system—the network—will be divided into segments small enough so that they can be considered isopotential and spatially uniform in their physical properties. Therefore, we can neglect the spatial structure of the cell and treat it as a point.

Considering each neuron as a vertex and the synapses as a binary relation over N (the set of edges), we obtain a graph $G = (N, W)$. Since the synapses are oriented in the

sense of pre-post synaptic neurons, $G = (N, W)$ is a directed graph with $(i, j) \in W$ whereas $w_{i \to j} \neq 0$.

Figure 2a shows two GABAergic pacemaker neurons spiking spontaneously and synaptic weight adjusted with the value from Table A1. The synaptic weight is the same at all synapses.

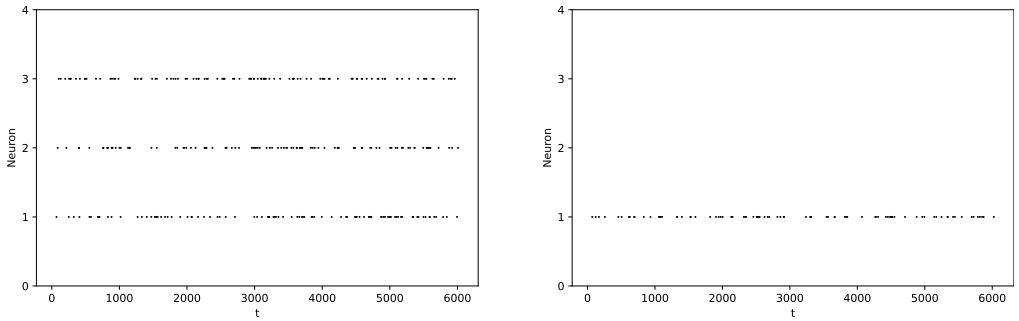
To validate the inhibitory component of the network, we set a high synaptic weight w = 1.5, showing that if the synapse is strong enough, it is capable of completely inhibiting the firing of the postsynaptic neuron Figure 2b.



(**a**) (**b**)

Figure 2. Spiking times of two GABAergic pacemaker neurons (Neuron 1 and Neuron 2) represented by black dots in a time interval of 6000 ms, with $V_i(0)$ chosen uniformly in $[-1, 0]$, $i = 1, 2$, $v_{rest} = -30$ and $\tau_M = 0.020$. (**a**) Synaptic weights adjusted so that the both neurons have action potentials, $w_{1 \to 2} = -0.9$ and $w_{2 \to 1} = 0$. (**b**) Synaptic weights adjusted to validate the inhibitory component of the network, $w_{1 \to 2} = -1.5$ and $w_{2 \to 1} = 0$.

The same sequence of experiments was reproduced for three connected neurons, and it was possible to validate the previously mentioned results, that is, with a moderate synaptic weight Figure 3a and then Figure 3b the weight increase to check if the inhibition spreads.



(**a**) (**b**)

Figure 3. Spiking times of three GABAergic pacemaker neurons in a network represented by black dots in a time interval of 6000 ms, with $V_i(0)$ chosen uniformly in $[-1, 0]$, $i = 1, 2, 3$, $v_{rest} = -30$ and $\tau_M = 0.020$. (**a**) Synaptic weights adjusted so that the neurons have action potentials, $w_{1 \to 2} = w_{2 \to 3} = w_{2 \to 3} = -0.9$ and equal do zero otherwise. (**b**) Synaptic weights adjusted to validate the inhibitory component of the network, $w_{1 \to 2} = w_{2 \to 3} = w_{2 \to 3} = -1.5$ and equal do zero otherwise.

Finally, Figure 4 presents a simulation of a network with the total N of SNr neurons and with the electrophysiological characteristics described above.

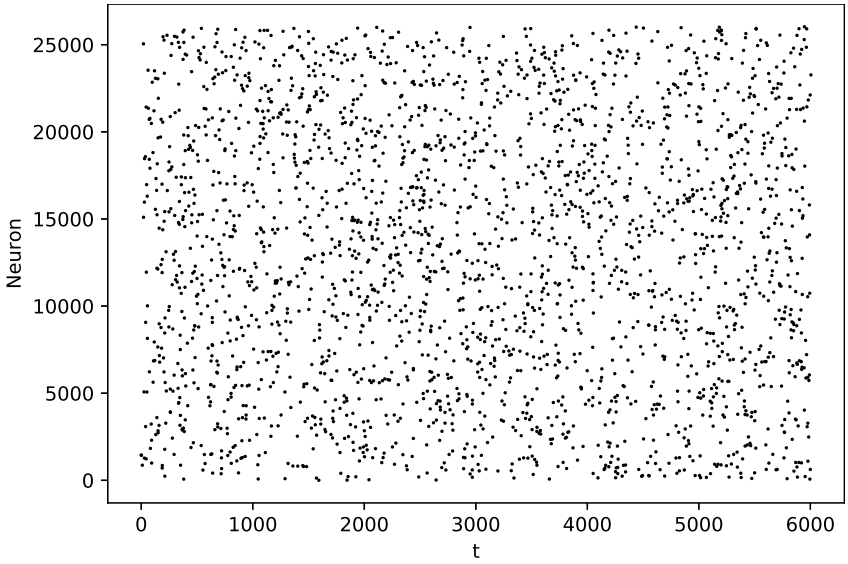


Figure 4. Spiking times of 26,300 GABAergic pacemaker neurons represented by black dots in a time interval of 6000 ms, with $V_i(0)$ chosen uniformly in $[-1, 0]$, $i = 1, \ldots, 26{,}300$, $v_{rest} = -30$, $\tau_M = 0.020$ and $w_{i \to j} = -0.9, i \neq j$.

Figure 4 represents a network of 26,300 GABAergic pacemaker neurons communicating via a complete graph. Since they all communicate with each other through inhibitory synapses, the inputs modulate the excitability of the network which implies that each single neuron receives many inhibitory synapses becoming inactive for a while. When a neuron becomes inactive, it stops inhibiting the others. This combination of inhibition, inactivity, and more activation, means that the network is not completely silent, however, it is sparse-asynchronous. For more details on this dynamic and its aspect of asynchrony, see [29,31,33]. Thus, the model reproduces the biological aspect of asynchrony in the firing pattern of the network of this region, that is, they do not fire at the same time.

Finite size effects have been studied analytically in the purely inhibitory system by Brunel et al. [34] when the system is stationary or deviations to stationarity are small. In [35] Brunel defines synchronous and asynchronous states and shows single-cell behavior (rasters). The analysis predicts qualitatively the behavior of the system in both cases (synchronous and asynchronous). The result shown in Figure 4 is similar to the graphical representation defined as asynchronous by the author.

The results we show so far are very important in order to validate the mathematical model since this is the first time that a numerical study of the model is being simulated taking into account an inhibitory network and aiming to make biological inferences. Once the model's ability to reproduce biological phenomena has been validated, next we will test the model's ability to predict realistic responses.

3.2. Pause Phenomenon

Here, starting from the previous experiment, without modifying any parameters of the network, we inserted an inhibitory external stimulus in the network to simulate the pause.

Consider a deterministic sequence of external stimulus, $(w_1^e, \ldots, w_N^e)$, for a while of acting, $0 < t_{min} < t_{ee} < t_{max} < T$, where t_{min} is the initial time of the external stimulus, t_{ee} represents the interaction of the afferent pathways of the striatum with the activity of the population of SNr neurons, i.e., the external stimulus, t_{max} is the final time of action of the external stimulus and T is the end time of the simulation. Since these synapses are also GABAergic, the consequence is a pause in the firing of all neurons in the network for a period of time. Figure 5 shows the network simulation with the pause phenomenon implemented.

In [29] the authors present a graphical representation of the spiking times of isolated neurons with more than 800 attempts aligned in the photostimulation. The graphic closely resembles the results we obtained from the networked neurons (Figure 5). It is possible to observe that after the pause there are no visual signs of network synchronization in both cases.

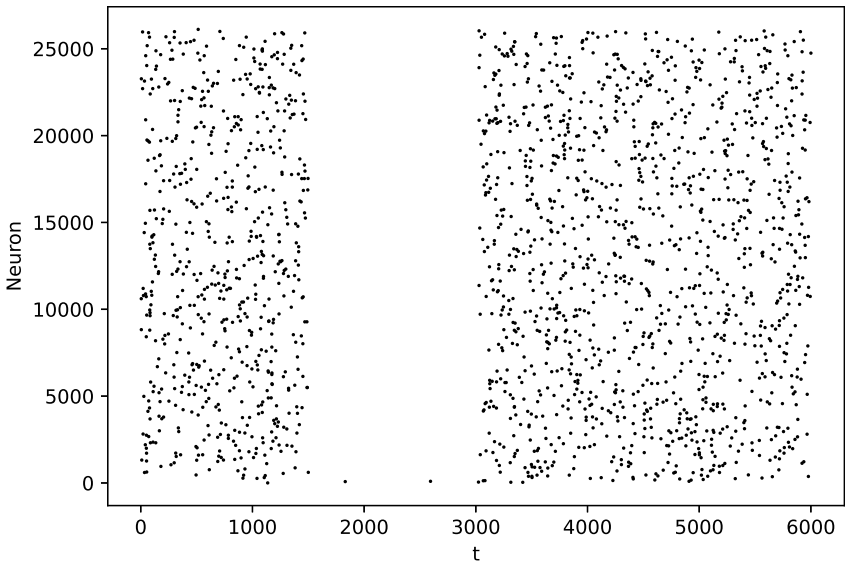


Figure 5. Spiking times of 26,300 GABAergic pacemaker neurons represented by black dots in a time interval of 6000 ms, with $V_i(0)$ chosen uniformly in $[-1, 0]$ $i = 1, \ldots, 26{,}300$, $v_{rest} = -30$, $\tau_M = 0.020$, $w_{i \to j} = -0.9, i \neq j$, t_{min} = 1500 ms, t_{max} = 3000 and $w_i^e = -10, i = 1, \ldots, 26{,}300$.

3.3. Random Graph

Autocorrelation analyses of spontaneous inhibitory postsynaptic currents in brain slices indicate that a given SNr neuron receives zero to four locally projected synaptic inputs on average [28]. Consequently, synaptic interactions between SNr neurons result in brief synaptic transients that can incrementally impact neuronal synchrony, modifying the oscillatory phase of the postsynaptic neuron. We implement a random graph whose number of local synapses is at most four.

Formally, consider $G = (N, W)$ a graph such that the sequence of out and in-degrees, $\overrightarrow{d}(i) = |\{j \in N; w_{j \to i} \neq 0\}|$ and $\overleftarrow{d}(i) = |\{j \in N; w_{i \to j} \neq 0\}|$ respectively, with $|\cdot|$ denoting the size of the set, satisfying

$$\begin{aligned} \overrightarrow{d}(i) &\sim \xi_i, \quad \text{for } \xi_k \in \{0, 1, 2, 3, 4\} \\ \overleftarrow{d}(i) &\sim \phi_i, \quad \text{for } \phi_k \in \{0, 1, 2, 3, 4\} \end{aligned}$$

with $i = 1, \ldots, N$. The choice of how many synapses each neuron will receive is random and limited to four. We will denote a random graph generated like the above as $\mathcal{G}$.

In Figure 6 we also observe that after the pause there are no visual indications of network synchronization.

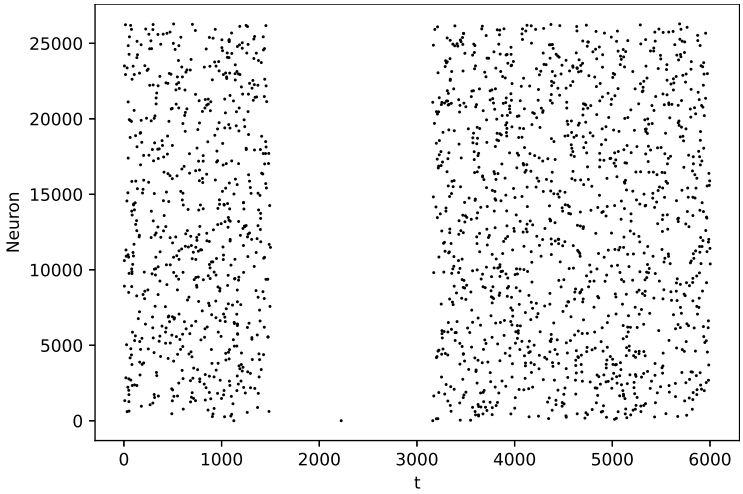


Figure 6. Spiking times of 26,300 GABAergic pacemaker neurons represented by black dots in a time interval of 6000 ms, with graph $\mathcal{G}$, $V_i(0)$ chosen uniformly in $[-1, 0]$ $i = 1, \ldots,$ 26,300, $v_{rest} = -30$, $\tau_M = 0.020$, t_{min} = 1500, t_{max} = 3000 and $w_i^e = -10, i = 1, \ldots,$ 26,300.

3.4. Sensitivity Analysis

Sensitivity analysis consists of studying the effect of the relationship between variations in the result of a mathematical model and the different sources of variation of the model's input data [36].

In this section, we present a sensitivity analysis of the variation of model parameters in order to identify a phase change related to the synchronization of the system. We use a local analysis, which only deals with a specific parameter varied at different levels, while all other parameters are kept constant. The other parameters are varied separately at each level.

The analysis was performed using parameters τ_{M}, $V(0)$ and γ and β given in (3). The parameters τ_{M}, $V(0)$ showed low sensitivity. With respect to the ϕ function, the translation parameter β also showed low sensitivity. However, with respect to the slope parameter γ, we observed that small variations led to a change in the behavior of the system. Figure 7 shows the simulation of the network with the change of the slope parameter of the activation function.

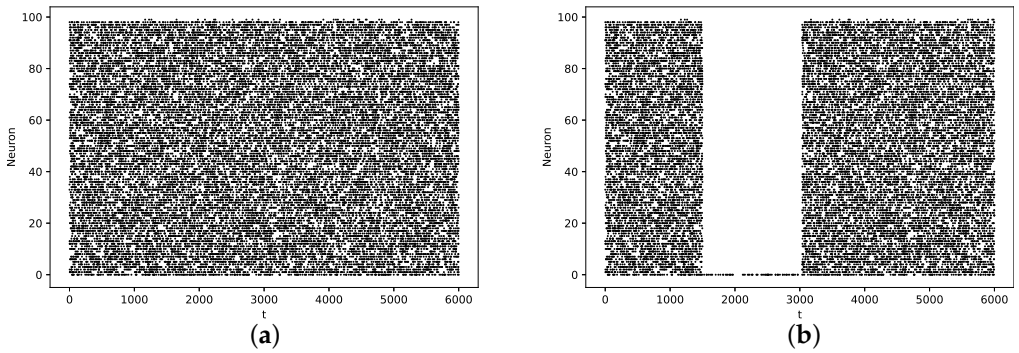


Figure 7. Spiking times of 100 GABAergic pacemaker neurons represented by black dots in a time interval of 6000 ms, with $V_i(0)$ chosen uniformly in $[-1, 0]$ $i = 1, \ldots, 100$, $v_{rest} = -30$, $\tau_M = 0.020$, $w_{i \to j} = -0.9, i \neq j$, t_{min} = 1500, t_{max} = 3000 and $w_i^e, i = 1, \ldots, 100$ and $\gamma = 3$. (**a**) Spiking times of one hundred neurons connected. (**b**) Spiking times of one hundred neurons connected with pause phenomenon.

The results of this simulation suggest a synchronized network by modifying parameters in the ϕ function.

Inducing synchronization implies increasing the probability of activation. This is because it is a GABAergic network, where locally the neurons are constantly inhibiting each other and the inactivation frequency is high. Because of this, they act like "Christmas lights", one group is active, then another, making synchronization more difficult. When we have more neurons with high activity frequency, the probability that they fire at the same time is greater (synchronization), because we will have many neurons sending inhibition at the same time, this implies in many neurons are being inhibited and becoming inactive, which would facilitate synchrony when they become active again-given that also when "returning" they are not being so inhibited on the first spike. Indeed, in [33] the authors show that in rates the regularity of the action potential firing of the SNr GABA neurons depended upon their firing frequency. At high discharge rates (around 20 Hz or above), these neurons displayed a very regular firing pattern.

4. Discussion

Employing computer modeling to simulate a phenomenon requires the development of a rigorous mathematical theory. Moreover, the validation of the mathematical framework through computational modeling is of vital importance to endorse the relationship of theoretical works with the real phenomenon. In this work, we simulate a GABAergic neural network of pacemaker neurons mathematically described by a stochastic models introduced by [6,7]. It is the first time that a numerical study of the continuous time model is being carried out taking into account a totally inhibitory network and with the objective of making biological inferences, the results obtained also have the role of validating the mathematical model.

In this study, we explored the hypothesis that after a brief pause produced by inhibition and subsequent disinhibition in the firing of SNr neurons, the network could synchronize. Our results suggest that in this SNr modeling context, the choice of the activation function ϕ seems to have an influence on what could be interpreted as network synchronization/asynchrony. In the context of our model, changes in the functioning of the intrinsic properties of spontaneous spiking seem to contribute to the phase shift.

These observations are consistent with the results found by [37], where the authors predict that inhibitory inputs into SNr may recruit currents that are activated by hyperpolarization, such as persistent sodium, low-voltage activated Ca^{++} or hyperpolarization-activated cyclic nucleotide–gated (HCN) channels. However, to verify the relevance of these ideas, future experiments would need to be carried out. Unfortunately, as the model is simplified and does not have the variety of channels mentioned, we have this simulation limitation.

Author Contributions: Conceptualization, K.G.; Methodology, K.G. and A.D.; Software, K.G.; Validation, K.G.; Writing—original draft, K.G.; Writing—review & editing, K.G. and A.D. All authors have read and agreed to the published version of the manuscript.

Funding: This article is supported by FAPESP grant 2019/22219-0 and was produced as part of the activities of FAPESP Research, Innovation and Dissemination Center for Neuromathematics (grant 2013/07699-0), São Paulo Research Foundation (FAPESP).

Data Availability Statement: The data presented in this study are available in this article in Table A1.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Parameters.

Parameters	Description	Value
$V(0)$	initial condition-uniform random variable	values in $[-1, 0]$
v_{rest}	resting potential	-30
τ_{M}	potential loss to the extracellular medium	0.020
w	synaptic weight	-0.9

References

1. Faisal, A.A.; Laughlin, S.B. Stochastic simulations on the reliability of action potential propagation in this axons. *PLoS Comp. Biol.* **2007**, *3*, 783–795. [CrossRef] [PubMed]
2. Goldwyn, J.H.; Imennov, N.S.; Famulare, M.; Shea-Brown, E. Stochastic differential equation models for ion channel noise in Hodgkin-Huxley neurons. *Phys. Rev. Stat. Nonlinear Soft Matter Phys.* **2011**, *83 Pt 1*, 041908. [CrossRef] [PubMed]
3. Luo, L. *Principles of Neurobiology*, 1st ed.; Garland Science: New York, NY, USA, 2016.
4. Mainen, Z.F.; Sejnowski, T.J. Reliability of spike timing in neocortical neurons. *Science* **1995**, *268*, 1503–1506. [CrossRef] [PubMed]
5. Schneidman, E.; Freedman, B.; Segev, I. Ion channel stochasticity may be critical in determining the reliability and precision of spike timing. *Neural Comput.* **1998**, *10*, 1679–1703. [CrossRef] [PubMed]
6. De Masi, A.; Galves, A.; Löcherbach, E.; Presutti, E. Hydrodynamic limit for interacting neurons. *J. Stat. Phys.* **2015**, *158*, 866–902. [CrossRef]
7. Galves, A.; Löcherbach, E. Infinite Systems of Interacting Chains with Memory of Variable Length—A Stochastic Model for Biological Neural Nets. *J. Stat. Phys.* **2013**, *151*, 896–921. [CrossRef]
8. Bolam, J.P.; Hanley, J.J.; Booth, P.A.C.; Bevan, M.D. Synaptic organization of the basal ganglia. *J. Anat.* **2000**, *196*, 527–542. [CrossRef]
9. Deniau, J.M.; Mailly, P.; Maurice, N.; Charpier, S. The pars reticulata of the substantia nigra: A window to basal ganglia output. *Prog. Brain Res.* **2007**, *160*, 151–172.
10. Guatteo, E.; Cucchiaroni, M.L.; Mercuri, N.B. Substantia nigra control of basal ganglia nuclei. *J. Neural Transm. Suppl.* **2009**, *73*, 91–101.
11. Hardman, C.D.; McRitchie, D.A.; Halliday, G.M.; Cartwright, H.R.; Morris, J.G. Substantia nigra pars reticulata neurons in Parkinson's disease. *Neurodegeneration* **1996**, *5*, 49–55. [CrossRef]
12. Hu, Y.; Ma, T.C.; Alberico, S.L.; Ding, Y.; Jin, L.; Kang, U.J. Substantia Nigra Pars Reticulata Projections to the Pedunculopontine Nucleus Modulate Dyskinesia. *Mov. Disord.* 2023, *Online ahead of print*. [CrossRef] [PubMed]
13. Wichmann, T.; DeLong, M.R. Pathophysiology of Parkinson's disease: The MPTP primate model of the human disorder. *Ann. N. Y. Acad. Sci.* **2003**, *991*, 199–213. [CrossRef] [PubMed]
14. Graybiel, A.M.; Rauch, S.L. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* **2000**, *28*, 343–347. [CrossRef] [PubMed]
15. Graybiel, A.M.; Canales, J.J. The neurobiology of repetitive behaviors: Clues to the neurobiology of Tourette syndrome. *Adv. Neurol.* **2001**, *85*, 123–131. [PubMed]
16. Parent, A. Extrinsic connections of the basal ganglia. *Trends Neurosci.* **1990**, *13*, 254–258. [CrossRef]
17. Hikosaka, O.; Tepper, J.M.; Abercrombie, E.D.; Bolam, J.P. GABAergic output of the basal ganglia. *Prog. Brain Res.* **2007**, *160*, 209–226.
18. Freeze, B.S.; Kravitz, A.V.; Hammack, N.; Berke, J.D.; Kreitzer, A.C. Control of basal ganglia output by direct and indirect pathway projection neurons. *J. Neurosci.* **2013**, *33*, 18531–18539. [CrossRef]
19. Naito, A.; Kita, H. The cortico-nigral projection in the rat: An anterograde tracing study with biotinylated dextran amine. *Brain Res.* **1994**, *637*, 317–322. [CrossRef]
20. Windels, F.; Kiyatkin, E.A. GABA, not glutamate, controls the activity of substantia nigra reticulata neurons in awake, unrestrained rats. *J. Neurosci. Off. J. Soc. Neurosci.* **2004**, *24*, 6751–6754. [CrossRef]
21. Deniau, J.M.; Kitai, S.T.; Donoghue, J.P.; Grofova, I. Neuronal interactions in the substantia nigra pars reticulata through axon collaterals of the projection neurons. *Exp. Brain Res.* **1982**, *47*, 105–113. [CrossRef]
22. Mailly, P.; Charpier, S.; Menetrey, A.; Deniau, J.-M. Three-Dimensional Organization of the Recurrent Axon Collateral Network of the Substantia Nigra Pars Reticulata Neurons in the Rat. *J. Neurosci.* **2003**, *23*, 5247. [CrossRef] [PubMed]
23. Surmeier, D.J.; Mercer, J.N.; Chan, S. Autonomous pacemakers in the basal ganglia: Who needs excitatory synapses anyway? *Curr. Opin. Neurobiol.* **2005**, *15*, 312–318. [CrossRef] [PubMed]
24. Seutin, V.; Engel, D. Differences in Na^+ Conductance Density and Na^+ Channel Functional Properties Between Dopamine and GABA Neurons of the Rat Substantia Nigra. *J. Neurophysiol.* **2010**, *103*, 3099–3114. [CrossRef] [PubMed]
25. Ding, S.; Zhou, F.-M. Molecular and functional differences in voltage-activated sodium currents between GABA projection neurons and dopamine neurons in the substantia nigra. *Soc. Neurosci. Abstr.* **2010**, *339*, 22. [CrossRef]
26. Ding, S.; Wei, W.; Zhou, F.-M. Kv3-like potassium channels are required for sustained high-frequency firing in basal ganglia output neurons. *J. Neurophysiol.* **2011**, *106*, 3019–3034. [CrossRef]
27. Zhou, F.M.; Lee, C.R. Intrinsic and integrative properties of substantia nigra pars reticulata neurons. *Neuroscience* **2011**, *198*, 69–94. [CrossRef]
28. Higgs, M.H.; Wilson, C.J. Unitary synaptic connections among substantia nigra pars reticulata neurons. *J. Neurophysiol.* **2016**, *115*, 2814–2829. [CrossRef]
29. Simmons, D.V.; Higgs, M.H.; Lebby, S.; Wilson, C.J. Predicting responses to inhibitory synaptic input in substantia nigra pars reticulate neurons. *J. Neurophysiol.* **2018**, *120*, 2679–2693. [CrossRef]
30. Lanciego, J.L.; Luquin, N.; Obeso, J.A. Functional neuroanatomy of the basal ganglia. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a009621. [CrossRef]
31. Wilson, C.J. Active decorrelation in the basal ganglia. *Neuroscience* **2013**, *250*, 467–482. [CrossRef]

32. Masuda, N.; Rocha, L.E.C. A Gillespie algorithm for non-Markovian stochastic processes. *Siam Rev.* **2018**, *60*, 95–115. [CrossRef]
33. Richards, C.D.; Shiroyama, T.; Kitai, S.T. Electrophysiological and immunocytochemical characterization of GABA and Dopamine neurons in the Substantia Nigra of the rat. *Neuroscience* **1997**, *80*, 545–577. [CrossRef] [PubMed]
34. Brunel, N.; Hakim, V. Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. *Neural Comput.* **1999**, *11*, 1621–1671. [CrossRef] [PubMed]
35. Brunel, N. Dynamics of Sparsely Connected Networks of Excitatory and Inhibitory Spiking Neurons. *J. Comput. Neurosci.* **2000**, *8*, 183–208. [CrossRef]
36. Saltelli, A.; Tarantola, S.; Campolongo, F. Sensitivity Analysis as an Ingredient of Modeling. *Stat. Sci.* **2000**, *15*, 377–395.
37. Phillips, R.S.; Rosner, I.; Gittis, A.H.; Rubin, J.E. A computational model explains and predicts substantia nigra pars reticulata responses to pallidal and striatal inputs. *bioRxiv* **2020**. [CrossRef]