Neural Dynamics in Parkinson's Disease: Integrating Machine Learning and Stochastic Modelling with Connectomic Data*

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Abstract. Parkinson's disease (PD) is a neurological disorder defined by the gradual loss of dopaminergic neurons in the substantia nigra pars compacta, which causes both motor and non-motor symptoms. Understanding the neuronal processes that underlie PD is critical for creating successful therapies. This work presents a novel strategy that combines machine learning (ML) and stochastic modelling with connectomic data to understand better the complicated brain pathways involved in PD pathogenesis. We use modern computational methods to study large-scale neural networks to identify neuronal activity patterns related to PD development. We aim to define the subtle structural and functional connection changes in PD brains by combining connectomic with stochastic noises. Stochastic modelling approaches reflect brain dynamics' intrinsic variability and unpredictability, shedding light on the origin and spread of pathogenic events in PD. We created a hybrid modelling formalism and a novel co-simulation approach to identify the effect of stochastic noises on the cortex-BG-thalamus (CBGTH) brain network model in a large-scale brain connectome. We use Human Connectome Project (HCP) data to elucidate a stochastic influence on the brain network model. Furthermore, we choose areas of the parameter space that reflect both healthy and Parkinsonian states and the impact of deep brain stimulation (DBS) on the subthalamic nucleus and thalamus. We infer that thalamus activity increases with stochastic disturbances, even in the presence of DBS. We predicted that lowering the effect of stochastic noises would increase the healthy state of the brain. This work aims to unravel PD's complicated neuronal activity dynamics, opening up new options for therapeutic intervention and tailored therapy.

Keywords: Brain networks · Machine learning · Laplacian operator · Neural dynamics · Wiener process · Neurodegenerative disorders

* Stochastic modelling of brain networks.

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1 Introduction

Parkinson's disease (PD) stands as one of the most prevalent neurodegenerative disorders, characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to debilitating motor symptoms such as tremors, rigidity, and bradykinesia [1, 2]. Despite significant advancements in therapeutic approaches, including pharmacological interventions and DBS, our understanding of the complex interplay between neuronal dynamics, disease progression, and treatment outcomes remains incomplete [3, 4].

Recent years have witnessed a paradigm shift in neuroscientific research, driven by the convergence of computational methodologies, artificial intelligence (AI) techniques, including ML tools, and advancements in neural engineering [5]. Among these approaches, ML holds promise in deciphering intricate patterns within vast datasets, offering insights into disease mechanisms and personalized treatment strategies. Concurrently, DBS has emerged as a potent therapeutic modality, modulating aberrant neuronal circuits to alleviate motor symptoms in PD patients [6]. The discipline of ML, which is a subdivision of AI, has experienced rapid growth and has recently impacted medical fields like neurosurgery [5]. A literature review focusing on the application of ML in DBS has not yet been published despite the field's growing interest in the area.

In parallel, stochastic modelling has gained traction to capture the inherent randomness and complexity of neuronal activity [7], shedding light on the dynamic nature of neurological disorders such as PD [8]. By integrating these diverse methodologies, researchers aim to unravel the underlying mechanisms governing neuronal dysfunction in PD, thereby paving the way for more effective interventions and improved patient outcomes. Furthermore, recent studies employing multiscale mathematical modelling have highlighted the efficacy of nonlinear reaction-diffusion equations in discerning neuropathological conditions [9]. Notably, connectomic data has revealed the extensive impact of DBS across various cortical and subcortical regions [10]. Discrete brain network models operating in a spatio-temporal domain elucidate the dynamics of model parameters, thereby simulating large-scale brain activity [3, 10, 11].

In essence, neurons constitute the fundamental units of our nervous system, with the basal ganglia (BG) comprising three critical nuclei: the subthalamic nucleus (STN), the globus pallidus internus (GPi), and the globus pallidus externus (GPe) [2]. Neurons utilize neurotransmitters for intercellular communication and employ action potentials to transmit signals within the cell upon receiving external stimuli (I_{app}). Notably, using a reduced number of neurons, such as 10 neurons per nucleus, yields similar outcomes to those obtained with 100 neurons. Thus, each nucleus in our study comprises 10 cells [2].

In the present study, we adopted a novel co-simulation approach utilizing a modified Rubin-Terman model for subcortical brain regions surrounding the basal ganglia across the entire cerebral hemisphere from our previous study [2]. This approach incorporates stochastic noise, explicitly incorporating a Wiener process, to capture additional variability and complexity in brain dynamics [12, 13]. Therefore, we integrate a discrete brain network model for each cortical

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region, incorporating stochastic noise at the macroscopic scale to better align with experimental data on neuron firing characteristics. Following the strategy outlined in [2], we explore critical aspects of the model dynamics, including the influence of stochastic noise on healthy and diseased states. Our findings demonstrate that the eigendecomposition of the Laplace operator, incorporating stochastic noise, can predict the collective dynamics of human brain activity at the macroscopic scale [2]. These findings suggest that the disruption of multivariate connection-wise functional connectivity patterns holds promise for discriminating PD patients based on cognitive status, supporting previous observations of altered functional connectivity associated with cognitive impairment in PD. Our research uncovers significant findings regarding the influence of stochastic noise on brain dynamics. Specifically, we observed that in the presence of stochastic noise, the activity of the thalamus reaches a critical threshold, contrasting with scenarios lacking noise. Furthermore, our analysis revealed that stochastic noise amplifies the membrane potential of the thalamus, potentially exacerbating brain disease states. This effect of stochastic noise is pronounced, leading to burst oscillations in the membrane potential across all selected regions, even in the presence of DBS. Our study highlights the brain's resilience as it endeavours to maintain a healthy state for a prolonged period following DBS despite stochastic noise.

The rest of the paper is organized as follows. In Section 2, we describe our model in its different components: (i) a discrete and (ii) a stochastic discrete brain network model of the CBGTH. Section 3 presents numerical results based on the developed stochastic discrete brain network model for the cortex-thalamus-basal-ganglia systems. The computational results were obtained using codes developed in C-language and SHARCNET supercomputer facilities, and the simulation results were visualized in MATLAB. Implications of these results and their importance are discussed in Section 4. Finally, we conclude our findings and outline future directions in Section 5.

2 Methods

This section highlights the discrete and stochastic brain network model of CBGTH. In this section, we present (a) the discrete model of the CBGTH network mediated by Laplacian terms and (b) the stochastic brain network model of the CBGTH system, giving particular attention to stochastic noises. We evaluated the behaviour of stochastic noises in the brain regions such as Gpe, GPi, STN and thalamus (TH) and firing patterns under healthy and pathological states to validate the features of the CBGTH model. We then use data to examine the firing rates of the coupled neurons on each node in the brain network. Finally, the effects of noise in the presence of DBS on STN and thalamus are evaluated.

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2.1 Discrete brain network model of CBGTH

The network comprises nodes delineated within the brain connectome, often corresponding to established brain atlas regions. We aim to construct a model capable of capturing temporal voltage variations across different nodal points.

The brain connectome is represented as a weighted network $\mathcal{G}$ consisting of V nodes and E edges, derived from diffusion tensor imaging (DTI) and tractography techniques [2], as adopted from the HCP dataset. The edges of this network symbolize axonal bundles within white-matter tracts. To generate a network approximation of the diffusion terms, we utilize a weighted graph Laplacian, where the weights of the weighted adjacency matrix $\mathbf{W}$ are determined by the ratio of the mean fibre number n_{ij} to the mean squared length l_{ij}^2 connecting nodes i and j, expressed as:

$$W_{ij} = \frac{n_{ij}}{l_{ij}^2}, \quad i = 1, \ldots, V. \tag{1}$$

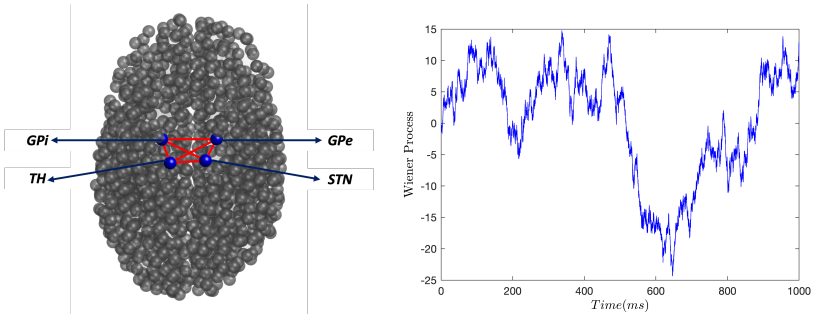
These weights align with the inverse length-squared dependency observed in the canonical discretization of the continuous Laplace (diffusion) operator [2]. Additionally, we define the diagonal weighted degree matrix as:

$$D_{ii} = \sum_{j=1}^{V} W_{ij}, \quad i, j = 1, \ldots, V. \tag{2}$$

Furthermore, the graph Laplacian $\mathbf{L}$ with (i, j)-entry is defined as:

$$L_{ij} = \rho(D_{ij} - W_{ij}), \quad i, j = 1, \ldots, V, \tag{3}$$

where ρ represents the diffusion coefficient.



(a) (b)

Fig. 1: (Color online) (a) Discrete brain network connectome in a healthy condition (left) (axial view from bottom). The four nodes are STN, GPe, GPi, and TH, and we replaced the spiking node "cortex" with the whole brain connectome (b) Stochastic noises applied to STN, GPe, GPi, and TH

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The adjacency matrix for simulations is derived from diffusion tensor magnetic resonance images obtained from 418 healthy HCP subjects sourced from the Budapest Reference Connectome v3.0 [2]. Fig. 1 (a) showcases a network composed of $V = 4$ nodes and $E = 6$ edges representing brain regions like the putamen, globus pallidus, and thalamus. Each node is assumed to occupy a surface area of 1.5cm^2. Each node linked with STN, GPi, GPe, and TH carries the voltage v^{sn}, v^{gi}, v^{ge}, and v^{th}, respectively. The network equations for the continuous model take the form of a system of first-order ordinary differential equations as follows:

$$\frac{dv^{sn}}{dt} = -d_{v^{sn}} \sum_{k=1}^{V} L_{1k} v_k + \frac{1}{c_m}\Big(-I_{Na}^{sn} - I_K^{sn} - I_L^{sn} - I_T^{sn} - I_{Ca}^{sn} - I_{ahp}^{sn} - I_{ge\to sn} + I_{snapp} \Big), \tag{4}$$

$$\frac{dv^{gi}}{dt} = -d_{v^{gi}} \sum_{k=1}^{V} L_{2k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{gi} - I_K^{gi} - I_L^{gi} - I_T^{gi} - I_{Ca}^{gi} - I_{ahp}^{gi} - I_{sn\to gi} - I_{ge\to gi} + I_{giapp} \Big), \tag{5}$$

$$\frac{dv^{ge}}{dt} = -d_{v^{ge}} \sum_{k=1}^{V} L_{3k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{ge} - I_K^{ge} - I_L^{ge} - I_T^{ge} - I_{Ca}^{ge} - I_{ahp}^{ge} - I_{sn\to ge} - I_{ge\to ge} + I_{geapp} \Big), \tag{6}$$

$$\frac{dv^{th}}{dt} = -d_{v^{th}} \sum_{k=1}^{V} L_{4k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{th} - I_K^{th} - I_L^{th} - I_T^{th} - I_{gi\to th} + I_{smc} \Big), \tag{7}$$

with non-negative initial conditions for all variables v^{sn}, v^{gi}, v^{ge}, and v^{th}. Additionally, $d_{v^{sn}}, d_{v^{gi}}, d_{v^{ge}}$, and $d_{v^{th}}$ represent the diffusion terms corresponding to each node. The weights in the weighted adjacency matrix represent the spread of transneuronal degeneration from one node to its neighbours. Next, we introduce stochastic noise into the discrete brain network model to observe its influence.

2.2 Stochastic brain network model of CBGTH

The integration of ML techniques with stochastic modelling in brain studies holds significant promise for advancing our understanding of neural dynamics and function [14]. In this section, we develop a discrete brain network model incorporating the addition of stochastic noise. The noise levels are crucial for ensuring the proper functioning of signals within the nervous system [15]. Studies have suggested that in computational models of neurodegenerative conditions such as PD, increased external noise levels are necessary for optimal function, reflecting the aging process and reduced plasticity [16]. Consequently, noise stimulation could be an alternative therapeutic approach for alleviating PD symptoms

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[15]. Therefore, based on the model presented in Section 2.1, we have added the noise terms as follows:

$$\frac{dv^{sn}}{dt} = -d_{v^{sn}} \sum_{k=1}^{V} L_{1k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{sn} - I_K^{sn} - I_L^{sn} - I_T^{sn} - I_{Ca}^{sn} - I_{ahp}^{sn} - I_{ge\to sn} + I_{snapp}\Big) + \sigma_1 \cdot dW_1(t), \tag{8}$$

$$\frac{dv^{gi}}{dt} = -d_{v^{gi}} \sum_{k=1}^{V} L_{2k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{gi} - I_K^{gi} - I_L^{gi} - I_T^{gi} - I_{Ca}^{gi} - I_{ahp}^{gi} - I_{sn\to gi} - I_{ge\to gi} + I_{giapp}\Big) + \sigma_2 \cdot dW_2(t), \tag{9}$$

$$\frac{dv^{ge}}{dt} = -d_{v^{ge}} \sum_{k=1}^{V} L_{3k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{ge} - I_K^{ge} - I_L^{ge} - I_T^{ge} - I_{Ca}^{ge} - I_{ahp}^{ge} - I_{sn\to ge} - I_{ge\to ge} + I_{geapp}\Big) + \sigma_3 \cdot dW_3(t), \tag{10}$$

$$\frac{dv^{th}}{dt} = -d_{v^{th}} \sum_{k=1}^{V} L_{4k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{th} - I_K^{th} - I_L^{th} - I_T^{th} - I_{gi\to th} + I_{smc}\Big) + \sigma_4 \cdot dW_4(t), \tag{11}$$

where $dW_i(t)$ represents the increment of the Wiener process $W_i(t)$ and σ_i are the scaling factors (representing the intensity of the noise) for each equation. When numerically integrating these stochastic differential equations, we generated increments of the Wiener process at each time step dt to represent the stochastic component using the Euler–Maruyama method. Incorporating noise into the CBGTH system within a discrete brain network model provides valuable insights into how the brain functions [16]. Fig. 1 (b) showcases a Wiener process or stochastic noises added into the CBGTH system. Since noise is present throughout various neural processes, from perceiving sensory signals to generating motor responses, it profoundly affects neuronal dynamics. Therefore, understanding the impact of noise is crucial for comprehending the brain's behaviour [17]. The significance of this impact will be explored further in the following Section 3. Moreover, the DBS current is added to the spatio-temporal model to the membrane potential equations of STN as follows:

$$\frac{dv^{sn}}{dt} = -d_{v^{sn}} \sum_{k=1}^{V} L_{1k} v_k + \frac{1}{c_m}\Big(- I_{Na}^{sn} - I_K^{sn} - I_L^{sn} - I_T^{sn} - I_{Ca}^{sn} - I_{ahp}^{sn} - I_{ge\to sn} + I_{snapp} + I_{DBS}\Big) + \sigma_1 \cdot dW_1(t), \tag{12}$$

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where $c_m = 1\mu F/cm^2$ and I_{DBS} is adopted from [2]. According to Eq. (12), the DBS electrode has been applied to the STN node in the discrete brain network connectome. The relevant parameters are given in Table 1 (the other relevant parameters are adopted from [2], (pd is a parameter, and $pd = 0$ indicates that the network is in healthy states, while $pd = 1$ shows that the network is in Parkinsonian states). The $--$ represents no connection to neurons.

Table 1: Parameter set for the CBGTH network [2].

	STN neuron	GPe/GPi neuron	TH neuron
I_{Ca}	$2(c^2)(v-140)$	$0.15(s_\infty(v))^2(v-120)$	$--$
I_{ahp}	$20(v+80)$ $(w/(w+15))$	$10(v+80)(w/(w+10))$	$--$
$I_{ge\to sn}$	$0.5S_{ge\to sn}(v+85)$	$--$	$--$
$I_{ge\to ge}$	$--$	$0.5Sge \to ge(v+85)$	$--$
$I_{ge\to gi}$	$--$	$0.5S_{ge\to gi}(v+85)$	$--$
$I_{sn\to ge}$	$--$	$0.15S_{sn\to ge}v$	$--$
$I_{sn\to gi}$	$--$	$0.15S_{sn\to gi}v$	$--$
$I_{gi\to th}$	$--$	$--$	$0.112S_{gi\to th}(v+85)$
I_{snapp}	$33-10pd$	$--$	$--$
I_{giapp}		$22-6pd$	$--$
I_{geapp}		$21-13pd+(-1.5)$	$--$

3 Results

In this section, we will investigate how stochastic noise impacts the CBGTH system in healthy and PD brain states by integrating ML and stochastic modelling with connectomic data.

Importantly, noise introduces stochastic fluctuations into the brain network, affecting the timing and reliability of neural signal transmission [18, 19]. In the context of the basal ganglia-thalamocortical circuit, where precise timing is crucial for motor control and cognitive processes, the impact of noise may lead to alterations in information processing and integration [18]. Moreover, neural noise, originating from various sources such as sensory input, cellular processes, and electrical activity, significantly influences the functioning of the nervous system. While it can hinder information processing, it also contributes to brain function by shaping functional networks, enhancing synchronization, and impacting task performance [19]. The brain's dynamics, characterized by subject-specific parameters and diverse outputs, make it a noisy dynamical system. Recent research indicates that noninvasive brain stimulation can alter the signal-noise relationship, but the precise relationship between noise amplitude and the global effects of local stimulation remains uncertain [18].

The impact of stochastic noise on the selected regions, namely the TH, STN, GPi, and GPe, in the healthy brain is illustrated in Fig. 2. It is observed that

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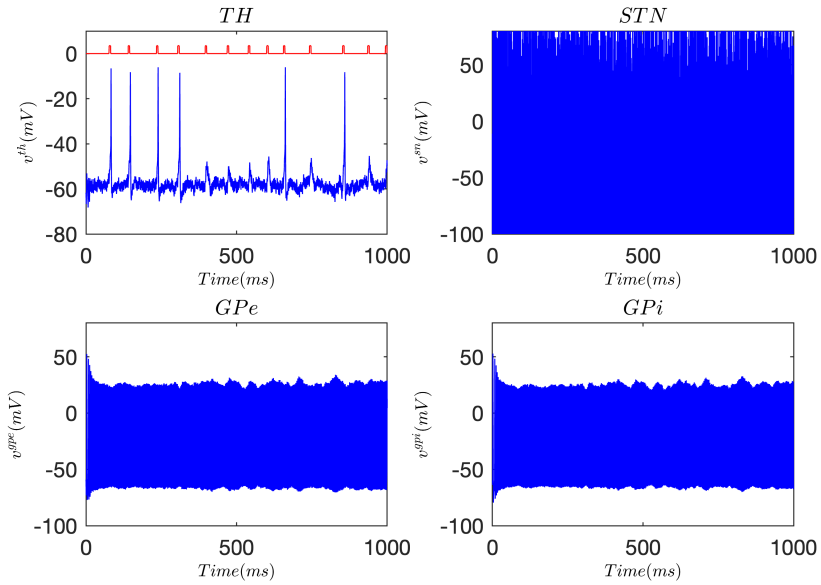

Fig. 2: (Color online) The effect of stochastic noise on the membrane voltages of the discrete brain network's TH, STN, GPe and GPi neurons in a healthy state. The red pulse trains in the top right panel denote SMC signal.

burst oscillations occur across all brain regions, particularly in the thalamus and subthalamic nucleus, where the oscillations persistently burst. Consequently, this heightened neural activity exacerbates the healthy state of the brain. As a result, it impairs membrane potential and disrupts the normal functioning of neurons. These findings underscore the significant adverse effects of stochastic noise on the brain and its constituent regions, potentially leading to the development or exacerbation of brain injury [20, 21].

In the Parkinsonian state, the membrane voltages of key neuronal populations, including STN, GPi, GPe, and TH neurons within a discrete brain network, exhibit dynamic fluctuations over time, as depicted in Fig. 3. The initial equilibrium has been set to $-65mV$; these neurons display varying voltage concentrations due to stochastic effects and diffusion processes. The color scale of voltage concentrations in Fig. 3 is plotted using MATLAB jet colormap. The recorded voltages at specific time points, such as $t = 354.56ms, 356.8ms, 356.23ms, 370ms$, $374.67ms, 383.2ms, 385.05ms$, and $385.57ms$, reveal temporal changes in neuronal activity. Notably, certain neuronal populations exhibit elevated voltages relative to others at different time points, as indicated by the color nodes. For instance, at $t = 356.23ms$, the voltage of TH neurons surpasses that of other neurons. In contrast, at $t = 356.8ms$, the GPe and TH neurons exhibit higher voltage concentrations within the CBTH circuitry in the Parkinsonian state.

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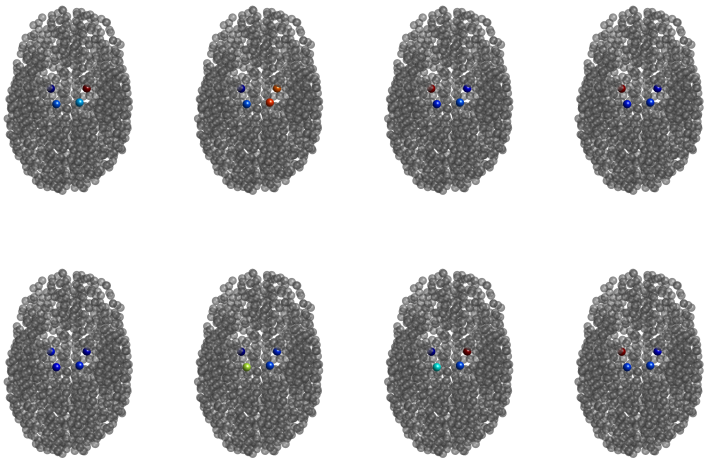

Fig. 3: (Color online) The effect of stochastic noise on the membrane voltage distributions of TH (top right), STN (top left), GPe (bottom right) and GPi (bottom left) neurons in the brain over time in Parkinson's state (axial views from below). Top panel (left to right): $t = 354.56\text{ms}, 356.8\text{ms}, 356.23\text{ms}, 370\text{ms}$, and for the bottom panel (left to right): $t = 374.67\text{ms}, 383.2\text{ms}, 385.05\text{ms}, 385.57\text{ms}$.

These voltage dynamics underscore the intricate interplay of stochastic noise and diffusion processes in shaping neuronal activity patterns associated with PD [2].

In Fig. 3, stochastic noise is crucial in modulating the membrane voltage distributions of key neuronal populations implicated in PD. Over time, stochastic fluctuations in membrane potentials within these neural networks can exacerbate pathological activity patterns in the Parkinsonian state. In the TH neurons involved in dopamine production, stochastic noise may contribute to the dysregulation of dopamine levels characteristic of Parkinson's. Similarly, in the STN, known for its involvement in motor control, stochastic noise might amplify aberrant firing patterns associated with movement dysfunction. Meanwhile, within the GPe and GPi, integral components of the basal ganglia circuitry, stochastic fluctuations could disrupt the delicate balance of inhibitory signalling, further exacerbating motor symptoms [14, 16]. These stochastic influences underscore the complexity of Parkinson's pathophysiology and highlight the importance of understanding noise modulation within neural circuits for developing effective therapeutic interventions [20].

Next, the DBS has been applied to STN neurons in the PD state of the brain. The application of DBS to STN neurons in the Parkinsonian state of the brain often results in a temporary restoration of healthy neural activity within

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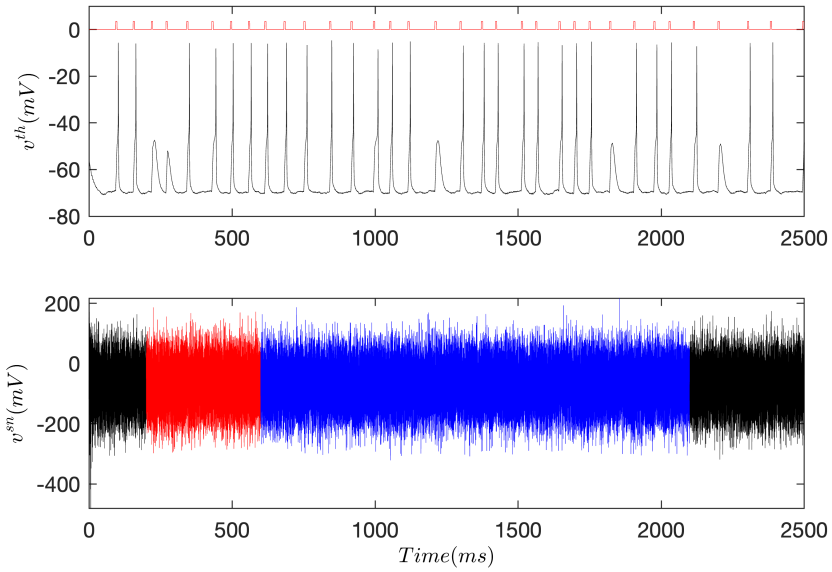

Fig. 4: (Color online) Effect of stochastic noise on membrane voltages of the TH (top) and the STN (bottom) neurons of discrete brain network in the Parkinson's state (black color). The effects of open-loop DBS on the STN neurons are presented in red color (bottom). However, the blue color shows a healthy state after the DBS is applied to the PD state. The red pulse trains in the top panel denote the SMC signal.

the basal ganglia circuitry, leading to symptom alleviation in PD patients. As depicted in Fig. 4, we applied the DBS in a spatio-temporal domain for a smaller amount of time. It is interesting to know that in the presence of a diffusion operator, neurons maintained a healthy state for a sufficient time after the DBS had been applied. We see the healthy state of STN neurons in blue color, as shown in Fig. 4. However, despite the therapeutic benefits of DBS, the long-term maintenance of a healthy state remains challenging. This is evident in the observed disturbances in thalamic activity characterized by bursts of oscillations and fluctuating membrane potentials, as shown in Fig. 4. Even with the presence of DBS, stochastic noise and diffusion processes continue to exert adverse effects on neural activity within the brain. Stochastic noise, arising from random fluctuations in ion channels and synaptic activity, can disrupt the finely tuned balance of excitation and inhibition within neural networks [21, 22]. Additionally, diffusion processes, which govern the spread of neurotransmitters and other signalling molecules, can lead to spatial and temporal variations in neuronal activity.

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In Fig. 4, the persistence of disturbances in thalamic activity despite DBS suggests that stochastic noise and diffusion processes may interact with the therapeutic intervention, leading to unintended consequences. These adverse effects underscore the complexity of neural dynamics in PD and highlight the need for further research to better understand and mitigate the impact of stochastic noise and diffusion on DBS efficacy [23, 24]. Additionally, advancements in DBS technology and optimization of stimulation parameters may help minimize these adverse effects and improve long-term therapeutic outcomes for Parkinson's patients.

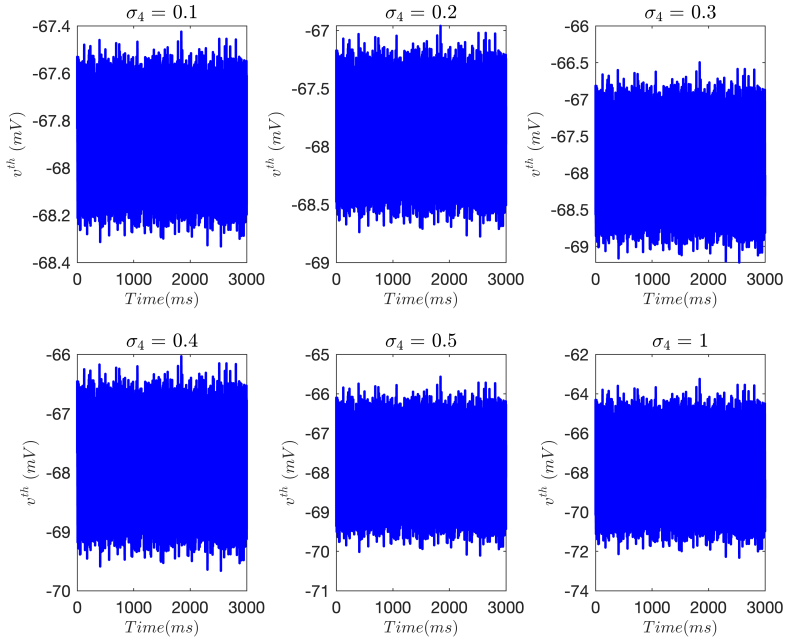

Fig. 5: Color online) The effect of stochastic noise on pathological activity patterns within the thalamus.

Stochastic noise can significantly impact thalamic activity, disrupting its normal functioning. As depicted in Fig. 5, the thalamus may exhibit erratic fluctuations in membrane potentials and firing patterns in the presence of stochastic noise. This can lead to disturbances in sensory processing, motor control, and cognitive functions that rely on thalamic signalling. Moreover, Fig.(2-5) were plotted using $\sigma_1 = 0.1, \sigma_2 = 0.4, \sigma_3 = 0.4, \sigma_4 = 0.5$. As seen in Fig. 5, we observed that stochastic noise tends to drive the membrane potential of thalamic neurons towards the PD state. The fluctuations in the membrane potential

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exhibit low-frequency oscillations. These oscillations appear to have a regular pattern but are modulated by the stochastic noise added to the system. The frequency and amplitude of these oscillations may vary depending on the system's parameters and the noise level. The stochastic noise introduced in the system causes the membrane potential to fluctuate randomly around a mean value. As the noise level (σ_4) increases, the amplitude of the fluctuations also increases. This suggests that noise can significantly influence the dynamics of the system. Incorporating stochastic noise in the thalamic membrane potential exacerbates the pathological activity patterns associated with PD. Conversely, when the noise is absent, the membrane potentials tend towards a healthier state, particularly in the presence of DBS. These observations underscore the critical role of stochastic noise in modulating thalamic activity, thereby influencing the balance between pathological and healthy states in neurological disorders such as PD.

4 Discussion

In the current work, we used resting-state functional connectomes and machine-learning approaches such as parallel computing in classifying brain connectomes in healthy and PD states, with and without the stochastic process. To solve the network model computationally, we utilized the Euler–Maruyama method with a time-step $dt = 0.001$, with consistent results across various time-step values. Throughout all simulations, we used brain connectome data sourced from https://braingraph.org, with no significant changes observed over time.

Additionally, obtaining precise data regarding cortical-BGTH tractography proves challenging due to various limitations in structural MRI data, as highlighted by Meier et al. [8]. Petersen et al. have recently introduced an advanced axonal pathway atlas for the human brain, integrating findings from histological studies, imaging data, and expert insights [25, 26]. Earlier work optimized connection probabilities and weights among BG regions to align with empirical fMRI data on an individual basis [2]. However, many studies resort to normative connectome atlases due to the complexities associated with acquiring and interpreting patient-specific diffusion-weighted imaging data. Yet, the potential benefits of patient-specific connection data remain uncertain.

In this work, we modified the Rubin and Terman model to better align with experimental evidence on neuron firing characteristics [2, 27]. Our study focuses on a network mathematical model that enables experimentalists to quickly evaluate membrane potentials throughout the cortex's four central nuclei and BGTH regions. Importantly, significant connection changes were detected in the PD brain, especially in stochastic noise, consistent with previous findings [14, 19, 20]. Unlike prior studies focusing on group differences, our study examined the discriminatory potential of resting-state functional connectivity at the individual level. This provides evidence that connectivity patterns with stochastic noise can distinguish PD patients with cognitive impairment from those without. Notably, our study is the sole one to show this capacity. In PD patients, functional

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connectivity reductions were observed across significant brain regions, with a disproportionate involvement of occipital-temporal and occipital-frontal connections compared to healthy controls. These findings contribute to the understanding of PD-associated cognitive impairment, corroborating previous neuroimaging modalities' observations.

Furthermore, this study underscores the potential of resting-state functional connectivity measures for individual-level discrimination in PD, providing valuable insights into the disease's pathophysiology. Our examination of stochastic noise's influence on various brain regions, including the STN, GPi, GPe, and thalamus, enhances our understanding of the complexities of PD. Moreover, noise can modulate the excitability of neurons within the brain network, influencing their firing patterns and synchronization properties. This modulation could change the overall network dynamics, affecting the balance between inhibitory and excitatory signals and potentially leading to dysregulated activity associated with neurological disorders such as PD. This discovery not only calls into question existing therapy options but also demonstrates the potential of our hybrid modelling approach for identifying subtle elements of brain dysfunction. Overall, investigating the influence of noise on the CBTH system using a discrete brain network paradigm gives valuable information on the system's resilience, flexibility, and susceptibility to dysfunction. It provides insights into the processes underpinning neurological diseases and may aid in developing therapeutic approaches to restore normal network function.

5 Conclusions

In conclusion, this study presents a novel approach utilizing a fusion of ML, stochastic modelling, and connectomic data to delve into the intricate neural pathways implicated in Parkinson's disease (PD) pathogenesis. By harnessing modern computational methodologies, we've endeavoured to decode the nuanced changes in structure and function within the PD-afflicted brain. Our findings shed light on the subtle alterations in neuronal activity patterns associated with PD progression, illuminating potential targets for therapeutic intervention. The hybrid modelling framework and innovative co-simulation technique developed in this research offer a deeper understanding of the impact of stochastic disturbances on the CBGTH network within the context of large-scale brain connectivity maps derived from the HCP. Notably, our analysis reveals that even in the presence of DBS, stochastic influences can lead to heightened activity in the thalamus, a key node in PD pathology.

In the future, we aim to analyze high temporal and spatially resolved cerebral data sources from functional near-infrared spectroscopy and EEG, PET, and MRI/fMRI data from healthy patients with neurodegenerative conditions such as PD. Also, the effect of stochastic noises in other regions, such as GPe, GPi and the whole cortex, will be analyzed. This work lays the groundwork for novel therapeutic strategies tailored to individual patients by elucidating the complex dynamics of neuronal activity underlying PD. The integration of ML, stochastic

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modelling, and connectomic data holds promise for advancing our understanding of PD pathophysiology and accelerating the development of personalized treatment approaches. Ultimately, the goal is to translate these insights into tangible clinical benefits, offering hope to those affected by this debilitating neurological disorder.

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