Final Report

MODELING NEUROPLASTICITY AND SYNAPTIC DYNAMICS IN PARKINSON'S DISEASE: INTEGRATING BRAIN ACTIVITY AND NERVE PATHWAYS

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Abstract

This research introduces a sophisticated computational model to investigate the complex dynamics of neuronal activity and calcium homeostasis in Parkinson's Disease (PD), blending inputs from both the central and peripheral nervous systems to mirror the intricacies of the condition. Through a detailed exploration of neuronal excitability, connectivity, and intracellular signaling, our study sheds light on the pivotal role of dopamine in modulating brain circuits, particularly emphasizing its influence on motor control and neural communication within the basal ganglia. The degeneration of dopaminergic neurons, as seen in PD, leads to significant disruptions in the functional patterns of key brain regions, contributing to hallmark motor symptoms like bradykinesia and rigidity. Moreover, the model underscores the critical nature of calcium balance, highlighting how dysregulation can lead to neuronal damage and emphasizing the importance of maintaining equilibrium for brain health. By providing a comprehensive multi-scale view of PD pathophysiology, this work not only deepens our understanding of the disease but also opens new pathways for developing diagnostic and therapeutic strategies, with the potential to significantly enhance treatment approaches and patient quality of life.

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1 Problem Statement

Problem Statement

The objective is to construct a computational model that elucidates the mechanisms of synaptic plasticity in Parkinson's disease, integrating afferent signals from the vagus nerve, spinal cord, and peripheral nervous system to simulate the resultant feedback signals, neuro-hormonal responses, and motor functions, and to accurately model spinal and cranial neural pathways for the induction of calcium spikes, thereby initiating molecular processes pertinent to the patho-physiology of Parkinson's disease.

Background

Given the complexity of modeling Parkinson's disease (PD) within a research paper context, it's essential to ground our approach in the current understanding of PD and the role of synaptic plasticity. Parkinson's disease is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to motor and non-motor symptoms. Synaptic plasticity, particularly in the basal ganglia, plays a crucial role in the disease's progression and symptoms expression, affecting motor control and learning processes.

Research has shown that alterations in synaptic plasticity mechanisms, such as long-term potentiation (LTP) and long-term depression (LTD), contribute significantly to the motor symptoms observed in PD. These alterations are influenced by the complex interplay between various neurotransmitters, including dopamine, acetylcholine, and glutamate (1) (2).

Moreover, the involvement of peripheral inputs, including those from the vagus nerve and spinal cord, in PD pathology has been increasingly recognized. The concept of a "gut-brain axis" suggests that early pathological changes in the enteric nervous system can ascend via the vagus nerve to the central nervous system, contributing to PD onset and progression(3).

Furthermore, computational models have been proposed to understand the disease's neural mechanisms better and predict the outcomes of interventions. These models often focus on the basal ganglia's circuitry, incorporating the dynamics of neurotransmitters and their impact on neural plasticity (4). However, there's a gap in models that comprehensively integrate inputs from the peripheral nervous system and detailed molecular mechanisms, such as calcium signaling pathways, which are pivotal in synaptic function and plasticity(5).

The proposed project aims to fill these gaps by developing a model that not only incorporates the central aspects of PD-related synaptic plasticity but also considers the peripheral influences and molecular underpinnings, such as calcium spikes, that drive the disease's pathology. By doing so, we aim to provide a more holistic understanding of PD mechanisms, offering potential insights into novel therapeutic targets.

Objectives

The proposed project aims to create a comprehensive computational model to simulate the synaptic plasticity associated with Parkinson's Disease (PD), incorporating inputs from the central and peripheral nervous systems to reflect the disease's complexity. This innovative approach includes modeling synaptic changes, calcium signaling pathways, and the potential for simulating therapeutic interventions. By integrating data from diverse biological sources such as the vagus nerve, spinal cord, and periphery, and simulating crucial outputs like feedback signals, neurohormones, and motor functions, the project seeks to provide a holistic view of PD and its systemic nature. The ultimate goal is to understand the mechanisms behind both motor and non-motor symptoms of PD and to use this model to explore new therapeutic interventions in a pre-clinical setting.

The benefits of this project are multi-fold, offering significant advances in the understanding of PD, especially in identifying the role of synaptic plasticity and peripheral influences. It holds the promise of innovation in treatment strategies by identifying new therapeutic targets, thereby potentially leading to more effective treatments. Additionally, the model is expected to reduce research costs and time by allowing rapid virtual testing of hypotheses and therapeutic strategies, mitigating the need for extensive in vivo studies. In the long run, this could pave the way for personalized medicine in PD treatment, adjusting therapeutic strategies to individual patient responses. This project, therefore, stands to not only enhance the quality of life for those living with PD but also serves as a pioneering model for researching other neurodegenerative diseases, highlighting its broad potential impact on neuroscience.

2 Literature Survey

The escalating prevalence of Parkinson's disease (PD) presents a formidable public health challenge, with significant implications for affected individuals and society at large. The disease's complexity, characterized by both motor and non-motor symptoms, necessitates advancements in our understanding of its underlying mechanisms to develop more effective treatments. The economic and social burden of PD is considerable, with the costs of care and lost productivity placing a heavy load on healthcare systems and families (6). Therefore, research aimed at elucidating the pathophysiological processes of PD, particularly those related to synaptic plasticity and the integration of nervous system inputs, is of paramount importance. Such efforts promise not only to enhance diagnostic and therapeutic strategies but also to mitigate the financial strain on society by improving patient outcomes and potentially slowing disease progression.

Advances in computational modeling of PD, focusing on the intricate balance of neurotransmission and synaptic plasticity, offer a promising avenue for uncovering novel therapeutic targets. The inclusion of peripheral inputs in these models, such as those from the vagus nerve, highlights the potential for identifying early intervention strategies

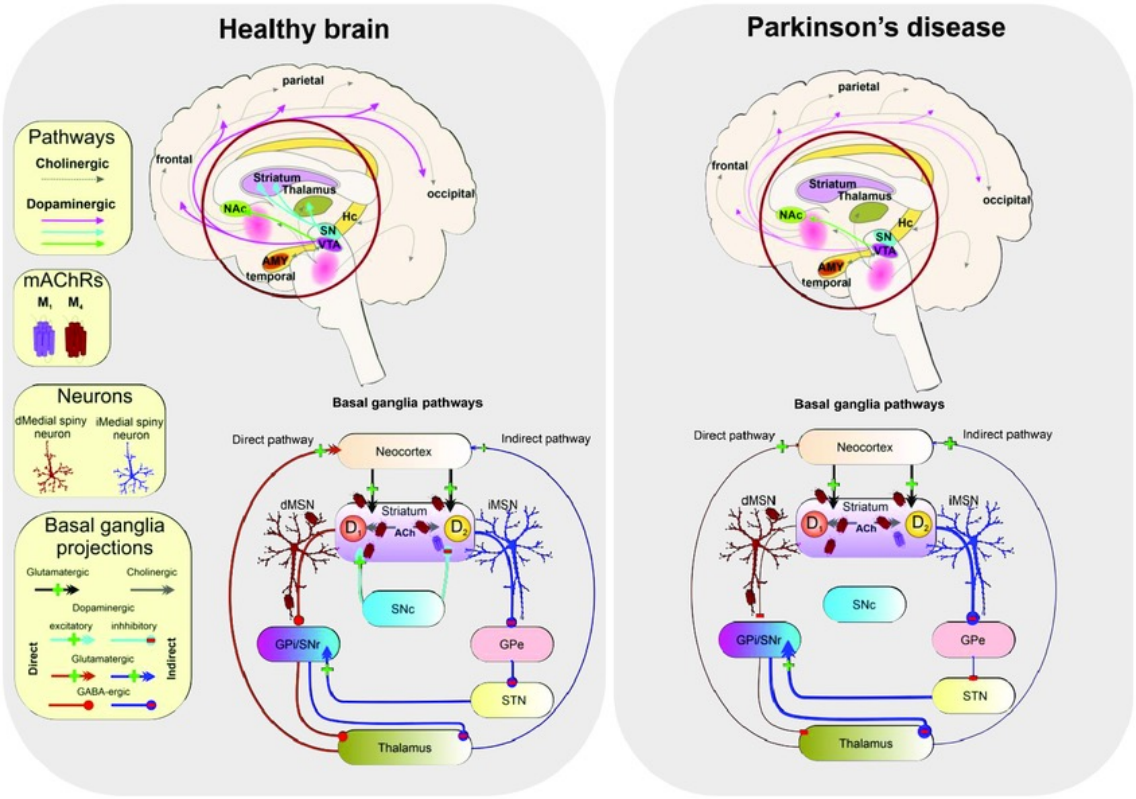

Figure 1: Difference between the brain of a healthy human and a human with Parkinson's disease

that could preempt central nervous system pathology (7). Furthermore, understanding the molecular mechanisms, like calcium signaling disruptions involved in neuronal degeneration, provides a critical foundation for developing drugs aimed at molecular and cellular targets. This holistic approach to modeling PD could revolutionize treatment paradigms, shifting from symptomatic management to addressing the disease's root causes, thereby significantly impacting patient quality of life and reducing the broader societal impacts of this growing pandemic (8).

Recent years have seen significant advancements in computational models aimed at understanding PD. These models have explored various aspects of the disease, from neural circuitry disruptions in the basal ganglia to the effects of neurodegeneration on motor and cognitive functions. For instance, Humphries and Gurney (9) developed a model that highlights the role of dopamine in modulating the basal ganglia's output, which is crucial for understanding PD's motor symptoms. Additionally, Pavlides et al. (10) proposed a computational framework for the dopaminergic system that simulates the effects of

dopaminergic neuron loss, offering insights into the disease's progression and potential therapeutic interventions.

The recognition of the peripheral nervous system's role in PD, particularly through the gut-brain axis, represents a paradigm shift in understanding the disease's etiology. Research by Sampson et al. (11) provided groundbreaking evidence of how gut bacteria can influence neuroinflammation and alpha-synuclein pathology in the brain, suggesting a potential pathway for disease initiation and progression. This work underscores the importance of incorporating peripheral inputs into models of PD to capture the disease's full systemic complexity.

Calcium signaling has been identified as a critical factor in the pathogenesis of PD, with implications for neuron health and synaptic plasticity. Surmeier et al.(12) have shown that aberrant calcium signaling in dopaminergic neurons contributes to cellular stress and vulnerability, leading to neurodegeneration. These findings highlight the need for models that accurately represent calcium dynamics within neurons to uncover novel therapeutic targets aimed at mitigating these effects.

The proposed project seeks to integrate these diverse strands of research into a unified computational model of PD. Unlike existing models that may focus on specific aspects of the disease, this project aims to incorporate inputs from the vagus nerve, spinal cord, and periphery, alongside simulating synaptic plasticity and calcium signaling pathways. This comprehensive approach is poised to offer novel insights into PD's multifactorial nature, potentially identifying new biomarkers and therapeutic targets. By doing so, the project not only advances existing solutions but also proposes a revolutionary framework for understanding and treating PD, emphasizing the disease's systemic and molecular complexity.

3 Research Methodology

This research aims to advance our understanding of Parkinson's disease (PD) through the development and analysis of computational models. These models simulate various aspects of neuronal function and dysregulation in PD, from individual neurons to complex networks involving central and peripheral nervous system inputs. The methodology is structured into four distinct stages, each building upon the insights gained from the preceding one, to dissect the neural underpinnings of PD and compare them with healthy brain function. The chosen simulations aim to elucidate the multifaceted nature of PD, focusing on synaptic plasticity, neurotransmitter dynamics, and the systemic integration of neural circuits.

Development of a Leaky Neuron Integrate-and-Fire Model

The first step involves creating a lean integrate-and-fire model for a single neuron. This simplified model captures the threshold-based firing mechanism crucial for neural communication. It represents the spiking behavior of neurons with minimal computational

complexity, allowing for rapid testing of hypotheses related to neuronal excitability and firing patterns in PD.

The Lean Integrate-and-Fire (LIF) model is a simplified yet powerful computational tool used to simulate the basic electrical activity of neurons (13). Central to this model is the equation describing the rate of change of the neuron's membrane potential over time, given by (14):

$$\frac{dV}{dt} = \frac{-(V - V_{\text{rest}}) + R_m I_{\text{ext}}}{\tau_m}$$

where:

- $\frac{dV}{dt}$ is the rate of change of the membrane potential over time.
- V is the membrane potential of the neuron.
- V_{rest} is the resting membrane potential, which is the potential the membrane tends to return to in the absence of any input.
- R_m is the membrane resistance, which determines how much the membrane potential will change in response to an input current.
- I_{ext} is the external current applied to the neuron, representing inputs from other neurons or external sources.
- τ_m is the membrane time constant, which is a measure of how quickly the membrane potential responds to changes in input. It is determined by the membrane resistance R_m and the membrane capacitance C_m (not explicitly shown in this equation but related by $\tau_m = R_m C_m$).

Choosing the LIF model as the foundation for this research is motivated by several strategic considerations. It strikes a balance between biological realism and computational feasibility, enabling the simulation of large neural networks without the prohibitive computational costs associated with more complex models. Furthermore, the LIF model's framework allows for the exploration of neuronal behavior under various conditions, setting the groundwork for progressively incorporating more sophisticated dynamics in later stages of the research. This approach ensures a systematic exploration of the neural mechanisms implicated in Parkinson's disease, starting from the most elemental aspects of neuronal function and gradually building towards a comprehensive understanding of the disease's complex neurobiology.

Two-Neuron Model with Hodgkin-Huxley Equations

Building on the single-neuron model, the second phase involves the development of a two-neuron model based on the Hodgkin-Huxley equations. This model incorporates the

detailed ionic mechanisms underlying action potential generation, with a specific focus on the roles of sodium and potassium currents. By simulating the interactions between two neurons, this model enables the examination of synaptic connectivity and the dependence of neuronal communication on ion channel dynamics. The choice of the Hodgkin-Huxley model reflects its comprehensive approach to neuronal electrophysiology, providing insights into the alterations in ionic currents that may contribute to the motor and non-motor symptoms of PD (15).

- **The Hodgkin-Huxley model equations are given by:**

- **Membrane Potential Equation:**

$$\frac{dV}{dt} = \frac{I_{\text{ext}} - I_{\text{Na}} - I_{\text{K}} - I_{\text{L}}}{C_m}$$

where V is the membrane potential, I_{ext} is the external applied current, C_m is the membrane capacitance, and I_{Na}, I_{K}, and I_{L} are the sodium, potassium, and leak currents respectively, defined as:

$$\begin{aligned} I_{\text{Na}} &= g_{\text{Na}} \cdot m^3 \cdot h \cdot (V - E_{\text{Na}}) \\ I_{\text{K}} &= g_{\text{K}} \cdot n^4 \cdot (V - E_{\text{K}}) \\ I_{\text{L}} &= g_{\text{L}} \cdot (V - E_{\text{L}}) \end{aligned}$$

- **Gating Variables Equations:**

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(V) \cdot (1 - m) - \beta_m(V) \cdot m \\ \frac{dh}{dt} &= \alpha_h(V) \cdot (1 - h) - \beta_h(V) \cdot h \\ \frac{dn}{dt} &= \alpha_n(V) \cdot (1 - n) - \beta_n(V) \cdot n \end{aligned}$$

where m, h, and n are the gating variables representing sodium and potassium channel states.

- **Rate Functions:**

$$\alpha_m(V) = \frac{0.1 \cdot (V + 40)}{1 - \exp\left(-\frac{V+40}{10}\right)}$$
$$\beta_m(V) = 4.0 \cdot \exp\left(-\frac{V + 65}{18}\right)$$
$$\alpha_h(V) = 0.07 \cdot \exp\left(-\frac{V + 65}{20}\right)$$
$$\beta_h(V) = \frac{1}{1 + \exp\left(-\frac{V+35}{10}\right)}$$
$$\alpha_n(V) = \frac{0.01 \cdot (V + 55)}{1 - \exp\left(-\frac{V+55}{10}\right)}$$
$$\beta_n(V) = 0.125 \cdot \exp\left(-\frac{V + 65}{80}\right)$$

- **Variable Definitions:**

- V: Membrane potential (mV)
- I_{ext}: External applied current ($\mu A/cm^2$)
- C_m: Membrane capacitance ($\mu F/cm^2$)
- $g_{\text{Na}}, g_{\text{K}}, g_{\text{L}}$: Maximum conductances for Na^+, K^+, and leak channels (mS/cm^2)
- $E_{\text{Na}}, E_{\text{K}}, E_{\text{L}}$: Reversal potentials for Na^+, K^+, and leak channels (mV)
- m, h, n: Gating variables, dimensionless probabilities ranging from 0 to 1

The importance of the Hodgkin-Huxley model lies in its ability to accurately simulate the electrical characteristics of neurons, including the action potential generation and propagation. This model's comprehensive approach to understanding the ionic bases of neuronal activity provides crucial insights into how alterations in ionic currents, such as those seen in Parkinson's disease, can lead to both motor and non-motor symptoms. By incorporating the Hodgkin-Huxley equations into our two-neuron model, we are able to explore the complex dynamics of neuronal communication and synaptic connectivity, shedding light on the pathophysiological mechanisms underlying PD.

Modeling Calcium Dynamics in PD

The third phase simulates calcium dynamics in a PD model by integrating mechanisms of calcium-induced calcium release (CICR) and calcium buffering into the two-neuron model.

This phase aims to uncover the dysregulation of calcium homeostasis in PD, highlighting potential therapeutic targets for modulating calcium signaling (16).

To model the complex interplay of calcium signaling pathways, we introduce equations that capture the essence of CICR and calcium buffering mechanisms:

- **Membrane Potential Equation for Each Neuron (V)**:

$$\frac{dV}{dt} = \frac{I_{\text{ext}} + I_{\text{syn}} - I_{\text{Na}} - I_{\text{K}} - I_{\text{L}} - I_{\text{Ca}}}{C_m}$$

- **Gating Variables for Na^+, K^+ Channels (m, h, n)**: The dynamics of m, h, and n are governed by their respective alpha and beta functions, similar to the standard Hodgkin-Huxley model.

- **Calcium Gating Variable (c)**:

$$\frac{dc}{dt} = \alpha_c(V) \cdot (1 - c) - \beta_c(V) \cdot c$$

- **Intracellular Calcium Concentration Dynamics ($Ca_{\textbf{intracellular}}$)**:

$$\frac{dCa}{dt} = \text{clamp}\left(-I_{\text{Ca}} + \text{CICR}_{\text{flux}} - \text{buffered}_{\text{Ca}} - \text{extruded}_{\text{Ca}}, \text{min} = 0.0\right)$$

Variable Definitions:

- V: Membrane potential (mV).
- I_{ext}: External applied current ($\mu A/cm^2$).
- I_{syn}: Synaptic current from other neurons, not explicitly modeled here.
- $I_{\text{Na}}, I_{\text{K}}, I_{\text{L}}$: Sodium, potassium, and leak currents, respectively.
- I_{Ca}: Calcium current through calcium channels.
- C_m: Membrane capacitance ($\mu F/cm^2$).
- $g_{\text{Na}}, g_{\text{K}}, g_{\text{L}}, g_{\text{Ca}}$: Maximum conductances for Na^+, K^+, leak, and Ca^{2+} channels (mS/cm^2).
- $E_{\text{Na}}, E_{\text{K}}, E_{\text{L}}, E_{\text{Ca}}$: Reversal potentials for Na^+, K^+, leak, and Ca^{2+} channels (mV).
- m, h, n: Gating variables for Na^+ and K^+ channels.
- c: Gating variable for Ca^{2+} channels.

- Ca: Intracellular calcium concentration.
- $\text{CICR}_{\text{flux}}$: Calcium-induced calcium release flux.
- $\text{buffered}_{\text{Ca}}$: Calcium buffering within the cell.
- $\text{extruded}_{\text{Ca}}$: Calcium extrusion out of the cell.
- Ca_{ER}: Calcium concentration in the endoplasmic reticulum.
- $k_{\text{CICR}}, k_{\text{buffer}}, k_{\text{extrusion}}$: Rate constants for CICR, buffering, and extrusion processes.

Understanding the dysregulation of calcium homeostasis in PD is crucial, as it offers insights into the cellular mechanisms that may contribute to neuronal degeneration. The integration of CICR and calcium buffering into our computational model allows

Comprehensive Neural Network Model Incorporating Central and Peripheral Inputs

The final phase expands to a comprehensive neural network model that simulates inputs from the cortex and outputs to key brain regions affected by PD, such as the striatum, thalamus, and substantia nigra. This model allows for the observation of circuit-level dysfunctions and evaluates how central and peripheral nervous system inputs are processed differently in PD compared to a healthy brain.

Thalamus (T)

- The activity of the thalamus (T) is inversely proportional to the activity in the GPi/SNr (G).

$$T' = -G$$

where:

$$T : \text{Thalamic activity}$$
$$G : \text{GPi/SNr activity}$$

Striatum (S)

- The activity of the striatum (S) is influenced by its membrane potential (V), sodium (Na^+), and potassium (K^+) concentrations.

$$S' = f_{\text{striatum}}(V, \text{Na}^+, \text{K}^+)$$

$$\frac{dS}{dt} = k_1 \cdot V + k_2 \cdot [\mathrm{Na}^+] - k_3 \cdot [\mathrm{K}^+]$$

where:

$$S : \text{Striatal activity}$$
$$V : \text{Membrane potential}$$
$$\mathrm{Na}^+, \mathrm{K}^+ : \text{Sodium and potassium concentrations}$$

GPi/SNr (G)

- The activity of the GPi/SNr (G) is dependent on the activity in the striatum (S).

$$G' = f_{\text{GPi/SNr}}(S)$$

where:

$$G : \text{GPi/SNr activity}$$

Cortex (C)

- The activity of the cortex (C) can be influenced by various factors such as sensory inputs, internal states, and network connectivity.

$$C' = f_{\text{cortex}}(\text{inputs})$$

where:

$$C : \text{Cortical activity}$$
$$\text{inputs} : \text{External inputs}$$

This advanced simulation approach enables the study of the intricate dynamics of neural circuits in PD, incorporating various factors such as synaptic plasticity, neurotransmitter dynamics, and the effects of neurodegeneration on network connectivity. By leveraging this model, researchers can gain insights into the systemic manifestations of PD and identify potential neural circuit targets for therapeutic intervention.

The image outlines the basal ganglia circuitry, emphasizing the direct and indirect pathways that regulate motor control. The direct pathway, signified by the release of glutamate (Glu) and dopamine (DA), facilitates movement by inhibiting the GPi/SNr, reducing its inhibitory influence on the thalamus and thereby promoting cortical activity. The indirect pathway, on the other hand, inhibits movement; the striatum dampens the

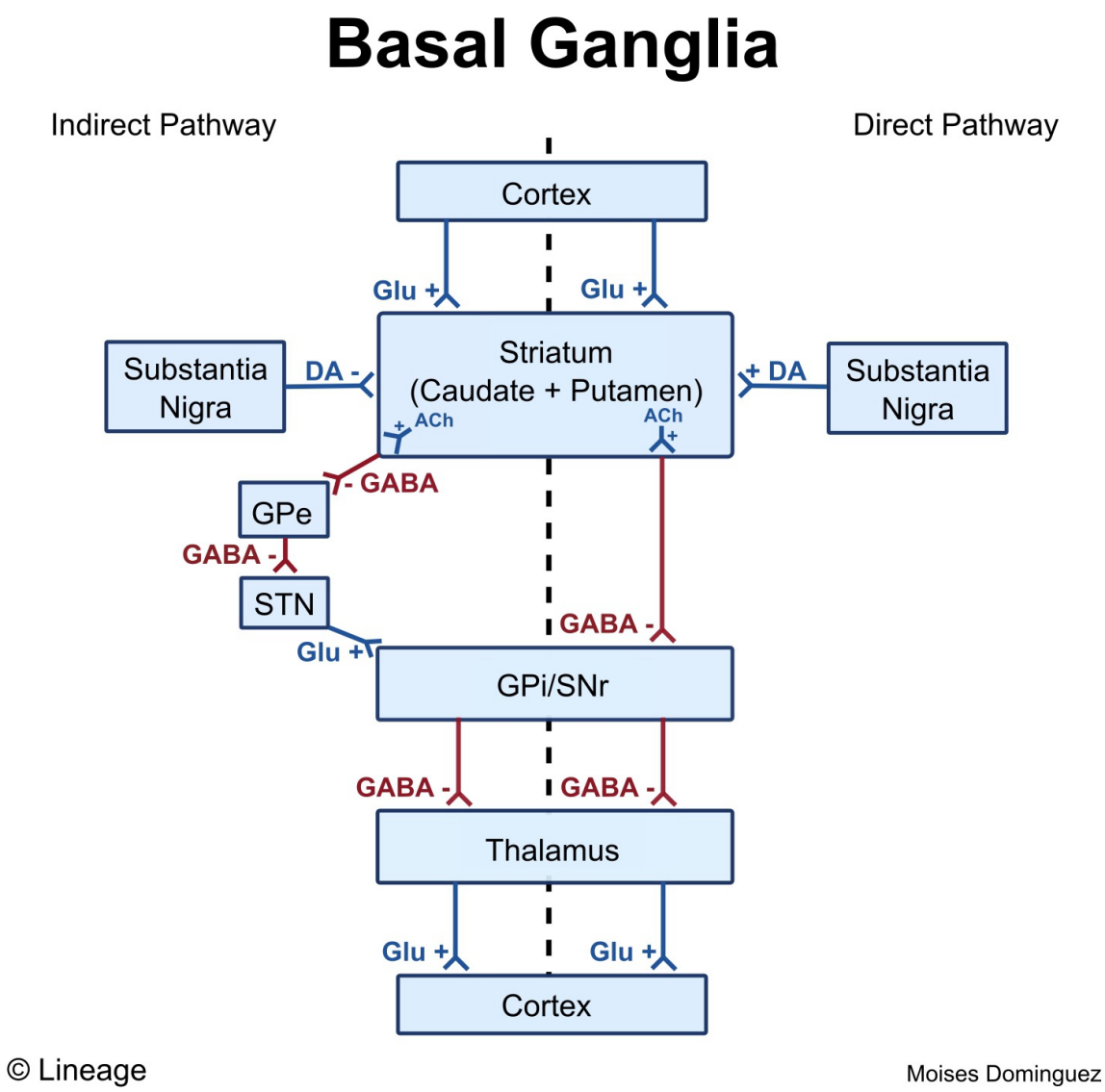

Figure 2: Direct and Indirect Pathways in Basal Ganglia Circuitry

GPe, leading to increased activity in the subthalamic nucleus (STN), which in turn excites the GPi/SNr, resulting in enhanced inhibition of the thalamus and suppressed cortical stimulation. This balance between pathways is crucial; disruptions, such as the dopaminergic neuron loss seen in Parkinson's disease, can lead to motor deficits characteristic of the

disorder.

Through these methodologically progressive steps, the research provides detailed computational insight into the pathophysiology of PD. By bridging the gap between molecular mechanisms and whole-brain dynamics, this approach offers a multi-scale perspective on the disease. It underscores the importance of understanding the complex interplay between different levels of brain organization and how disruptions at the molecular or cellular level can lead to the systemic manifestations observed in Parkinson's disease.

The comprehensive neural network model represents a significant advancement in our ability to simulate and understand the complex neurobiological underpinnings of PD. It opens new avenues for exploring the disease's progression, identifying biomarkers, and developing targeted therapies. As such, this research contributes significantly to the field of neurodegenerative disease study, providing a robust framework for future investigations into PD and potentially other neurological conditions.

4 Results and Discussion

Development of a Leaky Neuron Integrate-and-Fire Model

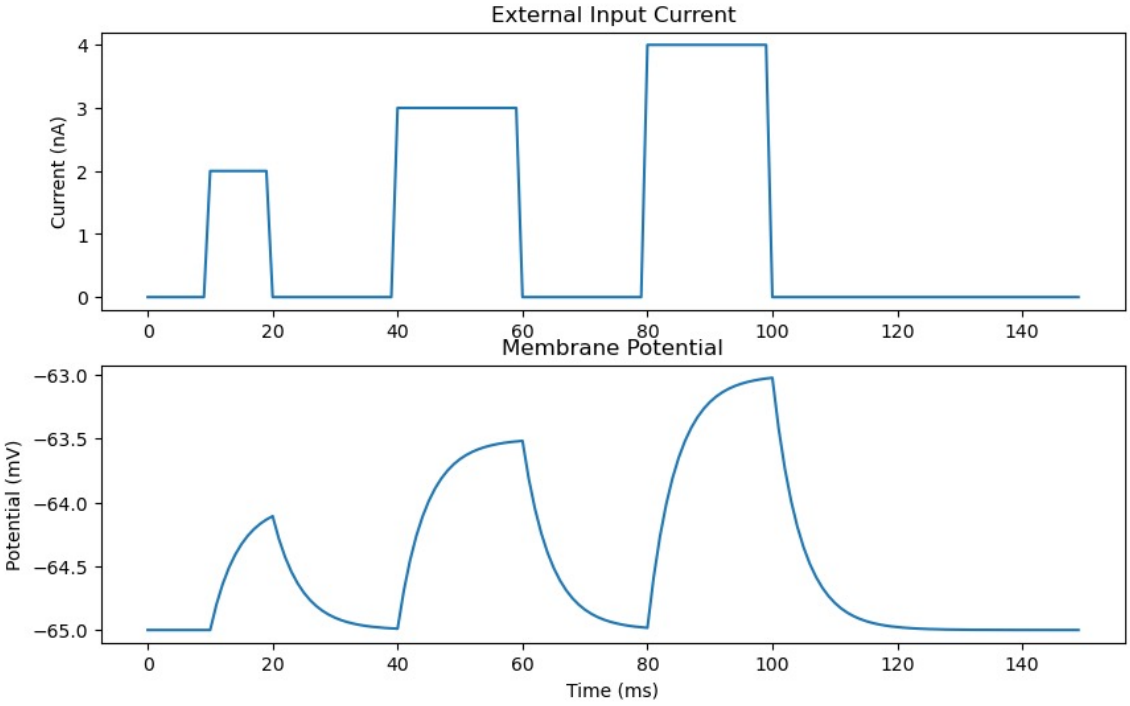

Figure 3: Simulation of LIF model

The generated plots shown in figure 3 represent the behavior of a neuron modeled by a leaky integrate-and-fire (LIF) model under the influence of external input currents over time.

In the first plot, we observe the periods of external input current applied to the neuron, depicted as three distinct bursts of varying magnitudes (2 nA, 3 nA, and 4 nA) at different time intervals. The first burst occurs between 10 and 20 ms, the second between 40 and 60 ms, and the third between 80 and 100 ms. These inputs simulate the kind of external stimulation a neuron might receive in a neural network.

The second plot shows the neuron's membrane potential in response to these input currents. Initially, the membrane potential is at the resting potential of -65 mV. Upon receiving each current burst, the membrane potential rises as the neuron integrates the incoming current. Once the potential reaches the spike threshold of -50 mV, the neuron fires (not explicitly shown due to the model's simplicity), and the potential is immediately reset to -65 mV, followed by a refractory period where the potential remains at the reset value despite ongoing external stimulation. This cycle repeats for each current burst, demonstrating the basic behavior of neuronal firing in response to external stimuli. The increase in input current amplitude leads to a higher frequency of firing, illustrating the neuron's responsiveness to the strength of the stimulation.

Two-Neuron Model with Hodgkin-Huxley Equations

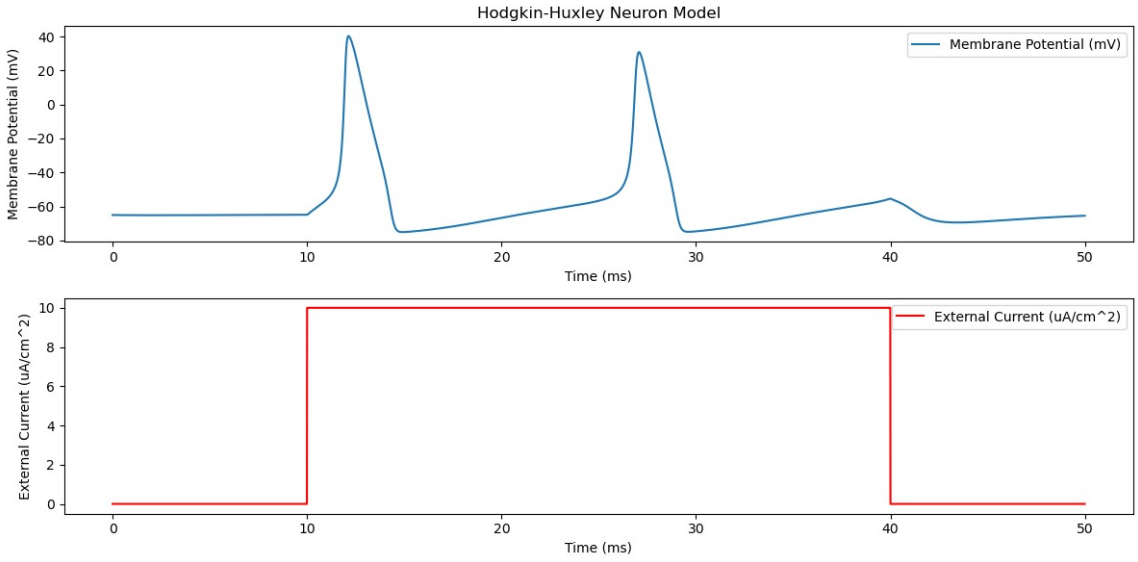

Figure 4: Simulation of Hodgkin-Huxley model

The plots generated in figure 4 from the Hodgkin-Huxley model simulation depict the

dynamics of a neuron's membrane potential in response to an applied external current, as well as the external current itself over time.

In the first plot, the membrane potential of the neuron exhibits characteristic spikes or action potentials during the period when the external current is applied (from 10 to 40 ms). These spikes are due to the depolarization and repolarization of the neuron's membrane. Depolarization occurs when the membrane potential becomes less negative, reaching a threshold that triggers the opening of sodium (Na+) channels. This leads to a rapid influx of Na+ ions, causing the membrane potential to rise sharply. Once the peak is reached, the sodium channels close, and potassium (K+) channels open, allowing K+ ions to exit the cell, leading to repolarization—where the membrane potential returns to its resting state. The overshoot below the resting membrane potential is due to the delayed closing of K+ channels, briefly making the interior of the cell more negative than at rest.

The second plot shows the external current applied over time, with a constant current of 10A applied between 10 and 40 ms. This external stimulus is what initiates the depolarization process, leading to the observed action potentials.

The Hodgkin-Huxley model provides a detailed mathematical framework for understanding these processes, incorporating the kinetics of Na+ and K+ channels and their impact on the neuron's membrane potential. This model not only explains how action potentials are generated and propagate along neurons but also highlights the fundamental role of ion channels in neuronal excitability and signaling. Through this simulation, we see the direct effect of external stimulation on neuron activity, showcasing the delicate balance between depolarization and repolarization phases crucial for action potential generation and neural communication.

Modeling Calcium Dynamics in PD

The plots in figure 5 show the membrane potential of each neuron over time. Initially, both neurons exhibit a resting membrane potential of approximately -65 mV. Upon application of external current to each neuron at different times), the neurons depolarize, potentially generating action potentials if the threshold is crossed. The external currents are applied at different intervals to each neuron, demonstrating the network's response to asynchronous stimuli. This dynamic reflects how neurons in a network can influence each other's firing patterns through synaptic connections, albeit the synaptic weights in this specific implementation might not lead to visible post-synaptic potentials due to their configuration or the absence of explicit synaptic current equations in the given simulation.

The calcium concentration shown in figure 6 within each neuron is influenced by calcium currents, CICR, buffering, and extrusion processes. The increase in intracellular calcium concentration would be evident during periods of neuronal activity (depolarization phases) due to calcium influx through voltage-gated calcium channels and CICR. Subsequently, buffering and extrusion mechanisms help to restore basal calcium levels, highlighting the role of calcium dynamics in neuronal signaling and its potential dysregulation in neurological

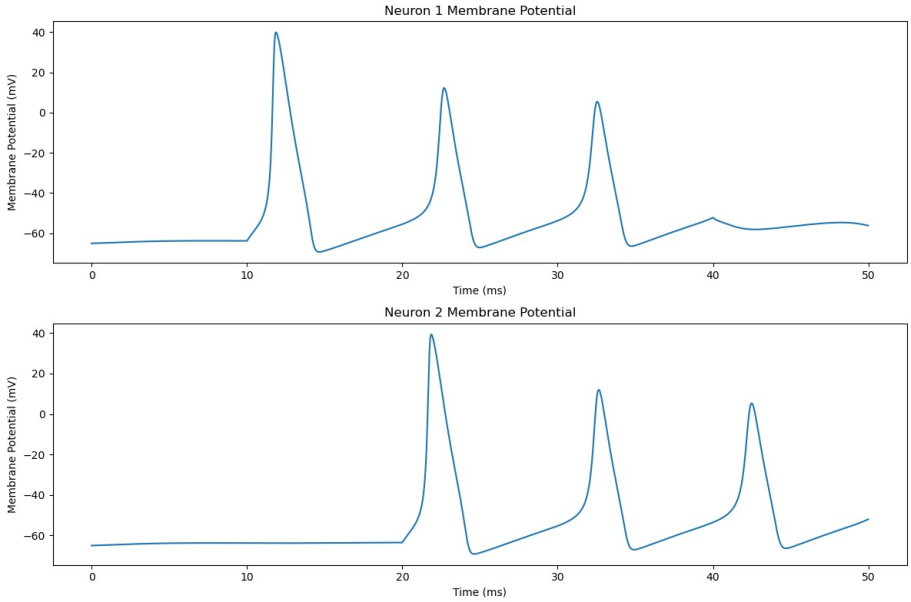

Figure 5: Simulation of neuron firing in PD model

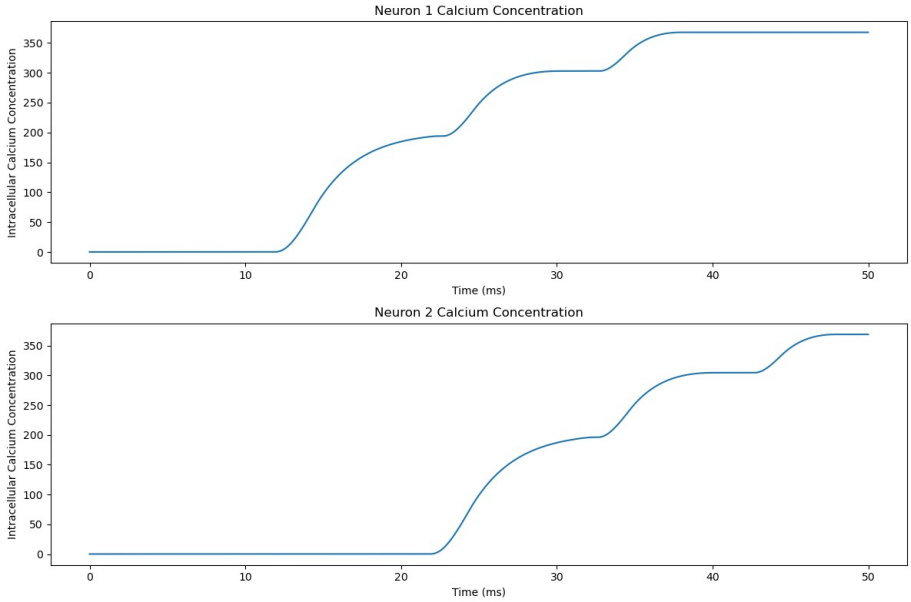

Figure 6: Simulation of Calcium Concentration in PD model

disorders. Due to absence of dopamine producing neurons in PD affected brain, the buffering and extrusion mechanisms are hindered which cause the calcium concentration to accumulate over time and cause abnormally high level of calcium in the brain. This leads to dysregulated calcium homeostasis.

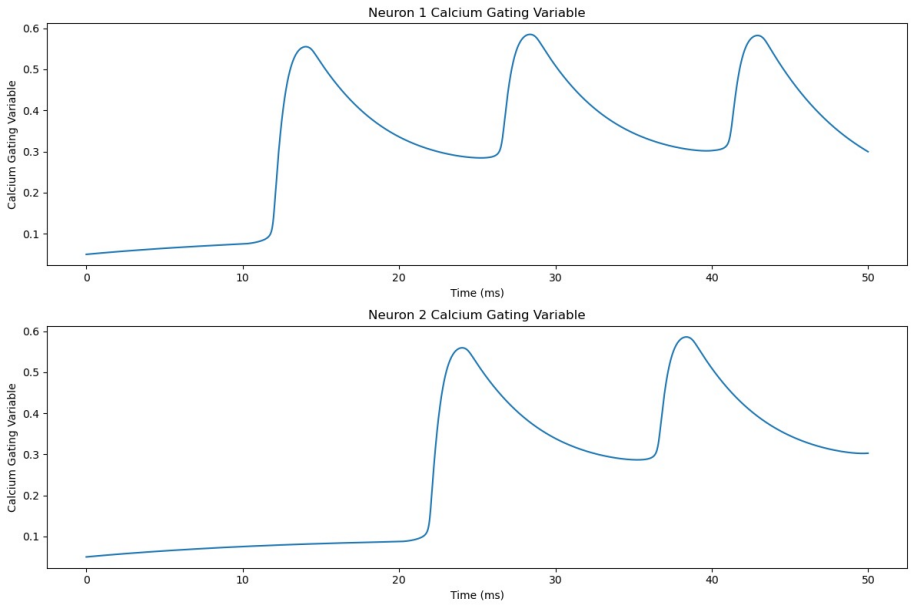

Figure 7: Simulation of Calcium concentration in healthy brain model

In a healthy brain, calcium dynamics are characterized by oscillations within a narrow range, crucial for maintaining neuronal function and communication as shown in figure 7. This regulation involves a delicate balance between calcium entry through channels and its removal via pumps and exchangers, with neurotransmitters like dopamine fine-tuning these processes. Dopamine modulates calcium levels through receptor-mediated pathways, ensuring that calcium oscillations support normal brain activities such as synaptic plasticity, signaling, and gene expression.

Comprehensive Neural Network Model Incorporating Central and Peripheral Inputs

The plotted results in figure 8 illustrate the dynamics of a neural circuit modeling Parkinson's disease (PD), emphasizing the interplay between the cortex, striatum, GPi/SNr (globus pallidus internus/substantia nigra pars reticulata), and thalamus.

Initially, there's a pulse of activity from the cortex, represented as a square wave where the activity level rises to 1 between 0.5 and 1.5 seconds, simulating a burst of excitatory

input. This input into the striatum is modulated by a PD-specific excitatory function, which accounts for reduced dopaminergic effect, evident in the diminished responsiveness of the striatum to cortical stimulation. The altered striatal activity then influences GPi/SNr activity, which in PD, tends to be overactive due to insufficient inhibition from the striatum. However, in this simple model, the GPi/SNr activity decreases as it's directly inhibited by the striatum's response. This in turn affects the thalamic output, which is modeled as inversely related to GPi/SNr activity, leading to increased thalamic activity when GPi/SNr activity is reduced. These dynamics are illustrative of the pathological changes in PD,

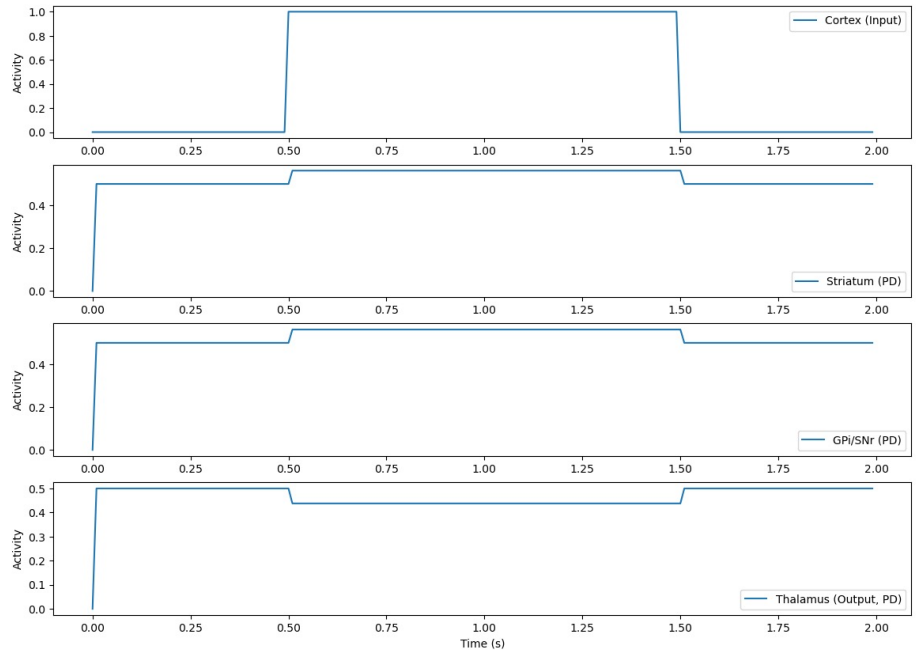

Figure 8: Simulation of basal ganglia circuitry in PD model

where dopaminergic neuron degeneration diminishes the modulatory effect of dopamine on striatal neurons. This leads to a disruption in the balance of direct and indirect pathways in the basal ganglia circuitry. Normally, dopamine facilitates the activation of the direct pathway (which promotes movement) and inhibits the indirect pathway (which suppresses movement). PD's dopaminergic loss results in reduced facilitation of movement, manifesting as the motor symptoms of PD—bradykinesia and rigidity. The simplified circuit model captures the essence of these alterations by showing how reduced dopaminergic modulation impacts the activity across the circuit, leading to changes in the output of the thalamus, which plays a crucial role in controlling motor activity.

In a healthy brain, the striatal response to cortical input is more robust, thanks to the optimal dopamine effect modeled in the provided function as shown in figure 9. This optimal

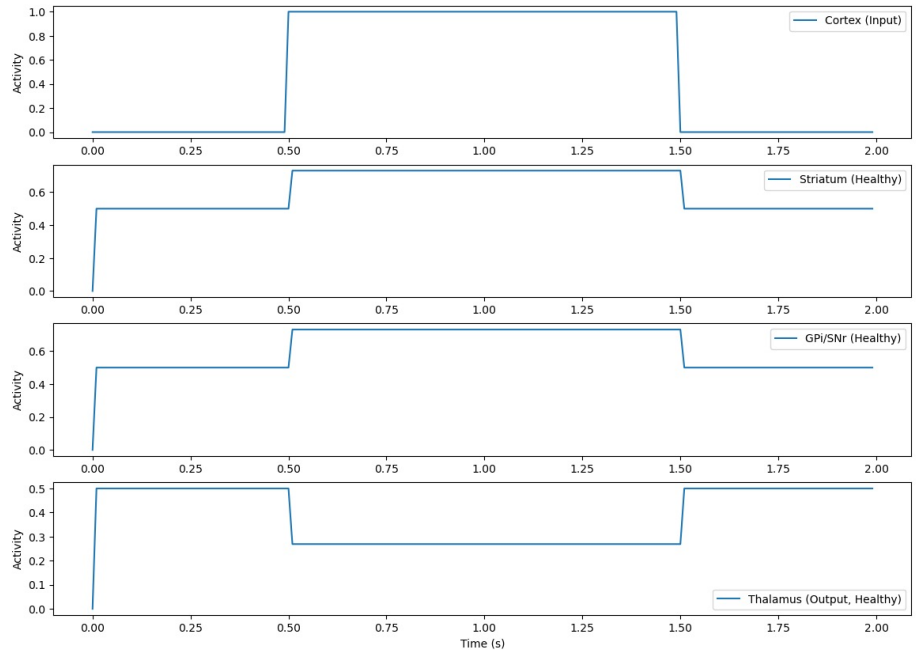

Figure 9: Simulation of basal ganglia circuitry in healthy model

dopaminergic modulation ensures a balanced activation of both the direct (movement-promoting) and indirect (movement-inhibiting) pathways of the basal ganglia. As a result, the GPi/SNr's activity is appropriately modulated, allowing for a more regulated thalamic output that facilitates normal movement. This contrasts with the PD model, where dopamine's reduced effect leads to diminished striatal response, excessive GPi/SNr activity, and thus impaired thalamic output, culminating in the motor deficits characteristic of PD.

These simulations highlight the critical roles of dopamine in maintaining the balance of basal ganglia circuitry and of calcium homeostasis in neuronal health. The contrasts between the healthy and PD models illustrate how deficits in these areas can lead to the characteristic pathophysiology of PD, including disrupted motor control and potential neuronal damage from dysregulated calcium levels.

5 Conclusion

This study has systematically explored the dynamics of neuronal activity and calcium homeostasis under conditions simulating both a healthy brain and Parkinson's Disease (PD) through computational modeling. By developing models ranging from a simple leaky integrate-and-fire neuron to a comprehensive neural network incorporating central and peripheral inputs, we have delineated the nuanced interplay between neuronal excitability,

synaptic connectivity, and intracellular signaling pathways. The simulations reveal the critical influence of dopamine on modulating neuronal circuits, particularly within the basal ganglia, and its profound impact on motor control and neural communication.

In the context of PD, our models highlight how the degeneration of dopaminergic neurons and the subsequent reduction in dopamine levels lead to marked disruptions in the activity patterns of the striatum, GPi/SNr, and thalamus. These disruptions underpin the motor symptoms characteristic of PD, such as bradykinesia and rigidity. Additionally, the simulated calcium dynamics offer insights into the potential neuronal damage arising from dysregulated calcium homeostasis, accentuating the role of calcium in neurodegeneration and the importance of maintaining its equilibrium for neuronal health.

Through these computational experiments, we bridge the gap between molecular mechanisms and whole-brain dynamics, providing a multi-scale perspective on the pathophysiology of PD. The insights gained from these models underscore the complexity of neural and molecular interactions involved in PD and the potential therapeutic targets within these systems. Moving forward, these models could serve as valuable tools for testing hypotheses about the disease's progression and response to treatments, ultimately contributing to the development of more effective diagnostic and therapeutic strategies for Parkinson's Disease and similar neurological conditions.

6 Future Scope

The exploration of neural dynamics and calcium homeostasis in Parkinson's disease (PD) through computational models opens a wide array of avenues for future research. An immediate and promising direction is to extend these models to incorporate synaptic plasticity using Hebbian learning principles. By simulating how synaptic strengths change in response to the activity of the neuron and its neighbors, this approach could shed light on the long-term alterations in neural networks associated with PD. Incorporating synaptic plasticity into the models will allow for a deeper understanding of how PD affects not only the individual neurons but also the connectivity and overall network function over time. This could lead to insights into the progression of the disease and the mechanisms behind the loss of motor and cognitive functions. Moreover, modeling synaptic plasticity could inform the development of new therapeutic strategies aimed at restoring neural network dynamics, potentially offering ways to counteract the effects of dopamine depletion. This integration of Hebbian learning principles into PD models represents a forward leap in creating more dynamic and adaptive simulations, paving the way for novel interventions and a better understanding of neurodegenerative diseases.

7 References

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