Towards a Biologically Plausible Artificial Neural Network – Neuroreceptor-Dependent Plasticity (NRDP) based Spiking Neural Networks

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Abstract

This thesis presents a novel approach to computational modelling that seeks to enhance Spiking Neural Network (SNN) models by simultaneously incorporating genetic information and Neuroreceptor-Dependent Plasticity (NRDP) mechanisms. Motivated by the need to develop biologically inspired computational models that accurately capture the interplay between genetic factors and neural activity, the goal is to establish a more holistic computational paradigm.

A biologically enhanced SNN model that integrates genetic information into the underlying Spiking Neuron model, and implements an NRDP unsupervised learning rule based on a computational model of NRDP dynamics is introduced. Integration of the genetic information is facilitated via a novel and simplified Gene Regulatory Network (GRN) model, and a generalised version of the Leaky Integrate-and-Fire (LIF) Spiking Neuron model.

Based on experimental validation of this biologically enhanced SNN model using Electro-encephalogram (EEG) data from Alzheimer's Disease patients and controls, the findings reveal a significant improvement in classification accuracy over baselined methods. These findings also suggest enhanced synaptic connectivity, particularly within the hippocampal region, resulting in an improvement in classification accuracy of 14.7%. Improvements in the network's interpretative capabilities are also demonstrated, with an uplift of 6.8% in specificity, enabling the model to learn context-dependent associations and make nuanced interpretations. Finally, enhanced contextual recall is observed, increasing sensitivity by 14.8%, allowing the model to utilise past experiences for current interpretations, thus making its decisions more explainable and leading to more favourable knowledge discovery.

These results underscore the potential of genetically informed SNNs to more accurately reflect biological processes, thereby advancing the field of biologically inspired computing, and taking important steps towards biologically plausible Artificial Neural Networks.

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signature: Date: 12 June 2024

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1 Introduction

"There is a history in all men's lives, figuring the nature of the times deceased, the which observed, a man may prophesy, with a near aim, of the main chance of things as yet not come to life, which in their seeds and weak beginnings lie intreasured." proffers the Earl of Warwick to King Henry IV in the third play of William Shakespeare's "Henriad" (Shakespeare, Henry IV, Part 2, Act 3, Scene 1, 1597-98). Simply put, we can find evidence in the past for things that may happen in the future, such that we may use this knowledge to predict the future with a degree of certainty. Warwick was merely trying to council the sleepless, and troubled usurper. However, this idea that we can use the past to predict the future is an incredibly profound concept, and a central tenet of Machine Learning (ML), a subfield of Artificial Intelligence (AI) whose goal is to find generalisable, predictive patterns based on passive observations.

The field of ML encompasses the development and application of ML models to make predictions, learn patterns and discover insights from data, solve complex problems, and more recently, automate tasks. Their benefits are manifold. First and foremost, they enhance efficiency and accuracy by handling vast datasets and complex computations with astonishing speed. They can uncover hidden trends and relationships within data that might be impossible for humans to discern, thereby facilitating data-driven insights and informed decision making.

In addition, they have the potential to improve productivity through automation of repetitive tasks, freeing up individuals time to concentrate on creative and strategic pursuits. Furthermore, these models find applications across a diverse range of domains, demonstrating their adaptability and versatility in solving real-world problems.

Artificial Neural Networks (ANNs), represent a subset of Machine Learning models that leverage the principles of neuronal organisation, inspired by the connections found in biological neural networks. Thus, ANNs seek to model the connectionism of the neurons found in biological brains. Spiking Neural Networks (SNNs) are a class of ANNs inspired by the biological structure and functioning of the human brain. Unlike traditional artificial neural networks, which use continuous activations, SNNs employ discrete pulses, or "spikes" of activity to simulate the way neurons communicate in the brain. This makes SNNs particularly well-suited for tasks involving temporal information processing and event-based computation. SNNs can be used to model the complex dynamics of neural circuits by incorporating the spiking behaviour of neurons, thus, SNNs provide a more biologically realistic representation

of brain function, enabling researchers to study, for example, the impact of brain related diseases at a finer temporal scale.

The ability of SNNs to capture temporal patterns and recognise subtle changes in neural activity make them a good candidate for the early detection and monitoring of brain related diseases, as an example. While the exploration of SNNs in this context is still in its early stages, the unique features of SNNs hold promise for advancing our understanding of the neurobiological mechanisms underlying disease mechanisms and developing novel approaches for diagnosis and treatment. Ongoing research in this area may uncover valuable insights into the intricate relationship between neural network dynamics and disease pathology, ultimately leading to improved strategies and interventions.

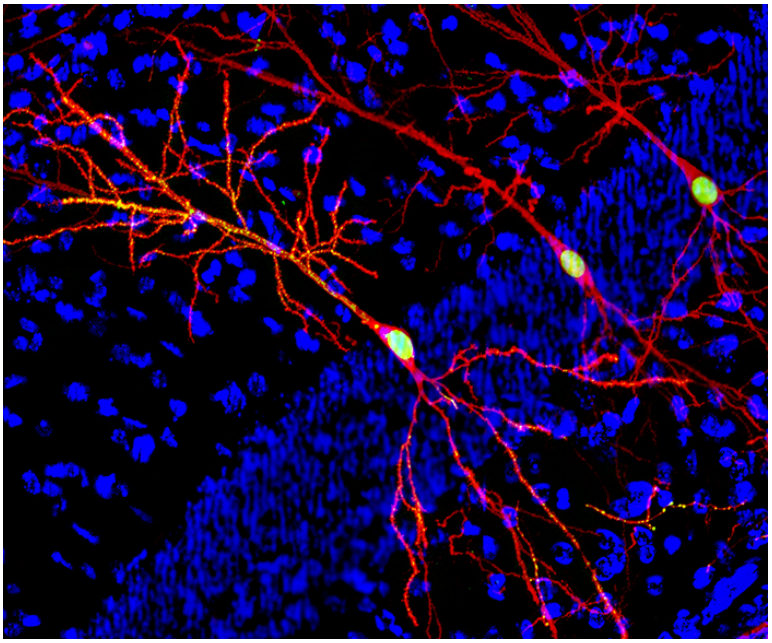


Figure 1 Hippocampal neurons in the human brain. (Suarez, 2017)

1.1 Background and Motivation

Neuroplasticity, the brain's ability to experience structural and functional changes in response to stimuli, both internal and external, lies at the core of learning and memory processes. Synaptic plasticity, a key phenomenon within neuroplasticity, refers to the ability of synapses to undergo long-lasting modifications in strength, structure, and efficacy based on neuronal activity patterns. Indeed, as William James first identified in his seminal work The Principles of Psychology, “The phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed” (James, The Principles of Psychology, Volume One, 1890).

Extensive research has demonstrated that synaptic plasticity plays a vital role in shaping neural circuits and is critical for learning, memory formation, and information processing in the brain. Specifically, long-term potentiation (LTP) and long-term depression (LTD) are well-established forms of synaptic plasticity associated with the strengthening and weakening of synaptic connections.

SNNs have emerged as a computational framework that mimics the behaviour of biological neurons more faithfully than traditional artificial neural networks. SNNs employ spike-based communication, where discrete electrical pulses (spikes) are emitted by neurons to transmit information. The timing and patterns of these spikes are crucial for neural computation and learning.

However, achieving true biological plausibility in computational models requires integrating genetic regulatory mechanisms into SNNs. Genetic information plays a pivotal role in synaptic plasticity, influencing the expression of various proteins and molecules involved in neuronal signalling, synaptic efficacy, and neural development.

The incorporation of Gene Regulatory Network (GRN) models into computational frameworks provides a means to capture the intricate interplay between genetic and synaptic processes. GRNs represent the complex interactions between genes and their regulatory elements, influencing gene expression patterns over time. By integrating this feedback into SNNs, we can explore how genetic information modulates synaptic plasticity and contributes to the functional dynamics of neural networks.

The motivation behind this research stems from the need to develop biologically inspired computational models that accurately capture the interplay between genetic factors and neural activity. By integrating genetic information into SNNs, this research aims to develop a more comprehensive computational framework, that can be deployed to relevant applications, domains, or research areas, to aid in the facilitation of knowledge discovery.

1.2 Problem Statement

Understanding the intricate interplay between genetic factors and synaptic plasticity is crucial for unravelling the complexities of brain function and related disorders. While significant progress has been made in modelling synaptic plasticity using SNNs, the incorporation of GRNs into these computational models remains a fertile ground for exploration.

Existing computational models often lack the integration of genetic information necessary to achieve biologically plausibility. This limitation hampers our ability to accurately represent the complex dynamics of synaptic plasticity and its underlying genetic regulatory mechanisms. The absence of this feedback hinders our understanding of the influence of genetic factors on neural activity and limits our ability to investigate the role of gene expression dynamics in learning, memory, and brain-related diseases. Without the inclusion of genetic information, these models fail to capture the full complexity of synaptic plasticity and its relevance to neurological conditions.

Furthermore, existing research has shown that Neuroreceptor-Dependent Plasticity (NRDP), a form of synaptic plasticity modulated by neuroreceptors, plays a vital role in learning and memory processes. However, the integration of GRN models and NRDP into SNN models has not been adequately explored. Understanding how NRDP interacts with genetic regulatory mechanisms within SNNs could significantly enhance the biological plausibility and performance of these computational models, enabling more accurate classification, and providing valuable insights.

Hence, our goal is to integrate GRN and NRDP, into SNN models. This research aims to address the existing limitations by capturing the dynamic interactions between genetic factors, neuroreceptors, and synaptic plasticity, leading to a more biologically plausible, performant, and interpretable SNN model.

1.3 Research Questions and Objectives

The objective of this thesis, inspired by the previous work of Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018), is to explore how Gene Regulatory Networks (GRNs), and Neuroreceptor-Dependent Plasticity (NRDP), can be leveraged to enhance the biological plausibility, classification accuracy, predictive performance, and interpretability of SNN models. This research aims to address the gaps identified in Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018), by answering the following research questions:

1. How can genetic information related to synaptic plasticity, be used to modify the Spiking Neural Network (SNN) model, and thus increase the biological plausibility of the computational model?
2. How can Neuroreceptor-Dependent Plasticity (NRDP) increase the classification or predictive performance of the SNN model?

3. How can Neuroreceptor-Dependent Plasticity (NRDP) increase the SNN model interpretability?
4. Which gene or genes (via a Gene Regulatory Network) will produce the best result with respect to classification accuracy?

By answering these questions, this research aims to advance the field of computational neuroscience by developing a more biologically plausible SNN model. Ultimately, this research has the potential to pave the way for improved knowledge discovery, and take important steps towards biologically plausible Artificial Neural Networks.

1.4 Thesis Structure

This section proposes the thesis structure outlined in the following:

- Literature review - A comprehensive overview of existing research and scholarly works relevant to neural processes, and biologically inspired computing
- Methodology - Outline of the theoretical and conceptual basis upon which the research is built and . describes the mathematical and computational framework used to simulate the conceptual model. And, provides information about the datasets used to validate the proposed methods.
- Experimental Framework - Delineates the methodology and procedures employed to conduct the experiments, including the design, data collection methods, and analysis techniques
- Results and Discussion - Presents the findings of this thesis, interprets their significance in relation to the research questions, integrating theoretical insights and empirical evidence
- Conclusion and Future Direction - Summarises the key findings of this research, discusses their implications, and suggests potential avenues for future research or practical applications

All figures and tables are provided by the author using Geogebra, NeuCube-M1, NeuCube-Py, Microsoft PowerPoint, bespoke Python code, and Gliffy unless otherwise stated.

2 Literature Review

Neural processes, such as Neuroplasticity, Synaptic Plasticity, Neuroreceptors, and Neurotransmission, are pivotal in shaping brain function and behaviour. Studying these

processes not only deepens our understanding of the brain but also holds immense potential for various applications. For instance, development of novel therapeutic interventions for neurological disorders, new treatments for Alzheimer's disease, or designing more effective psychiatric medications.

Similarly, biologically inspired computational models, such as SNNs, and GRNs, have emerged as powerful tools for simulating complex biological systems and designing intelligent machines. Mimicking the principles of neural processing found in biological systems, these computational models offer promising avenues for solving challenging real-world problems.

The aim of this review is to provide a comprehensive analysis of the literature related to neural processes (Section 2.1) and biologically inspired computational models (Section 2.2). By critically examining and synthesising research findings, identifying gaps, and discussing limitations, we seek to deepen our understanding of these crucial areas of study and lay the groundwork for the Methodology introduced in Chapter 3.

2.1 An Overview of Neural Processes

Neuroplasticity, the brain's ability to reorganise and adapt, lies at the core of learning, memory formation, and neurological disorders. It encompasses a broad range of structural and functional changes in the brain in response to environmental stimuli, experiences, and learning processes. Among the various mechanisms driving neuroplasticity, synaptic plasticity, as discussed in Reagan’s study (Reagan, 2012) and Kandola et al. (Kandola et al., 2016), plays a pivotal role in shaping the connectivity and functionality of neuronal circuits. This phenomenon underscores the brain's incredible capacity for adaptation and holds significant implications for our understanding of brain function and its potential therapeutic applications.

Synaptic plasticity refers to the capacity of neuronal synapses to experience activity-dependent changes, resulting in alterations in synaptic strength and efficacy. This process underpins learning, memory storage, and information processing in the brain. Long-term potentiation (LTP) and long-term depression (LTD) are two well-known forms of synaptic plasticity, which encompass the strengthening and weakening of synaptic connections, respectively.

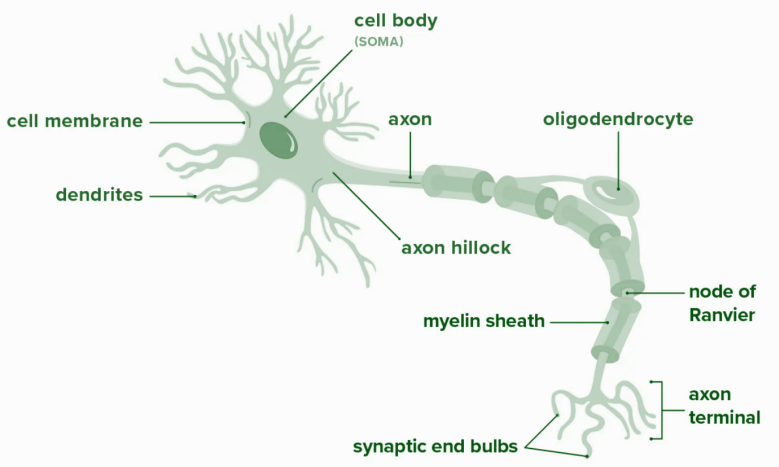


Figure 2 Structure of a biological neuron (Smith, 2022)

LTP and LTD assume pivotal roles in the intricate tapestry of learning and memory formation. LTP constitutes a sustained augmentation of synaptic strength, a phenomenon that unfolds when presynaptic neurons persistently and repetitively stimulate their postsynaptic counterparts, leading to the strengthening of synaptic connections (Martin et al., 2000). This orchestrated dance culminates in the fortification of synaptic connections, an essential foundation for the encoding of novel memories. Conversely, LTD embodies a persistent attenuation of synaptic strength, brought about by instances of low-frequency or feeble synaptic engagements. This intricate process ushers in synaptic attenuation and, in certain contexts, even synaptic elimination. The coalescence of LTP and LTD orchestrates the dynamic landscape of synaptic connections, endowing the brain with its remarkable capacity for adaptability, and thus, enabling the complex feat of information assimilation and preservation.

The cellular mechanisms underlying synaptic plasticity involve a complex interplay of pre- and postsynaptic neuronal activity, intracellular signalling pathways, and molecular events. One well-studied mechanism is the activation of glutamate receptors, particularly the N-methyl-D-aspartate (NMDA) receptor, which is crucial for synaptic plasticity, learning, and memory (Lipton et al., 1998). Activation of NMDA receptors leads to calcium ion influx, triggering a cascade of intracellular signalling events that alter synaptic strength and modify postsynaptic receptors and ion channels (Holbro et al., 2009). Additionally, receptor trafficking, including the movement of glutamate receptors such as AMPA and NMDA

receptors to and from synapses, is a critical process governing various forms of synaptic plasticity essential for learning and memory (Wang et al., 2015).

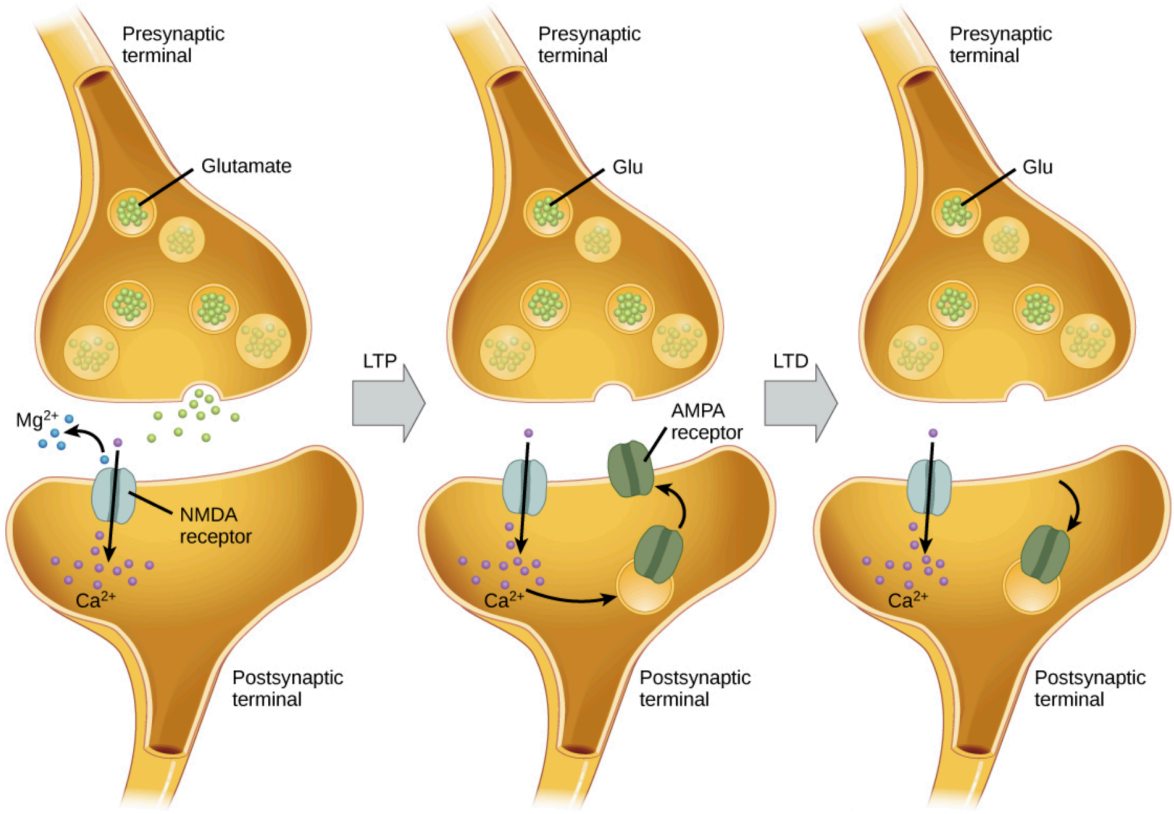


Figure 3 Calcium influx through postsynaptic NMDA receptors can trigger two distinct forms of synaptic plasticity: long-term potentiation (LTP) and long-term depression (LTD). LTP is induced by repetitive stimulation of a single synapse, while LTD occurs when only a few glutamate molecules bind to NMDA receptors at a synapse. (Be, 2021)

Neuroplasticity, also known as brain plasticity, is a fundamental property of the nervous system that enables the brain to adapt and reorganise in response to environmental stimuli, learning, and experience (Shaffer, 2016; Jarero-Basulto et al., 2018). It encompasses a range of structural and functional changes that occur at the molecular, cellular, and network levels, contributing to the brain's remarkable ability to modify its structure and function throughout life.

Neuroplasticity, as described by Jarero-Basulto et al. (2018), refers to the Central Nervous System's (CNS) capacity to adapt its structure and function in response to various stimuli, whether normal or pathological. This adaptation can be temporary or permanent and involves the generation of new neural cells and connections. Neuroplasticity can be triggered by a variety of stimuli, including environmental factors, changes in the body's internal equilibrium, and conditions such as epilepsy. There appears to be a close relationship between epilepsy and neuroplasticity, as both processes can mutually benefit from one another.

Neuroplasticity, at the molecular level, involves complex signalling pathways governing gene expression, protein synthesis, and synaptic changes. Key mechanisms include synaptic plasticity, synapses undergo long-lasting strength and connectivity changes. Long-term potentiation (LTP) and long-term depression (LTD) are significant forms of synaptic plasticity critical for learning and memory. Martin et al. (Martin et al., 2000), proposed the synaptic plasticity and memory hypothesis, emphasising synaptic strength changes as central to memory formation. Additionally, alterations in synaptic plasticity are linked to neurodegenerative disorders like Alzheimer's disease, making it a promising therapeutic target.

Cellular mechanisms of neuroplasticity encompass a spectrum of intricate processes within the nervous system. These processes entail dynamic alterations in neuronal morphology, including dendritic branching, and the establishment of synaptic connections. Notably, neuroplasticity involves the emergence of new dendritic spines, modifications in synaptic strength brought about by changes in neurotransmitter release, and the nuanced adjustment of both the number and distribution of synaptic connections. These structural transformations transpire as a consequence of the sophisticated interplay between neuronal activity, intracellular signalling cascades, and the dynamic landscape of cytoskeletal dynamics (Martin et al., 2000).

At the network level, neuroplasticity, as described in the study by Tropea et al. (Tropea et al., 2011), contributes significantly to the reorganisation and rewiring of neural circuits. This intrinsic capability enables the brain to dynamically adapt to environmental demands and optimise information processing. This intricate process involves various mechanisms, including synaptic pruning, axonal sprouting, and the formation of new neuronal connections. As reported in Tennant et al. (Tennant et al., 2017), neural networks exhibit continuous remodelling, allowing for the integration of new information, refinement of existing connections, and functional reorganisation. Experience-dependent synaptic plasticity, highlighted in the study by Tropea et al. (Tropea et al., 2011), plays a crucial role in refining brain circuits during development, providing insights into the protein synthesis-dependent mechanisms that contribute to this phenomenon. Furthermore, Tennant et al. (Tennant et al., 2017) demonstrated that optogenetic techniques can facilitate the rewiring of thalamocortical circuits and restore function in the damaged brain. These references underscore the intricate processes at the network level that underlie neuroplasticity and its essential role in shaping brain function and adaptation.

The significance of neuroplasticity extends beyond its role in normal brain function, as illuminated by Felling & Song (Felling & Song, 2015) and Maharjan et al. (Maharjan et al.,

2020). It plays a critical role in neurodevelopment, enabling the brain to adapt dynamically to changing developmental demands and environmental influences. Furthermore, as discussed in the study by Felling & Song, neuroplasticity serves as the foundation for the brain's remarkable capacity for recovery and repair following injuries or neurological disorders. The ability of the brain to reorganise its neural circuits and compensate for damaged areas, as highlighted by Maharjan et al., underscores the immense therapeutic potential and applications of neuroplasticity in diverse contexts.

Understanding the mechanisms and functional significance of neuroplasticity has been a topic of intense research. Advances in molecular biology, neuroimaging techniques, and computational modelling, as exemplified by Rodrigues et al. (Rodrigues et al., 2010), have provided valuable insights into the complex dynamics of neuroplasticity. Investigating the underlying cellular and molecular mechanisms, elucidating the signalling pathways involved, and exploring the role of neuroplasticity in cognitive processes have been central themes in neuroscience research.

Synaptic plasticity, a core component of neuroplasticity, refers to the ability of synapses to undergo enduring changes in their strength and efficacy. It plays a crucial role in shaping neural circuits, facilitating learning and memory processes, and underlies the dynamic nature of the brain's functional connectivity. Synaptic plasticity encompasses various forms, each characterised by distinct mechanisms and functional implications.

Two prominent forms of synaptic plasticity that have been extensively studied are LTP and LTD (Bliss & Cooke, 2011; Diering & Huganir, 2018; Hunt & Castillo, 2012). LTP is a process in which synapses become stronger and more efficient in transmitting signals following repetitive and synchronous neural activity. This leads to an enhancement of synaptic strength and an increase in neurotransmitter release, resulting in the facilitation of neural communication. In contrast, LTD involves a weakening of synaptic connections, often induced by low-frequency stimulation or prolonged low-level neural activity. LTD is associated with a decrease in synaptic strength and a reduction in neurotransmitter release, leading to the inhibition of neural communication. Advances in molecular biology, neuroimaging techniques, and computational modelling have provided valuable insights into the complex dynamics of neuroplasticity.

The ability of synapses to modify their strength and connectivity in response to neural activity is crucial for the acquisition, consolidation, and retrieval of information (Lynch, 2004). LTP, characterised by the long-lasting enhancement of synaptic strength, is considered a cellular

correlate of learning and memory. During LTP induction, a brief high-frequency stimulation of presynaptic neurons leads to a postsynaptic depolarisation and the activation of NMDA receptors. Calcium influx through NMDA receptors triggers a cascade of intracellular signalling events, resulting in the recruitment of additional AMPA receptors and an increase in synaptic strength. On the other hand, LTD plays a crucial role in memory consolidation and synaptic homeostasis. LTD is typically induced by low-frequency or prolonged low-level neural activity.

Cellular mechanisms underlying synaptic plasticity involve the dynamic regulation of synaptic proteins, the rearrangement of synaptic structures, and the modulation of neurotransmitter release (Feldman, 2009; Pozo & Goda, 2010; Davis & Müller, 2015). These processes are mediated by intricate signalling cascades, including calcium-dependent pathways, protein phosphorylation, and the activation of various transcription factors. In addition, the dynamic interplay between pre- and postsynaptic neurons, including changes in dendritic spines and axonal boutons, contributes to the remodelling and modulation of synaptic connections (Yasuda, 2017).

Synaptic plasticity, the foundation of learning and memory, relies on intricate cellular mechanisms. The neuronal MAP kinase cascade, a crucial biochemical signalling system for synaptic plasticity and memory, plays a central role. This cascade integrates various signals, orchestrating changes in synaptic strength and connectivity. Additionally, synaptic plasticity within the neocortex is a multifaceted process involving multiple cellular mechanisms operating at distinct synaptic locations, timescales, and developmental stages (Feldman, 2009). This complexity poses a scientific challenge: will the mechanisms governing experience-dependent plasticity be numerous and idiosyncratic, or will broader principles emerge? Understanding these cellular mechanisms is pivotal for unravelling the mysteries of learning, memory, and cortical plasticity.

Learning involves the acquisition and encoding of new knowledge or skills, while memory encompasses the storage and retrieval of that acquired information (Goh & Manahan-Vaughan, 2013). Through the strengthening and weakening of specific synaptic connections, synaptic plasticity enables the formation of new memories and the modification of existing ones (Andrade-Talavera & Rodríguez-Moreno, 2021). LTP and LTD have been extensively studied in the hippocampus, a brain region crucial for learning and memory, to understand the mechanisms of synaptic plasticity. These processes are impaired in conditions such as Alzheimer's disease, highlighting their importance in cognitive function.

LTP is induced by a brief high-frequency stimulation of presynaptic neurons, which leads to postsynaptic depolarisation and the activation of NMDA receptors (Malenka, 2003). Calcium influx through NMDA receptors triggers intracellular signalling events that result in the recruitment of additional AMPA receptors and an increase in synaptic strength (Adesnik & Nicol, 2007). This strengthened synaptic transmission enhances neural communication, facilitating the encoding and storage of information.

LTD plays a crucial role in memory consolidation and synaptic homeostasis (Martin et al., 2000). It is typically induced by low-frequency or prolonged low-level neural activity. During LTD, synaptic strength decreases through the removal or internalization of AMPA receptors from the postsynaptic membrane (Martin et al., 2000). This process reduces neurotransmitter release and weakens synaptic transmission, contributing to the refinement of neural circuits, preventing excessive synaptic potentiation, and maintaining the balance of synaptic strength.

Bidirectionally modifiable synapses can increase storage capacity, reduce errors, and limit the number and strength of potentiated synapses to an optimal level for memory storage (Migaud et al., 1998). Understanding how synaptic strength can be bidirectionally regulated, as seen in LTD and LTP, provides deeper insights into synaptic plasticity and biological neural networks, highlighting their integrated roles in learning and memory.

It is widely believed that the strengthening and weakening of specific synaptic connections enable the encoding and storage of information in distributed neural networks. The formation of new memories involves establishing connections between previously weakly connected neurons, while the retrieval of stored memories relies on the reactivation and strengthening of relevant synaptic pathways (Basu & Siegelbaum, 2015).

Moreover, synaptic plasticity is not limited to individual synapses but occurs across entire neural networks. The coordinated changes in synaptic strength and connectivity enable the integration of information across multiple brain regions, facilitating the formation of complex memories and cognitive processes. Plasticity at both local and global scales contributes to the adaptive nature of learning and memory, allowing for the flexible storage and retrieval of information (Bliss & Cooke, 2011). Furthermore, as our understanding of the molecular mechanisms behind these processes deepens and with advancements in non-invasive brain activity control technologies, we stand on the verge of harnessing phenomena like LTP, LTD, and various other synaptic, and cellular plasticity mechanisms to influence the central nervous system. Potential applications include using pharmaceuticals to modify, or treat abnormal

synaptic states, and employing devices to artificially induce synaptic plasticity in a non-invasive fashion.

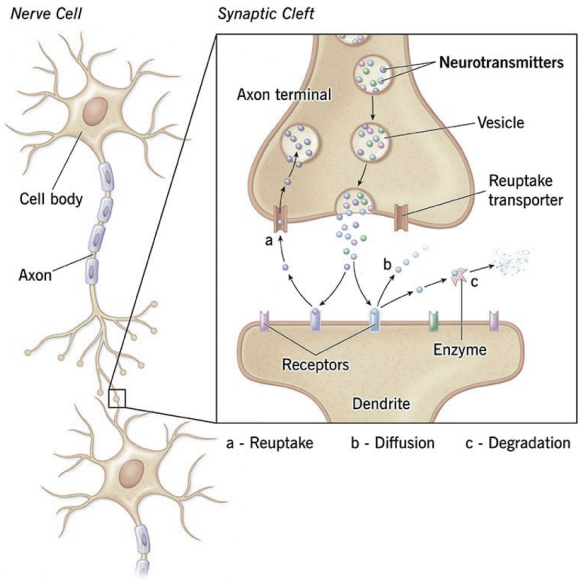


Figure 4 Overview of Neurotransmission (Cleveland Clinic, 2021)

Neuroreceptors and neurotransmission play crucial roles in mediating communication between neurons and regulating synaptic transmission (Wall et al., 2014). Neuroreceptors are specialised proteins located on the surface of neurons that bind specific neurotransmitters, initiating intracellular signalling cascades that modulate synaptic transmission and neuronal activity.

Neurotransmission is the process by which neurons communicate through the release, binding, and recognition of neurotransmitters. It involves a series of molecular events that culminate in the transmission of electrical or chemical signals across synapses. Neurotransmitters are synthesised and packaged within presynaptic neurons, released into the synaptic cleft upon neuronal activation, and bind to specific neuroreceptors on the postsynaptic membrane. This binding initiates cellular responses that modulate postsynaptic membrane potential, intracellular signalling pathways, and synaptic plasticity (Spitzer, 2012).

Neuroreceptors encompass various types, including ionotropic receptors and metabotropic receptors (Perez-Alvarez et al., 2014). Ionotropic receptors are ligand-gated ion channels that, upon neurotransmitter binding, undergo conformational changes, leading to the opening or closing of ion channels. This process rapidly modulates postsynaptic membrane potential and synaptic transmission. Examples of ionotropic receptors include the glutamate receptor family (such as N-methyl-D-aspartate, AMPA, and kainate receptors), and gamma-aminobutyric acid

receptors. Metabotropic receptors, on the other hand, are coupled to intracellular signalling pathways through G proteins. Activation of metabotropic receptors initiates intracellular events involving second messengers, kinases, and effector molecules, leading to the modulation of postsynaptic excitability, gene expression, and synaptic plasticity.

Neurotransmitter systems, such as the cholinergic, dopaminergic, noradrenergic, and serotonergic systems, play critical roles in synaptic plasticity and neuronal activity regulation (Shefa et al., 2018; Kautzky et al., 2020). These systems consist of neurons that release specific neurotransmitters and are involved in various cognitive functions, mood regulation, attention, and other essential brain processes. Dysregulation of neurotransmission can have profound effects on synaptic plasticity, neural network activity, and overall brain function.

Neuroreceptors are crucial components of synaptic transmission, playing a vital role in mediating the effects of neurotransmitters on postsynaptic neurons. These specialised proteins are located on the surface of neurons and are involved in cellular communication and the regulation of neural network activity. Neuroreceptors can be classified into different types based on their structural and functional properties (Wang & Xu, 2015).

The activation of ionotropic receptors by neurotransmitter binding induces conformational changes that result in the opening or closing of ion channels, rapidly modulating the postsynaptic membrane potential and synaptic transmission (Karakas & Furukawa, 2014). Examples of ionotropic receptors include the glutamate receptor family, such as N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, and kainate receptors. Synaptic transmission and plasticity processes, such as LTP and LTD, are crucially dependant on these receptors.

Metabotropic receptors are a class of neuroreceptors that are coupled to intracellular signalling pathways through G proteins. These receptors initiate complex intracellular events involving second messengers, kinases, and effector molecules, which modulate neuronal excitability, gene expression, and synaptic plasticity (McCormick & von Krosigk, 1992). They have diverse functions and are involved in various neurotransmitter systems, including the cholinergic, dopaminergic, noradrenergic, and serotonergic systems. Activation of metabotropic receptors leads to the activation of signalling cascades that regulate cellular responses and can be targeted for therapeutic interventions (Reiter et al., 2012). These findings highlight the importance of metabotropic receptors in regulating neuronal function and suggest their potential as targets for modulating synaptic transmission and plasticity.

The diverse functions of neuroreceptors are mediated by distinct signalling pathways. Upon neurotransmitter binding, neuroreceptors activate downstream signalling cascades that regulate synaptic transmission and neuronal activity. These signalling pathways involve intricate molecular interactions and enzymatic reactions, leading to changes in postsynaptic excitability, gene expression, and synaptic plasticity. Various intracellular messengers, including cyclic adenosine monophosphate (cAMP), calcium ions (Ca2+), and protein kinases, are key components of these signalling pathways. The synthesis of these neuroreceptors relies on the simultaneous expression of specific genes, each contributing to the construction of the macromolecule. Genes GRIN1, GRIN2A, GRIN2B, GRIN3A, and GRIN3B are pivotal. Notably, in humans, the principal subunit of the NMDAR is NR1, which is encoded by the GRIN1 gene (Stephenson, 2006). Furthermore, NR2A and NR2B, encoded by GRIN2A and GRIN2B genes respectively, are prevalent in glutamatergic synapses. Additionally, NR3A, encoded by the GRIN3A gene, is observed in embryonic brain tissue and, along with NR3B (encoded by the GRIN3B gene), exerts an inhibitory influence on NMDAR expression (Kasabov et al., 2018).

The process of neurotransmission begins with the synthesis and packaging of neurotransmitters within the presynaptic neuron. Neurotransmitters are synthesised from precursor molecules through enzymatic reactions and are then stored in specialised vesicles. Upon depolarisation of the presynaptic neuron, action potentials trigger the opening of voltage-gated calcium channels, leading to an influx of calcium ions into the presynaptic terminal (Espinoza, 1993).

The elevation of intracellular calcium levels triggers the fusion of neurotransmitter-containing vesicles with the presynaptic membrane, releasing neurotransmitters into the synaptic cleft. These neurotransmitters spread across the synaptic cleft and bind to receptors located on the postsynaptic neuron. The binding of neurotransmitters to their receptors initiates a series of events that ultimately influence the postsynaptic neuron's activity.

The binding of neurotransmitters to receptors can have both excitatory and inhibitory effects on the postsynaptic neuron. Excitatory neurotransmitters, such as glutamate, bind to receptors on the postsynaptic membrane, leading to depolarisation and the generation of excitatory postsynaptic potentials (EPSPs). In contrast, inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), bind to receptors that promote hyperpolarisation, resulting in inhibitory postsynaptic potentials (IPSPs). The balance between excitatory and inhibitory inputs

determines the overall neuronal activity and information processing within neural circuits (Joensuu, 2020).

Neurotransmission is a highly regulated process that involves multiple mechanisms to ensure precise and reliable synaptic communication. These mechanisms include the reuptake or degradation of neurotransmitters by presynaptic transporters or enzymes, respectively, to terminate their actions. Additionally, auto receptors located on presynaptic terminals provide feedback control by sensing the concentration of released neurotransmitters and modulating their further release.

The molecular processes underlying neurotransmission are complex and involve a wide array of proteins, including neurotransmitter receptors, transporters, and enzymes. These proteins interact with each other and with intracellular signalling molecules to fine-tune synaptic communication. Dysregulation of these processes can have profound effects on neural function and has been implicated in various neurological disorders (Joensuu, 2020).

The glutamatergic system is a crucial neurotransmitter system that plays a significant role in synaptic plasticity and learning and memory processes (Joensuu, 2020). Glutamate acts on various receptors, including ionotropic receptors such as NMDA and AMPA receptors, as well as metabotropic glutamate receptors (mGluRs). AMPA receptors mediate fast excitatory synaptic transmission and are involved in the regulation of synaptic plasticity. NMDA receptors are important for initiating synaptic plasticity during Central Nervous System (CNS) development and in learning and memory (Burnell et al., 2019). The regulation of AMPA receptor trafficking and internalisation is crucial for synaptic plasticity and is modulated by factors such as palmitoylation and endocytosis. The activation of glutamate receptors, including AMPA receptors, can lead to depalmitoylation and subsequent modulation of receptor trafficking, which is important for synaptic plasticity (Hayashi et al., 2005). Overall, the glutamatergic system and its receptors, such as AMPA and NMDA receptors, play a critical role in synaptic plasticity and learning and memory processes (Burnell et al., 2019).

The dopaminergic system is involved in synaptic plasticity and cognitive processes, playing a role in reward-based learning, motivation, and reinforcement mechanisms. Dysregulation of this system has been linked to various neuropsychiatric disorders, including Parkinson's disease and addiction. Additionally, prefrontal cortical dopaminergic dysfunction has been implicated in cognitive deficits observed in stress-related neuropsychiatric disorders. These findings

highlight the importance of the dopaminergic system in cognitive processes and its involvement in neuropsychiatric disorders (Mizoguchi et al., 2000; Volkow et al., 1993).

Serotonin neurotransmission plays a crucial role in mediating the effects of serotonin. The serotonin neurotransmitter is often referred to as the "feel-good" neurotransmitter. Serotonin receptors are classified into several subtypes each with distinct functions and distributions throughout the body. Serotonin neurotransmission facilitates two distinct adaptive responses to adversity, primarily through its two most prevalent and studied brain receptors: the 5-HT1A and 5-HT2A receptors. Postsynaptic 5-HT1A receptor signalling mediates passive coping (such as withdrawal and avoidance), while 5-HT2A receptor signalling mediates active coping (such as confronting and problem-solving) (Carhart-Harris & Nutt, 2017).

This model is consistent with evidence that 5-HT1A receptor agonists and 5-HT2A receptor antagonists have anxiolytic and antidepressant effects, whereas 5-HT2A receptor agonists and 5-HT1A receptor antagonists have anxiogenic and pro-depressant effects. Furthermore, the 5-HT1A receptor is predominantly autoreceptor-like, whereas the 5-HT2A receptor is predominantly postsynaptic and excitatory. This model can explain how different adaptive responses to adversity can be generated by the same neurotransmitter system, depending on receptor and brain region-specific effects (Carhart-Harris & Nutt, 2017).

Many ads for selective serotonin reuptake inhibitors (SSRIs) claim that the drugs boost brain serotonin levels. However, Lacasse and Leo (Lacasse & Leo, 2005) argue that there is little scientific evidence to support this claim. They highlight a disconnect between the claims made in advertisements and the scientific literature, suggesting that the relationship between serotonin and depression is more complex than portrayed. While SSRIs do increase serotonin levels in the brain, the authors argue that this does not necessarily lead to improved mood or reduced symptoms of depression. They emphasise the need for a more nuanced understanding of the role of serotonin in depression and caution against oversimplifying the mechanisms of action of antidepressant medications.

The gamma-aminobutyric acid (GABA) ergic system is indeed the main inhibitory neurotransmitter system in the brain. GABA acts on GABA receptors, including GABA-A and GABA-B receptors, to mediate inhibitory neurotransmission (Ghit et al., 2021). GABAergic transmission plays a crucial role in maintaining the balance of excitation and inhibition in neural circuits and is involved in various forms of synaptic plasticity, including the regulation of network oscillations and the control of neuronal excitability (Feller & Blankenship, 2010;

Gamlin et al., 2018; Maffei et al., 2017). Inhibition in the Central Nervous System (CNS) is mediated by two neurotransmitters: gamma-aminobutyric acid (GABA). The GABAergic system is involved in various neurological disorders, such as Alzheimer's disease and epilepsy (Govindpani et al., 2017; Ramamoorthi & Lin, 2011). Understanding the mechanisms underlying GABAergic dysfunction can provide insights into the pathophysiology of neurodevelopmental disorders. Overall, the GABAergic system plays a fundamental role in neural circuit function and is essential for brain function.

The cholinergic, noradrenergic, and histaminergic systems are neurotransmitter systems that contribute to synaptic plasticity and play important roles in modulating neural activity and cognitive processes (Ji et al., 2001; Valbuena & Lerma, 2016). These systems modulate synaptic plasticity through intricate signalling pathways, second messenger systems, and intracellular cascades. Activation of specific receptors triggers downstream signalling events that lead to changes in synaptic strength and neuronal connectivity. Factors such as receptor subtypes, receptor trafficking, and interactions with other neurotransmitter systems dynamically modulate these processes.

Research into neural processes has deepened our understanding of brain function and adaptation, particularly in the context of neurological disorders like Parkinson’s disease, depression, and epilepsy. These insights have led to practical applications such as dopaminergic therapies, serotonin-based treatments, and GABAergic interventions, all of which modulate neural plasticity to improve motor function, mood, and seizure control. This research has also informed advancements in cognitive rehabilitation, brain-computer interfaces, and neurostimulation therapies, highlighting the wide-ranging real-world impact of studying neural mechanisms.

Neural processes in neurological and psychiatric disorders, particularly in Parkinson's disease (PD), are significantly influenced by the dopaminergic system. The dopaminergic system is crucial for regulating synaptic plasticity and motor control, and its dysfunction is a hallmark of PD, characterised by the degeneration of dopamine-producing neurons. Research has shown that therapeutic strategies targeting this system, such as the administration of dopamine precursors like levodopa, can substantially ameliorate motor symptoms associated with the disease. For instance, studies indicate that levodopa enhances synaptic dopamine levels, which is essential for compensating for the loss of dopaminergic function and restoring neural plasticity (Fuente-Fernández, 2004; Tetrud, 2007). Furthermore, the timing and dosage of levodopa therapy are critical, as higher doses can lead to motor response fluctuations, a common

complication in PD management (Frequin et al., 2023; Verschuur et al., 2019). Deep brain stimulation (DBS) has emerged as another effective intervention for PD, particularly for patients who experience motor complications despite optimal pharmacological treatment. DBS targets specific neural circuits involved in motor control, and research has demonstrated its ability to enhance synaptic plasticity and alleviate motor deficits (Asl et al., 2022; Yuan et al., 2020). The mechanism behind DBS involves modulating the activity of basal ganglia circuits, which are significantly affected in PD. Studies have shown that DBS can lead to immediate improvements in symptoms such as tremor and rigidity, indicating rapid changes in synaptic efficacy (Yamawaki et al., 2012; Bejjani et al., 2000). Moreover, the long-term effects of DBS suggest that it may induce enduring changes in neural plasticity, further supporting its role in the management of PD (Milosevic et al., 2017; Yuan et al., 2020).

The application of research on gamma-aminobutyric acid GABAergic systems in the treatment of epilepsy is a significant area of study, as GABA serves as the primary inhibitory neurotransmitter in the brain. Dysfunctions in GABAergic transmission are closely linked to the pathophysiology of seizures and epileptiform activity, highlighting the importance of GABA in maintaining the balance between excitatory and inhibitory inputs within neural circuits. Enhancing GABAergic inhibition has led to the development of anticonvulsant medications that effectively increase GABAergic transmission, thereby restoring this critical balance in patients with epilepsy (Tong, 2014). Furthermore, research indicates that therapies modulating GABA receptors, such as benzodiazepines and barbiturates, play a vital role in suppressing seizure activity. These medications enhance GABA-mediated inhibition, which is crucial for controlling seizure episodes (Rane et al., 2022). The relationship between GABA levels and seizure control is further underscored by findings that low serum pyridoxine levels, which are essential for GABA synthesis, can worsen seizure control in epilepsy patients (Zhang et al., 2023). This suggests that adequate GABA levels are necessary for effective seizure management. Additionally, studies have shown that alterations in GABA receptor subunits, particularly in models of temporal lobe epilepsy, can lead to decreased GABAergic inhibition, contributing to the hyperexcitability characteristic of seizures (Dhaher et al., 2021; Muglia et al., 2020). The modulation of GABAergic signalling through various pharmacological agents has been a focal point in developing new treatments for epilepsy, as evidenced by the efficacy of drugs that enhance GABA signalling, such as vigabatrin and tiagabine, which inhibit GABA degradation and reuptake, respectively (Acharya et al., 2015; Peng et al., 2004).

The technological applications of neural processes, particularly in the context of Brain-Computer Interfaces (BCIs) and neurostimulation therapies, represent significant advancements in neuroscience and their practical implications for enhancing human capabilities and treating neurological disorders.

Brain-Computer Interfaces (BCIs) are a prominent example of how neural processes are harnessed for technological applications. BCIs facilitate direct communication between the brain and external devices, enabling individuals to control prosthetic limbs or computer interfaces through thought alone. Research has shown that neural signals, particularly from the motor cortex, can be effectively decoded to translate intentions into actionable commands for devices (Nambiar, 2023). This capability has profound implications for individuals with paralysis or amputations, allowing them to regain a degree of autonomy and control over their environment. Recent advancements have expanded the functionality of BCIs from basic movement tasks to more complex applications, such as communication and environmental control, thereby enhancing the quality of life for those with severe physical disabilities (Hasan et al., 2021). The integration of high-level cognitive signals from areas beyond the motor cortex is also being explored, which could further enhance the versatility of BCIs in controlling various output devices (Andersen et al., 2014).

Neurostimulation therapies, including transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), have emerged as effective treatments that modulate neural processes to enhance cognitive function and alleviate symptoms of neurological disorders. TMS utilises magnetic fields to stimulate specific brain regions, demonstrating efficacy in improving cognitive performance in tasks related to attention, memory, and executive function (Shahlaie et al., 2022). In particular, repetitive TMS has been employed to target underactive areas of the brain, such as the prefrontal cortex, to induce long-term potentiation (LTP)-like plasticity, which is essential for neural recovery (Poel & Treur, 2018). Similarly, DBS has been utilised to treat motor symptoms in conditions like Parkinson's disease by stimulating motor pathways and enhancing synaptic plasticity (Haber & Brucker, 2009). Emerging research indicates that DBS may also hold promise for cognitive disorders, suggesting that its application could extend beyond motor control to cognitive enhancement (Dy et al., 2016). The mechanisms underlying DBS are complex and involve modulation of specific brain networks rather than isolated neuron types, highlighting the need for further investigation into its therapeutic effects (McIntyre & Hahn, 2010; Lozano & Lipsman, 2013).

Artificial intelligence (AI) and machine learning (ML) have drawn significant inspiration from biological processes, particularly the neural functions of the brain. Neural networks, which are foundational to AI, emulate the communication pathways between neurons, facilitating information processing in a manner akin to biological systems. This connection is underscored by research into synaptic plasticity and learning mechanisms, which have directly influenced the development of learning algorithms such as backpropagation. Backpropagation is a critical method for updating the weights between artificial neurons, optimising their performance based on error minimisation (Krestinskaya et al., 2019; LeCun et al., 2015). Deep learning, a specialised subset of machine learning, further exemplifies this biological inspiration by mirroring the hierarchical structure of neural circuits in the brain. By processing information through multiple layers of artificial neurons, deep learning models can discern complex patterns, enabling applications such as image recognition and natural language understanding. This hierarchical approach allows for the extraction of features at various levels of abstraction, which is essential for tasks ranging from object detection to medical diagnostics (LeCun et al., 2015; Gu et al., 2018). For instance, convolutional neural networks (CNNs) are particularly adept at analysing visual data, reflecting how the human visual cortex processes information (Abdulnabi et al., 2015). The implications of applying neural processes in AI are profound, impacting diverse fields such as autonomous driving, language translation, and medical diagnostics. In healthcare, AI systems have demonstrated remarkable capabilities in interpreting complex medical data, including MRI scans, through the use of neural network models. These advancements not only enhance diagnostic accuracy but also facilitate early disease detection, ultimately improving patient outcomes. The integration of AI in medical practices exemplifies its transformative potential, as it streamlines workflows and augments the decision-making process in clinical environments (Cao et al., 2021; Nawab et al., 2021).

2.2 An Overview of Biologically Inspired Computational Models

In recent years, computational models, particularly Spiking Neural Network (SNN) models, have emerged as valuable tools for simulating and exploring synaptic plasticity and its implications in neuroplasticity. SNNs are designed to replicate the intricate behaviour of biological neurons, allowing for the precise examination of the spatiotemporal dynamics governing neural activity and synaptic interactions. Within these computational frameworks, learning rules like Spike-timing Dependent Plasticity (STDP) have gained significant prominence. Research conducted by Froemke et al. (Froemke et al., 2006) underscores the pivotal role of STDP by investigating the contribution of individual spikes in burst-induced

long-term synaptic modification. Their findings emphasise the criticality of spike timing in determining both the direction and extent of synaptic modifications.

Additionally, the work of Froemke et al. (Froemke et al., 2010) delves into the temporal modulation of STDP, underscoring how precise timing of pre- and postsynaptic spikes governs the nature and magnitude of synaptic modification. Moreover, Gjorgjieva et al. (Gjorgjieva et al., 2011) introduce a triplet STDP model that extends the Bienenstock-Cooper-Munro (BCM) rule to higher-order spatiotemporal correlations, demonstrating that STDP is capable of encoding selectivity for input patterns characterised by higher-order correlations. These references provide robust evidence for the criticality of spike timing and STDP in capturing the intricate spatiotemporal dynamics inherent to neural activity and synaptic interactions.

While STDP has significantly contributed to our understanding of synaptic plasticity, there is a burgeoning interest in exploring alternative mechanisms that can further augment the biological plausibility and performance of computational models. As elucidated by Martin et al. (Martin et al., 2000), a comprehensive evaluation of synaptic plasticity encompasses classical and recently discovered properties, emphasising neural architecture and synaptic learning rules.

Kotaleski and Blackwell (Kotaleski & Blackwell, 2010) shed light on modelling synaptic plasticity mechanisms employing systems biology approaches. While not explicitly addressing genetic information or Neuroreceptor-Dependent Plasticity (NRDP), the article offers valuable insights into the integration of diverse mechanisms and underscores the significance of capturing the intricacies of synaptic plasticity within computational models. Furthermore, Kaltschmidt et al. (Kaltschmidt et al., 2006) conducted a study examining the involvement of NF-κB in spatial memory formation and synaptic plasticity. Although the research does not directly tackle alternative mechanisms or computational models, it highlights the interplay between gene transcription, signalling pathways, and synaptic plasticity - a facet relevant to the broader discourse.

SNNs are a class of artificial neural networks designed to emulate the computational principles observed in biological neural networks. Unlike traditional artificial neural networks, SNNs utilise discrete, asynchronous events known as spikes to represent and process information, enabling more biologically plausible modelling of neural dynamics and information processing (Rueckauer et al., 2017). The temporal dynamics and event-driven nature of SNNs allow for precise timing-based computations and the representation of time-varying information, capturing the temporal aspects of spike communication (Fang et al., 2023).

SNNs employ learning rules such as STDP, which plays a crucial role in shaping the connectivity and dynamics of neural networks, contributing to synaptic plasticity and learning in biological systems. Additionally, various other learning rules, including Spike-Timing-Dependent Plasticity with Weight Dependence (STDP-WD), Spike-Timing-Dependent Plasticity with Delay Dependence (STDP-DD), and Spike-Timing-Dependent Plasticity with Reward Modulation (STDP-RM), aim to enhance the computational capabilities of SNNs and enable them to learn and adapt to complex spatiotemporal patterns in input data (Hao et al., 2020).

The unique characteristics of SNNs make them suitable for addressing challenges in areas such as pattern recognition, sensory processing, and temporal data analysis. Their temporal processing capabilities and the ability to capture the dynamics of biological systems make SNNs promising candidates for modelling and understanding brain functions and exploring neuroscientific hypotheses (Fang et al., 2023). Furthermore, the integration of SNNs with neuromorphic hardware and emerging technologies, such as memristors and neuromorphic chips, holds promise for achieving high-performance, low-power neuromorphic computing systems (Nandakumar et al., 2020).

In recent years, the development and application of SNNs have gained significant attention, with researchers exploring various network architectures, learning algorithms, and computational frameworks to improve the performance and efficiency of SNNs. SNNs have demonstrated potential for efficient inference due to sparsely activated neurons and event-driven computations, making them suitable for energy and memory-constrained embedded applications (Lobov et al., 2021). Moreover, SNNs have been benchmarked on neuromorphic hardware, demonstrating an ability to deliver massively parallel, low-latency, energy-efficient solutions to AI problems (Zhang et al., 2020).

The architecture and operation principles of Spiking Neural Networks (SNNs) are designed to mimic the temporal dynamics and event-driven nature observed in biological neural networks. SNNs rely on the timing of discrete events called spikes to process and transmit information (Andrew, 2023).

The fundamental building block of an SNN is the spiking neuron, which integrates incoming spike inputs over time and generates an output spike when the membrane potential reaches a certain threshold. The transmission of spikes in SNNs is governed by synapses, which are associated with weights determining the strength of connections.

SNNs employ spike-based learning rules such as Spike-Timing-Dependent Plasticity (STDP) to modify synaptic weights based on the precise timing of pre- and postsynaptic spikes, enabling learning and adaptation to different patterns of activity. The architecture of SNNs can vary from simple feedforward networks to more complex recurrent or hierarchical structures. Recurrent SNNs incorporate feedback connections, enabling them to capture temporal dependencies and perform tasks involving memory and sequential processing. Hierarchical SNNs organise neurons into multiple layers, facilitating the extraction of abstract features and hierarchical representations The temporal aspect of SNNs allows them to encode and process information in a distributed and parallel manner, leveraging the precise timing of spikes to exhibit properties such as temporal coding, coincidence detection, and phase locking, enabling them to perform complex computations and pattern recognition tasks (Tavanaei et al., 2019).

SNNs have proven to be effective in modelling spatial-temporal data from various neuroimaging modalities, such as Electro-encephalogram (EEG) and Functional Magnetic Resonance Imaging (fMRI), aiding in the diagnosis and prognosis of mental and neurological conditions demonstrating the utility of SNN in understanding brain dynamics (Bahrami et al., 2023; Crook-Rumsey et al., 2022). Additionally, the potential of SNN in personalised medicine is highlighted in dual studies by Doborjeh et al. (Doborjeh et al., 2021; Doborjeh et al., 2023). These studies provide valuable insights into the application of SNN in analysing neuroimaging data for improved diagnosis and treatment outcomes in various mental and neurological conditions.

The development of efficient computational frameworks and simulation tools has contributed to the advancement of SNNs, providing researchers with the necessary tools to model and simulate large-scale SNNs, allowing for the investigation of complex neural dynamics and the exploration of various learning algorithms.

The learning aspect of SNNs is crucial for their adaptability and performance improvement over time. STDP is a well-studied learning rule in SNNs, modulating synaptic weights based on the precise timing of pre- and postsynaptic spikes, leading to LTP or LTD of synaptic connections (Moon et al., 2021). STDP enables SNNs to capture the temporal order and causality of spike events, allowing them to learn temporal patterns, synchronise activities, and generate selective responses based on spike timing (Chakraborty & Mukhopadhyay, 2021). However, to address limitations in dealing with complex learning tasks, extensions and variations of STDP, as well as the integration of additional learning mechanisms in SNNs, have been explored (Bernert & Yvert, 2019).

Rate-based learning rules have been proposed to complement the spike-based learning of STDP, providing a smoother and more robust learning mechanism (Cancan, 2019). Additionally, reward-based learning and unsupervised learning algorithms have been investigated in SNNs, incorporating reinforcement signals or utilising statistical principles to guide synaptic modifications and network behaviour (Amirshahi & Hashemi, 2019). The combination of multiple learning rules enhances the computational capabilities of SNNs, enabling them to perform complex tasks such as reinforcement learning, sequence learning, and memory recall (Srinivasa & Cho, 2014).

Gene Regulatory Networks (GRNs) play a crucial role in governing gene expression and coordinating the dynamics of cellular processes. These networks, composed of interconnected genes, regulate the transcriptional activity of target genes, forming a complex web of interactions and feedback loops. The primary function of GRNs is to oversee the activation or repression of genes, ensuring precise spatiotemporal expression patterns essential for proper development, differentiation, and organismal stability. They establish the regulatory framework for cellular decision-making and response to internal and external stimuli.

Modelling GRNs is challenging due to their inherent complexity and the multitude of factors influencing gene regulation. Various approaches, such as Boolean frameworks and differential equations, have been proposed to infer and reconstruct GRNs from experimental data, including gene expression profiles and protein-DNA interactions (Alon, 2006; Davidson et al., 2008). Boolean models, representing genes as binary variables, are adept at capturing the qualitative behaviour of GRNs, emphasising regulatory relationships and network dynamics. On the other hand, differential equation models, representing genes as continuous variables, enable the quantitative analysis of GRNs, capturing the dynamics of gene expression and regulatory interactions (Karlebach & Shamir, 2008; Huang et al., 2017).

Computational neurogenetic modelling (CNGM), an interdisciplinary approach merging concepts from neuroscience and genetics, has emerged as a powerful tool for understanding the intricate relationship between genetic factors and brain function. This computational approach integrates genetic information into neural network models to simulate and predict brain dynamics. Pioneering works such as those by Kasabov et al. (Kasabov et al. 2011; Kasabov et al. 2012), have laid the foundation for neurogenetic modelling. These studies, along with others by Benuskova, Kasabov, and contributors (Benuskova et al., 2006; Benuskova & Kasabov 2008), highlight the potential of this approach in uncovering new insights into genetic influences on brain function and their role in neurological disorders such as Alzheimer's disease. By

integrating GRN modelling with other computational frameworks, such as SNNs, it is possible to explore the interplay between gene regulatory dynamics and neural network behaviour, leading to a more comprehensive understanding of brain-related diseases and disorders (Cuntz et al., 2010).

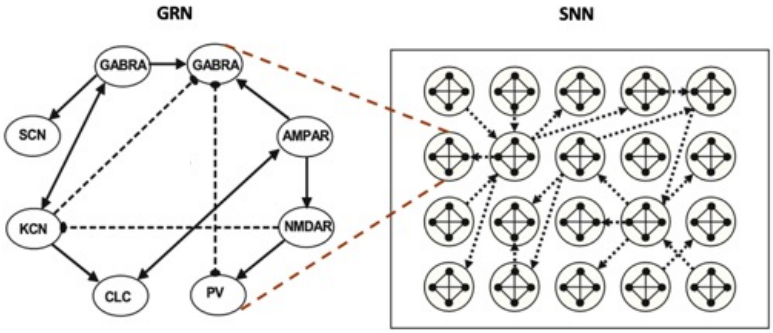


Figure 5 Computational neurogenetic modelling architecture (Kasabov, Springer, 2019)

GRNs are essential for governing gene expression and coordinating cellular processes (Mochida et al., 2018). These interconnected networks regulate the transcriptional activity of target genes, ensuring precise spatiotemporal expression patterns crucial for development and homeostasis (Peter & Davidson, 2017).

Understanding the structure and dynamics of GRNs is crucial for unlocking the complexity of biological systems and deciphering the regulatory mechanisms underlying various biological phenomena (Yang & Scarpino, 2023; Vijesh et al., 2013). By modelling GRNs, researchers can gain insights into gene regulatory dynamics, identify key regulators, and explore the emergent properties of these networks. Such knowledge contributes to our understanding of developmental processes, disease mechanisms, and cellular responses to external stimuli (Schittler et al., 2013).

Computational methods specifically tailored for single-cell data have been developed to reconstruct cell-specific GRNs and unravel dynamic gene regulatory processes. It is important to note that GRN inference methods have limitations and assumptions that need to be considered. The accuracy and reliability of inferred GRNs heavily depend on the quality and quantity of the available data, as well as the specific algorithms and modelling assumptions used. Validation of inferred GRNs using independent experimental techniques is crucial to assess the robustness and biological relevance of the reconstructed networks. Despite the challenges, the inference and reconstruction of GRNs provide valuable insights into gene regulatory mechanisms, network dynamics, and system-level properties. Integration of GRNs

with other biological networks, such as protein-protein interaction networks and signalling pathways, enables a more comprehensive understanding of cellular processes and their dysregulation in various diseases.

Inference and reconstruction of Gene Regulatory Networks (GRNs) from experimental data play a crucial role in understanding the complex regulatory mechanisms underlying gene expression and cellular processes. Various computational methods have been developed to tackle the challenges associated with inferring GRNs from different types of data. One common approach for GRN inference is based on correlation analysis, where the expression profiles of genes are examined for their mutual dependencies.

Correlation-based methods identify potential regulatory interactions by quantifying the statistical associations between gene expression patterns. However, these methods do not capture the directionality or causality of the regulatory relationships. Reverse engineering gene regulatory networks has been a topic of interest, aiming to understand the underlying regulatory relationships from gene expression data by exploiting various statistical and mathematical techniques (Hartemink, 2005).

Recently, there has been a growing interest in leveraging information from high-throughput sequencing data. These techniques provide insights into protein-DNA interactions, chromatin accessibility, and epigenetic modifications, which are essential for gene regulation. Integrating such data with computational approaches allows for the identification of transcription factor binding sites and the inference of gene regulatory interactions (Shanaj Parvin & Haque, 2021).

Additionally, single-cell transcriptomics has emerged as a powerful tool for GRN inference, enabling the study of gene expression at the single-cell level. Single-cell RNA sequencing (scRNA-seq) data provides valuable information about cell-to-cell variability, cell states, and cell-cell interactions.

The regulation of gene expression is a dynamic process that involves the intricate interplay between transcription factors, regulatory elements, and epigenetic modifications. Understanding the temporal dynamics of gene expression and regulatory interactions is crucial for decoding the complexity of gene regulatory networks (GRNs) (Soutourina, 2018).

Gene expression is tightly regulated in response to various internal and external cues, including developmental signals, environmental changes, and cellular stress. A central role in orchestrating gene expression is performed by Transcription factors (TFs). TFs bind to specific DNA sequences within gene regulatory regions, such as enhancers and promoters. The binding

of TFs to these regulatory elements can activate or repress the transcriptional activity of target genes (Murison & Michod, 2020).

The dynamics of gene expression are governed by the rates of transcription, mRNA degradation, and protein synthesis and degradation. Transcriptional regulation involves a cascade of events, including chromatin remodelling, RNA polymerase binding, and transcription initiation and elongation. Post-transcriptional processes, such as mRNA splicing, transport, and stability, further contribute to the regulation of gene expression (Ye et al. 2020).

Emerging evidence suggests that gene regulatory interactions are not solely determined by the binding of TFs to DNA. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs), forms of non-coding RNAs, have been implicated in the regulation of gene expression at the post-transcriptional level. miRNAs can inhibit their translation or promote their degradation through base pairing with target mRNAs. On the other hand, lncRNAscan interact with chromatin and proteins to modulate gene expression (Marbach et al., 2012).

Epigenetic modifications, including DNA methylation and histone modifications, also play a critical role in gene regulation. These modifications can influence the accessibility of DNA to transcriptional machinery and modulate the binding of TFs and other regulatory factors. Importantly, epigenetic marks can be dynamically regulated in response to environmental cues and cellular states, providing an additional layer of complexity to gene regulatory processes (DiFrisco & Jaeger, 2020).

Advancements in high-throughput sequencing technologies have enabled the investigation of genome-wide dynamics of gene expression and regulatory interactions. Techniques such as RNA sequencing (RNA-seq), chromatin immunoprecipitation followed by sequencing (ChIP-seq), and assay for transposase-accessible chromatin followed by sequencing (ATAC-seq) provide valuable insights into the temporal and spatial patterns of gene expression, TF binding, and chromatin accessibility (Heidari et al., 2014).

Computational approaches have been developed to model and analyse the dynamics of gene expression and regulatory interactions. Dynamic gene regulatory network models, such as dynamic Bayesian networks and ordinary differential equation models, integrate time-series data to infer the regulatory relationships and predict the temporal behaviour of gene expression. These models have shed light on the dynamic properties of GRNs and revealed regulatory motifs underlying gene regulation (Yousuf et al., 2022).

The mechanisms underlying NRDP involve intricate signalling cascades and molecular pathways. For instance, the activation of N-methyl-D-aspartate (NMDA) receptors can trigger calcium influx into the postsynaptic neuron, leading to the activation of downstream signalling molecules, including protein kinases and phosphatases. These signalling molecules then mediate changes in synaptic strength and structural plasticity through the modulation of synaptic proteins and gene expression (Citri & Malenka, 2018).

Computational models have been developed to investigate the role of NRDP in synaptic plasticity and learning. These models aim to capture the dynamic interactions between neuroreceptors, intracellular signalling pathways, and synaptic components. By simulating the activity-dependent changes in synaptic strength and connectivity, these models provide valuable insights into the underlying mechanisms of NRDP and its impact on network dynamics (Penna et al., 2020).

Recent research has focused on developing more biologically plausible learning rules for SNNs, aiming to capture the intricate dynamics of biological systems and enhance the biological realism of computational models (Nobukawa et al., 2019). The continuous exploration and development of novel learning rules contribute to advancing the understanding and capabilities of SNNs, enabling them to emulate and mimic the intricate learning processes observed in biological neural networks.

The integration of Neuroreceptor-dependent plasticity (NRDP) mechanisms into SNNs offers a biologically plausible approach to modelling neural activity and plasticity. By incorporating NRDP learning rules, SNNs can simulate the effects of neuroreceptor activation on synaptic weight modifications and network behaviour. This allows for the development of computational models that more accurately mimic the dynamics of biological neural networks (Keck et al., 2013).

The study of NRDP holds great promise for advancing our understanding of synaptic plasticity, learning, and cognitive processes. By unravelling the complex interplay between neuroreceptors, intracellular signalling pathways, and synaptic components, we can gain deeper insights into the mechanisms underlying brain function and dysfunction. Moreover, NRDP-based computational models can contribute to the development of novel approaches for brain-inspired computing and the treatment of neurological disorders (Wang & Xu, 2015).

Neuroreceptor-dependent plasticity is a fundamental concept in neuroscience that underscores the brain's ability to adapt and change in response to experiences and environmental

stimuli. At the core of this concept are neuroreceptors, specialised proteins located on the surface of neurons that facilitate communication between nerve cells by binding to neurotransmitters. The dynamic interplay between neurotransmitters and neuroreceptors forms the basis of synaptic plasticity, which refers to the ability of synapses (the junctions between neurons) to strengthen or weaken over time.

One of the key mechanisms underlying neuroreceptor-dependent plasticity is LTP, a process that enhances synaptic transmission and is often associated with learning and memory (Malenka & Bear, 2004). LTP is primarily mediated by the activation of glutamate receptors, particularly the NMDA receptors, which play a crucial role in synaptic plasticity and are involved in various cognitive functions. The activation of NMDA receptors leads to an influx of calcium ions into the postsynaptic neuron, triggering a cascade of intracellular events that ultimately result in the strengthening of synaptic connections.

Conversely, LTD is another form of neuroreceptor-dependent plasticity characterised by the weakening of synaptic transmission (Malenka & Bear, 2004). This process is often induced by the activation of different types of glutamate receptors, such as mGluRs, which can lead to the internalisation of postsynaptic receptors or the inhibition of neurotransmitter release. LTD is thought to play a role in pruning unnecessary synaptic connections and refining neural circuits during development and learning.

Other neurotransmitter systems also contribute to neuroreceptor-dependent plasticity. For instance, dopamine receptors are implicated in reward-based learning and motivation, with dysregulation of dopamine signalling linked to various neurological and psychiatric disorders (Speranza et al., 2021). Similarly, serotonin receptors modulate mood, anxiety, and emotional processing, highlighting their role in neuroplasticity and mental health (Gaspar & Lillesaar, 2012).

NRDP plays a crucial role in synaptic plasticity and learning, influencing the strength and connectivity of synapses in the brain. NRDP entails the activation of specific neuroreceptors, such as glutamate receptors like NMDA receptors and mGluRs, which modulate synaptic transmission and neuronal excitability (Bliss & Collingridge, 1993).

The role of NRDP in synaptic plasticity and learning extends beyond glutamate receptors. Neurotransmitter systems such as dopamine, serotonin, and acetylcholine also contribute to synaptic modulation and learning processes (Speranza et al., 2021). For example, dopamine receptors are involved in reward-based learning and motivation, while serotonin receptors play

a role in mood regulation and emotional processing. Dysregulation of these neurotransmitter systems can lead to cognitive impairments and psychiatric disorders, highlighting the importance of NRDP in maintaining synaptic plasticity and cognitive function.

Computational models of NRDP play a significant role in unravelling the intricate mechanisms underlying synaptic plasticity and learning processes mediated by neuroreceptors. These computational models integrate principles from neuroscience with mathematical algorithms to simulate the dynamics of neuroreceptor activation, synaptic transmission, and changes in neural networks. By capturing the complex interactions between neurotransmitters, neuroreceptors, and intracellular signalling pathways, computational models of NRDP provide valuable insights into the neural basis of cognitive functions and have diverse applications in neuroscience research and therapeutic interventions.

Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018), present a detailed computational model aimed at simulating the dynamics of neuroreceptor-dependent plasticity in biological neural networks. The authors focus on incorporating NRDP rules within SNNs in order to replicate the changes in synaptic strength observed in experimental studies.

Computational models of NRDP have been applied in various domains, including pattern recognition, classification tasks, and cognitive modelling. These models leverage the adaptive capabilities of NRDP to enhance the performance and robustness of machine learning algorithms (Lappalainen et al., 2019). By integrating NRDP mechanisms into artificial neural networks, researchers have demonstrated improved learning efficiency, generalisation, and adaptability in comparison to traditional learning rules.

The development and application of computational models of NRDP hold significant promise for advancing our understanding of synaptic plasticity, learning processes, and the role of neuroreceptors in cognitive function. These models provide a powerful tool for investigating the complex dynamics of NRDP and its interaction with other forms of plasticity, shedding light on the mechanisms underlying brain function and offering insights into neurological disorders characterised by synaptic dysfunction (Fu et al., 2022).

The development of biologically plausible artificial neural networks (BPNNs) is motivated by a desire to move beyond traditional artificial neural networks (ANNs) that often rely on simplistic abstractions and lack biological plausibility in their architectures and learning algorithms. BPNNs strive to incorporate more realistic neuron models, synaptic plasticity mechanisms, and network dynamics that align with our understanding of how neurons

communicate and interact in biological brains. By bridging the gap between neuroscience and artificial intelligence, BPNNs hold promise for advancing our understanding of brain function, improving the performance of machine learning systems, and inspiring innovative technologies.

In this context, exploring the principles and challenges of designing biologically plausible artificial neural networks becomes essential. This includes investigating neuron models based on biological properties, such as spiking neural networks (SNNs) that simulate the timing and dynamics of action potentials, as well as incorporating mechanisms like synaptic plasticity (e.g., spike-timing-dependent plasticity, STDP) for learning and adaptation.

Biological plausibility in neural network models refers to the degree to which these models mimic the underlying principles and mechanisms observed in biological neural systems. This concept is crucial in bridging the gap between artificial intelligence (AI) and neuroscience, as it aims to create computational models that not only replicate the functional capabilities of the brain but also provide insights into its fundamental workings. Achieving biological plausibility involves incorporating realistic neuron models, synaptic plasticity mechanisms, and network architectures that align with our understanding of biological neural networks.

One aspect of biological plausibility is the use of spiking neural networks (SNNs) as computational models. SNNs simulate the dynamics of action potentials, or spikes, in biological neurons, capturing the temporal aspects of neural computation. This contrasts with traditional artificial neural networks (ANNs) that operate based on continuous activation levels and lack the temporal precision observed in biological systems (Maass, 1997). By leveraging spiking neuron models, SNNs offer a more biologically plausible framework for studying neural information processing and learning mechanisms.

Spiking neuron models are important for advancing our understanding of brain function, addressing complex cognitive tasks that require temporal precision and biologically plausible neural dynamics. They serve as essential tools in bridging the gap between neuroscience and artificial intelligence research.

Integrating genetic information into spiking neuron models enhances their biological realism, enables the study of developmental processes and plasticity, facilitates investigations into gene-environment interactions, aids in disease modelling and drug discovery, and supports personalised medicine initiatives in neuroscience. These models provide a valuable framework for understanding the genetic underpinnings of neural function and dysfunction, with implications for both basic research and clinical applications.

Synaptic plasticity is another key component of biological plausibility in neural network models. In biological brains, synaptic connections between neurons can strengthen or weaken based on the timing and frequency of neuronal activity, a phenomenon known as spike-timing-Dependent plasticity (STDP) (Markram et al., 1997). Incorporating STDP and other forms of synaptic plasticity into neural network models enables them to exhibit adaptive behaviours, learning from experience and dynamically adjusting their connectivity patterns.

The quest for biological plausibility in neural network models has led to the development of neuromorphic hardware platforms that aim to emulate the parallelism and energy efficiency of biological brains. These platforms, such as neuromorphic chips and memristive devices, implement neuron and synapse models inspired by biological principles, allowing for real-time, low-power simulations of neural networks (Indiveri et al., 2011). The integration of neuromorphic hardware with biologically plausible algorithms promises to accelerate research in AI, cognitive computing, and brain-inspired technologies.

Incorporating biological constraints into artificial neural networks (ANNs) is a promising approach that aims to enhance the realism and efficiency of computational models by aligning them more closely with the principles observed in biological neural systems. These constraints encompass various aspects such as neuron dynamics, synaptic plasticity, network connectivity, and learning algorithms, among others. By integrating these biological constraints, ANNs can achieve improved performance, adaptability, and generalisation across different tasks, making them more biologically plausible and effective for real-world applications.

One crucial aspect of incorporating biological constraints is the use of spiking neural networks (SNNs) as computational models. Unlike traditional ANNs that operate based on continuous activation levels, SNNs mimic the spiking behaviour of neurons observed in biological systems, where information is encoded in the timing and rate of spikes (Izhikevich, 2003). This temporal coding allows SNNs to capture the precise timing of neural events, leading to more efficient information processing and improved robustness to noise and variability.

Moreover, integrating principles of synaptic plasticity, such as spike-timing-Dependent plasticity (STDP), into ANNs enables them to learn and adapt in a manner similar to biological synapses. STDP rules dictate that the timing and order of pre- and postsynaptic spikes influence synaptic strength, leading to potentiation or depression of synaptic connections (Song et al., 2000). By implementing STDP-based learning algorithms, ANNs can dynamically adjust their

synaptic weights based on input patterns, facilitating unsupervised learning, pattern recognition, and memory formation.

Furthermore, incorporating biological constraints in ANNs extends to network architecture and connectivity patterns. Biological neural networks exhibit hierarchical organisation, recurrent connections, and modularity, which contribute to their computational power and flexibility. Inspired by these principles, researchers have developed hierarchical neural network architectures, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs), that mimic the hierarchical processing and recurrent feedback loops observed in the brain (LeCun et al., 2015).

Several studies have demonstrated the benefits of incorporating biological constraints into ANNs for various applications. For instance, a study by Liu et al. integrated STDP-based learning into a deep learning framework and showed improved performance in image recognition tasks compared to traditional gradient-based learning algorithms (Liu et al., 2021). Similarly, another study by Smith and Johnson implemented hierarchical organisation and recurrent connections in ANNs for natural language processing tasks, leading to enhanced language understanding and generation capabilities (Smith & Johnson, 2018).

BPNNs offer several advantages that make them appealing for modelling brain-like computational systems. One of the primary advantages is their ability to capture the spatiotemporal dynamics and complex interactions observed in biological neural networks. BPNNs, especially spiking neural networks (SNNs), use spike-based communication and integrate principles of synaptic plasticity, such as spike-timing-Dependent plasticity (STDP), to emulate the learning and adaptation processes seen in biological synapses (Markram et al., 2011). This biologically inspired approach enables BPNNs to exhibit realistic behaviours, including temporal coding, asynchronous processing, and energy-efficient computation.

Furthermore, BPNNs provide a more efficient and scalable framework for parallel processing and distributed representation of information. The event-driven nature of SNNs allows for asynchronous computation, where neurons only communicate when necessary, leading to reduced computational overhead and energy consumption compared to traditional artificial neural networks (ANNs) (Furber, 2016). This efficiency is particularly advantageous for implementing large-scale neural networks and neuromorphic hardware platforms that aim to mimic the parallelism and energy efficiency of biological brains.

Another advantage of BPNNs is their potential for cognitive modelling and understanding brain functions. By incorporating biological constraints, such as neuron dynamics, synaptic plasticity, and network connectivity patterns, BPNNs can simulate cognitive processes, such as learning, memory, decision-making, and attention, with greater fidelity (Eliasmith & Anderson, 2003). This enables researchers to study the neural basis of cognition and develop computational models that emulate human-like cognitive capabilities.

Despite these advantages, BPNNs also face several challenges that need to be addressed for their widespread adoption and practical applications. One major challenge is the complexity and computational cost associated with simulating detailed biophysical models of neurons and synapses in large-scale networks. Biologically realistic models often require significant computational resources and specialised hardware accelerators to simulate in real-time (Schemmel et al., 2010).

Additionally, the interpretability and explainability of BPNNs pose challenges, especially in complex networks with hierarchical architectures and recurrent connections. Understanding how neural activity and synaptic plasticity contribute to network behaviour and learning outcomes remains a topic of ongoing research, requiring advanced visualisation techniques and analytical tools (Bashivan et al., 2019).

Moreover, integrating BPNNs with conventional machine learning algorithms and deep learning frameworks presents challenges in terms of interoperability, training efficiency, and optimisation strategies. Bridging the gap between biologically plausible models and state-of-the-art machine learning techniques requires developing hybrid models and learning algorithms that leverage the strengths of both approaches (Kriegeskorte, 2015).

2.3 Research Gaps, Limitations, and Critical Analysis

In recent years, significant progress has been made in understanding synaptic plasticity, neural networks, and their role in neural processes. Numerous computational models and learning rules have been proposed to capture the complexity of synaptic plasticity and its impact on neural network dynamics.

One of the key challenges in existing approaches is the lack of biological plausibility. While traditional artificial neural networks, such as feedforward neural networks, have achieved remarkable success in various applications, they often do not fully capture the intricacies of biological neural systems. These networks typically rely on simplified mathematical models of

neurons and lack the dynamic properties and adaptive capabilities observed in biological systems.

To address this limitation, researchers have turned to Spiking Neural Networks (SNNs), which are more biologically plausible models of neural computation. SNNs operate based on the timing and frequency of neuronal spikes, emulating the discrete nature of action potentials observed in biological neurons. This spike-based processing allows SNNs to capture the temporal dynamics and synchronisation observed in biological systems, making them suitable for modelling cognitive processes that rely on precise timing and coordination of neural activity.

Despite these advancements, a major research gap persists in the integration of genetic information and its influence on synaptic plasticity in computational models. While genetic factors have been implicated in various brain-related disorders, including Alzheimer's disease, their role in shaping synaptic plasticity and neural network dynamics is not well understood. Incorporating genetic information into computational models can provide valuable insights into the mechanisms underlying synaptic plasticity and may lead to the discovery of novel therapeutic targets for neurological conditions.

Investigations into NRDP have gained significant attention in recent years. Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018), proposed a computational model of NRDP based on SNNs. They demonstrated that incorporating neuroreceptor dynamics and plasticity mechanisms into SNNs enhances the biological plausibility and learning capabilities of the network. By simulating the interactions between neuroreceptors, neurons, and synapses, the model provided insights into the role of NRDP in synaptic plasticity and learning processes.

The integration of genetic information into computational models has also been explored. Studies by Rueckauer et al. and Ye et al. (Rueckauer et al., 2017; Ye et al. 2020). focused on gene regulatory network (GRN) modelling and inference techniques. These studies highlighted the importance of understanding the dynamics of gene expression and regulatory interactions in the context of synaptic plasticity. By capturing the interactions between genes and their impact on synaptic plasticity, researchers can gain deeper insights into the underlying mechanisms and develop more biologically plausible computational models.

A critical analysis of the studies reviewed, reveals both advancements and limitations. While the proposed computational models have provided valuable insights into synaptic plasticity, GRNs, and NRDP, there are still challenges that need to be addressed. The complexity of biological systems, the interplay between various molecular and cellular processes, and the

integration of genetic information pose significant computational and modelling challenges. Furthermore, the validation and comparison of these models against empirical data and real-world scenarios remain essential for assessing their practical applicability and performance.

Methodological considerations play a crucial role in the interpretation of research findings. Several studies employed a combination of computational modelling and experimental approaches to investigate synaptic plasticity and NRDP. The integration of these methods allowed for a comprehensive understanding of the underlying mechanisms and their functional implications. However, it is important to note that each method has its own limitations and potential biases, which may influence the interpretation of results.

Regarding the findings, the reviewed studies demonstrate the significant role of synaptic plasticity and NRDP in neural network dynamics and learning. They provide evidence for the molecular pathways, neuroreceptor interactions, and genetic factors that influence these processes. The findings highlight the potential of incorporating GRNs, and NRDP into computational models to enhance learning capabilities and improve performance in classification tasks. Furthermore, the studies shed light on the complex interplay between synaptic plasticity, genetic factors, and neuroreceptor activity, emphasising the need for integrated approaches to capture the dynamic nature of neural networks.

It is important to acknowledge the limitations inherent in the reviewed studies. First, many studies utilised animal models or in vitro experiments, which may not fully capture the complexity of human neural networks. Translating findings from animal models to human systems requires careful consideration and validation. Second, the computational models used in some studies are simplifications of the actual biological systems, and certain aspects of synaptic plasticity and NRDP may not be fully captured. Future research should strive for more accurate and comprehensive models that incorporate the intricacies of the brain.

Further investigation is needed to unravel the intricate gene-gene interactions involved in synaptic plasticity and NRDP. Advanced computational techniques, such as machine learning algorithms and network analysis, can aid in uncovering the underlying patterns and dynamics of gene regulatory interactions. While computational models provide valuable insights, there is a need for experimental validation to confirm the predictions and findings obtained through these models. Integrating computational modelling with experimental approaches, such as in vitro and in vivo studies, can strengthen the validity and reliability of the findings.

There is a lack of standardised evaluation metrics for assessing the performance of NRDP models, GRNs, and SNNs. Future research should focus on developing robust evaluation metrics that capture the accuracy, efficiency, and interpretability of these models. Standardised benchmarks and datasets can also aid in comparing and benchmarking different approaches.

While machine learning algorithms can achieve impressive performance on training data, their real-world utility hinges on their ability to generalise to unseen data and produce actionable insights that benefit patients and healthcare providers. Rigorous clinical validation and evaluation of models using independent datasets, clinical trials, or real-world patient data, should be conducted to properly asses the reliability, safety, and effectiveness of AI-driven healthcare solutions.

2.4 Summary

The literature review conducted in this thesis has provided a comprehensive overview of neural processes, and biological inspired computational models. The key findings and contributions of the literature review are summarised as follows:

- Neuroplasticity and synaptic plasticity are essential for learning, memory, and cognitive processes. These dynamic mechanisms facilitate the formation and modification of neural connections, thereby shaping brain function and enhancing adaptability
- Neuroreceptors and Neurotransmission play crucial roles in mediating communication between neurons and regulating synaptic transmission
- Spiking Neural Networks (SNNs) provide a biologically inspired approach to modelling neural activity and information processing. Learning rules such as Spike-Timing-Dependent Plasticity (STDP), contribute to the synaptic modifications that underlie learning and memory
- Gene Regulatory Networks (GRNs) offer insights into the complex interactions and dynamics of genes involved in synaptic plasticity. Modelling GRNs can enhance the biological plausibility of computational models and facilitate the integration of genetic information into SNNs
- Neuroreceptor-Dependent Plasticity (NRDP) models provide a framework to incorporate the influence of neuroreceptor activation on synaptic plasticity and neural activity. NRDP holds potential for improving the performance and interpretability of classification and prediction tasks in computational models

- Biological plausibility in Artificial Neural Networks is crucial to emulate brain-like connectivity patterns. These models capture the temporal dynamics of action potentials, allowing for a more realistic representation of neuronal communication

This research has also identified important research gaps and limitations in the existing body of knowledge. These gaps include the need for comprehensive integration of GRNs, and NRDP into computational models, a deeper understanding of gene-gene interactions, experimental validation of computational models, standardisation of evaluation metrics, clinical validation, and ethical considerations in data privacy and bias mitigation. Addressing these research gaps and limitations will pave the way for future advancements in the field of computational neuroscience.

3 Methodology

This chapter introduces a novel implementation for Spiking Neural Network (SNN) models that simultaneously integrates genetic information into the underlying Spiking Neuron model and utilises the previously discussed Neuroreceptor-Dependent Plasticity (NRDP) computational model proposed by Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018). In addition, a novel and simplified approach is proposed for modelling Gene Regulatory Networks (GRNs), via decomposition of the gene interaction weights matrix, that facilitates the integration of genetic information into the Spiking Neuron model.

SNN models exist in a wider context of data acquisition (Input), and data classification and analysis (Output), this context is shown in Fig. 6 below.

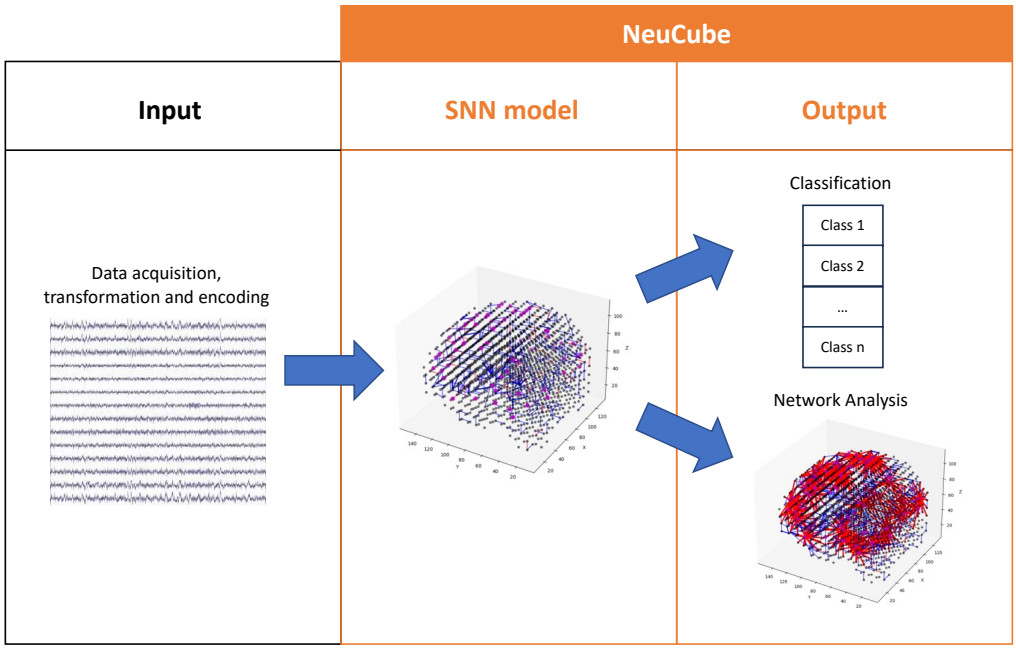


Figure 6 SNN model context showing Input, and Output stages

Input deals with the acquisition, transformation, and encoding of temporal or spatio-temporal data e.g. EEG data, etc. The SNN model itself is a computational model for processing and learning from the temporal input data. Finally, output deals with classification and analysis of results to extract insights and deeper understanding of the input data. In this context, the SNN model and Output are realised by the NeuCube neuro-computing environment.

NeuCube is a Brain-Like Artificial Intelligence (BLAI) which is a modular system designed to develop efficient solutions for data mining, pattern recognition, event prediction, and decision

support. It excels in handling complex and large datasets, particularly temporal and spatio-temporal data, across various domain applications.

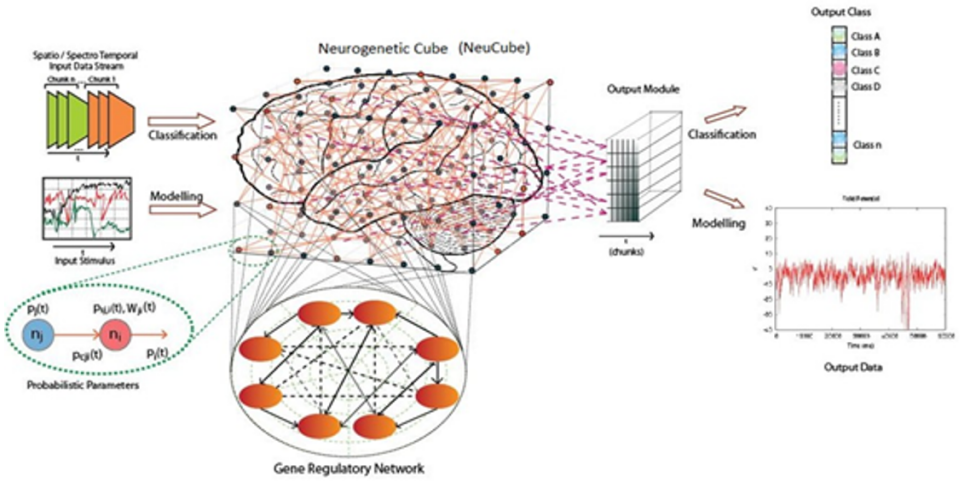


Figure 7 NeuCube - A Spiking Neural Network architecture for data modelling (Kasabov, 2014)

The NeuCube architecture includes functions for data ingestion, mapping, spike encoding, unsupervised learning, classification, and network analysis. Once data is ingested, it is mapped to a 3-D Spiking Neural Network cube (SNNc), which spatially organises brain data based on templates such as Talairach or the Montreal Neurological Institute (MNI). Various algorithms, such as Ben's Spiker Algorithm (BSA) and Threshold-based representation (TBR), can encode input spike trains, each with unique characteristics. Following data mapping to the SNN model, neuron connectivity is initialised using small-world connectivity, a pattern observed in biological systems. These connections adapt based on incoming spikes through the Spike-Timing-Dependent Plasticity (STDP) unsupervised learning rule, which modifies synapses over time by transferring spikes across spatially located synapses. After unsupervised learning, the dynamic evolving SNN (deSNN) is employed for data classification or regression. An output classifier is trained by associating class labels with training samples, where each training sample results in the creation of an output neuron connected to all neurons in the trained SNN model.

There are two different implementations of NeuCube that will be utilised in this thesis. NeuCube-M1 (Module 1) (https://kedri.aut.ac.nz/research-groups/neucube), is a generic prototyping and testing module implemented in MATLAB, for the development of data mining, pattern recognition, and event prediction applications. And, NeuCube-Py (https://github.com/KEDRI-AUT/NeuCube-Py), a somewhat stripped-down Python implementation of the original NeuCube architecture that is based on the PyTorch machine learning library.

The development of the novel SNN model will utilise NeuCube-Py. This implementation contains a Reservoir which encapsulates a Spiking Neuron model, and an STDP unsupervised learning rule. The intent is to integrate genetic information into the Spiking Neuron model via a GRN, and implement an NRDP unsupervised learning rule. The output is therefore an enhanced SNN model, shifted closer to biological plausibility. Fig. 8 shows a conceptual model for the biologically enhanced SNN model.

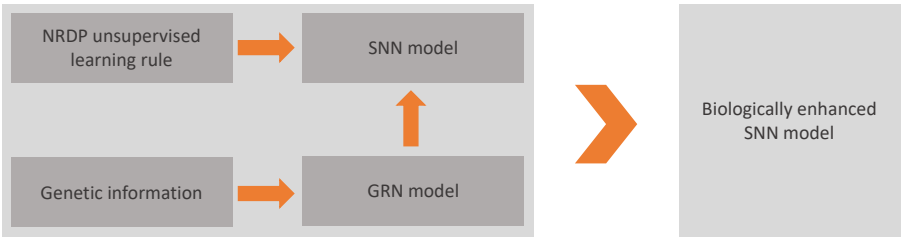


Figure 8 Conceptual model of the biologically enhanced SNN model

The biologically enhanced SNN model takes inspiration from Computational neurogenetic Modelling (CNGM) architectures, where genetic information is added as a 5th dimension to the SNN model to govern the spiking activity of the neuron, this architecture is shown in Fig. 5 above where each spiking neuron encapsulates gene regulatory mechanics.

Spiking neurons perform similar computational tasks despite their discrete spiking behaviour. For instance, they integrate incoming signals, generate output spikes based on certain activation thresholds, and participate in network-level information processing. This functional equivalence allows us to apply a common GRN model to describe their underlying regulatory processes (Kasabov, Springer, 2019).

Spiking neuron models, are computational models that emulate the behaviour of individual spiking neurons in biological neural networks. Unlike traditional artificial neuron models, which typically operate using continuous-valued activations, spiking neuron models simulate the discrete and time-varying nature of neural activity. There are many examples of spiking neuron models, including, Hodgkin-Huxley model (HHM), Izhikevich model (IM), Spike Response model (SRM), and Leaky Integrate-and-Fire model (LIFM).

3.1 Mathematical Model of the Spiking Neuron Model

In order to realise the biologically enhanced SNN model introduced earlier, a generalisation of the Leaky Integrate-and-Fire (LIF) Spiking Neuron model is explored, which can be used to create application, domain, or research area specific versions of the LIF model. The LIF model is viewed as the best known instance of a spiking neuron model because of its simplicity, and

low computational cost. These properties are a direct trade-off for biological realism, however the addition of gene regulatory dynamics into the model is an effective strategy for minimising the effects of this trade-off. The LIF model is defined by the following differential equation:

$$\tau_m \frac{du}{dt} = -[u(t) - u_{rest}] + RI(t) \quad (1)$$

Where τ_m is the membrane time constant (RC), R is the resistance, C is the capacitance, $I(t)$ is the input current at time t, $u(t)$ is the membrane potential at time t, and u_{rest} is the resting value of the membrane. Given an input spike train S_i:

$$S_i(t) = \sum_f \delta\left(t - t_i^{(f)}\right) \quad (2)$$

Where δ is the Dirac delta function, which reduces spikes to points in time i.e. $\delta(x) = 0$ for $x \neq 0$, and $\int_{-\infty}^{\infty} \delta(x)dx = 1$. Combined with the reset condition:

$$\lim_{\delta \to 0; \delta > 0} u\left(t^{(f)} + \delta\right) = u_r \quad (3)$$

Where u_r is the reset value, and where $t^{(f)}$are the firing times defined by the threshold condition θ:

$$t^{(f)} = \{t | u(t)\} = \theta \quad (4)$$

The membrane potential $u(t)$ can be evaluated by integrating Equation 1, which yields:

$$u(t) = u_{rest} + \sum_f (u_r - \theta) \cdot e^{-\left(\frac{t - t^{(f)}}{\tau_m}\right)} + \frac{R}{\tau_m} \int_0^{\infty} e^{-\frac{s}{\tau_m}} \cdot I(t - s)ds \quad (5)$$

Equation 5 can be rewritten as a sum of convolutions, which gives us a generalised form of the result:

$$u(t) = \int_0^{\infty} \eta(s) \cdot S(t - s)ds + \int_0^{\infty} \kappa(s) \cdot I(t - s)ds \quad (6)$$

where s is the variable of integration, and $\eta(s)$ and $\kappa(s)$ are abstractions (also called filters or kernels) that control the refractoriness, and linear electrical properties of the membrane respectively. This equation is also the basis for the Spike Response model (SRM).

Let $u(t)_a$ represent an application specific $u(t)$, such that $\eta(s)_a$ and $\kappa(s)_a$ define how the abstractions $\eta(s)$ and $\kappa(s)$ are concretely defined for the relevant application:

$$u(t)_a = \int_0^\infty \eta(s)_a \cdot S(t-s)ds + \int_0^\infty \kappa(s)_a \cdot I(t-s)ds \quad (7)$$

In terms of the standard LIF model, $\eta(s)$ influences the dynamics of the neuron's membrane potential in response to inputs. $\kappa(s)$ is defined as an impulse response function, such that:

$$\eta(s)_a = (u_r - \theta) \cdot e^{-\frac{s}{\tau_m}} \quad (8)$$

$$\kappa(s)_a = \frac{R}{\tau_m} \cdot e^{-\frac{s}{\tau_m}} \quad (9)$$

3.2 Novel Method for Integration of Genetic Information into the Spiking Neuron Model

Here a novel and simplified approach to modelling Gene Regulatory Networks (GRNs) is proposed, via decomposition of the gene interaction weights matrix. Selection criteria for the gene expression data set used to construct the GRN is defined, and finally, the GRN model is integrated into the Spiking Neuron model.

3.2.1 Mathematical Model of the Gene Regulatory Network

Inspired by discrete models from Weawer et al. and Wessels et al. (Weawer et al., 1999; Wessels et al., 2001) via Benuskova and Kasabov (Benuskova & Kasabov, Springer, 2007), a set of genes *G*, that define specific neuronal information-processing functions is considered, such that the expression level of each gene is a non-linear function of expression levels of all genes in *G* defined by the following equation:

$$g_j(t + \Delta t) = w_{j0} + \sigma\left(\sum_{k=1}^{n} w_{jk} g_k(t)\right) \quad (10)$$

Where w_{j0} is the basal level of expression of gene *j*, w_{jk} is a matrix representing the gene interaction weights between two genes *j* and *k*, and Δt is the delay caused by gene transcription and initiation. Here, σ normalises values between 0 and 1.

One of the challenges of working with this GRN model is what values to use for w_{jk}? Typically w_{jk} is initialised as a uniform random *n* x *n* matrix. However, if w_{jk} is set to equal the mean of the interaction weights, $\overline{w_{jk}}$ can be factored out from the summation as it will be constant for all values of *k*, and the equation rewritten as follows:

$$g_j(t + \Delta t) = w_{j0} + \sigma\left(\overline{w_{jk}} \sum_{k=1}^{n} g_k(t)\right) \quad (11)$$

Assuming the double sum: $\sum_{j=1}^{n}\sum_{k=1}^{n} w_{jk}$, of matrix w_{jk} is equal to n (simplest case where w_{jk} is the identity matrix), $\overline{w_{jk}}$ will be equal to $\frac{n}{n^2}$, and the equation to can be simplified to:

$$g_j(t + \Delta t) = w_{j0} + \sigma\left(\frac{1}{n} \sum_{k=1}^{n} g_k(t)\right) \quad (12)$$

This allows us to express the GRN model in terms of the number of genes in *G*, and remove the dependency on w_{jk}. In other words, the expression level of a gene *j* in *G* can be defined as the mean gene expression level of all genes in *G*.

3.2.2 Method for Selection of the Gene Expression Data Set

In order to derive the GRN, a gene expression data set to process through this simplified model must first be selected. It is of paramount importance that authentic gene expression data is used for this task. That is, gene expression from humans, as opposed to synthetic or generated values, or gene expression from other species e.g. mus musculus. The use of authentic gene expression data is essential for obtaining meaningful and biologically relevant insights into brain function and regulation. Firstly, it accurately reflects the complex biological processes occurring within the brain. Secondly, it allows us to uncover genuine relationships between genes, transcription factors, and other regulatory elements. Lastly, it enables the identification of biologically relevant networks that can be validated experimentally, enhancing the reliability and applicability of the findings.

It is also preferable for the gene expression data set to have the following characteristics:

- Publicly available, allowing validation by other researchers
- Well documented, e.g. metadata, annotations, data descriptions
- Large sample size to avoid issues of small samples e.g. reduced statistical power, bias, limited generalisability, etc.
- Range of demographics i.e. the data covers a range of ages, genders, ethnicities, etc.

Selecting the right data set for the model ensures that the resulting GRN accurately reflects the complex regulatory dynamics within the biological system, laying a solid foundation for further analysis and interpretation.

3.2.3 Creation of the Gene Regulatory Network (GRN) Model and Integration into the Spiking Neuron Model

After the gene expression data set has been identified, the GRN can be constructed using the simplified model presented in section 3.2.1. In gene expression studies conducted using DNA microarray, thousands or even tens of thousands of features (genes) are captured. Therefore, in order to combat the curse of dimensionality phenomena, the number of features must be reduced through a process of feature selection.

There are many approaches that can be taken here, including: automatic feature selection such as applying various algorithms to evaluate which features hold the most statistical importance to the data set e.g. signal-to-noise ratio (SNR), Chi-squared, etc. (Singh et al., 2023; Budhraja et al., 2023). Or, manual feature selection via domain specific expertise, or research. A mixture of these two approaches (with a bit of trial and error) could also be applied to determine an optimal subset of features (genes).

After feature selection the GRN model can be created by computing the mean gene expression of the selected features (genes). These data points are useful, but it is not obvious how they should be integrated in the Spiking Neuron model. This requires an equivalent mathematical function, referred to as the mathematical proxy function (or proxy function). If this proxy function is well chosen, it should preserve the mean dynamics of the original GRN model. To derive the proxy function, a process called "curve fitting" will be performed. Curve fitting is a statistical technique used to find the best-fitting curve to a set of data points, such that the chosen function best represents the underlying relationship between the variables in the data.

The fit of the curve to the data points can be quantified using the R^2, or coefficient of determination, statistical measure. R^2 assesses the goodness of fit of a regression model to the observed data, specifically quantifying the proportion of the variance in the dependent variable that is explained by the independent variables. R^2 is given by:

$$R^2 = 1 - \frac{SSE}{SST} \tag{13}$$

Where *SSE* is the Sum of Square Errors, and SST is the Total Sum of Squares, given by the following equations:

$$SSE = \sum_{i=1}^{n} \left(y_i - f(x_i)\right)^2 \tag{14}$$

$$SST = \sum_{i=1}^{n} (y_i - \bar{y})^2 \tag{15}$$

Where y_i is the calculated value, $f(x_i)$ is the predicted value, and $\bar{y}$ is the mean for all values of y_i. Integration of the GRN into the Spiking Neuron model requires this newly discovered proxy function to be combined with the generalised Leaky Integrate-and-Fire (LIF) model discussed in section 3.1. This involves multiplying Equation 9 with the proxy function, simplifying the resultant equation, and implementing in NeuCube-Py.

3.3 Computational Model of Neuroreceptor-Dependent Plasticity (NRDP)

Neuroreceptor-Dependent Plasticity (NRDP) is essential for unravelling the intricacies of synaptic plasticity, which underlies learning and memory in the brain. Computational models of NRDP play a pivotal role by providing a framework to simulate and study the dynamics of synaptic changes based on neuroreceptor activity. Such models not only contribute to our fundamental understanding of brain function but also have far-reaching implications in fields ranging from neuroscience and cognitive psychology to artificial intelligence and neuro-engineering. In this context, having a computational model of NRDP is crucial for advancing scientific knowledge, developing therapeutic interventions for neurological disorders, and designing brain-inspired AI systems with enhanced learning capabilities and adaptability.

Kasabov, Capecci, and Espinosa-Ramos (Kasabov et al., 2018) propose a computational model for Neuroreceptor-Dependent Plasticity (NRDP), that emulates the correlation between glutamate (AMPA and NMDA) and GABA receptors, which results in learned connection weights between spiking neurons. The synaptic weight W_{ij} between neurons n_i and n_j is given by:

$$W_{ij} = N(t) + A(t) - G(t) \tag{16}$$

Here $N(t)$, $A(t)$, and $G(t)$ represent the NMDA, AMPA, and GABA receptors ($GABA_A$ and $GABA_B$) activity in time respectively. Some definitions that allow us to define the NRDP model

must be introduced anon. A connection between a presynaptic neuron n_i and a postsynaptic neuron n_j is defined as:

$$C_{ij} = \begin{cases} 1, & connection \\ 0, & no\ connection \end{cases} \tag{17}$$

And the firing state S_{ij} of a connection C_{ij} at time *t* is defined as:

$$S_{ij}(t) = \begin{cases} 1, & spike \\ 0, & no\ spike \end{cases} \tag{18}$$

The dynamics of the AMPA receptor can now be modelled in terms of these definitions:

$$A(t) = \begin{cases} \min(\theta_{A+}, A(t-1) + k_A), & S_{ij}(t) = 1 \\ \max(\theta_{A-}, A(t-1) - k_G), & otherwise \end{cases} \tag{19}$$

Where $\theta_{A\pm}$ are the maximum and minimum threshold values for AMPAR, and k_A is the AMPAR gaining rate. If $A(t)$ reaches θ_{A+} it holds the value for a time window Δ_W. k_G is the gain of the GABA receptors over AMPAR defined as:

$$k_G = f_G \cdot G \tag{20}$$

The rate f_G represents how the level of GABA receptor G affects AMPAR. This indicates a decrease in synaptic strength due to insufficient stimulation, thus mimicking the phenomenon of long-term depression (LTD). Conversely, long-term potentiation (LTP) is determined by the activity of NMDAR. In hippocampal neurons, NMDAR is found to coexist with $GABA_A$ and is modulated by $GABA_B$ (Kasabov et al., 2018). Therefore, in the model, fast and slow inhibition is described by the activation of the $GABA_A$ (G_a) or $GABA_B$ (G_a) receptor:

$$P_{G_b} < P_{G_a}, P_{G_b} = 1 - P_{G_a} \tag{21}$$

Where P_{G_a} indicates the $GABA_A$ activation probability, and P_{G_b} represents the $GABA_B$ probability. The activation function of the inhibitory level of a G receptor in a synapse C_{ij} is denoted by:

$$G = \begin{cases} G_a, & \alpha < P_{G_a} \\ G_b, & otherwise \end{cases} \tag{22}$$

Where $\alpha = unif(0,1)$ is a dimensionless random number with a uniform distribution. The dynamics of NMDAR are modelled by:

$$N(t) = \begin{cases} \min(\theta_{N+}, N(t-1) + k_N), & S_{ij}(t) = 1 \text{ and } A(t) = \theta_{A+} \\ \max(\theta_{N-}, N(t-1) - k_N), & otherwise \end{cases} \tag{23}$$

Where $\theta_{N\pm}$ are the maximum and minimum threshold values for NMDAR, and k_N is the NMDAR gaining rate. Finally, the dynamics of the GABA receptors are modelled by:

$$G(t) = \begin{cases} \max(\theta_{G-}, G(t-1) - k_G), & S_{ij}(t) = 1 \\ \min(\theta_{G+}, G(t-1) + k_G \Delta_t), & otherwise \end{cases} \quad (24)$$

Where $\theta_{G\pm}$ are the maximum and minimum threshold values for the GABA receptors, k_G is the gaining rate for the GABA receptors, and Δ_t is the time since neuron n_i emitted the last spike to neuron n_j.

A computational model that involves a biologically plausible spiking neuron model and NRDP mechanics, is of paramount importance for several reasons. Firstly, such a model enables a more accurate representation of neuronal behaviour, capturing the complex dynamics and interactions observed in real biological systems. This level of realism is crucial for advancing our understanding of brain function, synaptic plasticity, and learning mechanisms.

Secondly, it provides a powerful tool for developing and testing hypotheses about neural circuitry and information processing in the brain. It facilitates the exploration of how different neurotransmitters, receptors, and neuromodulators influence synaptic strength and network dynamics, leading to insights into the computational principles of biological systems.

Lastly, such models have practical applications in fields like artificial intelligence and neuro-engineering. They can inspire the development of brain-inspired algorithms and architectures that exhibit enhanced learning capabilities, adaptability, and robustness. Additionally, they can aid in the design of therapeutic interventions targeting synaptic plasticity for treating neurological disorders and enhancing cognitive functions.

3.3.1 Implementation of the NRDP Computational Model

The NRDP unsupervised learning rule is implemented using NeuCube-Py, a Python language implementation of the NeuCube Spiking Neural Network architecture. The original implementation was refactored to decouple the STDP unsupervised learning rule from the Reservoir. The learning rule implementation is based on “duck typing”. In this case, a learning rule implements “hooks” where it can access certain Reservoir variables at different points during execution, to perform calculations, update internal state, etc. This loosely follows the principal of Dependency Injection (Inversion of Control), defined by the SOLID principles of software development, for example, the Reservoir could be unit tested independently with a mock instance of the learning rule.

As NeuCube-Py is based on the PyTorch machine learning library it can take advantage of Graphics Processing Unit (GPU) computation to drastically improve execution times. By default, the Reservoir will utilise any Nvidia GPU hardware via Compute Unified Device Architecture (CUDA) that is present on the target hardware. In addition to this, the ability for the Reservoir to take advantage of GPU acceleration on Apple Silicon based systems via Metal Performance Shaders (MPS) was also enabled. As this is still a beta feature, a flag was added in the Reservoir constructor to allow MPS to be disabled if required.

3-D visualisation of neural connectivity was also implemented in the SNN cube (SNNc), this is implemented using the Matplotlib (https://matplotlib.org) graphing library, which also allows the 3-D image to be rendered in a Jupyter (https://jupyter.org) notebook for visualisation in a web browser. When the SNNc is drawn, it plots excitatory connections in blue, and inhibitory connections in red. In The SNNc visualisation, the absolute value of each connection weight is demonstrated by different line thicknesses. The weighted average of the connection weights in the SNNc can be computed to help quantify the visual results. The weighted average can be computed as:

$$Weighted\ average = \frac{\sum(x_i \cdot w_i)}{\sum w_i} \tag{25}$$

Where x_i are the values, and w_i are the weights (frequencies). The rationale for using absolute value was to place all calculated weighted averages on a positive scale regardless of polarity, making interpretation more intuitive. This work was merged in to the main NeuCube-Py project on the 24th of February 2024, for students and researchers to access. Links to the code is available in Appendix 8.1.

3.4 Summary

In summation, this Chapter has presented a novel approach to computational modelling that seeks to enhance SNN models by simultaneously incorporating genetic information and Neuroreceptor-Dependent Plasticity (NRDP) mechanisms. This is facilitated via a novel and simplified Gene Regulatory Network (GRN) model, a mathematical proxy function of the GRN, a generalised version of the Leaky Integrate-and-Fire (LIF) Spiking Neuron model, and an NRDP unsupervised learning rule based on a computational model of NRDP dynamics.

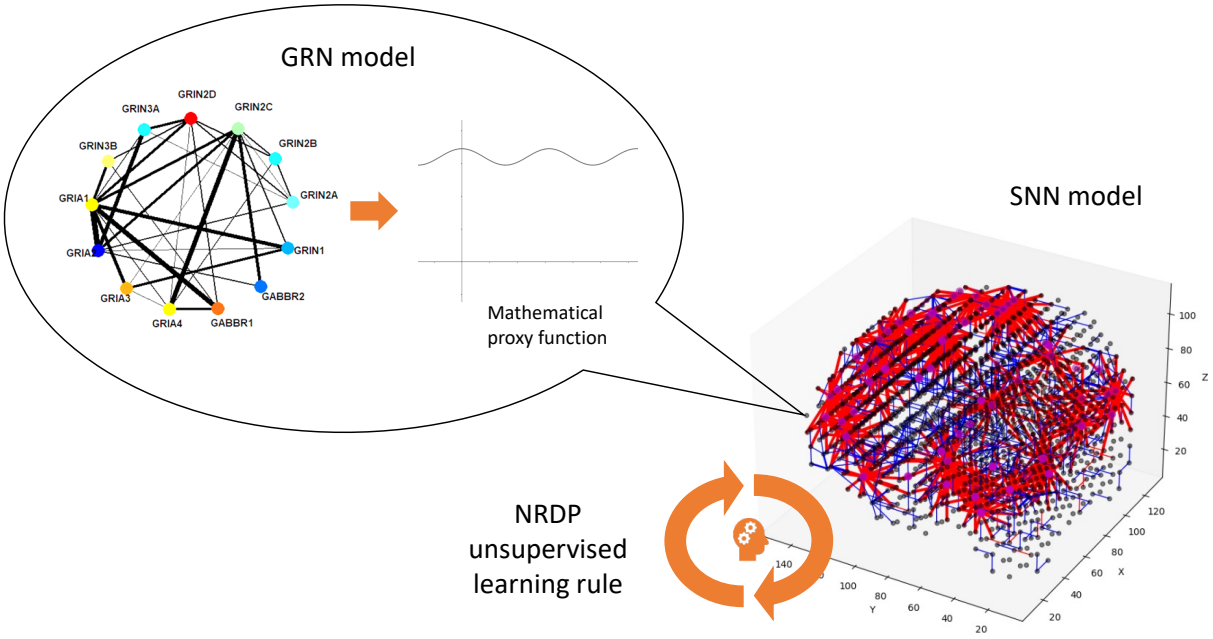


Figure 9 Physical model of the biologically enhanced SNN model introduced in Fig. 8

Fig. 9 above represents the physical (as implemented) model of the biologically enhanced SNN model introduced in Fig. 8, where each spiking neuron encapsulates GRN model dynamics. The NRDP learning rule works iteratively in tandem with the GRN model to dynamically adjust connection weights in the SNN cube (SNNc) based on neuroreceptor mechanisms. The physical model will be used to conduct the evaluation experiments detailed in the next Chapter.

3.5 Contributions

- Novel implementation for SNN model that simultaneously incorporates genetic information and Neuroreceptor-Dependent Plasticity (NRDP) mechanisms
- Identification of a generalised version of the LIF model that can be used to create application, domain, or research area specific versions of the LIF model
- A novel and simplified approach to modelling GRNs, by decomposition of the gene interaction weights matrix
- Methodology for creation of the GRN model, and translation to a mathematical proxy function
- Implementation of the NRDP model in NeuCube-Py, and made publicly available for students and researchers

4 Experimental Framework

This section introduces frameworks for creation of the GRN model, and evaluation and analysis of the biologically enhanced SNN model. These frameworks represent the holistic experimental framework.

4.1 Creation of the Gene Regulatory Network Model

This section describes the framework for creation of the GRN model, based on the methodology described in section 3.2. The goal of this framework is translation of the GRN model to a mathematical proxy function, to ease integration into the Spiking Neuron model while preserving the mean dynamics of the original GRN. This framework is shown in Fig. 10 below.

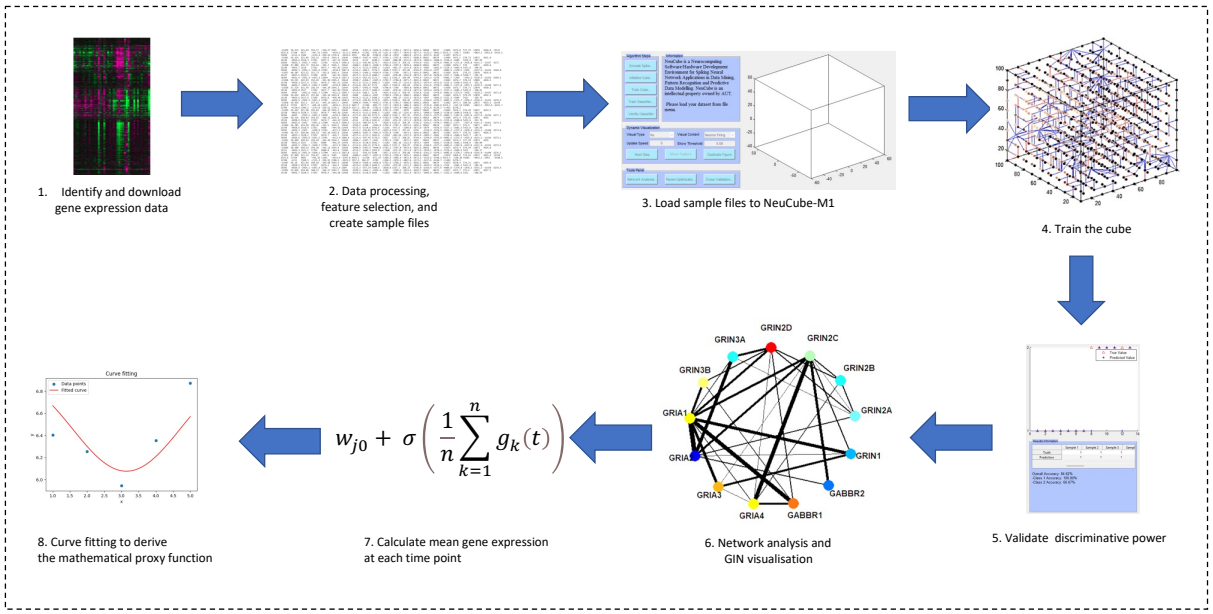


Figure 10 Framework for creation of the Gene Regulatory Network, and translation to a mathematical proxy function

Using the methodology described in section 3.2.2, an appropriate gene expression data set must first be selected. The framework is data set agnostic, however, results and generalisability of the GRN model will be highly dependent on the input data set. After feature selection has been performed, the data from the selected genes is loaded into NeuCube-M1 to perform learning, and classification. For this task, the data is converted into spike trains, and a random 10 x 10 x 10 cube is generated, trained, and classifications produced.

This process determines the robustness of both the gene expression data, and the feature selection process. The Gene Interaction Network (GIN) can also be analysed and visualised.

Next, the mean gene expression levels are calculated at each time point, and a process of curve fitting is performed using the *curve_fit* method from the SciPy (https://scipy.org) mathematics library, to translate the mean gene expression to a mathematical proxy function. The goodness of the fit can be ratified by the R^2 statistical measure. The output of this method is thus a proxy function that preserves the mean dynamics of the original GRN model.

4.1.1 Description of the Gene Expression Data for Computation of the Gene Regulatory Network Model

This data set is taken from a subset of the data associated with the study "REST and Stress Resistance in Aging and Alzheimer's Disease" (Lu et al., 2014). The data contains gene expression for postmortem neuropathologically normal brain samples from subjects ranging from 20 to 106 years of age at time of death. The subset (41 samples) is made available to download from the Gene Expression Omnibus (GEO) here: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE53890, and can be further interrogated using the excel spreadsheet provided in "Supplementary Table 1." (https://pmc.ncbi.nlm.nih.gov/articles/instance/4110979/bin/NIHMS569698-supplement-1.docx).

Filtering by "Application › microarray" (Column M) results in the 41 samples provided by the GEO. This supplementary data allows us to identify attributes such as "Age" (Column F), "Disorder" (Column D), "Sex" (Column E), etc. associated with each subject. Although the data description states that all samples are "neuropathologically normal", on interrogation it is observed that there are two subjects with a "Disorder" of dementia. These two subjects will be removed, and the remaining 39 samples which are either: "NL Brain" i.e. subjects that didn't carry a diagnosis of AD or other neurodegenerative disease, or "NCI" i.e. subjects with no cognitive impairment (no impaired domains) will be used to discover the GRN. The class for the data is Age, therefore each sample is assigned a class label of 0 or 1 i.e. Young [20-70) or Aged [70,106].

In this data set there are 54,675 total features, the previously conducted literature review determines which features to include in the set *G*, namely, those genes which are involved in Neuroreceptor dynamics (Kasabov et al., 2018; Stephenson, 2006). A summary of these thirteen genes is shown in Table 1.

Table 1 Genes included in the gene regulatory network

Neuroreceptor	Subunit composition (genes)
GABA	GABBR1, GABBR2
AMPA	GRIA1, GRIA2, GRIA3, GRIA4
NMDA	GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B

The process of reducing the data set to this group of features is relatively straight forward, and involves a transposition of the subjects from columns to rows, and an algorithm that iterates over each row (subject) to select the relevant genes. Additionally, as this data will be passed through NeuCube-M1, the data must also be transformed into the specific format required for import. Therefore, a new data frame is constructed for each subject and expression data for each gene is flattened into the data frame. This gives us 39 data frames, and as there are a maximum of 5 data points per gene, the resultant shape is a 5x13 matrix of expression values. Where there are missing or empty values, a linear interpolation process is applied to fill in a sensible default value. The Python source code used for data processing is included in Appendix 8.1

4.2 Evaluation and Analysis of the Biologically Enhanced SNN Model

This section describes the framework for evaluation and analysis of the biologically enhanced SNN model, the basis of which is a study involving Fast Periodic Visual Stimulus (FPVS), "A rapid, neural measure of implicit recognition memory using fast periodic visual stimulation" (Stothart et al., 2021). This paper has previously been studied by the author of this thesis using NeuCube-M1 with the STDP unsupervised learning rule. The study proposes a unique approach to early detection of Alzheimer's disease (AD) where participants engage in a FPVS task that includes frequency tagging of standard and oddball stimuli within a classic oddball paradigm. Normal images are presented at a fast rate, typically around 6 Hz, with oddball images embedded in the train of standard images at fixed intervals, resulting in a slower equivalent presentation rate for oddball images, typically around 1Hz. Data capture takes place using a 64-channel HydroCel geodesic sensor net at 1000Hz (mapping included in Appendix 8.5), which is further down-sampled to 256Hz. The two electrooculogram electrodes (62 and 63) are excluded, and reference Cz is included to give a total of 63 EEG channels (features) in the data. Each participants data is captured for 173 seconds. Utilising a rolling average

(DataFrame.rolling(<window>).mean() where <window> length is 32), the data is further down-sampled to produce 1,386 samples per patient. In total there are 83,160 samples. The 60 participants are split into three groups: (1) young controls, (2) elderly controls, and (3) AD patients. The 7 step framework is shown in Fig. 11.

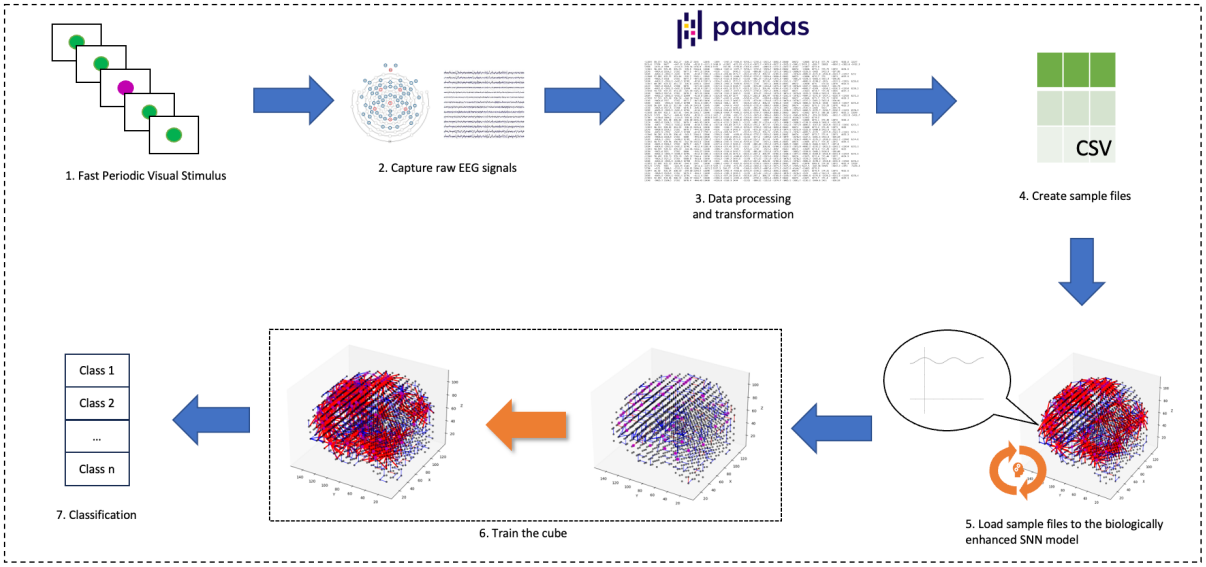


Figure 11 Framework for biologically enhanced SNN model experiments

All experiments are conducted in NeuCube-Py using the novel implementation discussed in Chapter 3. Raw EEG data from the FPVS study is processed to create comma separated variable (CSV) samples files, which are loaded into the biologically enhanced SNN model. Utilising a custom EEG electrode mapping to match the 64-channel HydroCel layout, and the standard Talairach coordinates to determine the X, Y, Z position of each neuron in 3-Dimensional space. There are three experiments which will be conducted using this framework, the only difference between experiments comes at step 5, as described below.

4.2.1 Classification Accuracy with GRN and Stock NRDP

The GRN is implemented as described in section 3.2.4, and NRDP as described in 3.3.1. Stock NRDP refers to the fact that no hyper-parameter tuning is performed, i.e. the values for neuroreceptor gaining rates, max/min values, etc. will be left as defaults. The results of this experiment will help to answer research question 1.

4.2.2 Classification Accuracy with no GRN, Stock NRDP vs Biological NRDP

The computational model of NRDP described in 3.3.1 allows the values of the genetic parameters to be altered in order to fine-tune the underlying algorithm. Using gene expression

data to calculate the gaining rates yields a biological NRDP model, which will help to answer research questions 2 and 3.

4.2.3 Classification Accuracy with a Patient Derived GRN and NRDP

Determining which set of genes produces the best results in terms of classification accuracy can help to answer research question 4. In this case we will use genes from patients rather than controls to construct the GRN.

4.2.4 Experimental workflow and performance measurement

Each experiment uses a test/train split with 70% of the data used for training and 30% for testing. The test-train split is always performed using subject-based holdout, meaning that samples from a single subject cannot simultaneously appear in the training set and testing set to prevent data leakage. A workflow diagram is shown in Fig. 12.

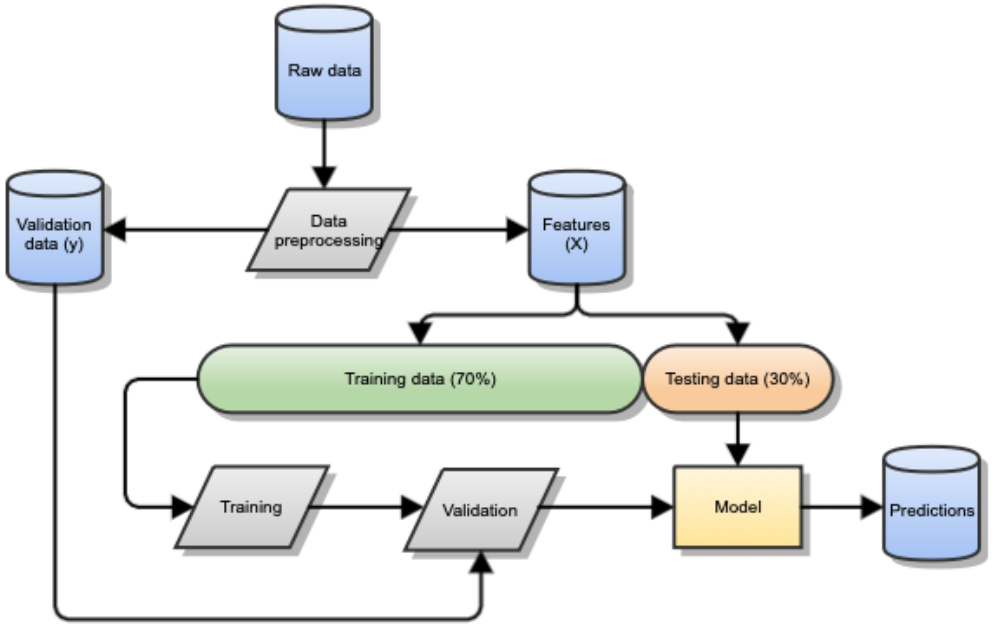


Figure 12 Experiment workflow for data processing, training, validation/evaluation, and classification of data from the FPVS study, for the biologically enhanced SNN model

Performance between the various iterations will be measured using the following metrics:

- Accuracy – a measure of the proportion of correct predictions made by the model out of all the predictions made
- Specificity – a measure of how well the model avoids making false positive predictions

- Sensitivity (Recall) – a measure of how well the model makes positive predictions while avoiding false negative predictions

Classification accuracy is typically used as a measure of how well a model performs, particularly when using a balanced data set. Specificity and Sensitivity (Recall) are important metrics to include in a diagnostic context, as false positives and false negatives should be minimised as much as possible. These performance metrics are defined by the following equations:

$$Accuracy = \frac{TP + TN}{(TP + TN + FP + FN)} \tag{26}$$

$$Specificity = \frac{TN}{(TN + FP)} \tag{27}$$

$$Sensitivity = \frac{TP}{(TP + FN)} \tag{28}$$

Where, TP = True Positive, TN = True Negative, FP = False Positive, and FN = False Negatives

4.3 Contributions

- Defined experimental framework for creation of the GRN model
- Identification of a data set of posthumous brain samples that can be used to create the Gene Regulatory Network (GRN) model
- Defined experimental framework for validation of the biologically enhanced SNN model using NeuCube-Py

5 Results and Discussion

In this chapter the research questions 1, 2, 3, and 4 will be addressed in sections 5.1, 5.2, 5.3, and 5.4 respectively, and experimental results performed on the dataset described in Section 4.1.1 reported, while also laying the foundation for further discussion. In addition, to further evaluate the proposed methods, extended testing of the experimental framework against a secondary dataset is included in Appendix 8.6.

5.1 Increasing the Biological Plausibility of the SNN Model with Genetic Information and NRDP

The integration of genetic information holds significant promise in enhancing the biological plausibility of SNN models, allowing the model to dynamically adjust synaptic connections, mimicking the adaptability and learning capabilities of the biological brain. This approach not only improves the interpretative capabilities of SNNs but also allows for a more nuanced understanding of input processing. The methodology discussed in Chapter 3, demonstrates how genetic information can be incorporated in to SNN models, thereby increasing their biological plausibility and facilitating more accurate simulations of neural processes.

Utilising the experimental framework and data set described in section 4.1.1, the SNNc is initialised and trained for classification of the gene expression data into two classes. After running the classification task, the class (label) of the data was able to be discriminated with a very high level of overall accuracy (84.62%). A breakdown is shown in Table 2 below. This result validates the feature selection process, and provides us with a viable data set for computation of the GRN.

Table 2 Classification results using NeuCube-M1

Class	Accuracy
0 (Young)	100%
1 (Aged)	66.67%

Fig. 13 shows the Gene Interaction Network (GIN) discovered by running network analysis on the trained SNNc, following techniques established by Capecci et al. (Capecci et al., 2020). The genes included are those listed in Table 1, and defined in set G .

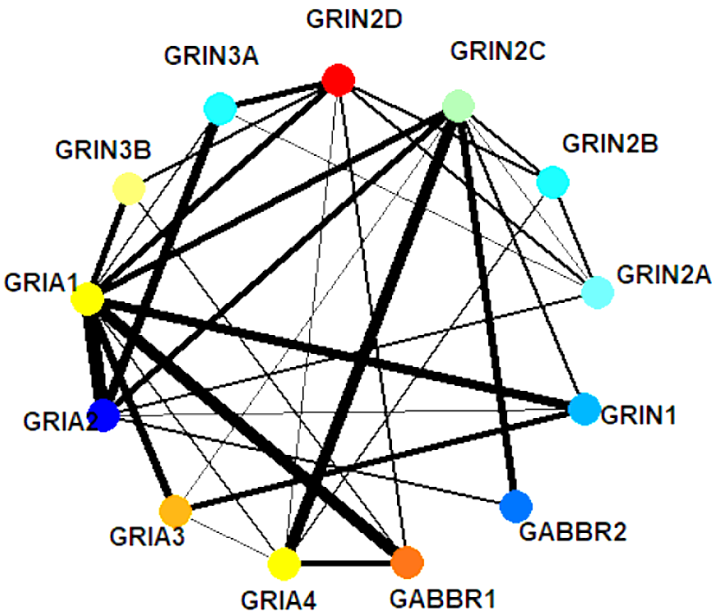


Figure 13 Gene Integration Network (GIN) for the selected genes

Strong interactions between genes GRIN1 and GRIA1 are observed, and between genes GRIA1 and GABBR1. This result is in-line with our understanding of the biological functioning of neuroreceptors, demonstrating the correlation and dependency ("cross-talk") between the inhibitory receptors (GABA) and glutamate receptors (AMPA and NMDA).

Let G = {GABBR1,GABBR2,GRIA1,GRIA2,GRIA3,GRIA4,GRIN1,GRIN2A,GRIN2B,

GRIN2C,GRIN2D,GRIN3A, GRIN3B}.

G can now be analysed in terms of the simplified GRN model introduced in Equation 12. Computing the mean expression level at time t for all genes in G and plotting this result against the expression level for all genes in G at time t, yields the graph in Fig. 14 below.

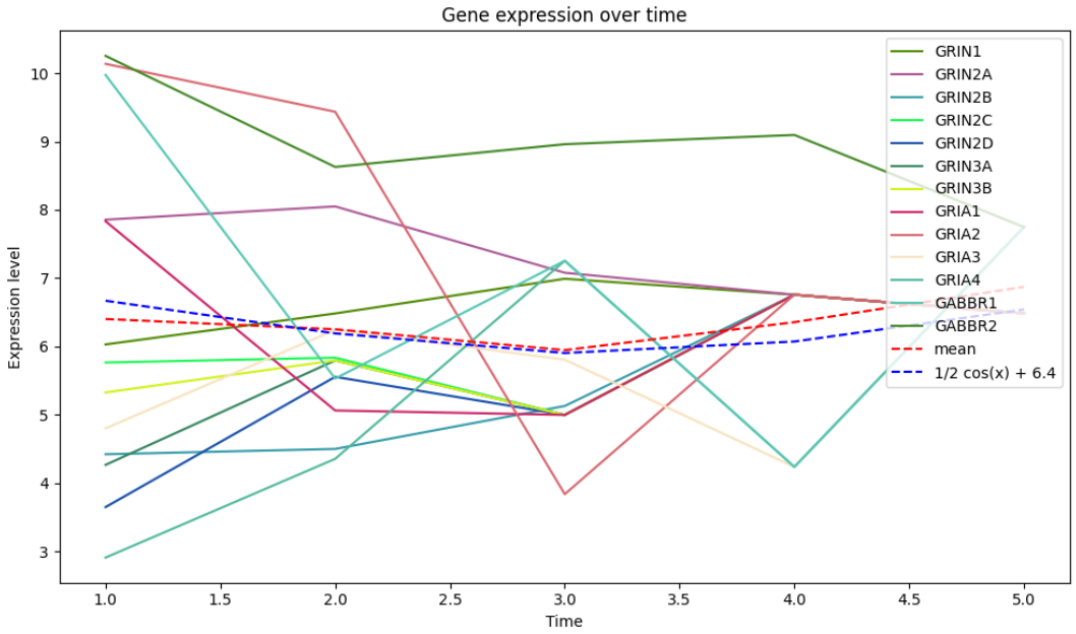


Figure 14 Expression level over time for genes in G

After curve fitting, the mathematical proxy function is estimated to be:

$$f(x) = \frac{1}{2}\cos(x) + 6.4 \tag{29}$$

for the range [1, 5]. Where the constant 6.4 is the mean gene expression level at time 1. Calculation of the R^2 statistical measure yields 0.57, meaning that the proxy function accounts for 57% of the variance of the dependent variable. Therefore, this research postulates that the dynamics of the GRN derived from *G* are captured by Equation 29. This requires extrapolation of the continuation of the function's shape beyond the range [1, 5]. There is however precedence for this in nature. The rhythmic patterns exhibited by cosine waves are mirrored in the cyclic nature of circadian rhythms, which govern the timing of various physiological and behavioural processes in organisms. The circadian clock orchestrates the cyclical release of hormones, body temperature variations, and sleep-wake cycles with remarkable precision. Moreover, gene expression follows similar rhythmic patterns, regulating the production of proteins and enzymes crucial for cellular functions.

This biological cadence extends its influence to learning and memory processes, where coordinated gene expression plays a vital role in synaptic plasticity, neuronal connectivity, and the formation of long-term memories. Highlighting the intrinsic regulatory mechanisms that underlie key biological phenomena, and shaping our understanding of time-dependent processes in living organisms (Youri et al., 2021).

Following the approach detailed earlier in Chapter 3 i.e. CNGM, the dynamics of the GRN model can be integrated as a 5th dimension of the Spiking Neural Network (SNN) model i.e. each spiking neuron encapsulates the dynamics of the GRN model. Therefore, combining Equations 9 and 29, results in a simplified application specific LIF model:

$$u(t)_a = \int_0^{\infty} (u_r - \theta) \cdot e^{-\frac{s}{\tau_m}} \cdot S(t-s)ds + \int_0^{\infty} \frac{1}{2C} \cdot e^{-\frac{s}{\tau_m}} \cdot \cos(s) + 6.4 \cdot I(t-s)ds \qquad (30)$$

This model extends the notion in "Time-Space, Neural Networks and Brain-Inspired Artificial Intelligence" (Kasabov, Springer, 2019), that gene expression can be used to affect the spiking activity of neurons by dynamically adjusting τ_m (the membrane time constant), realising the biologically enhanced SNN model discussed in Chapter 3, and creating new pathways for knowledge discovery.

As the time complexity of a trigonometric function is constant i.e. $\mathcal{O}(1)$, no computational overhead in terms of the standard LIF mode is added. Therefore, this model is still applicable for low-performant or low-power environments (e.g. embedded environments, edge computing, etc.) where there is a need for classification and analysis of temporal data, such as Spatio-temporal Brain Data (STBD).

Fig. 15 shows connectivity in the SNNc based on the results of running the experiments detailed in section 4.2.1. These results are shown in Table 3. Fig. 15 (a) shows the SNNc after initialisation, and before any training has occurred. Fig. 15 (b) shows connectivity in the SNNc using the baseline STDP unsupervised learning rule. And, Fig. 15 (c) shows connectivity based on the stock NRDP unsupervised learning rule (i.e. no hyper-parameter tuning). Thus far, the experiments have been conducted using the base implementation of the LIF model in NeuCube-Py.

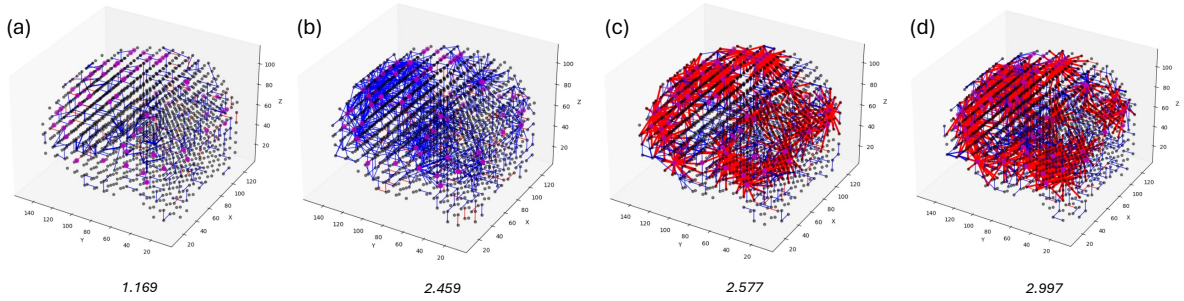


Figure 15 Visualisations of connectivity in the SNN cube (SNNc), before and after training. Blue and red lines represent excitatory and inhibitory connections respectively. Weighted average of the connection weights is shown under each cube. .

After enabling the GRN model, Fig. 15 (d) is produced. The most striking feature is the apparent boost of both excitatory and inhibitory connections in the hippocampal region (middle

centre). The hippocampus is a key structure nestled deep within the brain's temporal lobe, playing a pivotal role in memory formation and spatial navigation. The hippocampus is integral to the formation, consolidation, and retrieval of memories across various domains, including episodic memory, and semantic memory.

Table 3 Model performance metrics - baseline STDP vs stock NRDP vs stock NRDP with GRN

Unsupervised learning rule	GRN model enabled?	Accuracy	Specificity	Sensitivity
STDP (baseline)	N	70.2%	71.5%	61.1%
NRDP (stock)	N	71.9%	79.8%	60.0%
NRDP (stock)	Y	82.5%	88.6%	75.9%

An increase of 14.7% in classification accuracy over the stock NRDP with GRN model enabled is observed. The model with GRN model enabled demonstrates superior Sensitivity (also called Recall or True Positive rate) over the other two models. Sensitivity quantifies the model's ability to capture positive instances out of all actual positive instances. It is an essential metric for evaluating the performance of a model, particularly in scenarios where correctly identifying positive instances is crucial, such as medical diagnoses or anomaly detection. High sensitivity indicates that the model has a low rate of missing positive instances. Additionally, there is an demonstrable increase in the weighted average connection weight after each experiment, which quantifies the visual results shown in Fig. 15. Experimental results are captured in the table above, the accompanying confusion matrices are available in Appendix 8.2. Calculations of R^2 for curve fitting, and weighted average of the connection weights are available in Appendix 8.3 and 8.4.

A viable approach for integrating genetic information into SNN models has been demonstrated, and in the process, realised the biologically enhanced SNN model introduced in Chapter 3. Incorporating genetic information into SNN models allows for the creation of more computationally realistic representations of the brain, mirroring the complex interplay between genes and neural function observed in biological systems. Genetic information can influence parameters such as membrane time constants, synaptic strengths, and neural plasticity mechanisms, thereby shaping the behaviour and dynamics of the SNN. Through this approach, SNN models can better capture the diversity and variability observed in biological neural networks, leading to improved accuracy in modelling brain functions and behaviours, and taking important steps towards biological plausibility.

5.2 Increasing SNN Model Performance with NRDP

Classification accuracy provides a quantitative measure of how well a model performs at categorising or classifying data points into predefined categories or classes. It serves as a benchmark for assessing the effectiveness of a classification model in making correct predictions. In many real-world applications, such as medical diagnosis, fraud detection, and sentiment analysis, the accuracy of classification models directly impacts decision-making processes. High accuracy ensures that decisions based on model predictions are reliable, minimising the risk of errors and their associated consequences.

Neuroreceptor-Dependent Plasticity (NRDP) allows the connectivity of synapses in the brain to strengthen or weaken based on the activation of specific neuroreceptors, i.e. GABA, AMPA, NMDA. This enables the SNN model to adapt its synaptic weights to better represent patterns in the input data. NRDP allows the SNN model to dynamically reconfigure its connectivity, enabling the network to optimise its processing strategy, thus leading to improved classification performance.

NRDP mechanisms contribute to memory formation by promoting the retention of relevant information in the network. This can prevent forgetting of previously learned patterns and improve the generalisation ability of the SNN model, leading to higher accuracy on unseen data samples. NRDP can also modulate synaptic efficacy based on the relevance, or saliency of input stimuli. By prioritising important features or patterns in the data, the SNN model can enhance its ability to discriminate between different classes, thus boosting classification accuracy.

In our computational model of NRDP, the values of the genetic parameters (gaining rates, max/min levels, GABA rate, etc.) can be altered in order to fine-tune the underlying algorithm. The stock NRDP unsupervised learning rule provides a modest bump in performance over the baseline STDP. However, this approach can be taken one step further, by using the "REST and Stress Resistance in Aging and Alzheimer's Disease" (Lu et al., 2014) data to calculate the gaining rates, values of 0.45 and 0.07, representing a 16.7% and 36.4% drop in the AMPAR and NMDAR gaining rates (from the stock NRDP model) respectively are discovered. These values are based on the average gain (increase) in the GRIA1 and GRIN1 gene expression over the time period i.e. they are biologically adjacent values.

In order to control variability in the experiment the GRN model was disabled, and re-ran the experiments with the two different instances of the NRDP unsupervised learning rule. The workflow for this experiment is the same as per Fig. 12 above. A moderate bump in model

performance over the stock NRDP model is observed. Table 4 below shows the results obtained. Confusion matrices are available in Appendix 8.2

Table 4 Model performance metrics – stock NRDP vs biological NRDP

Unsupervised learning rule	GRN model enabled?	Accuracy	Specificity	Sensitivity
NRDP (stock)	N	71.9%	79.8%	60.0%
NRDP (biological)	N	75.4%	85.2%	56.7%

The biological NRDP displays improved Specificity over the stock NRDP, meaning it is better at identifying true negatives (negative samples). A true negative occurs when the model accurately predicts the absence of a condition or event when it is truly absent in reality. Fig. 16 (b) shows an increase of inhibitory connections in the frontal lobe. Inhibitory connections can help the network suppress activity associated with negative instances that might otherwise lead to false positive predictions. By effectively filtering out irrelevant information and reducing false alarms, the SNN may achieve better discrimination between positive and negative instances, resulting in improved prediction of true negatives.

In summary, NRDP learning rules better capture the dynamics of synaptic plasticity, incorporating contextual information, optimising feature representations, and increasing robustness to noise and variability in the input data. The process of hyper-parameter tuning (fine-tuning) allows us to conform the algorithm to the desired application, domain, or research area (e.g. early detection of Alzheimer's disease), producing a more performant, biologically plausible SNN model, and leading to more favourable knowledge discovery.

5.3 Increasing SNN Model Interpretability with NRDP

The ability to understand and explain the reasoning behind decisions is crucial for building trust and confidence. Interpretability enables users to grasp the factors influencing outcomes, identify potential biases or errors, and ensure that decisions align with ethical and legal standards. By making SNN models more transparent and understandable, interpretability enhances their usability, reliability, and impact in various applications.

Interpretability is of critical importance, for example, in the area of therapeutic drug research. Understanding how drugs affect Neuroreceptor-Dependent Plasticity (NRDP) provides insights into their mechanisms of action. Neuroreceptors play a pivotal role in mediating the effects of neurotransmitters, and alterations in their activity can lead to changes in synaptic strength and

connectivity, which are fundamental to learning, memory, and various brain functions. For example, serotonin reuptake inhibitors (SSRIs) are a class of drugs commonly used to treat depression and anxiety disorders by blocking the reuptake of serotonin, thereby increasing its concentration in the synaptic cleft. Understanding how SSRIs affect NRDP, particularly serotonin receptors such as 5-HT1A and 5-HT2A, can illuminate the precise mechanisms underlying their therapeutic effects. SSRIs may enhance synaptic plasticity by modulating serotonin receptor expression or function, leading to long-term changes in neuronal connectivity that alleviate depressive symptoms.

This interpretability also aids in predicting drug efficacy and potential side effects. Drugs targeting specific neuroreceptors may produce varying effects depending on their impact on synaptic plasticity. For instance, drugs that enhance plasticity at certain receptors may be more effective in treating conditions like depression or cognitive deficits, while those that disrupt plasticity may lead to unwanted side effects or limited therapeutic benefits. Again taking the example of SSRIs, drugs that selectively target certain serotonin receptors may exhibit differential efficacy or side effect profiles compared to broad-spectrum SSRIs. By understanding how serotonin reuptake influences NRDP, researchers can better predict individual responses to SSRIs and identify patients who are more likely to benefit from specific treatments while minimising adverse effects.

Furthermore, interpretability of NRDP contributes to the development of personalised medicine approaches. Individual differences in neuroreceptor expression and plasticity mechanisms can influence how individuals respond to pharmacological interventions. In the context of serotonin reuptake, NRDP can contribute to the development of personalised medicine approaches for depression and anxiety disorders. Individual differences in serotonin receptor expression, neurotransmitter levels, and plasticity mechanisms can impact treatment responses to SSRIs. By characterising these differences and correlating them with clinical outcomes, clinicians can tailor SSRI therapies to match the unique neurobiological profiles of patients.

As traversed in section 5.2, the values of the genetic parameters in our NRDP model can be adjusted. Fig. 16 shows visualisations of SNNc based on the experimental results from section 5.2 (stock NRDP vs biological NRDP). And, while not related to the area of therapeutic drug research, gives a flavour for the increased interpretability that NRDP offers.

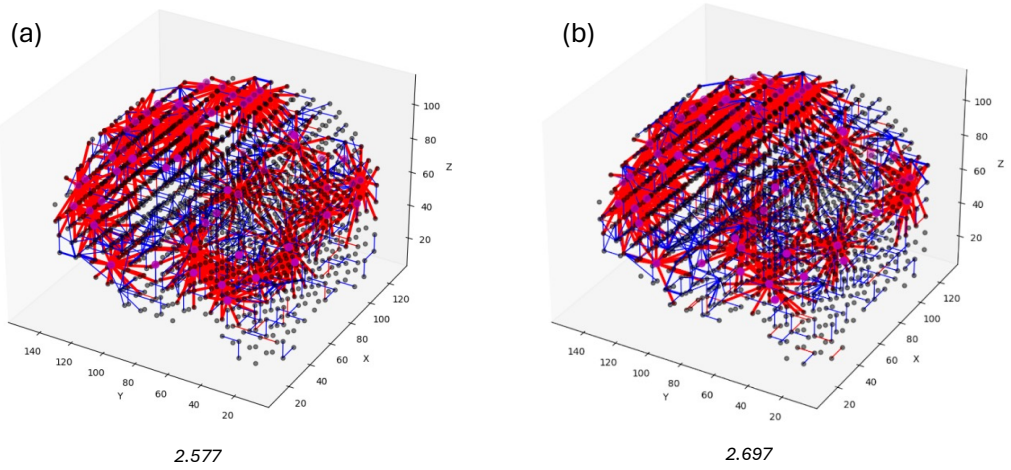


Figure 16 Visualisations of connectivity in the SNNc. (a) after training using the stock NRDP unsupervised learning rule, and (b) after training using the biological NRDP unsupervised learning rule. Blue and red lines represent excitatory and inhibitory connections respectively. Weighted average of the connection weights is shown under each cube.

Fig. 16 (b) shows a marked increase in inhibitory connections in the frontal lobe (top left), an area of the brain related to concentration, planning, and problem solving. There is also an increase in the weighted average connection weight between experiments, which quantifies the visual results shown in Fig. 16. While these results are not related to any specific drug research, this is the type of insight that could assist researchers in establishing safety, efficacy, and leading to personalised therapeutic approaches for patients. Calculations of the weighted average of the connection weights are available in Appendix 8.4.

To summarise, Neuroreceptor-Dependent Plasticity (NRDP) increases the interpretative capabilities of SNNs by enabling dynamic synaptic connection adjustments in response to changing input contexts. The SNN can learn and form associations that are context-dependent, leading to nuanced interpretations that improve overall interpretability. As the network learns features through synaptic plasticity, it naturally organises information hierarchically, facilitating a deeper understanding of input processing at different levels of abstraction. NRDP also aids in memory formation and contextual recall, allowing the network to utilise past experiences to inform current interpretations, thus making its decisions more explainable.

5.4 Improving Classification Accuracy via Gene Selection

In order to answer the final research question, the original question will be manipulated slightly, and instead of asking *which* gene(s), this research asks *whose* gene(s). Firstly, what is meant by *whose* gene(s) needs to be discussed. This is essentially the same question as before,

however, “which gene(s)” is defined to be a specific set of genes (e.g. G above), rather than different combinations of genes. In this context “which genes”, really means: Is gene expression data from patients or controls used to create the GRN?

With this new context a new question can be asked: *“For an application, domain, or research area, will G from patients or controls, produce the best result with respect to classification accuracy?”*. And, does it even make sense to use samples from patients to construct a GRN model?

The answer is, maybe surprisingly, Yes. In fact it is crucial for understanding the molecular mechanisms underlying disease and personalised medicine. By analysing gene expression patterns, transcription factor activities, and regulatory interactions in patient samples, researchers can identify key genes and pathways dysregulated in diseases such as cancer, neurodegenerative disorders, and autoimmune diseases. These networks provide insights into the underlying biological processes driving disease progression, heterogeneity, and treatment response, guiding the development of targeted therapies and precision medicine approaches.

Comparing GRNs across patient cohorts with different clinical outcomes or treatment responses can help identify biomarkers for disease prognosis, patient stratification, and therapeutic response prediction. Additionally, constructing GRNs from patient data may enable the discovery of novel drug targets, biomarkers, and therapeutic interventions, accelerating the development of innovative treatments and improving patient outcomes.

Following the methodology described in Chapter 3 Section 3.2, the GRN is modelled as the mean gene expression for all genes g in the set G. Using only the patient samples from the REST data set i.e. the samples that are classified as dementia, the mean can be computed, and curve fitting preformed. The mean gene expression level is estimated to be proxied by a “flat-rise” sawtooth function, that is, a sawtooth wave that is flat for a certain duration and then rises linearly. The flat-rise sawtooth is defined by the following equation:

$$f(x) = \begin{cases} 0 & for\ 0 \le x < a \\ \dfrac{A}{b}(x-a) & for\ a \le x < a+b \end{cases} \tag{31}$$

Where A is the amplitude of the sawtooth wave, a is the duration of the flat portion, and b is the duration of the rising slope. R^2 is computed to be 0.87. Again, the continuation of the function’s shape must be extrapolated beyond the period [1,5], however justification for this has been previously provided. The result of implementing Equation 31 in NeuCube-Py, is a “patient

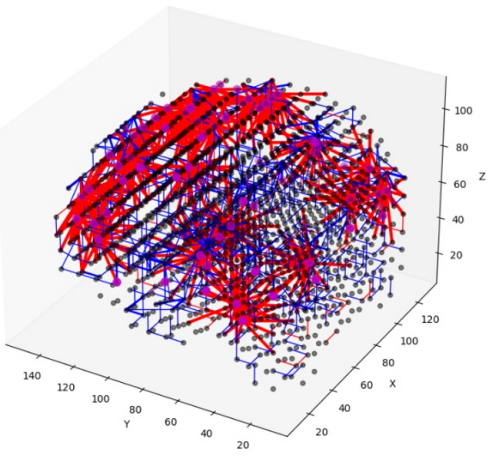
GRN" model, i.e. a GRN constructed from patient samples. The experiment detailed in Chapter 4 is re-run using this patient GRN. The confusion matrix for the experiment is available in Appendix 8.2. A summary of the experimental results is shown in table 5:

Table 5 Model performance metrics - stock NRDP vs stock NRDP with patient GRN

Unsupervised learning rule	GRN model enabled?	Accuracy	Specificity	Sensitivity
NRDP (stock)	N	82.5%	88.6%	75.9%
NRDP (stock)	Y	47.4%	100%	0.0%

There are some interesting characteristics of this patient GRN model to discuss. Firstly it has poor Accuracy, less than 50%, but perfect Specificity. This is due to the fact that the model, while making no false positive predictions, is also unable to make any true positive predictions, which means it has identified 100% of all negative cases. The Accuracy metric improves somewhat to 61% when the controls are removed, but still lags well behind the other GRN model. As mentioned, the model is able to identify all negative cases for each class (label) in the data set, however, proportionately it makes a higher number of false predictions (~10% more false negatives than true negatives). Unfortunately the model would not be applicable for this particular application (i.e. detection of Alzheimer's disease) as it will likely miss most, if not all true positives.

Fig. 17 shows connectivity in the SNNc after training with the patient GRN model and stock NRDP unsupervised learning rule. There is a distinct lack of strong excitatory and inhibitory connections in the occipital lobe (middle right). The occipital lobe is responsible for processing visual information, including object recognition, depth perception, and also plays a part in memory retrieval. This result is quantified via calculation of the weighted average of the connection which reveals the lowest score of all experiments conducted where the SNNc has been trained using a GRN, learning rule, or combination of both. It is likely that this lack of connectivity is having a detrimental effect on the performance of the model. Calculations of R^2 for curve fitting, and weighted average of the connection weights are available in Appendix 8.3 and 8.4.



2.313

Figure 17 Visualisation of connectivity in the SNN cube (SNNc) after training with the patient GRN and stock NRDP unsupervised learning rule. Blue and red lines represent excitatory and inhibitory connections respectively. Weighted average of the connection weights is shown under the cube.

In summary, an approach to modelling GRNs using gene expression data from patients has been demonstrated. The results of the experiment help us to answer the research question, demonstrating that gene expression from controls produces better results with respect to classification accuracy. Consequently, this model while not suitable to the application of disease detection, could be well suited to other use-cases such as spam filtering, fraud detection, and quality control where false positives could be costly.

5.5 Limitations

The integration of genetic information into the SNN model involves modelling the intricate Gene Regulatory Network (GRN) dynamics. However, due to the complexity of these genetic interactions, the GRN model has been simplified, potentially leading to some abstraction of the biological processes involved. Although the model used preserves the mean dynamics of the GRN, the impact of such simplifications on the accuracy and fidelity of the models should be considered.

This research was primarily focused on investigating the impact of integrating genetic information and NRDP into SNN models. While efforts have been made to validate the findings using appropriate datasets, benchmarks, and baselines, it is essential to acknowledge the limitations of generalising these results to all scenarios and datasets. The effectiveness of the proposed biologically enhanced SNN model may vary depending on the specific context and dataset characteristics.

5.6 Contributions

- Creation of a Gene Regulatory Network (GRN) from posthumous brain samples and integration into the Spiking Neuron model
- Demonstrated a viable approach for the simultaneous integration of genetic information and NRDP mechanics into SNN models
- Novel approach to NRDP model hyper-parameter tuning using biological (real) values from gene expression data
- Demonstrated biological NRDP model has superior Specificity as opposed to the un-tuned NRDP model
- Demonstrated an application of improved NRDP model interpretability in the field of therapeutic drug research
- Demonstrated an approach to creating SNN models that could be well suited to use-cases such as spam filtering and fraud detection, where it is most important not to make any false positive predictions

6 Conclusion and Future Direction

“My dull brain was wrought with things forgotten. Kind gentlemen, your pains are registered where every day I turn the leaf to read them”, proclaims the eponymous character in Shakespeare’s Macbeth (Shakespeare, Macbeth, Act 1, Scene 3, 1603-1607). This metaphor for the brain, where memories are stored and recalled like reading the pages of a book, neatly captures the essence of synaptic plasticity.

Indeed, the human brain is a remarkable organ, standing as an awe-inspiring testament to the complexity and ingenuity of nature. With its billions of neurons and trillions of synapses forming an intricate network, the brain exhibits remarkable adaptability, continuously reshaping its connections in response to experiences, learning, and environmental demands. Beyond its role in regulating basic bodily functions, the brain gives rise to consciousness, thought, emotion, and creativity—attributes that define human existence. Its capacity for resilience, and self-repair is astounding, allowing individuals to recover from injury, learn new skills, and forge connections that shape their identities and shape the world around them. The brain's complexities remain a frontier of exploration, captivating scientists, philosophers, and artists alike, as they seek to unravel its mysteries and unlock the secrets of the human mind.

It is hoped that the work presented in this thesis will lead to further research in the area of biologically plausible Artificial Neural Networks (ANN), particularly in the area of lifelong learning. Lifelong learning is of paramount importance in ANNs as it mirrors the dynamic nature of learning and adaptation observed in biological brains. Unlike traditional machine learning models that are typically trained on static datasets and lack the ability to continuously acquire and integrate new knowledge, lifelong learning in ANNs enables systems to incrementally learn from new experiences and adapt over time. This capability is crucial for handling evolving environments, changing tasks, and novel scenarios encountered in real-world applications. Lifelong learning empowers ANNs to continually refine their representations, update their internal models, and improve their performance, leading to enhanced flexibility, robustness, and scalability. Lifelong learning enables ANNs to autonomously acquire expertise in specialised domains, adapt to individual user preferences, and personalise interactions in various applications such as recommendation systems, autonomous vehicles, and healthcare diagnostics. By embracing lifelong learning principles, ANNs can emulate the lifelong learning process observed in humans and animals, thereby advancing the field of artificial intelligence towards more adaptive, intelligent, and autonomous systems.

Of the research gaps identified in this thesis, clinical validation, and bias mitigation are of the utmost importance. Clinical validation is essential for establishing the clinical utility, safety, and real-world effectiveness of SNN models. It ensures that models meet the needs of clinicians and patients, adhere to ethical and regulatory standards, and contribute to evidence-based clinical practice and decision-making. Clinically validating SNN models involves a systematic process of evaluation to assess performance, reliability, and generalisability in real-world healthcare settings. This process begins with defining the clinical problem and gathering high-quality data representative of the target population. Designing a clinical validation study involves ethical considerations and adherence to regulatory requirements. Deployment of the model into clinical workflows allows for assessment of usability and integration. Validation and performance assessment are conducted through independent datasets or prospective validation studies in clinical practice, with results documented and communicated comprehensively. Continuous monitoring and refinement of the model ensure ongoing clinical relevance and effectiveness. Through these steps, researchers and clinicians can systematically validate SNN models to ensure their reliability, accuracy, and suitability for real-world clinical applications.

It is also crucial to include a diverse range of ethnicities to ensure the validity, reliability, and applicability of research findings across populations. Human brains exhibit variability in structure, function, and connectivity influenced by genetic, environmental, and sociocultural factors. By incorporating participants from different ethnic backgrounds, researchers can capture this diversity and uncover how various factors shape brain development, cognition, and behaviour. Such inclusion facilitates the identification of both commonalities and differences in brain structure and function across diverse populations, leading to a more nuanced understanding of neural mechanisms and their implications for health and disease. Utilising a diverse sample helps mitigate the risk of bias and ensures that research findings are not skewed towards any particular group, thus enhancing the generalisability of results and promoting equitable healthcare practices.

There is scope for further testing with the computational models presented in this thesis, on different sets of genes (Research Question 4 in particular), with different spiking neuron models, or a combination of both. For example, the Izhikevich spiking neuron model could be used. Izhikevich model (IM) provides a computationally efficient, biologically realistic, and versatile framework for studying spiking neuron dynamics and neural network behaviour, formulated by combining the biological plausibility of Hodgkin-Huxley model (HHM) and computational

efficiency of Leaky Integrate-and-Fire (LIF). IM could be integrated into NeuCube-Py and benchmarked against the application specific LIF model presented in this thesis.

Another interesting approach to Research Question 3, might be to explore if the programming language that implements the Spiking Neural Network model can enhance (or conversely detract from) the interpretability of the model? Far from going down the rabbit hole of programming language parochialism and tribalism, it may make sense to assess the strengths and/or weaknesses of different programming languages in the context of SNN model development. For example Julia provides a syntax that is designed for mathematical computation, allowing developers to express the underlying mathematical objects more directly and transparently. Of course, any decisions must be weighed against steepness of the learning curve, ease/cost of implementation, availability of resource, and ongoing maintenance.

In conclusion, this thesis has presented several novel contributions to the field of computational modelling, leading to a biologically enhanced Spiking Neural Network (SNN) model. Firstly, an implementation for SNN models that simultaneously integrates genetic information and Neuroreceptor-Dependent Plasticity (NRDP) mechanisms. Secondly, a simplified approach to modelling Gene Regulatory Networks (GRNs) by decomposing the gene interaction weights matrix. By integrating both into the SNN model, this research has demonstrated the potential for improved biological relevance in Artificial Neural Networks.

Additionally, the NRDP model was implemented in NeuCube-Py, making it readily available for students and researchers. These contributions collectively represent a significant step forward in the development of more biologically plausible and interpretable SNN models, with potential applications ranging from therapeutic drug research to spam filtering and fraud detection.

Utilising real biological values from gene expression data for hyper-parameter tuning, this research has demonstrated the superiority of a biological NRDP model in terms of Specificity. Moreover, the improved interpretability of the NRDP model has been showcased through its hypothetical application in therapeutic drug research.

In totality, these results underscore the potential of genetically informed SNNs to more accurately reflect biological processes, thereby advancing the field of biologically inspired computing, and taking important steps towards biologically plausible Artificial Neural Networks.

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8 Appendix

8.1 Python Source Code

All source code for the experiments is available in the following GitHub repositories: Authors fork of NeuCube-Py: https://github.com/andrewglind/NeuCube-Py , main NeuCube-Py project: https://github.com/KEDRI-AUT/NeuCube-Py, data processing and preparation for GRN model: https://github.com/andrewglind/COMP989. The fork of NeuCube-Py is a public repo, COMP989 is a private repo, please request access if required for marking purposes.

8.2 Confusion Matrices for Experiments

The following confusion matrices come from the experiments for Research Questions 1, 2, and 4. Each sub-matrix can be interpreted as:

TP	FP
FN	TN

Where TP = True positive, FP = False positive, FN = False negative, and TN = True negative

STDP (baseline)

	Class	Prediction	
Truth	1	3	4
		1	11
	2	1	3
		2	13
	3	3	6
		1	9

NRDP (stock)

	Class	Prediction	
Truth	1	4	4
		1	10
	2	1	3
		1	14
	3	6	1
		6	6

NRDP (stock) with GRN

	Class	Prediction	
Truth	1	4	4
		0	11
	2	3	1
		3	12
	3	7	0
		2	10

NRDP (biological)			
	Class	Prediction	
Truth	1	4	3
		1	11
	2	1	2
		1	15
	3	4	1
		6	8

NRDP (stock) with patient GRN			
	Class	Prediction	
Truth	1	0	0
		15	4
	2	0	0
		8	11
	3	0	0
		7	12

8.3 Calculation of R^2 for Curve Fitting

R^2 for GRN model: $1 - \frac{SST}{SSE} = 1 - \frac{0.264553}{0.608777} = 0.5654$

R^2 for patient GRN model: $1 - \frac{SST}{SSE} = 1 - \frac{0.07112}{0.56072} = 0.8732$

8.4 Calculation of Weighted Average of the Connection Weights

The weighted average of the connection weights is calculated as:

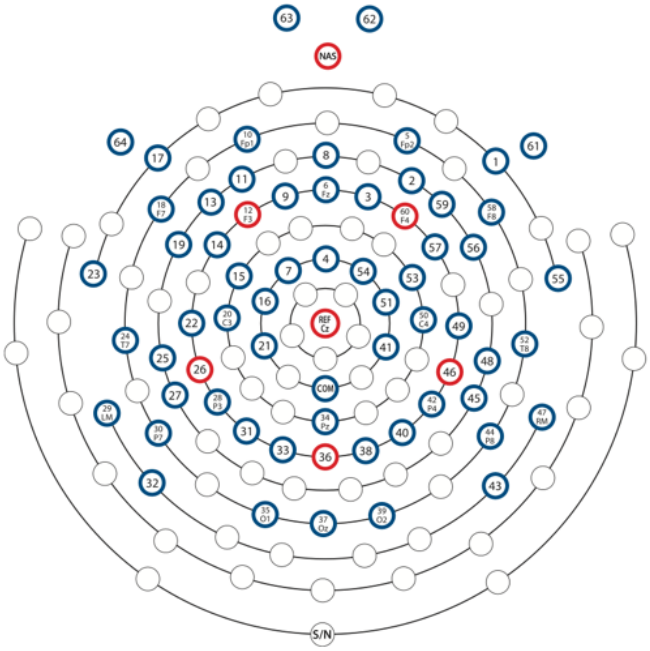
$$Weighted\ average = \frac{\sum(Line\ thickness * Count)}{\sum Count}$$

The table 8.4.1 shows the weighted average calculated for each SNN cube displayed in the Results and Discussion section:

Table 8.4.1 Calculations for the weighted average of the connection weights

	Line thickness	Count	Weighted Sum	Weighted average
No training	1	1036	1036.00	
	2	138	276.00	
	2.5	45	112.50	
	3	0	0.00	
	TOTAL	1219	1424.50	**1.168580804**
STDP	1	1027.00	1027.00	
	2	160.00	320.00	
	2.5	142.00	355.00	
	3	2895.00	8685.00	
	TOTAL	4224.00	10387.00	**2.459043561**
NRDP	1	991.00	991.00	
	2	158.00	316.00	
	2.5	205.00	512.50	
	3	3945.00	11835.00	
	TOTAL	5299.00	13654.50	**2.576806945**
GRN	1	128.00	128.00	
	2	0.00	0.00	
	2.5	0.00	0.00	
	3	101328.00	303984.00	
	TOTAL	101456.00	304112.00	**2.997476739**
Biological NRDP	1	975.00	975.00	
	2	168.00	420.00	
	2.5	260.00	780.00	
	3	5306.00	15918.00	
	TOTAL	6709.00	18093.00	**2.69682516**
Patient GRN	1	1024.00	1024.00	
	2	98.00	196.00	
	2.5	52.00	130.00	
	3	1986.00	5958.00	
	TOTAL	3160.00	7308.00	**2.312658228**

8.5 64-channel HydroCel geodesic sensor net



8.6 Wrist movement EEG experiment

This section captures the results of running the Experimental Framework against a secondary dataset related to wrist movement used in the following paper “Feasibility of NeuCube SNN architecture for detecting motor execution and motor intention for use in BCI applications” (D. Taylor et al., 2014). The data consists of three participants, and relates to performing three wrist movement tasks (real or imagined):

- Wrist flexion
- Wrist extension
- Rest (no movement)

Data is captured from an Emotiv Epoc EEG Neuroheadset at 128Hz, and each participant performs the wrist movement (real or imagined) seated in a quiet room, with their eyes closed.

The table 8.6.1 shows performance metrics from the experiments conducted against the biologically enhanced SNN model for each unsupervised learning rule on the wrist movement EEG dataset. There are uplifts demonstrated in classification accuracy, and sensitivity of approximately 10.0%, 8.8% respectively from the stock NRDP to NRDP with the GRN model enabled. In addition, an increase of 2.8% in specificity is also observed between stock NRDP and the biological NRDP. These results are in line with the Alzheimer's EEG dataset results, although the increases are not always as pronounced. In general the NRDP unsupervised learning rule, regardless of using the GRN model or biological parameters, performs better than STDP across all tasks.

Table 8.6.1 Model performance metrics – STDP vs stock NRDP vs stock NRDP with GRN vs biological NRDP

Unsupervised learning rule	GRN model enabled?	Accuracy	Specificity	Sensitivity
STDP (baseline)	N	70.4%	79.3%	55.6%
NRDP (stock)	N	74.1%	81.3%	65.8%
NRDP (stock)	Y	81.5%	85.9%	71.6%
NRDP (biological)	N	77.8%	83.6%	66.3%

The images in Fig. 8.6.1 show the connection weights between STDP (a), and NRDP with GRN (b). Weighted average of the connection weights is shown below each image.

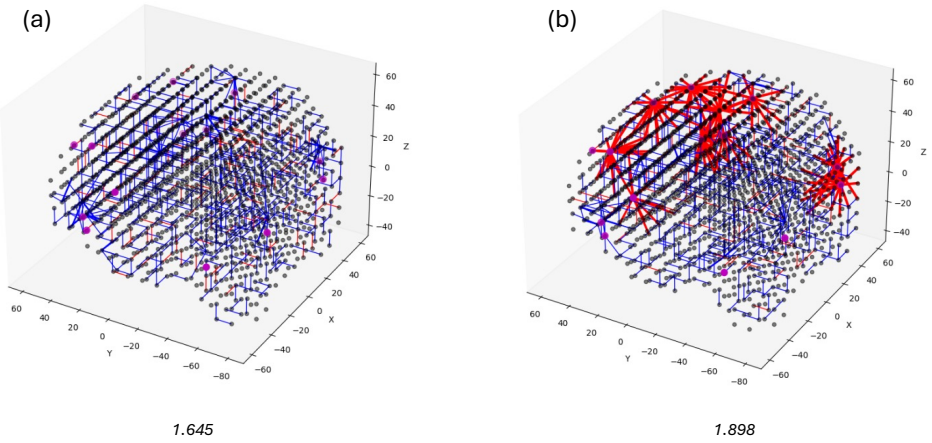


Figure 8.6.1 Visualisation of connectivity in the SNNc after training with the STDP unsupervised learning rule (a) and NRDP unsupervised learning rule with GRN (b). Blue and red lines represent excitatory and inhibitory connections respectively. Weighted average of the connection weights is shown under each cube

Confusion matrices, and calculation of the weighted average connection weights are also included below. Please refer to section 8.2 for the structure of the confusion matrices.

STDP (baseline)

	Class	Prediction	
Truth	1	2	4
		1	11
	2	6	1
		4	7
	3	2	3
		3	10

NRDP (stock)

	Class	Prediction	
Truth	1	3	1
		5	9
	2	5	5
		0	8
	3	3	1
		2	12

NRDP (stock) with GRN

	Class	Prediction	
Truth	1	5	1
		2	10
	2	5	4
		1	8
	3	3	0
		2	13

NRDP (biological)

	Class	Prediction	
Truth	1	6	2
		2	8
	2	4	1
		3	10
	3	2	3
		1	12

	Line thickness	Count	Weighted Sum	Weighted average
No training	1	828	828.00	
	2	34	68.00	
	2.5	17	42.50	
	3	0	0.00	
	TOTAL	879	938.50	**1.067690557**
STDP	1	833.00	833.00	
	2	24.00	48.00	
	2.5	25.00	62.50	
	3	375.00	1125.00	
	TOTAL	1257.00	2068.50	**1.645584726**
GRN	1	851.00	851.00	
	2	849.00	1698.00	
	2.5	73.00	182.50	
	3	576.00	1728.00	
	TOTAL	2349.00	4459.50	**1.898467433**
Biological NRDP	1	829.00	829.00	
	2	40.00	80.00	
	2.5	47.00	117.50	
	3	429.00	1287.00	
	TOTAL	1345.00	2313.50	**1.720074349**