

Computational Modelling of Spatio-Temporal EEG Brain Data with Spiking Neural Networks

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“...ipse se nihil scire id unum sciat...”

(ἐν οἶδα, ὅτι οὐδὲν οἶδα)

-Socrates

Abstract

The research presented in this thesis is aimed at modelling, classification and understanding of functional changes in brain activity that forewarn of the onset and/or the progression of a neurodegenerative process that may result in a number of disorders, including cognitive impairments, opiate addiction, Epilepsy and Alzheimer's Disease.

The study of neural plasticity and disease onset have been the centre of attention for researchers; especially as the population is ageing there is a need to deal with the increase in cognitive decline and the early onset of neurological diseases. As a consequence, large amounts of brain data has been collected and even more is expected to be collected, by means of novel computational techniques and biochemistry measurements. However, brain data is difficult to analyse and understand, especially since many of the traditional statistical and AI techniques are not able to deal with it appropriately.

Driven by these issues and aiming to achieve the proposed goals, this study undertook to explore the potential of an evolving spatio-temporal data processing machine called the NeuCube architecture of spiking neurons, to analyse, classify and extract knowledge from electroencephalography spatio-temporal brain data.

Firstly, the research undertaken in this thesis proposes a biologically plausible spiking neural network methodology for electroencephalography data classification and

analysis. Secondly, it proposes a methodology for understanding functional changes in brain activity generated by the spatio-temporal data in the spiking neural network model. Thirdly, a new unsupervised learning rule is proposed for the investigation of the biological processes responsible for brain synaptic activity with the aim of targeting pharmacological treatments.

The research undertaken achieved the following: high accuracy classification of electroencephalography data, even when fewer EEG channels and/or unprocessed data was used; personalised prognosis and early prediction of neurological events; the development of a tool for visualization and analysis of connectivity and spiking activity generated in the computational model; a better understanding of the impact of different drug doses on brain activity; a better understanding of specific neurological events by revealing the area of the brain where they occurred; and the analysis of the impact of biochemical processes on the neuronal synaptic plasticity of the model.

Further improvement of the understanding and use of the proposed methodologies would contribute to the advancement of research in the area of prediction of neurological events and understanding of brain data related to neurological disorders, such as Alzheimer's Disease.

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List of Acronyms and Abbreviations

AD	Alzheimer's Disease
AER	Address Event Representation
AI	Artificial Intelligence
AMPA	α-Amino-3-hydroxy-5-Methyl-4-izoxazole-Propionic Acid Receptor
AUTEC	AUT University Ethics Committee
BCI	Brain Computer Interfaces
BCM	Bienenstock Cooper Munro
BP	Back-Propagation
BSA	Ben's Spiker Algorithm
CAE	Childhood Absence Epilepsy
CNGM	Computational Neurogenetic Model
CNN	Convolutional Neural Networks
CNS	Central Nervous System
DBN	Deep Belief Networks
deSNN	Dynamic Evolving Spiking Neural Network
ECM	Evolving Clustering Method
ECOS	Evolving Connectionist Systems
EEG	ElectroEncephaloGraphy
ELM	Extreme Learning Machines
EPSC	Excitatory Post-Synaptic Current
eSNN	Evolving Spiking Neural Network
eSTDM	Evolving Spatio-Temporal Data Machine
fNIRS	Functional Near Infrared Spectrometry
GABA	γ-AminoButyric Acid
GRN	Gene Regulatory Network
HMM	Hidden Markov Model
HMMRF	Hidden Markov Random Field Model
IECF	Inductive Evolving Classification Function
IPSC	Inhibitory Post-Synaptic Current
kSVM-DT	Kernel Support Vector Machine Decision Tree
LDA	Linear Discriminant Analysis
LIF	Leaky Integrate and Fire
LOOCV	Leave One Out Cross Validation
LSM	Liquid State Machine
LTD	Long-Term Depression
LTP	Long-Term Potentiation
LVQ-SVM	Learning Vector Quantization with Support Vector Machine
MLR	Multiple Linear Regression
MCI	Mild Cognitive Impairment
MI	Motor Imagery
MLP	Multiple Layer Perceptron

MMT	M ethadone M aintenance T reatment
NRDP	N euroreceptor D ependent P lasticity
NMDAR	N - M ethyl- D - A spartate R eceptor
NN	N eural N etworks
PE	P ermutation E entropy
PM	P ersonalised M edicine
pSNM	P robabilistic S piking N eural M odel
PSP	P ost- S ynaptic P otential
RNA	R ibonucleic A cid
RNN	R ecurrent N eural N etworks
RRSV	R epeated R andom S ub-sampling V alidation
ROC	R eceiver O perating C haracteristics
RQ	R esearch Q uestions
SDSP	S pike D riven S ynaptic P lasticity
SNN	S piking N eural N etworks
SNNc	3D S piking N eural N etwork C ube
SPAN	S pike P attern A ssociation N euron
SCSP	S parse C ommon S patial P attern
STBD	S patio- T emporal B rain D ata
STDP	S pike T iming D ependent P lasticity
SVM	S upport V ector M achine
SW	S mall- W orld
TBR	T hreshold B ased R epresentation
TDNN	T ime- D elay N eural N etworks

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 of candidate

Publications

- Schliebs, S., **Capecchi, E.**, & Kasabov, N. (2013, January). Spiking Neural Network for On-line Cognitive Activity Classification Based on EEG Data. In *2013 International Conference on Neural Information Processing (ICONIP)*, Daegu, South Korea, 3-7 November (pp. 55-62). Springer Berlin Heidelberg.
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A mia madre, Loredana De Ascaniis...

lei sempre ha creduto in me e per lei nutro una profonda stima, a lei devo l'insegnamento di valori che hanno guidato la mia vita fino ad ora tra i quali la solerzia, la perseveranza e l'onestà

Chapter 1

Introduction

1.1 Rationale and Significance of the Study

Over the last several decades, researchers have been trying to understand and model the human brain. Lately, this is becoming not only a goal to pursue, but an issue that needs prioritizing, as the community has to deal with the dramatic rise of neurological disorders and above all cognitive impairment and early onset of Alzheimer's Disease (AD) (Vialatte, Dauwels, Maurice, Musha & Cichocki, 2011). As a consequence, serious health questions have emerged as well as a need for reorganization of social care services (Pritchard, Mayers & Baldwin, 2013).

In response, scientists from all over the world have focused their resources and efforts toward the understanding of the central nervous system (CNS) and especially the mechanisms involved in learning formation and synaptic plasticity, as neurological decline affects these functions as a start.

The efforts carried out and the improvement of the techniques used have resulted in a considerable amount of data now available. However, this has raised a new problem:

how to find a suitable technique in order to understand the information available and make adequate use of it.

In this context, the scientific contribution in the area of Information Science (IS) and especially Neuroinformatics plays a pivotal role. They have been developing and offering new computational techniques that model the data available, thus emulating cognitive and learning functions of natural intelligent systems such as the human brain.

On the one hand, many of the techniques already in use are not adequate, the data is heavily preprocessed at time and information cost; traditional artificial intelligence (AI) models lack biological plausibility and therefore they cannot represent the phenomena of study. On the other hand, new techniques developed appear to be expensive and made for scientific elite use only. On the contrary, they need to be affordable, understandable and accessible to a wider number of researchers.

This thesis proposes a few biologically plausible methodologies for modelling and understanding brain data by means of computational models of neurological systems. For the first time, a spiking neural networks (SNN) approach is used to analyse, classify and extract knowledge from Spatio-Temporal Brain Data (STBD) such as Electroencephalography (EEG) data.

1.2 Aims of the Study

Over the last six decades, numerous advances have been achieved by researchers using SNN machine learning approaches. Especially, Neuroinformatics experts have contributed to the advancement of the understanding of neurological disorders and the development of predictive system. Even so, many of the techniques that are still in use

do not make proper use of the available data and lack realistic representation of the events.

Considering all the above discussed, the study aims can be summarised as follows:

- to explore the potential of an evolving spatio-temporal data machine (eSTDM) for developing new biologically plausible methodologies for modelling and understanding EEG data and the neurological events that generate it.
- By developing a new computational model of a neurological system, we aimed at revealing the information concealed in the data and learning from it in a new way, so that it can be analysed and localised in the brain area where it was originally generated.
- We aim at combining the EEG information with the eSTDM-based methodology proposed providing a more accessible and reliable brain-computer interface (BCI) system that can help detecting and understanding the course of a neurological event, such as cognitive impairment, which is one of the first symptoms related with the appearance of AD, considered the most alarming neuropathology of the century (Hebert, Scherr, Bienias, Bennett & Evans, 2004; Wimo, Winblad, Aguero-Torres & von Strauss, 2003).

1.3 Research Questions

This study is comprised of innovative research that aims at contributing toward the advancement of neurological data mapping, modelling and understanding. The research questions (RQ) formulated during the study are the following:

RQ 1 Can we develop a methodology for EEG data classification and modelling in an eSTDM of spatially organised spiking neurons that can be used to properly

analyse and understand the STBD available and the brain processes that generated it?

- RQ 2** Can we identify the functional changes in neural activity generated when a subject affected by a particular neurological disorders and/or under a particular drug treatment is compared with a control subject or the absence of a neural event?
- RQ 3** Can we analyse the evolution of connectivity and/or spiking activity that occur in a trained eSTDM when comparing data of an individual subject or a group of subjects performing a task with data from another individual or another group?
- RQ 4** Can we identify the brain areas where the functional changes in neural activity is generated by the different classes using the computational model developed?
- RQ 5** Can the methodology be successfully applied on the analysis and the prediction of a specific neurological event?
- RQ 6** Can we elicit synaptic modifications based on biochemical mechanisms (*i.e.* based on the main glutamatergic and GABAergic receptors activity) to create an unsupervised learning rule that dynamically learns from the data?
- RQ 7** Can we use this methodology to study the impact of neuroreceptors' activity on the post-synaptic action potential of a spiking neuron in a eSTDM-based model and further interpret the findings for the study of brain conditions?
- RQ 8** Can a better understanding of how these neurotransmitters are involved in the computational learning processes be used to emulate therapeutic strategies for targeting mental diseases treatments?
- RQ 9** Can we use the proposed unsupervised learning rule together with an eSTDM to develop a computational neurogenetic model for knowledge extraction of both

STBD and genetic data?

1.4 Scientific Contribution

This study introduces new methodologies and a new learning rule to the set of techniques offered in the area of neuro- and bio- informatics that can be used for data analysis and learning. These are applied to several case studies that have reportedly proved their ability to properly classify different EEG patterns, localising the functional changes in the generated neural activity and extracting new knowledge from them.

Figure 1.1 shows how the thesis tackles aforementioned problems and where the methodologies were applied and discussed in the thesis chapters.

1.5 Contribution to IS as Peer-Reviewed International Conference and Journal Articles

The content of this thesis has been partially published in eight peer-reviewed international conference and journal papers and further two papers have been submitted for review.

1. Schliebs, S., **Capecci, E.**, & Kasabov, N. (2013, January). Spiking Neural Network for On-line Cognitive Activity Classification Based on EEG Data. In *2013 International Conference on Neural Information Processing (ICONIP)*, Daegu, South Korea, 3-7 November (pp. 55-62). Springer Berlin Heidelberg.
2. Taylor, D., Scott, N., Kasabov, N., **Capecci, E.**, Tu, E., Saywell, N., & Hou, Z. G. (2014). Feasibility of NeuCube SNN architecture for detecting motor execution and motor intention for use in BCI applications. In *2014 International*

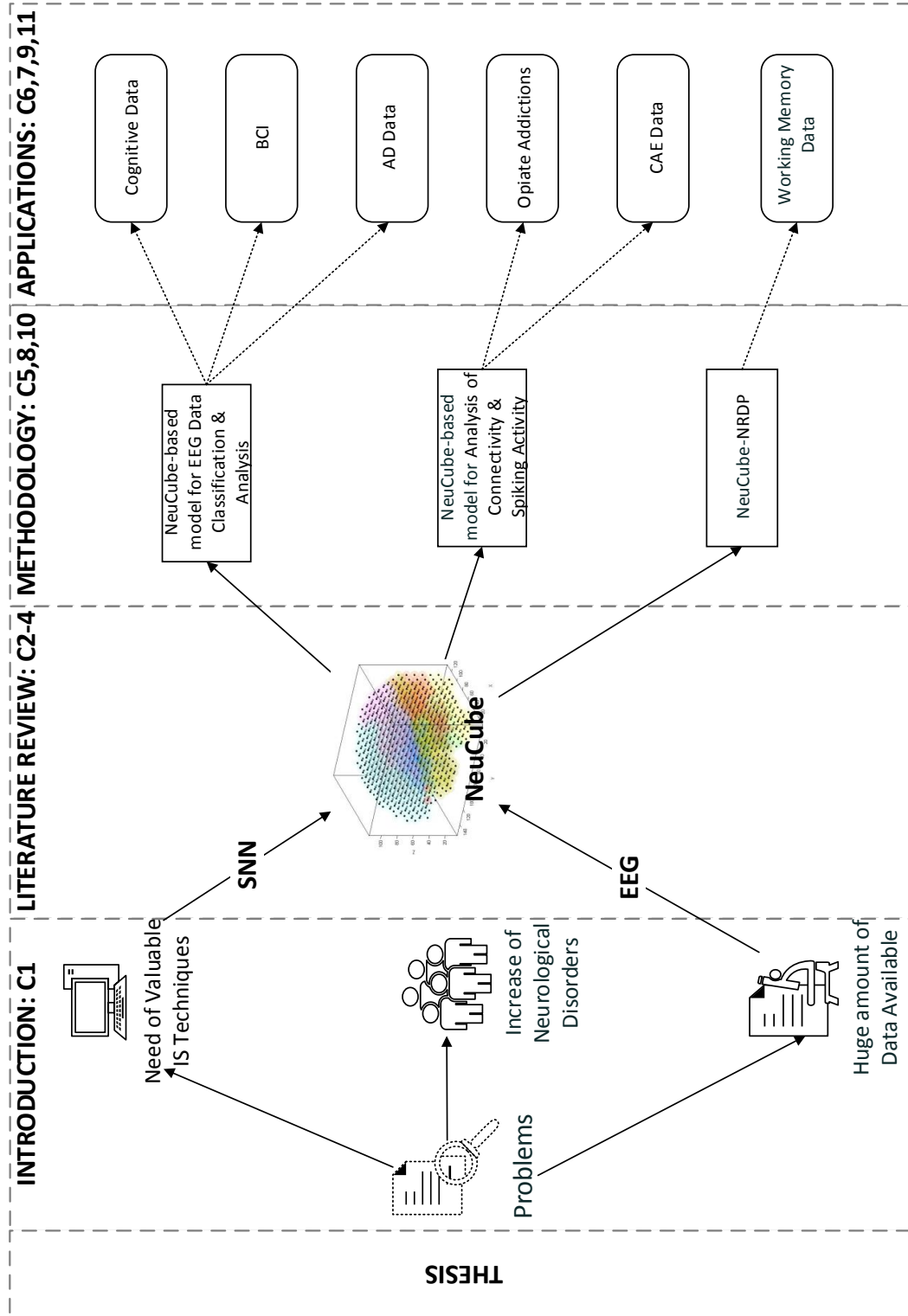


Figure 1.1: Diagram summarising the problems considered in the thesis, the approach used to study them, the methods developed and their applications. The thesis content is presented in 12 chapters (C1-12).

- Joint Conference on Neural Networks (IJCNN)*, Beijing, China, 6-11 July (pp. 3221-3225). IEEE.
3. Doborjeh, M. G., **Capecci, E.**, & Kasabov, N. (2014, December). Classification and segmentation of fMRI Spatio-Temporal Brain Data with a NeuCube evolving Spiking Neural Network model. In *2014 IEEE Symposium on Evolving and Autonomous Learning Systems (EALS)*, Orlando, Florida, USA, 9-12 December (pp. 73-80). IEEE.
 4. Kasabov, N., & **Capecci, E.** (2015). Spiking neural network methodology for modelling, classification and understanding of EEG spatio-temporal data measuring cognitive processes. *Information Sciences*, 294, 565-575. doi:10.1016/j.ins.2014.06.02
 5. **Capecci, E.**, Kasabov, N., & Wang, G. Y. (2015). Analysis of connectivity in NeuCube spiking neural network models trained on EEG data for the understanding of functional changes in the brain: A case study on opiate dependence treatment. *Neural Networks*, 68, 62-77. doi:10.1016/j.neunet.2015.03.009
 6. Kasabov, N., Scott, N., Tu, E., Marks, S., Sengupta, N., **Capecci, E.**, Othman, M., Doborjeh, M., Murli, N., Hartono, R., Espinosa-Ramos, J.I., Zhou, L., Alvi, F., Wang, G., Taylor, D., Feigin, V., Gulyaev, S., Mahmoud, M., Hou Z-H., Yang, J. (2015). Evolving spatio-temporal data machines based on the NeuCube neuromorphic framework: Design methodology and selected applications. *Neural Networks, Special Issue on Neural Networks Learning in Big Data*. Available online 17 October 2015, ISSN 0893-6080, doi:10.1016/j.neunet.2015.09.011
 7. **Capecci, E.**, Espinosa-Ramos, J.I., Mammone, N., Kasabov, N., Duun-Henriksen, J., Kjaer, T. W., Campolo, M., La Foresta, F., Morabito, F.C. (2015). Modelling Absence Epilepsy Seizure Data in the NeuCube Evolving Spiking Neural Network

Architecture. In *International Joint Conference on Neural Networks (IJCNN)*. Killarney, Ireland, 12-17 July (pp.1-8). IEEE. doi: 10.1109/IJCNN.2015.7280764

8. **Capecci, E.**, Morabito, F. C., Campolo, M., Mammone, N., Labate, D., Kasabov, N. (2015). A Feasibility Study of Using the NeuCube Spiking Neural Network Architecture for Modelling Alzheimer's Disease EEG Data. In *Advances in Neural Networks: Computational and Theoretical Issues* (pp. 159-172). Springer International Publishing.
9. Espinosa-Ramos, J.I., **Capecci, E.**, Kasabov, N. (2016). Computational Neuro-genetic Modelling Through Neuroreceptor Dependent Plasticity (NRDP) Based on Spiking Neural Networks. *Neural Networks*. (submitted).
10. **Capecci, E.**, Gholami-Doborjeh Z., Mammone, N., La Foresta, F., Morabito, F. C., Kasabov, N. (2016). Study of Alzheimer's Disease Degeneration through EEG Data Analysis with a NeuCube Spiking Neural Network Model. In *International Joint Conference on Neural Networks (IJCNN)*. Vancouver, Canada, 25-29 July. (submitted).

This thesis is presented by adapting selected papers into chapters. Table 1.1 presents a link between thesis chapters and their corresponding papers:

Table 1.1: Link between chapters and selected papers that were adapted into it.

Paper	Chapter
2	5
4	6
5	8
6	4
7	9
8, 10	7
9	11

1.6 Thesis Structure

This study is presented in twelve chapters as outlined below:

Chapter 1 introduces the research motivations, outlines the aims of the study, proposes the main research questions and identifies the proposed methodologies.

Chapter 2 reviews some of the main types of spatio-temporal and neurogenetic brain data used in Neuroinformatics and justifies the type of data used in this study to achieve the proposed objectives.

Chapter 3 discusses the main mechanisms that govern neural activity in the CNS and reviews how these mechanisms are viewed and modelled *in silico*, particularly in SNN, the method of choice to achieve the objectives proposed in this thesis.

Chapter 4 reviews the SNN NeuCube architecture, which is used in this thesis to develop the proposed new methodologies.

Chapter 5 proposes a new methodology for the classification and analysis of EEG data. The new methodology is first applied on a small dataset, a case study in BCI-based system for neurorehabilitation.

Chapter 6 presents a comparative analysis between the proposed methodology and some already published classification results on EEG data recorded during complex cognitive mental activities. The methodology demonstrated its potentiality to adapt to new data and new classes; additionally, it is shown that it can be used for the analysis of the learned data over various brain regions.

Chapter 7 explains how the proposed methodology was applied in order to classify and study neurological disorders. Functional changes in neural activity generated per class are analysed by identifying differences between subjects and/or the time of data collection. The promising results demonstrate the methodology potentiality to solve the classification task and propose its use for prediction of neurological disorders' onset.

Chapter 8 presents a new methodology for the analysis of functional changes in brain activity across different conditions and different groups of subjects. A case study of people undertaking drug-based treatment is also presented, which proved the methodology functionality for the analysis of the connectivity and spiking activity evolved in a specific area of the brain.

Chapter 9 explores the methodology potentiality for personalised modelling and events prediction. Data recorded from a person affected by an epileptic event, was analysed against the absence of it. The functional changes that produced the neural events are studied by means of stepwise connectivity and spiking activity analysis.

Chapter 10 presents a new biologically plausible unsupervised learning rule that is applied to the SNN NeuCube-based methodologies developed to dynamically learn the spatio-temporal relationship from the data.

Chapter 11 explains how the proposed methodology is applied to study cognitive brain processes in order to understand whether changes to neurotransmitters levels affect the computational learning process. Analysis of the evolved connectivity and spiking activity is used to study possible implications on mental diseases treatments.

Chapter 12 summarises the achieved goals and the contribution of this thesis to SNN research. Future work is also suggested.

1.7 Summary

This introductory chapter gives a background to the problems and the motivations that lead to the research presented in this thesis; the aims of the study are presented; the research questions are identified; and the contribution that this thesis brought about to research is outlined here.

Chapter 2 reviews some of the main STBD and neurogenetic data used in Neuroinformatics and focused on EEG data, which is used in this study to achieve its objectives.

Chapter 2

A Review on STBD and Information Processing in Neuroinformatics

2.1 Introduction

Dealing with the enormous amount of data available has been identified in the previous chapter as one of the major problems that motivates this study. In this chapter this problem will be analysed as follows: section 2.2 explains the limitations of STBD processing; section 2.3 reviews some of the most important types of STBD; section 2.4 focuses on EEG data, which has been identified as the most appropriate source of STBD to model for the purposes of this study; and section 2.5 provides a brief review of the main STBD processing approaches.

2.2 STBD Processing: Problems and Applications

Modelling STBD represents a challenge for IS, as it is complex to process; however, if properly used it constitutes a powerful source of information, as it contains knowledge about both where and when neurological events occur. This could help experts to

identify the cause of a problem and provides powerful decision support instruments for the health sector. Some important applications developed using STBD are:

- *BCI research.* This technology aims at decoding brain signals that represent neuronal processes to enable human-computer communication (Isa, Fetz & Mueller, 2009; Lotte, Congedo, Lecuyer, Lamarche & Arnaldi, 2007; Nicolelis, 2012) (Fig. 2.1-top). Many BCI systems still use traditional statistical and AI methods for the recognition of complex STBD. This often limits the functioning of the BCI and leads to poor performance (Keirn & Aunon, 1990; Nicolelis, 2012).
- *Early diagnosis and prevention of degenerative brain diseases.* Early detection is important, as it allows prompt treatments. This can be achieved by means of STBD analysis (Fig. 2.1-centre). In this context, more efficient machine learning techniques are needed to evaluate the cognitive ability of a person and to provide deeper understanding of the brain processes that cause it.
- *Personalised disease prognosis and neurorehabilitation.* Personalised medicine (PM) is a current trend in health care with a huge potential in many related areas (Chen, Hu, Kasabov, Hou & Cheng, 2013; Kasabov et al., 2014). Data from an individual is used to create a particular model that is able to estimate an unknown outcome for this individual. Neurorehabilitation systems help patients' healing by using mental movements rehearsal in order to encourage neural recovery (Jaeger, 2001) (Fig. 2.1-bottom). Still, new IS methods are needed for the efficient implementation of this concept as demonstrated in (Kasabov et al., 2014).

The main problem associated with the STBD signal is to preserve the intrinsic correlation between its spatial and temporal components. To make proper use of the information “hidden” in the data, this correlation needs to be preserved. However, traditional computational techniques fail to do that. Data is compressed (*e.g.* averaged) and

the location component is disregarded (*i.e.* once the data is processed the information about the brain area where the data was collected is lost); therefore, we could consider traditional machine learning methods not suitable for dealing with the spatio-temporal information in a proper way.

In this study, we investigate new methodologies that tackle these problems in a different way. To process STBD at a high level, we apply the neural basis of cognitive processes and information exchange to our computational model.

2.3 What STBD can be Measured and Modelled?

A vast amount of data has been collected so far for the study, understanding and modelling of the human brain at a cognitive level. Changes of electromagnetic signals, blood flow and metabolic processes caused by activity in the neural cell are the major source of STBD such as Functional Magnetic Resonance Imaging (fMRI), Magnetoencephalogram (MEG), Diffusion Tensor Imaging (DTI), EEG, etc. (Liu, Ding & He, 2006).

2.3.1 fMRI

fMRI data (Fig. 2.2) is powerful STBD that presents neuron localization with high resolution (Lindquist, 2008; Graner, Oakes, French & Riedy, 2013). This data is collected using magnetic resonance imaging to reveal changes in neuronal activities based on dynamics of blood flow. To start firing, active neurons demand high level of oxygen that is carried by blood cells. By increasing the number of spikes in activated brain regions, blood flow will be increased in those particular parts. fMRI data provides the spatial localizations of the brain in a three dimensional cell called voxel and temporal



Figure 2.1: (top) BCI used to register and analyse the brain waves recorded by an EEG device (Ferrando & Lammerhuber, 2009); (centre) a researcher studying the information from a high-resolution functional magnetic resonance (NIMH, 2008); (bottom) EEG-based Neurorehabilitation device for spinal cord injury recovery (Advanced Brain Monitoring, 2014)

information as the fourth dimension (Ogawa et al., 1992). Each of these voxels represents fluctuation of blood oxygenation level dependent (BOLD) intensity of thousands of neurons over time, while different regions of the brain are activated by means of different *stimuli*.

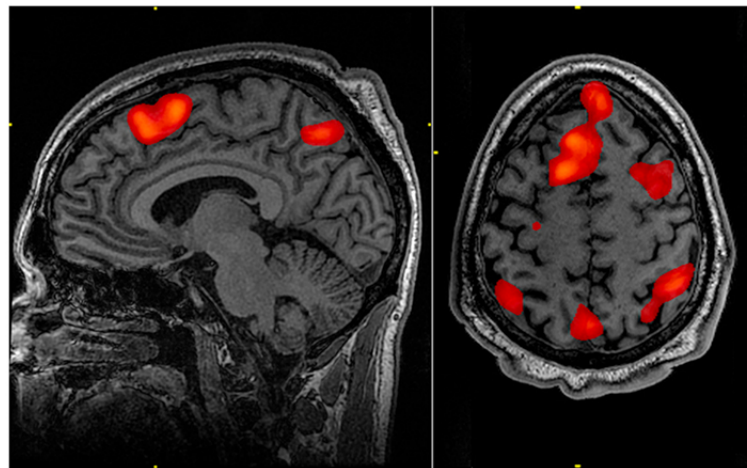


Figure 2.2: Example of fMRI STBD collected during a working memory task (Graner et al., 2013). The highlighted regions identify the brain areas activated during the recording.

2.3.2 MEG and EEG

From a biochemical point of view, the activity of the neural cell is generated by ionic currents. This activity produces magnetic and electric fields that can be measured as *MEG* and *EEG* signals respectively (Da Silva & Van Rotterdam, 1999). In contrast to fMRI technique, they possess high temporal resolution (as brain signals are recorded in the sequence of milliseconds), but less clear localization (Lindquist, 2008). The main features of both MEG and EEG signals are similar; however, they differ in properties such as frequency and phase. Also, the MEG technique allows to record signals emitted from smaller regions of the scalp, but it possesses angular limitations (*i.e.* MEG technique detects only dipoles parallel to the surface of the model), while the EEG technique is sensitive to larger regions only but it can detect dipoles independently from the

orientation (Cuffin & Cohen, 1979). Nevertheless, EEG data is really easy to collect and transport (see Fig. 2.3) making EEG the most commonly collected data for the study of brain processes (Anderson & Peterson, 2001; Forney & Anderson, 2011; Kasabov, 2014b; Nuntalid, Dhoble & Kasabov, 2011). In this study, we are especially interested in EEG data and we have dedicated the entire next section to it.



Figure 2.3: Example of MEG and EEG data collection procedure. Clearly, EEG data is easier to collect and more affordable than MEG data, which requires a voluminous and expensive scanner equipment to carry out the recording process. These images are from the public domain and are available from (NIMH, 2009) and (Myers, 2010).

2.3.3 A Relevant Non Spatio-Temporal Type of Brain Data

For our research, we consider important to introduce another type of data used for the study of the brain processes and the neurological disorders especially correlated with genetic compounds, namely *transcriptome data*. The transcriptome is the quantitative description of all ribonucleic acid (RNA) molecules expressed by a cell (Adams, 2008; Schwanhausser et al., 2011) and RNA molecules are the first products of all genes (Griffiths, Gelbart, Miller & Lewontin, 1999). The nature of any cell is dictated by the

genes that are expressed in it, connecting genes, with cells and anatomy; thus, modelling this information appropriately could help to unlock the mysteries of neurological diseases and disorders affecting millions of people worldwide.

Even though RNA-seq has emerged as method of choice for measuring transcriptome of organisms (Mortazavi, Williams, McCue, Schaeffer & Wold, 2008), DNA microarrays are still widely used for targeting the identification of already known common allele variants. Microarrays are “biochips”, each one consisting of DNA spots attached to a solid surface, the array. In more detail, in a Microarray two samples are marked by fluorescent methods and after being scanned, the ratio of each gene expression is calculated by computational statistical methods. The result is an image where each pixel from the picture represents the activity of a gene and the colour of each pixel shows how active a particular gene is (Fig. 2.4).

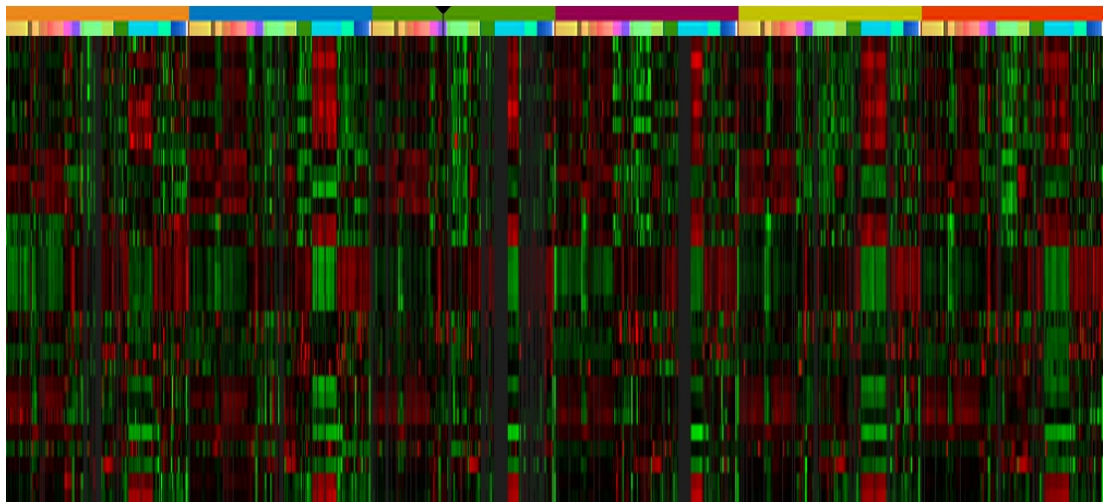


Figure 2.4: Microarray rendering of gene expression available from the Allen Brain Atlas (Allen Institute for Brain Science, 2014a). The example shows a Microarray of several genes under the category of AD. The first row identifies the data corresponding to each of the six donors in different colours; the second row represents areas of the brain each identified by a different colour band. In the heat map the red areas identify the over expressed gene expression, the green areas the under expressed and the black areas their average value (Allen Institute for Brain Science, 2014b)

Genes provide clues about how the brain works (Shen, Overly & Jones, 2012). Human beings possess 23 pairs of chromosomes and roughly 20000 genes encoded for proteins in our DNA (Pertea & Salzberg, 2010; Ezkurdia et al., 2013). The possibility to identify where a gene is turned on in the brain results in a better understanding of how brain diseases work (Shen et al., 2012). Because of that, the Allen Brain Institute of Seattle developed the first available on-line atlas (Allen Institute for Brain Science, 2014a) that maps gene expression with anatomical coverage of the human brain. They used measurements of Microarrays expressed as a z-score (*i.e.* a statistical parameter). These are available through the web page (Allen Institute for Brain Science, 2014a) and each of them contains around 60000 data points (Shen et al., 2012), an enormous quantity of data. Even though the transcriptome data provided by the Allen Brain Atlas is representative, as it is based on DNA of just a few individuals, the genome's sequence similarity over individuals is really high (about 99.9%), with the same genes in the same location (Feuk, Carson & Scherer, 2006). People are unique by phenotype; however, every human being shares the same genetic blueprint (Shen et al., 2012).

In (Benuskova & Kasabov, 2007; Kasabov, 2010, 2014a) a computational neurogenetic model (CNGM) has been proposed that combines the information provided by STBD and gene expression data. In this thesis section 11.3.1 on future work, we suggest a genetic study that can combine the new methodology proposed in our research and the CNGM.

2.4 Review of EEG Data as a Type of STBD for Neural Information Processing

EEG techniques coupled with BCI devices allow for the recording of electrical cortical activity and the study of the collected STBD by means of computational methods. Fig. 2.5 shows an example of a BCI-based EEG recording system, the Emotiv neuro-headset (*The Emotiv Systems*, 2014). In the cortical area, conscious sensations, abstract thought, reasoning, sounds (including word and music), even planning and working memory are processed (Carter, Aldridge, Page & Parker, 2009; Douglas & Martin, 2007). Thus, EEG can be considered a valuable data for the research and study of cognitive activity in the human cortex as well as for the study and advancement of cognitive impairments. EEG is also an affordable technique, easy to manage and carry, and it is not considered an aggressive method for the subjects being studied (Rodriguez, Copello, Vitali, Perego & Nobili, 1999); therefore, it has been used extensively for the study of brain functional changes under different conditions, including neurological disease and treatment with drugs, as published in (Labate et al., 2014; Morabito, Labate, Morabito, Palamara & Szu, 2013; Morabito et al., 2012; Mammone, Labate, Lay-Ekuakille & Morabito, 2012).

The relevance of oscillatory phenomena related to EEG functionality has been demonstrated in many studies, such as (Baaayar, Baaayr-Eroglu, Karakaay & Schrmann, 2001; Raghavachari et al., 2001; Onton, Delorme & Makeig, 2005). These phenomena correspond to rhythms of type delta ($0.5\text{-}3.5\text{ Hz}$, generally related to sleep or rest); theta ($3.5\text{-}7.5\text{ Hz}$, generally related to learning, memory and sensory motor processing); alpha ($7.5\text{-}12.5\text{ Hz}$, generally related to meditation); beta ($12.5\text{-}30\text{ Hz}$, generally related to mental calculation, anticipation or tension); and gamma ($30\text{-}60\text{ Hz}$, generally related to attention and sensory perception). These rhythms are associated with different cognitive

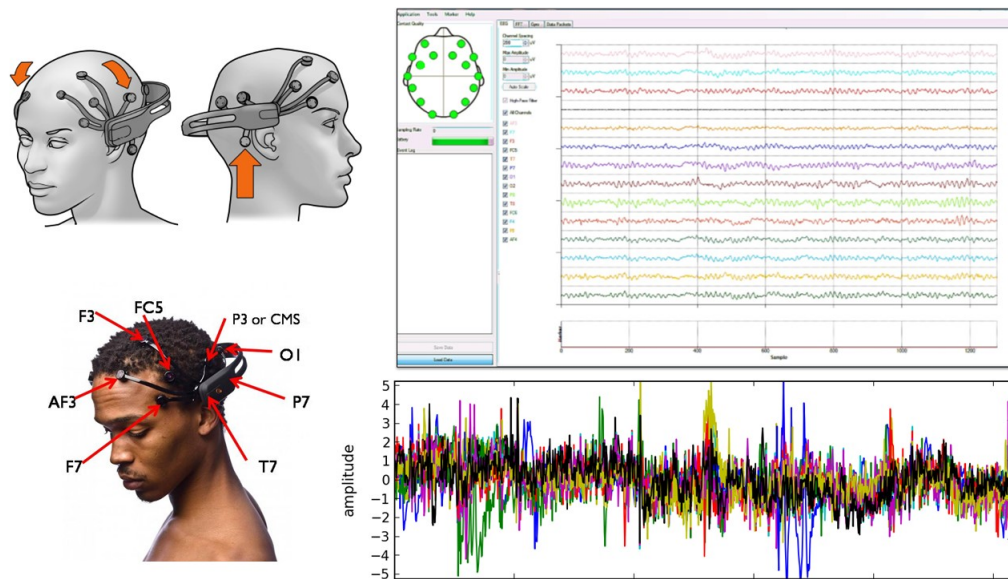


Figure 2.5: The pictures on the left (Jane, 2013) show the 14-channel Emotiv neuro-headset and the images on the right show the EEG signal recorded by using the Emotiv.

processes and communication between neuronal cells (Baaayar et al., 2001; Freeman & Quiroga, 2012) (Fig. 2.6). Encoding of new information, scanning through the short-term memory, and decision making are related to oscillation of alpha and theta bands in particular (Klimesch, 1999). However, alpha is the dominant frequency in the human brain of healthy adults and if there is a demand related to cognitive and memory processes, the power of alpha waves desynchronizes (*i.e.* it decreases), while theta synchronizes (*i.e.* it increases) (Klimesch, 1999). In fact, these two bands (alpha and theta) are often related to working memory and cognitive efforts and it is the hippocampus area of the brain that is known to be essential for these processes (Onton et al., 2005). People suffering from a cognitive impairment, such as MCI and AD in its early stages, have this region affected and consequently their cognitive and memory efficiency is altered too (Baddeley, 1992).

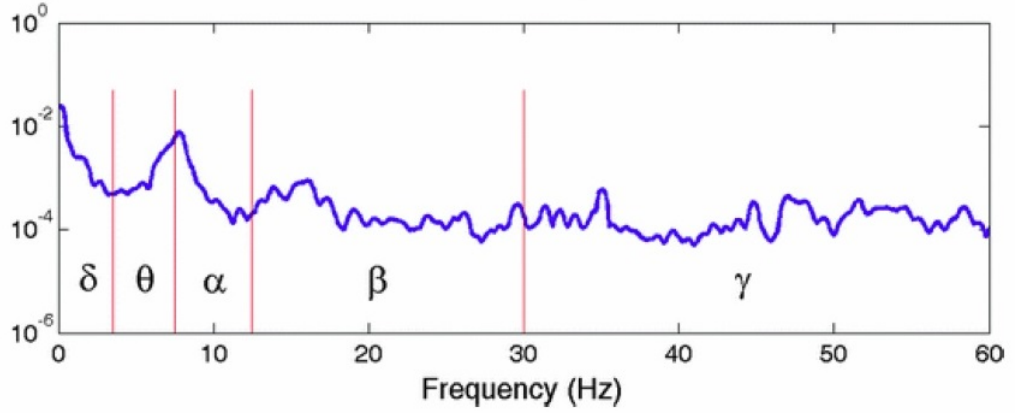


Figure 2.6: The picture shows the five EEG frequency bands of the EEG spectrum, such as δ rhythms (between 0.5 and 3.5 Hz), θ (between 3.5 and 7.5 Hz), α (between 7.5 and 12.5 Hz), β (between 12.5 and 30 Hz), γ (between 30 and 60 Hz). Picture from (Freeman & Quiroga, 2012).

Recently, a growing number of tools have been developed to process EEG data, including EEGLAB (Delorme & Makeig, 2004), LORETA (Pascual-Marqui, 2009) and PyEEG (Bao, Liu & Zhang, 2011). Classification of EEG data is often done with standard methods, such as Multiple Linear Regression (MLR), Support Vector Machine (SVM), Multilayer Perceptron (MLP), Evolving Clustering Method (ECM) (Song & Kasabov, 2001) and linear regression. All these techniques often require extensive preprocessing of the data and also signal averaging.

In this thesis, we explore new methodologies that process EEG data differently as they consider both EEG time and frequency dependency appropriately. In the next section, we will introduce some of the popular STBD processing approaches already in use, highlighting the technique of choice used in this research.

2.5 STBD Processing in Neuroinformatics

Researchers have struggled for many years to find the best technique for processing complex continuous signals developing several stochastic models. However, while

some of these are widely used, mining STBD with less spatio-temporal pattern loss is still a challenge for IS.

Most of the developed models are based on statistical approaches. Hidden Markov Models (HMM) is one of those and is a popular statistical modelling approach for mining temporal data; this model has been used for a long time in several applications such as speech recognition (Rabiner, 1989), computational sequence analysis (Churchill, 1989) and protein structural modelling (Stultz, White & Smith, 1993). HMM assigns a probability distribution to a set of available infinite states (Eddy, 1996). Even though these models are able to provide desired outputs in most circumstances, they possess some limitations (Trentin & Gori, 2001). Most importantly, a problem appears when defining more than one independent variable; thus, with STBD being inherently two-dimensional, HMM cannot be used to appropriately learn from it.

This problem was tackled by means of ANN techniques, extensions of connectionist models that use discriminative training, non-parametric estimation of patterns, and possess a limited number of features (Trentin & Gori, 2001). Several techniques emerged, such as time-delay neural networks (TDNN) (Waibel, Hanazawa, Hinton, Shikano & Lang, 1989) and recurrent neural networks (RNN) (Mozier, 1993), together with different training algorithms based on back-propagation (BP) of errors (Rumelhart, Hinton & Williams, 1988) such as recurrent BP (Pineda, 1989) and BP through time (Rumelhart, Hinton & Williams, 1986). However, ANN showed some limitations when long time-sequence data was to be modelled (Bengio, Simard & Frasconi, 1994; Trentin & Gori, 2001). The solution was found in hybrid architectures, which maintained the HMM structure and added ANN features making efficient output modelling possible and time recognition achievable (Trentin & Gori, 2001). Many hybrid architectures and training algorithms have been proposed in the literature, for instance deep machine

learning, which combines discriminative multi-layer neural networks, such as convolutional neural networks (CNN), and also probabilistic generative models, such as deep belief networks (DBN) (Arel, Rose & Karnowski, 2010). However, in the proposed architecture the input data is first filtered and then sub-sampled, thus losing the precious spatio-temporal information.

SNN techniques can be used to learn from the entire time-series data by using biologically inspired net of neurons. As a matter of fact, they have gained popularity and different algorithms for learning and classification of STBD have been proposed using SNN, for instance (Gerstner, 2001; Maass, Natschläger & Markram, 2002; Tsodyks, Pawelzik & Markram, 1998; Turrigiano, Leslie, Desai, Rutherford & Nelson, 1998; Markram, Gerstner & Sjöström, 2011). Several SNN models and applications have been developed so far, including models for spatio-temporal EEG data modelling and for the study of brain functional changes caused by different conditions, such as neurological disorders and also for predicting response to treatments (Ghosh-Dastidar & Adeli, 2007; Nuntalid et al., 2011; Hu, Hou, Chen, Kasabov & Scott, 2014; Kasabov, 2014b). This has been done with only partial success so far, as pointed out in (Gerstner, Sprekeler & Deco, 2012; Kasabov, 2014b, 2014a), increasing the need for development of new SNN methods for STBD modelling and analysis.

In this thesis, we propose some new methodologies for EEG data classification and modelling based on the SNN NeuCube architecture (Kasabov, 2014a).

2.6 Summary

This chapter introduces some of the most relevant types of STBD used for the study of brain cognitive activity and neurological impairments; it revises briefly how the

problems related to STBD modelling have been approached in the literature; also, SNN techniques are assessed as the most appropriate to accomplish the objectives proposed in this thesis as discussed in detail in Chapter 3.

Chapter 3

Overview of Spiking Neural Networks: Biological *versus* Artificial Neurons

3.1 Introduction

As discussed in the previous chapter, the vast amount of data in hand can proportionate great knowledge, when dealing with STBD; however, appropriate computational models are needed that are able to interpret and correctly represent this information. SNN techniques, named also third generation of brain-inspired neural network techniques (Maass, 1997; Ghosh-Dastidar & Adeli, 2007) have emerged as the method of choice, as they are able to learn time, space, and frequency from the STBD. As a matter of fact, they have been used in several applications such as neuromorphic design and implementation (Gerstner, 2001; Izhikevich, 2006; Furber & Temple, 2007; Gerstner et al., 2012), spatio-temporal pattern recognition (Humble, Denham & Wennekers, 2012; Kasabov, 2012b), encoding continuous input data into spike trains (Lichtsteiner & Delbruck, 2005; Chan, Liu & Van Schaik, 2007; Indiveri et al., 2011; Dhoble, Nuntalid, Indiveri & Kasabov, 2012), neurogenetic computation (Benuskova & Kasabov, 2007; Kasabov, 2010), and neurocomputational studies of brain pathology (Reggia, Ruppín &

Glanzman, 1999).

All SNN techniques developed are based on the emulation of some of the main principles that regulate information processing and plasticity in the CNS. Thus, in this chapter, first the functionality of SNNs will be assessed by introducing the main unit of information processing in the brain, the neural cell (section 3.1); then some of the most important computational models that have been derived from it will be discussed (section 3.3).

3.2 How Does the Human Brain Process Information?

To understand information processing in the CNS, we need to first understand how its main information processing cells (*i.e.* the neurons) work.

3.2.1 The Neural Cell

In the human brain there are roughly 86 billions of neurons (Azevedo et al., 2009), each connected up to 7000 others *via* synapses (Pakkenberg et al., 2003; Drachman, 2005), even though the exact number is still unknown (Azevedo et al., 2009) and it changes during the course of normal life (DeFelipe, Marco, Busturia & Merchán-Pérez, 1999).

Neurons' function is to receive, analyse, store and transmit information. The process by which these cells accomplish the transfer of the information along two systems is called neuronal signalling. The signalling process is performed along precise routes (Gazzaniga, Ivry & Mangun, 2009). It is how these cells are distributed and connected that underlies brain functions. Neurons with similar morphologies tend to be focussed in a specific region of the nervous system and have a similar function role (Carter et al., 2009).

Neurons' morphology consist of a cell body, or soma, and unlike other cells, it may possess additional structural extensions: dendrites and axons (Fig. 3.1). The soma, the dendrites and the axons share the same cytoplasm and for that reason neurons can perform electrical signalling, which means that their dynamic activity reside on their extensions (Gazzaniga et al., 2009).

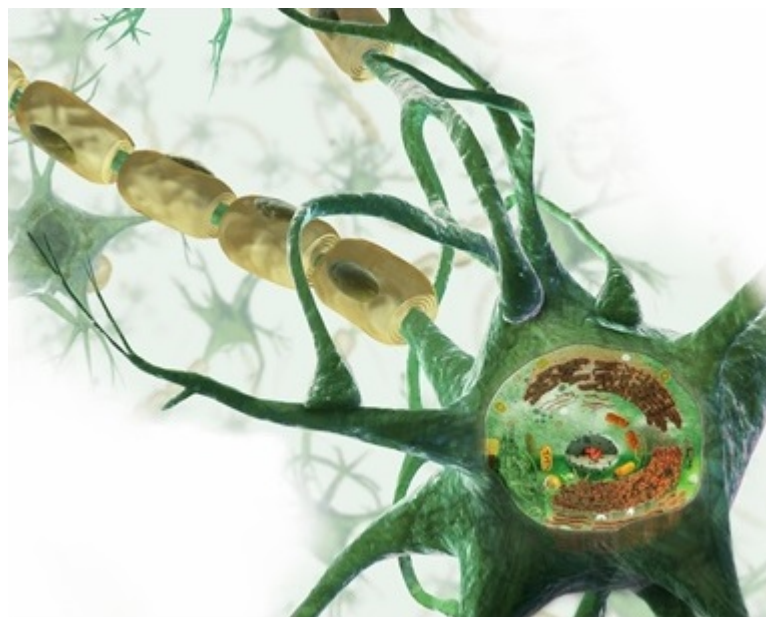


Figure 3.1: The cell body, like all other cells, contains all typical components of eukaryotic cells (nucleus, endoplasmic reticulum, ribosomes, mitochondria, Golgi apparatus, cell membrane etc.). From the body there are noticeable extensions of the cell membrane: the dendrites and the axon. Axons are identifiable by the myelin sheaths (in white) spaced out by nodes of Ranvier (*i.e.* the gaps between them). Figure from (Carter, 2009).

3.2.2 Neural Signalling and Action Potential

The force that generates neural activity is called action potential, or “spike”. As explained by (Hodgkin & Huxley, 1952c) more than 60 years ago, an action potential is created in the neuron's axon by regenerative changes in the membrane potential that occur throughout the length of its propagation. This is achieved by electrochemical

forces that are based upon diffusion of charged ions, especially Na^+ , K^+ , Ca^{2+} and Cl^- , through specific channels situated along the neural membrane (Brady, Siegel, Albers & Price, 2011). In Fig. 3.2, this complex process is summarised into five steps (Boundless, 2014; Brady et al., 2011):

1. Neurons receive *stimuli* (e.g. a visual, auditory or cognitive input) from other cells or from other neurons through dendrites. When this happens, a neural cell, which lies in a resting potential of about -70 mV, begin to depolarise (*i.e.* it increases), as a consequence of the synthesis of some enzyme, protein, vesicles, etc., required by the stimulus.
2. Inside the neural cell, there is a high concentration of K^+ cations, while outside the higher concentration is of Na^+ cations. If the stimulus is strong enough to depolarize the membrane up to its threshold (- 50 mV), this increases its permeability toward Na^+ temporarily by means of voltage-gated ion channels situated along the axon membrane.
3. At this point, the action potential will quickly reach its peak, at about 30 mV, and then sets into a short plateau.
4. At the same time, the membrane potential quickly starts a falling phase, as voltage-gated K^+ channels open, leaving the cations to exit, and Na^+ channels close.
5. As the K^+ cations are drained out, the membrane potential hyperpolarizes, setting into a refractory period, when the action potential cannot be generated again, and slowly come back into its resting potential.

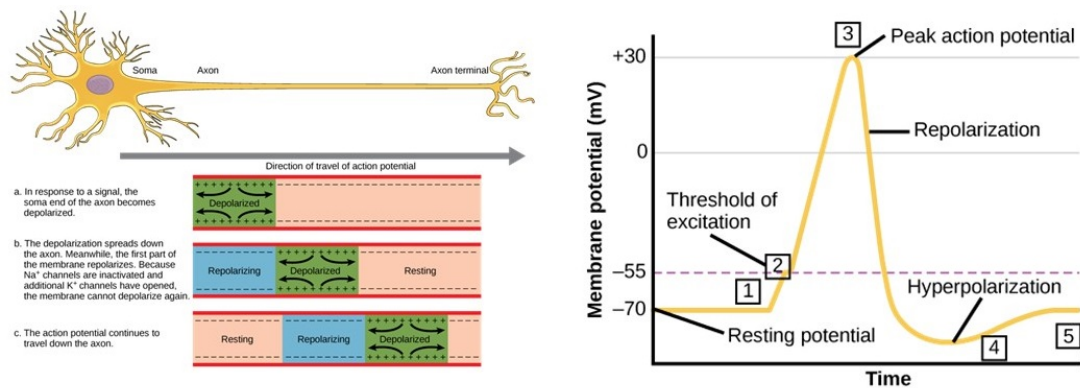


Figure 3.2: The left hand-side image shows how the action potential is transmitted through the axon's membrane by alternating waves of depolarization and repolarization, caused by Na^+ and K^+ diffusion, through the axon's membrane that directionally drives the electrical impulse toward the synaptic cleft. The right hand-side graphic represents the five steps that generate the action potential. Images from (Boundless.com, 2014a, 2014b).

3.2.3 Chemical Synapse

Although neuronal signalling occurs *via* electrical phenomena, at a synapse the signal is resolved through chemical transmissions (Gazzaniga et al., 2009), where the axon enables communication between the other cells releasing chemical substances. Axons and their terminals are called pre-synaptic structures, due to their location with respect to the information flow, while dendrites, which are located after the synapses in respect to the information flow, are named post-synaptic structures (Gazzaniga et al., 2009).

When the alternating electrical waves of depolarization and repolarization, caused by Na^+ and K^+ diffusion, finally reach the axon's end, another series of complex events take place, which can be summarised as follow:

- voltage-dependent Ca^{2+} channels open allowing Ca^{2+} cations influx inside the pre-synaptic terminal. Here, the molecules are transported by the action potential, like vesicles containing neurotransmitters, bound with Ca^{2+} ions, which help them to fuse into the membrane and flow into the synaptic cleft (*i.e.* a narrow

division between a pre-synaptic and a post-synaptic cell) (Ernst, 2012).

- Neurotransmitters released by the vesicles diffuse to the post-synaptic membrane. This is where the communication with the other neuron occur (*i.e.* the synapse).
- Each specific channel inserted in the post-synaptic membrane (*i.e.* the neuroreceptors) responds to a specific neurotransmitter, which is able to activate and open it.
- The opening of a specific channel allows ions, like Na^+ , Ca^{2+} or Cl^- , to flow inside the post-synaptic cell, causing a series of chain reactions, according to the type of stimulus.
- The latter can resolve into either an excitatory or an inhibitory post-synaptic potential (PSP) (Gilbert & Wiesel, 1983), as a specific neurotransmitter enables the transmission of the signal to the target cell (depolarizing its membrane) or disables it (inhibiting the depolarization process) (Carter, 2009). Channels located into either the pre- or the post- synaptic cell are responsible that one process occur instead of another (Carter, 2009).

What we have just described are the most popular type of synapses present in the CNS (Ernst, 2012), the so called axodendritic chemical synapses (Fig. 3.3). However, these are not the only types of synapses present in nature (Ernst, 2012). In reality, based on the place of communication between two cells, we can encounter axodendritic, axosomatic, axoaxonic, dendrodendritic, somatosomatic and somatodendritic synapses (Brady et al., 2011); while, based on the type of transmission, beside the chemical synapses, we can encounter the so called electrical synapses; however, these are really rare in the CNS (FitzGerald, Gruener & Mtui, 2012). These synapses occur by means of gap junctions, channels that permit direct continuity between the cytoplasm of two cells. They allow bidirectional electronic exchange between the pre- and the post-synaptic cell. They

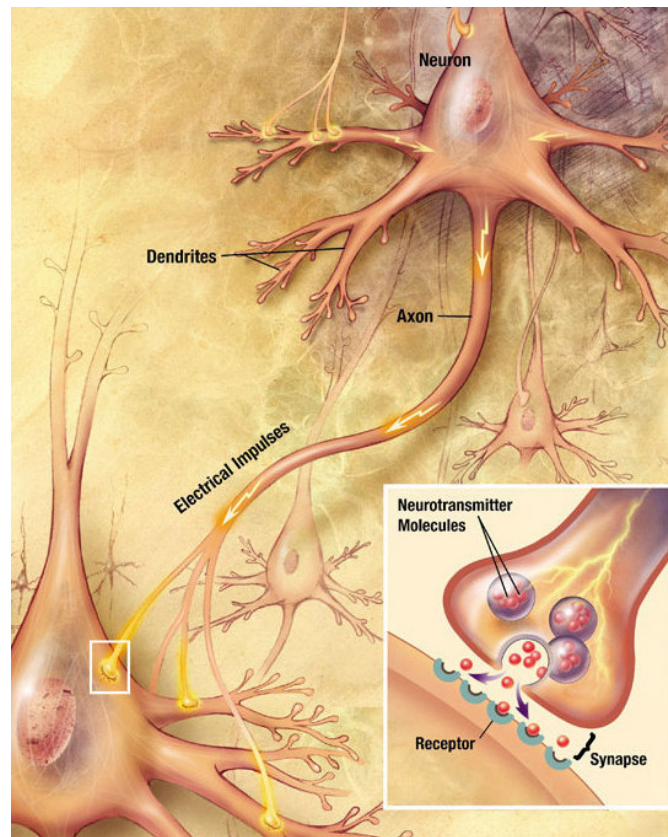


Figure 3.3: The image shows the main elements that determine a chemical synapse. Figure from (National Institute on Aging, 2009) and (Ernst, 2012).

ensure synchronous activity of neurons targeting the same stimulus (FitzGerald et al., 2012).

3.2.4 Neurotransmitters and Neuroreceptors Involvement in the Mechanisms of Learning

Neurotransmitters are molecules that are responsible to carry *stimuli* to the target cell. Once they bind to their corresponding receptors located in the post-synaptic cell's membrane, they can either depolarize the membrane (*i.e.* excitatory current) and propagate the signal, or hyperpolarize it (*i.e.* inhibitory current) and suppress the signal. One or the other occurs depending on the type of neurotransmitter released by the vesicles (Carter et al., 2009).

There are many types of neurotransmitters. The main excitatory neurotransmitter in the CNS is glutamate while the main inhibitory neurotransmitter is γ -aminobutyric acid (GABA) (FitzGerald et al., 2012). The most important neuroreceptors activated by glutamate are the α -amino-3-hydroxy-5-methyl-4-izoxazole-propionic acid receptors (AMPA) and the N -methyl-D -aspartate receptor (NMDAR) (Collingridge & Wang, 2004). The AMPAR mediates fast excitatory synaptic response (Chin, Roberson & Mucke, 2008), while NDMAR is a ligand-gated and voltage-dependent channel (Wieronska, Stachowicz, Nowak & Pilc, 2011). On the other hand, the GABA activates two main classes of neuroreceptors, GABA type A ($GABA_A$) and GABA type B ($GABA_B$). They regulate a fast and a slow inhibition of the neural action potential respectively (Nicoll, Malenka & Kauer, 1990; Mann, Kohl & Paulsen, 2009; Kantamneni, 2015). All these receptors are fundamental for the neural synaptic plasticity, which is strongly related with cognitive processes in the hippocampus.

In the hippocampus, complex biochemical mechanisms mediate and process cognitive activity, like learning and memory, through synaptic plasticity regulation (Brady et al., 2011). Several of those have been encountered to occur in both pre- and post-synaptic cells (Brady et al., 2011). Two phenomena involved in this process are known as long-term potentiation (LTP) and long-term depression (LTD). Memory formation and modelling synaptic plasticity in the mammalian brain is broadly thought to depend on this bidirectional activity (Tsai, Liu, Liu, Cheng & Chen-Jee, 2002; Cooke & Bliss, 2006). LTP is responsible for the transfer of information from short-term memory to long-term memory by means of long and persistent depolarization of the post-synaptic cell's membrane (*i.e.* repetitive firing stimuli); this mechanism is able to increase synaptic transmission efficiency (Lømo, 2003) and was studied by Hebb (Hebb, 1949), who postulated the theory known today as Hebbian learning rule.

These cognitive mechanisms, which have been extensively studied in the literature, involve the release of a high number of glutamate neurotransmitters by the pre-synaptic cell, which in turn provoke the post-synaptic cell to activate enough receptors and increase their synthesis according to the demand (Brady et al., 2011). In this scenario, NMDAR plays a pivotal role, as it is situated in the post-synaptic cell allowing the influx of a significant quantity of stimulatory Ca^{2+} into the cytoplasm (Francis, 2005). In fact, the influx of these cations is believed to start LTP induction by generating a series of cascade events that apparently are responsible to alter synaptic strength (Cooke & Bliss, 2006). NMDAR is a slow excitation receptor and its plasticity depends mainly on the fast excitation of AMPAR (Brady et al., 2011). In more details, glutamate neurotransmitters in the synaptic cleft bind to both NMDAR and AMPAR causing the opening of the latter channel. Subsequently, influx of Na^+ in the post-synaptic membrane causes its depolarization. Whether the depolarization event is strong enough, it can provoke the removal of the Mg^{2+} ion, which obstructs the NMDAR voltage-dependent channel, enabling Na^+ and Ca^{2+} to enter the cell (Cooke & Bliss, 2006) (Fig. 3.4). For this reason, the NMDA receptor is a slow excitation receptor and its plasticity, which determines LTP formation, depends on these properties.

In a single synapse, different types of receptors can be found coexisting (Gerstner & Kistler, 2002; Ernst, 2012). In hippocampal neurons, NMDAR is broadly found to coexist with $GABA_A$ (Shrivastava, Triller & Sieghart, 2011). However, $GABA_B$ can also modulate synaptic plasticity through NMDAR regulation in both pre-synaptic cells, by inhibiting Ca^{2+} and therefore limiting GABA release, and in post-synaptic cells, by mainly cooperating with $GABA_A$ in inhibiting NMDAR activation (Olsen & DeLorey, 1999; Collingridge & Wang, 2004; Kantamneni, 2015). The localization of both glutamate and GABA receptors in post-synaptic cells depends on neurotransmitters

demand, as they are found to move rapidly from where they are synthesized to where they are required in the membrane according to neurotransmitters level (Collingridge & Wang, 2004). The onset of glutamatergic post-synaptic currents suppresses inhibitory functions of GABA receptors and *vice versa*, inhibitory currents increase proportionally with excitatory activation (Y. Shu, Hasenstaub & McCormick, 2003; Haider, Duque, Hasenstaub & McCormick, 2006; Mann et al., 2009). The balance of these two forces modulate the period of the synaptic activity (Compte, Sanchez-Vives, McCormick & Wang, 2003; Mann et al., 2009; Wieronska et al., 2011) and that is why these neuroreceptors are highly correlated and modulated (Shrivastava et al., 2011; Wieronska et al., 2011). This dependency is defined also as “cross-talk” (Shrivastava et al., 2011; Kantamneni, 2015).

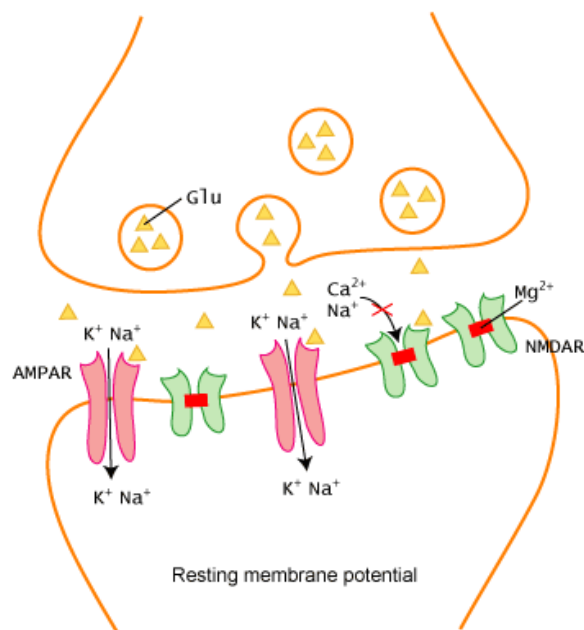


Figure 3.4: The image shows what happens after an action potential arrives at the pre-synaptic terminal. The electro-chemical current causes vesicles containing glutamate neurotransmitters to fuse with the membrane. Once released into the synaptic cleft, the neurotransmitter molecules bind to both AMPAR (in red) and NMDAR (in green). Images from (Diberri, 2004).

Hippocampal neurons mechanisms can be applied to many other neurons encountered in the brain, as they are considered representative of several types of synapses (Collingridge & Wang, 2004). Studying hippocampal activity is of high relevance for the understanding of neurological disorders, as this region is also one of the first to be affected by the onset of MCI and AD. One hypothesis upon AD focuses on the constant activation of NMDAR. High intracellular Ca^{2+} lead to mitochondrial dysfunction (Mohandas, Rajmohan & Raghunath, 2009). Consequently, the constant activation of this receptor leads to a chronic over-activity with an abnormally high synaptic glutamate level under resting condition and therefore a low amount of neurotransmitters left to be released into synaptic cleft during neural activity (Francis, 2005). These happenings lead to cellular dysfunction and neural death over a period of time (Mohandas et al., 2009).

The study of neural plasticity and its biochemical counterpart is fundamental for the analysis and understanding of cognitive brain activity and consequently the information provided by the STBD collected. In this thesis, we challenge ourselves by applying the main principles related to axodentritic chemical synapses to classify and extract new knowledge from the neural processes that generate the EEG data by means of SNN techniques.

3.3 Computational Models of a Spiking Neuron

Computer simulation has become one of the most powerful and relevant tools for the study and understanding of the mammalian brain. It significantly contributes to the discovery of new knowledge related to structure through dynamic simulation, and also allows for the reproduction of certain scenarios, which would be impossible to develop *in vivo* (Izhikevich & Edelman, 2008). Thus, the human brain has become a model to copy, a source of inspiration for researchers and especially for information scientists.

One of the valuable techniques being used *in silico* investigations over the last six decades is the machine-learning technique and specifically SNNs (Fig. 3.5). This computational technique is inspired by the human nervous system and it represents the third generation of the perceptron algorithm proposed by (Rosenblatt, 1957), an artificial neuron able to linearly classify real-valued input data into discrete binary events. Some of the main advantages that SNN techniques provide are: compact representation of space and time; fast information processing; time-based and frequency-based information representation; they are memory-based, so that they can be studied after training for data understanding (Kasabov, 2014a).

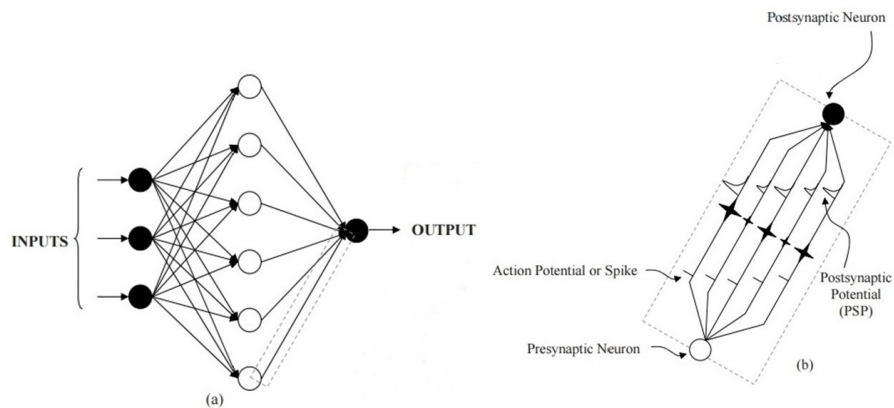


Figure 3.5: The image (left) shows a network of artificial spiking neurons represented as circular nodes. The arrows represent the neural connection from the output of one neuron to the input of another. The image (right) represents how in a synapse the connection weight increases as a consequence of a series of incoming spikes, which generates delayed PSPs. This process resembles the behaviour of a neural cell. Images are from (Ghosh-Dastidar & Adeli, 2007).

In the mammalian brain, neurons receive, analyse and transmit information *via* electrochemical signals. Synapses are where neurons exchange these signals between each other. In a network of artificial spiking neurons this process is computed using a mathematical function; thus each artificial neuron represents a computational unit of the network. Neural activity recorded from the brain, like EEG signals, is encoded in

the model as binary events (*i.e.* the spikes). The neurons (or nodes of the network) are interconnected and their spiking activity influences the neighbouring neurons. In this model, the spatio-temporal information is learnt from the encoded train of spikes and the synaptic connections between neurons of the network are modified accordingly *i.e.* the connection weight or efficiency of a synapse increases or decreases as a consequence of a series of incoming spike inputs, which are summed at each node of the network. It is how the spiking activity is computed in the neuron that identifies the different types of computational models of spiking neurons available.

3.3.1 Neuronal Models

Some significant neural models well known in the area of neuroscience and neural computation are:

- Hodgkin-Huxley Model
- Transmitter-Activated Ion Channels Synapses
- Synaptic Transmission Model
- Integrate-and-Fire Model
- Leaky Integrate-and-fire
- Izhikevich Model
- Thorpe's Model
- Probabilistic Spiking Neural Model
- Computational Neurogenetic Model

Hodgkin-Huxley Model

In 1952, the English scientists Alan L. Hodgkin and Andrew Huxley described in a series of studies (Hodgkin & Huxley, 1952c; Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952b, 1952a) a model of a spiking neuron by studying the electrochemical forces that mediate neural signalling in the giant axon of a squid. Their study described how the ionic current created by Na^+ and K^+ cations and a small “leakage” current created by Cl^- and/or other ions control the initialization and propagation of the action potential through the cell membrane (Hodgkin et al., 1952). This mechanism is described as an electrical circuit, which consists of a capacitor C , input sources I , resistors R and batteries E (Fig. 3.6). The model describes changes in membrane capacitance as a function of voltage V_m and input current described in a series of complex differential equations, including:

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_L (u - E_L) + I(t) \quad (3.1)$$

$$\tau_n \frac{dn}{dt} = -[n - n_0(u)] \quad (3.2)$$

$$\tau_m \frac{dm}{dt} = -[m - m_0(u)] \quad (3.3)$$

$$\tau_h \frac{dh}{dt} = -[h - h_0(u)] \quad (3.4)$$

where g_{Na} , g_K and g_L are the sodium, potassium and leakage conductance respectively; E_{Na} , E_K and E_L are the equilibrium potential for the sodium, potassium and the leakage current respectively; and m , n , h are dimensionless variables, which depends on other three differential equations (Awad & Khanna, 2015). This model can be considered

the *basis* of all the other models (Awad & Khanna, 2015); however, due to its complex mathematical nature, other models have been developed and become more popular for their simple computational implementation.

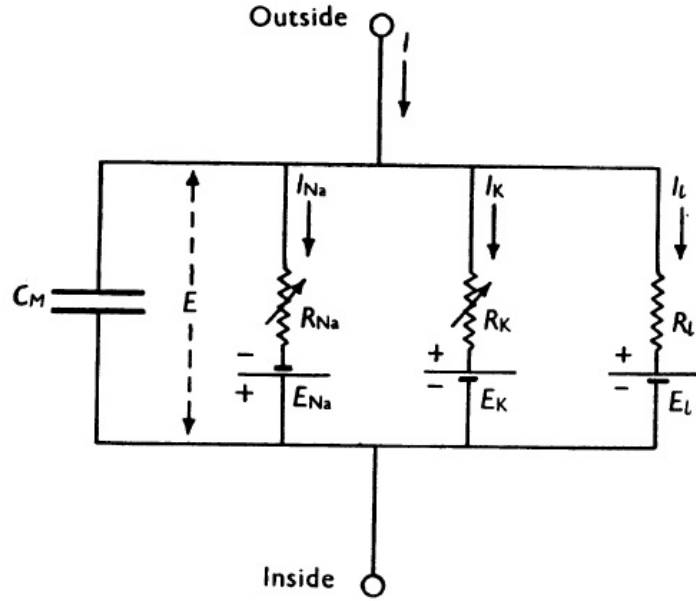


Figure 3.6: Hodgkin-Huxley model of a neural membrane described as an electrical circuit, where the cell membrane acts as a capacitor C_M that separates the inside of the cell from the outside cytoplasm where the input current I comes from. The Na^+ , K^+ and leakage L currents act as resistors R between the membranes. Image from (Hodgkin et al., 1952).

Transmitter-Activated Ion Channels Synapses

The *transmitter-activated ion channels synapses*, described in (Gerstner & Kistler, 2002), are an evolution of the Hodgkin-Huxley model (Hodgkin et al., 1952). This model proposes synaptic modifications based on neurotransmitters release and on the consequent activation of their neuroreceptors. These are responsible for the onset of either excitatory or inhibitory post-synaptic currents, named EPSC and IPSC respectively. Transmitters-activated ion channels synapses are described as time dependent, as the channels conductivity $g_{syn}(t)$ depends on the arrival of a pre-synaptic action potential. The following equation describes the current I dependence on the reverse

potential E and the actual membrane potential u for different type of synapses:

$$I_{syn}(t) = g_{syn}(t)(u - E_{syn}) \quad (3.5)$$

The conductance of inhibitory GABAergic synapses is also described as function of a fast and a slow component that decay with the time, as follows:

$$g_{syn}(t) = \sum_f \left(\bar{g}_{fast} e^{-(t-t^{(f)})/\tau_{fast}} + \bar{g}_{slow} e^{-(t-t^{(f)})/\tau_{slow}} \right) \Theta(t - t^{(f)}) \quad (3.6)$$

while the conductance of excitatory glutamatergic synapses in cerebral granular cells is described as function of a fast and a slower response regulated by AMPA and NMDA receptors respectively:

$$g_{AMPA}(t) = \bar{g}_{AMPA} \cdot N \cdot \left[e^{-(t-t^{(f)})/\tau_{decay}} - e^{-(t-t^{(f)})/\tau_{rise}} \right] \Theta(t - t^{(f)}) \quad (3.7)$$

$$g_{NMDA}(t) = \bar{g}_{NMDA} \cdot N \cdot \left[e^{-(t-t^{(f)})/\tau_{decay}} - e^{-(t-t^{(f)})/\tau_{rise}} \right] g_{\infty} \Theta(t - t^{(f)}) \quad (3.8)$$

Where g_{∞} represents the channel dependency of the Mg^{2+} blockage and is described as $g_{\infty} = (1 + e^{\alpha U} [Mg^{2+}]_o / \beta)^{-1}$. All the other parameters, such as N and Θ , are numerical constants (see (Gerstner & Kistler, 2002) for more details).

Synaptic Transmission Model

Another relevant extension of the Hodgkin-Huxley model (Hodgkin et al., 1952) is the *synaptic transmission model* proposed by (Koch & Segev, 1998). Koch & Segev modulate the dynamic of LTP and LTD in learning mechanisms based on neuroreceptors kinetic currents. In this model a series of equations are proposed to modulate fast

and slow activation of both excitatory *AMPA* and *NMDA* receptors, and inhibitory *GABA_A* and *GABA_B* receptors respectively. The ionic currents I are calculated as follows:

$$I_{AMPA}(t, V) = \bar{g}_{AMPA} \cdot [O] \cdot (V(t) - E_{AMPA}) \quad (3.9)$$

$$I_{NMDA}(t, V) = \bar{g}_{NMDA} \cdot B(V) \cdot [O] \cdot (V(t) - E_{NMDA}) \quad (3.10)$$

$$I_{GABA_A}(t, V) = \bar{g}_{GABA_A} \cdot ([O_1] + [O_2]) \cdot (V(t) - E_{Cl}) \quad (3.11)$$

$$I_{GABA_B}(t, V) = \bar{g}_{GABA_B} \cdot \frac{[G]^n}{[G]^n + K_d} \cdot (V(t) - E_K) \quad (3.12)$$

Where, for every neuroreceptor, E and $\bar{g}$ identify the equilibrium potential and the maximal conductance respectively; $[O]$ is the fraction of active receptor (*e.g.* as NMDAR is blocked by Mg^{2+} this is expressed by the term $B(V)$); and $[G]$ is the concentration of the G-protein activated by ion K^+ necessary for the activation of the metabotropic receptor *GABA_B*.

Integrate-and-Fire Model

This model is based on the neuronal model proposed by Luise Lapicque in 1907 (Lapicque, 1907; Brunel & van Rossum, 2007), long before the modern concept of action potential was known; however, the term integrate-and-fire was first used by (Knight, 1972). It presents a simplified mathematical model with respect to the Hodgkin-Huxley equations, as it considers all action potentials constant, but with a different time of occurrence (Fig. 3.7). In (Awad & Khanna, 2015), this model is expressed in terms of its membrane capacitance C and potential $u(t)$, as follows:

$$C \frac{du}{dt} = -\frac{1}{R}(u(t) - u_{rest}) + I(t) \quad (3.13)$$

$$u(t^{(f)}) = \theta \quad \text{when} \quad u'(t^{(f)}) > 0 \quad (3.14)$$

where R is the resistor, u_{rest} is the resting potential of the membrane; θ is the neuron firing threshold; $t^{(f)}$ is the time at which the spikes are emitted, $u(t^{(f)})$ describes the membrane potential of firing neuron, $u'(t^{(f)})$ is its derivative; and $I(t)$ is the input current (Awad & Khanna, 2015).

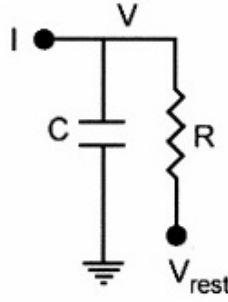


Figure 3.7: The image depicts the integrate-and-fire circuit, where C , R , V and V_{rest} identify the membrane capacitor, resistor, potential and resting potential respectively. The input current is denoted as I . Image from (Abbott, 1999).

Leaky Integrate-and-Fire Model

This model, called “forgetful” Integrate-and-Fire model by (Knight, 1972), adds to the constant potential described above a decaying period term. This is subtracted from the membrane potential $u(t)$ over time, when no incoming spikes are received by the neuron. A leaky integrate-and-fire (LIF) neuron emits a spike at a time $t^{(f)}$, when its potential $u(t)$ reaches a threshold θ and $u'(t^{(f)}) > 0$. After a spike is emitted, $u(t)$ “leaks”,

as a biological neuron does, entering in refractory period, where no new spike can be emitted, as the current is hyperpolarized. During this period, which lasts for a time d_{abs} , the potential is calculated as $u(t) = -u_{abs}$, where u_{abs} defines the refractoriness potential. The membrane reaches its resting potential u_{rest} again, after d_{abs} expires. This model can be also represented as an electrical circuit, where all ionic currents presented in the Hodgkin-Huxley model are considered as one individual current (Fig. 3.8).

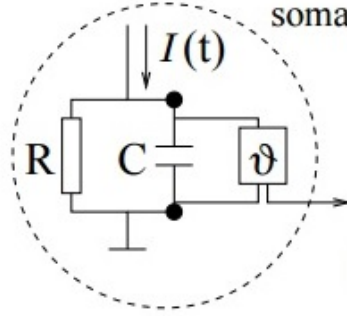


Figure 3.8: The diagram depicts the LIF model circuit. C , R , I and θ identify the membrane capacitor, its resistor, the input current and the threshold of firing respectively. Image from (Gerstner & Kistler, 2002).

In the LIF, the neuron action potential is calculated according to the following equation:

$$\tau_m \frac{du}{dt} = u_{rest} - u(t) + RI(t) \quad (3.15)$$

where τ_m , u_{rest} , $I(t)$ and R are the membrane time constant, its resting potential, the input current and the neural model's resistance.

The LIF neuron model is really popular in SNN techniques (Gerstner & Kistler, 2002), as it still maintains the biological plausibility, but it also improves the technique by making it less computationally expensive.

Izhikevich Model

In 2003, Eugene M. Izhikevich developed a model (Izhikevich, 2003) by combining the biological principles introduced by Hodgkin-Huxley and the computational efficiency of the integrate-and-fire model. In this model, he achieved an almost identical reproduction of firing patterns of neurons registered in a rat's motor cortex (Fig. 3.9). The model uses two differential equations to describe the membrane potential activity:

$$\frac{dv}{dt} = 0.04v(t)^2 + 5v(t) + 140 - u(t) + I(t) \quad (3.16)$$

$$\frac{du}{dt} = a(bv(t) - u(t)) \quad (3.17)$$

When the membrane action potential reaches a threshold $\theta=30\text{mV}$, then a spike is generated and v and u are reset according to the following equation:

$$\text{if } v \geq \theta \quad \text{then} \quad \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \quad (3.18)$$

In the equations, v represents the membrane potential and u is the membrane recovery variable, which provides negative feedback to v and resembles K^+ activation and Na^+ inactivation ionic currents respectively; and a , b , c and d are dimensionless parameters.

Several variants and extensions of the Izhikevich model have been proposed (Izhikevich, 2006; Izhikevich & Edelman, 2008); especially interesting is the work proposed by (Teramae & Fukai, 2007), where the general input current $I(t)$ described in equation 3.16 is expressed as a function of the excitatory or inhibitory conductances of AMPA and Gabaergic synapses respectively (Teramae & Fukai, 2007). In this model,

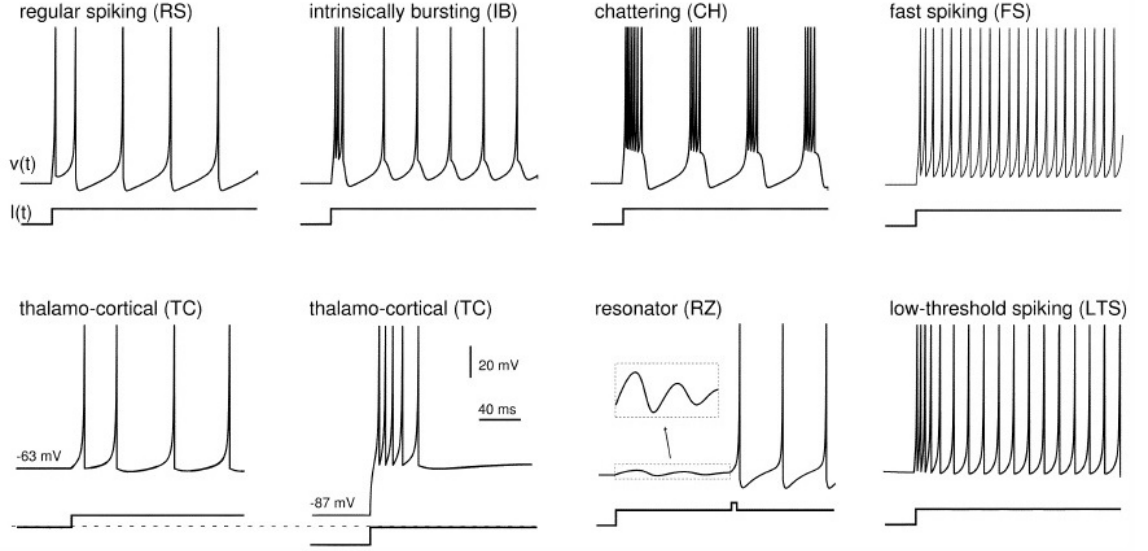


Figure 3.9: The image describes the different dynamic obtained by the Izhikevich model using different values of a, b, c, d parameters. Regular spiking (RS), intrinsically bursting (IB), and chattering (CH) represent cortical excitatory neurons. Fast spiking (FS) and low-threshold spiking (LTS) represent cortical inhibitory interneurons. Image from (Izhikevich, 2003).

the membrane potential v is calculated as follows:

$$\dot{v} = 0.04v^2 + 5v + 140 - u - g_{AMPA}(v - 0) - g_{GABA}(v + 70) \quad (3.19)$$

$$\dot{u} = a(bv - u) \quad (3.20)$$

The parameters a and b that influence the membrane recovery variable u are calculated as different constants for both excitatory and inhibitory neurons; and the net conductance $\dot{g}$ derives from:

$$\dot{g} = -\frac{g}{\tau} + g_{XY} \sum \delta(t - t_{spikes}) + g_{XY,b} \sum \delta(t - t_{random}) \quad (3.21)$$

In the equation, τ is a time constant that differs for excitatory and inhibitory neurons.

When v reaches the threshold $\theta=30\text{mV}$, then v and u are reset according to the parameters

c and d , which are also calculated as different constants for both AMPA and GABAergic synapses.

In Teramae & Fukai model, the synaptic connection between excitatory neuron j and inhibitory neuron i are generated as:

$$g_{ij} = \sum_{\mu=1}^P \sum_{k=1}^{l(\mu)-1} \xi_i^{\mu,k+1} \eta_j^{\mu,k} \quad (3.22)$$

Where P is the total number of synfire chain developed (*i.e.* the number of multi-layered feedforward subnetworks of neurons, which ensemble the main network) (Abeles, 1991); $l(\mu)$ is the length of the μ -number of chains; $\xi_i^{\mu,k} = \{\xi_i^{\mu,k}\}_{i=1,\dots,N}$ is a vector of neurons i that are inside the k -layer of the μ -synfire chain; and $\eta_j^{\mu,k}$ is a vector derived by the previous one.

Thorpe's Model

In the 1990, Simon J. Thorpe proposed a variation of the LIF model (Thorpe, 1990; Thorpe & Gautrais, 1998), where the PSP of a neuron only depends on the order of the incoming pre-synaptic spikes and early spikes have grater influence on the PSP then subsequent spikes. Stimuli and firing order are strongly correlated, especially in the visual cortex (Hubel & Wiesel, 1962; Thorpe & Gautrais, 1996; Thorpe, 1997, 1998), as only few spikes alone are actually capable of accomplishing complex processes. In this model the neuron PSP is calculated as follows:

$$PSP_i = \sum w_{ji} * mod^{order_j} \quad (3.23)$$

$$\Delta w_{ji} = mod^{order_j} \quad (3.24)$$

Where w_{ji} is the connection weight between neuron j and neuron i ; mod is a modulator

factor $\in [0, 1]$; $order_j$ is the rank order of the pre-synaptic neuron j , with $j \in [1, n - 1]$, where n is the number of neurons j connected to i .

The post-synaptic neuron i emits a spike when its PSP reaches the threshold θ , then it is reset immediately to 0 (*i.e.* the refractory time is disregarded in the model). Thus, the PSP is calculated as follows:

$$PSP_i = \begin{cases} PSP_i + P_{ji} & \text{when } PSP_i < PSP_{\Theta i} \\ 0 & \text{when } PSP_i \geq PSP_{\Theta i} \end{cases} \quad (3.25)$$

Where P_{ji} is the increment in strength of a connection between two neurons j and i . The computational simplicity of the model makes it really suitable for different applications, such as (Van Rullen, Gautrais, Delorme & Thorpe, 1998; Delorme & Thorpe, 2001; Thorpe, Delorme & VanRullen, 2001), as it is able to achieve fast and real-time simulation even in large neural networks.

Probabilistic Spiking Neural Model

N. Kasabov proposed in 2010 the probabilistic spiking neural model (pSNM) (Kasabov, 2010). This model adds to the synaptic connection weight $w_{j,i}(t)$, calculated according to the Thorpe's model, three probabilistic constraints (Fig. 3.10), defined as follows:

- a probability $p_{cj,i}(t)$ that a spike emitted from the pre-synaptic neuron j will reach the post-synaptic neuron i , which attributes to each connection a structural and functional uncertainty.
- a probability $p_{sj,i}(t)$ that a synapse $s_{j,i}$ contributes to the $PSP_i(t)$ after a spike is received, due to biochemical processes involved in the synaptic mechanism.
- a probability $p_i(t)$ that i will emit a spike after the threshold of the total $PSP_i(t)$

has been reached, which is known as the probability density for firing in a neural cell.

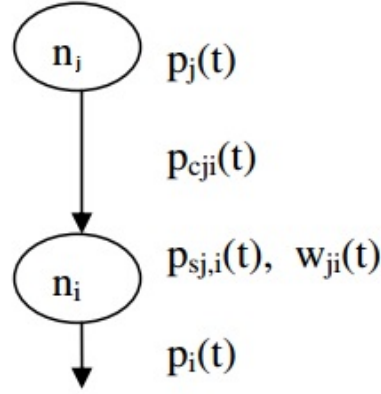


Figure 3.10: The image represents the connection between a pre-synaptic neuron j and a post-synaptic neuron i of a pSNM. Image from (Kasabov, 2010).

Then, the total $PSP_i(t)$ is calculated according to the following equation:

$$PSP_i(t) = \sum_{p=t_0, \dots, t} \sum_{j=1, \dots, m} e_j g(p_{cj,i}(t-p)) f(p_{sj,i}(t-p)) w_{ji}(t) + \eta(t-t_0) \quad (3.26)$$

Where $e_j = 1$, when a spike has been emitted from j , or $e_j = 0$ otherwise; the probability terms - $g(p_{cj,i}(t))$ and $f(p_{sj,i}(t))$ - are equal to 1, when the probability of their occurrence exists, otherwise they are 0; t_0 is the time of last spike emitted by i ; $\eta(t-t_0)$ is the decaying term associated to the PSP.

When all the probability parameters are set to 1, the pSNM is simplified as the LIF model.

Computational Neurogenetic Model

N. Kasabov also proposed a model of a spiking neuron that integrates the pSNM (Kasabov, 2010) with the neurogenetic model introduced by (Benuskova & Kasabov,

2007; Kasabov, Benuskova & Wysoski, 2005). In this model, the total PSP of a neuron is calculated as the contribution of four different types of synapses that affect the connection between neuron j and neuron i , as follows:

$$\xi_{ij}^{synapse}(s) = A^{synapse} \left(\exp\left(-\frac{s}{\tau_{decay}^{synapse}}\right) - \exp\left(-\frac{s}{\tau_{rise}^{synapse}}\right) \right) \quad (3.27)$$

Where ξ_{ij} is the PSP calculated for one of the four types of synapses of a neuron; $\tau_{decay/rise}^{synapse}$ are time constants, which represent the rise and fall of either a fast excitation, or a fast inhibition, or a slow excitation, or a slow inhibition synapse, established by *AMPA*, *GABA_A*, *NMDAR* and *GABA_B* respectively; A is the amplitude of the PSP; $\xi_{ij}^{synapse}(s)$ represents the type of activity of the synapse, which is affected by different genes and/or proteins, and can be measured and modelled separately for each type of synapse (Kasabov, 2014a).

When all the probability parameters or some of them are set to 1, and gene expression data are not available, the model is reduced to the LIF model. Alternatively, a dynamic gene/protein regulatory network (GRN) model organised as an ANN can be added to study the dynamic interactions between genes/proteins over time and how they affect the action potential of the neurons of the network.

3.3.2 Information Encoding in a Spiking Neuron

As showed in Fig.3.5, SNN architectures consist of an input layer, a hidden layer, and an output layer. Similarly to dendrites of a neural cell, the input layer is where the original *stimuli* are converted into a new number of features, which are then transmitted into the neurons of the hidden layer. It is crucial for the whole process how the data is processed in this first stage and the continuous real valued inputs converted into discrete trains of spikes. This process is called: “input encoding” (Ghosh-Dastidar & Adeli,

2007). Not only does the input data need to be encoded, but so does the output of the encoded information. Several encoding schemes have been proposed for both input and output data. While the first two generations of ANN used *rate* coding to compute neurons' output signals (*i.e.* averaging the firing rate, the temporal information, for a individual neuron), in SNNs *pulses* of spikes are used as encoding scheme (Maass & Bishop, 2001; Gerstner & Kistler, 2002; Vreeken, 2003).

Neural cells use action potentials to encode and transmit the information. This can be seen as a spike or pulse, which contains precise spatio-temporal information used by the neuron to encode their message that is then transmitted to another neuron (Maass, 1997; Gerstner, Kempter, Hemmen & Wagner, 1999; Vreeken, 2003; Bohte, 2004). It is well assumed that neural signalling is not due to frequency transmission only (rate coding), but the “code” is rather transmitted, at least partially, *via* precise timing of individual spikes (Bohte, 2004). Different schemes that use pulse timing information have been proposed (Fig. 3.11). They differ from each other in the way they believe the exact timing of the spike is transmitting the code. For instance:

- The *latency coding*, which recognises that it is the precise timing of a series of analogous spikes responsible for containing the information (Maass, 1997).
- Contrary to the above, the *rank order coding* considers the order of the incoming spike responsible for carrying the information (Thorpe & Gautrais, 1998; Delorme, Gautrais, van Rullen & Thorpe, 1999).
- The *synchrony code* is based on the principle that neurons spikes occur synchronously (*i.e.* as a population of spikes), as a consequence of a unique *stimulus* that evokes potent post-synaptic responses (Izhikevich, 2006), or to organize together different parts of the same information, which is not conveyed by the firing rate only (Sejnowski, 1999).

- The *resonant burst coding* believes that bursts (*i.e.* the generation of a group of subsequent spikes by a neuron) with certain resonant frequency oscillations influence post-synaptic activity and increase the character of the neural communication (Izhikevich, Desai, Walcott & Hoppensteadt, 2003).

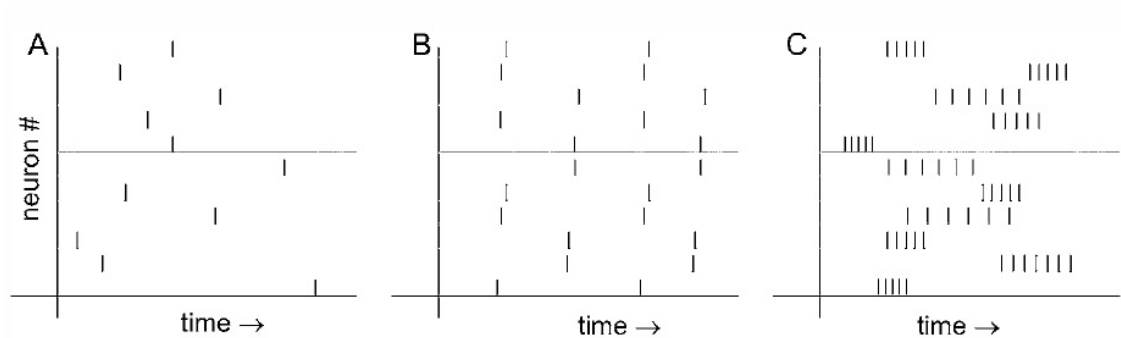


Figure 3.11: The image compares latency coding (A), with synchrony coding (B) and with burst-coding (C). Image from (Bohte, 2004).

Some popular encoding algorithms applied in SNN techniques are:

- address event representation (AER) (Delbruck, 2007; Chan et al., 2007; Dhoble et al., 2012).
- Ben's spiker algorithm (BSA) (Schrauwen & Van Campenhout, 2003; Nuntalid et al., 2011).
- population rank -coding (Bohte, 2004).

The main limitation related to input/output encoding schemes is the association of only one action potential per neuron (Ghosh-Dastidar & Adeli, 2007); however, a neural cell may have different types of spikes associated with different areas of its membrane (Brady et al., 2011).

3.3.3 Learning in SNN

Several difficulties emerge when training SNNs, as it is highly computationally expensive compared to traditional ANN techniques (Ghosh-Dastidar & Adeli, 2007). This is due to the mechanism responsible for the connection weight updating, which needs to be computed for all the synapses that connect a pre-synaptic neuron to a post-synaptic one; additionally, the simulation time (*i.e.* the simulation of the internal state of each neuron) needs to be computed continuously, which consequently affects the total computation time necessary to train the network (Ghosh-Dastidar & Adeli, 2007). Moreover, the error generated by small changes in PSP, has a high impact upon the output spike time of the post-synaptic neuron.

These problems have been approached in different ways, which generated different learning rules. Three different types of learning can be distinguished in SNNs:

- *Supervised learning.* In supervised learning both input data and desired outputs (*e.g.* a class label for classification problems or real numbers for regression problems) are given and the aim is to learn to produce a correct output for every new input (Ghahramani, 2004). Some examples of popular supervised learning algorithms are: the rank-order (RO) (Thorpe & Gautrais, 1998) learning rule, the Fusi's spike driven synaptic plasticity (SDSP) learning rule (Fusi, 2002), and error-backpropagation (SpikeProp) (Bohte, Kok & La Poutre, 2000).
- *Reinforcement learning.* The goal of the training is to produce "actions" and consequent "rewards" or "punishments" according to the success of the learning process (Ghahramani, 2004). Reinforcement learning is less popular than the other two types of training. It is mainly used in the field of decision theory, such as statistics and management science.

- *Unsupervised learning*. This training is based on learning only from unlabelled input patterns in order to interpret the output data and organize it in a way that can be used in applications such as decision making, prediction etc.

In this thesis, we are especially interested in applying unsupervised training approaches to an SNN environment for the purposes of extracting new information from the data analysed in a way that is biologically plausible and computational affordable.

Unsupervised Learning in SNN

Several unsupervised learning algorithms have been proposed. Most of them modify the synaptic activity based on global competition (*i.e.* between neurons' pre- and post-synaptic action potentials) as per the Hebbian type of learning (Hebb, 1949). Example of this is the *spike time dependent plasticity (STDP) learning rule* and its extensions. Other unsupervised learning algorithms are based on local competition (*i.e.* at a synaptic connection) through either synaptic current modifications, such as the *transmitter-activated ion channels synapses* and the *synaptic transmission model*; or dynamic mechanisms involving non-Hebbian rise and fall terms, such as the *phenomenological model of dynamic synapses* and the *activity-dependent synaptic scaling*.

The *STDP* learning rule is by far the most popular unsupervised training method applied in SNN techniques. Synaptic modifications are elicited through STDP-like rules as they accentuate the temporal character of the spike event (Awad & Khanna, 2015). The theory of STDP states that pre-synaptic activity that precedes post-synaptic firing can induce LTP, reversing this temporal order results in LTD (Markram et al., 2011). In (Song, Miller & Abbott, 2000), the STDP learning rule is described by the following

equation:

$$F(\Delta t) = \begin{cases} A_+ \exp(\Delta t / \tau_+) & \text{if } \Delta t < 0 \\ -A_- \exp(-\Delta t / \tau_-) & \text{if } \Delta t \geq 0 \end{cases} \quad (3.28)$$

Where $F(\Delta t)$ is the connection weight or the synaptic modification that occurs during a time Δt (*i.e.* from the arrival of the pre-synaptic spike to the moment that the post-synaptic spike is emitted); the parameters τ_+ and τ_- represent the decay constants in exponentials between the pre- and the post- synaptic spike respectively (when the synaptic connection strengthens, during LTP, or weakens, during LTD); and the parameters A_+ and A_- represent the maximum synaptic modification for $\Delta t \approx 0$. These four parameters need to be adjusted according to the neural model. In Fig. 3.12, we can observe how the synaptic modification changes according to the spike timing between a pre- and a post- synaptic action potential.

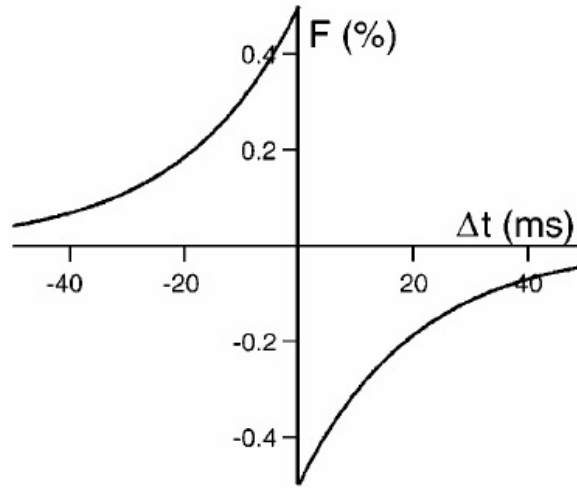


Figure 3.12: The graph represents the change in conductance F with respect to the time Δt during a pre- and post- synaptic action potential. We can observe how the synaptic modification depends on the spike timing. Image from (Song et al., 2000).

An interesting extension of the STDP rule, also discussed by (Mayr, Partzsch & Schuffny, 2009), is the *STDP model of metaplasticity* proposed by (Benuskova & Abraham, 2007). This model describes the spontaneous activity that occurs in the dentate gyrus combining the STDP rule with the Bienenstock, Cooper and Munro (BCM) sliding LTP/LTD modification threshold. The dentate gyrus is situated in the hippocampus and is responsible for differential storage of similar experiences and contexts (Stella, Cerasti & Treves, 2015). In this model, excitatory and inhibitory changes of synaptic weight, or, in other words, the amplitude of positive A_+ and negative A_- synaptic connection, are modified proportionally to the postsynaptic spiking activity of a neuron over some recent past.

The *phenomenological model of dynamic synapses* has been proposed by (Tsodyks et al., 1998). In this model, the synaptic modification is described in term of depression and facilitation of biochemical mechanisms. In other words, the release of a particular neurotransmitter by the pre-synaptic cell is responsible of decreasing or increasing the post-synaptic response, which in turn regulates the information transmission between neurons. This *phenomenon* was observed when stimulations occurred during a short period of time (Abbott, Varela, Sen & Nelson, 1997; Tsodyks & Markram, 1997; Torres & Kappen, 2013).

The *activity-dependent synaptic scaling* mechanisms have been discussed by (Turrigiano et al., 1998). This model also describes biochemical *phenomena* considered responsible for long-lasting changes in synaptic plasticity that determine memory formation. Such changes regulate synaptic strength through homeostatic scaling *i.e.* by increasing or decreasing neurotransmitters release or inducing alteration of their neuroreceptors in order to stabilise neuron's firing rate (Turrigiano et al., 1998; Desai, Cudmore, Nelson & Turrigiano, 2002).

3.4 Summary

This chapter introduces some of the main principles that regulate neural synaptic plasticity; additionally, it also introduces some of the models and techniques used in the SNN machine learning field of research, in order to justify the methods used in this thesis to address the research questions.

SNN methods and techniques provide a solid background for the development of new, brain-like information methods and systems for STBD. A model, able to take into account data feature and that is also biologically plausible and anatomically accurate, would offer the advantage of a better understanding of the data and the processes that generate them.

All of these challenges are being addressed in this study by the means of the SNN NeuCube model. This model is presented in details in the next chapter and is used in this thesis to develop new methodologies for cognitive EEG data modelling, classification and understanding.

Chapter 4

The NeuCube SNN Architecture for Modelling Spatio-/Spectro-Temporal Data

4.1 Introduction

Chapter 3 discusses how neuroscientific notions have been used by IS researchers to develop new SNN techniques. It also explains why SNNs are valuable methods to mine STBD properly and to advance brain data modelling and improve our knowledge about synaptic and neural processes.

In this chapter, Section 4.2 presents an eSTDM implemented in the Knowledge Engineering and Discovery Research Institute of the Auckland University of Technology by Prof.N.Kasabov and his group. It is named NeuCube. The NeuCube architecture is used in this research to develop novel methodologies for EEG data modelling, classification and interpretation, especially by gaining new knowledge from the neural functional pathways that generated the collected data.

A paper about eSTDMS based on the NeuCube architecture (Kasabov et al., 2015) has been submitted, peer-reviewed and accepted by *Neural Networks Journal* Special Issue: *Neural Network Learning in Big Data*. Copyright and permission from the publisher of the paper are included in Appendix B and full text of the preprinted version of the paper is provided in Appendix A.1.

4.2 NeuCube: Neurocomputing Development Architecture for Spatio-/Spectro-Temporal Data Processing

The introduction of a new eSTDM based on neuromorphic, brain-like SNN information processing principles, the NeuCube architecture (Kasabov, 2014a), resulted from the development of the evolving SNN (eSNN) architecture proposed by (Kasabov, 2007; Wysoski, Benuskova & Kasabov, 2010). Thus, the NeuCube architecture is part of the evolving connectionist systems (ECOS), multi-modular, adaptive and knowledge representation computer systems based on neural networks (Kasabov et al., 2015).

The whole NeuCube system works in an integrated mode for spatio-/spectro- temporal data pattern recognition and it consists of the following 10 modules:

- Module M1, for generic prototyping and testing.
- Module M2, with a pySNN simulator for small and large scale applications.
- Module M3, with a neuromorphic hardware for real time execution.
- Module M4, for 3D visualisation and mining.
- Module M5, where input/output information exchange.

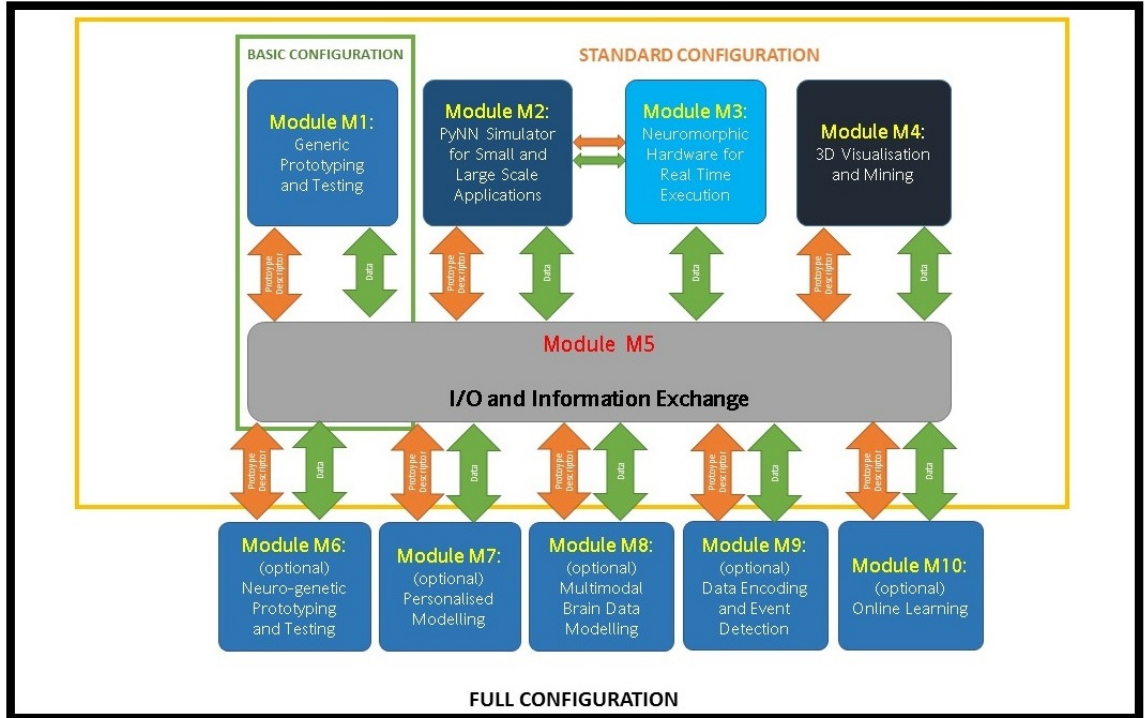


Figure 4.1: The conceptual diagram of the NeuCube multimodular development architecture for Spatio-/Spectro-Temporal data modelling with its 10 modules. The picture shows the NeuCube interface and relationship between the core and optional modules; it also identifies the NeuCube basic configuration (module M1), its standard configuration (module M1-M5) and its full configuration (module M1-M10). Figure from (Kasabov et al., 2015).

- Module M6, for neurogenetic prototyping and testing (optional).
- Module M7, for personalised modelling (optional).
- Module M8, for multi-modal brain modelling (optional).
- Module M9, for data encoding and event detection.
- Module M10, for on-line learning.

Figure 4.1 schematized the NeuCube architecture with its 10 modules and how information is exchanged between them.

This eSTDM system works based on the following scheme:

- It converts multiple features of input data into trains of spikes;
- The encoded spatio-temporal patterns are then learned in an SNN cube using unsupervised training;
- By supervised learning, the output data is classified (*i.e.* labelled) into the corresponding classes or regression variables;
- When necessary, the evaluated/tested output is optimized in an iterative way in order to improve the classification/regression accuracy.

4.2.1 The NeuCube Architecture for Modelling STBD

The basic configuration of the NeuCube (module M1) for STBD modelling and understanding was initially proposed in (Kasabov, 2012b) and then further developed in (Kasabov, 2014a; Chen et al., 2013; Tu et al., 2014). A diagram of the three main sub-modules of the NeuCube module M1 is depicted in Fig. 4.2. It consists of the following sub-modules:

- Input information encoding sub-module, where input data are encoded into trains of spikes that are then presented to the main sub-module.
- 3D spiking neural network cube (SNNc) sub-module (the Cube), where time and space characteristics of the STBD are captured and learned.
- Output sub-module for data classification (or regression) and new knowledge discovery from the SNNc visualization.
- GRN sub-module (optional).

In the encoding sub-module, the available STBD, ordered as vectors of real-valued data, are converted into trains of spikes using one of a number of algorithms, including

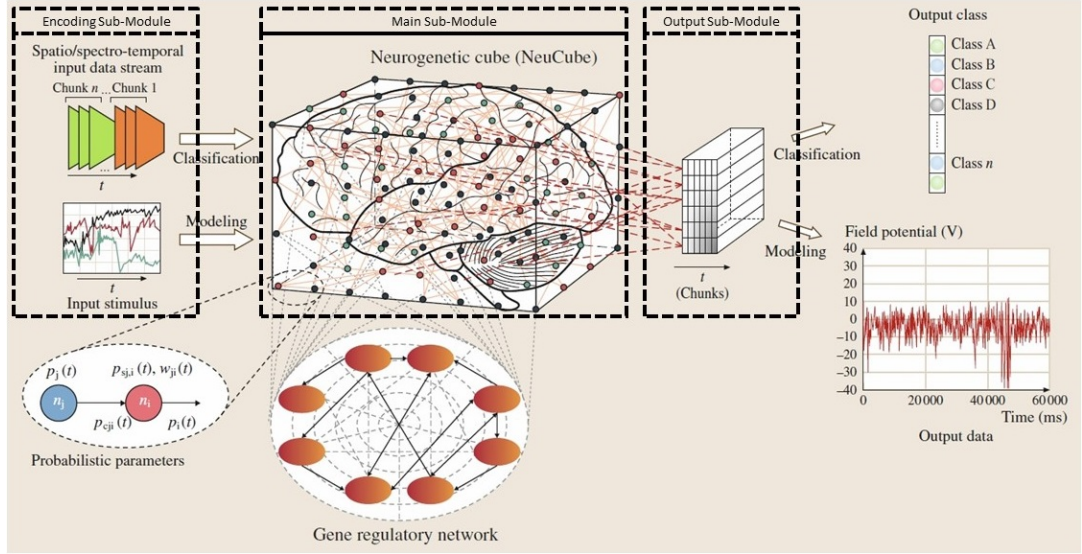


Figure 4.2: The NeuCube module M1 for STBD modelling with its three main sub-modules: input data encoding sub-module; a 3D SNN cube sub-module; an output evolving classification sub-module (Kasabov, 2014a). An optional GRN sub-module can be incorporated if gene information is available. The spiking neurons can be simple LIF neurons or probabilistic neurons (lower left hand-side of the image). Figure from (Kasabov, 2015).

AER algorithm (Delbruck, 2007; Chan et al., 2007; Dhoble et al., 2012), BSA method (Schrauwen & Van Campenhout, 2003; Nuntalid et al., 2011), population rank -coding (Bohte, 2004) and threshold based (TB) representation. One of the main advantages of NeuCube is that there is no need of additional pre-processing of the data, such as normalization, scaling, smoothing, etc. The architecture can also deal with noisy data, which is significantly time-saving.

The encoded spike trains are fed into spatially located neurons in the cube. The 3D SNNc is modelled with a population of LIF neurons separated by a small-world (SW) connectivity (Kasabov, 2014a) distance. The SW connectivity principle has been chosen here as it is based on the biological process that makes neighbouring neural cells to be highly and strongly interconnected; therefore, it is fundamental for the initialization, the capture of relevant patterns from the data and the learning process of

this architecture. The initial structure of the cube is scalable and it can evolve in size according to the data set and the study problem through the creation of new neurons and new connections based on the ECOS principles used in eSNN classifiers (Kasabov, 2003; Kasabov, Dhoble, Nuntalid & Indiveri, 2013; Mohemmed, Schliebs, Matsuda & Kasabov, 2013; Nuntalid et al., 2011). That may include known structural or/and functional connections between different areas of the brain represented in the data. Setting up a proper initial structural connectivity in a network of artificial spiking neurons is important, as it allows to properly learn from the spatio-temporal data and capture functional connectivity information from it. This preserves the spatio-temporal relationships within the data, which is a significant source of information generally overlooked by other techniques.

Learning in NeuCube is performed in two stages:

- Unsupervised learning of the SNNc sub-module. This process is performed to modify the initially set connection weights. The SNNc learns to activate same groups of spiking neurons when similar input *stimuli* are presented, also known as a polychronization effect (Izhikevich, 2006). Hebbian learning rules (Hebb, 1949) are applied at this stage, implementing STDP-like algorithms (Song et al., 2000). The STDP rule describes the connection between two neurons as stronger as their activation persists and repeats. The neurons become able to modify their initial connections and, after learning, the final connectivity and spiking activity generated in the network can be analysed and interpreted. This makes NeuCube useful for learning spatio-temporal patterns from the STBD, forming associative type of memory that can be further explored. The NeuCube can deal with noisy data also and with a low amounts of training; the training can be performed either on-line or off-line; in addition, its SNNc structure can

be visualised after unsupervised training for greater knowledge extraction that cannot be achieved with purely statistical or mathematical techniques. When protein/gene expression data are available, these can be added as a dynamic GRN that interact with the neurons of the SNNc. This can be used to study the dynamic interactions between genes/proteins over time. Especially, as per the CNGM (Benuskova & Kasabov, 2007; Kasabov, 2010), it can be used to study how fast excitatory, slow excitatory, fast inhibitory and slow inhibitory synapses related to *AMPA*, *NMDA*, *GABA_A* and *GABA_B* respectively, can affect the PSP of the neurons of the network.

- Supervised learning of the spiking neurons in the output classification sub-module. Here, the same STBD used for the unsupervised training is propagated again through the trained SNNc and output neurons are generated (evolved) and trained to classify the spatio-temporal spiking pattern of the cube into pre-defined classes (or output spike sequences). If new data do not sufficiently activate existing neurons in the output classifier, new neurons are created and allocated to match the data along with their new connections. As a special case, all neurons from the SNNc are connected to every output neuron. Feedback connections from output neurons to neurons in the SNNc can be created for reinforcement learning. Different SNN methods can be used to learn and classify spiking patterns from the SNNc, including the dynamic evolving spiking neural network deSNN(s,m) classifiers for simple class-based discrimination (Kasabov et al., 2013) and the multiSPAN classifier for defined output spike trains (Mohammed, Schliebs, Matsuda & Kasabov, 2012).

There are three types of memory in NeuCube:

- Short-term memory, represented as changes of the post-synaptic potentials (PSP) and temporary changes of synaptic efficacy;

- Long-term memory, represented as a stable establishment of synaptic efficacy - as LTP and LTD;
- Genetic memory, represented as a genetic code.

The STDP rule is responsible for short- and long- term memory formation in the NeuCube. Genetic memory can be generated by combining the NeuCube with a GRN so that protein/gene expression data can also be incorporated.

The NeuCube module M1 for STBD modelling allows for the creation of different models for STBD based on the following information processing principles as described in (Kasabov, 2014a):

1. The main sub-module has a spatial structure that maps the spatially located areas of the brain where STBD is collected.
2. The same information paradigm – spiking information processing that ultimately generates STBD at a low level of brain information processing, is used in the model to represent and to process this STBD.
3. Brain-like learning rules are used during training to learn STBD that is mapped into the designated spatial areas of the model.
4. A model is evolving in terms of new STBD patterns being learnt, recognised and added incrementally, which is also a principle of brain cognitive development.
5. A model always retains a spatio-temporal memory that can be mined and interpreted for a better understanding of the cognitive processes.
6. A visualisation of the model evolution during learning can be used as a bio-feedback.

Different NeuCube models and systems have been developed and applied for different types of problems such as:

- Spatio-/spectro- temporal pattern recognition (Kasabov, 2012a).
- Moving object recognition (Kasabov et al., 2013).
- Environmental and ecological modelling (Tu et al., 2014).
- EEG data modelling for neurorehabilitation (Chen et al., 2013).
- Neuromorphic SNN hardware (Indiveri et al., 2011).
- Neurogenetic models (Benuskova, Jain, Wysocki & Kasabov, 2006).
- Personalised modelling of neurodegenerative disorders (Kasabov et al., 2014).

All the above principles and applications make NeuCube a suitable eSTDM to learn and reveal complex spatio-temporal patterns “hidden” in STBD and that is why it has been chosen for the development of new methodologies for cognitive EEG STBD modelling and understanding.

4.3 Summary

This chapter introduces a class of ECOS eSTDM, called the NeuCube architecture, and described its functionality and main applications.

In the next chapter, the SNN NeuCube module M1 for STBD modelling and understanding is applied on EEG data and a new methodology for EEG data classification and understanding is proposed.

Chapter 5

A New Methodology for EEG Data Classification and Analysis in a NeuCube Model

5.1 Introduction

As seen in the previous chapter, NeuCube is an SNN architecture in which both spatio and temporal neurogenetic brain data can be encoded according to the location of the *stimulus* and reflecting the timing of their spiking activity (Kasabov, 2014a). NeuCube is capable of learning noisy data and it can be used not only for modelling and classification of STBD, but also for extracting knowledge from it.

In this chapter, a new NeuCube-based methodology is proposed in section 5.2 for the classification and analysis of EEG STBD and for the understanding of the brain processes that generate it. In section 5.3, the proposed methodology is applied on a small data set for a case study in neurorehabilitation. Summary of the chapter and conclusions are drawn in section 5.5.

This study was peer-reviewed and published by IEEE in the *Proceedings of the 2014 International Joint Conference on Neural Networks (IJCNN)*. Copyright and permission from the publisher of the paper are included in Appendix B and full text of the paper is provided in Appendix A.2.

5.2 eSTDM for EEG STBD Modelling and Understanding

The approach used in this research to model EEG data is based on the eSTDM called the NeuCube architecture. Previously, eSNNs have been successfully applied to classify cognitive EEG data (Nuntalid et al., 2011) and other type of spatio-temporal data, such as in moving object recognition (Dhoble et al., 2012), personalised disease prognosis (Kasabov et al., 2014) and knowledge extraction (Soltic & Kasabov, 2010). Now, by extending some of the methods available for the NeuCube module M1 for generic prototyping and testing (introduced in chapter 4.2 and depicted in Fig. 4.1), we propose here a new methodology for EEG data modelling, classification and understanding. This is applied here on a small dataset for a BCI-based neurorehabilitation system.

Figure 5.1 shows a diagram for the proposed methodology, which is explained in details in the next section.

5.2.1 The Methodology

The proposed methodology here consists of the following procedures and parameters:

1. The time series data obtained from the EEG device is first ordered as a sequence of real-value data vectors. Every data vector is transformed into a spike train using the TB representation algorithm (Tu et al., 2014), which is based on the

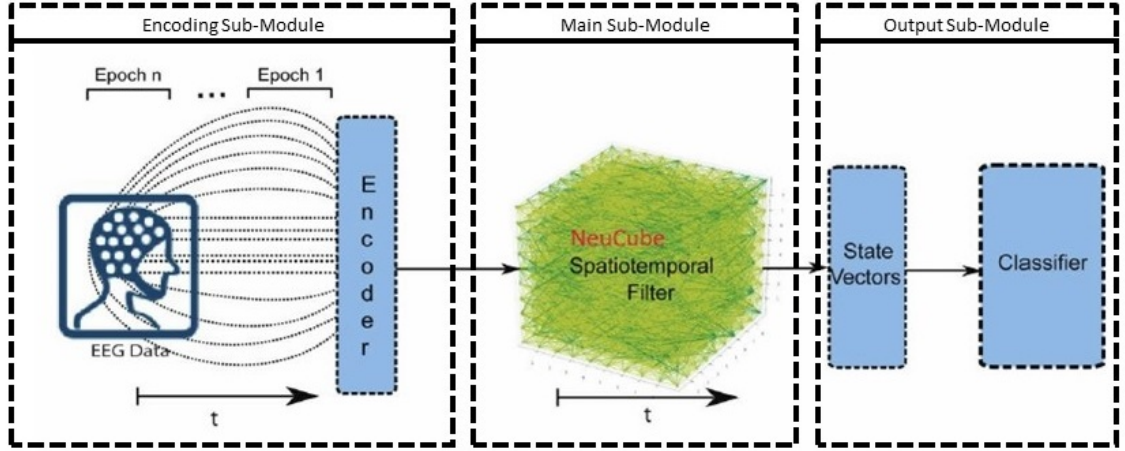


Figure 5.1: The image shows the NeuCube architecture for EEG data classification and knowledge extraction. The picture shows the NeuCube three principal sub-modules: the input encoding sub-module, where EEG data is encoded into trains of spikes that are then presented to the main sub-module, the SNNc; the NeuCube main sub-module, where time and space characteristics of the data are captured and learned; and the output sub-module for data classification and new knowledge discovery from the SNNc visualization. Image from (Kasabov, 2014a).

AER encoding method (Delbruck, 2007; Dhoble et al., 2012; Chan et al., 2007).

This algorithm suits EEG STBD well, since it identifies only the differences in consecutive values, as demonstrated and implemented in the artificial silicon retina chip (Delbruck, 2007; Dhoble et al., 2012) and the artificial cochlea chip (Chan et al., 2007). The TB algorithm is calculated as a bi-directional threshold (TBR_{thr}), which is applied to the signal $x(t)$ (*i.e.* for each vector of real-valued data), according to the following equation:

$$TBR_{thr} = \dot{x} + s \sigma \quad (5.1)$$

where $\dot{x} = x(t) = \{x_{t_2} - x_{t_1}, x_{t_3} - x_{t_2}, \dots, x_{t_n} - x_{t_{n-1}}\}$ is the mean of the differential signal with respect to time calculated by using all samples $x(t)_n$; σ is the standard deviation calculated for each vector of real-valued data $x(t)_n$; and s is a scale parameter of σ .

The TBR_{thr} is used to generate two types of spike sequences: a positive spike train corresponding to the signal increment, which is mapped to a specific input neuron in the SNNc; and a negative spike train, corresponding to the signal decline, which is mapped into another input neuron of the SNNc that is placed in the same position as the positive one.

2. For mapping the spatial locations of the EEG channels into the SNNc, we use the Talairach template (Koessler et al., 2009; Lancaster et al., 2000; Talairach & Tournoux, 1988). The number of neurons in the cube is set as 1471 neurons, as each neuron represents 1 cm^3 of population of human neural cells. The neurons are located in the cube following the same (x,y,z) coordinates of the Talairach template. The EEG channels are mapped according to the standard mapping suggested in (Koessler et al., 2009). The spike sequences that represent the data from EEG channels are presented to an evolving brain-mapped SNNc that reflects the number of input variables (e.g. the EEG channels), the functional brain areas associated with them and the size of the data available.
3. The neurons in the cube are initialised as SW connected networks. Neurons' initial connection weights are calculated as the product of a random number $[-0.1, +0.1]$ and the multiplicative inverse of the Euclidean distance $d(i, j)$ between a pre-synaptic i and a post-synaptic neuron j (calculated according to their (x, y, z) coordinates). Twenty percent of these weights are selected to be negative (inhibitory connections weights), as in the mammalian brain the number of GABAergic neurons is found to be about 20-30% (Capano, Herrmann & de Arcangelis, 2015), while 80% are positive (excitatory connections weights). The $d(i, j)$ also depends on a distance threshold D_{thr} calculated as:

$$D_{thr} = \max (d(i, j)) p \quad (5.2)$$

The distance threshold depends also on a SW connectivity distance or parameter p (a numerical constant).

4. The neurons in the cube are implemented as LIF neurons (Gerstner, 2001). If an initial connection $c_{i,j}$ between two neurons is established, then, the membrane potential v_j of a neuron j increases according to the time and the order of the incoming spike S_i from neuron i . v_j increases until a firing threshold Θ is reached, then, it resets itself and an output spike S_j is emitted.

$$S_i = \begin{cases} 1 & v_j \geq \Theta \\ 0 & \text{otherwise} \end{cases} \quad (5.3)$$

The membrane potential will stay zero for the length of its refractory time r . Between spikes, the membrane potential leaks according to the potential leak rate (l).

$$v_j(t) = \begin{cases} v_j(t-1) + w_j & r = 0 \\ v_j(t-1) - l & \text{otherwise} \end{cases} \quad (5.4)$$

where w_j is the connection weight of a post-synaptic neuron j .

5. The SNNc is trained in an unsupervised mode using the STDP (Song et al., 2000) learning rule, as it allows spiking neurons to learn consecutive temporal associations from the EEG data within and across EEG channels. The STDP is implemented here as follows:

$$w_j(t) = \begin{cases} w_j(t-1) \pm \alpha/\Delta t & t_j \neq t_i \\ w_j(t-1) & t_j = t_i \end{cases} \quad (5.5)$$

where α is the STDP learning rate parameter, Δ_t is the time elapsed since the

last spike was emitted by neuron j . If a neuron i fires before a neuron j , then its connection weight $w_{j,i}$ increases; otherwise, it decreases.

6. The output classifier is trained in a supervised mode using deSNN (Kasabov et al., 2013) algorithm, which combines the RO (Thorpe & Gautrais, 1998) and the STDP (Song et al., 2000) learning rules. This allows each output neuron to learn from the spatio-temporal patterns using only one pass of data propagation. According to this algorithm, every trained sample is associated to an output neuron that is connected to every other neuron of the cube. In this case, all neurons of the SNNc are connected to the output neurons as inputs to the deSNN classifier. Initially, the connection weights $w_{i,j}$ between the input neuron i and the output neuron j are all set to zero. Then, according to the RO rule, they are computed as follows:

$$w_{i,j} = mod^{order(i,j)} \quad (5.6)$$

where mod is a modulation factor and $order(i, j)$ is the order of the incoming spike (starting from 1). The connection weights are modified according to the SDSP learning rule (Fusi, 2002). This is implemented as:

$$w_{i,j}(t) = \begin{cases} w_{i,j}(t-1) + drift & S_j(t) = 1 \\ w_{i,j}(t-1) - drift & S_j(t) = 0 \end{cases} \quad (5.7)$$

where $drift$ is a parameter used to modify the connection weights and $S_i(t)$ represents the occurrence of the spikes arriving from neuron i at a time t after the first one was emitted.

7. The classification results are evaluated using repeated random sub-sampling validation (RRSV), leave one out cross validation (LOOCV) or other optimization

methods.

8. Steps (3) to (6) are repeated using different parameter values in order to optimize the classification output. The best performing model is then recorded for further uses.
9. The trained SNNc is visualised, its connectivity and the dynamic spiking activity are analysed for a better understanding of the data and the brain processes that generated it, including changes of brain functionality across conditions and different groups of subjects.

It is important to highlight that the SNNc sub-module is a stochastic model (*i.e.* initial connections between the neurons in the cube are randomly generated) and therefore the model is sensitive to parameter settings. Some of the major parameters that highly influence the model are:

- The bi-directional encoding threshold TBR_{thr} , as the spike rates depends on this threshold, which can be determined either as a particular value for every input variable or as a global threshold to be applied to all of them.
- The SW connectivity parameter p , as each neuron in the SNNc is initially connected to its neighbouring neurons within this parameter as distance.
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model, as when a LIF neuron of the network receives a spike, its PSP increases gradually with every input spike according to the time, until it reaches an established threshold of firing; then, an output spike is emitted and the membrane potential is reset to an initial state (refractory time); and between spikes, the membrane potential leaks.

- The STDP rate parameter α , as according to the STDP learning rule the firing activity of two connected neurons causes their connection weights to increase or decrease depending on the order of firing in order to emulate the temporal relationship between the activity of these neurons.
- The number of times that the NeuCube is trained in an unsupervised mode, as different values may cause either over-training of the SNNc, producing outputs that fit only the specific data set, or under-training, when the learning is not enough to detect a pattern in a complex data set.
- The variables *mod* and *drift* of the deSNN classifier, as connection weights are modified according to the RO learning rule, which is calculated depending on the modulation factor, *mod*, of the order of the incoming spikes; and connection weights increase or decrease according to the number of spikes that follow the first one, which is expressed as the *drift* parameter.

A crucial step in obtaining desirable results from the NeuCube model is the optimisation of these parameter values. Parameter optimisation can be achieved *via* grid search method, genetic algorithm, or quantum-inspired evolutionary algorithm (Platel, Schliebs & Kasabov, 2009; Nuzly Abdull, Kasabov & Shamsuddin, 2010).

In the following section, the methodology herein introduced is applied on a small EEG data set for a case study in BCI-based neurorehabilitation study.

5.3 A Case Study on EEG Data Classification of Imaginary Movement of an Upper Limb

5.3.1 Problem Specification

A focal neurological insult that causes changes to cerebral blood flow, such as in a stroke, can result in mild to severe motor dysfunctions on the contra-lateral side of the body. Although some spontaneous recovery usually occurs in the first six months after stroke only about 14% of people with stroke recover normal use of the upper limb (Kong, Chua & Lee, 2011). The driver of functional recovery after stroke is neural plasticity, the propensity of synapses and neuronal circuits to change in response to experience and demand (Kleim & Jones, 2008; Fox, 2009; Kerr, Cheng & Jones, 2011). Whilst it is known that frequency and intensity of intervention following stroke is important, high intensity rehabilitation is resource-limited. In order to deliver interventions at a high enough intensity and frequency for neural plasticity we need to develop devices that can assist with rehabilitation without the concentrated input of rehabilitation professionals.

Motor imagery (MI), or the mental rehearsal of a movement, is an approach used by rehabilitation professionals to encourage motor practice in the absence of sufficient muscle activity (Jeannerod, 2001; Rizzolatti, Fogassi & Gallese, 2001; Jeannerod et al., 1994). MI is thought to activate similar cortical networks as activated in a real movement, including activation of the primary motor cortex, premotor cortex, supplementary motor area and parietal cortices (Fadiga, Fogassi, Pavesi & Rizzolatti, 1995; Grush, 2004). Recent evidence suggests that although there are common cortical networks in real and imagined movement (frontal and parietal sensorimotor cortices) there are also important differences, with ventral areas being activated in imagined movement, but not in real movement. These specific additional activations in the extreme/external capsule

may represent an additional cognitive demand of imagery based tasks.

Recovery of movement control is greater after motor execution training than after MI training alone. Interestingly the combination of MI training with even passive movement generates greater recovery than MI alone (Page, Levine, Sisto & Johnston, 2001). Combining motor imagery with functional electrical muscle stimulation, *via* BCI devices, may result in greater neural plasticity and recovery than motor imagery alone, or motor imagery combined with passive movement. The additional feedback to the brain provided by executing a movement may enhance plasticity and reduce the cognitive demand of motor imagery. Many people following stroke or other neurological disorder have some residual muscle activity but fail to recruit enough motor units at an appropriate speed and pattern, to generate sufficient force to complete the desired movement (V. Gray, Rice & Garland, 2012; Chang, Zhou, Rymer, Li et al., 2013). A BCI device in which motor imagery triggers an appropriate signal in a functional electrical stimulation system would facilitate the practice of real movements and potentially result in greater neural plasticity and functional recovery.

EEG records brain signals through electrodes on the scalp and is the most widely used method for recording brain data used in BCI devices. EEG is non-invasive and has good temporal and spatial resolution. However, EEG systems have been criticized because of the time consuming and complex training period for the potential user (Zimmermann et al., 2013). One advantage of the NeuCube framework is that intensive training of the user is not required as NeuCube classifies naturally elicited cortical activity, rather than a specific component of the EEG signal, such as the P300 wave, the production of which has to be learned by the user. In addition, NeuCube is capable of learning in an on-line fashion, training as it is used.

We are investigating the feasibility of using NeuCube with EEG data to develop a functional electrical stimulation BCI system that is able to assist in the rehabilitation of complex upper limb movements. Two methods of use are under consideration: firstly, for people who have no voluntary activity in a limb and who would drive the device using MI; secondly, for people who have some residual activity in their muscles that, in addition to using MI, may augment the device with their own muscle activity. To do this it is important to establish a high degree of accuracy of classification of movement intention and movement execution to ensure that the appropriate electrical stimulation output is then provided. One of the challenges to any BCI system is the extent to which it accurately classifies the input signal.

In (Zimmermann et al., 2013) real movement, consisting of a pinch grip to a specified force level, compared to a resting state, was used. Data were collected using functional near infrared spectrometry (fNIRS) combined with other physiological data, such as blood pressure and respiratory information. Using HMMs as the classifier framework, accuracies ranging between 79.6% and 98.8% over two classes were achieved. Using fNIRS in a trial of MI (Zimmermann et al., 2013) investigated the classification accuracy of a simple imagined tap of the thumb on a keyboard versus a complex multi-digit tapping sequence. Linear discriminant analysis (LDA) was used in combination with careful selection of the best performing data channel (out of 3 possible channels) and best 4 features for each participant. The study in (Holper & Wolf, 2011) reported classification accuracies in a 2-class model (simple imagined movement or complex imagined movement) of between 70.8% and 91.7%. A sparse common spatial pattern (SCSP) optimization technique that reduced EEG channels by disregarding noisy channels and channels thought to be irrelevant was reported in (Arvaneh, Guan, Ang & Quek, 2011), however this approach results in a loss of data that could be informative.

We were interested in determining if it was feasible to use the NeuCube framework as a driver of BCI devices. As a first step, we wanted to determine if NeuCube was at least equivalent in classifying movement tasks to other commonly used methods. As proof of concept, we designed a study that required NeuCube to classify imagined and real movements in two different directions and at rest (wrist flexion, extension or rest). The general hypothesis is that NeuCube using EEG data can correctly identify brain patterns corresponding to specific movements. In a previous work (Chen et al., 2013), the potential of NeuCube to identify different EEG patterns relating to different imagined movements from a commercially available 14 channel EEG headset was assessed. In this trial imagined wrist extension, rest and wrist flexion achieved accuracy in 1 individual of 88%, 83% and 71% respectively (Chen et al., 2013).

The specific hypothesis for this study was that NeuCube would accurately classify both single joint real and imagined movements of the hand into one of three classes, flexion, extension or rest. This paradigm built on the earlier work in (Chen et al., 2013) by increasing the complexity of the task by requiring the NeuCube to distinguish three conditions, two different muscle contraction patterns (flexion or extensor muscle activity) or rest (Chen et al., 2013). A secondary hypothesis was that NeuCube would perform better than other classification methods, including MLR, SVM, MLP and ECM (Song & Kasabov, 2001), along with offering other advantages such as adaptability to new data on-line and interpretability of results.

5.3.2 Data Collection

Three coauthors of the paper, that resulted from this case study, were used as healthy volunteers to collect the data. None had any history of neurological disorders and all were right handed.

All measures were taken in a quiet room with participants seated in a dining chair. The task consisted of either performing the specified movements or imagining the movements, or remaining at rest. All tasks were completed with eyes closed to reduce visual and blink related artefacts. The movement for the execution task involved the participant resting, flexing the wrist or extending the wrist. The starting position was from midpronation with the forearm resting on the persons lap. The movement intention task involved the participant imagining or performing the movements as described above. Participants were required to imagine or perform each movement in 2 seconds and to repeat that 10 times.

A low-cost commercially available wireless Emotiv Epoc EEG Neuroheadset was used to record EEG data. The Epoc records from 14 channels based on International 10 – 20 locations (AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4). Two additional electrodes (P3, P4) were used as reference. Data were digitized at 128 Hz sampling rate and sent to the computer via Bluetooth. An important factor was that no filtering was applied to the data, either online or offline.

5.3.3 Data Processing

The data was separated into classes denoting each task. Each set of 10 samples was then evenly divided into a training (seen) and a testing (unseen) set. The data was then converted into trains of spikes (one train per channel, 14 in total) with the Address Event Representation algorithm, utilizing a spiking threshold of six. No other data processing was applied.

Each training sample was presented to NeuCube once, entered as 14 input streams of

EEG continuous data collected at the $msec$ time unit, encoded using TB representation method with a global $TBR_{thr} = 6$. The spiking activity of every neuron was recorded over the time of the sample, and these were presented to the deSNNs classifier. The deSNNs was initialized with a $mod = 0.9$ and $drift = 0.25$ (empirically established values for this dataset). The synaptic weights for both NeuCube and the deSNNs were then fixed at their final (learned) values for the validation phase. The unseen data samples were presented in the same way, and the predicted classes recorded. The predicted classes were then compared to the actual classes of those samples.

5.3.4 Comparative Study

NeuCube described above was compared to some popular machine learning methods: MLR, SVM, MLP and ECM. The SVM method uses a Polynomial kernel with a rank 1; the MLP uses 30 hidden nodes with 1000 iterations for training. The ECM (Song & Kasabov, 2001) uses $m = 3$; $R_{max} = 1$; $R_{min} = 0.1$. Data for these methods is averaged at 8 milliseconds intervals and a single input vector is formed for each session, as is the general practice.

5.3.5 Results

The classification accuracy of NeuCube was on average 76%, with individual accuracies ranging from 70 to 85%. There was a consistent rate of recognition between the real and the imagined movement. In terms of the comparison with other classification approaches, it is clear from the results shown in Table 5.1 that NeuCube performed significantly better than the other machine learning techniques with the highest average accuracy over all subjects and samples, whilst the closest competitor was SVM with the second highest average accuracy of 62%. MLR was the poorest performing algorithm, with an average accuracy of 50.5%, or just over the chance threshold.

Table 5.1: Results of the comparative study; accuracy expressed as percentage for real and imagined movements.

Subject/Session	MLR	SVM	MLP	ECM	NeuCube
1/Real	55	69	62	76	80
1/Imagined	63	68	58	58	80
2/Real	55	55	45	52	67
2/Imagined	42	63	63	79	85
3/Real	41	65	41	45	73
3/Imagined	53	53	63	53	70
Average (appr.)	52	62	55	61	76

In Fig. 5.2, the resulting connectivity and spiking activity generated between the neurons of the network during unsupervised learning is visualised for a better understanding of the data and the brain processes that generated it. The analysis of the SNNc offers the possibility to interpret and extract knowledge from the model for the purpose of a better understanding of the data and the cognitive brain processes.

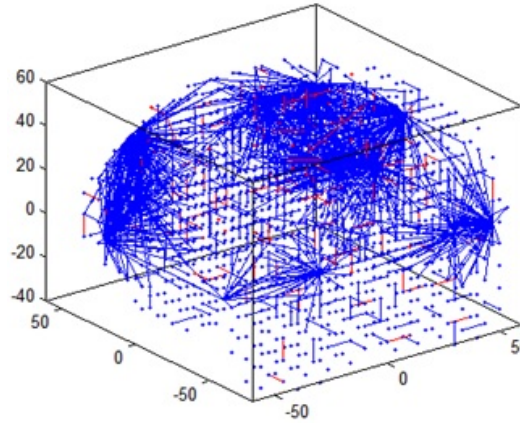


Figure 5.2: Example visualisation of the trained 3D SNNc. Blue lines show strong excitatory connections between two neurons, and red lines show strong inhibitory connections.

5.4 Discussion and Conclusion

The research herein presented investigates the potential of the NeuCube-based methodology proposed in section 5.2.1 by means of a feasibility study in BCI-based rehabilitation system.

When considering the classification accuracies, which ranged from 70 to 85%, it is important to take into account three factors. Firstly, the data were collected in an unshielded room using a commercially available gaming EEG headset, resulting in an EEG signal with relatively high signal to noise ratio. Secondly, there was no processing or feature extraction performed on the data prior to classification; the raw, noisy EEG data was used as the input. Thirdly, all comparative methods in this study, except NeuCube, were validated using LOOCV, while NeuCube was validated with RRSV, a more disadvantageous 50/50 (half used for training, half for testing) split. The accuracy of NeuCube was still significantly higher than the other techniques and would likely rise when trained using leave-one-out approach.

Bearing these three factors in mind, the classification accuracies obtained using NeuCube are in a similar range to those reported in other research and demonstrates that NeuCube is capable of accurately classifying noisy and relatively low-quality data. In addition, unlike many other approaches, NeuCube does not require a lengthy feature extraction process; instead it use all the raw data for classification, thus utilizing a rich data set that does not lose any potentially useful data.

We chose to use a relatively cheap and accessible EEG headset because two major factors that prevent the adoption of high technology interventions into rehabilitation practice are cost and complexity. EEG systems commonly used in research and clinical

situations are expensive and unlikely to be widely available to rehabilitation specialists. The Emotiv neuroheadset (*The Emotiv Systems*, 2014) has a limited number of channels with a fixed electrode placement, which may serve to improve usability as it reduces the preparation time and is easy for users to put on themselves.

An advantage of the NeuCube is that it allows for interpretation of results and understanding of the data and the brain processes that generated it. This is illustrated in Fig. 5.2 where the connectivity of a trained SNNc is shown for further analysis. The SNNc and the deSNN classifier have evolvable structures, *i.e.* a NeuCube model can be trained further on more data and recalled on new data not necessarily of the same size and feature dimensionality. This allows in theory for a NeuCube structure to be partially trained on highly accurate data captured in a controlled manner with medical devices, and then further trained and adapted to the particular subject with a cheaper, less accurate device such as Emotiv. This will increase potential uses in clinical and rehabilitation applications.

The large number of parameters that need to be optimized for every experiment to achieve the best results limits the current NeuCube architecture. The results presented in this study are obtained through manual parameter optimization. To mitigate this, adaptive and evolutionary techniques (including the GRN discussed earlier and quantum-inspired optimization) are being developed for this system, so that parameter selection is automated in a desirable way.

5.5 Summary

This chapter presents a new methodology for the classification and analysis of EEG data in order to answer *RQ1* proposed in Chapter 1: *Can we develop a methodology for EEG*

data classification and modelling in an eSTDM of spatially organised spiking neurons, such the NeuCube architecture, that can be used to proper analyse and understand the STBD available and the brain processes that generated it?

The results of this study demonstrated that the proposed NeuCube-based methodology is indeed feasible to use in BCI-based rehabilitation devices by classifying and analysing a small EEG data set. Especially, the SNN NeuCube-based methodology has been demonstrated to provide a significantly better accuracy of classification and interpretation of brain data than traditional machine learning techniques, suggesting its potential application to neurological clinical research. Moreover, the ability of NeuCube for representing the brain data both spatially and temporally has been demonstrated to be useful in future applications. Observing changes in neural representation and spike timing throughout rehabilitation interventions could provide valuable information on human learning and adaptation to advance rehabilitation interventions. This may facilitate understanding of recovery from neurological injury and recovery related to rehabilitation.

In the next chapter, the proposed methodology is applied on a bigger data set of complex cognitive EEG data and the classification outputs are compared with already published results on the same data set.

Chapter 6

Application of the Proposed Methodology for Modelling, Classification and Understanding of Cognitive EEG Data

6.1 Introduction

Chapter 5 proposes a new SNN NeuCube-based methodology for the classification and analysis of EEG STBD. The methodology is now applied on a bigger data set to model, recognise and understand complex cognitive EEG data recorded during mental tasks.

Cognitive brain processes are difficult to analyse and understand with the use of a computational model, unless a technique is available that is able to deal with the data in a proper way. Many applications related to STBD still rely on traditional AI techniques; however, more efficient techniques are required, as cognitive tests and memory screening can provide powerful information that, if understood, can be used to stage

and diagnose cognitive impairments such as AD (Reggia et al., 1999). In fact, one of the first symptoms that follow the onset of the pathology is cognitive decline and memory loss. Early detection is important, as it allows for initial treatments. In this field, Neuroinformatics research can play a pivotal role. A major contribution that can be brought about by a much more efficient methodology based on machine learning techniques that can be used to evaluate the cognitive ability of a person with a deeper understanding of the underlying brain processes.

In this chapter, we first apply the NeuCube-based methodology on a benchmark data recorded during cognitive tasks (section 6.2). The results obtained are also compared to already published classification results on the same data set. In section 6.3, conclusions and future work are drawn. Section 6.4 summarises the chapter.

This study resulted in a peer-reviewed paper publication, which appeared in *Information Sciences Journal*. Copyright and permission from the publisher of the paper are included in Appendix B and the full text of the paper is presented in Appendix A.3.

6.2 A Case Study on EEG Cognitive Data

6.2.1 Data Description

The data used for this study are made freely available on-line by the University of Colorado (Anderson & Kirby, 2003). Data was collected in an earlier experiment by Z.A. Keirn (Keirn, 1988; Keirn & Aunon, 1990) and further studied in (Anderson & Peterson, 2001; Anderson & Sijercic, 1996; Nan-Ying, Paramasivan, Guang-Bin & Narasimhan, 2006). The EEG data was collected from the cortex of seven healthy subjects (between 20 and 48 years old; six men and one woman; all right-handed except

for one subject) following five different scenarios, one resting task and four cognitive tests. A BCI device was used to collect the EEG data. The designed mental task scenarios consisted of: a “resting” task – a subject is relaxing, avoiding thoughts as much as possible (class 1); a “letter composition” task (class 2) – a subject is tasked with imagining writing a letter to someone without verbally expressing it; a “multiplication” task (class 3) – a subject is performing a non-simple two digit mental multiplication; a “counting” task (class 4) – a subject is visualising a blackboard on top of which numbers were sequentially being written; a “rotation” task (class 5) – a subject is mentally rotating a 3D geometric figure. Each recording session was carried out using six electrodes: C3, C4, P3, P4, O1 and O2. Data was recorded for 10 seconds at 250 Hz, resulting in 2500 data points collected per session. Every task was repeated five times during a daily session. Some of the subject data was recorded in a one-day session, while other subjects repeated the five trial tasks for a second or third day session. The data of subject 4 was excluded from the experiment, as according to a previous study (Nan-Ying et al., 2006) the signal was repeatedly saturated or invalidated in several trials.

6.2.2 Experimental Design and Implementation

For our study, we resized each session dataset into two samples of 5 seconds each, 1250 data points per channel on every sample. We assumed that half of the information can be considered enough to represent the mental activity measured. Thus, for each of the five classes we had 10 samples of 1250 data points per six EEG channels; in total, we obtained 50 samples per subject and per session.

For the model implementation we have used a software simulator of NeuCube written in MATLAB® (Chen et al., 2013; Tu et al., 2014). Figure 6.1 illustrates the procedures

applied to the experiment as explained in details in Chapter 5.

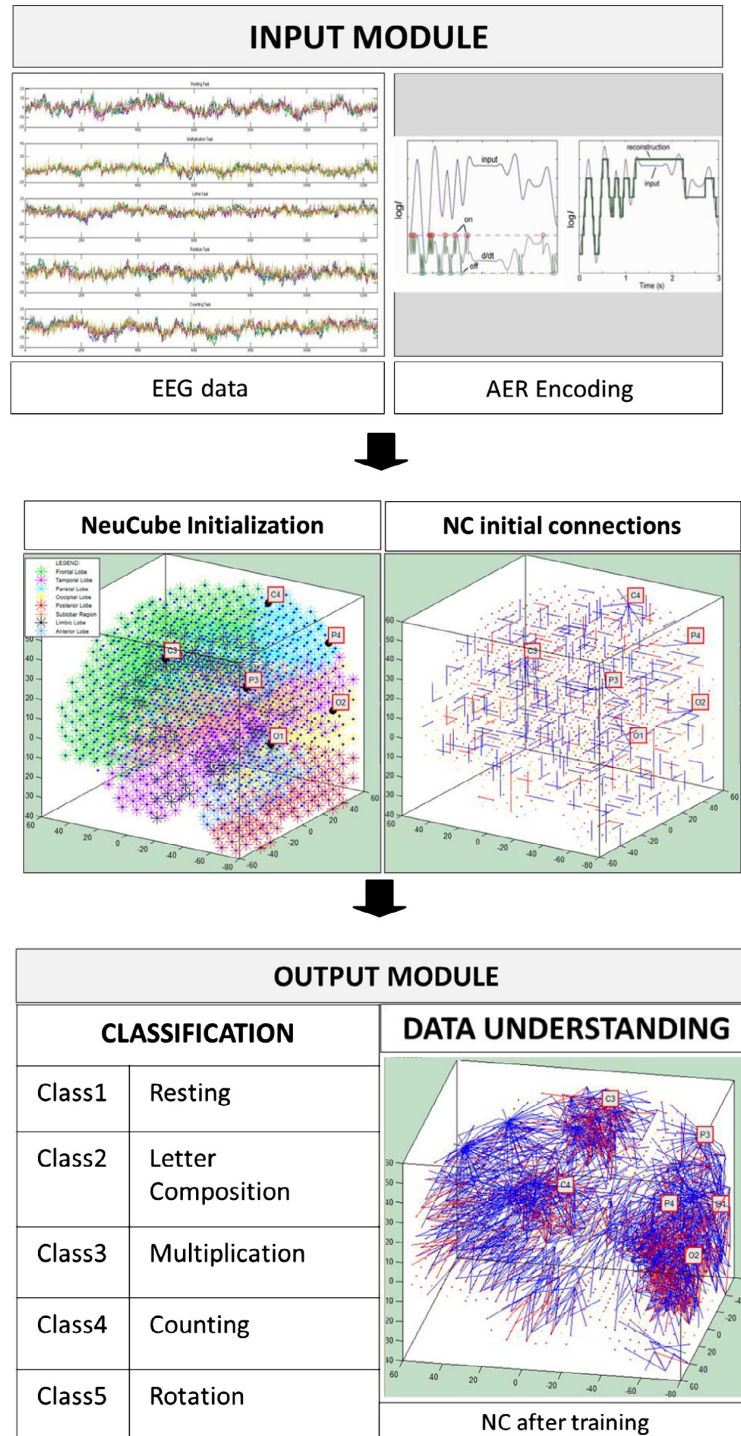


Figure 6.1: A graphical representation of the different steps from the proposed methodology applied on the case study problem.

To summarise:

- In the NeuCube's input module, the available EEG data are transformed into spike sequences using an encoding algorithm, such as AER method, as this algorithm suits well the cognitive EEG data as it only identifies differences in consecutive values.
- In the NeuCube's main module, the spike trains are presented to the 3D brain-like cube of 1471 LIF neurons mapped using the Talairach template (Koessler et al., 2009). This reflects the number of input variables (*i.e.* the six EEG channels: C3, C4, P3, P4, O3 and O4) and the size of the data available. Then, the SNNc is stochastically initialised using the SW connectivity rule and trained on the spike data using an unsupervised learning method, such as the STDP learning rule, as it allows the spiking neurons of the cube to learn consecutive temporal associations from the EEG data within and across EEG channels. As a consequence, new connections are formed between neurons that can be further interpreted in the context of different cognitive tasks. This makes the NeuCube architecture useful for learning spatio-temporal patterns from the EEG data, forming associative type of memory that can be further explored (Kasabov, 2014a).
- In the output module, the classifier is trained in a supervised mode and the output results are validated. In this study, the deSNN (Kasabov et al., 2013) algorithm was used to classify the EEG STBD into the five brain cognitive states (classes) and the classification results were evaluated using both RRSV and LOOCV.

In order to optimise the numerous parameters of NeuCube, the unsupervised and supervised learning procedures are repeated using different parameter values until desired classification results are achieved and the best performing model is retained. Here, we evaluated the model *via* grid search first. We randomly selected 50% of

the entire time series for training and the other 50% for testing. We assessed the classification accuracy of 20 model configurations for each subject and for each session optimizing the AER threshold (AER_{Thr}) values only, while the other parameters were set as per default, as follows:

- The SW connectivity parameter p was set at 0.15;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.5, 6 ms and 0.02 respectively;
- The STDP rate parameter α was set at 0.01;
- The variables *mod* and *drift* of the deSNN classifier were set at 0.4 and 0.25 respectively.

These parameters were empirically established values for this dataset and used together with the optimised AER threshold value to evaluate the classification output using both RRSV and LOOCV evaluation methods.

6.2.3 Experimental Results

Table 6.1 summarises classification results per subject and per session. For this study, the average CPU time for execution has also been measured. The CPU time used by the main NeuCube's algorithms during the entire experiment was 48.46 seconds for the unsupervised training (per sample and per iteration); 20 seconds (per sample) for the supervised training; and 5854.51 seconds for testing the classifier. These values were obtained by measuring the CPU time under the following settings: a software simulator of NeuCube written in MATLAB R2012b®; a 64-bit Microsoft®Windows 7 machine, with processor Intel®core™ i5-2400 CPU 3.10 GHz ; 8 GB of memory (RAM).

Table 6.1: Experimental results with the NeuCube-based model per subject and per session. Results reveal the classification accuracy percent obtained per sample. These can be identified by the corresponding “Subject/Session” label (S/S). The outputs were assessed by using both RRSV (per class type and as average over all classes) and LOOCV (as average over all classes). The results were optimised by finding the AER_{Thr} value that led to the best classification accuracy result.

S/S	AER_{Thr}	NeuCube (random 50/50 cross validation accuracy)					RRSV	LOOCV
		Class 1	Class 2	Class 3	Class 4	Class 5	Overall	Overall
1/1	2.00	80	100	100	60	100	88	80
1/2	1.99	100	100	100	100	100	100	100
2/1	1.30	100	100	100	100	20	84	74
3/1	4.07	80	40	80	40	40	56	52
3/2	2.94	80	40	100	80	100	80	80
5/1	5.23	100	80	80	80	80	84	70
5/2	2.95	20	60	100	100	80	72	54
5/3	5.89	80	100	60	100	60	80	94
6/1	6.48	60	80	40	100	80	72	56
6/2	5.57	80	100	100	80	60	84	86
7/1	1.70	60	100	100	100	80	88	82

In Fig. 6.2 and 6.3, we can observe both the seven areas of the SNNc that spatially represent the regions of the brain allocated in the Talairach’s template and the evolved connectivity obtained after unsupervised learning of the SNNc respectively. From

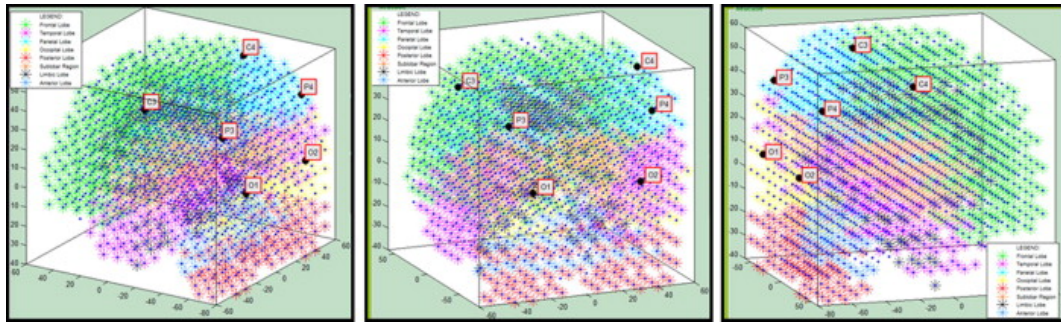


Figure 6.2: Different views of the SNNc of 1471 neurons and the six input neurons for the case study EEG data and problem. Seven particular areas from the SNNc that correspond spatially to brain regions according to the Talairach Atlas are also shown: in green – the frontal lobe; in magenta – the temporal lobe; in cyan – the parietal lobe; in yellow – the occipital lobe; in red – the posterior lobe; in orange – the sub-lobar region; in black – the limbic lobe; in light blue – the anterior lobe.

Fig. 6.3, we can notice that new connections are formed around the input neurons of the SNNc which were allocated so that they spatially mapped the spatial location of the EEG electrodes. Studying the picture, we could also deduce some additional information, *e.g.* subjects where using actively their visual cortex (occipital lobes, allocated

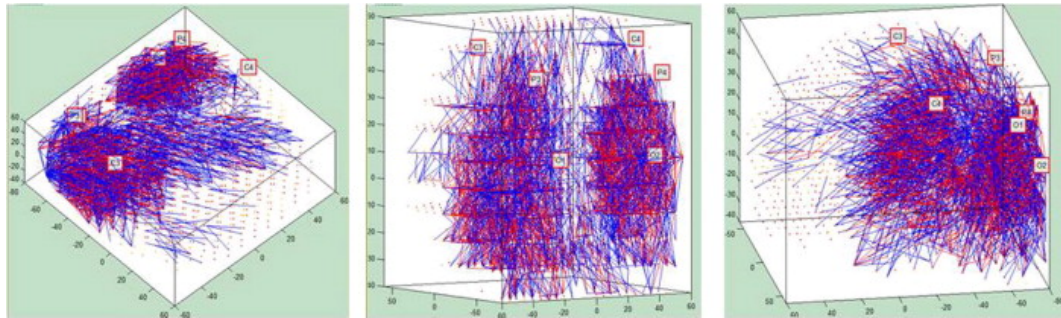


Figure 6.3: The SNNc connectivity after training can be analysed and interpreted for a better understanding of the cognitive EEG data to identify differences between brain states representing different mental tasks performed by different subjects. Connections represent spatio-temporal correlations between spiking neurons that correspond to brain areas. Using only EEG data for training, deeper structural connections are evolved that reveal new information about the cognitive processes.

by electrodes O3 and O4). Effectively, the subjects were performing each cognitive scenario with open eyes. We can also observe from the picture a high activity on the parietal lobe (allocated by electrodes P3 and P4) where integration of visual and other information occurred during the cognitive tasks related to this data.

As the data set was of a small size, it is not appropriate to draw any scientific conclusions about the mental tasks performance by different subjects, and that was not the goal of this study. We rather conclude that it is feasible to consider the NeuCube-based method for further analysis and further experimental data modelling; it could become a widely used method for EEG data analysis related to mental tasks and cognitive processes across applications. The results from this experiment still confirmed some expected phenomena:

- Subjects perform differently for different complex mental tasks (classes).
- Data for class 1 (relax) was the best classified across all subjects.
- The accuracy of classification increased with some manual parameter tuning showing that this is not the full potential of the NeuCube-based model and it still

needs to be further optimised.

The results from the NeuCube-based methodology were compared with the ones obtained in previous experiments carried out by other researchers on the same data set (Nan-Ying et al., 2006). With the proposed NuCube-based methodology, we obtained higher classification accuracy on the data per session, per subject and overall (see Table 6.2) when compared with other methods such as SVM and extreme learning machines (ELM) (tested in a LOOCV mode). When the SVM and the ELM methods were applied, the EEG data was first pre-processed (smoothed) and then “compressed” into smaller number of input vectors, rather than treated as spatio-temporal stream data as it is in the NeuCube-model case.

Table 6.2: Outputs obtained using the NeuCube-based methodology *versus* the best accuracy obtained by Nan-Ying et al. (2006) with two other methods. Results are expressed as best percentage of classification accuracy obtained per subject and per session (labelled as S/S).

S/S	NeuCube	(Nan-Ying et al., 2006)	Types of other Methods
1/2	100	86.70	ELM with smoothing
2/1	84	78.76	SVM with smoothing
3/2	80	64.60	SVM with smoothing
5/1	84	63.43	SVM with smoothing
6/2	84	69.47	ELM with smoothing
7/1	88	79.77	SVM with smoothing

We can conclude that, in addition to the above, the NeuCube-based methodology has several other important advantages namely:

- It requires only one iteration of data propagation for learning, while the classical methods of SVM and ELM require hundreds of iterations;
- The NeuCube-based model is adaptable to new data and new classes, while the other models are fixed and difficult to adapt to new data;
- The NeuCube-based model allows for a good interpretation of the data through the analysis of the SNNc.

6.3 Conclusion and Future Directions

NeuCube constitutes a biologically inspired three-dimensional environment of SNN for on-line learning and recognition of spatio-temporal data. This ability of the NeuCube models will allow to trace the development/decline of cognitive processes over time and to extract new information and knowledge about them.

Moreover, NeuCube offers the following advantages when compared to traditional information processing methods:

- Fast learning of STBD (only one pass data propagation);
- Higher accuracy of classification;
- Ability to adapt to new data through incremental learning (an evolving SNN is used as an output classifier) (Kasabov, 2003; Kasabov et al., 2013; Mohemmed et al., 2013), that includes learning of new input patterns from data and new classes;
- Interpretation of the model for a better understanding of the EEG STBD and the processes that generated it.

Future research could cover:

- Experimentation of NeuCube-based models on other EEG data;
- Parameter optimisation using quantum inspired evolutionary algorithms, as developed by (Platel et al., 2009; Nuzly Abdull et al., 2010; Schliebs, Defoin-Platel, Worner & Kasabov, 2009).
- Adding genetic information in terms of GRN to the model, as explained in (Benuskova & Kasabov, 2007; Hawrylycz et al., 2012; Henley, Barker & Glebov, 2011; Kasabov, 2014b; Kasabov, Schliebs & Kojima, 2011), to help study the

impact of genes on cognitive abilities, *e.g.* how much gene expression levels of neuro-receptors affect certain cognitive tasks.

- Testing the proposed method on new types of BCI, including neuro-rehabilitation, as proposed in (Chen et al., 2013; Van Essen et al., 2012).
- Testing the proposed method in clinical environment for early diagnosis of cognitive decline.
- Extending the proposed method for predictive modelling and personalised prognosis (Kasabov et al., 2014).
- Improved visualisation of the SNNc and the classifier during the training and recall procedures for an improved understanding of the data and the brain processes.
- Implementation of the proposed method on neuromorphic hardware to explore its potential for a highly parallel computation (Furber & Temple, 2007; Furber, 2012; Indiveri et al., 2011; Neftci, Chicca, Indiveri & Douglas, 2011).

6.4 Summary

The aim of this research has been to extend the proposed methodology in Chapter 5 for modelling and interpretation of EEG data that represents brain activities during cognitive tasks. As demonstrated, this approach leads to faster data processing, improved accuracy of the EEG data classification and improved understanding of the brain information and the cognitive processes that generated it when compared to traditional information processing methods.

All of this proved that the new proposed methodology can constitute an important contribution to the IS field of research, as it allows for the creation of new types of BCI

and also for early detection of cognitive decline to be used by clinicians in everyday diagnosis.

The next chapter discusses the proposed methodology is applied on EEG data recorded from a subject affected by AD in order to classify and study neurological disorders.

Chapter 7

The NeuCube-based Methodology for EEG Data Analysis of a Neurodegenerative Disorder

7.1 Introduction

In this chapter, we challenge ourselves with the problem of finding functional changes in brain activity that forewarn of the onset and/or the progression of a neurodegenerative process that may result in a number of disorders, including AD. This particular problem is of high importance for society, especially since the increase in human lifespan has been followed by the dramatic rise of cognitive impairments and neurodegenerative diseases. While AD has been the pathology affecting most victims in both developing and developed countries (Pritchard et al., 2013), EEG has been for long used to analyse and stage AD decline from MCI, as reported by (Labate, Foresta, Morabito, Palamara & Morabito, 2013; Morabito, Labate, Bramanti et al., 2013; Morabito et al., 2012). We believe that by classifying and analysing EEG data by means of the SNN NeuCube-based methodology proposed in Chapter 5, we can achieve a better understanding of

the neurodegenerative process and develop a predictive system.

This chapter is constructed in the following way: Section 7.2 presents the case study and the data used for the analysis following three methodologies; Section 7.3 discusses the conclusion and future work; and the chapter is summarised in Section 7.4.

The study presented in Section 7.2.3 was peer-reviewed and published in the *Springer Series of Smart Innovation, Systems and Technologies* for the *22nd Italian Workshop on Neural Networks (WIRN) 2014*. Copyright and permission from the publisher of the paper are included in Appendix B and the full text of the paper is presented in Appendix A.4. Also, the study presented in Section 7.2.5 has been submitted to the *2016 International Joint Conference on Neural Networks (IJCNN)*.

7.2 The NeuCube-based Methodology for Modelling AD EEG Data

7.2.1 Data Collection and Description

The EEG data was collected by the Scientific institute for Research, Hospitalization and Health Care (IRCCS) Neurolesi Centre of Messina, Italy.

The data collection protocol was approved by the local Ethical Committee and consent forms were signed by the patients under the study. Standard inclusion criteria were followed to select patients for the analysis. They underwent cognitive and clinical assessments, including Mini-Mental State Examination (MMSE). Diagnosis of AD was made according to the criteria of the National Institute of Aging-Alzheimer's Association. After diagnostic confirmation, patients were discriminated by gender, age,

education, dementia onset, marital status and MMSE scores. All patients were under the influence of drug treatments such as cholinesterase inhibitors (ChEis), Memantine, anti-depressants, anti-psychotics and anti-epileptic drugs. The dosage of each drug administered for the three month period prior to the experiment was carefully monitored.

Before data collection, all patients and their caregivers went through a semi-structured interview, which included questions regarding the quality and duration of their sleep the night before the experiment along with the food consumed and the time it was consumed.

Each recording session was carried out using 19 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 and the G2 electrode was used as reference. Electrodes were placed according to the sites defined by the standard 10–20 international system. A brain computer interface device was used to collect the EEG data, which was recorded under resting condition. Data was collected during the morning with subjects sitting with eyes closed and always under vigilant control.

7.2.2 Methodology of the Study

Data was processed following three methodologies: initially, a preliminary analysis was carried out on a small data set to determine the feasibility of the model to classify and analyse the neurodegenerative event (Section 7.2.3); secondly, a comparative analysis was performed to prove the methodology reliability and validity in an extended study (Section 7.2.4); finally, the methodology was applied to extract degeneration markers from the data collected during a longitudinal study (section 7.2.3).

The methodology proposed in Chapter 5 was applied as summarised below:

- The raw time series data, obtained from the EEG device, is directly fed into the

model as ordered sequence of real-valued data vectors. Each real value input stream of data is encoded into a spike train using AER-like algorithm (Chan et al., 2007; Dhoble et al., 2012).

- Due to the size of the data set, we generated a 3D cube of 1471 brain mapped LIF neurons; 19 of these mapped neurons were the input neurons, which corresponded to the number of EEG channels, as per the Talairach Atlas coordinates (Koessler et al., 2009).
- The SNNc is initialised according to the SW connectivity rule and trained on the input spike trains *via* unsupervised learning method, using the STDP (Song et al., 2000) learning rule.
- The output classifier is trained *via* supervised method. For this experimental study, deSNN algorithm (Kasabov et al., 2013) was used.
- The classification results are evaluated using both RRSV and LOOCV.
- The numerous parameters of NeuCube need to be optimised. Therefore, unsupervised and supervised training are repeated changing parameters' values until the desired classification output is achieved. In this study, this was obtained *via* grid search method.
- The trained SNNc is visualized and its connectivity and spiking activity analysed for a better understanding of the data and the brain processes that generate it.

7.2.3 A Case Study on AD EEG Data

For this preliminary analysis, we decided to use just the data recorded from one healthy subject (class 1) and one subject diagnosed as having AD (class 2). This were recorded for 65 seconds at 256 Hz, resulting in 16640 data points collected per session. The

control was a male subject of 58 years of age and the AD patient was a female subject of 80 years of age. They were both picked at random. The EEG data available was resized into 3 seconds epochs. Thus, for each of the two classes, we had 21 samples of 768 data points recorded for every of the 19 EEG channels. In total, we used 42 samples to run the NeuCube experiments.

Data was band-pass filtered between 0.5 and 32 Hz, which includes the relevant bands for AD diagnosis. No further pre-processing of the data was applied, as the NeuCube model is able to accommodate raw data directly; however, screening and selection of the signals that were visually artefact-free was performed prior to data analysis to avoid misleading results. Then, the original EEG signal was treated to avoid sub-effects related to the inevitable information loss implied by excluding some components.

Results and Discussion

In this study, we evaluated the feasibility of the NeuCube-based model proposed in Chapter 5 for the correct classification of data with known pattern and for extracting knowledge from the spatio-temporal EEG signals of a subject affected by AD *versus* a healthy control. Our aim is to develop an analysis and prediction tool to be used by clinicians for identifying the appearance of MCI and predict the onset of AD.

To achieve satisfying classification results, the numerous parameters of NeuCube need to be accurately selected. Based on previous studies that we have conducted, some critical variables were identified which required careful optimization and selection of values that corresponded to some of them. Taking into account that the tuning of every parameter involves a considerable amount of processing time, we needed to carefully select the proper number of variables to be optimised. The AER threshold parameter

was chosen for this study, as it is applied to the entire signal gradient reflecting the timing; therefore, the rate of the generated spike trains depend on this threshold. Moreover, since NeuCube is a stochastic model, altering this value means also altering the initial model configuration each time. Thus, using a grid search, we evaluated the classification accuracy of 10 model configurations adjusting the AER parameter for every new configuration. For that, we used 50% of the entire time series for training and the other 50% for testing. The parameter values used after optimization were the following:

- The AER_{Thr} was set at 0.94;
- The SW connectivity parameter p was set at 0.15;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.5, 6 ms and 0.02 respectively;
- The STDP rate parameter α was set at 0.01;
- The variables *mod* and *drift* of the deSNN classifier were set at 0.4 and 0.25 respectively.

Classification accuracy was calculated by statistical processing of the information obtained from the confusion table. Classifier outputs were evaluated using both RRSV and LOOCV, as reported in Table 7.1.

Table 7.1: NeuCube’s classification accuracy obtained for both healthy control and AD class. Results are obtained using both 50/50%-Training/Testing and LOOCV. Accuracy is presented in %

NeuCube Classification Accuracy		
CLASS	(50/50%-Tra/Test.)	(LOOCV)
Control	100	100
AD	100	100
Average Accuracy	100	100

Comparison of Results with Popular AI Methods

NeuCube results have been compared with other traditional AI approaches, such as MLP, SVM, ECM and inductive evolving classification function (IECF) (Song & Kasabov, 2001; Kasabov, 2007).

To apply the above traditional AI approaches on the available data sets, the NeuCom platform was used (Kasabov, 2007); NeuCom is a self-programmable, learning and reasoning computer environment freely available on-line (www.theneucom.com). The LOOCV method was used to evaluate the classifier outputs and the datasets were normalised prior to the experiments to ensure the highest classification accuracy: the normalisation protocol applied to each method consisted of a linear standardization of the data's vectors using values between 0 and 1 as a scale.

Classification accuracy was analysed *via* supervised learning method, which is based on classification of data with a known pattern. The results obtained are presented in the confusion table as number of True Positives (TP) and True Negatives (TN) against False Positive (FP) and False Negative (FN). An analysis of the classification outputs obtained by all different methods was performed based on this information, which was further processed to calculate the following metrics:

- Accuracy percent (A %):

$$A \% = (TP + TN) / (TP + FN + FP + TN) * 100 \quad (7.1)$$

- Sensitivity (S):

$$S = TP / (TP + FN) \quad (7.2)$$

- Specificity (SP):

$$SP = TN / (FP + TN) \quad (7.3)$$

Results obtained are summarised in Table 7.2 and they were used to plot a Receiver Operating Characteristics (ROC) graph (Fig. 7.1) (Fawcett, 2006). The parameters settings used for each method are reported in Table 7.3.

Table 7.2: Comparison of the results obtained *via* NeuCube *versus* traditional machine learning methods (MLP, SVM, IECF and ECMC), confusion table and resulted metrics.

Confusion Tables					
Control	AD	MLP		SVM	
TP	FN	11	14	11	14
FP	TN	10	7	10	7
IECF		ECMC		NeuCube	
21	13	21	1	21	0
0	8	0	20	0	21
METRICS					
	NeuCube	MLP	SVM	IECF	ECMC
A% (1)	100	43	43	69	98
S (2)	1	0.52	0.52	1	1
SP (3)	1	0.33	0.33	0.38	0.95
1-SP	0	0.67	0.67	0.62	0.05

Table 7.3: Traditional machine learning methods (MLP, SVM, IECF and ECM) parameter settings used to classify AD data *versus* healthy control data.

MLP parameters		SVM parameters	
Normalization	yes	Normalization	yes
Number of Hidden Units	3.0000	kernel	Polynomial
Number of Training Cycles	300.0000	Degree, γ	1
Output Value Precision	0.0001		
Output Function Precision	0.0001		
Output Activation Function	linear		
Optimization	scg		
IECF parameters		ECM parameters	
Normalization	yes	Normalization	yes
Max. Influence Field	1.00	Max. Influence Field	1.00
Min. Influence Field	0.01	Min. Influence Field	0.01
M of N	3.00	M of N	3.00
Membership Function	2.00		
Epochs	4.00		

As far as the ROC graph is concerned, each classifier produces a sensitivity and a

specificity value, which results in a single point on the graph's space. Classifiers falling in the top-left area of the graph are considered achieving desirable results (Fawcett, 2006). NeuCube appears on the top-left hand side of the graph (point 0,1) performing as a perfect classifier. High performance is also achieved by the ECM method, while the IECF method, even though classifying nearly all positives correctly, returns high false positive, which brings it too far on the top right hand side of the graph.

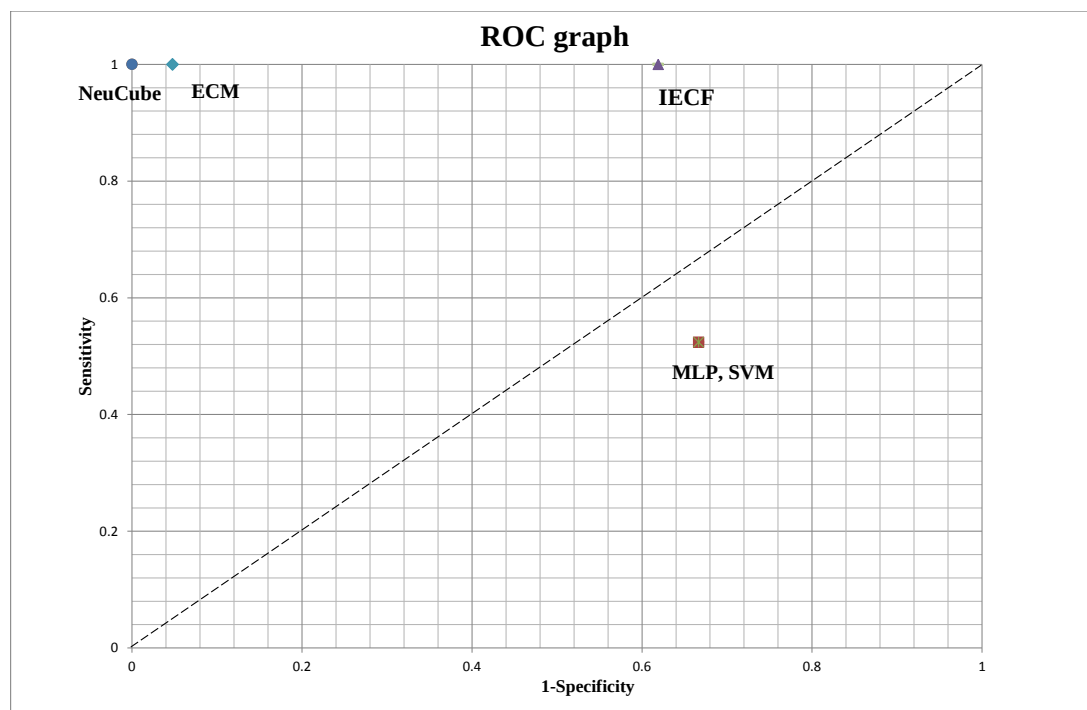


Figure 7.1: ROC graph. 1-Specificity is plotted on the X axis and Sensitivity is plotted on the Y axis.

When comparing NeuCube performance to the traditional AI approaches, we can conclude that NeuCube performed significantly better with the highest accuracy, sensitivity and specificity over all. In terms of these metrics, the closest to NeuCube's result was shown by ECM, whilst the poorest performing methods were MLP and SVM.

Optimization of the results obtained *via* traditional AI techniques is not a trivial process

and it requires more sophisticated optimization methods. In fact, the few parameters that influence these methods cannot be tuned independently; one of the reasons is that some of them are discrete values and others are continuous. Thus, it is not viable to improve the output results of these methods.

Model Interpretation and Data Understanding

The NeuCube model constitutes an SNN architecture based on some of the most important principles governing the neural activity in the human brain. Thus, it is a valuable architecture for on-line learning and recognition of STBD. It also takes into account data features, offering a better understanding of the information and the phenomena of study. In fact, one of the main advantages of the NeuCube architecture is that after training the SNNc can be visualized and its connectivity and spiking activity can be observed. This ability of the NeuCube architecture allows us to trace the development/decline of neurological processes over time and to extract new information and knowledge about them.

Illustrated in Fig. 7.2 is the SNNc state obtained after it was trained with data from a control subject (top picture) and then after it was trained with data from the subject affected by AD (bottom picture).

We can observe that new connections are formed between the neurons of the network and especially around the input neurons, which were mapped according to the Talairach coordinates of the 19 EEG electrodes. We can observe in Fig. 7.2 that the neural activities of the healthy subject and the subject suffering from AD are quite different. In fact, in the case of the healthy control, the evolved connections are equally distributed in every brain region. On the other hand, in the case of the patient affected by AD, we can observe that this activity decreased in the left hemisphere and there

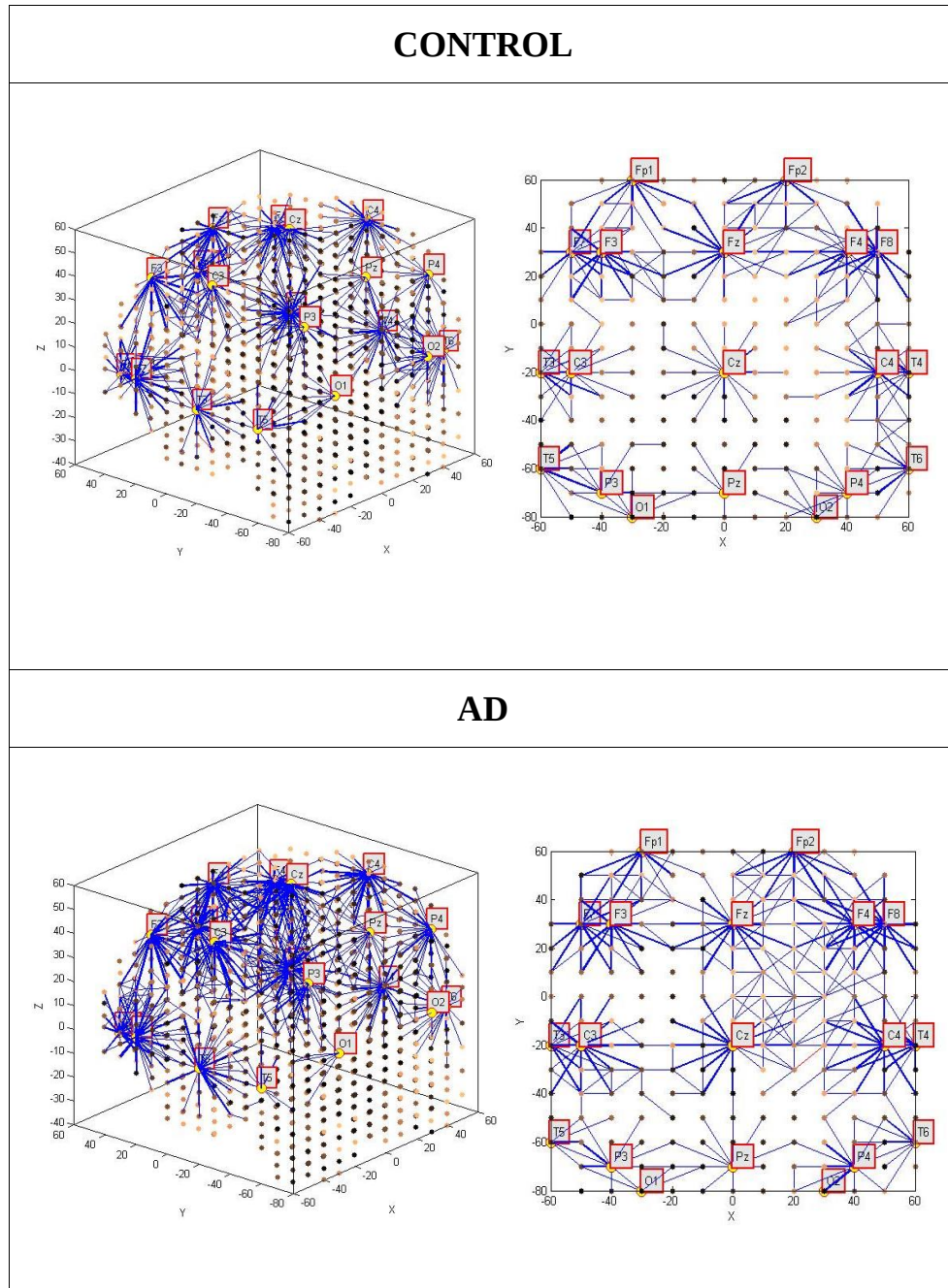


Figure 7.2: SNNc connectivity obtained after training it with the data belonging to the healthy subject (top) and the AD patient (bottom) individually. The image shows both the 3D cube and the (x,y) plane only of the SNNc. Blue lines represent excitatory synapses, while red lines represent inhibitory synapses. The brighter the colour of a neuron the stronger its interactivity with a neighbour neuron. Thickness of the lines also indicates the strength of neurons' connectivity. The 26 input neurons are labelled in yellow according to their corresponding EEG channels.

is a higher activity evolved in the right hemisphere, maybe to compensate the lack of activity in its counterpart and therefore as a consequence of the degeneration of the AD brain.

7.2.4 Comparative Analysis: H versus MCI and AD

For this study, five healthy/control subjects (H group), 20 patients diagnosed as having MCI (MCI group) and 25 subjects affected by AD (AD group) were selected. Resting data was recorded at 1024 Hz. Data was band-pass filtered at 0.125 – 64 Hz and down-sampled to 256 Hz by creating an average based on four samples. The resting data was recorded for several minutes, although only the first 10 seconds were used to carry out the experiments with the NeuCube, as this information was considered enough for a preliminary analysis over the data sets. We obtained a total of 50 samples, each representing the data of an individual subject (2560 data points per 19 EEG channels).

Data was entered into the NeuCube in the form of an ordered sequence of real-valued data vectors. Experiments were run by using 50% of the data for training and 50% for testing. A grid search algorithm of 100 loops was used to evaluate the best combination of parameters that resulted in the highest classification accuracy. The parameters values used after optimization were as follows:

- The AER_{Thr} was set at 3.98;
- The SW connectivity parameter p was set at 0.15;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.5, 6 ms and 0.02 respectively;
- The STDP rate parameter α was set at 0.013;

- The variables *mod* and *drift* of the deSNN classifier were set at 0.4 and 0.25 respectively.

Results and Discussion

In Table 7.4, we report the classification accuracy obtained with this combination of parameters. The results, obtained after testing, are expressed in the confusion table as the number of correctly classified samples *versus* the number of misclassified samples. It is interesting to observe that none of the samples belonging to the healthy subjects were classified correctly. However, only three samples were available from the H group and this number may not be sufficient for the unsupervised algorithm to learn from the data. Also, we can observe that three of the 10 samples belonging to the MCI group were misclassified as AD, while two of the 12 samples belonging to the AD group were misclassified as MCI.

Table 7.4: NeuCube confusion table results obtained by classifying the three groups: H, MCI and AD. The correctly predicted classes are located in the diagonal of the table.

Confusion Table			
	H	MCI	AD
H	0	0	0
MCI	3	7	2
AD	0	3	10

Even though the confusion table provides information about the classification of the data; it is through visualization of the SNNc that we can actually study how the time-series data has been learned during unsupervised training and extract knowledge from it. Our aim is to understand whether the misclassified samples have evolved connectivity and spiking activity that is comparable to the class that they were classified into (Fig. 7.3).

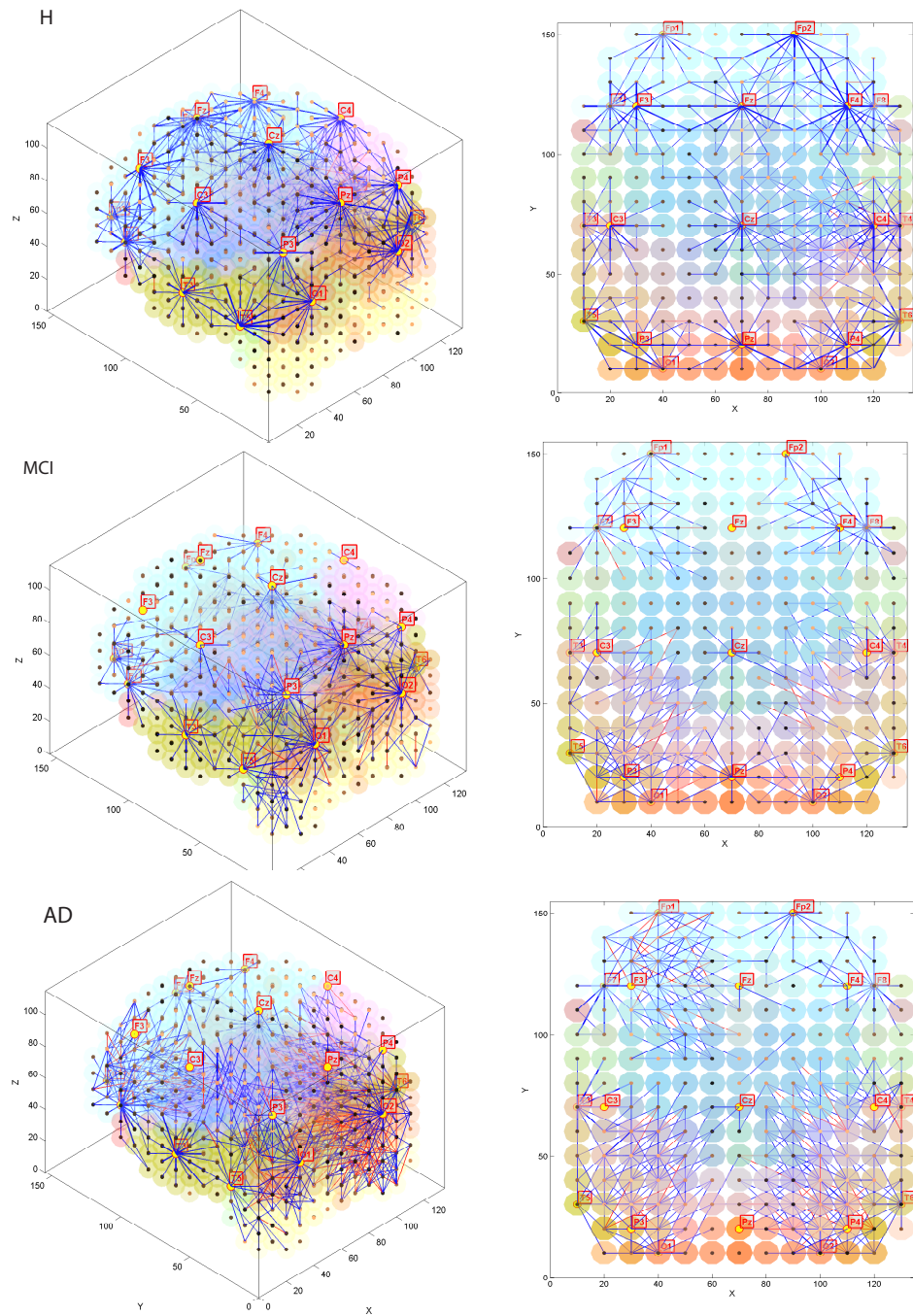


Figure 7.3: SNNc connectivity evolved after unsupervised learning of the data belonging to the H, the MCI and the AD group separately. The figures on the left hand-side show the 3D brain-like SNNc, while the figures on the right hand-side only show the (x,y) projection.

Fig. 7.3 depicts the 3D brain-like SNNc and its (x,y) projection along with the corresponding 12 brain functional areas (*i.e.* yellow-green, temporal lobe; pink, parietal lobe; light-blue, frontal lobe; red, fronto-temporal space; light-yellow, posterior lobe; orange, occipital lobe; green, anterior lobe; blue, sub-lobar region; grey, limbic lobe; purple, pons; blue-green, midbrain; brown, medulla). Also, the blue lines represent excitatory synapses, while the red lines represent inhibitory synapses. The 19 input neurons are labelled in yellow according to their corresponding EEG channels. The figures compare the activity obtained after training the cube with the data belonging to the H group, the MCI group and the AD group individually.

Similarly to the preliminary analysis reported in Section 7.2, the connectivity generated by the H group data is equally distributed in every brain region, especially around the input neurons. Also, we can observe in Fig. 7.3 that the neural activity generated by the three groups is quite different. Interestingly, the pattern of activity generated in the fronto-temporal neurons (associated with cognitive activity) and in those associated with the central line (*i.e.* electrodes Pz , Cz and especially Fz) substantially decreases for the MCI and the AD groups. However, more activity is generated between the parieto-occipital neurons; we can assume that this compensates for the lack of activity in the other areas of the brain. We can also assume that some decreased activity generated by the AD group data could be a sign of degeneration caused by the progress of the disease in AD patients.

7.2.5 Longitudinal Study

A total of seven patients were selected for the longitudinal study: three affected by AD and four diagnosed as suffering from MCI. They were all followed longitudinally for three months. During this period of time, the EEG data was recorded twice, at the

beginning of the study and at the end, denoted as t_0 and t_1 . This data was recorded at a sampling rate of 1024 Hz for 5 minutes and a 50 Hz notch filter was applied during collection. Then, data was downsampled to 256 Hz and processed using a 5 seconds sliding temporal window (*i.e.* one window includes 1280 EEG samples). The EEG signal was divided into rhythms of type δ , θ , α and β by using a set of four band-pass filters implemented in Matlab that use inverse Fast Fourier Transform (FFT). Data was divided into four of the main EEG sub-bands (α , β , δ and θ rhythms) that are considered relevant for the case study problem. The four sub-bands were partitioned into m non-overlapping windows, where m depends of the length of the recording, which was 5 minutes on average.

Classification

To investigate whether the data collected during the two different sessions (t_0 and t_1) identifies four different stages of neural degeneration (from early MCI to advanced AD), we classified the entire EEG signal from 0-64 Hz. Data was divided into four classes: data collected at t_0 from subjects diagnosed as having MCI was labelled as class 1 (MCI t_0), while the data collected at t_1 from the same subjects was labelled as class 2 (MCI t_1); and data collected at t_0 from AD patients was labelled as class 3 (AD t_0), while the data collected as t_1 from the same patients was labelled as class 4 (AD t_1). In total we obtained 14 samples, two for each of the seven subjects, one at t_0 and one at t_1 . Even though, every subject underwent several minutes of data recording, we resized each samples to 42240 data points for 19 EEG channels, as this was the size of the smallest sample available.

NeuCube's parameters were optimised *via* grid search method that evaluated the best combination of parameters that resulted in the highest classification accuracy. Experiments were run by using 50% of the data for training and 50% for testing. The resulting

best parameters were set as follows:

- The TBR_{Thr} for encoding algorithm was set at 0.5;
- The SW connectivity radius was set at 2.5;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.5, 6 ms and 0.002 respectively;
- The STDP rate parameter α of the unsupervised learning algorithm was set at 0.01; rate was set at 0.001;
- The variables *mod* and *drift* of the deSNN classifier were set at 0.8 and 0.005 respectively.

In Table 7.5, we report the classification accuracy obtained with this combination of parameters.

Table 7.5: NeuCube results expressed in percentage of classification accuracy obtained amongst the four classes: MCI t_0 , MCI t_1 , AD t_0 and AD t_1 .

Class	Accuracy %
MCI t_0	100
MCI t_1	50
AD t_0	100
AD t_1	100
Overall Accuracy	83.33

These results demonstrated the capability of the NeuCube to achieve high classification accuracy, but also that the four classes were in effect identifying four different stages of neural degeneration (from early MCI to advanced AD).

Analysis of Functional Changes in Brain Activity

To better extract degeneration features from the data, we analysed the SNNc connectivity generated after unsupervised learning. As a case study, we selected the EEG data

collected from a patient affected by AD (a woman of 83 years of age). This patient scored 16, at t_0 , and 13, at t_1 , in the MMSE test, which indicates decline in cognitive ability. However, more information can be obtained from the EEG data by discriminating relevant EEG sub-bands. Our goal is to better understand the advancement of the disease and to localize specific areas of the brain that are more seriously affected by neural degeneration.

Data was visualised after STDP learning by applying a threshold of 0.2 to the total amount of connection weight generated. By lowering this threshold the images would be difficult to analyse (in this case study). Fig. 7.4 and Fig. 7.5 show the SNNc along with the corresponding 12 brain functional areas. Yellow-green denotes the temporal lobe; pink the parietal lobe; light-blue the frontal lobe; red the fronto-temporal space; light-yellow the posterior lobe; orange the occipital lobe; green the anterior lobe; blue the sub-lobar region; grey the limbic lobe; purple the pons; blue-green the midbrain; and brown the medulla. Also, the 19 input neurons are labelled according to their corresponding EEG channels. In the figures, blue lines indicate the excitatory synapse and red lines the inhibitory synapse; the thickness of these lines indicates the strength of activity between neurons.

Fig. 7.4 shows the SNNc connectivity generated after unsupervised learning of the EEG signal (0-64 Hz) at t_0 and t_1 . The figures show significant decrease in neural activity from t_0 to t_1 . Quantitative measures of these results are also available in Appendix C.

More information can be extracted from the data by identifying relevant EEG sub-bands for AD to study the patient neural activity. Fig. 7.5(a)-(h) shows the SNNc connectivity generated after unsupervised learning of the EEG data in α , β , δ and θ sub-bands at t_0 and t_1 .

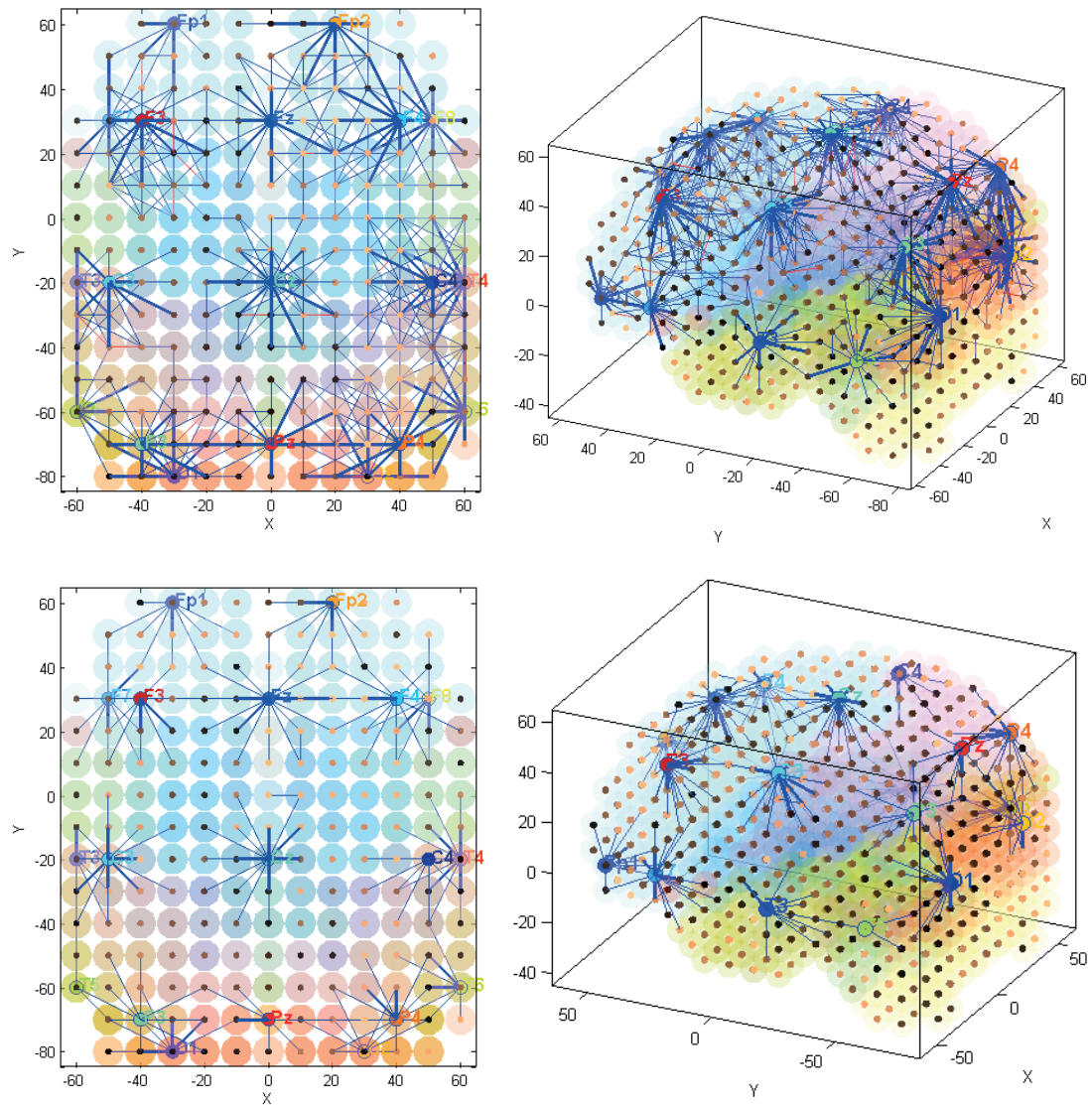


Figure 7.4: Connectivity generated after unsupervised learning of the SNNc was performed on the encoded EEG signal (0-64 Hz) at t_0 (top figures) and at t_1 (bottom figures). The figure shows the (x,y) plane and the 3D SNNc.

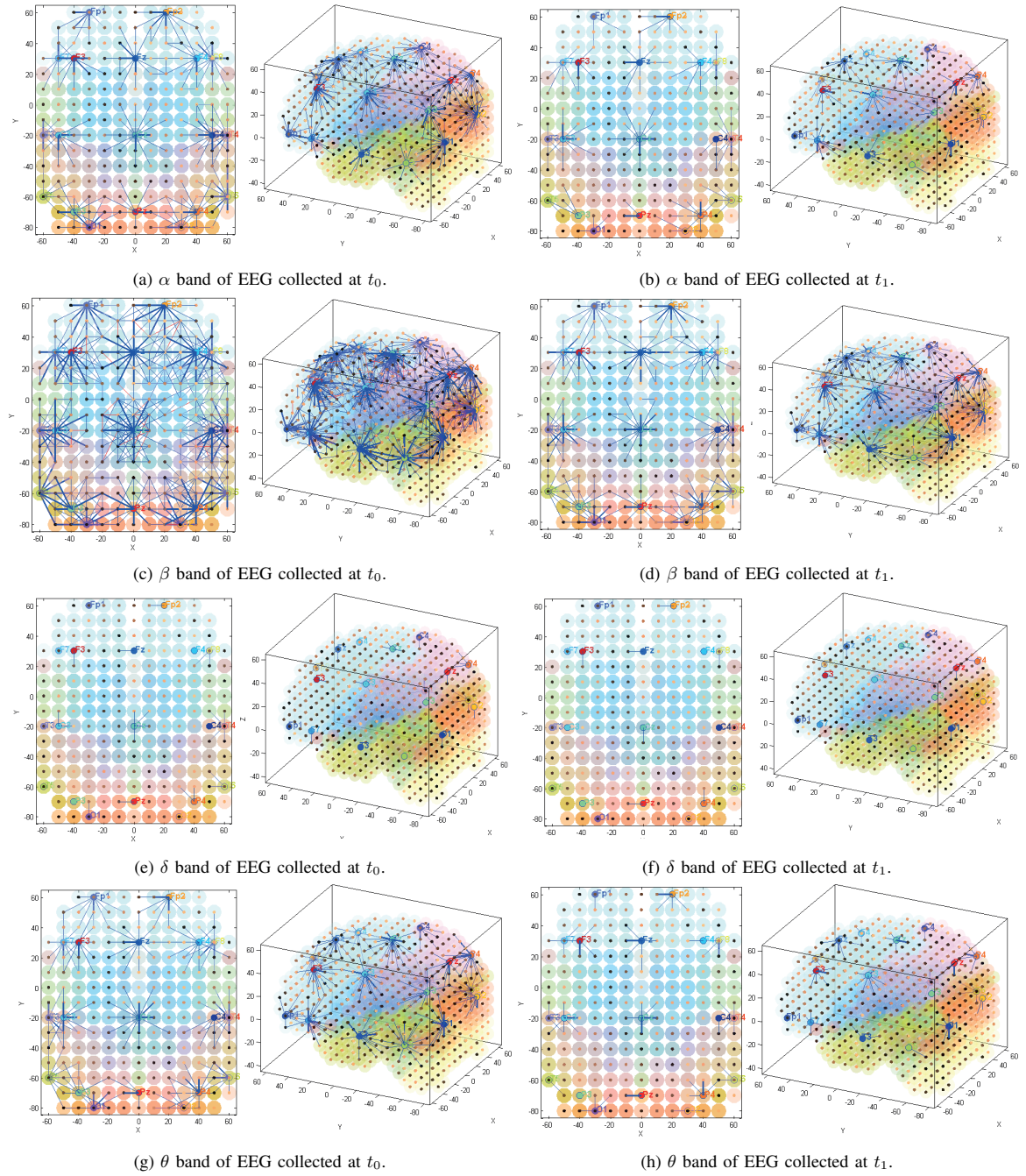


Figure 7.5: Connectivity generated after unsupervised learning of the SNNc was performed on every EEG sub-band of interest (α , β , δ and θ) at t_0 and t_1 . The figure shows the (x,y) plane and the 3D SNNc.

As we can study from the figures, functional connectivity decreases as the disorder advances (from t_0 to t_1). The disease affects both α and θ sub-bands, decreasing the connectivity across the brain regions. This effect is especially evident for the δ sub-band, where almost no connectivity is generated over the brain regions. On the other hand, higher frequency bands, such as β sub-band, show an increase in activity.

This analysis provides new evidence that can be used to improve our understanding of AD. Thus, the NeuCube can provide a powerful decision making tool that can support clinicians to target efficient drug treatments.

7.3 Conclusions and Future Directions

The goal of the proposed study has been to analyse how the proposed NeuCube-based methodology can be used for the classification and analysis of EEG data collected from people affected by a neurodegenerative disorder. This is important for the creation of new types of BCI-based systems and also for the early detection of the onset of a neurological disorder. Further improvement of the understanding and use of the model proposed herein would significantly contribute to the advancement in machine learning for the prediction and understanding of brain data and more specifically for data related to neurodegenerative pathologies, such as AD.

The NeuCube-based methodology revealed important benefits:

- When compared with traditional AI techniques, it requires only one pass data propagation for learning, while traditional methods require numerous iterations.
- The NeuCube-based methodology is adaptable to new data and new classes, while traditional AI techniques are fixed and difficult to adapt to new data.

- The NeuCube model achieved better classification accuracy per class than the other traditional AI techniques.
- The NeuCube model also offers a better understanding of the data and therefore of the brain processes that generate it through visualization and analysis of the output SNNc state.

There are different scenarios and avenues to be taken in the future such as:

- Extending the model by adding genetic information in terms of GRN, as proposed by (Benuskova & Kasabov, 2007), to be used as an optimization module to help study the impact of genes on cognitive abilities, *e.g.* how much gene expression levels of neuroreceptors effect certain cognitive tasks.
- Visualization and/or virtual reality of the SNNc can be used by clinicians to evaluate how effectively patients improve their neurological activity before and after treatments when compared to healthy controls.
- Comparison of the developed model with other techniques used for AD classification, such as Random Forest (Gray, Aljabar, Heckemann, Hammers & Rueckert, 2013), kernel Support Vector Machine Decision Tree (kSVM-DT) (Zhang, Wang & Dong, 2014) Learning Vector Quantization using Support Vector Machine (LVQ-SVM) (Ortiz, Gorriz, Ramirez & Martinez Murcia, 2013), Hidden Markov Random Field (Shu, Nan, Koeppe et al., 2014).
- Implementation of the proposed method on neuromorphic hardware to explore its potential for a highly parallel computation (Indiveri et al., 2011).

7.4 Summary

This chapter investigates the feasibility of the methodology proposed in Chapter 5 to be used as an indicator of the onset and/or the progression of a neurodegenerative process.

The results obtained demonstrated that the proposed NeuCube-based methodology better model, classify, interpret and understand the EEG data and the brain processes involved. It also begins to address *RQ2* formulated in Chapter 1: *Can we identify the functional changes in neural activity generated when a subject affected by a particular neurological disorders (and/or under a particular drug treatment) is compared with a control subject or the absence of a neural event?*

Aiming at exploring the possibilities offered by the analysis of the SNNc evolved after learning and therefore giving an exhaustive answer to the question mentioned, in the next chapter we extend the proposed methodology by developing a new methodology for the analysis of functional changes in brain activity across different conditions and different groups of subjects.

Chapter 8

A New Methodology for the Analysis of Connectivity and Spiking Activity in a NeuCube Model for the Understanding of Functional Changes in the Brain

8.1 Introduction

In this chapter, by extending the NeuCube-based methodology proposed in Chapter 5, we introduce a new methodology for the understanding of functional changes in the brain. The methodology is applied on EEG data to analyse the connectivity and spiking activity evolved in the SNN module under different conditions and across different groups of subjects.

Using standard statistical or machine learning techniques to classify EEG data from

groups of patients under different treatment can suggest whether there is a functional improvement, as a result of treatment. As demonstrated in already published studies (Wang, Wouldes, Kydd & Russell, 2012; Wang, Wouldes & Russell, 2013; Wang, Wouldes, Kydd, Jensen & Russell, 2014), cognitive functions improved in patients dependent on illicit opiates who are undergoing methadone maintenance treatment (MMT) in contrast to those dependent on illicit opiates that do not undergo any treatment. By comparing these two groups of patients with healthy controls, they also demonstrated that the MMT patients' cognitive functions are comparable to healthy subjects. In (Wang et al., 2012, 2013, 2014), groups' difference was investigated by analysing spectral power of EEG data using traditional statistical methods (*i.e.* analysis of covariance, independent sample t-test, etc.) and the results revealed the fluctuation of neural activity within an individual channel only.

Traditional statistical and AI methods applied to the study of functional brain changes lack the ability to explain which functional areas of the brain are affected during treatment, how much they are affected and what are the changes of the dynamics of the brain as a chain of spiking activity over time. Time information is present in STBD such as EEG data, but when the data is processed (*e.g.* classified) this information is obscured and there is no explanation of the final results related to the time component. In this respect traditional methods can be considered "black boxes" in a sense (Kasabov, 2014a). These are important questions that need to be addressed for a better understanding of functional changes in the brain under various conditions, including: neurological disease progression, disease treatment over time and ageing.

Methadone has been used as a pharmacological substitute for the treatment of opiate dependence since the mid-1960s. As a substitute for illicitly used opiates, the purpose of MMT is not to achieve a drug-free state but to reduce the harm associated

with illicit drug use and to improve life quality and psychosocial functioning for the individual (Lobmaier, Gossop, Waal & Bramness, 2010). The benefits of MMT have been demonstrated by many studies. For example, MMT has been shown to effectively reduce the use of other drugs, injection-related risky behaviour, criminal activity, mortality, and the transmission of HIV and other blood-borne pathogens, such as hepatitis-B (Ball, Lange, Myers & Friedman, 1988; Bell, Hall & Byth, 1992; Marsch, 1998; Gibson, Flynn & McCarthy, 1999). Consequently, MMT is now the most common treatment for opiate dependence in many countries, including the United States of America, Australia, the United Kingdom and New Zealand (Adamson et al., 2012; Joseph, Stancliff & Langrod, 1999).

Despite methadone's effective clinical use, it remains uncertain whether MMT has negative effects on cognitive functions, given that methadone has clinically similar actions and analgesic effects to morphine (Dole, 1988). Methadone primarily binds to μ receptors that are found throughout the brain and are densely concentrated in the periaqueductal gray, amygdalae, hippocampus, thalamus and striatum (Martin, Hurley & Taber, 2007; McBride, Chernet, McKinzie, Lumeng & Li, 1998). In humans, these areas are critical for pain perception, visual and sensory processing, memory and attention. Therefore, there is particular concern whether long-term use of a sedative opiate antagonist, such as methadone, has effects on cognitive function.

In this chapter, these problematics are addressed by means of a new NeuCube-based methodology, which makes use of EEG data to identify differences between healthy subjects, patients with opiate addiction and those undertaking substitution treatment for opiate addiction. The chapter is constructed in the following way: section 8.2 presents the new NeuCube-based methodology for connectivity and spiking activity analysis. Section 8.3 presents a case study on EEG data. Changes in functional brain

activity are analysed across groups of opiate addicts and those who have taken MMT in comparison with control subjects. This section also presents and discusses the results. The conclusion in section 8.4 clearly identifies the NeuCube methodology as being advantageous for the purpose of revealing functional brain changes and the prediction of response to treatment.

This study was peer-reviewed and published by *Neural Networks Journal*. Copyright and permission from the publisher of the paper are included in Appendix B and the full text of the paper is presented in Appendix A.5.

8.2 Connectivity and Spiking Activity Analysis in a NeuCube Model Trained on EEG STBD

8.2.1 The Methodology

The new methodology proposed for the analysis of connectivity and spiking activity generated by revealing the “hidden” EEG patterns consists of the following procedures:

1. The time series data obtained from the EEG device is first ordered as a sequence of real-value data vectors. One of the main advantages of the NeuCube is that there is no need for pre-processing of the EEG data, such as normalisation, scaling, and smoothing. The model can also deal with noisy data, which is significantly time-saving.
2. In order to obtain an input compatible with the SNNc, each real-value input time series (*e.g.* the measured EEG data in one electrode) is transformed into a spike train (*i.e.* sequence of binary events) using a spike encoding method, and more specifically, using the TB representation algorithm, as implemented in Chapter 5.

This algorithm is based on the AER principle and is well suited for EEG STBD, since it only identifies the differences in consecutive values, as demonstrated and implemented in the artificial silicon retina chip (Delbruck, 2007; Dhoble et al., 2012) and the artificial cochlea chip (Chan et al., 2007).

3. The input spike sequences are presented to an evolving brain-mapped SNNc that reflects the number of input variables (*e.g.* the 26 EEG channels in the case study from section 8.3), the functional brain areas associated with them and the size of the data available.
4. The SNNc is implemented using the LIF type of neurons (Gerstner, 2001) and is initialised as SW connected network, as implemented in Chapter 5. The SW connectivity principle has been chosen here as it is based on the biological process that makes neighbouring neural cells to be highly and strongly interconnected to each other, therefore, it is fundamental for the initialization, the capture of relevant patterns from the data and the learning process of this model.
5. The SNNc is trained in an unsupervised mode using STDP (Song et al., 2000) learning rule. This algorithm allows spiking neurons to learn consecutive temporal associations from the EEG data within and across EEG channels. The neurons become able to form new connections in the architecture, which can then be analysed and interpreted. This makes the NeuCube-based methodology useful for learning spatio- temporal patterns from EEG data, forming associative type of memory that can be further explored.
6. The output classifier is trained in a supervised mode (*i.e.* method based on classification of data with a known pattern) using deSNN (Kasabov et al., 2013) algorithm to classify the EEG STBD into the respective classes. As implemented in Chapter 5, this classification method combines the RO learning rule (Thorpe

& Gautrais, 1998) and the STDP (Song et al., 2000) temporal learning for each output neuron to learn a spatio-temporal pattern using only one pass of data propagation.

7. The classification results are evaluated using RRSV or LOOCV.
8. Steps (4) to (7) are repeated using different parameter values in order to optimize the classification output. The best performing model can then be recorded for further uses.
9. The trained SNNc is visualised, its connectivity and the dynamic spiking activity are analysed for a better understanding of the data and the brain processes that generated it including changes of brain functionality across different conditions and groups of subjects.

It is important to highlight that the NeuCube model is a stochastic model (*i.e.* the initial connections between the neurons of the network are randomly generated) and therefore the output classification accuracy depends on the parameters settings. These parameters are:

- The TB parameter TBR_{thr} ;
- The SW connectivity parameter p was set at 0.15;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model parameters, which in our experiments were set at 0.5, 6 *ms* and 0.02 respectively after optimisation;
- The STDP rate parameter α ;
- The variables *mod* and *drift* of the deSNN classifier that were set at 0.4 and 0.25 respectively.

In this study, a grid search method was applied, mainly to find the best value associated to the TBR_{thr} , as this threshold is applied to the entire signal gradient according to the time and therefore the rate of generated spike trains depends on it. Moreover, since the NeuCube is a stochastic model, altering this value means also modifying the initial model configuration each time. Default parameters were not set up prior to the experiment, but they were chosen in consistence with the range of figures reported by previous neuroscientific reports. For instance, the refractory time suggested by our model was 6 *ms*. In general, the refractory time interval for neural spiking reported by a previous study is about 5 *ms*, however, it might require more time in response to certain events (Berry & Meister, 1998).

8.2.2 The Study of Brain Functional Changes with the Proposed Methodology

A NeuCube model can accommodate data in one pass learning to dynamically evolve an output classifier. A new output neuron can be generated in the output classifier for every new input pattern learned in the SNNc and trained in one pass learning mode (Kasabov et al., 2013). This ability of the NeuCube models enables the brain processes to be traced over time and to extract new information and knowledge about them. The procedure proposed can be summarised in the following two main steps:

- First, a NeuCube model is trained until satisfactory performance (*e.g.* classification) of the EEG data is achieved, following the methodology presented above.
- Then, the SNNc connectivity structure is analysed for a better understanding of the dynamics of the data across different subjects and different groups of subjects. In fact, the connectivity of the SNNc represents dynamic spatio-temporal associations of the brain activities represented by the value of the input variables (the EEG channels).

Through the analysis of NeuCube evolved connectivity, the following research questions can be addressed and studied in general:

- a) Can we analyse the evolution of connectivity and/or spiking activity that occur in a trained NeuCube when comparing data of an individual subject or a group of subjects performing a task with data from another individual or another group?

Fig. 8.1 presents an example of a step-wise SNNc connectivity evolution during unsupervised training on EEG data recorded from all subjects who belonged to all three groups – healthy (H), opiate addicted (O) and people using methadone (M) as treatment – during an eyes open (EO) resting state.

- b) Can we identify the brain areas where the functional changes in neural activity is generated by the different classes using the computational model developed?

In our case study this question is addressed as follows: Fig. 8.2 (left) illustrates the different SNNc connectivity generated after a SNNc model which was trained with EEG data recorded from all subjects who belonged to the M group *versus* the same initial SNNc trained with EEG data recorded from all subjects who belonged to the H group during an EO resting state; Fig. 8.2 (right) shows different SNNc connectivity resulted after a SNNc was trained with EEG data recorded from all subjects who belonged to the M group *versus* the connectivity generated with data recorded from all subjects of O group during the EO state; and Fig. 8.3 presents the connectivity of a SNNc after training it with EEG data recorded from patients who have been treated with a different dose of methadone before completing the same trial.

These research questions are addressed here on EEG data related to the case study problem and explained in more detail in the following section. The above research questions are generic and can be studied in relation to other brain disorders and patients' response to respective treatments.

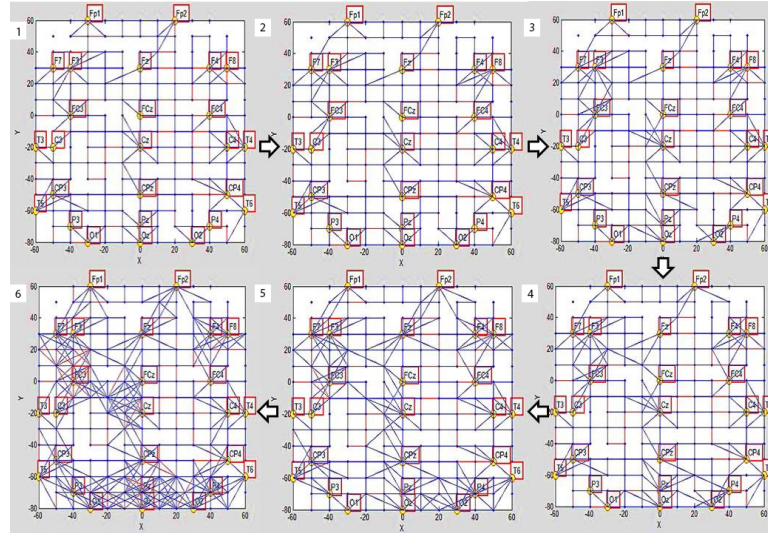


Figure 8.1: Example of a step-wise connectivity evolution in a SNNc activity during STDP learning on EEG data recorded from all subjects who belonged to all three groups – H, O and M – during an EO state (for interpretation — see next section).

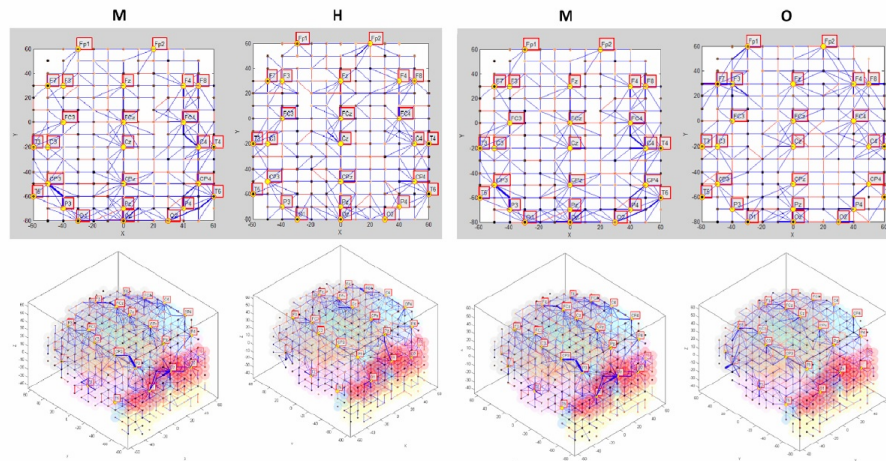


Figure 8.2: Examples of the SNNc connectivity after unsupervised training is finished. A SNNc was trained using EEG data recorded from all subjects who belonged to the M group and from all subjects who belonged to either the control H group (left) or the O group (right) during an EO state (for interpretation — see next section).

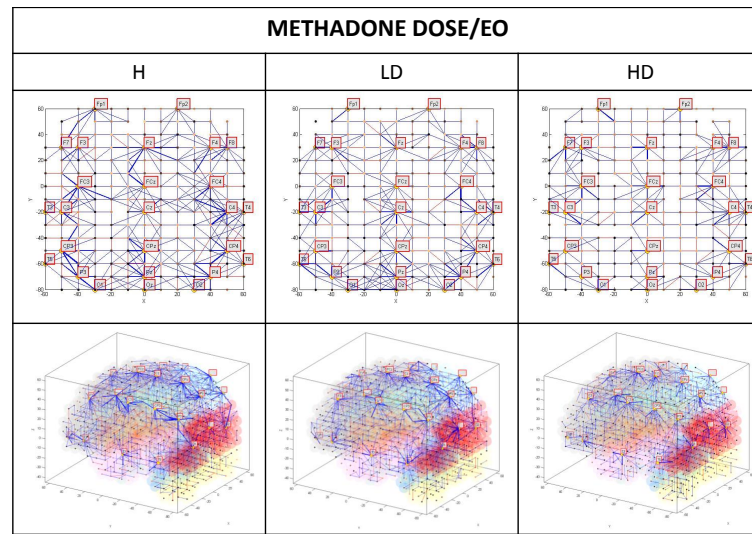


Figure 8.3: Examples of the SNNc after unsupervised training is finished. The SNNc was trained using EEG data recorded during the EO state, from 12 subjects who belonged to the control group (H), from patients taking low dose (below 60 *mg*) of methadone (LD) and from M patients taking high dose (60 *mg* or above) of methadone (HD) (for interpretation — see next section).

8.3 Connectivity Analysis of NeuCube Models Trained on EEG Data for the Understanding of Functional Changes in the Brain and Predicting Patients Response to Treatment

8.3.1 EEG Data Collection

Prior to commencing this research, ethical approval was granted by the Health and Disability Ethics Northern X Committees of New Zealand to Dr. G.Y. Wang who collected the data and published other work using the same data set such as in (Wang, Kydd & Russell, 2015). As reported in Wang, Kydd, and Russel (2015), all EEG recordings were conducted between 12 pm and 4 pm, apart from three participants (one was from the opiate user group and two were from the healthy control group) who completed

EEG recording at 6 pm, due to their availability. All EEG recordings were conducted on a one-to-one basis in a sound and light attenuated laboratory. A QuickCap (Neuroscan 4.3) 40 sensor shielded cap was used to acquire EEG data from the cephalic sites. The 26 cephalic sites included Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, Cpz, C3, C4, CP3, CP4, FC3, FCz, FC4, T3, T4, T5, T6, Pz, P3, P4, O1, O2, and Oz electrode sites (10-20 International System). A further 14 channels recorded other data, *e.g.* VPVA and VPVB vertical electrooculogram (EOG), HPHL and HNHR horizontal EOG, heart rate (HR), muscle movements and events, etc. HR is considered as one of the most sensitive measures of withdrawal, which has been shown to be positively correlated with severity of opiate withdrawal (Zilm & Sellers, 1978). EEG was recorded relative to the average of A1 and A2 (mastoid) electrode sites. Horizontal eye movements were recorded with electrodes placed 1.5 *cm* lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 *mm* above the middle of the left eyebrow and 1.5 *cm* below the middle of the left bottom eye-lid. Skin resistance was kept at $< 5\text{ k}\Omega$. Scalp and EOG potentials were amplified and digitised continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 *Hz* (above which attenuating by 40 *dB* per decade), and a sampling rate of 500 *Hz*. Electrical impedance was always $< 5\text{ k}\omega$.

Resting EEG data was collected with patients undertaking MMT (M group), people currently using illicit opiates (O group) and healthy volunteers (H group) in two states: eyes open (EO) and eyes closed (EC). In the EO condition, participants were asked to fixate on a red dot in the centre of the computer screen for two minutes. In the EC condition, participants were asked to sit still with their eyes closed for two minutes (Wang et al., 2015).

The M group consisted of 18 males and 14 females, with a mean age of 39.36 (SD

= 5.14) years. Their mean duration of education was 12.06 (SD = 2.00) years; mean duration of opiate use was 10.03 (SD = 6.08) years; mean duration of MMT 7.29 (SD = 6.39) years; and current methadone dose 70.86 (SD = 40.61; range 8-180) *mg/day* (Wang et al., 2015).

All the participants recruited were between 18-45 years of age, had basic English literacy skills and were able to provide written informed consent. Inclusion criteria for the M group was undertaking methadone for a minimum of six months and being stabilised on their current dose for at least 2 weeks. Participants in the opiate user group were required to meet the DSM-IV criteria for opiate dependence and were not allowed to be currently undertaking MMT. The inclusion criteria for healthy control subjects was no current or lifetime history of drug or alcohol abuse other than nicotine dependence (Wang et al., 2015).

8.3.2 A NeuCube Model to Analyse EEG Data from H, O and M Groups

For our study, we resized the raw EEG data to 26 ordered vectors of real value data, as 26 were the EEG channels used during the EEG recording. Data from 20 healthy subjects, 15 subjects addicted to opiates and 22 subjects under MMT was available for the EC state. On the other hand, data from 20 healthy subjects, 17 subjects addicted to opiates and 25 subjects under MMT was available for the EO state. Every EEG STBD sample fed into the NeuCube was labelled to represent one of the subjects. We averaged every subject's neural activity per channel every 2048 data points, which means every four seconds of recordings. We considered this information enough for the analysis of the problem. We obtained a total of 37 and 33 data points per channel and per sample for the two resting state EC and EO respectively (as this was the lowest number of data

points after averaging the signal).

For the experiments, we generated a SNNc of 1471 brain mapped spiking neurons. We used the 3D Talairach Atlas (Talairach & Tournoux, 1988; Lancaster et al., 2000; Koessler et al., 2009) to map 1471 brain areas of 1 cm^3 each into single spiking neurons of the SNNc and then entered the data from the EEG channels into the corresponding input neurons of the SNNc.

Results can be affected by subjects' poly-drug use, a common complication in a population with drug dependence and it is unlikely that patients or opiate users have no history of use of other types of drugs. The question is, while this is true, what more can we learn from the SNNc about the brain functional differences (changes) between these groups?

For a better understanding of the data and to address the research questions raised in the previous section, different analysis of the connectivity of the SNNc have been performed and reported below.

8.3.3 Analysis of Spiking Neuronal Activity and Connectivity Generated in EC *versus* EO Resting State Across the Groups of Study

The cube connectivity can be analysed and interpreted for a better understanding of the EEG data to identify differences between brain states during the execution of either the EC or the EO state. Fig. 8.4 shows the initial connections and the connectivity evolved after the STDP learning rule was applied to either H, O or M group. Table 8.1 reports the parameters settings used to obtain these results. In Fig. 8.4, excitatory synapse

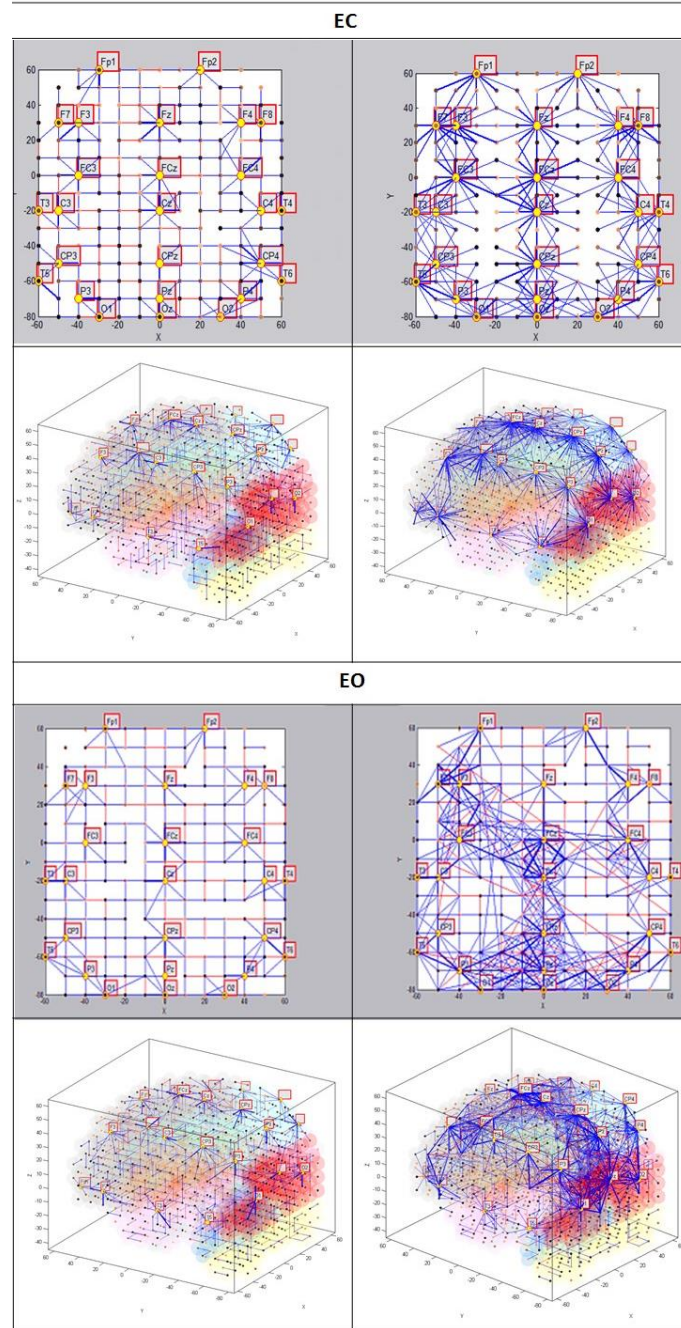


Figure 8.4: NeuCube connectivity before (left) and after training (right) the SNNc with the EEG data recorded from all subjects who belonged to all three groups - H, O and M - during either the EC (top) or the EO state (bottom). For both resting states, the top images show the (x, y) projection only of the 3D SNNc, while the bottom images show the 3D SNNc together with the corresponding eight brain functional areas.

Table 8.1: Parameters settings of the SNNc models used for training the data of all groups during EC and EO state.

SNNc Parameters Settings		
Parameters \ State	EC	EO
TBR_{thr}	7.94	52.62
p	0.15	0.15
Θ	0.50	0.40
l	0.02	0.02
α	0.10	0.10
Weight Threshold	0.15	0.07

are indicated by blue lines, while inhibitory synapse are indicated by red lines; the thickness of these lines indicates the strength of activity between neurons, while the interactivity between neurons is indicated by the brightness of the colour of the neurons. Each 3D SNNc of Fig. 8.4 highlights eight brain functional areas by different colours (*i.e.* grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe); also, the 26 input neurons are labelled in yellow according to their corresponding EEG channels. Doing so, we can study the functional changes in neural activity, while identifying the brain areas where these changes occurred.

As shown in Fig. 8.4, after training the system on data from all three groups (H, O, M), the two resting states (EC and EO) demonstrated to produced quiet different neural activity. Both states manifested high activity around the input neurons - which were allocated so that they spatially mapped the brain-location of the 26 EEG electrodes - and along the central area (Fz, Cz, Pz, etc.); although, the neural activity generated during the EO was significantly different from that generated during the EC, having a greater connectivity on the left frontal, central and occipital-parietal regions. This was also confirmed by the step-wise analysis of the SNNc (shown in Fig. 8.1). We can observe that the initial connections in the cube are firstly generated around the

input neurons represented by the 26 EEG channels. Then, as the unsupervised learning proceeds, more connections evolved in the frontal lobe of the left hemisphere (T3, C3, FC3, F2 and F3), the central areas (FCz and Cz) and the occipital-parietal regions (O1, O2, Oz, Pz, P3 and P4). As a result of the activity observed during the EO state, we decided to focus our subsequent analysis on the data collected during this state only.

8.3.4 Analysis of NeuCube Connectivity with the Aim of Discovering Functional Changes of Brain Activities in Subjects Under Treatment (M) Compared with Control Subjects (H)

Fig. 8.5 depicts the neural activity obtained after the SNNc was trained with EEG data corresponding to the M and the H group separately (EO only). The parameters settings used to obtain these results were set in accordance with the ones reported in Table 8.1.

As per Fig. 8.4, in Fig. 8.5 excitatory synapse are indicated by blue lines, while inhibitory synapse are indicated by red lines; the thickness of these lines indicates the strength of activity between neurons, while the interactivity between neurons is indicated by the brightness of the colour of the neurons. Each 3D SNNc of Fig. 8.5 highlights eight brain functional areas by different colours (*i.e.* grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe); also, the 26 input neurons are labelled in yellow according to their corresponding EEG channels. In addition to the information above, the different connectivity generated by the H group and the M group is studied by overlapping their images in different colour bands. The resulting composite image shows the regions where the two groups have equal intensities in grey and the regions where intensities are different in magenta (for M group) and green (for H group).

We can observe that in Fig. 8.5 there are differences between the SNNc connectivity of the M and H groups, indicating alternations of neural activity induced by history of opiate exposure. A better understanding of the data can be achieved by studying the

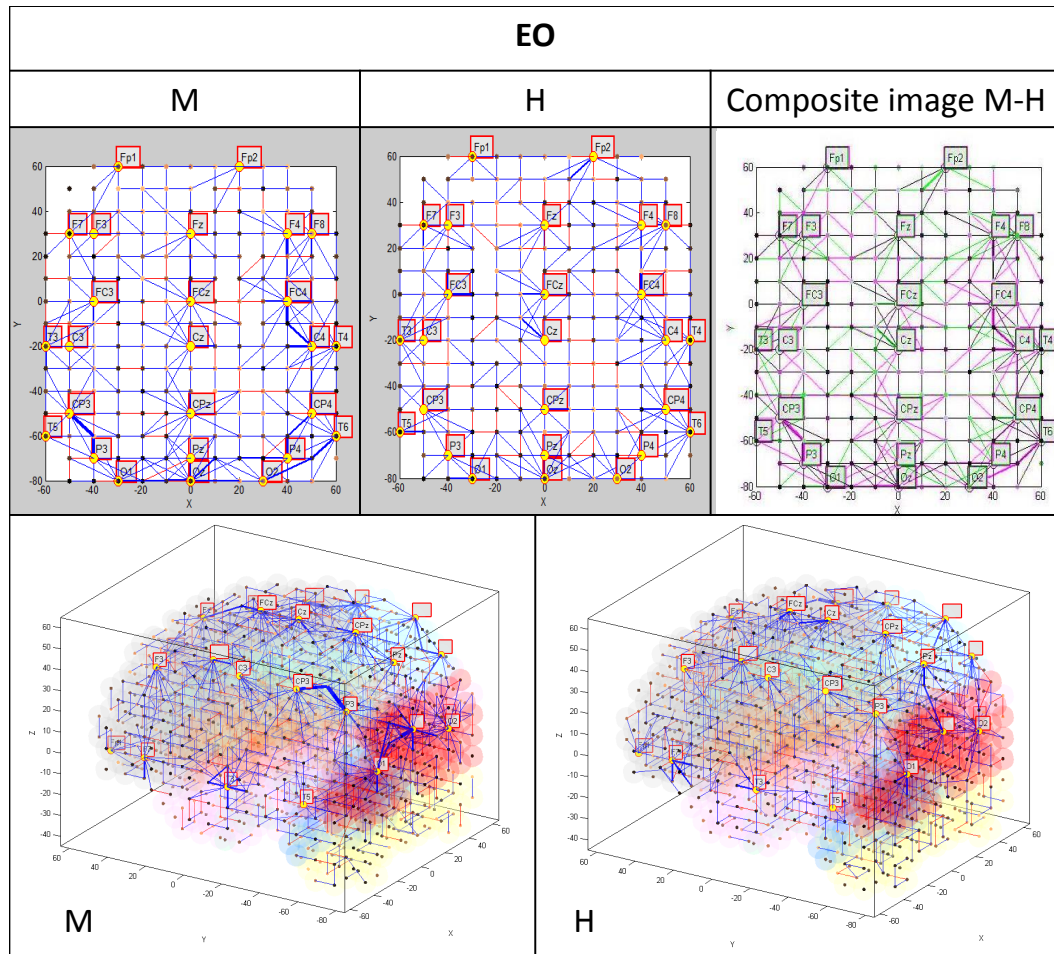


Figure 8.5: NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the control H group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding eight brain functional areas. The composite image is shown on the top right figure.

NeuCube network analysis per class, as illustrated in Fig. 8.6. The parameters settings used for the network analysis are listed in Table 8.2.

In Fig. 8.6 both spike spreading level between input neurons and their maximum spike gradient are depicted. The images show the activity generated by the 10 EEG channels

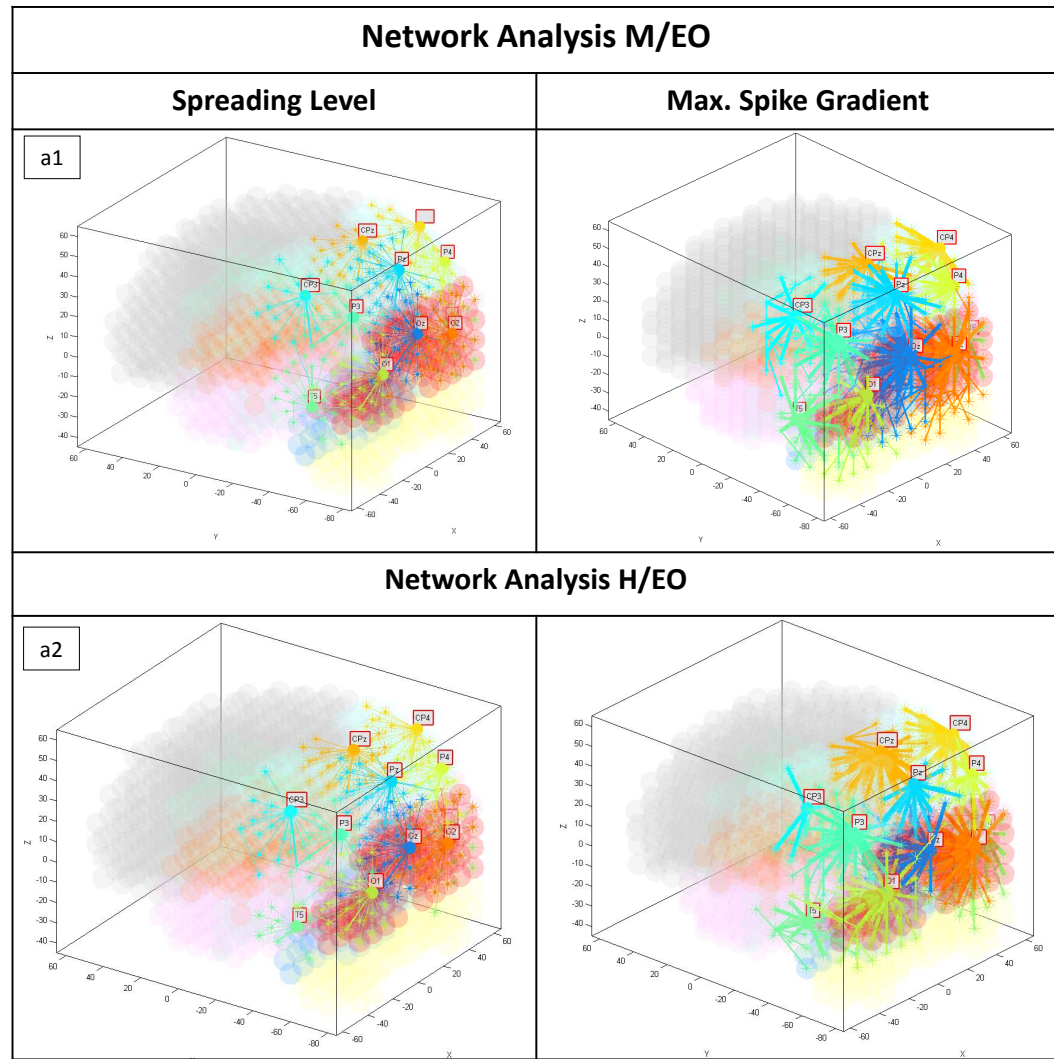


Figure 8.6: NeuCube connectivity and spiking activity analysis per class - M group (a1) and H group (a2) - obtained for the EO state. The images show the 3D SNNc together with the corresponding eight brain functional areas, the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated to the visual cortex.

allocated to the visual cortex only (*i.e.* CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz and O2) and highlight their activity by different colour lines. Analogous to the previous images, the thickness of the lines indicates the strength of activity between neurons, which are located in eight brain functional areas, also highlighted by different colours. We can observe, in Fig. 8.6, that the pathway of spiking activity of the M group is similar to the H group, despite their greater level of intensity.

Table 8.2: Parameters settings of the NeuCube models used for connectivity and spiking activity analysis for class M, class H and class O subjects (EO states only).

Network Analysis Parameters Settings	
TBR_{thr}	52.62
p	0.15
Θ	0.40
l	0.02
α	0.10
Weight Threshold	0.07
Number of Inputs	10
Spreading Level	2

8.3.5 Analysis of NeuCube Connectivity with the Aim of Discovering Functional Changes of Brain Activities in Subjects Under Treatment (M) Compared with Subjects without Treatment (O)

Fig. 8.7 shows the neural activity obtained after the SNNc was trained with the data corresponding to the M and the O group separately (EO only). The parameters were set in accordance with the ones reported in Table 8.1.

According to the previous sections, in Fig. 8.7, excitatory synapse are indicated by blue lines, while inhibitory synapse are indicated by red lines; the thickness of these lines indicates the strength of activity between neurons, while the interactivity between neurons

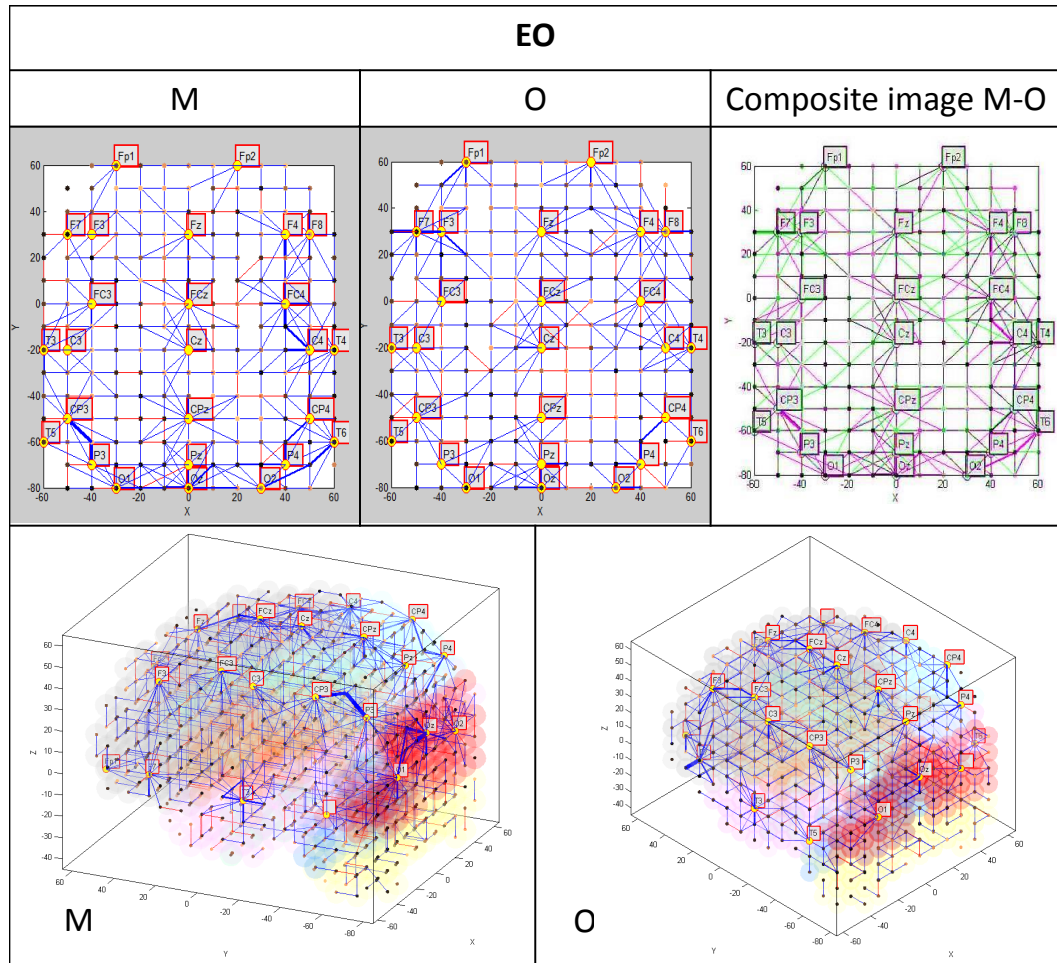


Figure 8.7: NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the O group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc. The composite image is shown on the top right figure.

is indicated by the brightness of the colour of the neurons. Each 3D SNNc of Fig. 8.7 highlights eight brain functional areas by different colours (*i.e.* grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe); also, the 26 input neurons are labelled in yellow according to their corresponding EEG channels. Additionally, the different connectivity generated by the M group and the O group is studied by overlapping their images in different colour bands. The resulting composite image shows the regions where the two groups have equal intensities in grey and the regions where intensities are different in magenta (for M group) and green (for O group).

As shown in Fig. 8.7, the neural activity of the M group was different from the O group; in particular, greater excitation in the parietal and occipital regions was observed in the M group. According to these results, we focused on these regions only analysing the maximum spike gradient between input neurons and their information spreading level (Fig. 8.8). Thus, Fig. 8.8 show only the activity generated by the 10 EEG channels allocated to the visual cortex (*i.e.* CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz and O2) and highlight their activity by different colour lines. Analogous to the previous images, the thickness of the lines indicates the strength of activity between neurons, which are located in eight brain functional areas, also highlighted by different colours. The parameter settings used are reported in Table 8.2. Consistent with the previous studies (Wang et al., 2012, 2013, 2014), our findings implicate that there are different cognitive-related effects between methadone and illicit opiates.

To further test this hypothesis, we have classified the O group *versus* M group (Table 8.4) for both resting states (EC and EO). The high classification accuracy obtained *via* the NeuCube methodology proved the model ability to manifest this difference and also

that the two classes were in fact two distinguishable groups. We compared the results obtained using the proposed NeuCube model with traditional machine learning methods, such as MLR, SVM, MLP and ECM. The parameters that influence these methods are: class performance variance (CPV); the use of signal noise ratio (SNR) for feature selection method; normalised minimum radius of influence field cluster (MIF); normalised maximum radius of a cluster (MxIF); SVM kernel (Kernel); MLP training cycles (Tr.Cycles), hidden units (HU) output value precision (OVP), output function precision (OFP) and output activation function (OAF).

We used the NeuCom platform (Kasabov, 2007) to carry out the experiments; NeuCom is a self-programmable, learning and reasoning computer environment freely available on-line (www.theneucom.com). The LOOCV method was used to evaluate the classifier outputs and the datasets were normalised prior to the experiments to ensure the highest classification accuracy. Table 8.3 lists the parameters settings used to obtain the results. When training a NeuCube model on the EEG data, we used 26 input features/variables (the EEG channels) and entered the times series of each input variable to train the SNNc. In contrast, the other methods could not take time series data without transforming it into a static and fixed length data vectors, used to train a model one after another. The results in Table 8.4 were obtained using LOOCV method when the best top 20 features were selected for every traditional machine learning method tested (MLR, SVM, MLP, ECM) and for every sample in the LOOCV procedure. Selecting features in time series processing is not recommended though as once a model is trained these features will be fixed and any change in the dynamics of the EEG data in future experiments would not be tolerated for incremental learning and model adaptation.

In this respect NeuCube offers a certain advantages from the point of view of adaptive and incremental learning of STBD. But the most important difference between a

Table 8.3: Parameters settings used to classify O group *versus* M group (EC and EO state) in a NeuCube classifier using RSSV method and in traditional machine learning classification methods (MLR, SVM, MLP and ECM) using LOOCV method.

Method \ State		EC	EO
MLR	CPV	0.05	0.14
SVM	Type of Method	inductive	inductive
	CPV	0.32	0.56
	Kernel	polynomial	polynomial
	Degree γ	1	1
MLP	CPV	0.01	0.04
	HU	5	5
	Tr.Cycles	500	500
	OVP	0.0001	0.0001
	OFP	0.0001	0.0001
	OAF	linear	linear
ECM	CPV	0.41	0.18
	MxIF	1	1
	MIF	0.01	0.01
	M of N	3	3
NeuCube	TBR_{thr}	145.3	33.16
	p	0.15	0.15
	Θ	0.5	0.5
	r	6	6
	l	0.02	0.02
	α	0.01	0.01
	mod	0.4	0.4
	$drift$	0.25	0.25

NeuCube model and the traditional machine learning methods is that a NeuCube model has a brain-like structure and uses brain-like learning methods to learn STBD, so that the model can be interpreted for new discoveries related to the source of the EEG data the brain. In contrast, the traditional machine learning methods, being successfully applied on many problems so far, cannot be of much use for STBD modelling, analysis, model interpretation and knowledge discovery.

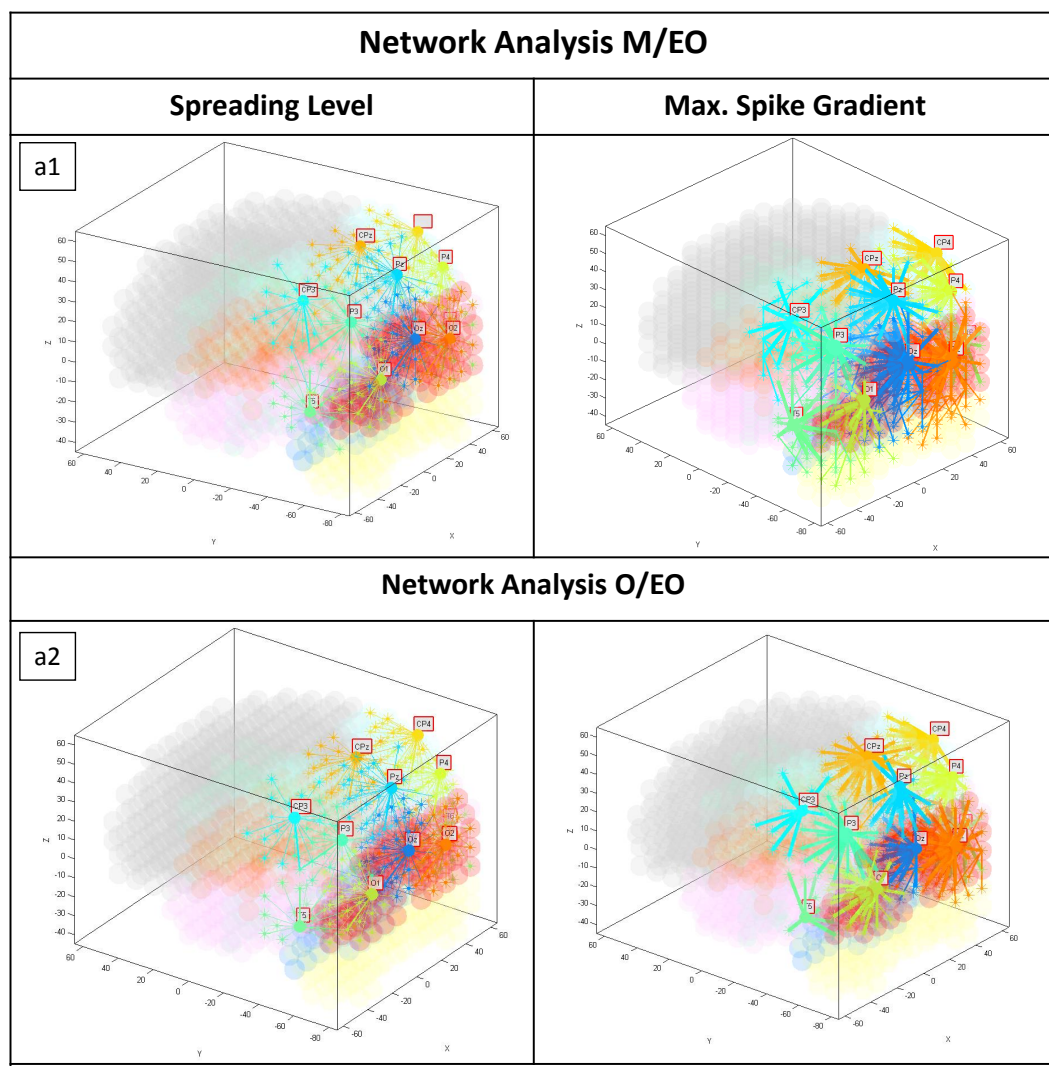


Figure 8.8: NeuCube network connectivity and spiking activity analysis per class - M group (a1) and O group (a2) - obtained for the EO state. The images show the 3D SNNc together with the corresponding eight brain functional areas, the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated to the visual cortex.

Table 8.4: Classification accuracy percentage obtained for the two classes O and M, and overall. The table compares the results achieved by using NeuCube and traditional machine learning methods (MLR, SVM, MLP, and ECM).

Method \ State	EC	EO	Class
MLR	53	59	O
	50	48	M
	51	52	overall
SVM	40	29	O
	64	68	M
	54	52	overall
MLP	60	53	O
	59	56	M
	59	55	overall
ECM	40	53	O
	73	68	M
	59	62	overall
NeuCube	67	75	O
	100	82	M
	86	79	overall

8.3.6 Connectivity Analysis of NeuCube Aiming at Discovering Functional Changes in Brain Activities Related to Different Doses of the Drug Administered

Since every EEG sample was an identifiably-labelled subject and there are potential dose-related effects suggested by the literature, we further analysed the methadone dose-related effect on spiking activity in our M group through the analysis of the connectivity of the NeuCube trained model with these EEG data. Data corresponding to the M group were divided into two subgroups, low dose (LD) and high dose (HD) of methadone, according to their daily dose of drug administered (high-dose $\leq 60\text{ mg}$ < low-dose). For the EO task, we obtained 14 samples for the low dose class and 11 samples for the high dose class. We also compared these two groups with 13 subjects of the healthy control group. Thirteen subjects were randomly chosen from the healthy control group

to minimise the possible confounding effects associated with sample size.

In order to study these effects, we analysed the SNNc activity and connectivity obtained after training the SNNc with the EEG data corresponding to the H, LD and HD group separately. Fig. 8.9 depicts the SNNc activity generated per class after setting the parameters according to Table 8.5.

Table 8.5: Parameters settings of the SNNc models used for training the data who belonged to one of three groups (H, LD or HD) during EO state. The parameter optimised was TBR_{thr} while the other parameters were set at default value.

Methadone dose EO	
Parameters \ State	EO
TBR_{thr}	32.44
p	0.15
Θ	0.50
l	0.02
α	0.50
Weight Threshold	0.07

In Fig. 8.9, the composite images depict differences between connectivity of the two groups of subjects overlaid in different colour bands. The regions where both groups have equal intensities in grey and the regions where intensities are different in magenta (for H group) and green (for either LD or HD group). As shown in Fig. 8.9, there are similarities and differences between groups (H *versus* HD or H *versus* LD). It appears that there is a greater reduction of connectivity in the HD group when compared to either the H or the LD group. Our findings suggest that the dose administered may play a role in treatment response and it needs to be addressed in treatment planning.

To further study the network connectivity, we focused on the occipital-parietal regions to extract new knowledge from the trained SNNc (for visualisation and analysis, as opposed to training purposes). Fig. 8.10 depicts the networks connectivity by means

of its maximum spike gradient between input neurons and their information spreading level. Fig. 8.10 shows the activity generated by the 10 EEG channels allocated to the visual cortex only (*i.e.* CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz and O2) and highlight their activity by different colour lines. The thickness of the lines indicates the strength of activity between neurons, which are located in eight brain functional areas, also highlighted by different colours. The results consistently support our argument showing a greater difference between the HD and the H group when compared to the difference between LD group and the H group. The parameters settings used to plot these images are the same as per Table 8.2.

8.4 Discussions, Conclusion and Further Directions

The NeuCube constitutes a brain-inspired three-dimensional architecture of SNN for on-line learning and recognition of STBD (Kasabov, 2014a). It takes into account the spatial coordinates of the sources of the STDB using a standard brain-template, offering a better understanding of the information and the phenomena under study.

The goal of this study has been to develop a method for the analysis of the connectivity and the dynamic activity of a NeuCube model trained on EEG STBD in order to understand changes in brain activities across different subjects and different groups of subjects undertaking different treatments. Traditional data mining/machine learning algorithms are not able to properly deal with this kind of data. Our results demonstrated that a NeuCube model can not only achieve a better sensitivity and specificity when classifying EEG data when compared to traditional AI methods, but it is also interpretable for a better understanding of the EEG data and the processes that generated it. This makes the NeuCube modelling approach widely applicable for neuroscience research across data and problems. In particular, the study demonstrated:

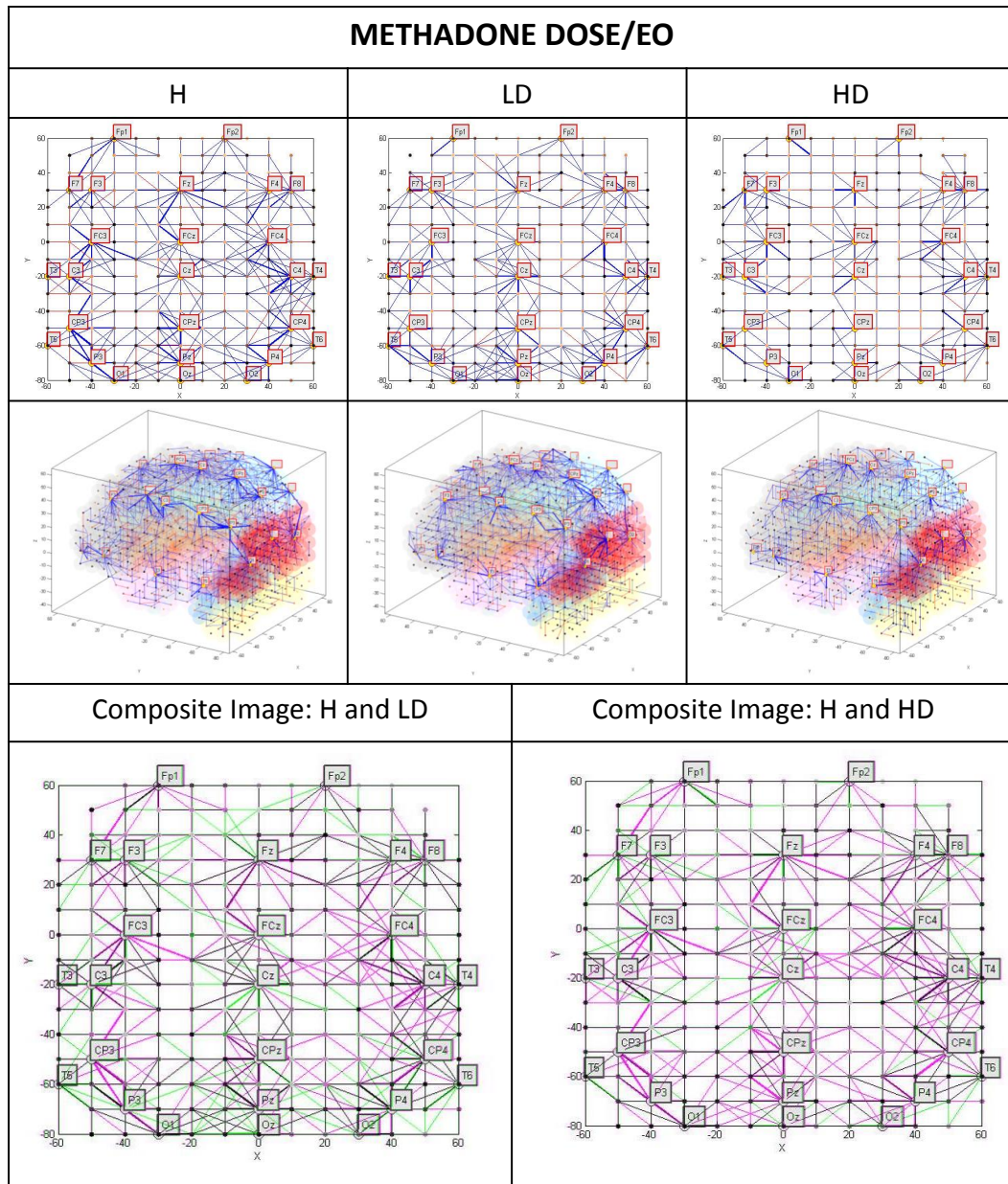


Figure 8.9: The SNNc connectivity after training it with EEG data corresponding to the EO task for the three classes (H, LD or HD) of methadone. The top figures show the (x, y) projection only of the 3D SNNc, while the middle figures show the 3D SNNc together with the corresponding eight brain functional areas. The composite image is shown on the lowest images.

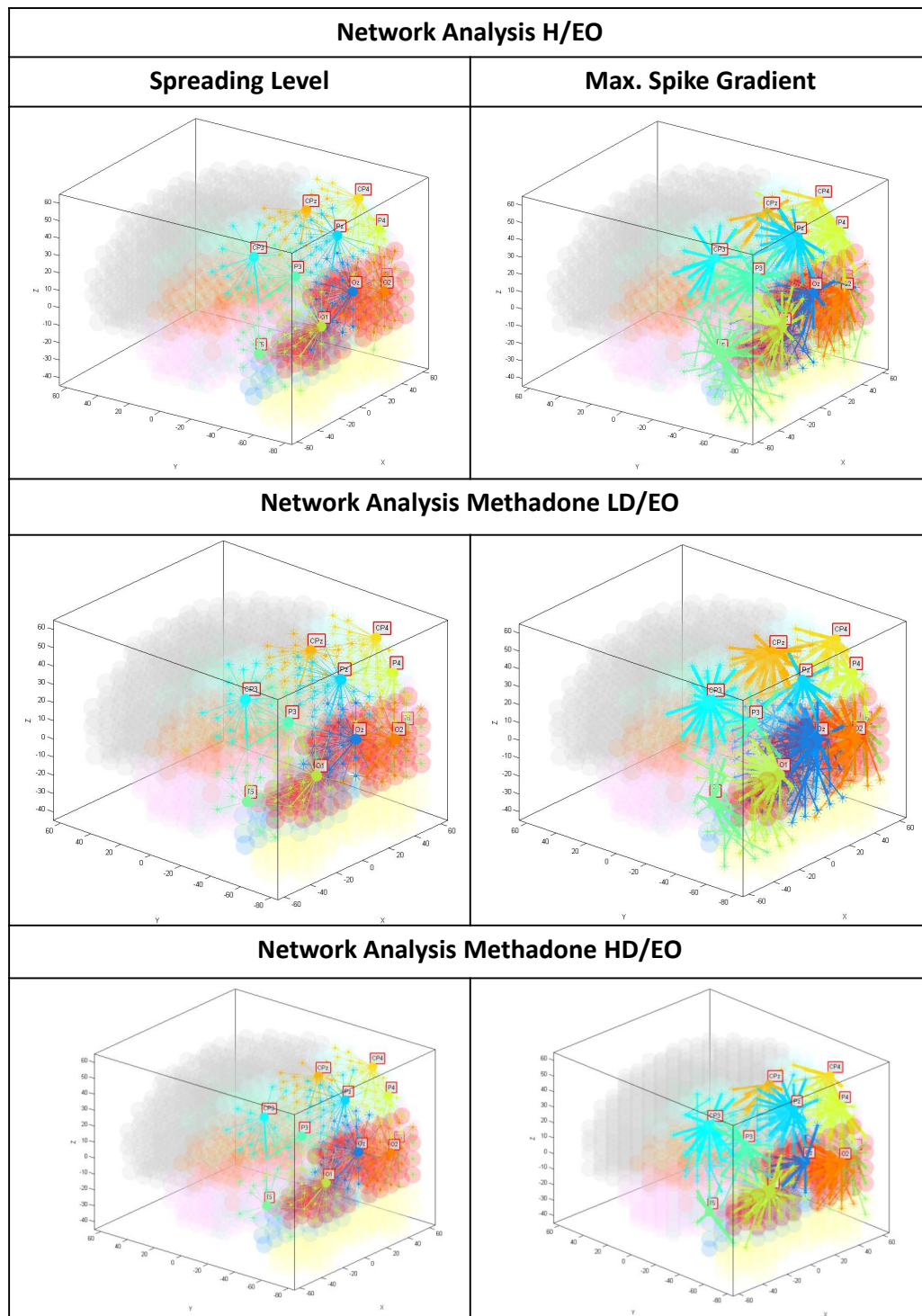


Figure 8.10: NeuCube model connectivity and spiking activity analysis per class - H, LD and HD groups - obtained for the EO task. The figures show the 3D SNNc together with the corresponding eight brain functional areas, the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated to the visual cortex.

- The NeuCube ability to classify EEG data collected from different groups of patients and healthy subjects.
- The ability to extract new knowledge and to study the brain regions involved based on connectivity analysis of an SNNc after training with EEG STBD from different groups of subjects;
- Understanding the correlation between a dose of treatment and results of treatment based on connectivity analysis;
- Understanding the impact of different dose of treatment on brain activities and at predicting response to treatment.

Some further development and research in the area could be suggested:

- Further development of the methods of the NeuCube framework, including: analysis of the ability of a NeuCube model in terms of how “deep in time” spatio-temporal patterns “hidden” in STBD can be efficiently learned; how different “time lags” can be represented in the NeuCube; spatio-temporal rule extraction from a trained NeuCube model; analysis and interpretation of the output connectivity along with the SNNc connectivity in relation to a better understanding of brain differences across groups of subjects.
- Further application for the study of EEG STBD in relation to understanding brain functionality, *e.g.* longitudinal study on patients undertaking methadone treatment in terms of defining any cognitive fluctuation across time; development of a GRN optimisation module as part of the SNNc to improve the results and to study how certain genes may influence treatment; analysis of EEG data collected from people taking a single oral dose of “party pill” using NeuCube; analysis of EEG data collected from people with depression; analysis of brain data collected from people with schizophrenia.

8.5 Summary

In this chapter, by exploring and extending the methodology proposed in Chapter 5, we propose a methodology for the analysis of connectivity and spiking activity obtained *via* unsupervised learning of the spatio-temporal information generated by the indicated brain regions. The aim of the study was to address *RQ3* and *RQ4* proposed in Chapter 1:

- *Can we analyse the evolution of connectivity and/or spiking activity that occur in a trained eSTDM when comparing data of an individual subject or a group of subjects performing a task with data from another individual or another group?*
- *Can we identify the brain areas where the functional changes in neural activity is generated by the different classes using the computational model developed?*

In the next chapter, we explore the methodology potentiality for stepwise personalised modelling and events prediction of EEG data.

Chapter 9

Application of the NeuCube-Based Methodology for Modelling Absence Epilepsy Seizure Data

9.1 Introduction

In this chapter, we explore the potentiality of the NeuCube-based methodology proposed in Chapter 8 for personalised modelling and events prediction. The methodology is applied here on a case study on epilepsy data.

Epilepsy is the most diffuse brain disorder that can affect people's lives even in its early stage. Many studies reported in the literature suggest that seizures are part of a complex network phenomenon, a sort of "epileptogenic process" that, for unknown reasons, arises, evolves, and finally results in a seizure. So far, no tool has been developed in order to monitor such mechanisms which, if discovered and explored, would allow for a much deeper understanding of the pathology that could lead to novel therapeutic

perspectives. With this information in hand and by utilising the NeuCube-based methodology proposed, we aim at studying the development of a seizure. This could potentially lead to automatically marking the critical events on the EEG data to provide deep and novel diagnostic information about brain networks (off-line utility) and a warning tool in case of high probability of an impending seizure (on-line utility).

The chapter is constructed in the following way: section 9.2 presents the case study problem and the available data, and reports the results obtained by using a small data set; section 9.3 draws the conclusions and proposes future work; a summary of the chapter is presented in section 9.4.

This study was peer-reviewed and published by IEEE in the *2015 International Joint Conference on Neural Networks (IJCNN)*. Copyright and permission from the publisher of the paper are included and full text of the paper is provided in Appendix A.6.

9.2 Analysis of Connectivity and Spiking Activity of Epileptic EEG Data with the Proposed NeuCube-Based Methodology

9.2.1 Problem Specification

Epileptogenic processes in the brain are hyper-synchronization of the electrical neural activity. Although the cause that produces them is still unknown there is a hypothesis that they may occur in different areas of the brain indiscriminately. The critical area associated with the epileptogenetic event is called epileptogenetic zone. This is responsible for recruiting other areas until the brain triggers the seizure. This process can be

seen as a network-event rather than a local event. Thus, the problem to localise and study the epileptogenic zone is of great interest to neuroscientists.

STBD and especially EEG data is widely used to record changes of brain activity during seizures at a millisecond time scale. It allows us to obtain information about frequency, time and space of the epileptogenic events.

When a subject experiences a seizure, he/she needs to undergo recording of several EEGs. This implies inpatient or day hospital care and, if epilepsy is diagnosed, the patient must undergo several further EEG recordings in order to assess the evolution of the disease and to monitor the effects of the treatment.

Once the EEG has been recorded (recording can last from minutes to days) a careful review of the entire recording is needed, in order to detect the presence of critical events and to come up with a diagnosis. In clinical practice, while reviewing the EEG, the neurologist manually scrolls through the EEG and visually detects seizures (ictal states) and seizure-free intervals (inter-ictal states), so that he/she can evaluate the events and locate them electrode per electrode.

The neurologist usually can only observe 20 *seconds* worth of recording at a time, scrolling ahead till the end of the recording. Thus, working with EEG data means handling “big data” and all the technologies that can support the neurologist in dealing with this huge amount of data, will certainly improve epileptic people’s quality of life as well as facilitate the neurologist’s work. Additionally, to understand the epileptogenic process, we need to know *when*, *where* and *why* abnormalities in the electrical activity arise in the brain and *how* they evolve recruiting other areas. Thus, a method is needed that is able to extract the mathematical descriptors from EEG signals and which would

be able to follow the evolution of the dynamics of cerebral electrical activity and to identify the transition from the inter-ictal stage to the pre-critical stage, thus detecting possible impending seizures (early seizure detection).

Aiming to achieve this goal, in this study we propose a methodology for modelling spatio-temporal data to study the development of seizures step by step, in order to automatically mark the critical events on the recording and to provide an off-line and on-line utility for seizures detection.

In already published studies (Mammone et al., 2011, 2012), spatio-temporal EEG signals have been analysed based on ordinal measures of patterns through permutation entropy (PE) features. There, long EEG recordings (minutes to hours before seizure onset) have been analysed in order to check whether the epileptogenic process in absence seizures actually corresponds to the model of a “jump” transition of the underlying dynamical system or a gradual transformation is detectable in advance. PE was used to convert real EEG signals into motifs neglecting amplitude of signals and excluding any dependence on the effect of the reference electrode. In this study, the NeuCube framework is used for analysing the dynamics of the epileptic events through the PE topographies.

9.2.2 Absence Epilepsy Seizures

Childhood Absence Epilepsy (CAE) disease is a common idiopathic generalized epilepsy syndrome. CAE is usually present in children between age of 4 and 10 years, peaking at age 6-7 years (Duun-Henriksen, Madsen et al., 2012; Duun-Henriksen, Kjaer et al., 2012). A strong genetic predisposition is evident, with occurrence more often in girls than in boys. The very frequent absences (several to hundreds a day) exert a

negative impact on an otherwise normal child. Untreated children often exhibit learning and attention difficulties because of their alterations of consciousness. The pediatric neurologist's main objective is to neutralize all absences as well as the side effects.

9.2.3 EEG Data Description

Data was collected by HypoSafe A/S, Denmark and made available to us from the researchers of the Neurophysiology Center, Department of Neurology, Roskilde University Hospital, Denmark. They published another study on the same data set (Mammone et al., 2015) and coauthored the paper that resulted from this study.

Standard EEG recording from a patient diagnosed with CAE was used for training and testing. The patient was a young girl and her age was nine. The EEG was acquired using a 16-channel device (Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1 and O2) according to the international 10/20 system with Cadwell Easy II (Cadwell Laboratories, Inc., Kennewick, WA). All channels were filtered with a pass band of 0.53 – 25 Hz, and digitised at a rate of 200 Hz. In total, eight paroxysms longer than 2 seconds were identified by a board-certified clinical neurophysiologist. In total, 15.8 minutes of electroencephalogram data were recorded. All data analysis was performed using MATLAB®.

9.2.4 Permutation Entropy

The n -channels EEG recording was processed by means of sliding temporal windows. The EEG samples were buffered in 5 seconds non-overlapping windows (since the sampling rate is 200 Hz, a window includes $N=1000$ EEG samples), then PE was estimated, channel by channel and window by window. Each EEG time window includes n time series, where n is the number of EEG channels. This window is stored

in the computer as a nxN matrix. Within each window, a sample of PE per channel is computed and the n values are arranged in an nxI PE vector, therefore, a nxN EEG matrix corresponds to a nxI PE vector thus a compressed temporal representation of the original time series is produced. In order to calculate PE, each time series x was mapped into an m -dimensional space, with m being the embedding dimension and L being the time lag. Vectors X_t were constructed selecting m equally spaced samples from x , starting from time point t :

$$X_t = [x(t), x(t+L), \dots, x(t+(m-1)L)]^T \quad (9.1)$$

The values of X_t are reshaped in an increasing order, the time points are renamed yielding Xr_t , a reshaped version of X_t : $Xr_t = [x(t+(t_1-1)L), x(t+(t_2-1)L), \dots, x(t+(t_m-1)L)]^T$. Therefore, each vector X_t can be considered uniquely mapped onto a symbol vector $\pi = [t_1, t_2, \dots, t_m]$. The vector π is a sequence of time points, hence a symbol. The frequency of occurrence of each possible π is indicated as $p(\pi)$, which represents the frequency of occurrence of the specific vector π in the time series under analysis, normalized by $N - (m-1)L$ where N is the number of samples of the time series x . PE is finally computed as:

$$H(m) = - \sum_{i=1}^{m!} p(\pi_i) \ln(p(\pi_i)) \quad (9.2)$$

Where $\ln$ is the natural logarithm and $m!$ is the number of the possible permutations. Since $H(m)$ can maximally reach $\ln(m!)$, PE is generally normalized as:

$$H_n(m) = - \frac{\sum_{i=1}^{m!} p(\pi_i) \ln(p(\pi_i))}{\ln(m!)} \quad (9.3)$$

9.2.5 NeuCube-based Methodology for the Study of CAE PE Data

Fig. 9.1 presents a diagram of the adopted methodology, which for the case study problem can be summarised as follows:

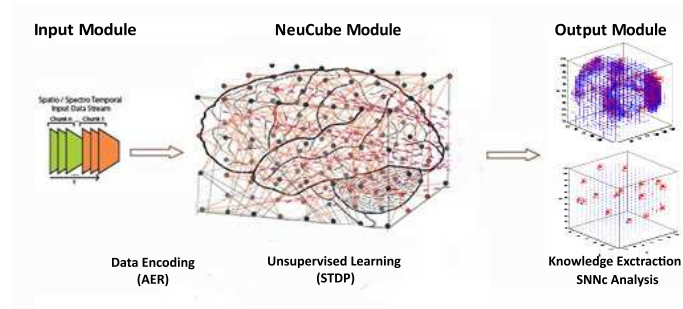


Figure 9.1: A diagram of the NeuCube-based methodology used for PE data modelling and brain connectivity analysis.

- In the input module, the available 187 PE vectors data are transformed into spike sequences by using the AER method, which ability to encode STBD in a proper way has already been proved in several studies, such as (Chan et al., 2007; Dhoble et al., 2012).
- In the NeuCube module, the encoded spike trains are entered into a 3D grid of 1471 LIF neurons by feeding them to the 16 corresponding brain-mapped input neurons (*i.e.* the 16 EEG channels). Each of these neurons are mapped according to the Talairach brain atlas (Talairach & Tournoux, 1988; Lancaster et al., 2000; Koessler et al., 2009) to reflects the Brodmann areas and the size of the data available. Here, the SNNc is stochastically initialised using the SW connectivity rule. Then, it is trained in a unsupervised mode on the spike trains using the STDP learning rule (Song et al., 2000). Thus, the data is propagated through the cube generating a spiking activity according to the time and frequency of the encoded spike trains. (*i.e.* a trained NeuCube represents a person's dynamic model of epileptic event progression over a short period of time).

- In the output module, the classifier is trained in a supervised mode and the output results are validated using LOOCV. In this study, the deSNN (Kasabov et al., 2013) algorithm was used to classify the data, to establish the effectiveness of the PEs as classification features. Then, the SNNc was visualised and analysed in a step-wise mode to study the activity and connectivity generated during learning.

In order to optimise the NeuCube parameters, the unsupervised and supervised training procedures were repeated until a high classification accuracy was achieved and then the best performing model was recorded. The parameters that underwent optimisation were:

- The AER threshold AER_{thr} ;
- The SW connectivity parameter p (generally set at 0.15);
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model parameters (generally set at 0.5, 6 ms and 0.02 respectively after optimisation);
- The STDP rate parameter α ;
- The variables mod and $drift$ of the deSNN classifier (generally set at 0.4 and 0.25 respectively).

9.2.6 Results and Discussion

As shown in Fig. 9.2, the 187 PE vectors calculated from the 16-channel EEG data corresponded to seven ictal (PE 2-5, 25, 34-41, 63-67, 95-99, 129-132 and 179-183) and eight equivalent interictal states.

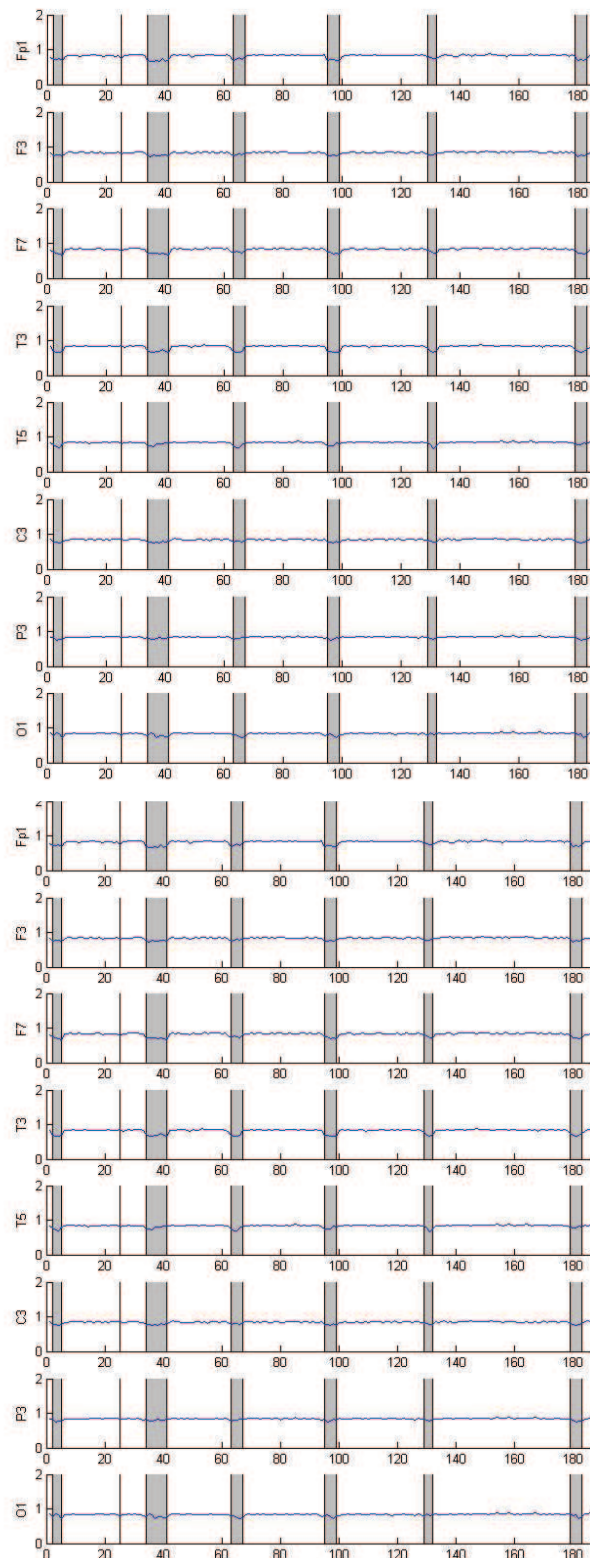


Figure 9.2: Sequence of PE obtained from the 16-channel EEG data. In grey colour are the PE corresponding to the ictal state, while the other PE are associated with the interictal states.

Accordingly, the 187 PE levels were divided into two respective classes for the classification experiments. Excluding the samples containing just one of the PE topography, we obtained six samples for class 1 (ictal state) and seven samples for class 2 (interictal state). The classification results were evaluated using LOOCV and the classification accuracy achieved by using the NeuCube-based was the following:

- Ictal State 100%.
- Interictal State 71%.
- Overall accuracy 86%.

Table 9.1 reports the NeuCube parameters used to obtain these results. These parameters were found after running a grid search in which 100 SNNc network configurations were evaluated regarding their test accuracy using RRSV (50% of the data was used for training and 50% was used for testing) changing the AER threshold and the STDP parameter each time.

Table 9.1: Parameter Setting used to obtain the results reported as NeuCube classification accuracy.

SNNc Parameters Settings	
AER_{thr}	0.003
p	0.15
r	2.50
Θ	0.50
l	0.02
α	0.50

The high classification accuracy (100% for class 1 and 71% for class 2) obtained *via* the NeuCube-based methodology proved the model ability to accurately classify the data and also that the two classes were in fact two distinguishable groups when using PE values as features.

To analyse the SNNc, we looked first at the dynamic of both spiking activity and connectivity during learning using the information available from the PE topographies. This threw more light on the functional changes in the brain provoked by the epileptic event and more importantly it helped to locate where these changes took place.

Figure 9.3 shows the NeuCube connectivity and spiking activity evolution over the 187 time points obtained during STDP learning. Table 9.2 lists the parameters settings used to obtain these results.

Table 9.2: Parameters settings of the NeuCube model used to study the evolution of connectivity and spiking activity analysis.

Network Analysis Parameters Settings	
AER_{thr}	0.003
r	2
Θ	0.50
l	0.002
α	1
Weight Threshold	0.08

Fig. 9.3 depicts the evolution of both SNNc connectivity and spiking activity during STDP learning. We can observe that, the SNNc connectivity evolves with the formation of either new excitatory synapses (blue lines) or new inhibitory synapses (red lines) during learning. The neuron activity represents when a spike is emitted (red coloured neurons) and when there is no spike (blue coloured neurons). The input neurons are identified in yellow and their labels corresponding to the 16 EEG channels are also presented. When an input neuron activity is excitatory, it is highlighted in magenta and when an input neuron activity is inhibitory, it is highlighted in cyan.

On the entire series of PE topographies, we are interested in the spiking activity and connectivity generated by each of the six ictal states and the seven relative interictal states. The first two sequences of PE topographies associated with a seizure (PE 2-5

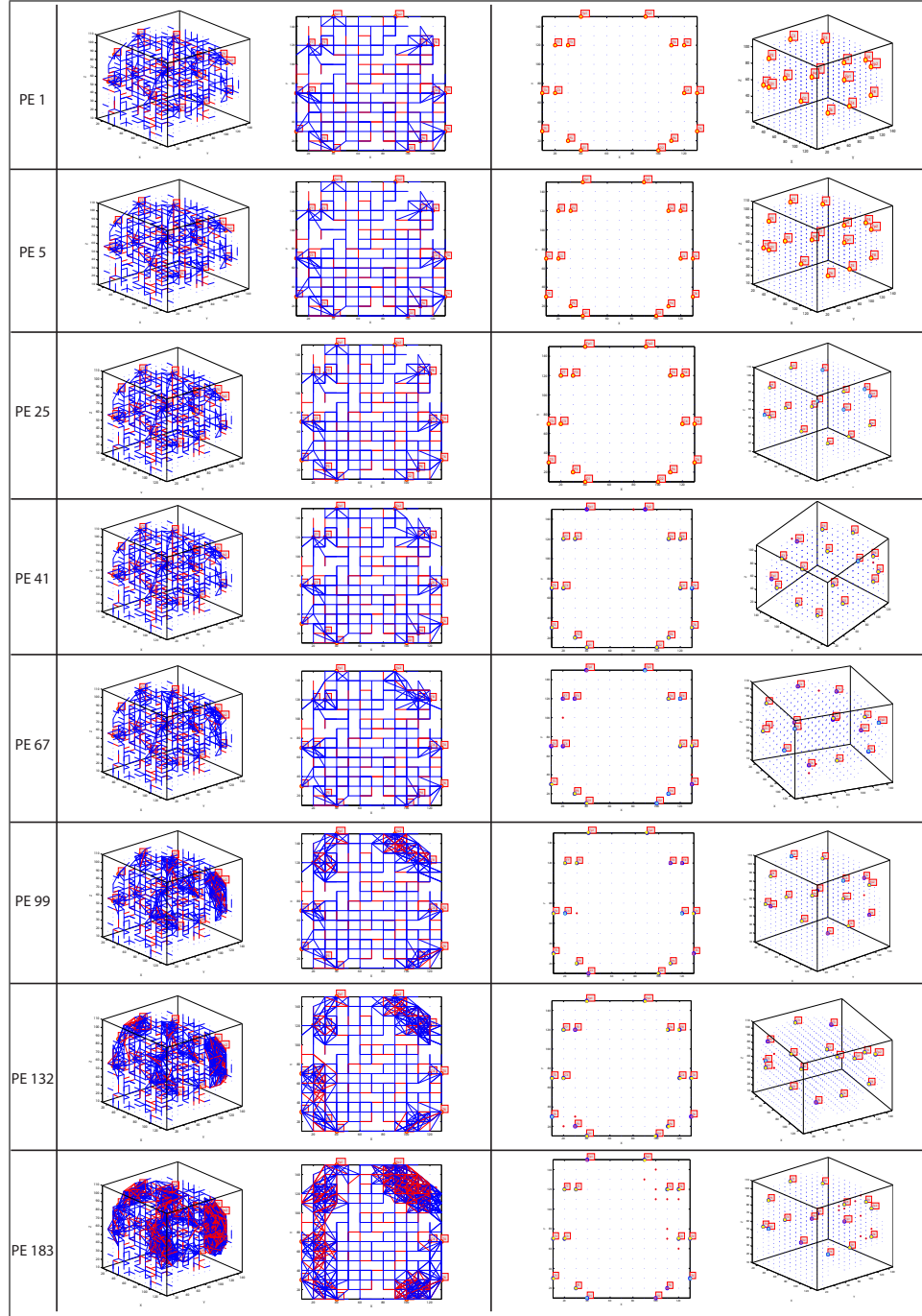


Figure 9.3: Evolution of connectivity (left) and spiking activity (right) of the 3D SNNc and its (x, y) projection during STDP learning. The top figures show the initial interictal state (PE 1) and the following figures the subsequent seven ictal states (PE 5, 25, 41, 67, 99, 132 and 183).

and PE 25) do not show a particular change in terms of connectivity or spiking activity. The third series of PE related to an epileptic event (PE 34-41) represents the longest sequence of PE topographies. Here, the F4 electrode appears to be the focal point in terms of enhanced connectivity. Also, new connections are formed in the (right) frontal polar area, electrode Fp2. The subsequent ictal state (PE 63-67) provokes the establishment of new connections in the right hemisphere especially in the anterior region of the frontal area, but also by the left hemisphere, at F7, F3 and FP1 positions. By the next sequence of ictal PE topographies (PE 95-99), the new connections have now consolidated and also new are formed by the (right) occipito-parietal area, channels O2 and P4. By the next ictal section (PE 129-132), most of the connections generated by the (right) frontal and occipito-parietal cortex and the (left) centro-temporal area keep consolidating, while the central regions are not affected. The last series of PEs associated with a seizure (PE 179-183), clearly show that most of the connections in the SNNc model are formed around the input neurons especially in the right frontal portion of the brain, while no connections are evolved in the central line at all.

Given a certain electrode and its PE level, we did not expect high PE to be linked to high degree of connections, we only expected PE to match the complexity degree of the electrical activity of the cerebral region covered by that electrode. PE levels can give us information that is local in space, depicting the topography over the scalp. It is a way to see which electrodes showed similar PE levels, but we obtained information about brain connectivity only through our proposed NeuCube model.

Neurologists address the frontal-temporal regions as “critical” in absence seizure patients and this seems to be in line with our modelling results and in particular with the ictal states associated to the PE 67, 99, 132, 183.

9.3 Conclusion and Future Work

The goal of the proposed study has been to develop a personalised model able to properly learn over time epileptic events in terms of space and time, so that the information can be dynamically visualised and analysed and possibly the epileptogenetic events predicted.

Our results demonstrated that the methodology constitutes a valuable tool for epileptic EEG data analysis and understanding. However, more extensive evidence is needed to establish the feasibility of a purely data driven diagnosis method for CAE diagnosis. So far, our results are promising and the proposed NeuCube-based methodology is planned to be used for molecular and genetic analysis of the disease and as a personalised model for the understanding of functional changes in the brain and for the prediction of epileptic events from new data.

More specifically, we propose the methodology to be used to CAE data to study how the regulation of GABA-mediated inhibitory mechanisms, which are believed to be involved in the neural hyper-synchronization responsible for type of epilepsy, can affect the post synaptic potential of a neuron (Crunelli & Leresche, 2002). This type of mechanisms are mediated by pharmacological treatments (Manning, Richards & Bowery, 2003) and we believe the NeuCube-based methodology could be of great help to clinicians for the analysis of possible changes in neural connectivity.

Also, NeuCube can be used for dynamic predictive modelling based on neuromorphic learning. The acquisition of more CAE data and their comparison to data from healthy subjects can be used to create such model that learns the progression of the epileptic events of a person over time. The brain-like mapping of the cube can be used to

study the specific characteristics of the epileptic events, the area of the brain where the event occurs and eventually to predict future epileptogenetic events based on the initial information.

9.4 Summary

In this chapter, we have explored the methodology proposed in Chapter 8 to achieve a stepwise personalised modelling and events prediction of spatio-temporal data generated by an epileptic event and the absence of it.

The methodology revealed to be able to achieve the goals proposed and addressed *RQ5* from Chapter 1: *Can the methodology be successfully applied on the analysis and the prediction of a specific neurological event?*

In the next chapter, a new biologically plausible unsupervised learning rule to be applied to the SNN NeuCube-based methodologies is used for the study of biochemical mechanisms involved in chemical synapses and to determine how these mechanisms can influence the PSP of a spiking neuron.

Chapter 10

A Novel Spiking Neural Network Learning Rule based on Neuroreceptor Dependent Plasticity

10.1 Introduction

As emerged in Chapter 9, the new SNN NeuCube-based methodology proposed for connectivity and spiking activity analysis could be used, if extended, to study the effect of neuroreceptors' modifications on the learning ability of an SNN model.

In this chapter, we propose a more biologically plausible system, which incorporates the dynamic mechanisms responsible for modifying neuronal synaptic plasticity through neurotransmitters/neuroreceptors cross-talk. To achieve that, we implement a new unsupervised learning algorithm based on local synaptic competition between biochemical processes.

The chapter is constructed in the following way: section 10.2 introduces the proposed new learning rule and reports the results obtained by applying it on a small recurrent network of four spiking neurons; section 10.3 presents the conclusions; and in section 10.4 the chapter is summarised.

10.2 Modelling Synaptic Plasticity through Neuroreceptor Dependent Plasticity Learning Rule

In the human brain, neuronal processes are mediated by complex biochemical mechanisms involving the transmission of ionic currents, which can be interpreted as a balance between excitatory and inhibitory forces. The glutamate and the GABA are the main excitatory and inhibitory neurotransmitters of the CNS. The most important receptors activated by glutamate are the AMPAR and the NMDAR (Collingridge & Wang, 2004). The AMPAR mediates fast excitatory synaptic response (Chin et al., 2008), while NDMAR is a ligand-gated and voltage-dependent channel (Wieronska et al., 2011). On the other hand, the GABA activates two main classes of receptors, $GABA_A$ and $GABA_B$. They regulate a fast and a slow inhibition of the neural action potential respectively. All these receptors are fundamental for the synaptic plasticity which is strongly related with the learning and memory processes in the hippocampus.

Some cognitive processes are modelled with SNN using Hebbian learning rules. An important mechanism in Hebbian learning is the competition among different synapses, *i.e.* when some synapses are strengthened due to pre-synaptic action potentials other are weakened. Several studies related to temporal pattern recognition have successfully utilised the STDP learning rule to control the timing of post-synaptic action potentials (Song et al., 2000). However, other mechanisms that regulate the synaptic activity

are based on local competition (*i.e.* at a synaptic connection) through either synaptic current modifications (Koch & Segev, 1998; Gerstner & Kistler, 2002); or dynamic mechanisms involving molecular rise and fall terms (Turrigiano et al., 1998; Tsodyks et al., 1998).

In this study, we propose a new learning rule for learning in SNN that models synaptic neuronal plasticity based on the dynamic changes in the neuroreceptors AMPAR, NMDAR, $GABA_A$ and $GABA_B$ as results of neuronal spiking activity. In (Benuskova & Kasabov, 2007) a CNGM of a spiking neuron is proposed that has four types of synapses defined by the activation of the above four neuroreceptors. But there was no learning rule or method proposed for this early CNGM.

A phenomenological model for the short-term dynamics of synapses was proposed in the literature (Tsodyks et al., 1998). The model, which is based on experimental data collected from biological synapses, suggests that the synaptic efficiency (weight) is a dynamic parameter that changes with every pre-synaptic spike due to two short-term synaptic plasticity processes: facilitation and depression. This inherent synaptic dynamics empower neural networks with a remarkable capability for carrying out computations on complex temporal patterns (*i.e.* time series) and spatio-temporal patterns.

In this chapter, we propose a new learning rule so that the synaptic connection weights are calculated and modified based on the dynamic changes of neuroreceptors as a result of spiking neuronal activity. The method is called neuroreceptor dependent plasticity (NRDP). In this context, our NRDP learning rule can automatically balance the synaptic strengths making post-synaptic firing sensitive to pre-synaptic potentials such as the STDP learning rule, but it also offers more options to study the effect of neurotransmitters and neuroreceptors on an SNN model that models brain data including gene and

protein data, thus offering new tools to study the effect of these neurotransmitters and neuroreceptors on brain cognitive functions.

The feasibility of the NRDP method is analysed here through a comparison with the STDP learning rule, both implemented in the evolving brain-inspired SNN architecture, NeuCube (Kasabov, 2014a). NeuCube has proved to be an efficient data modelling architecture for neurological clinical research (Kasabov, 2014a). We have implemented the NRDP learning rule as an unsupervised learning algorithm and compared results with the STDP learning rule and in scenarios when neuroreceptors took abnormal values. The implemented NeuCube-NRDP facilitates a better brain data modelling and a better understanding of how neurotransmitters are involved in cognitive processes.

This research is aimed to help scientists to achieve better understanding of brain processes where neurogenetic data is available and to develop novel management strategies for glutamate and/or GABA receptor-based disease. Targeting these molecular mechanisms could form the basis for new therapeutic strategies for the treatment of mental diseases since glutamate and GABA receptors are essential for many important physiological functions.

10.2.1 The NRDP learning rule

The proposed NRDP learning rule expresses mathematically the dynamic relationship between excitatory and inhibitory neuroreceptors that results in learned connection weights between spiking neurons and is manifested through spiking neural activity. This relationship generates a persistent increase or decay in the synaptic strength which influences the post-synaptic potential (action potential) and thus the spiking activity of the post-synaptic neuron, which in this case is an integrate-and-fire type neuron. Here,

we define the equations to calculate the synaptic strength between two neurons in a given time period as a function of four major neuroreceptor levels.

A connection C_{ij} between a neuron n_i and a neuron n_j is denoted by:

$$C_{ij} = \begin{cases} 1, & \text{connection;} \\ 0, & \text{no connection;} \end{cases} \quad (10.1)$$

The firing state $S_{i,j}$ of a connection C_{ij} (pre-synaptic spike) at a time t is defined as:

$$S_{ij}(t) = \begin{cases} 1, & \text{spike;} \\ 0, & \text{no spike;} \end{cases} \quad (10.2)$$

Now, let $M = \{A, N\}$ be the set of glutamate receptors where A and N are respectively the AMPAR and the NMDAR, and let $G = \{G_a, G_b\}$ be the set of GABA receptors where G_a and G_b are the $GABA_A$ and the $GABA_B$ receptor respectively.

The activation of the inhibitory receptors is modelled so that the probability P of activating receptor G_a is higher than the probability of activating receptor G_b :

$$P_{G_b} < P_{G_a}, \quad P_{G_b} = 1 - P_{G_a} \quad (10.3)$$

Then, the inhibitory level of a GABA receptor in the synapse between n_i and n_j neurons is determined according to the following activation function:

$$G = \begin{cases} G_a, & \alpha < P_{G_a}; \\ G_b, & \text{otherwise;} \end{cases} \quad (10.4)$$

where P_{G_a} indicates the $GABA_A$ activation probability and $\alpha = unif(0, 1)$ is a dimensionless random number with a uniform density probability.

The level of an inhibitory receptor activity with respect to time $G(t)$ is defined by:

$$G(t) = \begin{cases} \max(\theta_{G^-}, G(t-1) - k_{G_l}), & S_{ij}(t) = 1; \\ \min(\theta_{G^+}, G(t-1) + k_{G_d}\Delta_t), & \text{otherwise}; \end{cases} \quad (10.5)$$

where t is the training elapsed time, k_{G_l} and k_{G_d} are the losing and the gaining rate respectively; Δ_t is the elapsed time after n_i emitted the last spike to neuron n_j ; $\theta_{G^\pm}$ is the maximum and minimum threshold value for each GABA receptor respectively. The $\max$ and $\min$ functions are computed so that the receptor activation does not surpasses its threshold value. As far as the excitatory receptors are concerned, we made several assumptions to compute their values at a time t . If $S_{ij}(t) = 1$ then the level of A is calculated as:

$$A(t) = \min(\theta_{A^+}, A(t-1) + k_A) \quad (10.6)$$

where t is the elapsed time; and k_A is the AMPAR gaining rate. If A reaches its maximum threshold value θ_{A^+} , then it maintains this value during a time window Δ_w , even if n_i has not emitted a spike. In this case the AMPAR is completely activated. On the other hand, if a connection C_{ij} lacks of a *stimulus* for a longer time than Δ_w , *i.e.* $A = \theta_{A^+}$ and $\Delta_t > \Delta_w$, then the excitatory receptor will manifest a behaviour according to Equation 10.7:

$$A(t) = \max(\theta_{A^-}, A(t-1) - k_G) \quad (10.7)$$

where θ_{A^-} is the minimum level of AMPAR, and $k_G = f_G \cdot G$ is the gain of the inhibitory receptors over this receptor. Here, f_G is the rate that inhibitory receptor level G affects

AMPA. This implies a decay on the synaptic weight due to a lack of sufficient *stimuli*, and therefore simulating the phenomenon of loss of memory.

Regarding the NMDAR, it is known that its activation often depends on the AMPAR, especially in mechanisms that involve memory formation in the hippocampus (Hebert et al., 2004; Collingridge & Wang, 2004; Chin et al., 2008; Wieronska et al., 2011). Here, we propose a simplified model where the NMDAR is activated after the AMPAR reaches its maximum level. If $S_{ij}(t) = 1$ and $A = \theta_{A+}$ then:

$$N(t) = \begin{cases} \min(\theta_{N+}, N(t-1) + k_N) \end{cases} \quad (10.8)$$

otherwise:

$$N(t) = \begin{cases} \max(\theta_{N-}, N(t-1) - k_N) \end{cases} \quad (10.9)$$

where $\theta_{N\pm}$ is the maximum and the minimum level of NMDAR; and k_N is the gaining rate for NMDAR.

Finally, the synaptic weight $W_{ij}(t)$ of the connection from neuron n_i to n_j at a time t is computed as:

$$W_{ij}(t) = N(t) + A(t) - G(t) \quad (10.10)$$

The post-synaptic potential or membrane potential $u(t)$ of a neuron n_j at a time t is calculated in the standard way for the leaky integrate-and-fire type of spiking neuron:

$$u_j(t) = u(t-1) + \sum_{i=1}^m W_{ij}(t) S_{ij} \quad (10.11)$$

where: m the number of spiking neurons connected to the neuron n_j .

The membrane potential increases with every input spike at a time t , until it reaches a

threshold θ . Then, the neuron emits a spike and the membrane potential is reset to an initial state u_r as described in the Equation 10.12.

$$\text{If } u_j(t) \geq \theta \text{ then } u_j(t) = u_r \quad (10.12)$$

Afterwards, the dynamics described in the Equation 10.11 are interrupted during an absolute refractory time δ and restart the integration at time $t + \delta$ with the new initial condition u_r .

10.2.2 The NRDP Rule Behaviour in SNN

As a starting point, we assumed that equivalent model behaviour can be achieved by using the NRDP or the STDP learning rule. Both NRDP and STDP learning rules, can automatically balance the synaptic strengths making post-synaptic firing sensitive to pre-synaptic potentials. In order to produce the same behaviour (spike sequences) when using either STDP and NRDP learning rules, we fitted the NRDP parameters by means of the differential evolution (DE/rand/1/bin) algorithm (Storn & Price, 1997) on a small recurrent SNN as shown in Fig. 10.1. From the figure, we can observe how the excitatory and inhibitory forces affect the neurons' behaviour over time. Both the synaptic weight and the corresponding neurons' action potential decrease (*i.e.* GABA increases) if a pre-synaptic spike is not emitted. Consecutive pre-synaptic spikes cause AMPAR to increase and consequently also the synaptic weight and the respective action potential increase.

The aim was to maximise the spike time coincidences between the spike trains produced by each neuron using the STDP rule with a learning rate $r = 0.01$, and then using the NRDP rule proposed with optimised parameters. These parameters are related to the maximum θ_+ and the gain k values for each neuroreceptor; the probability of

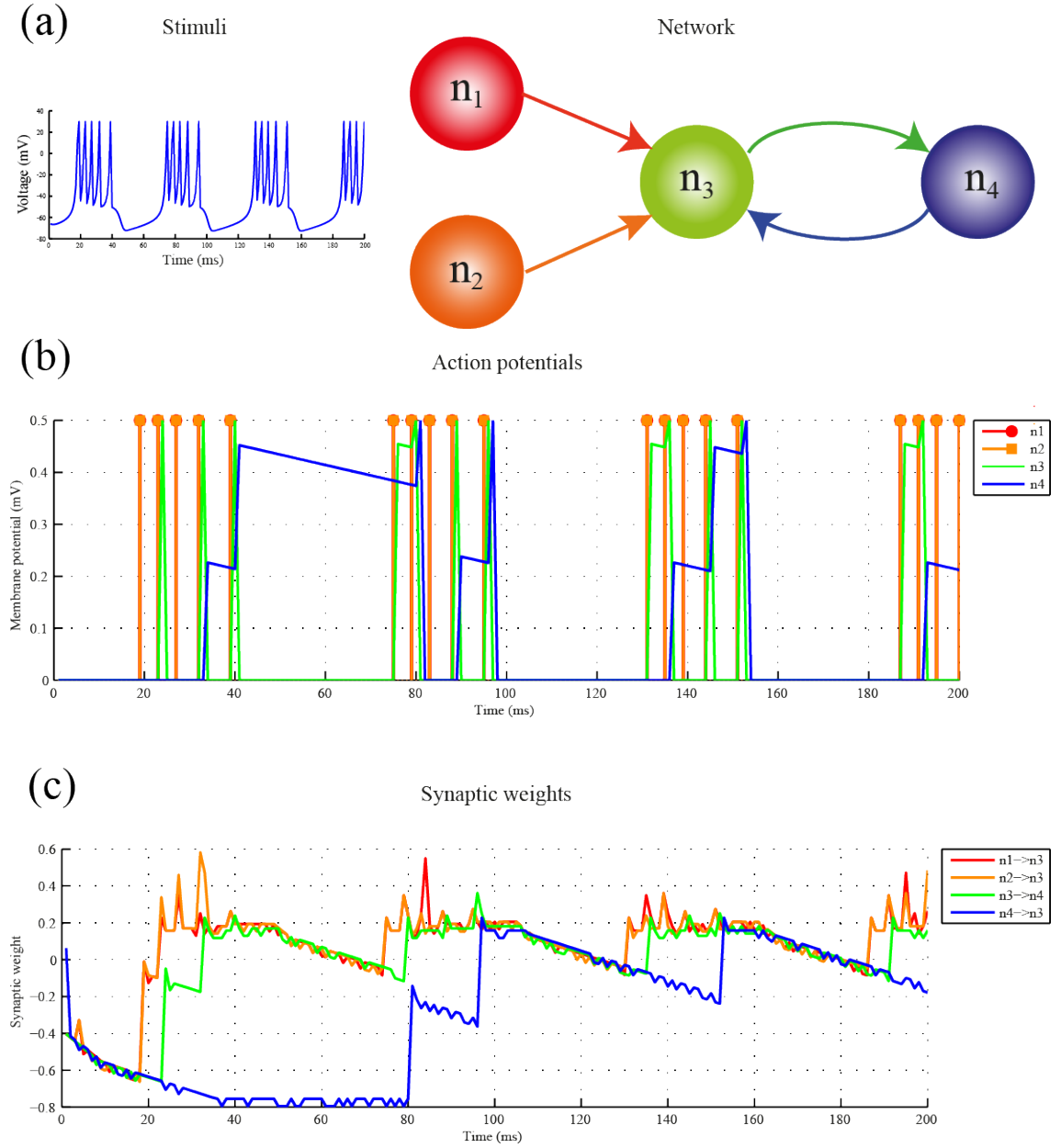


Figure 10.1: Illustration of the NRDP learning rule on four connected neurons: (a) a recurrent SNN network where n_1 and n_2 are input neurons emitting a periodic burst of spike and n_3 and n_4 are the output neurons; (b) The action potentials of neurons n_3 and n_4 calculated using the STDP or NRDP learning rule.

$GABA_A$ to be expressed P_{G_A} ; and the inhibitory rate f_G . Each neuron on the SNN was a leaky integrate-and-fire neuron model that fired when the membrane potential reached a threshold value of 0.5, using a leak value of 0.02 and a refractory time 6 *ms*. Table 10.1 shows the optimised NRDP parameters to produce the same spike trains when using the STDP rule.

Table 10.1: NRDP learning rule parameters settings.

Neuroreceptors	Parameters	Values
AMPA	θ_{A^-}	0
	θ_{A^+}	0.901680
	k_A	0.542872
NMDAR	θ_{N^-}	0
	θ_{N^+}	0.230013
	k_N	0.011660
$GABA_A$	$\theta_{G_a^-}$	0
	$\theta_{G_a^+}$	0.755415
	k_{G_a}	0.385908
	P_{G_a}	0.7
$GABA_B$	$\theta_{G_b^-}$	0
	$\theta_{G_b^+}$	0.795471
	k_{G_b}	0.110321
Inhibitory Rate	f_G	0.01

We can conclude that through setting suitable parameters in a NeuCube-NRDP, we can achieve the same performance as in the NeuCube-STDP. In addition to that a NeuCube-NRDP can facilitate studying the effect of unusual modifications of neuroreceptors on the learning ability of an SNN model trained on brain data, making possible to draw conclusions about the impact of these neuroreceptors on the connectivity and spiking activity of the brain as a source of the data.

10.2.3 NeuCube-NRDP for Computational Neurogenetic Modelling

The NeuCube module M1 for STBD modelling proposed by (Kasabov, 2014a) has three main sub-modules (as shown in Fig. 4.2): the input data encoding sub-module,

where continuous stream data is encoded into spike trains; a 3D SNNc sub-module, where unsupervised learning is applied to learn spatio-temporal patterns from the input spiking sequences; an output evolving classification sub-module (Kasabov et al., 2013) for classification or regression of the dynamic spiking states of the SNNc. Also, an optional GRN sub-module (Benuskova & Kasabov, 2007) can be incorporated, if gene information is available in relation to input data; and the pSNM (Kasabov, 2010) can be implemented as an alternative model to the simple LIF model of a spiking neuron used with the STDP learning rule. The GRN sub-module and the pSNM can be implemented in the future, but for this purpose a neurogenetic learning rule is needed, such as the proposed here NRDP.

To construct a biologically plausible computational neurogenetic model, the proposed NRDP needs to be implemented in the NeuCube-based methodology introduced, to obtain a NeuCube-NRDP system for computational modelling of spatio-temporal and neurogenetic data. This would allow for the creation of a valuable technique that is not only able to properly classify the available STBD, but also to extract new knowledge from the functional changes of brain activity that produced the data.

10.3 Conclusions

The proposed NRDP learning rule has been successfully applied here on integrate-and-fire spiking neurons for modelling their synaptic plasticity by means of dynamic changes in neuroreceptors activity.

According to the obtained results, the NRDP learning rule can be viewed as an extension of the STDP rule (Song et al., 2000), as it can be used to achieve similar spike timing as the STDP through a suitable selection of the neuroreceptor parameters.

Additionally, the NRDP rule can be implemented in a NeuCube SNN architecture to create a NeuCube-NRDP system for computational neurogenetic modelling. This system would allow to model EEG and other brain data, but more importantly, it would allow to study the impact of the neuroreceptors on the machine learning of the data and to further interpret the findings for the study of brain conditions. Targeting these molecular mechanisms could form the basis for new therapeutic strategies for the treatment of mental diseases since glutamate and GABA receptors are essential for many important physiological functions.

To draw more conclusions, the NeuCube-NRDP model needs to be applied on EEG data to study the model behaviour, the resulting classification and connectivity or spiking activity outputs.

10.4 Summary

In this chapter, a new learning rule has been proposed with the aim of improving the understanding of brain processes and to develop novel management strategies for glutamate and/or GABA receptor-based disease.

Here, *RQ6* proposed in Chapter 1 was addressed: *Can we elicit synaptic modifications based on biochemical mechanisms (i.e. based on the main glutamatergic and GABAergic receptors activity) to create an unsupervised learning rule that dynamically learns from the data?*

Chapter 11 explains how the NeuCube-NRDP is applied on complex cognitive EEG data to properly study its functionality.

Chapter 11

Neuroreceptor Dependent Plasticity

Learning Rule for Modelling EEG

Data of Cognitive Brain Processes

11.1 Introduction

In the previous chapter, we presented a new biologically plausible unsupervised learning rule, called NRDP rule, that if combined with the proposed NeuCube-based methodologies can dynamically learn the spatio-temporal relationship from the data. The combined NeuCube-NRDP system allows for computational neurogenetic modelling and this is demonstrated here on a case study on cognitive EEG data.

This chapter is constructed in the following way: section 11.2 explains how the proposed learning rule is applied to a case study on cognitive EEG data and presents some preliminary results; in section 11.3 conclusions are drawn and future work are planned; finally, section 11.4 summarises the chapter.

The study presented in this chapter has been submitted to *Neural Networks Journal* and full text of the paper is provided in Appendix A.7.

11.2 Modelling EEG Data and the Effect of Neuroreceptors in the NeuCube-NRDP Model

The use of NeuCube-NRDP for computational neurogenetic modelling is demonstrated here in cognitive EEG data.

11.2.1 EEG Data Collection

I personally collected the EEG data from 21 healthy volunteers. Ethical approval was granted by the Auckland University of Technology Ethics Committee (AUTEC). A copy of the approval (number **13/283**) is provided in Appendix D.

The subjects were aged between 28 and 50 years. They had all undertaken undergraduate university study as a minimum, had no history of cognitive impairment, and were all right handed. All measurements were taken in a quiet room with the participants seated in a dining chair and using a computer screen. Data was collected following two scenarios (a resting task and a cognitive task) using the Emotiv EPOC (<http://emotiv.com/>) device, a standard EEG system with 14 feature channel names based on the international 10-20 electrodes location system, which are AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4 *plus* two references in the P3/P4 location. No filtering was applied to the data, neither on-line nor off-line, and the recordings were made at a sampling rate of 128 *Hz* per channel. Data was collected in one session. The length of each session was 30 *seconds* per scenario, chosen in accordance with the duration of the memory/cognitive task.

The resting data was recorded with eyes closed, in order to avoid disturbing artefacts (*e.g.* blinking of the eyes) and each subject was asked to avoid thinking or planning thoughts as much as possible. For the memory task a modified Stenberg's Memory Scanning Test (SMT) (Van Der Elst, Van Boxtel, Van Breukelen & Jolles, 2007) was used. In this experiment, each subject was asked to sit comfortably and to look at the screen. A fixation cross appeared for 3 *seconds*; after that, a "positive set" of three random letters was displayed for 5 *seconds*, to give the subjects enough time to memorized them. After a 3 *seconds* pause, when the screen turned blank, a single "test set" was presented that may, or may not, have been shown previously. Every subject was asked to decide (to keep in mind) if the test set was included in the positive set or not. The experiment was repeated increasing the number of elements in the positive set (from three to five and finally to seven letters).

11.2.2 Experimental Design

For this study, only the last 15 *seconds* of the 30 *seconds* recorded were used to run the experiments in order to eliminate any possible noise related to the initial experimental settings. Also, one data point for every three was selected from the entire EEG sequence, obtaining one sample of 640 data points per 14-EEG channels per class and per subject. This information was considered enough for the algorithm to discriminate the resting scenario from the cognitive task. In total, we obtained 21 samples for class 1 (C1, resting) and another 21 samples for class 2 (C2, memory).

To perform the experiments, we created a SNNc with 1471 brain mapped LIF neurons, each representing 1 cm^3 of the 3D Talairach Atlas (Talairach & Tournoux, 1988; Lancaster et al., 2000; Koessler et al., 2009). The 14 EEG data channel variables were encoded as spike trains using the TB algorithm (Chan et al., 2007; Kasabov, 2010)

and the spike sequences were entered into the SNNc into predefined 14 corresponding input neurons that have the same 3D coordinates as the Talairach coordinates of the EEG channels (Koessler et al., 2009). The SW connectivity algorithm was used to initialise the connections in the SNNc with small random numbers attached to them as connection weights. 80% of the connections were made excitatory and 20% - inhibitory.

11.2.3 Results and Discussion

The NeuCube-NRDP parameters were optimised by a grid search algorithm that evaluated the model based on the best classification accuracy result. The resulting best parameters were set as follows:

- The TBR_{Thr} for encoding algorithm was set at 22.518;
- The SW connectivity parameter p was set at 0.075;
- The threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.306, 5 ms and 0.02 respectively;
- The variables *mod* and *drift* of the deSNN classifier were set at 0.4 and 0.25 respectively.

After the optimisation procedure, we retained the best NeuCube-NRDP model to perform the final experiments. We used 50% of the data randomly selected for training and the remaining 50% for testing in a cross validation mode for 30 runs. We also performed two more experiments increasing the parameter θ_{A+} (defining the maximum value for the AMPAR) by 10% and decreasing it by 10%. With the latter experiments we demonstrated the ability of the NeuCube-NRDP to model the effect of neuroreceptors on the connectivity of the learned SNN model from EEG data, therefore to offer some meaningful interpretations of the model in terms of brain learning and memory functions.

Classification

The NRDP model, along with the NeuCube architecture allowed us to analyse both the data and the brain processes that generated it across different conditions and groups of subjects. When we modified the excitatory and inhibitory levels, we were able to observe how the neuroreceptors affected the spiking activity and the connectivity of the SNNc, and therefore the classification results. In Table 11.1, we report the classification accuracy results obtained by using the optimised parameter values and the modified θ_{A^+} values.

Table 11.1: Classification accuracy. The results are presented as classification accuracy percentage for class 1 (resting), class 2 (memory) and overall.

Experimental Settings	Results		
	class 1	class 2	Overall
Optimised	91	64	77
$\theta_{A^+} + 10\%$	36	73	55
$\theta_{A^+} - 10\%$	73	36	55

We observe that optimised parameter values resulted in a good classification accuracy of 77% overall. Considering the short training period, the noisy nature of the data, its rather informal collection method, and the technical limitations of the EEG recording device, this result is satisfactory. Thus, the NRDP algorithm demonstrated its ability to properly distinguish between the resting and the memory tasks. However, modifying the maximum value of AMPAR expression, the θ_{A^+} parameter, affects the classification accuracy by both class and overall. After increasing θ_{A^+} value by 10% the classification accuracy for class 1 (the resting state) considerably decreased. This is because increasing excitatory currents prevents the subjects to get into a resting state. In contrast, decreasing the θ_{A^+} value by 10% makes the samples belonging to class 2 (the memory task) difficult to classify. A simple explanation is that decreasing excitatory currents does not support memory activity.

Analysis of the Connectivity of the SNNc in the NeuCube-NRDP Model

By visualising the connectivity of the training SNNc models in the experiment above (see Table 11.1), we can study how time-series EEG data is learned during unsupervised training and possibly extract new knowledge from it. We aim at understanding how spiking activity and connectivity evolve during learning, for each of the two classes.

Fig. 11.1 to 11.3 shows the 3D SNNc along with the corresponding 12 brain functional areas. Yellow-green denotes the temporal lobe; pink the parietal lobe; light-blue the frontal lobe; red the fronto-temporal space; light-yellow the posterior lobe; orange the occipital lobe; green the anterior lobe; blue the sub-lobar region; grey the limbic lobe; purple the pons; blue-green the midbrain; and brown the medulla. Also, the 14 input neurons are labelled in yellow according to their corresponding EEG channels. In the figures, blue lines indicate the excitatory synapse and red lines the inhibitory synapse; the thickness of these lines indicates the strength of activity between neurons.

We observe that modifying the threshold of the maximum value of AMPAR caused the SNNc to evolve different connectivity for both classes across the brain regions. In Fig. 11.1, we show the connectivity when the NeuCube-NRDP model was trained with optimised parameters settings. We observe that there is a significant difference between the SNNc connectivity generated by the two groups of subjects. The neural activity recorded during the resting task generated an equally distributed connectivity over the entire brain. Contrarily, the memory task evolved most of the connections in the (right) occipito-parietal cortex and centro-temporal area. These findings are consistent with those reported in the literature, as the parietal-temporal-occipital (PTO) area of the human brain is linked with associative type of memory/knowledge related

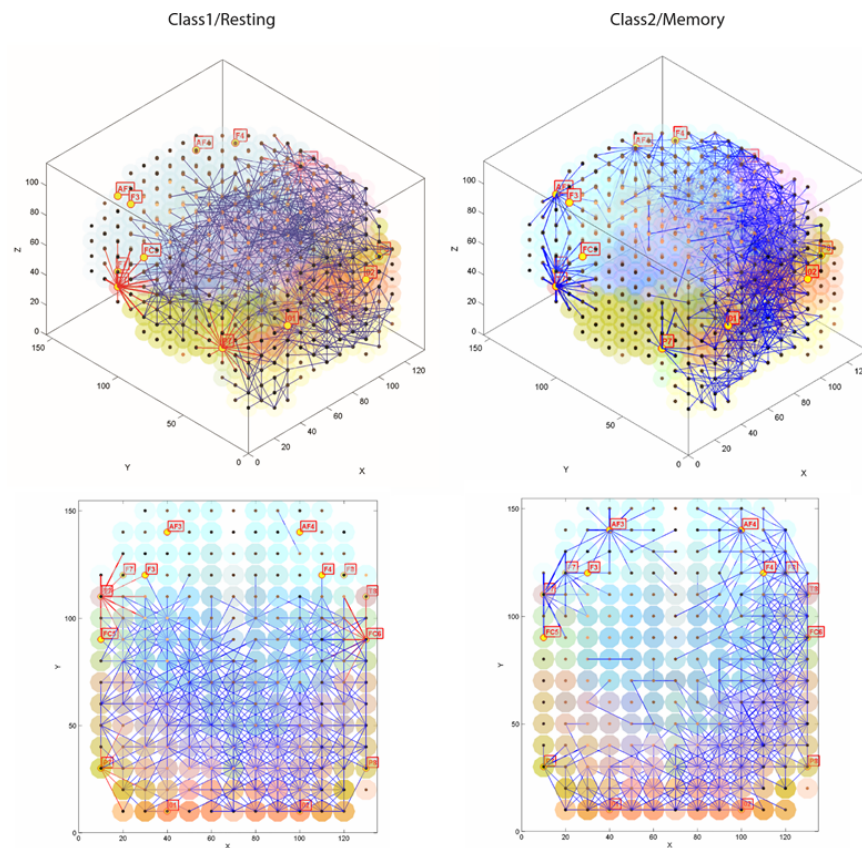


Figure 11.1: NeuCube-NRDP connectivity obtained after training the SNNc with the EEG data recorded during either the resting task (class 1), or the memory task (class 2). The figures show the 3D SNNc together with the corresponding 12 brain functional areas.

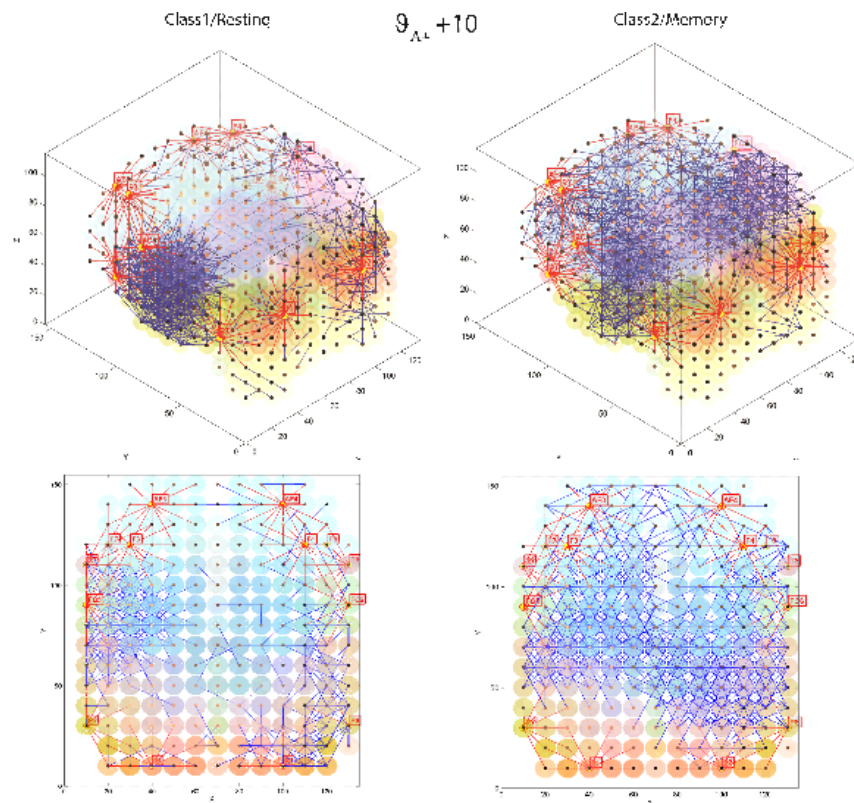


Figure 11.2: NeuCube-NRDP model with 10% higher θ_{A+} obtained after training the SNNc with the EEG data recorded during either the resting task (class 1), or the memory task (class 2). The figures show the 3D SNNc together with the corresponding 12 brain functional areas.

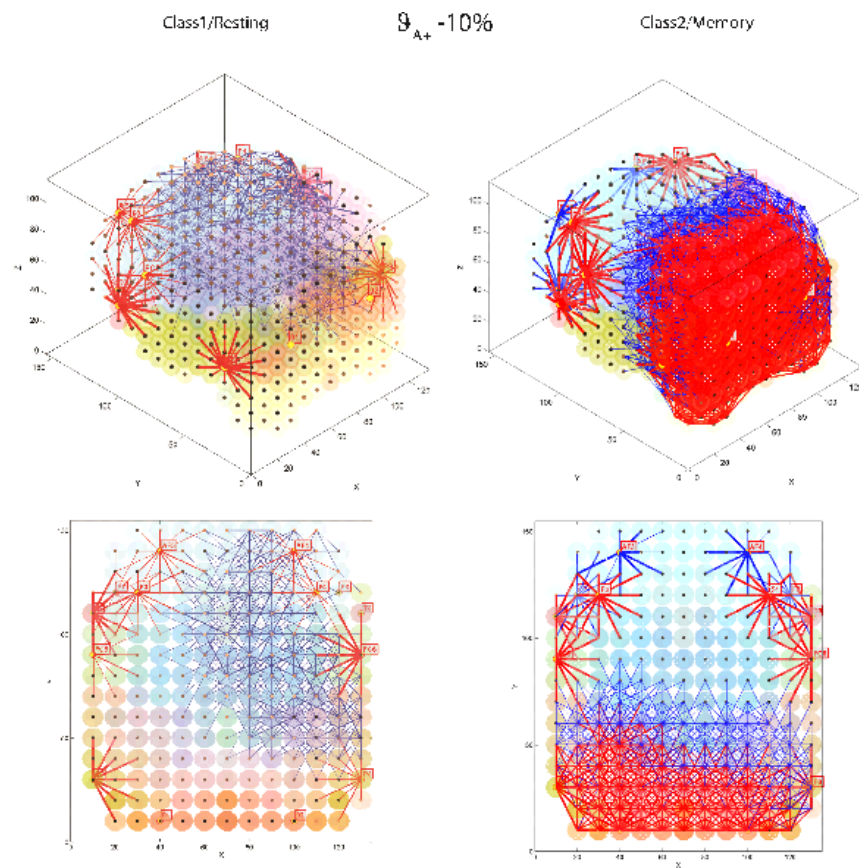


Figure 11.3: NeuCube-NRDP model with 10% lower θ_{A+} obtained after training the SNNc with the EEG data recorded during either the resting task (class 1), or the memory task (class 2). The figures show the 3D SNNc together with the corresponding 12 brain functional areas.

to perception/execution processes (Fuster, 2014). Analysing the connectivity of the evolved NeuCube models may lead to new findings about the data and the brain processes that generated it. Each connection in the SNN cube represents a spatio-temporal causal relationship between the connected neurons that represent corresponding brain areas. When we increased the AMPAR threshold by 10% of its initial value (Fig. 11.2), we observed that the evolved connectivity in the 3D SNN cube differed between the two groups. Inhibitory connections increased for both classes. The resting task data generated an increased connectivity in the temporal area of the left hemisphere, whilst the other areas decreased their connectivity. The memory task data showed increased inhibitory connections in the occipital area (especially by the electrodes O1 and O2), while excitatory connections increased in the right fronto-temporal area. In fact, over expression of AMPAR was responsible for affecting the resting state data, as it increases the connectivity, making the classification task more difficult. On the other hand, decreasing the AMPAR threshold by 10% of its initial value (Fig. 11.3), resulted in increased inhibitory connections around the input neurons in the resting task data; and in excitatory connections to be generated by the fronto-temporal (right) area. The memory task data generated remarkably increased inhibitory connections in the occipital area. Thus, it is the increased activity of GABAergic synapses that affects the classification results; as inhibitory activity prevails over excitatory affecting the normal neural equilibrium. However, cognitive functions and neural synchronisation are also mediated by GABA transmission, which is important for the correct evolution of the neural process (Gonzalez-Burgos, Fish & Lewis, 2011).

11.3 Conclusion and Future Work

In this study, computational modelling of EEG data was achieved by implementing the proposed NRDP learning rule in the NeuCube architecture. Using this system, EEG

and other brain data could be used to study the impact of neuroreceptor activity on the PSP of the neurons that form the SNN cube. Importantly, the evolved connectivity and spiking activity learned could be further interpreted and new knowledge about functional brain conditions could be revealed.

In future work, it would be useful to conduct more experiments using data sets related to the progression of neurodegenerative brain diseases, such as AD or vascular dementia.

In addition, future research could cover:

- Extension of the proposed methodology with the introduction of the probabilistic model of a neuron as proposed in (Kasabov, 2010);
- Extension of the proposed methodology with a GRN module to study how gene expression data can be used to modify the SNNc neural activity (as explained in details in the next subsection).

11.3.1 A GRN for Studying the Impact of NMDAR in AD

As emerged in this thesis, the expression of certain genes triggers mechanisms that are fundamental for the activities of the brain. When a gene is turned on in the neural cell, this is the starting engine of the various brain processes which determine its functions and development. Proteins influence the spiking activity of the neural cells, which consequently is reflected in the collected STBD. Genetic parameters are extremely useful especially if we aim to develop a valid neurological computational model. To construct a biologically plausible computational model with the use of SNN, we believe that a GRN sub-model is of pivotal importance.

This approach is shared by several researchers, who have been demonstrating that

even modelling just a single gene (Benuskova & Kasabov, 2007) or constructing a GRN (Benuskova & Kasabov, 2007) contributes to the optimization of the results and to a better understanding of the phenomena of study. In (Benuskova & Kasabov, 2007; Kasabov, 2010), a neurogenetic model of a neuron is proposed and studied. The model utilises information about how the main neuroreceptors, and the genes that affect their expression, related to the spiking activities of a neuron in terms of fast excitation, fast inhibition, slow excitation, and slow inhibition. This model can be also optimised using a gene/protein regulatory network, controlling the dynamic interactions between genes/proteins over time, which affect the PSP of the neurons in the SNNc.

The NeuCube-NRDP model proposed here could be extended by adding genetic information, related to NMDAR in particular, in term of a GRN. NMDAR plays a pivotal role in memory plasticity (Tsai et al., 2002; Cooke & Bliss, 2006) and it is well known that people affected by AD suffer from cognitive decline and disorientation as first symptoms (Cooke & Bliss, 2006). In the human brain, the information transmitted by neurons is processed and consolidated in the hippocampus from short-term memory to long-term memory; therefore, this is one of the first regions to suffer damage as AD advances. The human brain has two hippocampi, which are part of the limbic system and located in the medial temporal lobe. One of the processes associated with the development of AD is the constant activation of the NMDAR. This event is thought to lead to an abnormal over-activity during neural processes (Francis, 2005) leading to cellular dysfunction and neural death over a period of time (Mohandas et al., 2009). Moreover, these processes and related mechanisms are known to contribute to the effects of Amyloid-beta, which is the major component of senile plaques, one of the typical features of AD formation and degeneration (Rowan, Klyubin, Cullen & Anwyl, 2003; Collingridge & Wang, 2004; Francis, 2005).

It is important to outline that NMDAR is a channel with a quaternary-structure (*i.e.* three-dimensional or spatial structure of different proteins). Each of these proteins is encoded by a different gene (Ishii, 1993) (Fig. 11.4). The synthesis of this neuroreceptor is possible only due to the simultaneous expression of these genes, as they are responsible for each unit that forms the macromolecule. To construct a GRN for the NMDAR, gene GRIN1, GRIN2A, GRIN2B, GRIN3A and GRIN3B could be used; since, in humans, the NMDAR principal sub-unit is NR1 (encoded by GRIN1 gene) (Stephenson, 2006); NR2A and NR2B (encoded by GRIN2A and GRIN2B gene respectively) are found in glutamatergic synapses (Collingridge & Wang, 2004); NR3A (encoded by GRIN3A gene) has been found in embryonic brain tissue and together with NR3B (gene GRIN3B) have an inhibitory influence in NMDAR expression (Bendel, Meijer, Hurd & von Euler, 2005). The NRDP model proposed here, implemented in the NeuCube architecture, constitutes only a preliminary step towards further development of new neurogenetic computational models, representing more closely biological neural networks in order to allow for a better understanding of brain cognition.

11.4 Summary

In this chapter, we apply the proposed NeuCube-NRDP methodology to study cognitive brain processes in order to understand whether changes to neurotransmitters levels affect the computational learning process. Through the analysis of the NeuCube evolved connectivity and spiking activity, possible implications on mental diseases treatments have also been suggested. Thus, RQ7-9 proposed in Chapter 1 were addressed here:

- *Can we use this methodology to study the impact of neuroreceptors' activity on the post-synaptic action potential of a spiking neuron in a eSTDM-based model and further interpret the findings for the study of brain conditions?*

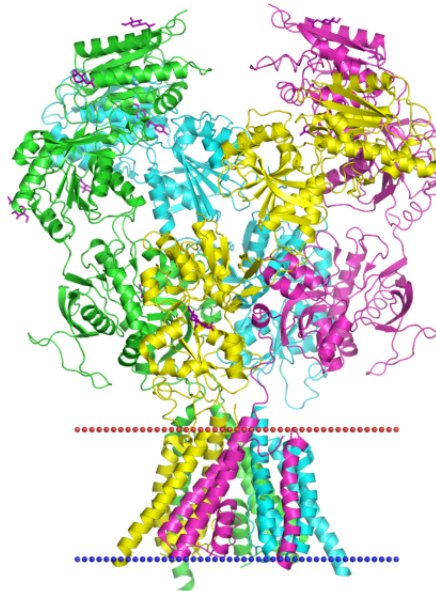


Figure 11.4: The image represents the crystal structure of the NMDAR channel. NMDAR four sub-units are highlighted in the image by different colours. Figure from (Lomize et al., 2005)

- *Can a better understanding of how these neurotransmitters are involved in the computational learning processes be used to emulate therapeutic strategies for targeting mental diseases treatments?*
- *Can we use the proposed unsupervised learning rule together with an eSTDM to develop a computational neurogenetic model for knowledge extraction of both STBD and genetic data?*

The next chapter summarises the research presented in this thesis and the achievements attained.

Chapter 12

Conclusion and Future Directions

12.1 Introduction

The chapter concludes the presented work by summarising the main achievements obtained throughout this research thesis (section 12.2) and suggesting future work to be undertaken (section 12.3).

12.2 Summary of Achievements

The research carried out and reported in this thesis's chapters was aimed at addressing the questions raised in Chapter 1 by achieving the proposed objective. Table 12.1 links these questions with the chapters where they were answered.

As noted earlier in the thesis, the increase in the average human life span has brought up the problem of dealing with a population ageing phenomenon and, as a consequence, the risk of early onset of cognitive impairments and neurological disorders. Researchers have been struggling to improve their understanding of the neural processes that govern the human brain and neurodegeneration. For this purpose, large amount of brain data has been collected and even more are expected to come, by means of novel electrophysiological

Table 12.1: The table lists the research questions raised in Chapter 1 and links them to the chapters where these were answered.

Research Questions	Chapters
RQ 1. Can we develop a methodology for EEG data classification and modelling in an eSTDM of spatially organised spiking neurons that can be used to properly analyse and understand the STBD available and the brain processes that generated it?	5, 6
RQ 2. Can we identify the functional changes in neural activity generated when a subject affected by a particular neurological disorders and/or under a particular drug treatment is compared with a control subject or the absence of a neural event?	7
RQ 3. Can we analyse the evolution of connectivity and/or spiking activity that occur in a trained eSTDM when comparing data of an individual subject or a group of subjects performing a task with data from another individual or another group?	8
RQ 4. Can we identify the brain areas where the functional changes in neural activity is generated by the different classes using the computational model developed?	8
RQ 5. Can the methodology be successfully applied on the analysis and the prediction of a specific neurological event?	9
RQ 6. Can we elicit synaptic modifications based on biochemical mechanisms (<i>i.e.</i> based on the main glutamatergic and GABAergic receptors activity) to create an unsupervised learning rule that dynamically learns from the data?	10
RQ 7. Can we use this methodology to study the impact of neuroreceptors' activity on the post-synaptic action potential of a spiking neuron in a eSTDM-based model and further interpret the findings for the study of brain conditions?	11
RQ 8. Can a better understanding of how these neurotransmitters are involved in the computational learning processes be used to emulate therapeutic strategies for targeting mental diseases treatments?	11
RQ 9. Can we use the proposed unsupervised learning rule together with an eSTDM to develop a computational neurogenetic model for knowledge extraction of both STBD and genetic data?	11

measurements and biochemistry techniques. However, modelling the data and interpretation of the results still remain a challenge due to the lack of appropriate machine learning techniques (Kasabov, 2012b; Izhikevich & Edelman, 2008; Reggia et al., 1999).

It is rather difficult to find studies where all these challenges are taken on. Proposed models often fail due to the lack of biological details and therefore have insufficient ability to represent the phenomena being studied (Reggia et al., 1999). Also, STBD, the most commonly collected data for the study of brain behaviours, are often mined with techniques that suffer from loss of details and patterns, which leads to incoherence in the analysis of results.

Driven by this problematics, we have investigated the development of a new biologically plausible SNN methodology for spatio-temporal EEG data modelling, classification and understanding (Chapter 5). The research extended further into the creation of an additional methodology for the analysis of connectivity and spiking activity generate in the SNN model with the aim of understanding functional changes in brain activity generated by the available spatio-temporal information (Chapter 8). Additionally, a new unsupervised learning rule has been proposed to better deal with the data and to investigate the biological processes responsible for brain synaptic activity to target pharmacological treatments (Chapter 10).

12.2.1 A NeuCube-based Methodology for EEG Data Classification and Analysis

As part of the research objectives, we explored the potentiality offered by eSTDM NeuCube architecture to develop new biologically plausible methodologies for modelling and understanding EEG data and the neurological events that generate it. This is important

for the creation of new types of BCI-based systems and also for early detection of cognitive decline to be used by clinicians in everyday diagnosis. Further improvement of the understanding and use of the proposed methodology would contribute to the advancement on IS research for the prediction and understanding of brain data and more specifically for data related to neurodegenerative disorders, such as AD.

NeuCube constitutes a biologically inspired 3D environment of SNN for on-line learning of spatio-temporal brain data and recognition of patterns within the data. It takes into account data features, offering a better understanding of the information and the phenomena of study. The proposed methodology is based on the NeuCube architecture and has demonstrated to be capable of accurately classifying even noisy and relatively low-quality data. An advantage of the NeuCube-based methodology is that it allows for interpretation of results leading to understanding of the data and the brain processes that generated it. NeuCube could be partially trained on highly accurate data captured in a controlled manner with medical devices, and then further trained and adapted to a particular subject, which will increase potential uses in clinical applications allowing to trace the development/decline of cognitive processes over time and to extract new information and knowledge about them.

Moreover, the NeuCube-based methodology has demonstrated to offer several advantages when compared to traditional AI methods, such as:

- No need of pre-processing of the data (such as normalization, scaling, smoothing, etc.);
- Fast learning of STBD with one iteration data propagation only;
- Better classification accuracy;

- Ability to adapt to new data and new classes through incremental learning;
- Interpretation of the model for a better understanding of the EEG STBD and the processes that generated it.

12.2.2 A NeuCube-based Methodology for the Analysis of Connectivity and Spiking Activity, for the Understanding of Functional Changes in the Brain

By developing a new NeuCube-based methodology for the analysis of connectivity and spiking activity for EEG STBD, we achieved a better understanding of changes in brain activity across different groups of subjects undertaking treatments.

This makes the NeuCube modelling approach widely applicable for neuroscience research. Especially, the new methodology proposed in this thesis demonstrates:

- The model ability to classify EEG data collected from different groups of patients and healthy subjects;
- Connectivity analysis of a SNNc after unsupervised training of EEG data from different groups of subjects/classes to extract new knowledge and to study the brain regions involved;
- Connectivity analysis for the understanding of drug-based treatments;
- Connectivity analysis for the understanding of the impact of different drug doses on brain activity and at predicting response to treatment;
- The model capability for use in neuromorphic learning, for personalised prognosis, and early prediction of a neurological event;

- The model capability for use in brain-like mapping, to study the specific characteristics of neurological events, revealing the area of the brain where it occurs. Leading eventually to future prediction of neurological events based on the initial information;

12.2.3 NeuCube-NRDP

This research explored and proposed a new unsupervised learning rule for SNN, called NRDP where the synaptic plasticity is modelled based on neuroreceptors dependent plasticity.

The proposed NRDP learning rule has been successfully applied on LIF neurons by achieving similar classification results as the STDP rule. Additionally, it offers the possibility of modelling dynamic changes in neuroreceptors synaptic activity. This could be further studied by means of a NeuCube-NRDP system for computational neurogenetic modelling.

The NeuCube-NRDP model allows mining of STBD to study the impact of neuroreceptors activity on the PSP of the neurons and further interpreting the findings for the study of brain conditions. This could potentially help the understanding of molecular mechanisms involved in neurodegeneration and treatments of neurological disorders.

12.3 Future Directions

This thesis reports a number of promising results and valuable insights that have been obtained in the course of the study. However, some further research and analysis need to be carried out.

Future research could cover:

- Testing the proposed methodology on new types of BCI in a clinical environment, using larger data sets collected from a higher number of subjects affected by AD and MCI, for early diagnosis of cognitive decline and to possibly extract degeneration markers;
- Development of a NeuCube-based model for the analysis of “deep in time” spatio-temporal patterns that are hidden in the brain data;
- Extending the analysis and interpretation of the output connectivity and spiking activity for a better understanding of brain functionality and brain activity. This can be achieved by adding quantitative measures to the results. For instance, by using the graph theory approach, we could measure the maximum degree of a vertex, the graph density, the clustering coefficient, the path length, etc.
- Spatio-temporal rule extraction from a trained NeuCube model;
- Parameter optimisation using genetic algorithm and/or quantum inspired evolutionary algorithms as suggested by (Platel et al., 2009; Nuzly Abdull et al., 2010; Schliebs et al., 2009);
- Comparison of the methodology developed with other techniques used for AD classification, such as Random Forest (Gray et al., 2013), kSVM-DT (Zhang et al., 2014), LVQ-SVM (Ortiz et al., 2013), HMRF model (Shu et al., 2014);
- Improved visualisation of the SNNc and the classifier during the training and recall procedures for an improved understanding of the data and the brain processes through visualization and/or virtual reality of the SNNc. This could be used by clinicians to study how patients effectively improve their neurological activity before and after treatments when compared to healthy controls;

- Implementation of the proposed method on neuromorphic hardware to explore its potential for a highly parallel computation as developed by (Furber & Temple, 2007; Furber, 2012; Indiveri et al., 2011; Neftci et al., 2011);
- Extending and improving the NeuCube-NRDP model by replacing the simple LIF neural model with the probabilistic spiking neuron model proposed by (Kasabov, 2010) and adding genetic information in terms of a GRN as per (Benuskova & Kasabov, 2007; Hawrylycz et al., 2012; Henley et al., 2011; Kasabov, 2014b; Kasabov et al., 2011). This model would help study the impact of genes on cognitive abilities. This would improve the molecular and genetic analysis of a disease and it could be used as a personalised model for the understanding of functional changes in the brain and for the prediction of neurological events from new data.

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Appendix A

Published Papers

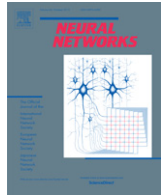
A.1 Evolving Spatio-Temporal Data Machines Based on the NeuCube Neuromorphic Framework: Design Methodology and Selected Applications

The paper presented in Chapter 4 resulted in a paper (Kasabov et al., 2015) that was published by *Neural Networks Journal* Special Issue: *Neural Network Learning in Big Data*. Copyright and permission from the publisher of the paper are provided in Appendix B.



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Evolving spatio-temporal data machines based on the NeuCube neuromorphic framework: Design methodology and selected applications

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ABSTRACT

The paper describes a new type of evolving connectionist systems (ECOS) called evolving spatio-temporal data machines based on neuromorphic, brain-like information processing principles (eSTDM). These are multi-modular computer systems designed to deal with large and fast spatio/spectro temporal data using spiking neural networks (SNN) as major processing modules. ECOS and eSTDM in particular can learn incrementally from data streams, can include 'on the fly' new input variables, new output class labels or regression outputs, can continuously adapt their structure and functionality, can be visualised and interpreted for new knowledge discovery and for a better understanding of the data and the processes that generated it. eSTDM can be used for early event prediction due to the ability of the SNN to spike early, before whole input vectors (they were trained on) are presented. A framework for building eSTDM called NeuCube along with a design methodology for building eSTDM using this is presented. The implementation of this framework in MATLAB, Java, and PyNN (Python) is presented. The latter facilitates the use of neuromorphic hardware platforms to run the eSTDM. Selected examples are given of eSTDM for pattern recognition and early event prediction on EEG data, fMRI data, multisensory seismic data, ecological data, climate data, audio-visual data. Future directions are discussed, including extension of the NeuCube framework for building neurogenetic eSTDM and also new applications of eSTDM.

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1. Introduction: Spatio & spectro temporal data and the challenges for information sciences

Most problems in nature require spatio- and/or spectro-temporal data (SSTD) that include measuring spatial or/and spectral variables over time. SSTD is described by a triplet (X, Y, F) , where: X is a set of independent variables measured over

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consecutive discrete time moments t ; Y is the set of dependent output variables, and F is the association function between whole segments ('chunks') of the input data, each sampled in a time window Δt , and the output variables belonging to Y , such that

$$F : X(\Delta t) \rightarrow Y$$

where $X(t) = (x_1(t), x_2(t), \dots, x_n(t))$ and $t = 1, 2, \dots, m$.

It is important for a computational model to capture and learn whole spatio- and spectro-temporal patterns from data streams in order to most accurately predict future events from new input data. Examples of problems involving SSTD are: brain cognitive state evaluation based on spatially distributed EEG electrodes (Kasabov, 2014); fMRI data (Chu, Ni, Tan, & Ashburton, 2011; Gholami Doborjeh & Kasabov, 2015; Just, 2001; Mitchell, Hutchinson, Just, Niculescu, & Wang, 2003; Murli, Kasabov, & Handaga, 2014); moving object recognition from video data (Delbruck & Lichtsteiner, 2007); evaluating risk of disease, e.g. heart attack, stroke (Kasabov et al., 2014); evaluating response of a disease to treatment based on clinical and environmental variables; modelling the progression of a neuro-degenerative disease, such as Alzheimer's Disease; modelling and prognosis of the establishment of invasive species in ecology. The prediction of events in geology, astronomy, economics and many other areas also depend on accurate SSTD modelling.

The most commonly used models for dealing with temporal information, based on Hidden Markov Models (HMM) and traditional artificial neural networks (ANN), have limited capacity to achieve the integration of complex and long temporal spatial/spectral components because they usually either ignore the temporal dimension or over-simplify its representation. A new trend in machine learning is currently emerging and is known as deep machine learning (Schmidhuber, 2014). Most of the proposed models still learn SSTD by entering single time point frames rather than learning whole SSTD patterns. They are also limited in addressing adequately the interaction between temporal and spatial components in SSTD. Some recent developments in SSTD modelling have been proposed (e.g. (Liu et al., 2013; Liu, Wang, Jayarajah, Misra, & Krishnan, 2013)) but these are limited in their application – typically these methods are targeted towards one specific source of data, and do not show the broad level of application required in the contexts we seek to address.

The human brain has the amazing capacity to learn and recall patterns from SSTD at different time scales, ranging from milliseconds, to years, and possibly to millions of years (*i.e.* genetic information, accumulated through evolution). Thus, the brain is the ultimate inspiration for the development of new machine learning techniques for SSTD modelling. Indeed, brain-inspired Spiking Neural Networks (SNN) (Buonomano & Maass, 2009; Gerstner, Kreiter, & Markram, 1997; Gerstner, Sprekeler, & Deco, 2012) have the potential to learn SSTD by using trains of spikes (binary temporal events) transmitted among spatially located synapses and neurons. Both spatial and temporal information can be encoded in an SNN as locations of synapses and neurons and time of their spiking activity, respectively. Spiking neurons send spikes via connections that have a complex dynamic behaviour, collectively forming an SSTD memory. Some SNN employ specific learning rules such as Spike-Time-Dependent-Plasticity (STDP) (Song, Miller, & Abbott, 2000) or Spike Driven Synaptic Plasticity (SDSP) (Fusi, 2003).

In Kasabov (2014) a NeuCube framework was presented for spatio-temporal brain data and in Kasabov et al. (2014) an application for personalised modelling stroke prediction was published. This paper further extends the published works into a generic and systematic methodology for a new type of solutions to any spatio-temporal stream data problems and the solution is called here for the first time—evolving spatio-temporal data machine (eSTDM). Various novel aspects of this

approach are developed and presented here such as: the analysis of encoding methods; 3D VR visualisation; GA optimisation; along with a novel NeuCube development system that consists of 10 different functional modules including a hardware module and a description of a hardware implementation of a developed application prototype model. The NeuCube development system is announced here for the first time to be publically available online: <http://www.kedri.aut.ac.nz/neucube>. New applications are presented here for the first time, such as: earthquake prediction; age detection from face video data, along with previously published applications that have been cited and briefly explained here.

Organisation of this paper:

In Section 2 we introduce classical evolving connectionist systems, the conceptual predecessor of this work, including the evolving spiking neural network which this work is based around. The primary contribution of this paper is established in Section 3, where our design methodology for eSTDM in the NeuCube computational framework is proposed. An immersive visualisation for this framework is discussed in Section 4. In the following sections we apply this methodology to build example eSTDM for case studies, in: eSTDM for brain data, including EEG and fMRI (Section 5); neurogenetic models (Section 5.3); personalised modelling, including stroke prediction (Section 6); environmental applications, including invasive pest population prediction and earthquake prediction (Section 7); video data (Section 8); and general spectro-temporal data, including radioastronomy (Section 9). An implementation of the framework for neuromorphic hardware is discussed in Section 10.

2. Principles of evolving connectionist systems and their development

2.1. Principles of ECOS

The human brain uniquely combines low level neuronal learning in the neurons and the connections between them, and higher level rule abstraction leading to adaptive learning and abstract concept formation. This is the ultimate inspiration for the development of intelligent evolving connectionist systems (ECOS) where specially constructed artificial neural networks (NN) are trained on data, so that after training abstract knowledge representation can be derived that explains the data and can be further interpreted as a knowledge-based system.

ECOS are modular connectionist based systems that evolve their structure and functionality in a continuous, self-organised, on-line, adaptive, interactive way from incoming data (Kasabov, 1998, 2007). They can process both data and knowledge in a supervised and/or unsupervised way. ECOS learn local models from data through clustering of the data and associating a local output function for each cluster represented in a connectionist structure. They can learn incrementally single data records or chunks of data and also incrementally change their input features. ECOS further develop some connectionist information processing principles already introduced in classical NN models, such as SOM, RBF, FuzzyARTMap, Growing Neural Gas, Neuro-Fuzzy Systems, or RAN (Kasabov, 2007).

ECOS perform *adaptive local learning*—neurons are allocated as centres of data clusters and the system creates local models in these clusters. The clustering used in ECOS is on-line, one-pass, evolving clustering, which is in contrast to the traditional fuzzy clustering methods that use pre-defined number of clusters and many iterations (Bezdek, 1987; Yager & Filev, 1994).

The following are the main principles of ECOS as stated in Kasabov (1998):

1. Fast learning from large amount of data, e.g. using 'one-pass' training, starting with little prior knowledge;
2. Adaptation in a real time and in an on-line mode where new data is accommodated as it comes based on local learning;
3. 'Open', evolving structure, where new input variables (relevant to the task), new outputs (e.g. classes), new connections and neurons are added/evolved 'on the fly';
4. Both data learning and knowledge representation is facilitated in a comprehensive and flexible way, e.g. supervised learning, unsupervised learning, evolving clustering, 'sleep' learning, forgetting/pruning, fuzzy rule insertion and extraction;
5. Active interaction with other ECOS and with the environment in a multi-modal fashion;
6. Representing both space and time in their different scales, e.g.: clusters of data, short- and long-term memory, age of data, forgetting, etc.;
7. System's self-evaluation in terms of behaviour, global error and success and related knowledge representation.

2.2. ECOS development: EFuNN, DENFIS, eSNN

The development of ECOS, as a trend in neural networks and computational intelligence that started in 1998 (Kasabov, 1998) continued as many improved or new computational methods that use the ECOS principles have been developed along many applications.

While the classical ECOS such as EFuNN and DENFIS (Kasabov, 2007) use a simple McCulloch and Pitts model of a neuron, where data is represented as scalars, the further developed evolving spiking neural network (eSNN) architectures use a spiking neuron model, while applying the same or similar ECOS principles. eSNN uses data represented as temporal sequences of spikes.

A single biological neuron and the associated synapses is a complex information processing machine that involves short term information processing, long term information storage, and evolutionary information stored as genes in the nucleus of the neuron. A spiking neuron model assumes input information represented as trains of spikes over time. When sufficient input information is accumulated in the membrane of the neuron and the neuron's postsynaptic potential exceeds a threshold, the neuron emits a spike at its axon. Some of the state-of-the-art models of a spiking neuron include: early models by Hodgkin and Huxley (Hodgkin & Huxley, 1952); more recent models by Maass, Gerstner, Kistler, Izhikevich and others, e.g.: Spike Response Models (SRM); Integrate-and-Fire Model (IFM); Izhikevich models (Izhikevich, 2004); adaptive IFM; probabilistic neurogenetic model (Kasabov, 2010).

Based on the ECOS principles, an evolving spiking neural network architecture (eSNN) was proposed (Kasabov, 2007; Wysoski, Benuskova, & Kasabov, 2010). It was initially designed as a visual pattern recognition system. The first eSNNs were based on the Thorpe's learning rule (Thorpe, 2001), in which the importance of early spikes (after the onset of a certain stimulus) is boosted, called rank-order coding and learning. Synaptic plasticity is employed by a fast supervised one-pass learning algorithm.

The main advantage of the eSNN when compared with other supervised or unsupervised SNN models is that it is computationally inexpensive and boosts the importance of the order in which input spikes arrive, thus making the eSNN suitable for on-line learning with a range of applications. For a comprehensive study of eSNN see Wysoski et al. (2010).

Different eSNN models have been developed, including:

- Dynamic eSNN (deSNN)—an architecture that uses both rank-order and time-based learning methods to account for spatio-temporal learning (Dhoble, Nuntalid, Indiveri, and Kasabov (2012) and Kasabov, Dhoble, Nuntalid, and Indiveri (2013);

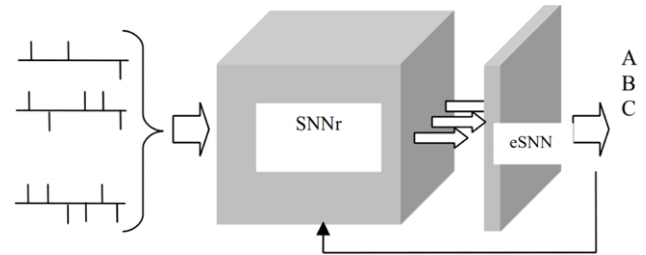


Fig. 1. A principle diagram of an eSTDm.

- Reservoir-based eSNN for spatio- and spectro-temporal pattern recognition (for principles of reservoir computing, see Verstraeten, Schrauwen, D'Haene, and Stroobandt (2007));
- Specialised architectures for EEG modelling and moving object recognition systems (Kasabov & Dhoble, et al., 2013).

3. A design methodology for evolving spatio-temporal data machines (eSTDm) using the NeuCube framework

3.1. General architecture and functionality of eSTDm

Our approach here to modelling large and fast stream SSTD is based on a common architecture of eSTDm as depicted in Fig. 1. The functionality of an eSTDm is based on the following procedures:

1. Converting multivariable input stream data into spike sequences;
2. Unsupervised learning of spatio-temporal patterns from data in a SNN reservoir (the "Cube");
3. Supervised learning of classification/regression output system for classification/regression problems;
4. Optimisation using the evaluated/tested accuracy of the system as a feedback for improving the performance of this system in an iterative way (if necessary).

The structure of the eSTDm resembles the structure of a LSM (Verstraeten et al., 2007), but the methodology for building such eSTDm in a specially proposed SNN computational framework called NeuCube departs significantly from the classical neuro-computation and artificial intelligence approaches.

3.2. NeuCube: A framework for eSTDm

The latest development in the direction of eSNN systems was proposed as a new architecture called NeuCube (Kasabov, 2014). It was initially proposed for spatio-temporal brain data modelling, but then it was further developed for other types of data as presented in this paper.

A block diagram of the NeuCube architecture is provided in Fig. 2. It consists of the following modules:

- Input information encoding module;
- 3D SNN module (the Cube);
- Output classification/regression module;

and other optional modules, including:

- Gene regulatory network (GRN) module;
- Parameter optimisation module;
- Visualisation and knowledge extraction module (not shown in Fig. 2).

The input module transforms input data into trains of spikes. Spatio-temporal data (such as EEG, fMRI, climate) is entered into the main module—the 3D SNNcube (SNNc). Different types of data

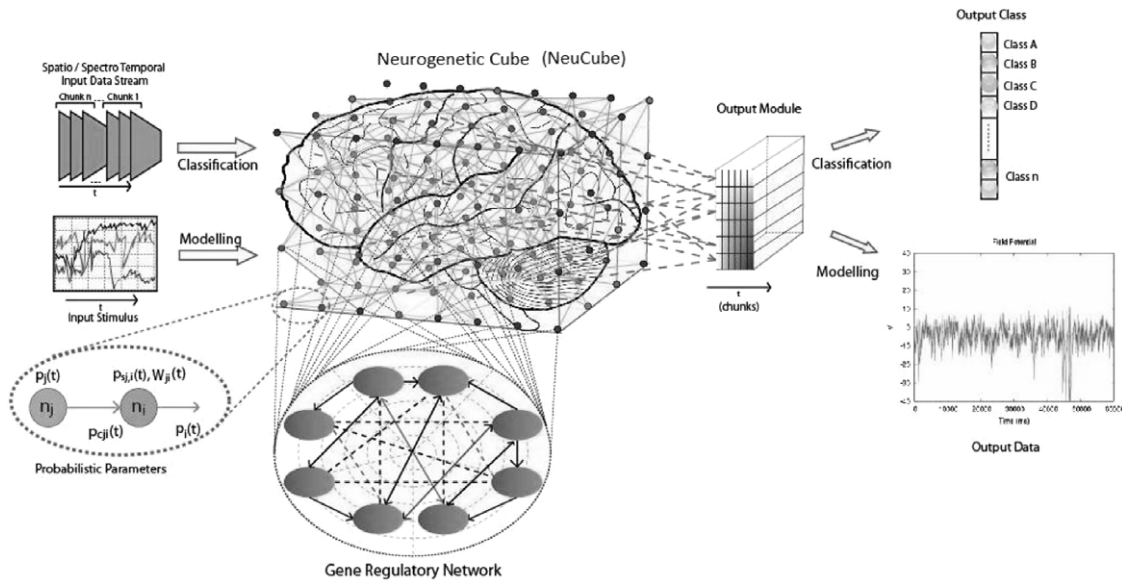


Fig. 2. A block diagram of the NeuCube architecture initially proposed for brain data modelling but later used for a wide range of SSTD (Kasabov, 2014).

can be used. This data is entered (“mapped”) into pre-designated spatially located areas of the SNNc that correspond to the spatial location of the origin where data was collected (if such a location exists).

Learning in the SNN is performed in two stages:

1. Unsupervised training, where spatio-temporal data is entered into relevant areas of the SNNc over time. Unsupervised learning is performed to modify the initially set connection weights. The SNNc will learn to activate same groups of spiking neurons when similar input stimuli are presented, also known as a polychronization effect (Izhikevich, 2004).
2. Supervised training of the spiking neurons in the output module, where the same data that was used for unsupervised training is now propagated again through the trained SNN and the output neurons are trained to classify the spatio-temporal spiking pattern of the SNNc into pre-defined classes (or output spike sequences). As a special case, all neurons from the SNN are connected to every output neuron. Feedback connections from output neurons to neurons in the SNN can be created for reinforcement learning. Different SNN methods can be used to learn and classify spiking patterns from the SNNc, including the deSNN (Kasabov, Hu, Chen, Scott, & Turkova, 2013) and SPAN models (Mohammed & Kasabov, 2012). The latter is suitable for generating motor control spike trains in response to certain patterns of activity of the Cube.

In an eSTDM similar activation patterns (called ‘polychronous waves’) can be generated in the SNNc with recurrent connections to represent short term memory. When using STDP learning, connection weights change to form LTP or LTD, which constitute long-term memory (see Song et al. (2000) for more detail of STDP).

Results of the use of the NeuCube suggest that the NeuCube architecture can be explored for learning long spatio-temporal patterns and to be used as associative memory. Once data is learned, the SNNc retains the connections as a long-term memory. Since the SNNc learns functional pathways of spiking activities represented as structural pathways of connections, when only a small initial part of input data is entered the SNNc will ‘synfire’ and ‘chain-fire’ learned connection pathways to reproduce learned functional pathways. Thus a NeuCube can be used as an associative memory and as a predictive system for event prediction when only some initial new input data is presented.

3.3. Design methodology of eSTDM in NeuCube

In order to design an appropriate eSTDM for a given data source, a number of factors must be taken into consideration. Here, we identify these considerations.

- Which input transformation function do we use to encode the data as trains of spikes?
- Which input variable mapping into the SNNc is used? Is there some a-priori information we can use to spatially locate these input variables in the SNNc?
- Which learning method do we use in the SNNc?
- Which output function is appropriate? Is it classification or regression?
- How to visualise an eSTDM for an improved understanding?
- Which parameter optimisation method will we apply?

For rapid prototyping and exploration of a NeuCube model, a generic prototyping and testing module has been implemented and is discussed later in this paper.

3.3.1. Data encoding

There are different coding schemes for SNN, primarily rate (information as mean firing rates) or temporal (information as temporally significant) coding. For NeuCube, we use temporal coding to represent information. So far four different spike encoding algorithms have been integrated into the existing implementation of the NeuCube, namely the Ben’s Spiker Algorithm (BSA), Temporal Contrast (Threshold-based), Step-Forward Spike Encoding Algorithm (SF) and Moving-Window Spike Encoding Algorithm (MW). Fig. 3a(a) shows different results of the same SSTD, in this case an EEG signal, encoded by these four algorithms.

Different spike encoding algorithms have distinct characteristics when representing input data. BSA is suitable for high frequency signals and because it is based on the Finite Impulse Response technique, the original signal can be recovered easily from the encoded spike train. Only positive (excitatory) spikes are generated by BSA, whereas all other techniques mentioned here can also generate negative (inhibitory) spikes. Temporal Contrast was originally implemented in hardware (Delbruck & Lichtsteiner, 2007) in the artificial silicon retina. It represents significant changes in signal intensity over a given threshold, where the ON and OFF events are dependent on the sign of the changes. However

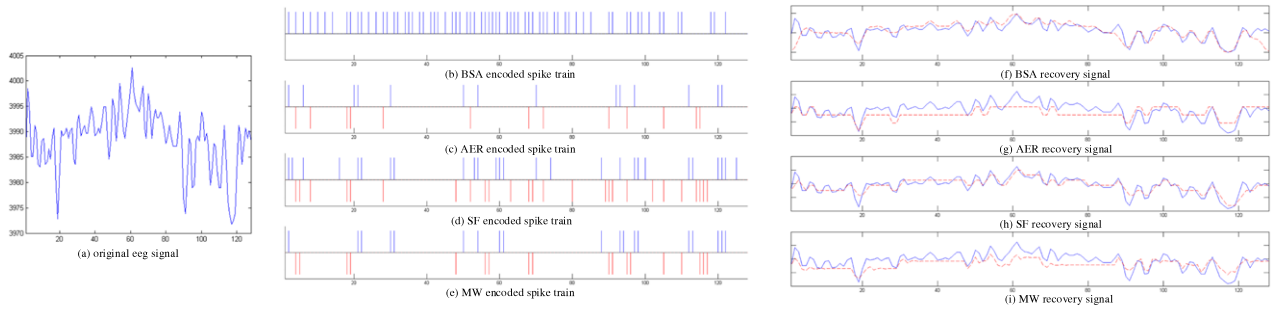


Fig. 3a. Spike trains generated by four different spike encoding algorithms in NeuCube with corresponding recovery signals. The blue(red) lines in (b), (c), (d), (e) are positive(negative) spikes, and the blue lines in (f), (g), (h), (i) are the original signals while the red dash lines are the signals reconstructed by corresponding spike trains.

if the changes of the signal intensity vary dramatically, it may not be possible to recover the original signal using the encoded spike train generated by AER. Therefore, we propose here an improved spike encoding algorithm, SF, to better represent the signal intensity.

For a given signal $S(t)$ where $(t = 1, 2, \dots, n)$, we define a baseline $B(t)$ variation during time t with $B(1) = S(1)$. If the incoming signal intensity $S(t_1)$ exceeds the baseline $B(t_{1-1})$ plus a threshold defined as Th , then a positive spike is encoded at time t_1 , and $B(t_1)$ is updated as $B(t_1) = B(t_{1-1}) + Th$; and if $S(t_1) \leq B(t_{1-1}) - Th$, a negative spike is generated and $B(t_1)$ is assigned as $B(t_1) = B(t_{1-1}) - Th$. In other situations, no spike is generated and $B(t_1) = B(t_{1-1})$.

As to the Moving-Window Spike Encoding Algorithm, the baseline $B(t)$ is defined as the mean of previous signal intensities within a time window T , thus this encoding algorithm can be robust to certain kinds of noise.

Before choosing a proper spike encoding algorithm, we need to figure out what information the spike trains shall carry for the original signals, like AER for significant changes. After that, the underlying spike patterns in the spike trains will be better understood.

3.3.2. Input variable mapping

Mapping input variables into spatially located spiking neurons in the SNNc is a new approach towards modelling SSTD introduced in Kasabov (2014) and is a unique feature of the eSTDM. The main principle is that if spatial information about the input variables is known it can help in (a) building more accurate models of the SSTD collected through these variables and (b) a much better interpretation of the model and a better understanding of the SSTD. This is very important for data such as brain data such as EEG (see Kasabov (2014) and Kasabov and Capecchi (2015)) and for fMRI data (see Fig. 3d) where patterns of interaction of brain signals can be learned and discovered. In some implementations we have used the Talairach brain template, mapped spatially into the SNNc (see Fig. 2). Another way of mapping, when there is no spatial information available for the input variables, is to measure the temporal similarity between the variables to map variables with similar patterns into closer neurons in the SNNc. This is the vector quantisation principle, where by ‘vector’ here we use time series, which do not necessarily have the same length.

3.3.3. Learning

Learning in a eSTDM is a two-phase process as it was described in the NeuCube framework (cf. Section 3.2). The accuracy of a NeuCube model depends a great deal with the SNNc learning parameters and the classifier/regressor parameters. Optimisation procedures are discussed in Section 3.3.5.

3.3.4. Output classification or regression

We use an SNN for the output model of the type eSNN. An eSNN evolves its structure and functionality in an on-line manner, from incoming information. For every new input data sample, a new output neuron is dynamically allocated and connected to the input neurons. The neuron’s connections are initially established using the RO rule for the output neuron to recognise this vector (frame, static pattern) or a similar one as a positive example. The weight vectors of the output neurons represent centres of clusters in the problem space and can be represented as fuzzy rules (Soltic & Kasabov, 2010). Then these connection weights are further adapted to the following spikes (Kasabov & Dhoble, et al., 2013).

In some implementations neurons with similar weight vectors are merged based on the Euclidean distance between them. That makes it possible to achieve a very fast learning (only one pass may be sufficient), in both supervised and unsupervised modes (Kasabov & Dhoble, et al., 2013). When in an unsupervised mode, the evolved neurons represent a learned pattern (or a prototype of patterns). The neurons can be labelled and grouped according to their class membership if the model performs a classification task in a supervised mode of learning.

Weights are calculated based on the order of the incoming spikes on the corresponding synapses using the RO learning rule:

$$w_{i,j} = \alpha \text{mod}^{\text{order}(j,i)}$$

where: α is a learning parameter (in a partial case it is equal to 1); mod is a modulation factor that defines how important the order of the first spike is; $w_{j,i}$ is the synaptic weight between a pre-synaptic neuron j and the postsynaptic neuron i ; $\text{order}(j, i)$ represents the order (the rank) of the first spike at synapse j , i ranked among all spikes arriving from all synapses to the neuron i ; $\text{order}(j, i) = 0$ for the first spike to neuron i and increases according to the input spike order at other synapses.

While the input training pattern (example) is presented (all input spikes on different synapses, encoding the input vector are presented within a time window of T time units), the spiking threshold Θ of the neuron i is defined to make this neuron spike when this or a similar pattern (example) is presented again in the recall mode. The threshold is calculated as a fraction (C) of the total PSP_i (denoted as PSP_i^{max}) accumulated during the presentation of the input pattern:

$$PSP_i^{\text{max}} = \sum_j \text{mod}^{\text{order}(j,i)}$$

$$\Theta = C PSP_i^{\text{max}}.$$

The eSNN (deSNN) learning is adaptive, incremental, theoretically ‘lifelong’, so that the system can learn new patterns through creating new output neurons, connecting them to the SNNc neurons, and possibly merging the most similar ones. The deSNN implements the 7 ECOS principles from Section 1.

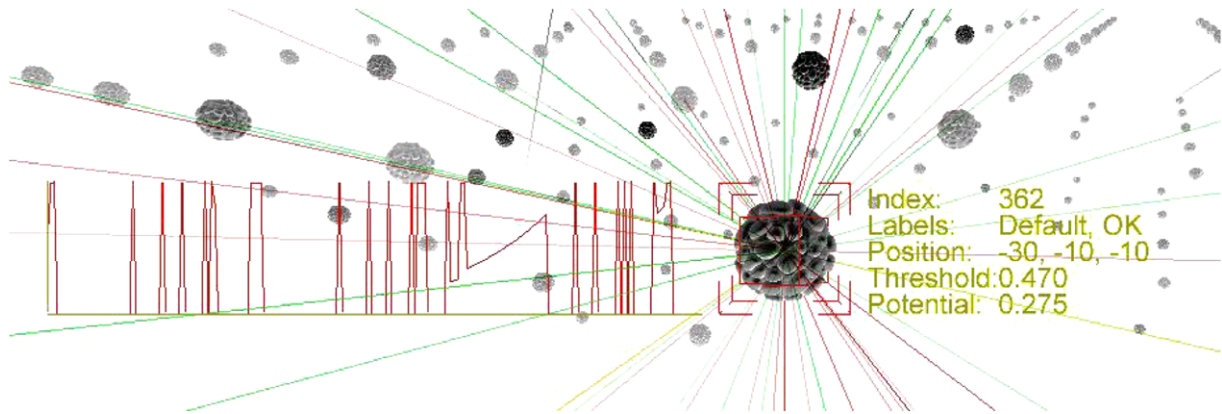


Fig. 3b. The cursor node can be used to view additional information about a specific neuron and its activity in the SNNc.

During the recall phase, when a new spike sequence is presented, the spiking pattern is submitted to all created neurons of the SNNc. An output spike is generated by neuron i at a time l if the $PSP_i(l)$ becomes higher than its threshold Th_i . After the first neuron spikes, the PSP of all neurons are set to an initial value (e.g. 0) to prepare the system for the next pattern for recall or learning.

3.3.5. Parameter optimisation of NeuCube models

eSTDM behaviours can be easily manipulated by changes in their large number of parameters. For example, differing neuron reset voltages can lead to a number of different spiking dynamics, and differing encoding parameters can significantly change the information density of the spike trains. Different 'mod' and 'drift' parameters in a deSNN can result in different classification accuracy. To this end, a parameter search is usually performed in order to extract the best performance. Three primary techniques are discussed here: Grid Search; Genetic Algorithm search; and the Quantum-Inspired search.

Grid search. Grid search is a straightforward but effective method to tune parameters. Suppose there are P parameters that have to be optimised simultaneously. For each parameter there are three hyperparameters to be specified manually: the minimal value m and the maximal value M of the searching interval, and the searching step size s . Given these three hyperparameters of each optimizing parameter, we first create a P -dimension matrix, each dimension of which corresponding to a optimizing parameter, from m to M divided into $(M - m)/s$ entries. In this case, each entry of the matrix corresponds to a group of values of the optimising parameters. Then we randomly split the training set into two equal-size parts, a training part and a validation part. For a specific group of values, we run the NeuCube system in a two-fold cross-validation way and the error rate of the cross-validation is added to the entry of the P -dimension matrix corresponding to that group of parameter values.

Instead of directly choosing the group of parameter values corresponding to the minimal entry in the matrix, we adopt another more robust method to determine the optimal parameters. We first apply a low pass filter by replacing each matrix entry with the average of its adjacent neighbouring entries, and then, after all entries are filtered, we choose the group of parameter values corresponding to the minimal entry of the filtered matrix as the optimal one. The justification is that the performance surface of the system varies smoothly in parameter space, and after filtering some highly unstable points (entry whose value is extremely larger or smaller than its all adjacent neighbouring entries) will be reduced. Thus the minimal value of the matrix can capture the general trend of the performance surface.

Genetic algorithms. Standard Genetic Algorithm techniques can be used to optimise the parameters of a NeuCube model.

Quantum-inspired evolutionary methods. These methods use the principle of superposition of states to represent and optimise parameters of SNN models (Kasabov, 2007). Such a method is the quantum inspired genetic algorithm or QiPSO (Defoin-Platel, Schliebs, & Kasabov, 2009).

4. Dynamic and immersive visualisation of NeuCube models

The number of neurons and connections within NeuCube as well as the 3-dimensional structure requires a visualisation that goes beyond a simple 2D connectivity/weight matrix or an orthographic 45-degree view of the volume. We created a specialised renderer for NeuCube datasets using JOGL (Java Bindings for OpenGL) and GLSL (OpenGL Shading Language) shaders to be able to render up to 1.5 million neurons and their connections with a steady frame rate of 60 fps. In this view, neurons are displayed as stylised spheres, and connections are rendered as lines with green colour for excitatory connections and red for inhibitory connections. Spiking activity is shown as signals travelling along the connections.

In conjunction with a 3D stereoscopic HMD (Head Mounted Display) like the Oculus Rift, it is easy for users to perceive the spatial structure of the network and the neuron positions. Furthermore, interaction mechanisms allow for playback of spiking patterns and the development of connection weights throughout the learning period. In addition, the visualisation includes analysis functionality for the usage of connections to find 'hot paths', connection length analysis, and the ability to view the 3D structure in 'slices'. A 3D cursor metaphor is employed to look at neurons individually, their parameters, and their spiking history (see Fig. 3b).

The NeuCube visualisation can run as a standalone program on a PC with a reasonable modern 3D graphics card and can be used with keyboard and mouse control. However, the full potential of the visualisation is possible in a motion capture space, where the camera perspective and the cursor node position and orientation are controlled by markers that are attached on the actual HMD and a cursor implement (see Fig. 3c). This setup makes it possible for the user to literally walk through NeuCube and point out individual neurons with the cursor in a natural manner.

In comparison to other scientific visualisation tools for neural networks such as BrainGazer (Bruckner et al., 2009) and Neuron Navigator (NNG) (Lin et al., 2011), our solution differs in that the user can naturally navigate through the 3D space by simply walking and gesturing instead of using mouse and keyboard shortcuts.

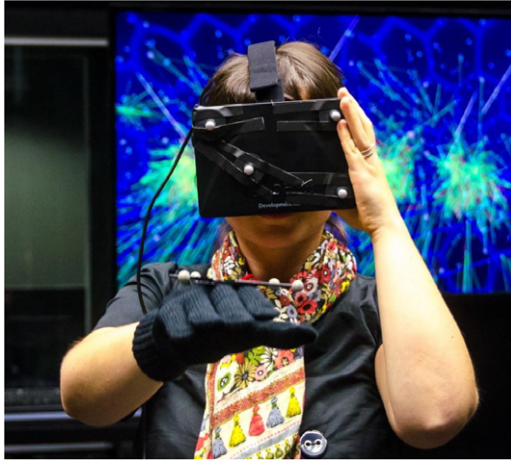


Fig. 3c. A user navigating through the virtual representation of the NeuCube network, using an intuitive, hand position based 3D cursor.

Closer to our visualisation is the work of von Kapri, Rick, Potjans, Diesmann, and Kuhlen (2011), who are using a Computer Assisted Virtual Environment (CAVE) to visualise the spatial structure and activity of a spiking neural network. However, due to the limited space within a cave environment, navigation by simply walking is not possible and requires indirect ways, e.g., by using a controller.

We have not yet conducted a systematic user study, but so far, around 50 visitors of the Immersive VR space have experienced this visualisation. We have observed that, in general, people quickly start to move around and look at structures and point out individual neurons using the 3D cursor. The visualisation and interaction metaphors are very intuitive for new and experienced users.

5. eSTDM for spatio-temporal brain data modelling and understanding

5.1. eSTDM for EEG STBD

EEG has been used for the study of human neural activity recorded from the scalp for nearly a century. It can measure functional changes in the brain that occur over a period of milliseconds, is easy to manage, and is considered non-invasive for the subject. For these reasons, EEG has been used in brain computer interface (BCI) based systems to allow users to control devices, for studying and staging of neurodegenerative disorders, and for other clinical diagnostic purposes. As the increase in average human lifespan has been followed by the dramatic rise in the appearance of neurological diseases, the importance of such tools is clear.

EEG data contains temporal, spatial, and spectral information that is difficult to truly explore using standard statistical or ML techniques. Though these techniques are often used to process STBD, they lack the ability to classify differences in neurological dynamics that occur over time, to identify the functional brain areas involved, and to quantify the information involved. SNN, however, are shown to be capable of such tasks (Hu, Hou, Chen, Kasabov, & Scott, 2014; Kasabov & Hu, et al., 2013; Taylor et al., 2014).

In Kasabov and Capecchi (2015) for example, an SNN methodology based in the NeuCube eSTDM was used for the study of 6-channel EEG data recorded from the scalp of seven subjects performing different mental tasks. This research identifies that the NeuCube is able to classify and analyse changes in functional brain activities. This is significant, as it allows for the identification of the appearance of mild cognitive impairment (MCI) to stage its degeneration towards Alzheimer's Disease (AD).

To study the EEG data, we have used a 3D SNNc of 1471 brain-mapped spiking neurons. Each of these neurons represented the centre coordinates of 1 cm^3 of the Talairach Atlas, a human brain template (Talairach & Tournoux, 1988). The spike trains, obtained after encoding the real time EEG data using the Temporal Contrast (Threshold-based) algorithm, were entered into the SNNc to the corresponding brain-mapped input neurons. The data was first learned in an unsupervised way using Spike Time Dependent Plasticity Learning Rule (STDP) (Song et al., 2000) and then classified via supervised learning with the Dynamic Evolving SNN (deSNN) (Kasabov & Dhoble, et al., 2013). After training, the SNNc connectivity can be analysed and interpreted for a better understanding of the data and to identify differences in brain activity. A methodology diagram is given in Fig. 4. The proposed method and the obtained results have been compared with traditional approaches resulting in a significantly better classification accuracy, but also in a better interpretation of the model and a better understanding of the complex cognitive processes that generate the EEG data. See the paper by Kasabov and Capecchi (2015) for detailed results.

In another study (Capecchi et al., 2015), the same NeuCube-based model has been used to study neural degeneration by means of EEG data collected amongst two groups: control and Alzheimer's Disease patients. Excellent classification results of 100% test accuracy have been achieved. These have also been compared with other traditional machine learning approaches, such as the Multi Layer Perceptron (MLP), Support Vector Machine (SVM), Evolving Classification Function (ECF) (Kasabov, 2007) and Evolving Clustering Method for Classification (ECMC). The leave-one-out cross-validation method was used to verify the results. See the paper by Capecchi et al. (2015) for detailed results.

A NeuCube model performed significantly better compared with the other methods and with the highest accuracy, sensitivity and specificity over all. Thus, we believe that the NeuCube eSTDM can be successfully used for on-line learning and recognition of STBD. It also offers a better interpretability of the information and the phenomena of study. Further improvement of the understanding and use of the model proposed are believed to contribute to the advancement in machine learning for the prediction and understanding of brain data and more specifically for data related to neurodegenerative pathologies, such as AD.

5.2. eSTDM for fMRI STBD

Recently there has been a huge interest in using functional magnetic resonance imaging (fMRI) to understand, analyse and predict behaviour and cognition. The ability of fMRI to sample high resolution spatial information over time has been successfully used in correlating high-resolution neural activity with behaviour. Several attempts have been made (Haxby et al., 2001; Mitchell et al., 2003), not only to identify the spatial distribution of activation across brain regions associated with cognitive tasks, but also to build computational models to distinguish them. The PBAIC 2007 competition was designed to detect cognitive tasks such as 'seeing a dog', 'picking up a weapon' etc. in a virtual reality environment.

Traditional machine learning algorithms like Gaussian Naive Bayes (Mitchell et al., 2003), or the SVM (Chu et al., 2011) has been used previously for this purpose. Some current research also focuses on the transformation of time series information to transformed space like shapelet-similarity, similarity in frequency domain etc. All of these techniques are focused mainly on classification accuracy (prediction), rather than *understanding* the spatio-temporal dynamics of the brain.

In contrast to statistical analysis and traditional machine learning methods, NeuCube is a rich computational model for

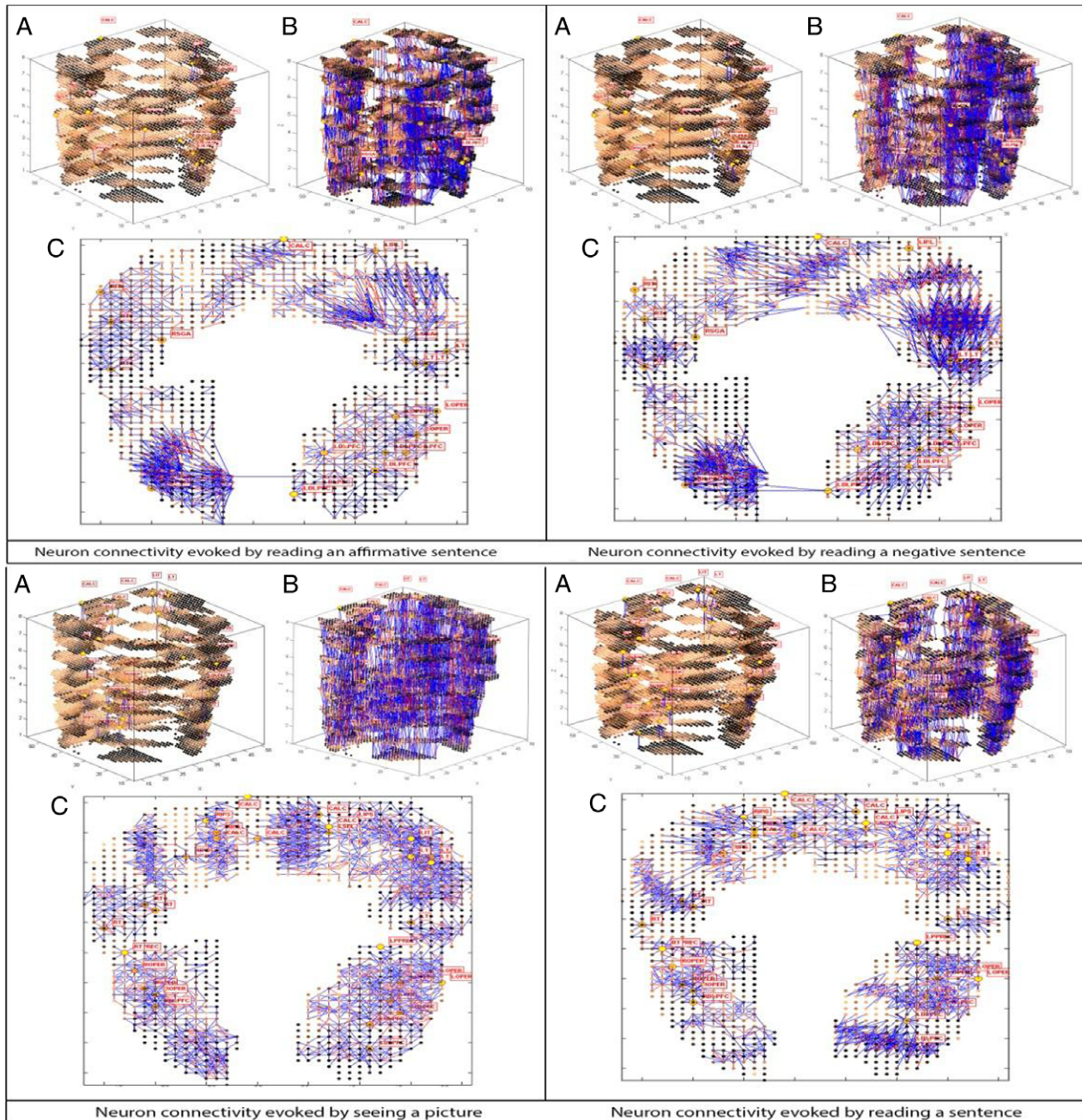


Fig. 3d. Illustrative mapping of 5062 voxels of a single individual fMRI data to the SNNc and the spatio-temporal connectivity which evolved through unsupervised learning from the spike sequences of 20 input voxels of the affirmative/negative sentence presentation and 33 input voxels of the picture/sentence presentation: (A) 3D visualisation of the initial connections between neurons before SNNc training; (B) 3D visualisation of the spatio-temporal connections after SNNc training; (C) 2D visualisation of the spatio-temporal connections after the SNNc training. Blue lines are positive connections while red lines represent negative connections. The brighter the colour of a neuron, the stronger its activity with neighbouring neurons. Thicknesses of the lines also identify the neuron's enhanced connectivity. Zooming on particular areas of the connections in the SNNc would reveal more information about the brain processes related to the task.

fMRI data analysis (Gholami Doborjeh & Kasabov, 2014). This method can be applied to fMRI data across areas of brain study and applications. The NeuCube neuromorphic spatiotemporal data machine has been used successfully on one of the benchmark datasets reported in Gholami Doborjeh and Kasabov (2015).

We mapped and analysed a known benchmark fMRI data called STAR/PLUS (Just, 2001). The 3D size of the SNNc is scalable. This SNNc is composed of $51 \times 56 \times 8$ spiking neurons corresponding to the maximum values of the x , y and z coordinates of the STAR/PLUS fMRI data.

In this experiment, we selected subject number “05780” from the STAR/PLUS fMRI datasets. This data consists of 5062 voxels from the entire brain data. In order to visualise the whole brain structure's activity, we loaded all voxel coordinates into an SNNc. Then, we fed the spiking activity sequences of the pre-selected voxels into the corresponding allocated input neurons inside the SNNc. Fig. 3d is a comparative illustration of the neuron connections created after the snnc learning procedure with different fMRI data streams related to different mental activities of the same subject.

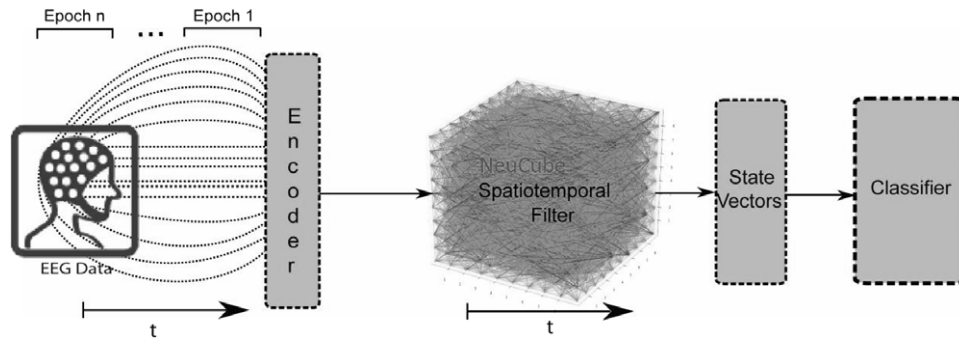


Fig. 4. The NeuCube framework for EEG data classification and knowledge extraction. The picture shows the cube's three principal modules: the input module, where input data are encoded into trains of spikes that are then presented to the main module, the SNN; the NeuCube module, where time and space characteristics of the STBD are captured and learned; and the output module for data classification (or regression) and new knowledge discovery from the SNNc visualisation.

Classification of a subject looking at a picture or looking at a sentence was conducted for 6 subjects (Murli et al., 2014). Comparing with the standard machine learning techniques (i.e. SVM and MLP), NeuCube has achieved more than 80% classification accuracy across all subjects. Neuron connectivity before and after training can help in understanding the data. The results suggest that a NeuCube model is more appropriate in handling complex fMRI data even without filtering the noise from the data. The noise may carry valuable information in defining the association between STBD samples, but failed to be recognised and processed in the standard machine learning techniques. Further work is in progress which not only uses fMRI, but also simultaneously uses other modalities like DTI and EEG for better prediction accuracy and understanding.

5.3. Neurogenetic eSTDM

A neurogenetic model of a neuron is proposed and studied in Benuskova and Kasabov (2007). It utilises information about how some proteins and genes affect the spiking activities of a neuron such as fast excitation, fast inhibition, slow excitation, and slow inhibition. An important part of the model is a dynamic Gene-Protein Regulatory Network (GRN) model of the dynamic interactions between genes and proteins over time that affect the spiking activity of the neuron (see Fig. 2).

Currently, NeuCube-based models implement the STDP learning rule, based on the Hebbian theory, which defines a synaptic connection with respect to the order of incoming spikes, leading to control of the postsynaptic action potentials over time (Song et al., 2000).

In the Central Nervous System, these mechanisms are regulated by two opposite forces controlling the synaptic plasticity. Spiking activity amongst neurons is intrinsically related with Glutamate and GABA neurotransmitters, and their receptors. While AMPA and NMDA Glutamate receptors mediate a fast and a slow excitatory synaptic response, the GABA_A and the GABA_B receptors regulate a fast and a slow inhibitory synaptic transmission. Additionally, these receptors are related to learning and memory in the hippocampus.

To study how the spiking neuron postsynaptic action potentials are affected by the dynamics of these four macromolecules, a new learning rule called neuroreceptor dependent plasticity (NRDP) has been developed. The model can automatically balance the synaptic strengths, making postsynaptic firing irregular but sensitive to presynaptic potentials similar to the STDP family of rules, but also taking into account neuroreceptor irregularities.

After a spike is emitted by a neuron n_i and received by a neuron n_j , the activation of the excitatory receptors in neuron n_j increases up to a maximum threshold value. If no spike is emitted,

the inhibitory receptors activity increases in function to the time elapsed after the last spike is emitted. A probability determines the activation of the GABA receptors; if GABA_A is activated then GABA_B is not, and the opposite. The inhibition speed (fast or slow) is also determined by this probability; a higher activation probability means a faster inhibition, and therefore, the GABA_A probability must be higher than the GABA_B probability.

Threshold values of each neuroreceptor can be modified according to the problem of interest and the data available. The possible effects that this change may have on the entire model connectivity and spiking activity can therefore be studied.

This approach needs to be further developed in terms of both theory and applications, as it can be used for modelling and prediction of neurodegenerative diseases, such as cognitive impairment and memory loss that leads to serious disorders such as Alzheimer's Disease (AD). In addition to brain data they make possible the study of gene data related to the same profile.

5.4. eSTDM for brain-machine interfaces

The feasibility of using a NeuCube model trained on EEG data to develop a functional BCI/BMI system that is able to assist in the rehabilitation of complex upper limb movements was shown in Taylor et al. (2014). A primary modality of the device is for subjects who have no voluntary activity in a limb, who would drive the device using mental imagery. However, the same model could be used for arbitrary output, to control a cursor or speaking device, for example. In order to provide an effective tool for this purpose, a NeuCube eSTDM was trained on EEG data for a series of relatively complex muscle movements.

The preliminary experiments suggest that a NeuCube model is much more efficient for this task than standard machine learning techniques, resulting in high recognition accuracy, a better adaptability to new data, and a better interpretation of the models, leading to a better understanding of the brain data and the processes that generated it.

5.5. eSTDM for neurorehabilitation

eSTDM based on the NeuCube are uniquely applicable for neurorehabilitation. Their biomimetic learning and information processing timescales are appropriate for integration with mentally-driven tasks. In addition, they offer the fast and incremental (continuous) learning required to adapt to the user's changing abilities as their rehabilitation progresses. This application is a natural extension of eSTDM's use in a BCI/BMI context.

Repetitive practice of activities of daily living (ADL) is commonly practised in the rehabilitation of paretic patients, and robotic active assisted training is increasingly being used. Both

Table 1

Comparative experimental results for all modelling methods (Othman et al., 2014) when applied to predicting a stroke occurrence.

Method	Overall accuracy (%)				
	SVM	MLP	kNN	wKNN	NeuCube
1 day earlier (100%)	55 (70, 40)	30 (50, 10)	40 (50, 30)	50 (70, 30)	95 (90, 100)
6 days earlier (75%)	60 (70, 30)	25 (20, 30)	40 (60, 20)	40 (60, 20)	70 (70, 70)
11 days earlier (50%)	50 (50, 50)	25 (30, 20)	45 (60, 30)	45 (60, 30)	70 (70, 70)

these approaches have shown some efficacy in the recovery of locomotor function in impaired limbs. Classification of ADL from EEG is of interest for the active robotic rehabilitation of patients with spinal cord injuries (SCI). This classification is a significant challenge with classical techniques, as these cannot deal effectively with the high noise, variability, and gradual change (due to the subject learning the task) in the EEG signals.

Hu et al. (2014) performed an experiment using the NeuCube eSTDm to identify the upper-limb ADL of three classes with 14-channel EEG data. The continuous real-number signals are firstly encoded into spike trains through Ben's Spike Algorithm (BSA). The generated spikes are then submitted into the SNNc reservoir. Spike trains from all neurons of the trained reservoir are finally classified using the dynamic evolving spiking neural network (deSNN) classifier. Classification accuracy using this technique is shown to be promising despite the highly noisy, low resolution EEG data (Hu et al., 2014). This experiment indicates strong potential for further exploration of the eSTDm for neurorehabilitation tasks.

6. eSTDm for personalised modelling and personalised event prediction

6.1. Personalised modelling

A special direction of ECOS is transductive reasoning and personalised modelling. Instead of building a set of local models (e.g. prototypes) to cover the whole problem space and then use these models to classify/predict any new input vector, in transductive modelling for every new input vector a new model is created based on selected nearest neighbour vectors from the available data. Such ECOS models are the Neuro-Fuzzy Inference model, NFI, and the Transductive Weighted Neuro-Fuzzy Inference Model, TWNFI (Kasabov, 2007).

In Kasabov et al. (2014), a methodology for personalised model creation is proposed based on the NeuCube framework. It builds an eSTDm for every individual based on both static and temporal data.

6.2. A case study on personalised early stroke prediction

The problem formulation for stroke occurrences is stated as: Given a set of individuals' data (static variables) and a set of environmental data (temporal variables), produce a model for an individual that predicts the earliest time point that individual is likely to suffer a stroke.

A feasibility study on the applicability of NeuCube eSTDm was published in Othman et al. (2014) where the dataset was taken from Auckland Regional Community Stroke Study population, consisting of 2805 patients data that suffered a stroke between the years 1981–1982, 1991–1992 and 2002–2003.

The subjects in this experiment are described by eighteen variables which consist of six static features (age, gender, history of hypertension, smoking status, season, date of stroke); along with twelve environmental (temporal) features (continuous daily data) including eight daily mean weather data (e.g. wind speed, min & max temperature, humidity); three daily mean air pollution data (e.g. NO² concentration); planetary geomagnetic activity, and solar radiation.

As NeuCube eSTDm functionality enables us to do predictive modelling, experiments were designed in three ways:

1. One day earlier prediction where the whole 100% time period of 20 days was taken for analysis.
2. Six days earlier prediction (75% of the whole time period was taken).
3. Eleven days earlier prediction (50% of the whole time period was taken).

As a comparative experiment, tests were also designed for conventional machine learning methods (SVM, MLP, kNN, wKNN). Table 1 shows the best obtained accuracy from all experiments.

The results clearly show that NeuCube eSTDm performed better than conventional machine learning methods (for 1 day prior prediction) since it achieved an overall accuracy of 95% for high risk of stroke with a misclassification of low risk.

Through visualisation tools in NeuCube eSTDm, patterns of temporal features can be analysed further. In NeuCube we can visualise input feature interactions, not only at group level but also on a personalised level leading to increased understanding of the relationships within the data and how these affect the individual risk of stroke.

7. Ecological and environmental event prediction

A NeuCube eSTDm would be suitable for learning the complex spatio-temporal relationships inherent in ecological and environmental data; for ecological applications to predict pest or crop populations; for seismic applications to potentially predict earthquake occurrence; and so on.

7.1. Case study on prediction of risk of aphid population

In this section we consider how to use the NeuCube architecture to model and predict the population of a harmful species, *Rhopalosiphum padi*, in Southern New Zealand based on weather and climate factors.

We study a concrete case on aphid population prediction to demonstrate the capability of the NeuCube architecture for modelling ecological and environmental spatio-temporal data. In this study we use 14 weather variables which are recorded week by week from year 1982 to 2004 at the Canterbury Agricultural Research Centre, Lincoln, New Zealand (Hartono, Pears, Kasabov, & Worner, 2014). Data preprocessing consisted of bad data removal, and time point alignment. Feature selection was applied to make sure the data was useful before entering the next phase.

The real valued weather variables were transformed into spike trains with the Temporal Contrast (Threshold-based) encoding algorithm. A $5 \times 20 \times 20$ SNNs was generated and initialised according to small world connection rule to learn the temporal patterns in the spike trains. Then all the weather variables were mapped into the SNNs using a graph matching algorithm to ensure that the temporally dependent weather variables were mapped into nearby input neurons. The input data was propagated, and after the synaptic weights were learned using STDP, the weights were fixed and the spike trains fed to the SNNc again to obtain each neuron's firing state vector, which serves as the transformed feature of the original input signals in the following learning stage.

Table 2

Aphid population prediction accuracy (%).

	Accuracy of each training and testing time length (weeks)		
	52 (full)	41.6 (early)	39
MLR	36.36	64.63	72.73
SVM	72.73	72.73	63.64
MLP	81.82	81.82	81.82
kNN	72.73	63.64	63.64
wkNN	72.73	63.64	63.64
NeuCube	100	90.91	81.82

The firing state vector of the SNNc is fed to a dynamic evolving spike neural network (deSNN) classifier to learn the underlying temporal pattern. After the whole system was trained, we used a validation dataset to verify the validity of the system. The accuracy of the performance was evaluated by comparing the ground truth results with the predicted results.

Table 2 shows the results of predicting the autumn aphid population amount with the NeuCube system, as well as results of other traditional methods as a comparison. The testing time length means how many weeks weather measurements we used to predict the autumn aphid population. The fewer weeks used, the harder to predict accurately in the autumn, as shown in the last two columns.

7.2. A feasibility evaluation of using eSTDM for seismic data modelling

Earthquake prediction is a challenging problem but compelling nonetheless. The immense capacity for destruction of earthquakes prompts for the ability to predict, within a reasonable time horizon, the occurrence of significant earthquakes so preemptive and anticipative actions could be taken to minimise the damage.

One of the potential uses of eSTDM in this field is to analyse the seismogram readings from multiple sites spread spatially across a geographical region to predict the occurrence of large earthquakes. A preliminary study using the waveform data obtained from the New Zealand GeoNet project web services (www.geonet.org.nz) has been done for the Canterbury region of New Zealand. After selecting the appropriate earthquakes from the earthquake catalog, the seismic waveform data collected prior to these earthquakes are fetched from four selected seismograph stations (Fig. 5) which were picked for their high uptime and availability.

To predict ahead of the actual event, the data fetched is offset by around twelve hours. The duration of the observation is 120 h or five days long. The experiment is done by selecting 24 samples of earthquakes in the Canterbury region which are equally put into two categories based on the severity of the case (i.e. Strong – historically notable, and Weak – low energy seismic events unnoticed by the general population). The small number of samples is the consequence of the fact that strong earthquakes happen very rarely throughout the history and earthquakes before the year 2010 were not included because the availability and quality of the seismic activity data is not as good compared to those which happen after. The performance of the classifiers are measured in terms of the F -measure, which is the harmonic mean of precision and sensitivity of binary classification problems with the formula $F1 = 2TP/(2TP + FP + FN)$. The testing scheme is Leave-one-out cross validation, since the number of samples is small.

The result shown in Table 3 gives us the confidence that seismicity data might be a viable precursor for short-term earthquake prediction. The peak F -score of 0.92 means that the classifier successfully predict 11 out of 12 strong earthquakes and raises only 1 false alarms. Though the experiment is in a very preliminary stage, this research has shown a promising way to

Table 3

Preliminary results of earthquake prediction on a small dataset using a NeuCube eSTDM in comparison with traditional techniques: SVM, MLP, NB.

Measure	SVM	MLP	ECF	NeuCube
Accuracy (%)	54.16	58.33	66.67	91.67
F -Score	0.58	0.58	0.58	0.92

predict the occurrence of strong earthquakes by training an eSTDM model to differentiate between strong and moderate earthquakes based on spatiotemporal seismicity precursors. For future works, it is important to fine-tune the models to get a better discriminating capability and using a larger dataset and getting more inputs from more seismic monitoring sites across the globe and running the analysis in real-time as the data is collected to produce a useful and practical disaster prediction system. A more comprehensive experiment should also be done to verify the accuracy and find the best prediction horizon and observation period. An interesting aspect is the extraction of spatiotemporal knowledge or rules pertaining to how the seismic activities in different sites affect each other.

8. eSTDM for video data recognition

Video SSTD can be successfully learned in an eSTDM subject to the availability of quality data and the NeuCube eSTDM parameter optimisation. Here we demonstrate the feasibility of NeuCube for this purpose on a case study problem. Specifically, a model is created to classify a given video data into one of three age groups based on its assessed age.

Ageing is a slow process and its effects are visible only after a few months or a few years. But in spite of being slow, it remains a spatiotemporal phenomenon. The facial features of a person itself can be considered as a subspace and their ageing over the years a temporal process. It would be very useful to incorporate the temporal, as well as spatial, patterns in ageing data as an important part in classification.

The raw data which has been used in this study is from (Cerniello, 2013). It is five minutes of video containing 8943 frames of size 1920×1080 pixels. First the video is converted into greyscale frames. The nose tip of the subject in the image is manually annotated. The purpose was to locate a small region on the face which remains at a fixed distance from the annotated point. That same region is used for all the images in our study. This region is a part of the texture information of the face image, namely a small part of cheek portion of the face. This is chosen as facial skin is naturally smooth in youth and becomes wrinkled with age, thereby resulting in a change in the textural information present in this area. Based on this assumption 50 pixels are selected from cheek area of each face image.

All frames are divided into three classes. 128 frames of each sample are chosen, for each in a total of 60 samples. Thus the whole data comprises some 7680 images. The first 20 samples comprise young age, the next 20 samples adult age, and the third set of 20 samples represent old age.

In this experiment, the size of the SNNc is 1000 neurons, a relatively simple $10 \times 10 \times 10$ cube. It is trained and tested in a hold out method. Firstly we converted the video data into discrete spike trains using the Temporal Contrast encoding method to discretise the continuous signal, following the example of the silicon retina (Delbruck & Lichtsteiner, 2007). The deSNN classified mentioned previously is used here as an output classifier, because deSNN is computationally efficient and emphasises the importance of the first spike, which has been observed in biological vision systems.

We conducted experiments to compare between traditional modelling methods (SVM and MLP) and our proposed method for

Table 4
Age group classification accuracy (%) from video data.

Method	Accuracy (%)
SVM	55
MLP	26
NeuCube	78

age group classification. We designed two experiments for these baseline algorithms. Note that for these baseline algorithms, the time length of training samples and testing samples have to be the same as these methods cannot tolerate different lengths of feature vectors for training and testing.

It was observed that the classification achieved with NeuCube was better than other techniques. See Table 4 for results. Note that the techniques mentioned (other than NeuCube) do not have the capability of representing the spatio-temporal problem space effectively. These traditional techniques are only suitable for static data within a given time segment. Since an eSTDM models the relationships between and within spatio-temporal data, even a small input data will be able to trigger the spiking activities in SNNc, for an accurate pattern (class) recognition from video data.

9. eSTDM for spectro-temporal data

9.1. eSTDM for audio information processing

Audio data is spectro-temporal. It consists of temporal sequences of the intensity of the signal at different frequencies. How to map the frequencies into an SNNc is the first challenge. And then—training the SNNc on spike sequences that represent the audio signals is another challenge.

9.2. Radioastronomy data

Radioastronomy data is massively spectro-temporal. The timescale of meaningful background radiation in space is billions of years, and the volume of data to be processed to identify a small event is immense. eSTDM are currently being explored for applications in radioastronomy, as they are effective at learning in a noisy and dynamic environment, and explicitly incorporating the spatial, spectral, and temporal characteristics of such data.

10. Implementing the NeuCube on neuromorphic hardware

A system like the NeuCube, with its highly scalable architecture, requires a highly scalable computation platform. As traditional Von Neumann computational architectures reach their limits (Esmailzadeh, Blem, St Amant, Sankaralingam, & Burger, 2011; Perrin, 2011) in terms of power consumption, transistor size, and communication, new approaches must be sought. Neuromorphic hardware systems, especially designed to solve neuron dynamics and able to be highly accelerated compared to biological time are a response to these concerns. Systems such as analog VLSI or the SpiNNaker are advantageous by comparison to software based simulations on commodity computing hardware in areas such as biophysical realism; density of neurons per unit of processing power; and significantly lowered power consumption (Furber, 2012; Indiveri et al., 2011). This is not to say that simulations of the NeuCube cannot occur on traditional computing architectures; merely that dedicated hardware is advantageous in these areas and may be more appropriate for large-scale modelling. Subsequent to the modular framework for the development of NeuCube neuromorphic implementations written in Python first introduced in Scott, Kasabov, and Indiveri (2013), a cross platform version was written utilising the PyNN API.

PyNN (Davison et al., 2008) is a generic SNN simulation markup framework that allows the user to run arbitrary SNN models on a number of different simulation platforms, including software simulators PyNEST and Brian, and some neuromorphic hardware systems such as SpiNNaker and FACETS/BrainScaleS. It provides a “write once, run anywhere” (where “anywhere” is the list of simulators it supports) facility for the development of SNN simulations. A version of the NeuCube has been implemented in this environment, for application on both commodity Von Neumann computing systems and dedicated neuromorphic hardware.

A key target of this NeuCube version is the SpiNNaker device currently in development. SpiNNaker is a general-purpose, scalable, multichip, multicore platform for the real-time massively parallel simulation of large scale SNN (Furber, 2012). Each SpiNNaker chip contains 18 ARM968 subsystems responsible for modelling up to one thousand neurons per core, at very low power consumption. These chips communicate through a custom multicast packet link fabric, and an arbitrary number of these chips can be linked together, with the assumption that the networks simulated exhibit some kind of connection locality. The small-world structure used in the NeuCube and its scalable nature are appropriate for implementation on this type of hardware.

An alternative implementation of the NeuCube eSTDM for embedded applications is currently being explored using the INI Neuromorphic VLSI chip (Indiveri et al., 2011).

11. NeuCube development system for SNN applied to spatio- and spectro-temporal data

11.1. Technical challenges

Effective eSTDM performance is reliant on the correct combination of a large number of hyperparameters. To account for this sensitivity, automated optimisation techniques have been developed for the system defined here. These have been discussed in Section 3.3.5, and at present a grid search and genetic algorithm approaches have been implemented. Future development in this space will explore the more efficient quantum-inspired optimisation technique (Defoin-Platel et al., 2009).

Computational scaling is also a concern with systems such as the NeuCube. Concerns must be paid primarily to computational speed, power consumption, and in the case of certain applications (e.g. robotics control) the system’s physical size. In order to address these concerns, the neuromorphic hardware systems described in Section 10 are being explored. While such systems require specialised knowledge and an investment in dedicated hardware, the advantages provided in the three main areas of concern (particularly computational speed and power consumption) warrant further exploration.

As a general statement regarding SNN, as there is not yet a robust information theory supporting the design and implementation of these networks, much of the decision making regarding network structure and composition must be based on heuristic measures. In the case of the eSTDM described here, network structure must be based on some a-priori knowledge of the dataset. This is, in our case, an advantage, as it allows us to represent the spatial and/or spectral components of the data sources explicitly, retaining the relationship between these and the temporal aspect of the data.

11.2. System architecture

The NeuCube has been implemented in a modular fashion, with each separate module communicating through JSON-format files. In this way, new modules can be added easily, in any language, in a

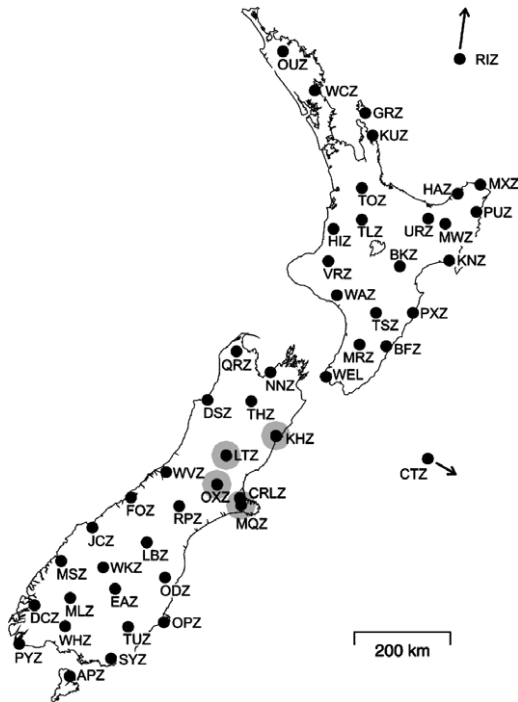


Fig. 5. Seismograph sites across New Zealand with the 4 selected sites greyed.

cross platform manner. Already the system has modules written in MATLAB, Python, and Java, and has been tested on both Windows and Linux environments.

The standard form of the NeuCube software environment (Fig. 6) is Module M1, responsible for Prototyping and Testing of NeuCube models and SNN applications. This module is implemented in MATLAB and is intended for prototyping and model exploration. From here a developed model can be saved and deployed to the M2 and M3 modules, utilising large scale computing or neuromorphic hardware for greater efficiency in either model optimisation or implementations. These models can be then visualised immersively with module M4, which incorporates the capacity to use virtual-reality headsets or even a full-scale motion capture system. Additional specialised modules for neurogenetic modelling, personalised modelling, and so on, can be added when required and will communicate with all other modules.

A version of Module M1 for research and teaching purposes can be found free of charge at <http://www.kedri.aut.ac.nz/neucube>. For commercial use or access to the full set of modules, please contact the authors directly or via this web page. The NeuCube is PCT patent protected.

12. Conclusion, contributions, and future directions

The main goal of ECOS is to facilitate the creation of computational models and systems for adaptive learning and knowledge discovery from complex data. ECOS principles are derived from the integration of principles from neural networks, fuzzy systems, evolutionary computation, quantum computing and brain information processing. ECOS applications are manifold, but perhaps most welcome in the medical, environmental and health sciences, where the diagnostic phenomena are chaotic in nature and the datasets are massive and often incomplete. Here we present a new development of ECOS: the eSTDM, created in the NeuCube SNN environment.

eSTDM is a promising approach to deal with big, stream data. Massive (so called 'big') datasets with the characteristics

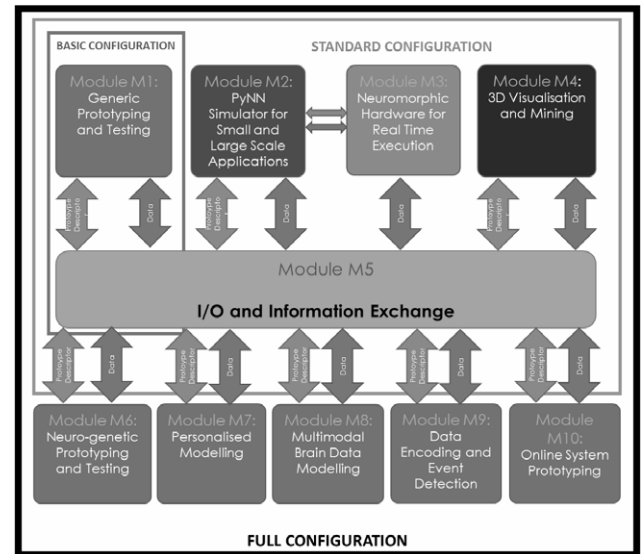


Fig. 6. A conceptual diagram of the NeuCube multimodular development system, demonstrating the interface and relationships between the core and optional modules.

just described need to be analysed, virtually in real time, for prognoses to be made and solutions to the issues sought at a level of urgency. In this sense, eSTDM for adaptive learning and knowledge discovery can make a great contribution to the methodologies employed by the emerging trans-disciplinary, integrative, systemic and problem-solving science. Herein we have presented a system to incorporate spatial, spectral, and temporal data components for the learning, classification, prediction, and visualisation of such data.

There are some challenging questions that need to be further explored, for example:

1. What is the capacity of a NeuCube eSTDM in terms of both spatial and temporal characteristics of the data?
2. How much noise can be tolerated in an eSTDM?
3. How do we model transitions between spatio-temporal states triggered by external stimuli?
4. How early and accurately can an eSTDM predict an event from SST?

These are some of the questions that need to be addressed as a future work.

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A.2 Feasibility of NeuCube SNN architecture for detecting motor execution and motor intention for use in BCI applications

The case study presented in Chapter 5 resulted in a paper (Taylor et al., 2014), which was published by IEEE in the *2014 International Joint Conference on Neural Networks (IJCNN)*. Copyright and permission from the publisher of the paper are provided in Appendix B.

Feasibility of NeuCube SNN architecture for detecting motor execution and motor intention for use in BCI applications

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Abstract—The paper is a feasibility analysis of using the recently introduced by one of the authors spiking neural networks architecture NeuCube for modelling and recognition of complex EEG spatio-temporal data related to both physical and intentional (imagined) movements. The preliminary experiments reported in the paper suggest that NeuCube is much more efficient for the task than standard machine learning techniques, resulting in high recognition accuracy, a better adaptability to new data, a better interpretation of the models, leading to a better understanding of the brain data and the processes that generated it.

I. INTRODUCTION

NeuCube is a spiking neural network (SNN) architecture in which both spatial and temporal neuroinformatics data can be encoded as both locations of synapses and neurons, as well as the timing of their spiking activity. NeuCube is capable of learning noisy data either on-line or with low amounts of training. In addition, its brain-like structure can be visualized for greater knowledge extraction than purely statistical or mathematical techniques. NeuCube is based on the idea of physiological Hebbian plasticity, which states that neurons that fire together wire together [1]. Contemporary research indicates that the temporal relationship of firing between the neurons is important in determining the firing association between the neurons. The theory of spike-time dependent plasticity states that pre-synaptic activity that precedes post-synaptic firing can induce long-term potentiation (LTP), reversing this temporal order results in long-term depression (LTD) [2]. The NeuCube is consistent with the theory of spike-timing dependent plasticity as temporal information about spike timing is retained. This advantage may facilitate understanding of recovery from neurological injury and recovery related to rehabilitation. NeuCube was first published in [3] then further developed in [4] and [5]. A block diagram is depicted in Fig.1. The NeuCube architecture consists of the following modules:

- Input information encoding module;
- 3D spiking neural network reservoir (SNNr) module (the Cube);

- Output/classification module;
- Gene regulatory network (GRN) module (Optional).
- Optimisation module (optional)

The input encoding module converts neuroinformatic data into trains of spikes using one of a number of algorithms, including the BSA [6], Population Encoding [7], and Address Event Representation [8] methods. The 3D SNNr is modelled after the human brain, with a population of Leaky-Integrate-and-Fire neurons spatially located according to the Talairach stereotactic atlas. Collected neuroinformatic data is used as inputs to spatially located neurons in the SNNr. The spatial location of these neurons correspond to spatial location of the sections of the brain where the corresponding data was collected (e.g. the location of the EEG electrodes). For example, EEG input channel data are entered into neurons from the SNNr according to the excellent mapping provided in [9]. This preserves the spatio-temporal relationships within the data that is a significant source of information, generally overlooked by other techniques. The number of neurons in the SNNr is scalable. It is set in our experimental NeuCube SNNr at 1471 neurons, each representing 1cm³ of brain tissue [4].

The output module contains a number of classifiers, which are chosen based on the desired output type. These include the deSNN(s,m) classifiers for simple class-based discrimination [10] and the multiSPAN classifier for defined output spike trains [11]. The GRN module was not included in this experiment. In principle, it includes some information on how AMPA, GABAA, GABAB, and NMDA neuronal receptors can modulate the simulated neurons activity much as they do in the real brain.

A focal neurological insult that causes changes to cerebral blood flow, such as in a stroke, can result in mild to severe motor dysfunctions on the contralateral side of the body. Although some spontaneous recovery usually occurs in the first 6 months after stroke only about 14% of people with stroke recover normal use of the upper limb [12]. The driver of

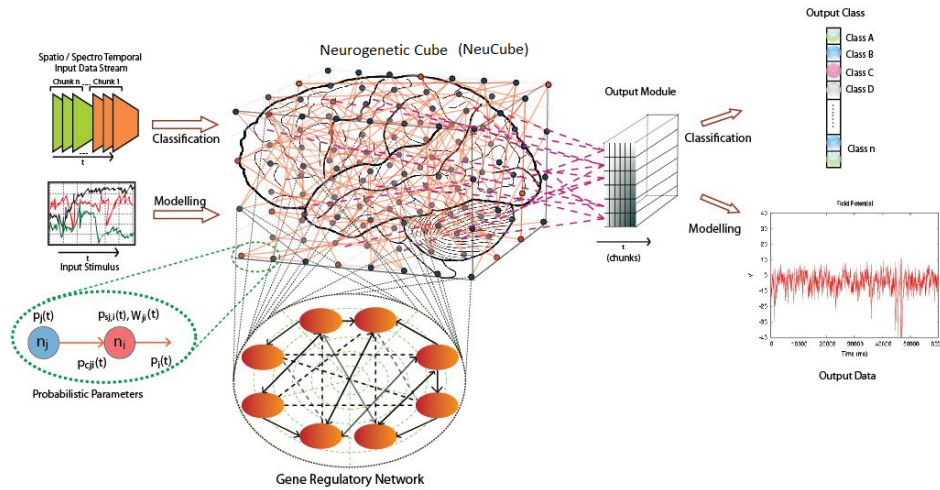


Fig. 1. A block diagram of the NeuCube architecture from [3]

functional recovery after stroke is neural plasticity, the propensity of synapses and neuronal circuits to change in response to experience and demand [13]–[15]. Whilst it is known that frequency and intensity of intervention following stroke is important high intensity rehabilitation is resource-limited. In order to deliver interventions at a high enough intensity and frequency for neural plasticity we need to develop devices that can assist with rehabilitation without the concentrated input of rehabilitation professionals.

Motor imagery (MI), or the mental rehearsal of a movement, is an approach used by rehabilitation professionals to encourage motor practice in the absence of sufficient muscle activity [16]–[18]. MI is thought to activate similar cortical networks as activated in a real movement, including activation of the primary motor cortex, premotor cortex, supplementary motor area and parietal cortices [19], [20]. Recent evidence suggests that although there are common cortical networks in real and imagined movement (frontal and parietal sensorimotor cortices) there are also important differences, with ventral areas being activated in imagined movement, but not in real movement. These specific additional activations in the extreme/external capsule may represent an additional cognitive demand of imagery based tasks.

Recovery of movement control is greater after motor execution training than after MI training alone. Interestingly the combination of MI training with even passive movement generates greater recovery than MI alone [21]. Combining motor imagery with functional electrical muscle stimulation, via Brain Computer Interface (BCI) devices, may result in greater neural plasticity and recovery than motor imagery alone, or motor imagery combined with passive movement. The additional feedback to the brain provided by executing a movement may enhance plasticity and reduce the cognitive demand of motor imagery. Many people following stroke or other neurological disorder have some residual muscle activity but fail to recruit enough motor units at an appropriate speed and pattern, to generate sufficient force to complete the desired movement [22], [23]. A BCI device in which motor imagery triggers an appropriate signal to a functional electrical stimulation system would facilitate the practice of real movements

and potentially result in greater neural plasticity and functional recovery.

EEG records brain signals through electrodes on the scalp and is the most widely used method for recording brain data used in BCI devices. EEG is non-invasive and has good temporal and spatial resolution. However, EEG systems have been criticized because of the time consuming and complex training period for the potential user [24]. One advantage of the NeuCube framework is that intensive training of the user is not required as NeuCube classifies naturally elicited cortical activity, rather than a specific component of the EEG signal, such as the P300 wave, the production of which has to be learned by the user. In addition, the NeuCube is capable of learning in an on-line fashion, training as it is used.

We are investigating the feasibility of using NeuCube with EEG data to develop a functional electrical stimulation BCI system that is able to assist in the rehabilitation of complex upper limb movements. Two methods of use are under consideration, firstly for people who have no voluntary activity in a limb who would drive the device using MI, and secondly for people who have some residual activity in their muscles that, in addition to using MI, may augment the device with their own muscle activity. To do this it is important to establish a high degree of accuracy of classification of movement intention and movement execution to ensure that the appropriate electrical stimulation output is then provided. One of the challenges to any BCI system is the extent to which it accurately classifies the input signal.

In [24] real movement, consisting of a pinch grip to a specified force level, compared to a resting state, was used. Data were collected using functional Near Infrared Spectrometry (fNIRS) combined with other physiological data, such as blood pressure and respiratory information. Using hidden Markov Models (HMMs) as the classifier framework accuracies ranging between 79.6% and 98.8% over 2 classes were achieved. Using fNIRS in a trial of MI [24] investigated the classification accuracy of a simple imagined tap of the thumb on a keyboard versus a complex multi-digit tapping sequence. Linear discriminant analysis (LDA) was used in combination

with careful selection of the best performing data channel (out of 3 possible channels) and best 4 features for each participant. The study in [25] reported classification accuracies in a 2-class model (simple imagined movement or complex imagined movement) of between 70.8% and 91.7%. A Sparse Common Spatial Pattern (SCSP) optimization technique that reduced EEG channels by disregarding noisy channels and channels thought to be irrelevant was reported in [26], however this approach results in a loss of data that could be informative.

We were interested in determining if it was feasible to use the NeuCube framework as a driver of BCI devices. As a first step we wanted to determine if the NeuCube was at least equivalent in classifying movement tasks as other commonly used methods. As proof-of concept we designed a study that required NeuCube to classify imagined and real movements in two different directions and at rest (wrist flexion, extension or rest). The general hypothesis is that NeuCube using EEG data can correctly identify brain patterns corresponding to specific movements. Previous work from our lab in association with research collaborators has indicated the potential of NeuCube to identify different EEG patterns relating to different imagined movements from a commercially available 14 channel EEG headset. In this trial imagined wrist extension, rest and wrist flexion achieved accuracy in 1 individual of 88%, 83% and 71% respectively [27].

The specific hypothesis for this study was that the NeuCube would accurately classify both single joint real and imagined movements of the hand into one of three classes, flexion, extension or rest. This paradigm built on the earlier work in [27] by increasing the complexity of the task by requiring the NeuCube to distinguish three conditions, two different muscle contraction patterns (flexion or extensor muscle activity) or rest [27]. A secondary hypothesis was that the NeuCube would perform better than other classification methods, including Multiple Linear Regression (MLR), Support Vector Machine (SVM), Multilayer Perceptron (MLP) and Evolving Clustering Method (ECM) [28], along with offering other advantages such as adaptability to new data on-line and interpretability of results.

II. METHOD

A. Participants

Three healthy volunteers from our laboratory group participated in the study. None had any history of neurological disorders and all were right handed.

B. Protocol

All measures were taken in a quiet room with participants seated in a dining chair. The task consisted of either performing the specified movements or imagining the movements, or remaining at rest. All tasks were completed with eyes closed to reduce visual and blink related artifacts. The movement execution task involved the participant resting, flexing the wrist or extending the wrist. The starting position was from mid-pronation with the forearm resting on the persons lap. The movement intention task involved the participant imagining or performing the movements as described above. Participants were required to imagine or perform each movement in 2 seconds and to repeat that 10 times.

C. Data acquisition

A low-cost commercially available wireless Emotiv Epoc EEG Neuroheadset was used to record EEG data. The Epoc records from 14 channels based on International 10-20 locations (AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4). Two additional electrodes (P3, P4) were used as reference. Data were digitized at 128 Hz sampling rate and sent to the computer via Bluetooth. An important factor was that no filtering was applied to the data, either online or offline.

D. Data processing

The data was separated into classes denoting each task. Each set of ten samples was then evenly divided into a training (seen) and a testing (unseen) set. The data was then converted into trains of spikes (one train per channel, 14 in total) with the Address Event Representation algorithm, utilizing a spiking threshold of 6. No other data processing was applied.

E. Classification

Each training sample was presented to the NeuCube once, entered as 14 input streams of EEG continuous data collected at the msec time unit, encoded using AER with a step size of 6. The spiking activity of every neuron was recorded over the time of the sample, and these presented to the deSNNs classifier. The deSNNs was initialized with a Mod of 0.9 and drift factor of 0.25 (empirically established values for this dataset). The synaptic weights for both the NeuCube and the deSNNs were then fixed at their final (learned) values for the validation phase. The unseen data samples were presented in the same way, and the predicted classes recorded. The predicted classes were then compared to the actual classes of those samples.

F. Comparative Study

The NeuCube described above was compared to some popular machine learning methods: MLR, SVM, MLP and ECM. The SVM method uses a Polynomial kernel with a rank 1; the MLP uses 30 hidden nodes with 1000 iterations for training. The ECM (Kasabov and Song, 2002) uses $m=3$; $R_{max}=1$; $R_{min}=0.1$. Data for these methods is averaged at 8 msec intervals and a single input vector is formed for each session, as is general practice.

III. RESULTS

The classification accuracy of the NeuCube was on average 76%, with individual accuracies ranging from 70-85%. There was a consistent rate of recognition between the real and the imagined movement. In terms of the comparison with other classification approaches, it is clear from the results shown in Table 1 that the NeuCube performed significantly better than the other machine learning techniques with the highest average accuracy over all subjects and samples, whilst the closest competitor was SVM with the second highest average accuracy of 62%. MLR was the poorest performing, with an average accuracy of 50.5%, or just over the chance threshold.

TABLE I. RESULTS OF THE COMPARATIVE STUDY; ACCURACY EXPRESSED AS PERCENTAGE FOR REAL AND IMAGINED MOVEMENTS.

Subject/Session	MLR	SVM	MLP	ECM	NeuCube
1-Real	55	69	62	76	80
1-Imagined	63	68	58	58	80
2-Real	55	55	45	52	67
2-Imagined	42	63	63	79	85
3-Real	41	65	41	45	73
3-Imagined	53	53	63	53	70
Average (appr.)	52	62	55	61	76

IV. DISCUSSION

This was a feasibility study to investigate the potential of using NeuCube in BCI based rehabilitation devices. In considering the classification accuracies, which ranged from 70-85%, it is important to consider three factors. Firstly, the data were collected in an unshielded room using a commercially available gaming EEG headset, resulting in an EEG signal with relatively high signal to noise ratio. Secondly, there was no processing or feature extraction performed on the data prior to classification, the raw, noisy, EEG data was used as the input. Thirdly, all comparative methods in this study, excepting NeuCube, were validated using Leave-One-Out (all but one sample used for training), while the NeuCube was validated with a more disadvantageous 50/50 (half used for training, half for testing) split. The accuracy of the NeuCube was still significantly higher than the other techniques and would likely rise when trained with leave-one-out paradigms.

Bearing these three factors in mind the classification accuracies obtained using NeuCube are in a similar range to those reported in other research and demonstrates that NeuCube is capable of accurately classifying noisy and relatively low-quality data. In addition, unlike many other approaches NeuCube does not require a lengthy feature extraction process, instead using all the raw data for classification, thus utilizing a rich data set that does not lose any potentially useful data.

We chose to use a relatively cheap and accessible EEG headset because two major factors that prevent the adoption of high technology interventions into rehabilitation practice are cost and complexity. EEG systems commonly used in research and clinical situations are expensive and unlikely to be widely available to rehabilitation specialists. The Emotiv neuroheadset has a limited number of channels with a fixed electrode placement, which may serve to improve usability as it reduces the preparation time and is easy for users to put on themselves.

An advantage of the NeuCube is that it allows for interpretation of results and understanding of the data and the brain processes that generated it. This is illustrated in Fig.2 where the connectivity of a trained SNNr is shown for further analysis. The SNNr and the deSNN classifier have evolvable structures, i.e. a NeuCube model can be trained further on more data and recalled on new data not necessarily of the same size and feature dimensionality. This allows in theory for a NeuCube to be partially trained on highly accurate data captured in a controlled manner with medical devices, and then further trained and adapted to the particular subject with a cheaper, less accurate device such as the Emotiv. This will increase potential uses in clinical and rehabilitation applications.

The large number of parameters that need to be optimized for every experiment to achieve the best results limits the

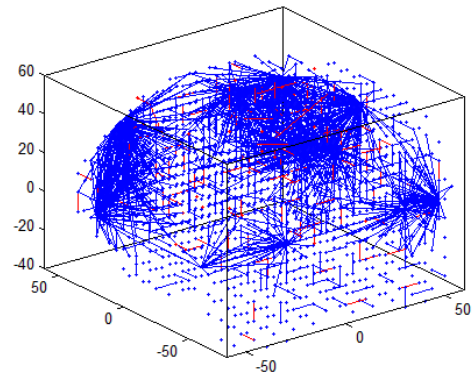


Fig. 2. Example visualisation of the connectome of the trained NeuCube. Blue lines show strong excitatory connections between two neurons, and red strong inhibitory.

current NeuCube. The results presented in this study are obtained through manual parameter optimization. To mitigate this, adaptive and evolutionary techniques (including the GRN discussed prior and quantum-inspired optimization) are being developed for this system, so that parameter selection is automated in a desirable way.

V. CONCLUSION

The results of this study support the premise that NeuCube is feasible to use in BCI based rehabilitation devices. Additionally, the ability of the NeuCube to both spatially and temporally represent brain data and provide visualization of the data could be useful in future applications. Observing changes in neural representation and spike timing throughout rehabilitation interventions could provide valuable information on human learning and adaptation to advance rehabilitation interventions.

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A.3 Spiking neural network methodology for modelling, classification and understanding of EEG spatio-temporal data measuring cognitive processes

The study presented in Chapter 6 resulted in a paper (Kasabov & Capecci, 2015) that was published by *Information Science Journal*. Copyright and permission from the publisher of the paper are provided in Appendix B.



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Spiking neural network methodology for modelling, classification and understanding of EEG spatio-temporal data measuring cognitive processes



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ABSTRACT

The paper offers a new methodology for modelling, recognition and understanding of electroencephalography (EEG) spatio-temporal data measuring complex cognitive brain processes during mental tasks. The key element is that mental tasks are performed through complex spatio-temporal brain processes and they can be better understood only if we model properly the spatio-/spectro temporal data that measures these processes. The proposed methodology is based on a recently proposed novel spiking neural network architecture, called NeuCube as a general framework for spatio-temporal brain data modelling. The methodology is demonstrated on benchmark cognitive EEG data. The new approach leads to a faster data processing, improved accuracy of the EEG data classification and improved understanding of this data and the cognitive processes that generated it. The paper concluded that the new methodology is worth exploring further on other spatio-temporal data, measuring complex cognitive brain processes, aiming at using this method for the development of the next generation of brain–computer interfaces and systems for early diagnosis of degenerative brain disease, such as Alzheimer's Disease (AD), and for personalised neuro-rehabilitation systems.

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1. Introduction

Modelling brain data, for the purpose of recognising and understanding of complex brain processes is a major problem in information sciences related to important applications, such as:

- Brain–computer interfaces (BCI) [1,44,54].
- Early diagnosis and prevention of degenerative brain diseases, such as Alzheimer's Disease (AD) [42,49,50,58].
- Personalised disease prognosis and neuro-rehabilitation [6,37].

Cognitive brain processes are characterised by complex spatio-/spectro-temporal brain data (STBD) that is difficult to process and understand in a computer model, unless we have a proper computational model that is relevant to the data. Many

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brain data related applications from the above listed still use inappropriate techniques and require more efficient ones as discussed below.

BCIs aim at decoding brain signals that represent cognitive processes to enable human–computer communication [1–4,25,29,44,54]. BCIs still use traditional statistical and artificial intelligence (AI) methods for the recognition of complex STBD. This often limits the functioning of the BCIs and leads to poor performance [40,54].

The increase in longevity of people's lives in modern society brought also the urgency to face the problem of dealing with the dramatic rise of neurological disorders and above all AD even in early onset [29,38,42,49,50,58]. This is becoming a major public health problem that raises serious health questions and would require reorganisation of social care services. Cognitive tests and memory screening are commonly used to stage and diagnose cognitive impairment, such as AD [57]. In fact, one of the first symptoms that follow the onset of the pathology is cognitive decline and memory loss. Early detection is important, as it allows for initial treatments. In this field, neuroinformatics research can play a pivotal role. A main contribution that can be brought by information scientists is a much more efficient machine learning technique that can be used to evaluate the cognitive ability of a person with a deeper understanding of the brain processes that cause it.

Personalised medicine is a current trend in health care with a huge potential in many health related areas, including BCI and neuro-rehabilitation robotics [6,70]. Still new information science methods are needed for the efficient implementation of this concept as it has already been demonstrated in [37].

Electroencephalogram (EEG) data is the most commonly collected data for the study of brain processes [1,9,10,13,25,29,55] related to both BCI and brain diseases. However, this data is the product of complex spatio-temporal brain signal pathways that are time dependant events related to the brain structure and its functioning [29,64,67,68]. In principle, EEG data is spatio-/spectro temporal brain data (STBD) and it has to be processed as such in order to be properly understood. This has been done with only partial success so far which raises the need for the development of new information science methods as pointed in [19,29,34].

In this paper we propose a novel methodology for the classification of EEG STBD recorded during different cognitive activities (Section 2). The methodology is based on the brain inspired spiking neural networks (SNN) and more specifically – on a recently proposed SNN architecture NeuCube [32,34]. In Section 3 we demonstrate the methodology on a benchmark data recorded during cognitive tasks [9]. Section 4 compares the proposed method and the obtained results on the benchmark data with traditional approaches, with the conclusion that the new method not only results in a significantly better accuracy of classification, but also in a better interpretation of the model and a better understanding of the data and the cognitive processes that generated it. Accurate classification results can be interpreted as an indicator for the detection of memory related cognitive problems. Section 4 highlights future directions for research based on the proposed methodology.

2. A spiking neural network methodology for modelling of EEG spatio-temporal data of brain cognitive activities

2.1. Brain-like SNN for modelling spatio-temporal data

There is a vast amount of information about structural and functional characteristics of the human brain accumulated so far, including: synaptic processes [29]; information encoding [65]; connectivity [27]; structural and functional atlases [43,46,47,67]; cortical projections [41]; genetics and proteomics [5,21]; neuro-genetic atlases [20,28]; brain disorders and conditions [57]. All this can be valuable information when processing cognitive data if our computational models can represent it.

From information science point of view, the brain represents and processes information at a 'low level' in the form of many trains of temporal electrical potentials that can be considered binary events (spikes) and are transferred between neurons through synaptic connections. Through learning from data the synaptic connections are modified to reflect more precisely the timing of the data from the sensory inputs. And this is one of the principles of SNN, considered the third generation of brain-inspired neural network techniques [16–19]. SNN methods have been developed for: learning from data [17,22,26,45,62,66]; system design and implementation [17,19,59]; encoding continuous input data into spike trains, such as the silicon retina [8] and the silicon cochlea sensory devices; neurogenetic computation [5,31,35,38]; high performance and neuromorphic engineering systems [14,15,24,53]. Promising features of SNN are: compact representation of space and time; fast information processing; time-based and frequency-based information representation. Methods of SNN for spatio-temporal pattern recognition have been already developed [11,23,26,33], including: evolving SNN (eSNN) classifiers [30,36,48,59,71]; pilot applications for moving object recognition [36,59]; pilot applications for simple EEG data classification [6,55]; SNN reservoir computing and liquid state machines [59,61,69]; finite automata modelling [52,53].

SNN methods and techniques provide a solid background for the development of new, brain-like information methods and systems for STBD. One of them, called NeuCube, is described below and used in the next sections for the proposed in this paper methodology for cognitive EEG data modelling, classification and understanding.

2.2. The NeuCube SNN architecture for modelling STBD

NeuCube is a SNN architecture for STBD, initially proposed in [32] and then further developed in [6,34,37,61]. A block diagram of the NeuCube model is depicted in Fig. 1. The NeuCube architecture consists of the following modules: input

information encoding module; 3D SNN cube module (SNNc); output (classification) module; gene regulatory network (GRN) module (optional); optimisation module (optional).

The input module transforms input data into trains of spikes that are entered then into the main module – the 3D SNNc. The SNNc is structured to spatially map brain areas for which STBD is available. That may include known structural or/and functional connections between different areas of the brain represented in the data. Setting up a proper initial structural connectivity in a model, in our case the SNNc, is important in order to learn properly spatio-temporal data and capture functional connectivity. More specific structural connectivity data can be obtained using for example diffusion tensor imaging (DTI) method.

The initial structure of the SNNc can be preliminary defined based on the available brain data and the problem or/and generated as a small-world connectivity [34]. The structure is also evolving through the creation of new neurons and new connections based on the ECOS principles used in eSNN classifiers [30,36,48,55]. If new data do not sufficiently activate existing neurons in the output classifier, new neurons are created and allocated to match the data along with their new connections.

Learning in the NeuCube is performed in two stages:

- Unsupervised learning, where STBD in the forms of spike trains, is entered into corresponding areas of the SNNc. Unsupervised learning is performed to modify the initially set connection weights. The SNNc will learn to activate same groups of spiking neurons when similar input stimuli are presented, also known as a polychronization effect [26].
- Supervised learning of the spiking neurons in the output classification module, where the same STBD used for the unsupervised training, is now propagated again through the trained SNNc and output neurons are generated (evolved) and trained to classify the spatio-temporal spiking pattern of the SNNc into pre-defined classes (or output spike sequences). As a special case, all neurons from the SNNc are connected to every output neuron. Feedback connections from output neurons to neurons in the SNNc can be created for reinforcement learning. Different SNN methods can be used to learn and classify spiking patterns from the SNNc, including: eSNN [30,71]; dynamic evolving SNN (deSNN [36]); spike pattern association neuron (SPAN [48]); other SNN classifiers [59]. All these options are implemented in some preliminary NeuCube implementations [6,34,61]).

Memory in a NeuCube-based model is represented as:

- Short-term memory, represented as changes of the post-synaptic potentials (PSP) and temporary changes of synaptic efficacy.
- Long-term memory, represented as a stable establishment of synaptic efficacy – long-term potentiation (LTP) and long-term depression (LTD).
- Genetic memory, represented as a genetic code.

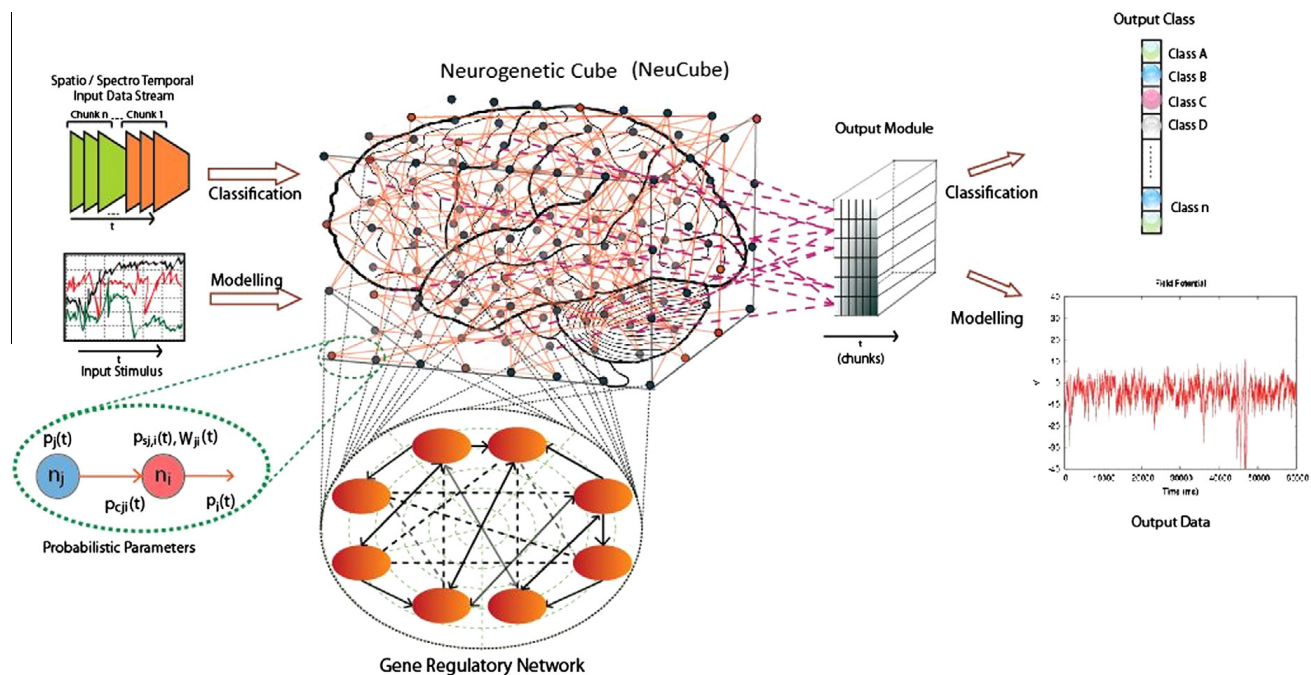


Fig. 1. A block diagram of the NeuCube architecture (from [34]).

NeuCube is a new type of computational architecture, which allows the creation of different models for STBD based on the following information processing principles as listed in [34]:

- (1) The model has a spatial structure that maps approximately the spatially located areas of the brain where STBD is collected.
- (2) The same information paradigm – spiking information processing that ultimately generates STBD at a low level of brain information processing, is used in the model to represent and to process this STBD.
- (3) Brain-like learning rules are used in the model to learn STBD, mapped into designated spatial areas of the model.
- (4) A model is evolving in terms of new STBD patterns being learnt, recognised and added incrementally, which is also a principle of brain cognitive development.
- (5) A model always retains a spatio-temporal memory that can be mined and interpreted for a better understanding of the cognitive processes.
- (6) A visualisation of the model evolution during learning can be used as a bio-feedback.

All the above principles make NeuCube a suitable SNN architecture to learn and reveal complex spatio-temporal patterns ‘hidden’ in STBD and that is why it has been chosen for the development of the new methodology to model cognitive EEG STBD as outlined in the next sub-section.

2.3. A NeuCube-based methodology for modelling EEG spatio-temporal data of brain cognitive activities

The proposed here methodology for modelling, classification and understanding of EEG cognitive data consists of the following procedures:

- (1) Collecting EEG STBD representing relevant to the study brain cognitive processes.
- (2) Encoding the EEG data into spike sequences.
- (3) Mapping the spike sequences into a specially designed SNNc that reflects on the number of input variables (channels) and the data available.
- (4) Training the SNNc on the spike STBD using unsupervised learning method, e.g. STDP [62].
- (5) Training of an output classifier in a supervised mode.
- (6) Validation of the classification results.
- (7) Repeating steps (2) to (6) for different parameter values in order to optimise the classification performance. Record the best performing model.
- (8) Visualise the trained SNNr and analyse its connectivity and spiking activity for a better understanding of the data and the brain processes that generated it.

For mapping the spatial locations of the EEG channels into the SNNc, we use the Talairach template [41,43,63]. The neurons in the SNNr are located following the same (x,y,z) coordinates of the Talairach template and the EEG channels are mapped according to the standard mapping suggested in [41]. The spike sequences that represent data from EEG channels (after transformation of continuous value signals into spike trains) are entered into the correspondingly located neurons in the SNNc during the unsupervised training procedure.

The above methodology is applied step-wise on a case study problem of cognitive EEG data modelling in the next section. Figs. 2–4 illustrate the procedures above.

3. A case study on EEG cognitive data modelling

3.1. Data description

The data used for this study was recorded in an earlier experiment [9,39,40] and further studied in [1,3,51]. This data was collected from the cortex of seven healthy subjects (between 20 and 48 years old; six men and one woman; all right-handed except for one subject) following five different scenarios, one resting task and four cognitive tests. A brain computer interface device was used to collect EEG data. The designed mental task scenarios consisted of: a “resting” task – a subject is relaxing, avoiding thoughts as much as possible (class 1); a “letter composition” task (class 2) – a subject is tasked with imagining writing a letter to someone without verbally expressing it; a “multiplication” task (class 3) – a subject is performing a non-simple two digit mental multiplication; a “counting” task (class 4) – a subject is visualising a blackboard on top of which numbers were sequentially being written; a “rotation” task (class 5) – a subject is mentally rotating a 3D geometric figure. Each recording session was carried out using six electrodes: C3, C4, P3, P4, O1, O2. Data was recorded for 10 s at 250 Hz, resulting in 2500 data points collected per session. Every task was repeated five times during a daily session. Some of the subject data was recorded on a one-day session, while other subjects repeated the five trial tasks for a second or third day session. The data of subject 4 was excluded from the experiment, as according to a previous study [51], the signal was repeatedly saturated or invalidated in several trials.

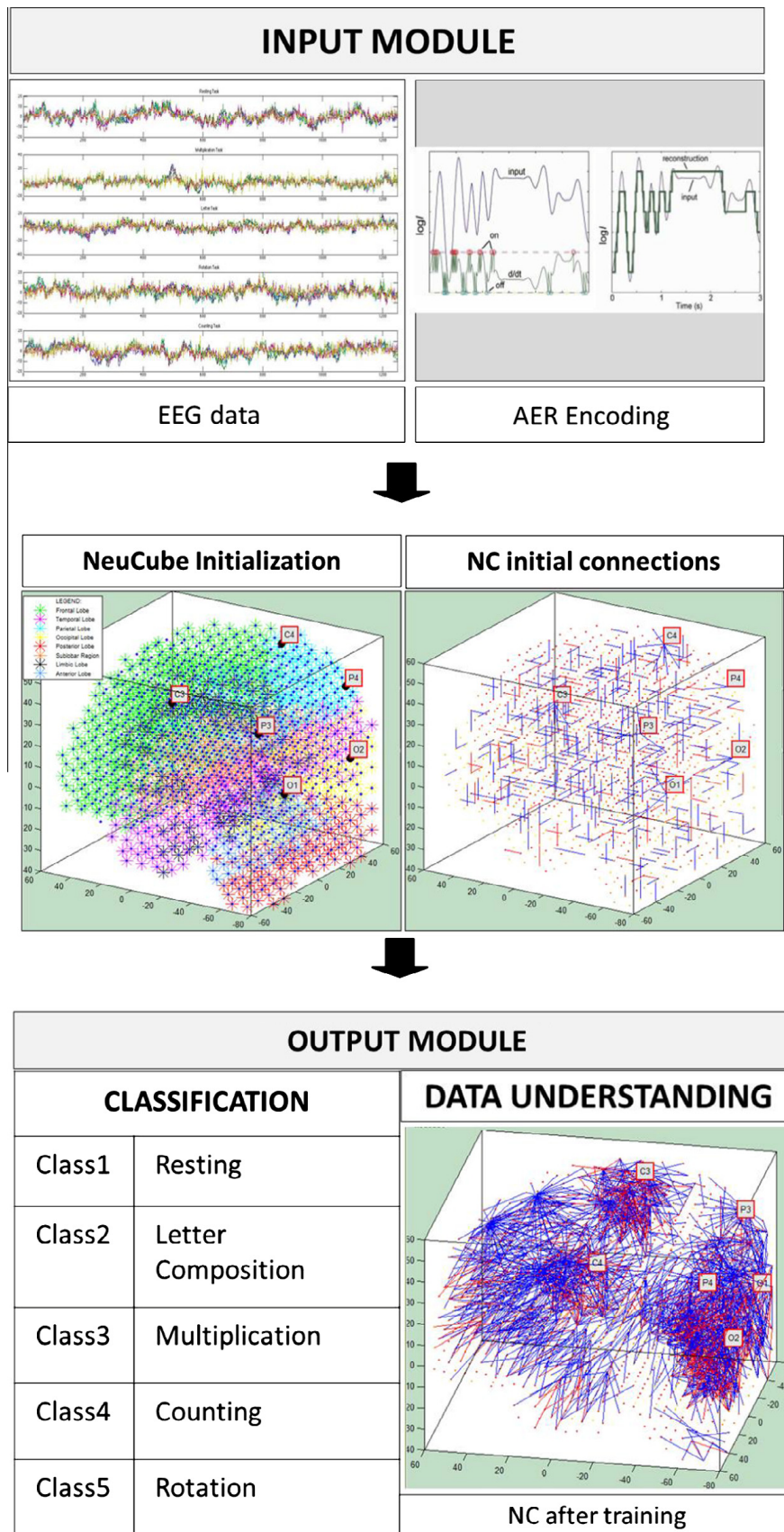


Fig. 2. A graphical representation of the different steps from the proposed methodology applied on the case study problem.

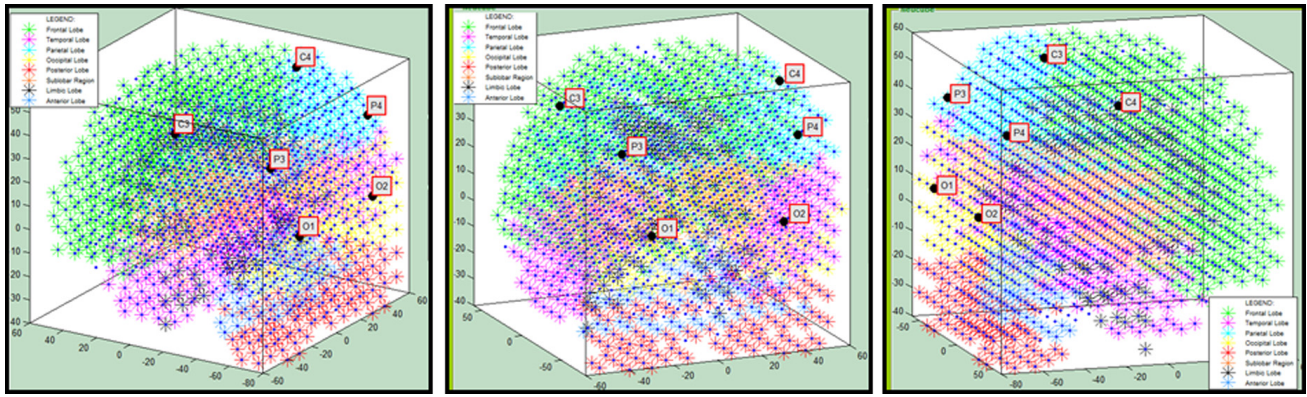


Fig. 3. Different views of the SNNc of 1471 neurons and the 6 input neurons for the case study EEG data and problem. Seven particular areas from the SNNc that correspond spatially to brain regions according to the Talairach Atlas are also shown: in green – the frontal lobe; in magenta – the temporal lobe; in cyan – the parietal lobe; in yellow – the occipital lobe; in red – the posterior lobe; in orange – the sub-lobar region; in black – the limbic lobe; in light blue – the anterior lobe. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

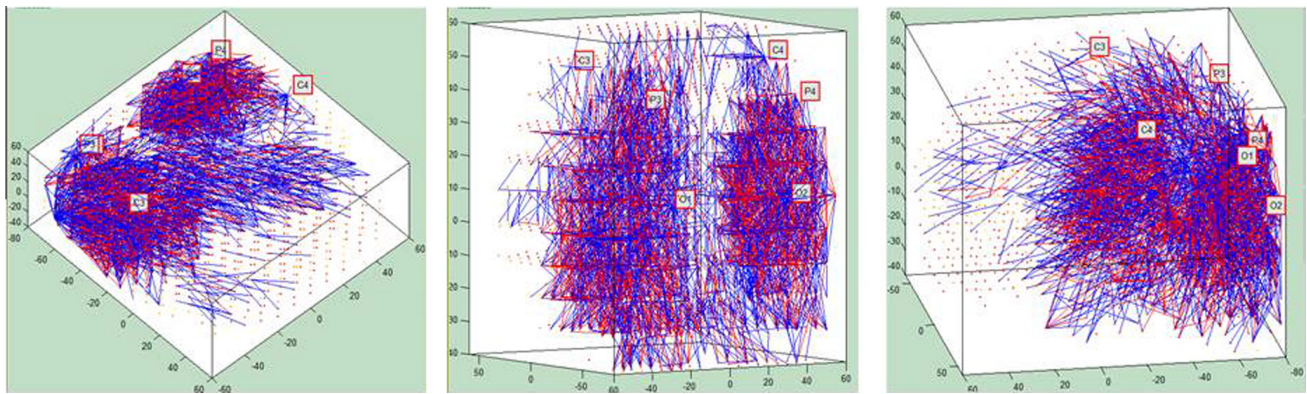


Fig. 4. The SNNc connectivity after training can be analysed and interpreted for a better understanding of the cognitive EEG data to identify differences between brain states representing different mental tasks performed by different subjects. Connections represent spatio-temporal correlations between spiking neurons that correspond to brain areas. Using only EEG data for training, deeper structural connections are evolved that reveal new information about the cognitive processes.

For our study, we resized each session dataset into two samples of 5 s each, 1250 data points per channel on every sample. We assumed that half of the information can be considered enough to represent the mental activity measured. Thus, for each of the 5 classes we had 10 samples of $1250 \text{ data points} \times 6 \text{ EEG channels}$, in total, we obtained 50 samples per subject and per session.

3.2. Model design and implementation

We applied the methodology from Section 2 on the above experiment as shown graphically in Fig. 2. For the model implementation we have used a software simulator of NeuCube written in MATLAB (see [6,34] for more details).

EEG STBD was classified per subject and per session using a NeuCube-based model that had a SNNc of 1471 spiking neurons using the Talairach EEG electrode mapping template [41]. One of the advantages of the NeuCube framework is that in many cases there is no need of pre-processing (such as normalisation of the data, scaling, and smoothing). The raw data is fed into the model as time series and transformed into spike trains using address event representation method (AER [8]), and then the transformed spike trains are mapped into the SNNr for unsupervised training. The AER method is suitable for EEG cognitive STBD, as this algorithm identifies just differences in consecutive EEG values.

The input spike sequences are presented to the SNNc, which was implemented using leaky integrate and fire (LIF) neurons, which is less computationally expensive [17,24,61]. The SNNc was trained using the spike timing dependant plasticity (STDP [62]) learning rule. The STDP learning rule allows the spiking neurons of the SNNc to learn consecutive temporal associations from the EEG data within-, and across EEG channels, and therefore forming new connections in the architecture that can be analysed and interpreted. This makes the NeuCube architecture useful for learning spatio-temporal patterns from EEG data, forming associative type of memory that can be further explored [34].

Although the SNNc can be evolving in size, for this research we have explored the classification ability of the NeuCube architecture of 1471 spiking neurons, each representing the centre coordinates of a one cubic centimetre area from the 3D Talairach Atlas [43,63].

The 3D architecture of the SNNc is initialised as “small-world” (SW) connected networks. The SW connectivity principle is fundamental for the initialization, the learning processes of this model and for the process of capturing relevant patterns from the data. The encoded into spike sequences data from the six EEG recording device channels (C3, C4, P3, P4, O3 and O4) is entered as time series into spatially allocated neurons following the Talairach coordinates as suggested in [41] (Fig. 3). Fig. 3 also shows different areas of the SNNc that spatially represent regions of the brain according to the Talairach's template: frontal lobe, temporal lobe, parietal lobe, occipital lobe, posterior lobe, sub-lobar region, limbic lobe, anterior lobe, coloured in different colours.

As an output classifier we used the dynamic evolving SNN (deSNN [36]) algorithm to classify the EEG STBD into the 5 brain cognitive states (classes). This classification method combines the rank-order learning rule [66] and the STDP [62] temporal learning for each output neuron to learn a spatio-temporal pattern using only one pass of data propagation. The classification results were evaluated using both repeated random sub-sampling validation (RRSSV) and leave-one-out cross-validation (LOOCV).

The last picture of the diagram in Fig. 2 represents another key advantage that NeuCube offers: the possibility of model interpretation and knowledge extraction for the purpose of a better understanding of the data and the cognitive brain processes. The state of the SNNc after training can be visualised in different ways and analysed. It can be observed that new connections are formed between neurons that can be further interpreted in the context of different cognitive tasks.

It is important to highlight that the NeuCube model is a stochastic model (*i.e.* initial connection between the neurons of the reservoir are randomly generated) and therefore the model is sensitive to parameter settings. Some of the major parameters that highly influence the model are:

- The AER threshold of the encoding spike trains – a bi-directional threshold, which is applied to the signal's gradient according to the time. When input EEG data is loaded, it is transformed into spike strains. The spike rates depend on the AER threshold, which can be determined either as a particular value for every input variable or as a global threshold to be applied to all of them.
- Connectivity between neurons of the network. Depending on a SW connectivity parameter, each neuron of the SNNr is initially connected to its neighbouring neurons within this parameter as distance. We have used a value of 0.15.
- The threshold of firing, the refractory time and the potential leak rate of the LIF neurons. When a LIF neuron of the reservoir receives a spike, its PSP increases gradually with every input spike according to the time, until it reaches an established threshold of firing. Then, an output spike is emitted and the membrane potential is reset to an initial state (refractory time). Between spikes, the membrane potential leaks. In our experiments the three parameters are set to 0.5, 6 and 0.02 respectively.
- The STDP rate parameter. According to the STDP learning rule (see [62] for more details), the firing activity of two connected neurons causes their connection weight to increase or decrease depending on the order of firing, so that the connection weight will reflect on the temporal relationship between the activities of these neurons. The experiment here uses a value 0.01.
- The number of times that the NeuCube is trained in an unsupervised mode. This is set by default as 2, as higher values may cause over training of the SNNc.
- The variables *mod* and *drift* of the deSNN classifier. According to [36], every training sample is associated to an output neuron, which is connected to each and every other neuron of the cube. The initial connection weights of these output neurons are all set to zero. New connection weights are formed according to the rank-order (RO) learning rule. This are calculated depending on a modulation factor (the variable *mod*) of the order of the incoming spikes. The new connection weights will then increase or decrease according to the number of spikes that follow the first one (the *drift* value). We have used for these parameters values of 0.4 and 0.25 correspondingly.

A crucial step in obtaining good results from the NeuCube model is the optimisation of these parameter values. Parameter optimisation can be achieved *via* grid search method, genetic algorithm, or quantum-inspired evolutionary algorithm [7,56]. In this study we applied a grid search using 50% of the entire time series for training and the other 50% for testing, both randomly selected. We assessed the classification accuracy of 20 model configurations for each subject and for each session using different AER values and used the AER that resulted in the best accuracy (Table 1). The other parameter values were set as explained above. These optimized parameters were used to evaluate the classification output in all experiments including LOOCV method.

3.3. Experimental results

In this study, we measured the classification accuracy of the NeuCube-based models (Table 1) and the average time for execution (Table 2). Table 1 summarises classification results per subject and per session. Results are expressed as a percentage of accurately classified samples per class type and over all classes. The results are obtained using randomly selected 50/50% train/test data and LOOCV method.

As the data set was of a small size, it is not appropriate to draw any scientific conclusions about the mental tasks performance by different subjects, and that was not the goal of this paper. We rather conclude that it is feasible to consider the NeuCube-based method for further analysis and further experimental data modelling to become a widely used method

Table 1

Experimental results with the NeuCube-based model per subject and per session. Results reveal the classification accuracy percent obtained using RRSSV (per class type and as average over all classes) and using LOOCV (as average over all classes).

Samples		Parameter setting	NeuCube classification accuracy using random 50/50 cross validation method						
Subject and session		AER threshold	Class 1 (%)	Class 2 (%)	Class 3 (%)	Class 4 (%)	Class 5 (%)	Average accuracy over all classes (%)	LOOCV (%)
1	Session 1	2.00	80	100	100	60	100	88	80
	Session 2	1.99	100	100	100	100	100	100	100
2	Session 1	1.30	100	100	100	100	20	84	74
	Session 2	4.07	80	40	80	40	40	56	52
3	Session 1	2.94	80	40	100	80	100	80	80
	Session 2	5.23	100	80	80	80	80	84	70
5	Session 1	2.95	20	60	100	100	80	72	54
	Session 2	5.89	80	100	60	100	60	80	94
6	Session 1	6.48	60	80	40	100	80	72	56
	Session 2	5.57	80	100	100	80	60	84	86
7	Session 1	1.70	60	100	100	100	80	88	82

Table 2

CPU time in seconds for the main NeuCube's algorithms (data encoding, neucube initialization, unsupervised training of the cube and supervised training-testing of the classifier).

CPU time (s)				
Data encoding	NeuCube initialization	Unsupervised training	Classifier ST and T	
(whole data)		48.46 (per sample per iteration)	20 (per sample)	5854.51

for EEG data analysis related to mental tasks and cognitive processes across applications. The results from this experiment still confirmed some expected phenomena:

- Subjects perform differently for different complex mental tasks (classes).
- Data for class 1 (relax) was the best classified across all subjects.
- The accuracy of classification increased with some manual parameter tuning showing that this is not the full potential of the NeuCube-based model and it still needs to be further optimised.
- Even dealing with very complex mental tasks, the classification accuracy was better when compared to previously used classification models.

The above comparison was confirmed as the results from the NeuCube based method were compared with the results obtained in previous experiments carried out the same data set [51]. With the proposed NuCube-based method we obtained higher classification accuracy on the data per session, per subject and overall (see Table 3) when compared with other methods such as support vector machines (SVM) and extreme learning machines (ELM) (tested in a leave-one-out cross validation mode). When the SVM and the ELM methods were applied, the EEG data was first pre-processed (smoothed) and then – ‘compressed’ into smaller number of input vectors, rather than treated as spatio-temporal stream data as it is in the NeuCube-model case.

The reported in Table 2 average CPU time has been measured under the following settings: a software simulator of NeuCube written in MATLAB R2012b®; a 64 bit Windows 7 machine, with processor Intel® core™ i5-2400 CPU 3.10 GHz; 8 GB of memory (RAM).

In addition to the above, the NeuCube-based model has several other important advantages:

- It requires only one iteration data propagation for learning, while the classical methods of SVM and ELM require hundreds of iterations.
- The NeuCube-based model is adaptable to new data and new classes, while the other models are fixed and difficult to adapt on new data.
- The NeuCube-based model allows for a good interpretation of the data as discussed next.

3.4. Model interpretation for a better understanding of data

NeuCube constitutes a biologically inspired three-dimensional environment of SNN for on-line learning and recognition of spatio-temporal brain data. It takes into account data features, offering a better understanding of the information and the phenomena of study. This is illustrated in Fig. 4 which was obtained after the SNNc was trained with one of the data sets. From Fig. 4 we can notice that new connections are formed around the input neurons of the SNNr which were allocated so that they spatially map the spatial location of the EEG electrodes. Studying the picture, we could also deduce some additional

Table 3

NeuCube best classification results versus Nan-Ying et al. [51] results.

Subjects	Session	NeuCube method (%)	Nan-Ying et al. [51] (%)	Method used in [51]
1	Session 2	100	86.70	ELM with smoothing
2	Session 1	84	78.76	SVM with smoothing
3	Session 2	80	64.60	SVM with smoothing
5	Session 1	84	63.43	SVM with smoothing
6	Session 2	84	69.47	ELM with smoothing
7	Session 1	88	79.77	SVM with smoothing

information, e.g. subjects where using actively their visual cortex (occipital lobes). Effectively, the subjects were performing each scenario with open eyes. We can also observe from the picture a high activity on the parietal lobe (integration of visual and other information) during the cognitive task related to this data.

The NeuCube model can be further trained incrementally on new data, including new classes, due to the capacity of the SNNr to accommodate data in one pass learning and to the evolvability of the output classifier. The latter will generate a new output neuron for every new input pattern learned and will train it in one pass learning mode [30,34,36]. This ability of the NeuCube models will allow to trace the development/decline of cognitive processes over time and to extract new information and knowledge about them.

4. Conclusion and future directions

The aim of this research has been to develop a methodology and a framework for modelling and interpretation of EEG data that measures brain activities during cognitive tasks. This is important for the creation of new types of BCI and also for early detection of cognitive decline to be used by clinicians in everyday diagnosis. For this purpose, we selected as a benchmark data EEG STBD on complex cognitive tasks [9,39,40]. In this study we proposed a methodology based on the novel SNN architecture called NeuCube [34], for classifying spatio-temporal EEG data collected while subjects were performing 4 types of cognitive tasks and a relax mode.

NeuCube offers several advantages when compared to traditional information methods:

- Fast learning of STBD (only one pass data propagation).
- Higher accuracy of classification.
- Ability to adapt to new data through incremental learning (an evolving SNN is used as an output classifier [30,36,48]), that includes learning of new input patterns from data and new classes.
- Interpretation of the model for a better understanding of the EEG STBD and the processes that generated it.

Future research directions include:

- Experimentation of NeuCube-based models on other EEG data, e.g. [12].
- Parameter optimisation using quantum inspired evolutionary algorithms [7,56,60].
- Adding genetic information in terms of GRN [5,20,21,29,38] to the model to help study the impact of genes on cognitive abilities, e.g. how much gene expression levels of neuro-receptors affect certain cognitive tasks.
- Testing the proposed method on new types of BCI, including neuro-rehabilitation [6,70].
- Testing the proposed method in clinical environment for early diagnosis of cognitive decline.
- Extending the proposed method for predictive modelling and personalised prognosis [37].
- Improved visualisation of the SNNr and the classifier during the training and recall procedures for an improved understanding of the data and the brain processes.
- Implementation of the proposed method on neuromorphic hardware to explore its potential for a highly parallel computation [14,15,24,53,61].

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A.4 A Feasibility Study of Using the NeuCube Spiking Neural Network Architecture for Modelling Alzheimer's Disease EEG data

The study presented in Chapter 7 resulted in a paper (Capecci, Morabito et al., 2015), which was published in *Springer Series of Smart Innovation, Systems and Technologies - 22nd Italian Workshop on Neural Networks (WIRN) 2014*. Copyright and permission from the publisher of the paper are provided in Appendix B.

A Feasibility Study of Using the NeuCube Spiking Neural Network Architecture for Modelling Alzheimer's Disease EEG Data

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Abstract. The paper presents a feasibility analysis of a novel Spiking Neural Network (SNN) architecture called NeuCube [10] for classification and analysis of functional changes in brain activity of Electroencephalography (EEG) data collected amongst two groups: control and Alzheimer's Disease (AD). Excellent classification results of 100% test accuracy have been achieved and these have also been compared with traditional machine learning techniques. Outputs confirmed that the NeuCube is better suited to model, classify, interpret and understand EEG data and the brain processes involved. Future applications of a NeuCube model are discussed including its use as an indicator of the early onset of Mild Cognitive Impairment(MCI) to study degeneration of the pathology toward AD.

Keywords: Spiking Neural Networks, NeuCube, EEG data classification, Alzheimer's Disease.

1 Introduction and Problem Specification

During the past few decades, researchers from all-over the world have been concentrating their efforts towards understanding of the human brain. As a consequence of the efforts made, a relevant progress has been achieved and a huge amount of brain data is becoming available. Neuroinformatics researchers have been playing a pivotal role in the advancement of these studies and especially with the use of machine learning techniques. Some of the major contributions are the improvements in the understanding of the Spatio-Temporal Brain Data (STBD) available and the development of predictive systems. These are of high importance for society, as the increase in human lifespan has been followed by the dramatic rise in the appearance of neurological disorders such as AD [18].

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We have used spatio-temporal EEG as a type of brain data to study this pathology and its degeneration, as it is one of the most commonly collected data for studying the neural processes and it has been for long used to analyse and stage the decline from MCI to AD (e.g. [11,14,15]). Moreover, it is an affordable technique, easy to manage and it is not considered aggressive for the subjects being studied [19].

In this paper, we analyse and classify the spatio-temporal information available (described in section 2) by use of the brain inspired SNN model called NeuCube [10]. In section 3, we introduce the NeuCube model and the experimental design of the study. Section 4 presents the classification results, which are then compared with traditional approaches. Particularly, in section 4.2, through visualization and analysis of the SNN cube (SNNc) after training, new knowledge is also extracted from the data. Finally, conclusions and future directions based on the proposed methodology are presented in section 5.

2 Data Collection and Description

The EEG data has been collected and made available by the IRCCS Centro Neurolesi of Messina, Italy. For this preliminary analysis, we decided to use just the data recorded from one healthy subjects and one subject diagnosed as having AD. The control was a male subject of 58 years of age and the AD patient was a female subject of 80 years of age. They were both at random selected. Each recording session was carried out using 19 electrodes: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2 and the G2 electrode was used as reference. Electrodes were placed according to the sites defined by the standard 10–20 international system. Data was recorded for 65 seconds at 256 Hz, resulting in 16640 data points collected per session. A brain computer interface device was used to collect the EEG data, which was recorded under resting condition. During the experiment, the subjects were sitting with the eyes closed and always under vigilant control.

The data was band-pass filtered between 0.5 and 32 Hz, which includes so the relevant bands for AD diagnosis. No further pre-processing of the data was applied, as the NeuCube model is able to accommodate raw data directly; however, screening and selection of the signals that were visually artefact-free was performed prior to data analysis to avoid misleading results. Then, the original EEG signal concatenated was treated to avoid sub-effects related to the inevitable information loss implied by excluding some components.

For this preliminary study, the EEG data was resized into 3 seconds epochs. Thus, for each of the two classes we had 21 samples of 768 data points recorded for every of the 19 EEG channels. In total, we used 42 samples to run the NeuCube experiments.

3 The NeuCube Spiking Neural Network Architecture

This paper evaluates the ability of the NeuCube SNN framework [10] (Fig. 1) to classify and analyse the functional brain activity produced by the EEG data

recorded from a subject affected by AD and a healthy control. This methodology allows for the creation of different models for STBD based on the following information processing principles as listed in [10]:

- The model has a spatial structure that maps approximately the spatially located areas of the brain where STBD is collected.
- The same information paradigm - spiking information processing, that ultimately generates STBD at a low level of brain information processing. This is used in the model to represent and to process this STBD.
- Brain-like learning rules are used in the model to learn STBD, mapped into designated spatial areas of the model.
- A model is evolving in terms of new STBD patterns being learnt, recognised and added incrementally, which is also a principle of brain cognitive development.
- A model always retains a spatio-temporal memory that can be mined and interpreted for a better understanding of the cognitive processes.
- A visualization of the model evolution during learning can be used as a bio-feedback.

Such models can be used to learn and reveal complex spatio-temporal patterns “hidden” in the STBD, which would not be possible to achieve using other information processing methods. As a result a significantly improved understanding of complex brain processes that generates the data can be gained, along with improved classification and/or prediction accuracy.

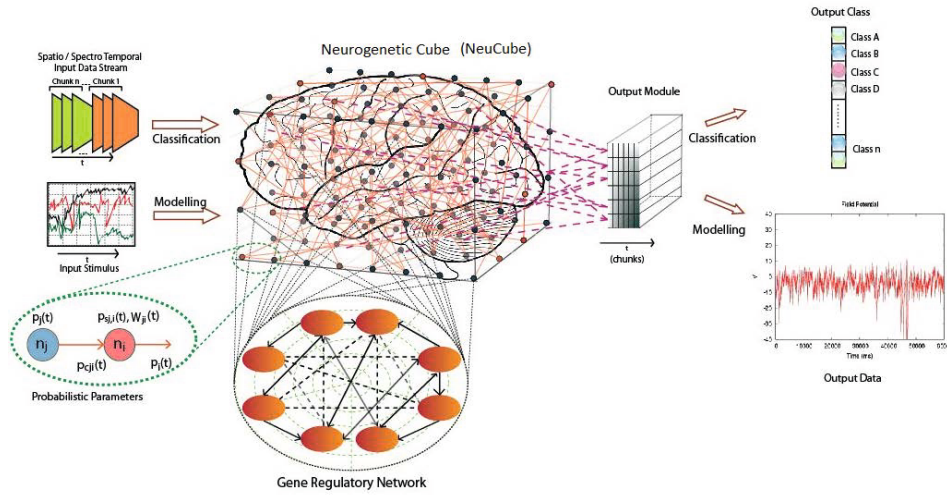


Fig. 1. The NeuCube architecture with its three main modules: input data encoding module; a 3D SNN cube module; an output classification module. Also, an optional Gene Regulatory Network (GRN) module can be incorporated if gene information is available. The spiking neurons can be simple leaky integrate and fire model or probabilistic models (shown in the lower left section).

3.1 Experimental Design and Implementation

The NeuCube-based model used for this study was implemented with a software simulator written in MATLAB [27]. This particular NeuCube consists of three modules:

1. An input information encoding module.
2. The NeuCube 3D SNNc module.
3. An output module for data classification and knowledge extraction.

The process scheme in Fig. 2 summarises the experimental design applied to the study.

- I. The raw time series data, obtained from the EEG device, is directly fed into the model as ordered sequence of real-valued data vectors. One of the great advantages of the NeuCube framework is that in many cases there is no need of pre-processing (such as normalization of the data, scaling, smoothing, etc.).
- II. Each real value input stream of data is transformed into a spike train using Address Event Representation (AER) method [2]. AER is more convenient when using continuous input data, such as EEG STBD, as this algorithm identify just differences in consecutive values.
- III. The spike sequences are then presented to the SNNc, which was implemented using Leaky Integrate and Fire (LIF) neurons [13], as that mimics the information processing of the human brain and it is less computational expensive [20,5]. The SNNc can also evolve according to the number of input variables (i.e. the EEG channels) and the data available.
Due to the size of the data set used for this study, we generated a 3D cube of $13 \times 15 \times 11$ spiking neurons. 1471 of these spiking neurons were mapped according to a brain atlas, the Talairach Atlas [12,24]. Each of these neurons were representing the centre coordinates of a one cubic centimetre area from the 3D Talairach Atlas, including the 19 EEG channels, which also identified the input neurons of the network.
- IV. The SNNc is then trained on the input spike trains *via* unsupervised learning method, using Spike Timing Dependant Plasticity (STDP) [23] learning rule. Unsupervised learning is performed to modify the initially set connection weights. The SNNc will learn to activate same groups of spiking neurons when similar input *stimuli* are presented [6]. This makes the NeuCube architecture useful for learning consecutive spatio-temporal patterns and therefore representing a more biologically plausible associative type of memory [10].
- V. The output classifier is then trained *via* supervised method. The same STBD used for the unsupervised training is now propagated again through the trained SNNc and output neurons are generated (evolved) and trained to classify the spatio-temporal spiking pattern of the SNNc into pre-defined classes (or output spike sequences). Different SNN methods can be used to learn and classify spiking patterns from the SNNc. For this experimental study, Dynamic Evolving SNN (deSNN) algorithm [9] was used.

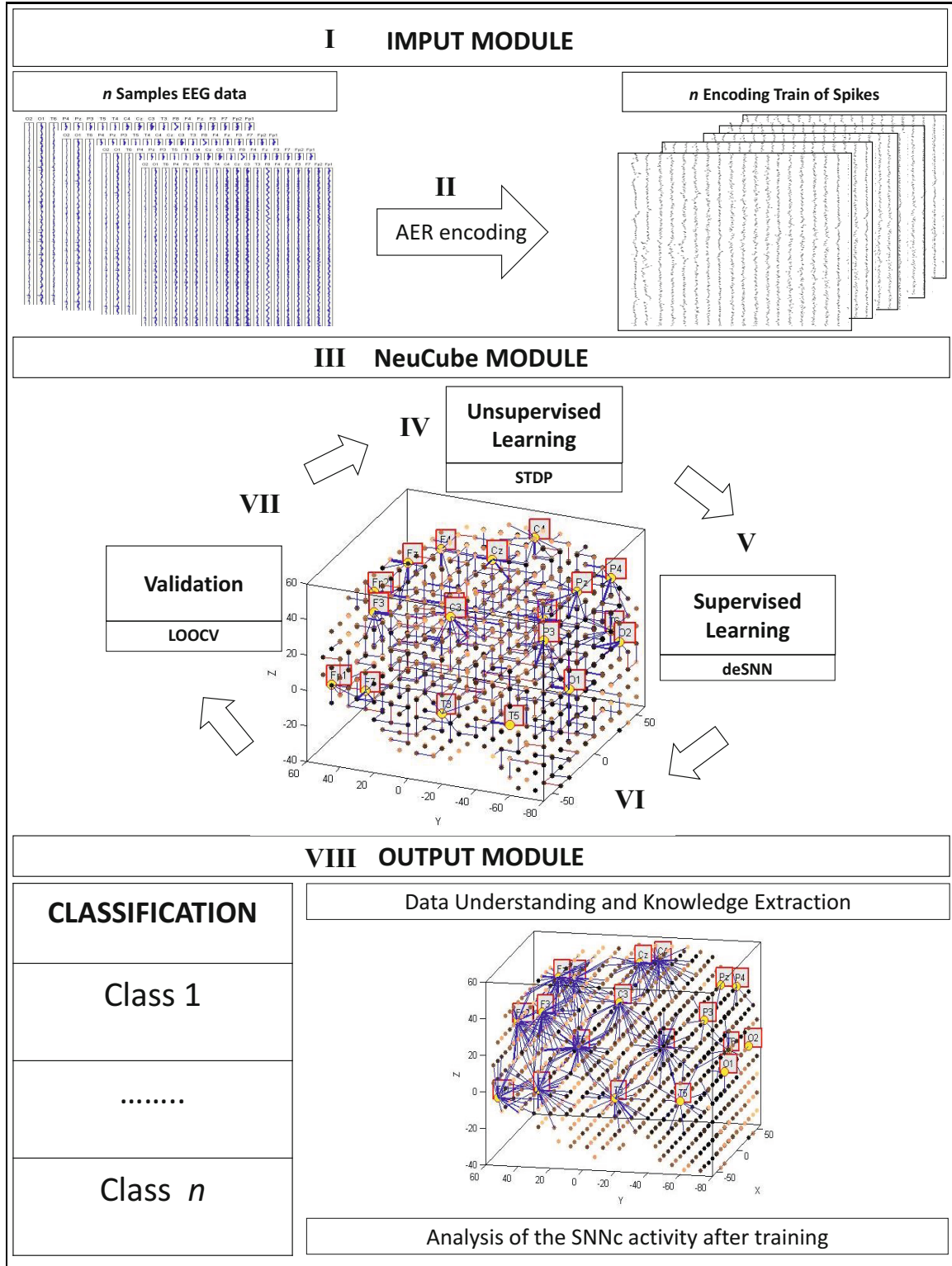


Fig. 2. Process scheme of the NeuCube framework with its three principal modules: the input module, where input data are transformed into trains of spikes that are then presented to the main module, the SNNc; the NeuCube module, where time and space characteristics of the STBD are captured and learned to extract new knowledge from them through the SNNc visualization; and the output module for data classification and understanding. In the scheme are also indicated the VIII processes involved in the NeuCube experiment.

This classification method combines the rank-order learning rule [26] with the STDP [23] temporal learning, for each output neuron to learn a how spatio-temporal pattern using only one pass of data propagation.

- VI. The classification results are evaluated using repeated random sub-sampling validation or Leave-One-Out Cross-Validation (LOOCV) respectively.
- VII. In order to achieve a desirable classification accuracy, the numerous parameters of the NeuCube needs to be optimized. Therefore, steps (III) to (VI) are repeated changing parameter values. That can be done using a grid search method, a genetic algorithm or the Quantum-Inspired Evolutionary Algorithm [17]. In this study, we have used a grid search, as we will explain in the next section.
- VIII. The trained SNNc is visualized and its connectivity and spiking activity analysed for a better understanding of the data and the brain processes that generates it. In fact, it can be observed that new connections are formed between the neurons and this can be further interpreted in the context of different neural activity. Therefore, this represents another key advantage that NeuCube offers: the possibility of knowledge extraction.

4 Results and Discussion

The NeuCube framework has been used and promising results on the analysis of cognitive mental activity [8] and the classification of complex muscular movements for neuro-rehabilitation [25] has been reported. In this paper, we evaluated the feasibility of a NeuCube-based model to correctly classify data with known pattern and extract knowledge from the spatio-temporal EEG signals of a subject affected by AD *versus* a healthy control. Our aim is to develop an analysis and prediction tool to be used by clinician for identifying the appearance of MCI and predict the onset of AD.

To achieve satisfying classification results, the numerous parameters of the NeuCube need to be accurately selected. Based on previous studies that we have conducted (e.g. [8]), we have identified some critical variables requiring careful optimization and we have selected the values that correspond to some of them, making them default. Taking into account that every parameter tuned also involves a considerable amount of processing time, we need to select the proper number of variables to be optimised. The AER threshold was chosen for this study, as it is applied to the entire signal gradient according to the time and therefore the rate of the generated spike trains depend on this threshold. Moreover, since the NeuCube is a stochastic model, altering this value means also altering the initial model configuration each time. Thus, using a grid search, we evaluated the classification accuracy of 10 model configurations adjusting the AER threshold at every new configuration. For that, we have used 50% of the entire time series for training and the other 50% for testing. The parameter's settings which were obtained after optimization are summarised in Tab.1.

Table 1. NeuCube Parameters

NeuCube Parameters			
AER threshold	Conn. Distance	STDP rate	Firing threshold
0,94	0,15	0,01	0,5
Refractory Time	Training Time	deSNN mod	deSNN drift
6	1	0,4	0,25

Table 2. NeuCube’s classification results expressed by accuracy percent. Results are obtained using both 50/50%-Trainin/Testing and LOOCV.

NeuCube RESULTS		
CLASS	(50/50%-Tra/Test.)	(LOOCV)
Control	100%	100%
AD	100%	100%
Average Accuracy	100%	100%

As common practice in machine learning, classification accuracy was calculated by statistical processing of the information obtained from the confusion table. Classifier outputs were evaluated using both random sub-sampling validation and LOOCV, as reported in Tab.2.

4.1 Comparative Analysis

NeuCube results have been also compared with other approaches, such as Multi Layer Perceptron (MLP), Support Vector Machine(SVM), Inductive Evolving Classification Function (IECF)[7] and Evolving Clustering Method for Classification (ECMC)[22].

To process these experiments, the NeuCom platform was used [7], which is a self-programmable, learning and reasoning computer environment freely available on-line (www.theneucom.com).

The LOOCV method was used to evaluate the outputs and datasets were normalised prior to the experiments to ensure the highest classification accuracy result. (i.e. the normalisation protocol applied to each method consisted in a linear standardization of the data’s vectors using values between 0 and 1 as a scale).

Classification accuracy was analysed *via* supervised learning method, which is based on classification of data with a known pattern. The results obtained are expressed in the confusion table as number of True Positives (TP) and True Negatives (TN) against False Positive (FP) and False Negative (FN). An analysis of the classification outputs obtained by all different methods was performed based on this information, which was further processed to calculate the following metrics:

- Accuracy percent (A %):

$$A \% = (TP + TN) / (TP + FN + FP + TN) * 100 \quad (1)$$

- Sensitivity (S):

$$S = TP / (TP + FN) \quad (2)$$

- Specificity (SP):

$$SP = TN / (FP + TN) \quad (3)$$

Results obtained are summarised in Tab. 3 and they were used to plot a Receiver Operating Characteristics (ROC) graph (Fig.3) [3]. The parameter's settings used for each method are reported in Tab. 4.

Table 3. Comparison of the results obtained *via* NeuCube *versus* traditional machine learning methods (MLP, SVM, IECF and ECMC), confusion table and resulted metrics.

Confusion Table					
Control	AD	MLP		SVM	
TP	FN	11	14	11	14
FP	TN	10	7	10	7
IECF		ECMC		NeuCube	
21	13	21	1	21	0
0	8	0	20	0	21
METRICS					
	NeuCube	MLP	SVM	IECF	ECMC
A% (1)	100	43	43	69	98
S (2)	1	0.52	0.52	1	1
SP (3)	1	0.33	0.33	0.38	0.95
1-SP	0	0.67	0.67	0.62	0.05

Table 4. Traditional machine learning methods (MLP, SVM, IECF and ECM) parameter's settings

MLP parameters		SVM parameters	
Normalization	yes	Normalization	yes
Number of Hidden Units	3	kernel	Polynomial
Number of Training Cycles	300	Degree, γ	1
Output Value Precision	0.0001		
Output Function Precision	0.0001		
Output Activation Function	linear		
Optimization	scg		
IECF parameters		ECMC parameters	
Normalization	yes	Normalization	yes
Max. Influence Field	1	Max. Influence Field	1
Min. Influence Field	0.01	Min. Influence Field	0.01
M of N	3	M of N	3
Membership Function	2		
Epochs	4		

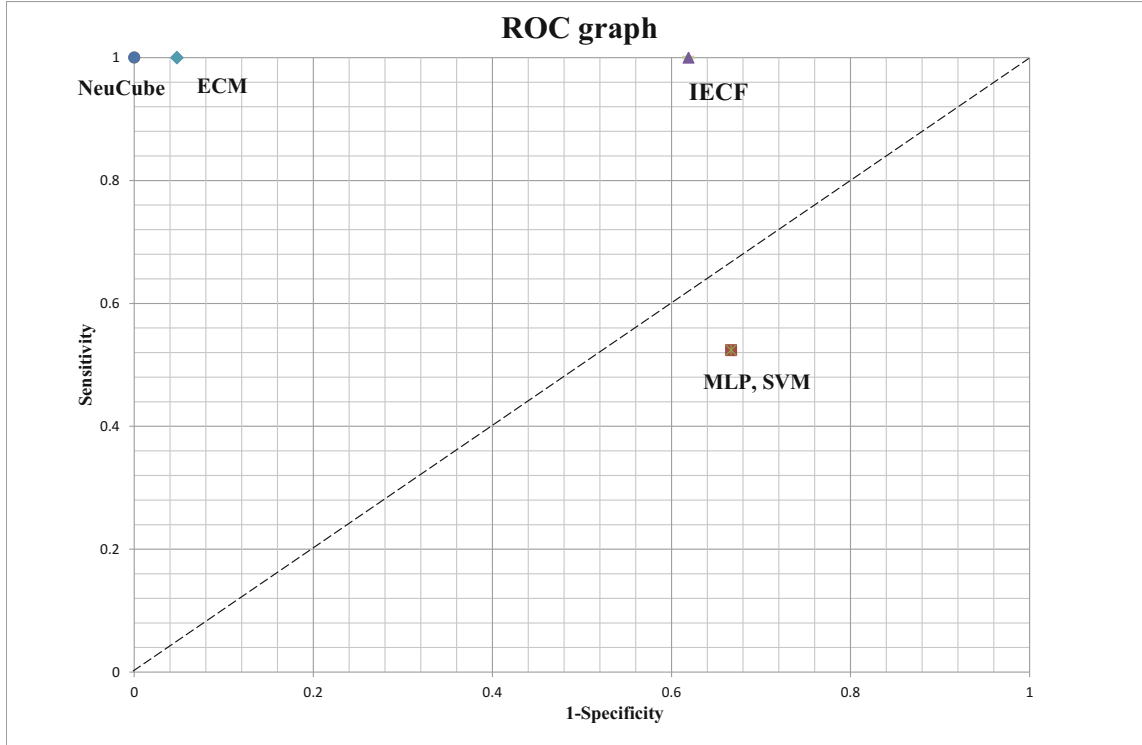


Fig. 3. ROC graph. 1-Specificity is plotted on the X axis and Sensitivity is plotted on the Y axis

As far as the ROC graph is concerned, each classifier produce a sensitivity and a specificity value, which results in a single point on the graph's space. Classifiers falling on the top-left area of the graph are considered achieving desirable results [3]. The NeuCube appears on the top-left hand side of the graph (point 0,1) performing as a perfect classifier. Interesting performance is also reported by ECMC method, while IECF method, even classifying nearly all positives correctly, it reports high false positive, which bring it too far on the right hand side of the graph.

Optimization of the results obtained *via* these techniques is not a trivial process and it requires more sophisticate optimization methods. In fact, the few parameters that influence these methods cannot be tuned independently, one of the reasons is that some of them are discrete values and others are continuous. Thus, the work involved to improve the output results is not viable.

We can conclude that, in terms of the comparison with the other classification methods, NeuCube performed significantly better with the highest accuracy, sensitivity and specificity over all. By means of these metrics, the closest to NeuCube's results was ECMC, whilst the poorest performing were MLP and SVM.

In addition to the above, the NeuCube-based model has other important benefits, such as:

- It requires only one iteration data propagation for learning, while traditional methods as SVM requires numerous iterations.
- The NeuCube-based model is adaptable to new data and new classes, while the other models are fixed and difficult to adapt on new data.
- There is no need of pre-processing of the data (such as normalization, scaling, smoothing, etc.) with the NeuCube model. The raw data can be fed directly into the model as time series transformed into spike trains.
- The NeuCube model demonstrated to be able to achieve a better classification accuracy per class than the other methods.
- The NeuCube model also offers a better understanding of the data and therefore the brain processes that generates it through visualization and analysis of the output SNNc state, as discussed in the following section.

4.2 Model Interpretation and Data Understanding

The NeuCube model constitutes a SNN environment based on some of the most important principles governing the neural activity in the human brain.

Thus, it constitutes a valuable model for on-line learning and recognition of STBD. It also takes into account data features, offering a better understanding of the information and the phenomena of study. In fact, one of the main advantages of the NeuCube model is that after training the SNNc can be visualized and its connectivity and spiking activity observed. This ability of the NeuCube models allows us to trace the development/decline of neurological processes over time and to extract new information and knowledge about them.

Illustrated in Fig. 4 is the SNNc state obtained after it was trained with data from a control subject (top picture) and then after it was trained with data from the subject affected by AD (bottom picture).

We can observe that new connections are formed between the neurons of the network and especially around the input neurons, which were mapped according to the Talairach coordinates of the 19 EEG electrodes. We can depict from Fig. 4 that the neural activity of both the healthy subject and the subject suffering from AD is quite different. In fact, in the case of the healthy control, the connections evolved are equally distributed in every brain region. On the other hand, in the case of the patient affected by AD, we can observe that this activity decreased in the left hemisphere and so there is a higher activity evolved in the right hemisphere, maybe to compensate the lack of its counterpart and therefore as a consequence of the degeneration of the pathology.

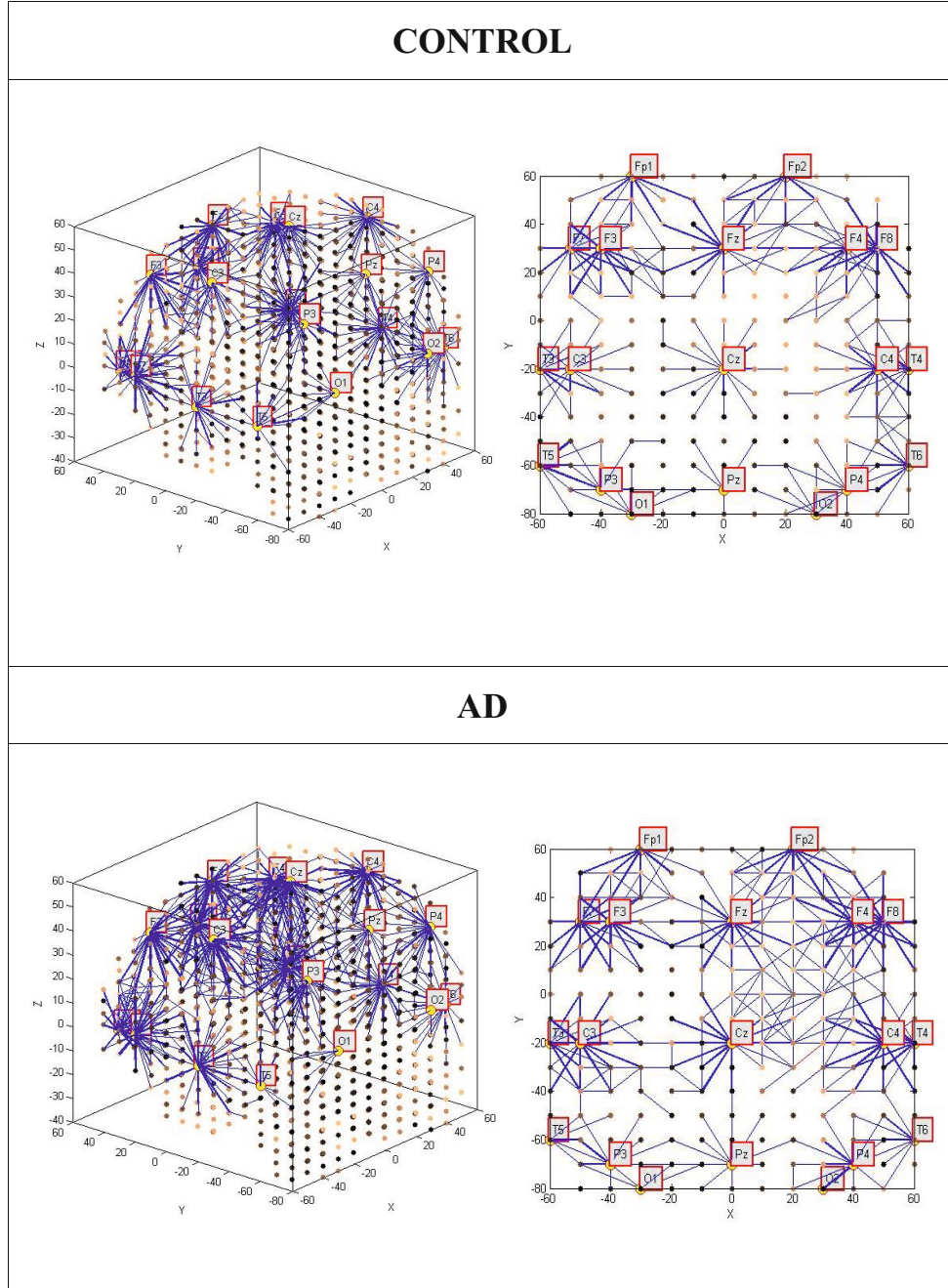


Fig. 4. The SNNc connectivity after training (top control, bottom AD). The figure shows both the 3D cube and the (x,y) plane only of the SNNc. The SNNc can be analysed and interpreted for a better understanding of the EEG data to identify differences between brain states. Blue lines are positive connections, while red lines are negative connections. The brighter the color of a neuron the stronger its activity with a neighbour neuron. Thickness of the lines also identify the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 19 EEG channels.

5 Conclusions and Future Directions

The goal of the proposed study has been to analyse how the NeuCube model can be used for classifying and analyse AD EEG data. This is important for the creation of new types of BCI and also for early detection of cognitive decline to be used by clinicians in everyday diagnosis. Further improvement of the understanding and use of the model proposed here are believed to significantly contribute to the advancement in machine learning for the prediction and understanding of brain data and more specifically for data related to neurodegenerative pathologies, such as AD.

There are different scenarios and avenue to be taken in the future, some of those includes:

- Extending the proposed methodology using a higher number of data sets from subjects affected by AD and also by MCI, in order to observe the SNNc state and possibly extract degeneration markers.
- Extending the model adding genetic information in terms of gene regulatory networks [1] as an optimization module to help study the impact of genes on cognitive abilities, e.g. how much gene expression levels of neuroreceptors effect certain cognitive tasks.
- STBD modelling and understanding also through visualization and/or virtual reality of the SNNc, which can be used by clinicians to study how patients effectively improve their neurological activity before and after treatments when compared to healthy control.
- Comparison of the model developed with other techniques used for AD classification, such as Random Forest (e.g. [4]), kernel Support Vector Machine Decision Tree (kSVM-DT) (e.g. [28]), Learning Vector Quantization using Support Vector Machine (LVQ-SVM) (e.g. [16]), Hidden Markov Random Field (e.g. [21]).
- Testing the proposed method in a clinical environment for prediction and early diagnosis of cognitive decline.
- Implementation of the proposed method on neuromorphic hardware to explore its potential for a highly parallel computation [5].

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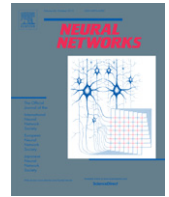
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A.5 Analysis of connectivity in NeuCube spiking neural network models trained on EEG data for the understanding of functional changes in the brain: A case study on opiate dependence treatment

The study presented in Chapter 8 resulted in a paper (Capecci, Kasabov & Wang, 2015) that was published by *Neural Networks Journal*. Copyright and permission from the publisher of the paper are provided in Appendix B.



Analysis of connectivity in NeuCube spiking neural network models trained on EEG data for the understanding of functional changes in the brain: A case study on opiate dependence treatment



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ABSTRACT

The paper presents a methodology for the analysis of functional changes in brain activity across different conditions and different groups of subjects. This analysis is based on the recently proposed NeuCube spiking neural network (SNN) framework and more specifically on the analysis of the connectivity of a NeuCube model trained with electroencephalography (EEG) data. The case study data used to illustrate this method is EEG data collected from three groups—subjects with opiate addiction, patients undertaking methadone maintenance treatment, and non-drug users/healthy control group. The proposed method classifies more accurately the EEG data than traditional statistical and artificial intelligence (AI) methods and can be used to predict response to treatment and dose-related drug effect. But more importantly, the method can be used to compare functional brain activities of different subjects and the changes of these activities as a result of treatment, which is a step towards a better understanding of both the EEG data and the brain processes that generated it. The method can also be used for a wide range of applications, such as a better understanding of disease progression or aging.

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1. Introduction

Over the last four decades, EEG has been used extensively for the study of brain functional changes under different conditions, including neurological disease and treatment with drugs. In principle, EEG data can show changes of cortical activity that occur during milliseconds (Gevins et al., 2011; Smith et al., 2006), and it is recognised as a sensitive measure of drug effects on the brain and, in particular, of drug effects on the size and on the time course of post-synaptic potentials (Gevins et al., 2011; Smith et al., 2006). Nevertheless, localisation of changes in cognitive activity is limited in EEG in contrast to magnetic resonance imaging (MRI). Recently, a growing number of methods have been developed to localise the generators of EEG components, for example low resolution brain electro-magnetic tomography (LORETA) (Pascual-Marqui et al., 1999; Pascual-Marqui, Michel, & Lehmann, 1994) and

statistical parametric mapping (SPM) (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011).

Using standard statistical or machine learning techniques to classify EEG data from groups of patients under different treatment can suggest whether there is a functional improvement, as a result of treatment. For example, in already published studies (Wang, Wouldes, Kydd, Jensen, & Russell, 2014; Wang, Wouldes, Kydd, & Russell, 2012; Wang, Kydd, Wouldes, Jensen, & Russell, 2015), we demonstrated that improved cognitive functions in patients undertaking methadone maintenance treatment (MMT) in contrast to those dependent on illicit opiates. Additionally, we demonstrated that MMT cognitive functions are comparable to healthy subjects. Previously, we have investigated group difference on spectral power of EEG data using traditional statistical methods (i.e. analysis of covariance, independent sample t-test, etc.), and the results only reveal the fluctuation of neural activity within an individual channel. Traditional statistical and AI methods applied to study functional brain changes lack the ability to explain which functional areas of the brain are affected during treatment, how much they are affected and what are the changes of the dynamics of the brain as a chain of spiking activity over time. Time information is present in spatio-temporal brain data (STBD), such as EEG data, but when the data is processed (e.g. classified) this information is

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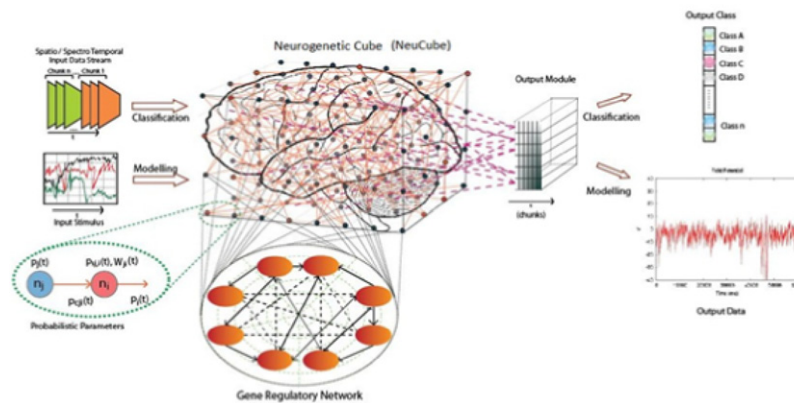


Fig. 1. The NeuCube architecture with its three main modules: input data encoding module; a 3D SNN cube module; an output evolving classification module (Kasabov, 2014). An optional Gene Regulatory Network (GRN) module can be incorporated if gene information is available. The spiking neurons can be implemented as a simple leaky integrate and fire model or probabilistic models (shown in the lower left section).

compressed and there is no explanation of the final results related to the time component. In this respect traditional methods can be considered “black boxes” in a sense (Kasabov, 2014). These are important questions that need to be addressed for a better understanding of functional changes in the brain under various conditions, including: neurological disease progression, disease treatment over time and ageing.

Recently, a new methodology, the “NeuCube framework”, based on the connectivity analysis of evolving brain-inspired spiking neural networks (eSNN) models has been proposed (Kasabov, 2014). It has been demonstrated that the NeuCube provides significant accuracy of classification and interpretation of the brain data, suggesting its potential application to neurological clinical research. In this study, we introduce a new method for the connectivity analysis of NeuCube model trained on EEG data to reveal brain functional changes under different conditions and across different groups of subjects. As a case study, we take the problem of identifying differences between people with opiate addiction and those undertaking substitution treatment for opiate addiction.

The paper is constructed in the following way: Section 2 describes the functional characteristics of the NeuCube eSNN framework. Section 3 presents a methodology for connectivity analysis of a NeuCube model. Section 4 presents a case study of EEG data analysis of functional brain changes across groups of opiate addicts and those who have taken MMT in comparison with control subjects. This section presents results of the analysis and discussions based on a comparative analysis between NeuCube models and traditional statistical and machine learning techniques. The conclusion in Section 5 clearly identifies the NeuCube models as being superior to other methods, for the purpose of revealing functional brain changes and the prediction of response to treatment across applications.

2. The NeuCube spiking neural network framework

2.1. Spiking neural networks (SNN)

Some of the most valuable techniques used in *in silico* investigations are brain inspired machine-learning techniques, such as SNN. These techniques are potentially able to learn and reveal time, space and frequency information “hidden” in the STBD. In fact, the neural activity recorded can be represented as binary events, called spikes, which are then fed into a model. Each neuron of the network represents a computational unit, which is able to modify and evolve connections with the other neighbouring neurons to reflect the timing of the data from the sensory inputs (Kasabov, 2014). This is one of the main principles of SNN, considered the third

generation of brain-inspired neural network techniques (Gerstner, 1995, 2001; Gerstner, Sprekeler, & Deco, 2012). Some of the main advantages that SNN techniques provide are: compact representation of space and time; fast information processing; time-based and frequency-based information representation; memory-based, so that they can be studied after training for data understanding.

2.2. The NeuCube SNN framework

The main principles of the NeuCube framework were first presented in Kasabov (2012, 2014) and further developed in Chen, Hu, Kasabov, Hou, and Cheng (2013), Scott, Kasabov, and Indiveri (2013) and Tu et al. (2015). A NeuCube model (Fig. 1) consists of: input data encoding module; a 3D SNN cube (SNNc); an eSNN classifier; and an optimisation module.

NeuCube has already been applied successfully for the classification and knowledge extraction of both EEG (Capecci et al., *in press*; Kasabov & Capecci, 2015) and functional MRI (fMRI) (Doborjeh, Capecci, & Kasabov, 2014) cognitive data, and to other type of spatio-temporal data for personalised disease prognosis (Kasabov et al., 2014; Othman et al., 2014) and neuro-rehabilitation (Chen et al., 2013; Taylor et al., 2014). This paper contributes to the set of methods related to the NeuCube with the introduction of a new methodology for connectivity analysis in relation to brain functions represented in the EEG STBD. The proposed method is applied on EEG data collected from people with drug addiction to reveal the possible changes of neural cognitive activity related to the treatment and the dose of drug administered. More specifically, we quantified the differences between groups on functional connectivity (e.g. positive/negative connection between neurons). Information processing in the brain involves multiple neurons and neural pathways distributed across different regions. To perform a particular task, there is a need to combine individual neuronal signals into a cognitive process. In this study, we did not examine the neural activity elicited by a cognitive task, however, the connection between neurons during resting state would implicate the potential difference between groups on cognitive function.

The NeuCube framework allows for the creation of different computational models for STBD based on the following information processing principles as listed in Kasabov (2014):

- The model has a 3D spatial structure that maps approximately the spatially located areas of the brain where STBD is collected.
- The same information paradigm—spiking information processing that ultimately generates STBD at a low level of brain information processing, is used in the model to represent and to process this STBD.

- Brain-like learning rules are used in the model to learn STBD, mapped into designated spatial areas of the model.
- A model is evolving in terms of new STBD patterns being learned, recognised and added incrementally, which is also a principle of brain cognitive development.
- A model always retains a spatio-temporal memory that can be mined and interpreted for a better understanding of the cognitive processes.
- A visualisation of the model evolution during learning can be used as a bio-feedback.

All the above principles make the NeuCube a suitable SNN architecture to learn and reveal complex spatio-temporal patterns, which justify its choice for the development of the new methodology to model EEG data and to extract knowledge from it in this paper.

Specific formulas used in the current version of NeuCube for the experiments in this paper are given in the [Appendix](#).

3. Connectivity analysis of a NeuCube spiking neural network model trained on EEG STBD

3.1. Modelling EEG data in the NeuCube

The EEG data modelling procedure used here is shown graphically on [Fig. 2](#) and it consists of the following procedures:

1. The time series data obtained from the EEG device is first ordered as a sequence of real-value data vectors. One of the main advantages of the NeuCube is that there is no need of additional pre-processing of the EEG data, such as normalisation, scaling, and smoothing. The model can also deal with noisy data, which is significantly time-saving.
2. In order to obtain an input compatible with the SNNc, each real-value input time series (e.g. the measured EEG data in one electrode) is transformed into a spike train (i.e. sequence of binary events) using a spike encoding method, and more specifically, the Threshold-Based representation method (TBR). This algorithm well suits EEG STBD, since it identifies just differences in consecutive values, as demonstrated and implemented in the artificial silicon retina chip ([Delbruck, 2007](#); [Dhoble, Nuntalid, Indiveri, & Kasabov, 2012](#)) and the artificial cochlea chip ([Chan, Liu, & Van Schaik, 2007](#)).
3. The input spike sequences are presented to an evolving brain-mapped SNNc that reflects the number of input variables (e.g. the 26 EEG channels in the case study from [Section 4](#)), the functional brain areas associated with them and the size of the data available.
4. The SNNc is implemented using leaky integrate and fire (LIF) model ([Gerstner, 2001](#)) neurons and is initialised as “small-world” (SW) connected networks. The SW connectivity principle has been chosen here as it is based on the biological process that makes neighbouring neural cells to be highly and strongly interconnected to each other, therefore, the initialisation is fundamental for the learning process of this model.
5. The SNNc is trained in an unsupervised mode using spike timing dependent plasticity (STDP) ([Song, Miller, & Abbott, 2000](#)) learning rule. This algorithm allows spiking neurons to learn consecutive temporal associations from the EEG data within- and across-EEG channels. The neurons become able to form new connections in the architecture, which can then be analysed and interpreted. This makes the NeuCube architecture useful for learning spatio-temporal patterns from EEG data, forming associative type of memory that can be further explored.

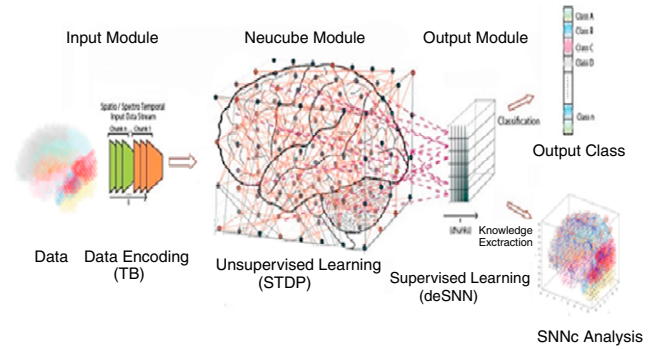


Fig. 2. A graphical representation of the NeuCube-based methodology used for EEG data modelling and connectivity analysis.

6. The output classifier is trained in a supervised mode (i.e. method based on classification of data with a known pattern) using dynamic evolving SNN (deSNN) ([Kasabov, Dhoble, Nuntalid, & Indiveri, 2013](#)) algorithm to classify the EEG STBD into the respective classes. This classification method combines the rank-order (RO) learning rule ([Thorpe & Gautrais, 1998](#)) and the STDP ([Song et al., 2000](#)) temporal learning for each output neuron to learn a spatio-temporal pattern using only one pass of data propagation.
7. The classification results are evaluated using repeated random sub-sampling validation (RRSV) or leave one out cross validation (LOOCV).
8. Steps (4)–(7) are repeated using different parameter values in order to optimise the classification output. The best performing model can then be recorded for further uses.
9. The trained SNNc is visualised, its connectivity and the dynamic spiking activity are analysed for a better understanding of the data and the brain processes that generated it including changes of brain functionality across different conditions and groups of subjects.

It is important to highlight that the NeuCube model is a stochastic model (i.e. initial connection between the neurons of the network are randomly generated) and therefore the output classification accuracy depends on the parameters settings. Based on previous studies that we have conducted, we have identified some critical variables requiring careful optimisation. These parameters are:

- The TBR which is applied to the input EEG data streams transforming them into spike trains. The rates of the spikes depend on the TBR threshold, which can be determined either as a particular value for every input variable or as a global threshold to be applied to all of them (Eq. (A.1) described in [Appendix A](#)).
- Connectivity between neurons of the network. Depending on the SW connectivity rule, each neuron of the SNNc is initially connected to its neighbouring neurons within a distance that depends of a SW connectivity parameter (Eq. (A.2) described in [Appendix A](#)).
- The threshold of firing, the refractory time and the potential leak rate of the LIF neurons (Eqs. (A.3)–(A.4) described in [Appendix A](#)). When a LIF neuron of the SNNc receives a spike, its post synaptic potential (PSP) increases gradually with every input spike according to the time of the spike arrival, until it reaches an established threshold of firing. An output spike is then emitted and the membrane potential is reset to an initial state (refractory time). Between input spikes, the membrane potential also leaks. In our experiments, the three parameters were set to 0.5, 6 ms and 0.002 respectively after optimisation.

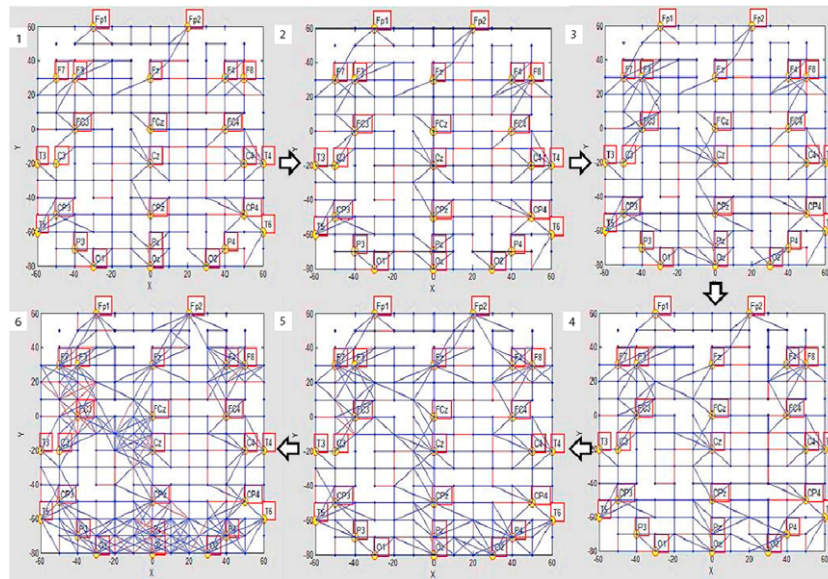


Fig. 3a. Example of a step-wise connectivity evolution in a SNNc activity during STDP learning on EEG data recorded from all subjects who belonged to all three groups – H, O and M – during an EO state (for interpretation—see next section). The figure shows the (x, y) projection only of the 3D SNNc. The six pictures visualise the cube connectivity during STDP learning from the initial randomly generated connections (1) until unsupervised training is finished—(6). Blue lines are positive connections (excitatory synapses) generated, while red lines are the evolved negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels. A video of the step-wise connectivity evolution is included with the supplementary data available online (see [Appendix C](#)).

- The STDP learning rate parameter. According to the STDP learning rule (see [Song et al., 2000](#) for more details), the firing activity of two connected neurons causes their connection weight to increase or decrease depending on the order of firing, so that the connection weight will reflect on the temporal relationship between the activities of these neurons (Eq. (A.5) described in [Appendix A](#)).
- The number of times that the NeuCube is trained in an unsupervised mode. This is set by default as 1 which is suitable for incremental, on-line adaptive learning.
- The parameters *mod* and *drift* of the deSNN classifier ([Kasabov et al., 2013](#)) (Eqs. (A.6)–(A.7) described in [Appendix A](#)). The values of these parameters depend on the data and problem in hand and need to be optimised for an optimal performance.

Optimisation of these parameters can be achieved via grid search method, genetic algorithm, or quantum-inspired evolutionary algorithm ([Platel, Schliebs, & Kasabov, 2009](#)). Taking into account that every parameter tuned also involves a considerable amount of processing time, we need to select the proper number of variables to be optimised. In this study, a grid search method was applied, mainly to find the best value associated to the TBR parameter, as this threshold is applied to the entire signal gradient according to the time and therefore the rate of generated spike trains depends on it. Moreover, since the NeuCube is a stochastic model, altering this value means also modifying the initial model configuration each time.

Default parameters were not set up prior to the experiment, but they were chosen as considered the ones leading to the optimal results and in consistence with information reported in previous neuroscience reports. For instance, the refractory time suggested by our model was 6 ms. In general, the refractory time interval for neural spiking reported by previous study is about 5 ms, however, it might require more time in response to certain events ([Berry & Meister, 1998](#)).

3.2. Connectivity analysis of a NeuCube model trained on EEG STBD for the study of brain functional changes

A NeuCube model can accommodate data in one pass learning to dynamically evolve an output classifier. A new output neuron

can be generated in the output classifier for every new input pattern learned in the SNNc and trained in one pass learning mode ([Kasabov et al., 2013](#)). This ability of the NeuCube models enables the brain processes to be traced over time and to extract new information and knowledge about them. First, a NeuCube model is trained until satisfactory performance (e.g. classification) of the EEG data. Then, the SNNc connectivity structure is analysed for a better understanding of the dynamics of the data across different subjects and different groups of subjects. In fact, the connectivity of the SNNc represents dynamic spatio-temporal associations of the brain activities measured by the input variables (the EEG channels). Through the analysis of NeuCube evolved connectivity, the following research questions can be addressed and studied in general:

- (a) How the connectivity evolves in a SNNc trained with data of all subjects from groups ([Fig. 3a](#)) versus training a model on data of an individual subject or a group of subjects performing a task, when compared to another individual or another group? [Fig. 3a](#) represents an example of a step-wise SNNc connectivity evolution during unsupervised training on EEG data recorded from all subjects who belonged to all three groups – healthy (H), opiate addicted (O) and people using methadone (M) as treatment – during an eyes open (EO) resting state.
- (b) What is the functional change of brain activities when a subject with history of drug use is compared with a control (healthy) subject? [Fig. 3b](#) (left) illustrates the different SNNc connectivity generated after a SNNc model which was trained with EEG data recorded from all subjects who belonged to the M group *versus* the same initial SNNc trained with EEG data recorded from all subjects who belonged to the H group during an EO resting state.
- (c) What are the differences in the activities of brain regions between subjects undertaking treatment for drug addictions and those without treatment. In our case study, these are opiate addicts *versus* those undertaking treatment for addiction. [Fig. 3b](#) (right) shows different SNNc connectivity resulted after a SNNc was trained with EEG data recorded from all subjects who belonged to the M group *versus* the connectivity generated with data recorded from all subjects of O group during the EO state.

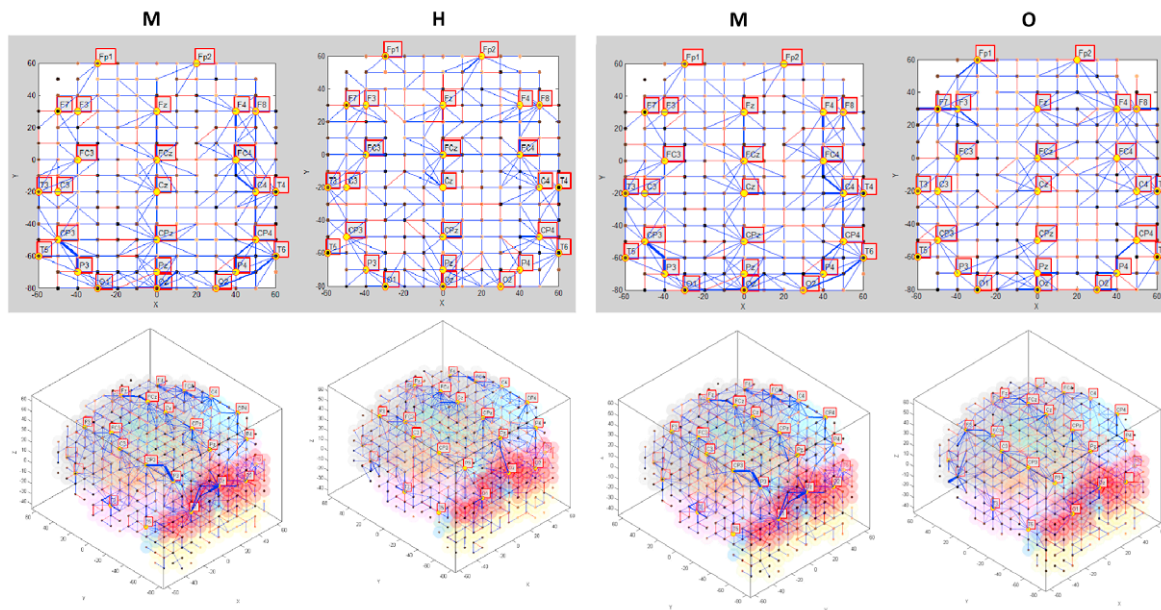


Fig. 3b. Examples of the SNNc connectivity after unsupervised training is finished. A SNNc was trained using EEG data recorded from all subjects who belonged to the M group and from all subjects who belonged to either the control H group (left) or the O group (right) during an EO state (for interpretation—see next section). The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines represent positive connections (excitatory synapses), while red lines represent the evolved negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels.

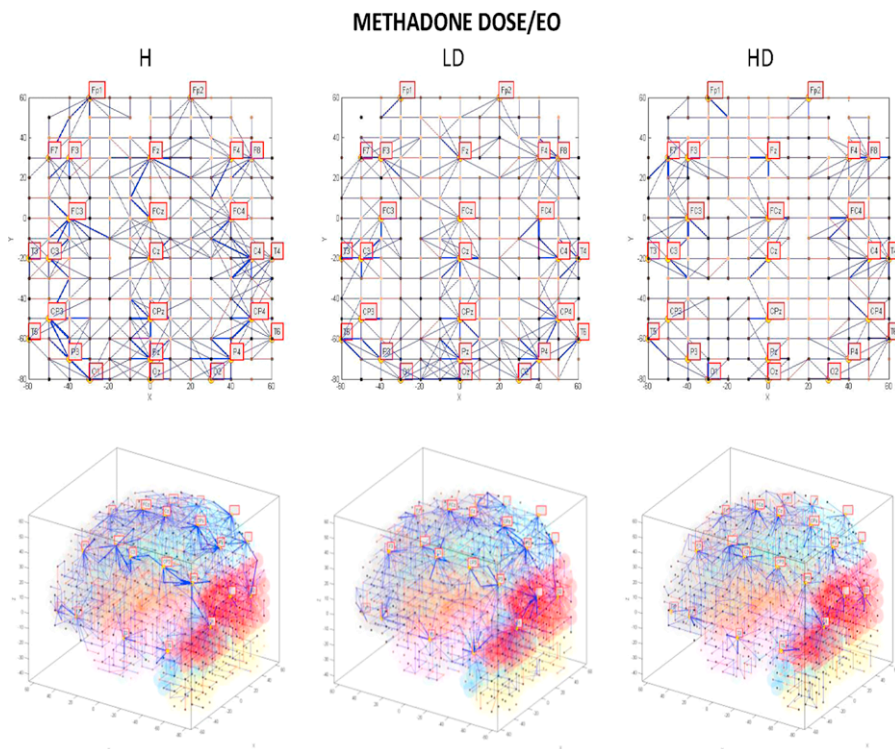


Fig. 3c. Examples of the SNNc after unsupervised training is finished. The SNNc was trained using EEG data recorded during the EO state, from 12 subjects who belonged to the control group (H), from patients taking below 60 mg of methadone (LD) and from M patients taking 60 mg or above of methadone (HD) (for interpretation—see next section). The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines represent positive connections (excitatory synapses), while red lines represent negative connections (inhibitory synapses). In yellow are the input neurons with their labels corresponding to the 26 EEG channels.

(d) What is the functional change of brain activities when a different dose of drug is administered? Fig. 3c represents the connectivity of a SNNc after training it with EEG data

recorded from patients who have been treated with a different dose of methadone before completing the same trial.

These research questions are illustrated here on EEG data related to the case study problem and explained in more detail in the following section. The above research questions are generic and can be studied in relation to other brain disorders and patients response to respective treatments.

4. Connectivity analysis of NeuCube models trained on EEG data for the understanding of functional brain changes related to opiate substitution treatment (methadone) and predicting patients response to treatment

4.1. Case study problem definition

Methadone has been used as a pharmacological substitute for the treatment of opiate dependence since the mid-1960s. As a substitute for illicitly used opiates, the purpose of MMT is not to achieve a drug-free state but to reduce the harm associated with illicit drug use and to improve life quality and psychosocial functioning for the individual (Lobmaier, Gossop, Waal, & Bramness, 2010). The benefits of MMT have been demonstrated by many studies. For example, MMT has been shown to effectively reduce the use of other drugs, injection-related risky behaviour, criminal activity, mortality, and the transmission of HIV and other blood-borne pathogens, such as hepatitis-B (Ball, Lange, Myers, & Friedman, 1988; Bell, Hall, & Byth, 1992; Gibson, Flynn, & McCarthy, 1999; Marsch, 1998). Consequently, MMT is now the most common treatment for opiate dependence in many countries, including the United States of America, Australia, the United Kingdom and New Zealand (Adamson et al., 2012; Joseph, Stancliff, & Langrod, 1999).

Despite methadone's effective clinical use, it remains uncertain whether MMT has negative effects on cognitive function, given that methadone has clinically similar actions and analgesic effects to morphine (Dole, 1988), for a review (Wang, Woules, & Russell, 2013). Methadone primarily binds to receptors that are found throughout the brain and are densely concentrated in the periaqueductal gray, amygdale, hippocampus, thalamus and striatum (Martin, Hurley, & Taber, 2007; McBride, Chernet, McKinzie, Lumeng, & Li, 1998). In humans, these areas are critical for pain perception, visual and sensory processing, memory and attention. Therefore, there is particular concern whether long-term use of a sedative opiate antagonist, such as methadone, has effects on cognitive function. To address this question, a more detailed analysis of EEG data collected from different groups of patients and healthy subjects is performed in this study, using the NeuCube modelling framework and its connectivity and activity analysis.

4.2. EEG data collection

Prior to commencing this research, ethical approval was granted by the Northern Regional X Ethics Committee of New Zealand and informed consent was given by all participants. All EEG recordings were conducted between 12 pm and 4 pm, apart from three participants (one was from the opiate user group and two were from the healthy control group) who completed EEG recording at 6 pm, due to their availability. All EEG recordings were conducted on a one-to-one basis in a sound and light attenuated laboratory. A QuickCap (Neuroscan 4.3) 40 sensor shielded cap was used to acquire EEG data from the cephalic sites. The 26 cephalic sites included Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, Cpz, C3, C4, CP3, CP4, FC3, FCz, FC4, T3, T4, T5, T6, Pz, P3, P4, O1, O2, and Oz electrode sites (10–20 International System). A further 14 channels recorded other data, e.g. VPVA and VPVB vertical electro-oculogram (EOG), HPHL and HNHR horizontal EOG, heart rate (HR), muscle movements and events, etc. HR is considered as one of the most sensitive measures of withdrawal, which has been shown to

be positively correlated with severity of opiate withdrawal (Zilm & Sellers, 1978). EEG was recorded relative to the average of A1 and A2 (mastoid) electrode sites. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eye-lid. Skin resistance was kept at $<5 \text{ k}\Omega$. Scalp and EOG potentials were amplified and digitised continuously by a system (NuAmps, SCAN 4.3) having a frequency response from DC to 100 Hz (above which attenuating by 40 dB per decade), and a sampling rate of 500 Hz. Electrical impedance was always $<5 \text{ k}\Omega$.

Resting EEG data was collected with patients undertaking MMT (M group), people currently using illicit opiates (O group) and healthy volunteers (H group) in two states: eyes open (EO) and eyes closed (EC). In the EO condition, participants were asked to fixate on a red dot in the centre of the computer screen for two minutes. In the EC condition, participants were asked to sit still with their eyes closed for two minutes.

The M group consisted of 18 males and 14 females, with a mean age of 39.36 (SD = 5.14) years. Their mean duration of education was 12.06 (SD = 2.00) years; mean duration of opiate use was 10.03 (SD = 6.08) years; mean duration of MMT 7.29 (SD = 6.39) years; and current methadone dose 70.86 (SD = 40.61; range 8–180) mg/day.

All the participants recruited were between 18 and 45 years of age, had basic English literacy skills and were able to provide written informed consent. Inclusion criteria for the M group was undertaking methadone for a minimum of six months and stabilised on their current dose for at least 2 weeks. Participants in the opiate user group were required to meet the DSM-IV criteria for opiate dependence and were not allowed to be currently undertaking MMT. The inclusion criteria for healthy control subjects was no current or lifetime history of drug or alcohol abuse other than nicotine dependence.

4.3. A NeuCube model to analyse EEG data from H, O and M groups

For our study, we resized the raw EEG data to 26 ordered vectors of real value data, as 26 were the EEG channels used during the EEG recording. Data from 20 healthy subjects, 15 subjects addicted to opiates and 22 subjects under MMT was available for the EC state. On the other hand, data from 20 healthy subjects, 17 subjects addicted to opiates and 25 subjects under MMT was available for the EO state. Every EEG STBD sample fed into the NeuCube was labelled to represent one of the subjects. We averaged every subjects neural activity per channel every 2048 data points, which means every 4 s of recordings. We considered this information enough for our analysis. We obtained a total of 37 and 33 data points per channel and per sample for the two resting state EC and EO respectively (as this was the lowest number of data points after averaging the signal).

For the experiments, we generated a SNNc of 1471 brain mapped spiking neurons. We used the 3D Talairach Atlas (Koessler et al., 2009; Lancaster et al., 2000; Talairach & Tournoux, 1988) to map 1471 brain areas of 1 cm^3 each into single spiking neurons of the SNNc and then entered the data from the EEG channels into the corresponding input neurons of the SNNc (see Kasabov, 2014).

Results can be affected by subjects' poly-drug use, a common complication in a population with drug dependence and it is unlikely that patients or opiate users have no history of use of other types of drugs. The question is, while this is true, what more can we learn from the SNNc about the brain functional differences (changes) between these groups?

For a better understanding of the data and to address the research questions raised in the previous section, different analysis of the connectivity of the SNNc have been performed and reported below.

Table 1

Parameters settings of the SNNc models used for training the data of all groups during EC and EO state.

SNNc parameters settings	
EC	
Threshold of firing: 0.5	Potential leak rate: 0.02
STDP: 0.1	TBR: 7.94
Long Dist. possibility: 0.01	Weight threshold 0.15
EO	
Threshold of firing: 0.4	Potential leak rate: 0.02
STDP: 0.1	TBR: 52.62
Long Dist. possibility: 0.01	Weight threshold 0.07

Table 2

Parameters settings of the NeuCube models used for connectivity and spiking activity analysis for class M versus class H and class O subjects (EO states only).

Network analysis parameters settings	
Threshold of firing: 0.4	Potential leak rate: 0.02
STDP rate: 0.1	Long Dist. possibility: 0.01
Connection distance: 0.15	Times to train: 1
TBR threshold: 52.62	Weight threshold 0.07
Max. spike gradient	Spreading level
10 inputs	2

4.4. Analysis of spiking neuronal activity and connectivity generated in EC versus EO resting state across the studied subject groups

To analyse and visualise the SNNc activity generated by the resting EEG data recorded when subjects are with EC or EO, Fig. 4a shows the initial connections and the connectivity evolved after STDP learning rule was applied to either H, O or M group. The cube connectivity can be analysed and interpreted for a better understanding of the EEG data to identify differences between brain states during the execution of either the EC or the EO state. Table 1 reports the parameters settings used to obtain these results. According to Fig. 4a, the neural activity generated during the two scenarios was different. Both states manifested high activity around the input neurons – which were allocated so that they spatially mapped the brain-location of the 26 EEG electrodes – and along the central area (Fz, Cz, Pz, etc.). The neural activity generated during the EO was significantly different from the EC, having a greater connectivity on the left frontal, central and occipital–parietal regions. This was also confirmed by the step-wise analysis of the SNNc (shown in Fig. 3a). We can observe that the initial connections in the cube are firstly generated around the input neurons represented by the 26 EEG channels. Then, as the unsupervised learning precede, more connections evolved in the frontal lobe of the left hemisphere (T3, C3, FC3, F2 and F3), the central areas (FCz, Cz) and the occipital–parietal regions (O1, O2, Oz, Pz, P3, P4). As a result of the activity observed during the EO state, we decided to focus our subsequent analysis on the data collected during this state only.

4.5. Analysis of NeuCube connectivity with the aim of discovering functional changes of brain activities in subjects under treatment (M) compared with control subjects (H)

Fig. 4b illustrates the neural activity obtained after the SNNc was trained with EEG data corresponding to the M and the H group separately (EO only). The parameters settings used to obtain this results were set in accordance with the ones reported in Table 1.

Analysing the figure, we can observe that there are differences in the SNNc connectivity between the M and H groups, indicating alternations of neural activity induced by history of opiate exposure.

Table 3

Classification accuracy percentage obtained using a NeuCube classification model versus traditional machine learning methods (MLR, SVM, MLP, and ECM).

Samples/classes-EC	MLR	SVM	MLP	ECM	NC
15 samples Opiate (% accuracy)	53	40	60	40	67
22 samples Methadone (% accuracy)	50	64	59	73	100
Overall accuracy (%)	51	54	59	59	86
Samples/classes-EO	MLR	SVM	MLP	ECM	NC
17 samples Opiate (% accuracy)	59	29	53	53	75
25 samples Methadone (% accuracy)	48	68	56	68	82
Overall accuracy	52	52	55	62	79

The NeuCube network analysis per class is illustrated in Fig. 4c. Table 2 reports the parameters settings used for the network analysis. The networks connectivity identifies higher spiking activity in the 10 EEG channels allocated in the visual cortex. Both spike spreading level and maximum spike gradient are reported. As shown in Fig. 4c, the pathway of spiking activity of the M group is similar to the H group, despite their greater level of intensity.

4.6. Analysis of NeuCube connectivity with the aim of discovering functional changes of brain activities in subjects under treatment (M) compared with subjects without treatment (O)

Fig. 4d shows the neural activity obtained after the SNNc was trained with the data corresponding to the M and the O group separately (EO only). The parameters were set in accordance with the ones reported in Table 1.

As shown in Fig. 4d the neural activity of the M group was different from the O group, in particular, greater excitation in the parietal and occipital regions was observed in the M group. According to these results, we focused on these regions analysing the maximum spike gradient of the input channels and their information spreading level (Fig. 4e). The parameter settings used are reported in Table 2. Consistent with the previous studies (Wang et al., 2014, 2012, 2015), our findings implicate that there are different cognitive-related effects between methadone and illicit opiates. To further test this hypothesis, we have classified the O group versus M group (Table 3) for both resting states (EC and EO). The high classification accuracy obtained via the NeuCube methodology proved the model ability to manifest this difference and also that the two classes were in fact two distinguishable groups. We compared the results obtained using the proposed NeuCube model with traditional machine learning methods, such as multiple linear regression (MLR), support vector machine (SVM), multilayer perceptron (MLP) and evolving clustering method for classification (ECM). We used the NeuCom software environment for the experiments (<http://www.theneucube.com>). Tables B.1 and B.2 in Appendix B report the parameters settings used to obtain these results for either EC and EO state.

When training a NeuCube model on the EEG data, we used 26 input features/variables (the EEG channels) and entered the times series of each input variable to train the SNNc. In contrast, the other methods could not take time series data without transforming it into a static and fixed length data vectors, used to train a model one after another. The results in Table 3 were obtained using LOOCV method when the best top 20 features were selected for every traditional machine learning method tested (MLR, SVM, MLP, ECM) and for every sample in the LOOCV procedure. Selecting features in time series processing is not recommended though as once a model is trained these features will be fixed and any change in the dynamics of the EEG data in future experiments would not be tolerated for incremental learning and model adaptation. In this respect NeuCube offers a certain advantages from the point of view of adaptive and incremental learning of STBD. But the most important difference between a NeuCube model and the

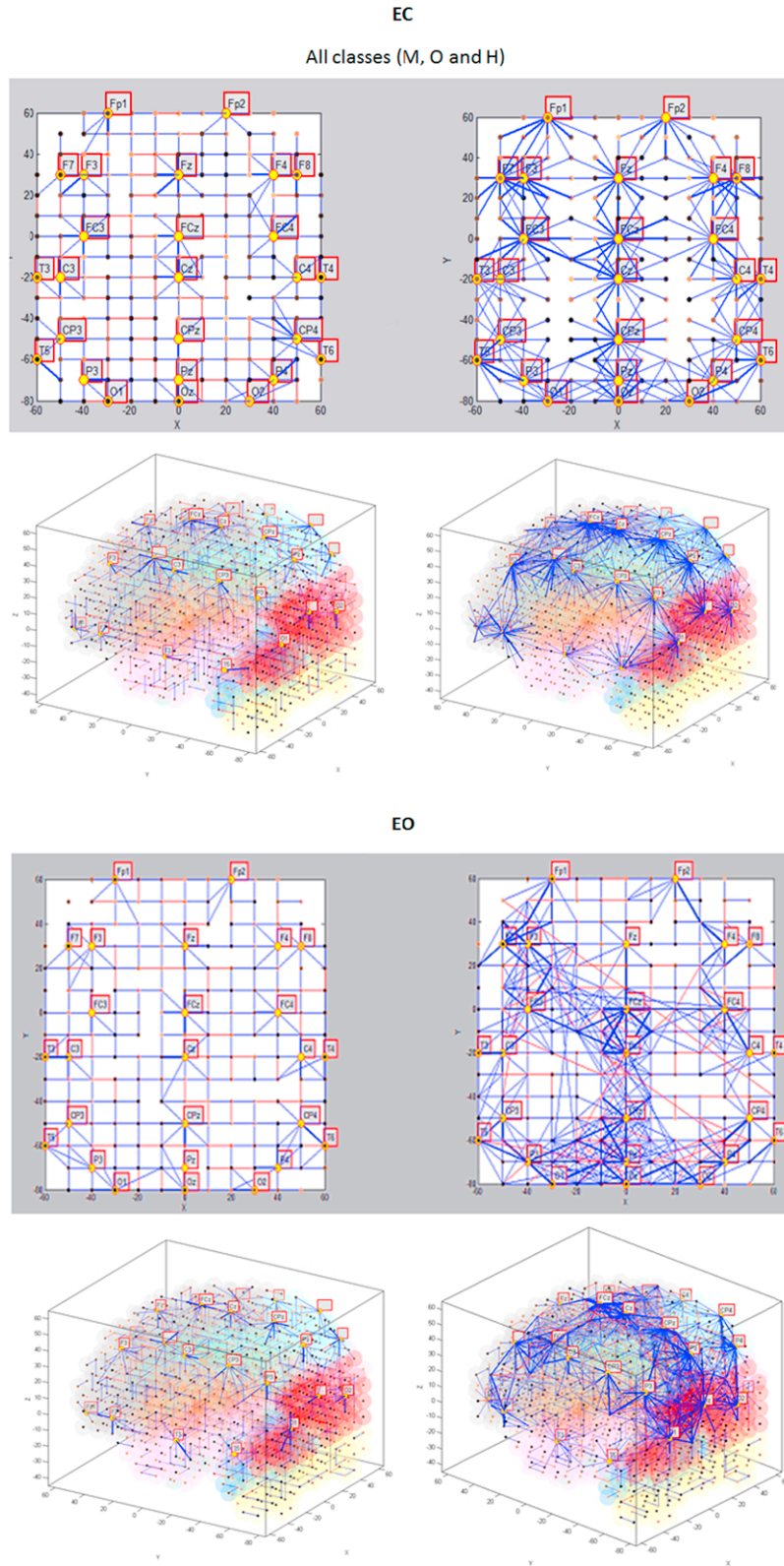


Fig. 4a. NeuCube connectivity before (left) and after training (right) the SNNc with the EEG data recorded from all subjects who belonged to all three groups – H, O and M – during either the EC (top) or the EO state (bottom). For both resting states, the top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). In yellow are the input neurons with their labels corresponding to the 26 EEG channels. Blue lines are positive connections (excitatory synapse), while red lines are negative connections (inhibitory synapse). The brighter the colour of a neuron, the stronger its activity with a neighbour neuron. Thickness of the lines also identifies the neurons enhanced connectivity.

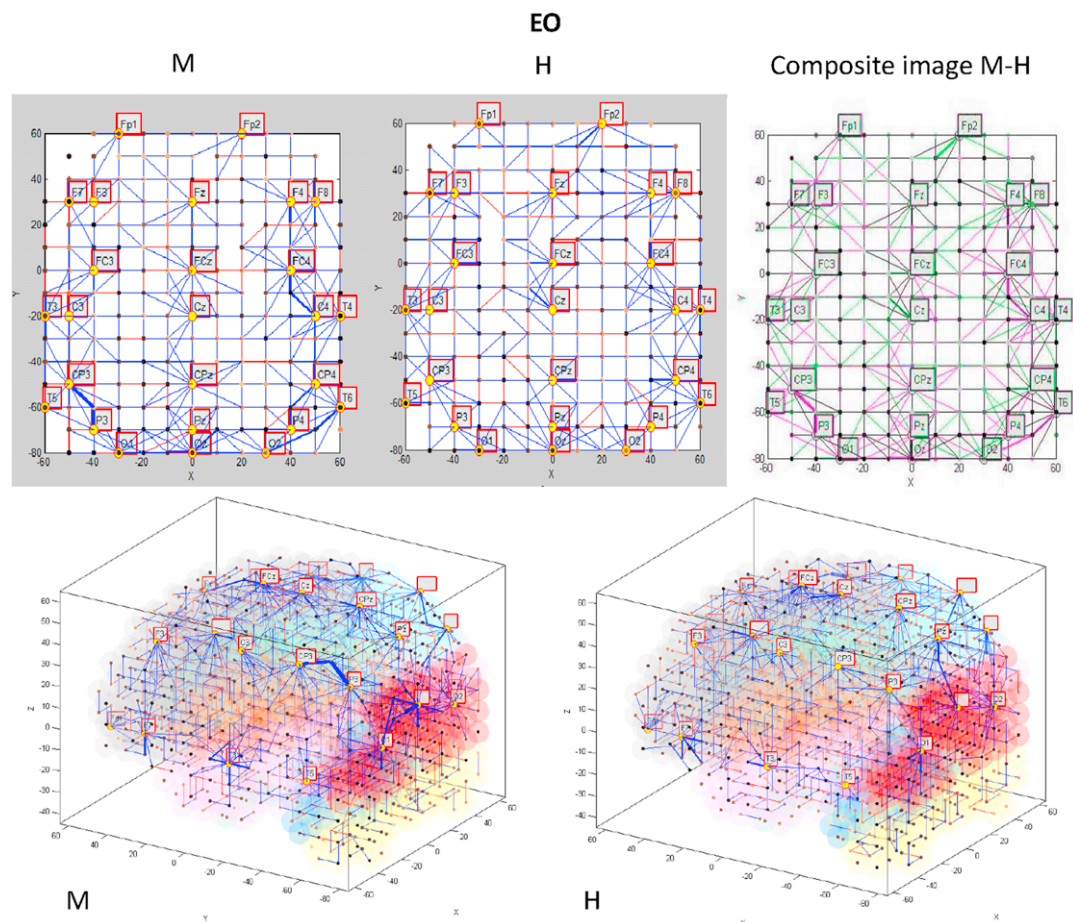


Fig. 4b. NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the control H group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite image (top right-hand side figure) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for M group) and green regions (for H group) show where the intensities are different.

traditional machine learning methods is that a NeuCube model has a brainlike structure and uses brain-like learning methods to learn STBD, so that the model can be interpreted for new discoveries related to the source of the EEG data the brain. In contrast, the traditional machine learning methods, being successfully applied on many problems so far, cannot be of much use for STBD modelling, analysis, model interpretation and knowledge discovery.

4.7. Connectivity analysis of the NeuCube model aiming at discovering functional changes in brain activities related to different doses of the drug administered

Since every EEG sample was an identifiably-labelled subject and there are potential dose-related effects suggested by the literature, we further analysed the methadone dose-related effect on spiking activity in our M group through the analysis of the connectivity of the NeuCube trained model with these EEG data. Data corresponding to the M group were divided into two subgroups, low dose (LD) and high dose (HD) of methadone, according to their daily dose of drug administered (high – dose ≤ 60 mg < low – dose). For the EO task, we obtained 14 samples for the low dose class and 11 samples for the high dose class. We also compared these two groups with 13 subjects of the healthy

Table 4
Parameters settings of the SNNc models used for training the data who belonged to one of three groups – H, LD, HD – during EO state. The parameter optimised was TBR while the other parameters were set as default value.

SNNc analysis parameters settings	
Methadone dose EO	
Thr. of firing: 0.5	Pot. leak rate: 0.002
STDP: 0.5	TBR: 32.44
Long Dist. possibility: 0.01	Weight Thr.: 0.07

control groups. Thirteen subjects were randomly chosen from the healthy control group to minimise the possible confounding effects associated with sample size.

In order to study these effects, we analysed the SNNc activity and connectivity obtained after training the SNNc with the EEG data corresponding to the H, LD and HD group separately. Fig. 4f reports the SNNc activity generated per class after setting the parameters according to Table 4.

As shown in Fig. 4f, there are similarities and differences between groups (H versus HD or H versus LD). It appears that there is a greater reduction of connectivity in the HD group when compared to either the H or the LD group. Our findings suggest that the dose administered may play a role in treatment response and it needs to be addressed in treatment planning.

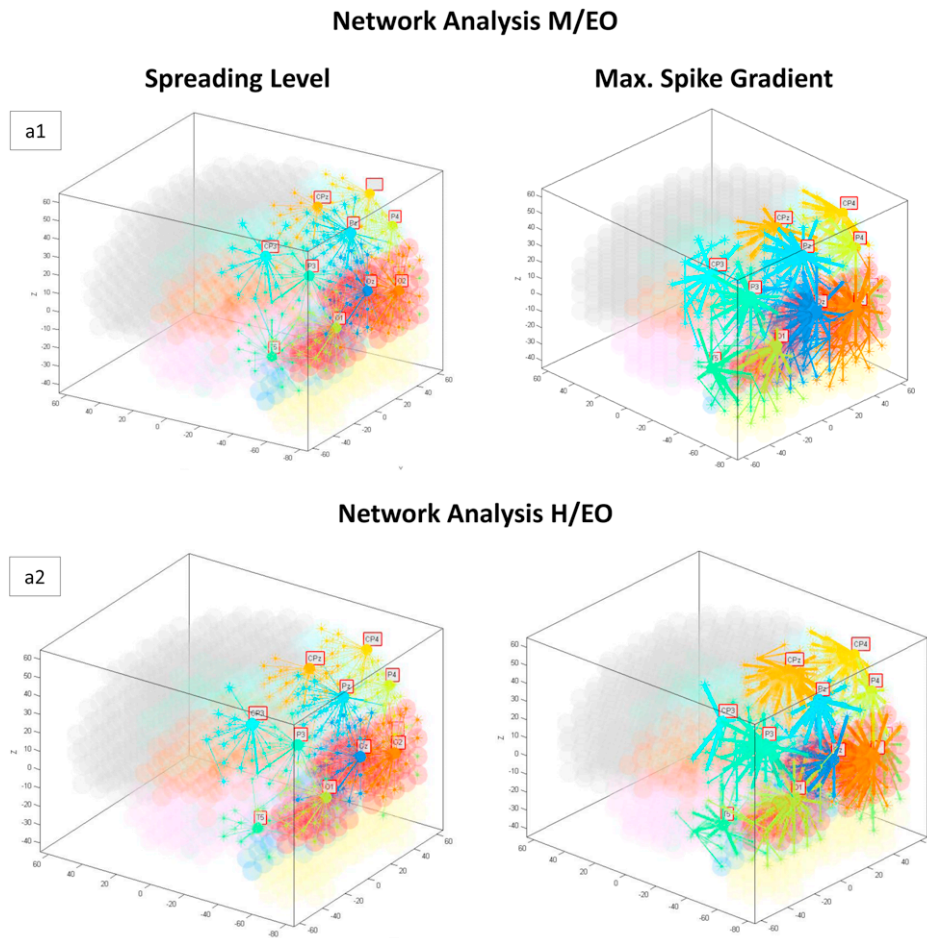


Fig. 4c. NeuCube connectivity and spiking activity analysis per class – M group (a1) and H group (a2) – obtained for the EO state. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

To further study the network connectivity, we focused on the occipital–parietal regions to extract new knowledge from the trained SNNc (for visualisation and analysis, as opposed to training purposes). Fig. 4g illustrates the network's connectivity by means of its spike spreading level and its maximum spike gradient emitted by class over the 10 EEG channels allocated in the particular brain area of interest.

The parameters settings used to plot these figures are the same as per Table 2. The results consistently support our argument showing a greater difference between the HD and the H groups compared to the difference between LD and the H groups.

5. Discussions, conclusion and further directions

The NeuCube constitutes a brain-inspired three-dimensional structure of SNN for on-line learning and recognition of spatio-temporal brain data (STBD) (Kasabov, 2014). It takes into account the spatial coordinates of the sources of the STBD using a standard brain-template, offering a better understanding of the information and the phenomena of study. The goal of the proposed study was to develop a method for the analysis of the connectivity and the dynamic activity of a NeuCube model trained on EEG STBD in order to understand changes in brain activities across subjects and groups. Traditional data mining/machine learning algorithms are not able to properly deal with this kind of data. Our results demonstrated that a NeuCube model not only achieves a better

sensitivity and specificity in classifying EEG data compared to traditional AI methods, but it is also interpretable for a better understanding of the EEG data and the processes that generated it. This makes the NeuCube modelling approach widely applicable for neuroscience research across data and problems. In particular, the paper demonstrated:

1. The NeuCube ability to classify EEG data collected from different groups of patients and healthy subjects.
2. Connectivity analysis of a SNNc after training with EEG STBD from different groups of subjects (different classes) to extract new knowledge and to study the brain regions involved.
3. Connectivity analysis aiming at the understanding the correlation between a dose of treatment and results of treatment.
4. Connectivity analysis aiming at the understanding the impact of different dose of treatment on brain activities and at predicting response to treatment.

A further development and research are planned including:

- Further development of the methods of the NeuCube framework, including: analysis of the ability of a NeuCube model in terms of how “deep in time” spatio-temporal patterns, “buried” in STBD, can be efficiently learned; how different “time lags” can be represented in the NeuCube; spatio-temporal rule extraction from a trained NeuCube model; analysis and interpretation of the output connectivity along with the SNNc connectivity in relation to a better understanding of brain differences across groups of subjects.

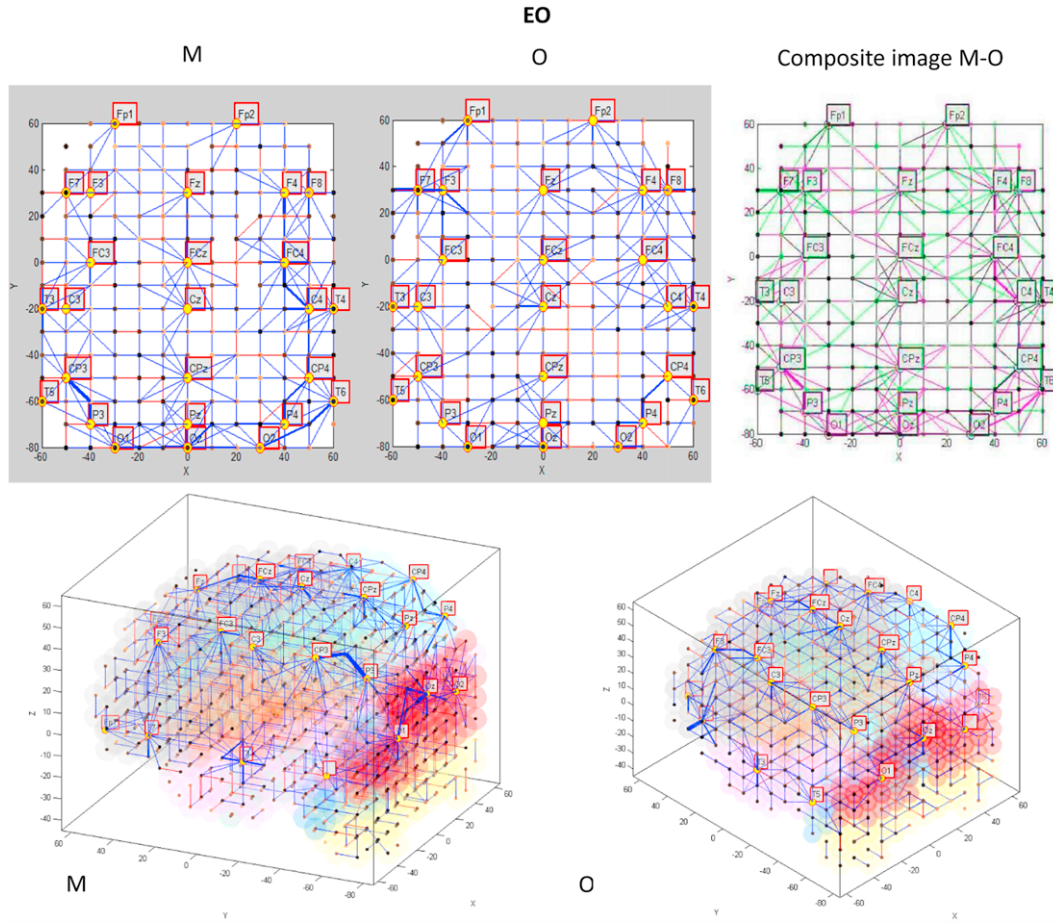


Fig. 4d. NeuCube connectivity obtained after training the SNNc with the EEG data recorded during the EO state from all subjects who belonged to either the M group or the O group. The top figures show the (x, y) projection only of the 3D SNNc, while the bottom figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite image (top right-hand side figure) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for M group) and green regions (for O group) show where the intensities are different.

- Further application for the study of EEG STBD in relation to understanding brain functionality, e.g. longitudinal study on patients undertaking methadone treatment in terms of defining any cognitive fluctuation across time; development of a gene regulatory network (GRN) optimisation module as part of the SNNc to improve the results and to study how certain genes may influence treatment; analysis of EEG data collected from people taking a single oral dose of “party pill” using NeuCube; analysis of EEG data collected from people with depression; analysis of brain data collected from people with schizophrenia.

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Appendix A. Some equations detailing the functionality of NeuCube (Kasabov, 2014)

The following equations describe the implementation of the main algorithms of the NeuCube-based model used in this study. The spike encoding method used in this study is the TBR encoding algorithm. A self-adaptive bi-directional threshold (TBR_{thr}), which is applied to the EEG signal $x(t)$ as follows:

$$TBR_{thr} = \mu + s\sigma \quad (A.1)$$

where μ is the mean of the differential signal with respect to time, $x(t) = \{x_{t_2} - x_{t_1}, x_{t_3} - x_{t_2}, \dots, x_{t_n} - x_{t_{n-1}}\}$, calculated by using all samples; σ is its standard deviation; s is a scale parameter of σ .

The TBR_{thr} is used to generate two types of spike sequences, a positive spike train corresponding to the signal increment, which is mapped to a specific input neuron in the SNNc; a negative spike train, corresponding to the signal decline, which is mapped into another input neuron of the SNNc that is placed in the same position as the positive one. Both kinds of input neurons are further connected with other neurons through connectivity initialisation and STDP learning.

The small world (SW) connectivity rule is applied to the NeuCube initialisation. In the SNNc, let i and j be a pre-synaptic and post-synaptic neuron respectively. Then, the distance

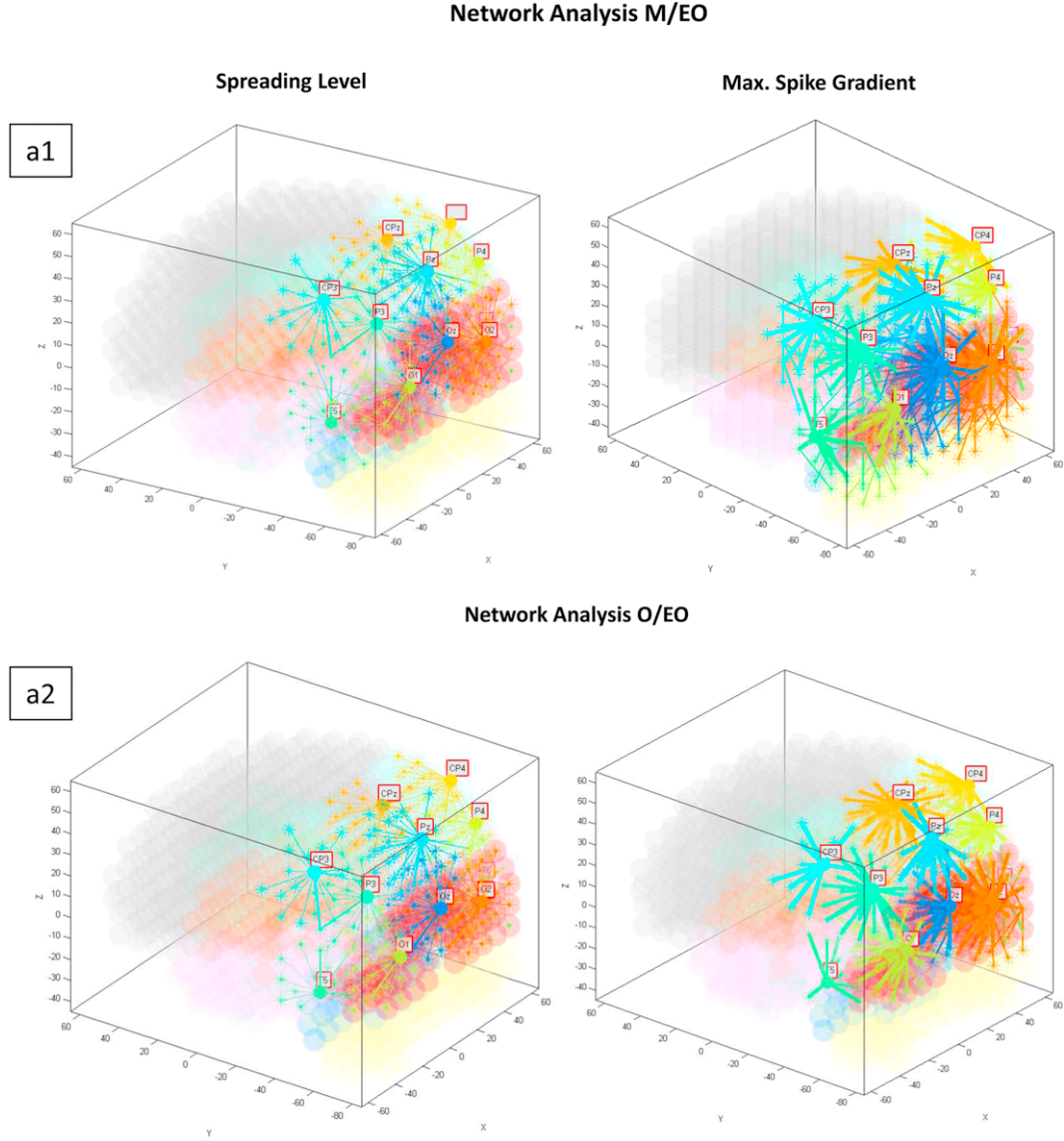


Fig. 4e. NeuCube network connectivity and spiking activity analysis per class – M group (a1) and O group (a2) – obtained for the EO state. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, Oz, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

between these two neurons is calculated as the Euclidean distance $d(i, j)$, based on their (x, y, z) coordinates. Initial connections are randomly generated, however, each neuron of the cube can connect only to its neighbouring neurons within a distance threshold D_{thr} , which is a proportion of the maximum Euclidean distance between two neurons. This is compute in Eq. (A.2):

$$D_{thr} = \max(d(i, j)) p \quad (A.2)$$

where p is the SW connectivity parameter. The initial connections weights are calculated as the product of a random number $[-1, 1]$ and the multiplicative inverse of $d(i, j)$. 20% of these weights are randomly selected to be negative, which represents the inhibitory connections weights, while 80% of them are positive, which represents the excitatory connections weights. To emphasise the significance of the input neurons in the SNNc, their connection weights are doubled with respect to the other neurons.

The neurons of the cube are modelled as LIF neurons. The action potential v_j of a neuron j increases with every input spike S_i from neuron i according to its connection ($c_{i,j}$) and depending on the frequency/time of the incoming spikes. When the v_j reaches the

firing threshold Θ , then an output spike S_j is emitted and the neuron potential is reset to zero.

$$S_i = \begin{cases} 1 & v_j \geq \Theta \\ 0 & \text{otherwise.} \end{cases} \quad (A.3)$$

The membrane potential will keep to zero for the length of its refractory time (r). Between spikes, the membrane potential leaks according to the potential leak rate (l).

$$v_j(t) = \begin{cases} v_j(t-1) + w_j & r = 0 \\ v_j(t-1) - l & \text{otherwise.} \end{cases} \quad (A.4)$$

The STDP learning rule is applied in an unsupervised mode of learning for the SNNc to capture spatio-temporal relationships from the encoded data. The STDP follows the Hebbian learning rule, which describes the connection established between two neurons as stronger as their activation persists and repeats. In this study, this algorithm has not been implemented as a standard

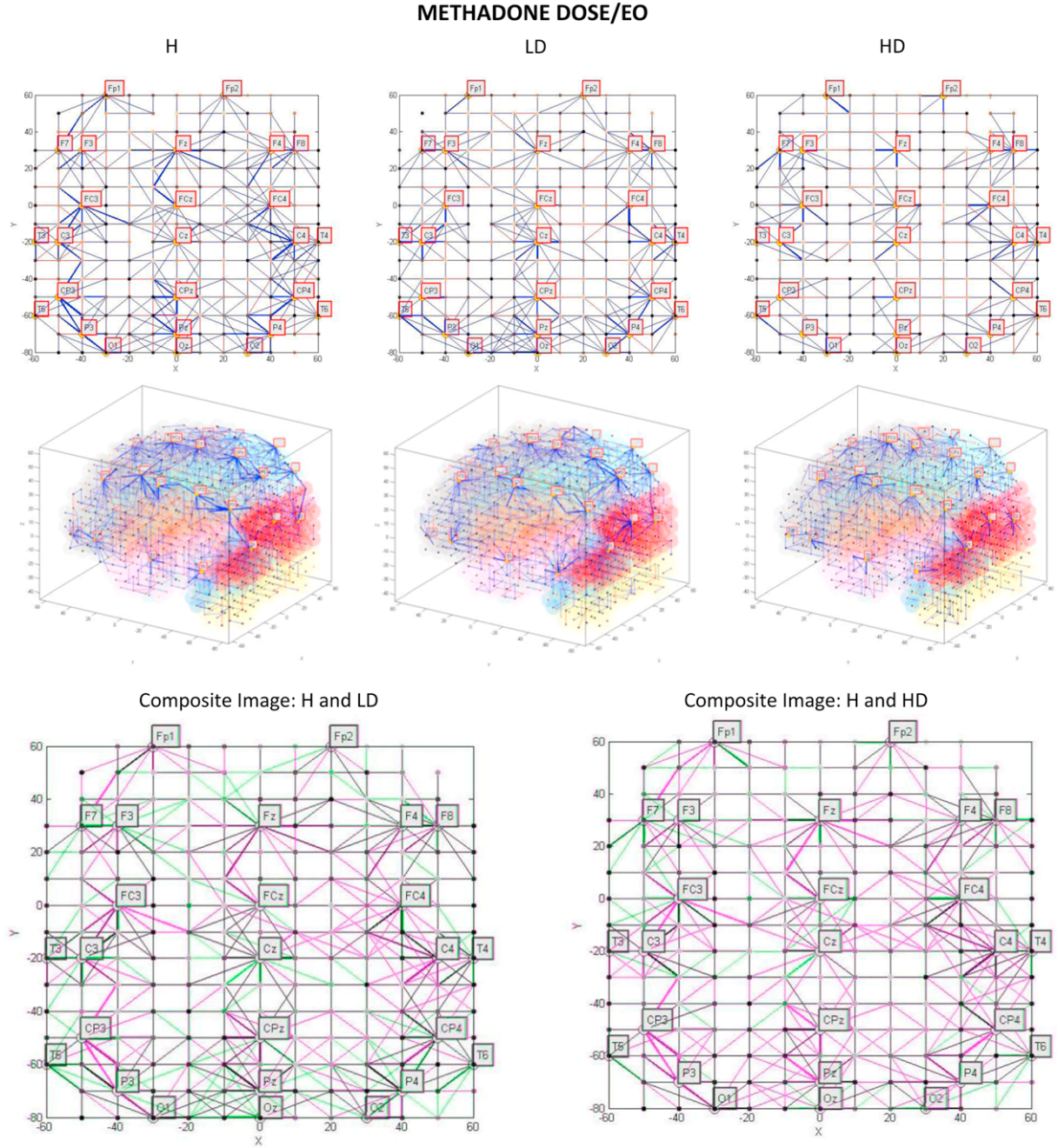


Fig. 4f. The SNNc connectivity after training it with EEG data corresponding to the EO task for the three classes—H, LD and HD of methadone. The top figures show the (x, y) projection only of the 3D SNNc, while the middle figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe). Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The brighter the colour of a neuron, the stronger its activity with a neighbouring neurons. Thickness of the lines also identifies the neurons enhanced connectivity. In yellow are the input neurons with their labels corresponding to the 26 EEG channels. The composite images (lowest figures) identify differences between connectivity of two groups of subjects overlaid in different colour bands. Grey regions in the composite image show where the two models have the same intensities. Magenta (for H group) and green regions (for either LD or HD group) show where the intensities are different.

exponential model, but described as follows:

$$w_j(t) = \begin{cases} w_j(t-1) \pm \alpha / \Delta t & t_j \neq t_i \\ w_j(t-1) & t_j = t_i. \end{cases} \quad (\text{A.5})$$

Depending on the order of the first incoming spike, if a neuron i fires before a neuron j then, its weight w_j increase otherwise it decreases, with respect to the STDP learning rate (α). This parameter linearly decays with respect to time variation: $\Delta t = t_j - t_i + 1$, the time elapsed between a spike was received from neuron i and a spike was emitted by the neuron j .

The deSNN classification algorithm (Kasabov et al., 2013) is applied here in a supervised mode of learning. According to this classifier, every training sample is associated to an output neuron, which is connected to each and every other neuron of the SNNc. The connection weights of these output neurons are all set to zero initially. Then, according to the rank-order (RO) learning rule, a connection weight between neuron i to neuron j , ($w_{i,j}$), is computed depending on a modulation factor mod and the order of

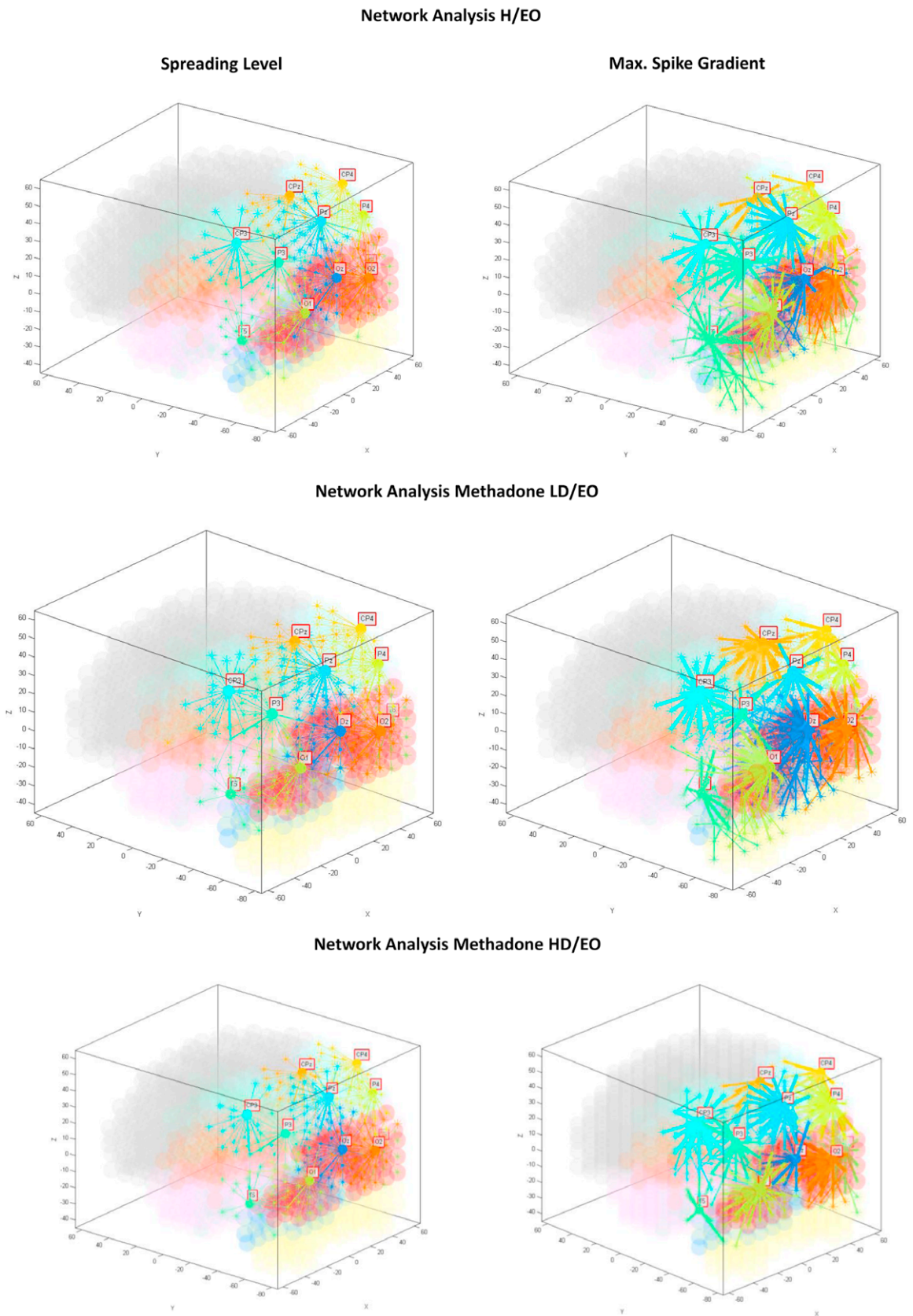


Fig. 4g. NeuCube model connectivity and spiking activity analysis per class – H, LD and HD groups – obtained for the EO task. The figures show the 3D SNNc together with the corresponding 8 brain functional areas (grey, frontal lobe; pink, temporal lobe; light-blue, parietal lobe; red, occipital lobe; light-yellow, posterior lobe; orange, sub-lobar region; light-green, limbic lobe; blue, anterior lobe), the spike spreading level (left) and the maximum spike gradient (right) of the 10 EEG channels allocated in the visual cortex (CP3, CPz, CP4, T5, T6, P3, Pz, P4, O1, O2) highlighted by different colours. Thickness of the lines identify a stronger activity between neurons.

Table B.1

Parameters settings used to classify O group versus M group (EC state) in a NeuCube classifier using RSSV method and in traditional machine learning classification methods (MLR, SVM, MLP and ECM). The parameters that influence traditional machine learning models are: class performance variance (CPV); the use of signal noise ratio (SNR) for feature selection method; normalised minimum radius of influence field cluster (MIF); normalised maximum radius of a cluster (MxIF); SVM kernel (Kernel); MLP training cycles (Tr. Cycles), hidden units (HU) output value precision (OVP), output function precision (OFP) and output activation function (OAF).

EC			
MLR		SVM	
CPV	0.05	Method	Inductive
		CPV	0.32
		Kernel	Polynomial
		Degree γ	1
MLP		ECM	
CPV	0.01	CPV	0.41
HU	5	MxIF	1
Tr. Cycles	500	MIF	0.01
OVP	0.0001	M of N	3
OFP	0.0001		
OAF	Linear		
NeuCube			
TBR	145.3	Con. Dist.	0.15
Refr. time	6	P. leak rate	0.002
STDP	0.01	Thr. of firing	0.5
Mod	0.4	Drift	0.25

Table B.2

Parameters settings used to classify O group versus M group (EO state) in a NeuCube classifier using RSSV method and in traditional machine learning classification methods (MLR, SVM, MLP and ECM). The parameters that influence traditional machine learning models are: class performance variance (CPV); the use of signal noise ratio (SNR) for feature selection method; normalised minimum radius of influence field cluster (MIF); normalised maximum radius of a cluster (MxIF); SVM kernel (Kernel); MLP training cycles (Tr. Cycles), hidden units (HU) output value precision (OVP), output function precision (OFP) and output activation function (OAF).

EO			
MLR		SVM	
CPV	0.14	Method	Inductive
		CPV	0.56
		Kernel	Polynomial
		Degree γ	1
MLP		ECM	
CPV	0.04	CPV	0.18
HU	5	MIF	1
Tr. Cycles	500	MIF	0.01
OVP	0.0001	M of N	3
OFP	0.0001		
OAF	Linear		
NeuCube			
TBR	33.16	Con. Dist.	0.15
Refr. time	6	P. leak rate	0.002
STDP	0.01	Thr. of firing	0.5
Mod	0.4	Drift	0.25

the first incoming spike, $order(i, j)$, as follows:

$$w_{i,j} = mod^{order(i,j)}. \quad (A.6)$$

Then, the new connection weights will change according to the spike driven synaptic plasticity (SDSP) learning rule using a drift parameter, which is used to modify the connection weights to take into account the occurrence of following spikes with respect to time $S_i(t)$; i.e. if there is a spike arriving from neuron i at time t after the first one was emitted the weight increases otherwise it

decreases.

$$w_{i,j}(t) = \begin{cases} w_{i,j}(t-1) + drift & S_j(t) = 1 \\ w_{i,j}(t-1) - drift & S_j(t) = 0. \end{cases} \quad (A.7)$$

Appendix B

See Tables B.1 and B.2.

Appendix C. Supplementary data

Supplementary material related to this article can be found online at <http://dx.doi.org/10.1016/j.neunet.2015.03.009>.

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A.6 Modelling Absence Epilepsy Seizure Data in the NeuCube Evolving Spiking Neural Network Architecture

The study presented in Chapter 9 resulted in a paper (Capecci, Espinosa-Ramos et al., 2015) that was published by IEEE in the *2015 International Joint Conference on Neural Networks (IJCNN)*.

Modelling Absence Epilepsy Seizure Data in the NeuCube Evolving Spiking Neural Network Architecture

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Abstract—Epilepsy is the most diffuse brain disorder that can affect people’s lives even on its early stage. In this paper, we used for the first time the spiking neural networks (SNN) framework called NeuCube for the analysis of electroencephalography (EEG) data recorded from a person affected by Absence Epileptic (AE), using permutation entropy (PE) features. Our results demonstrated that the methodology constitutes a valuable tool for the analysis and understanding of functional changes in the brain in term of its spiking activity and connectivity. Future applications of the model aim at personalised modelling of epileptic data for the analysis and the event prediction.

Keywords—Spiking Neural Networks, EEG, NeuCube, Epilepsy, Childhood Absence Seizures.

I. INTRODUCTION

Epileptogenic processes are hyper-synchronization of the electrical neural activity. It is still unknown the cause that produces them, however, there is a hypothesis that they may occur in different areas of the brain indiscriminately. The critical area associated with the epileptogenetic event is called epileptogenetic zone. This is responsible of recruiting other areas until the brain triggers the seizure. This process can be seen as a network-event rather than a local event. Thus, the problem to localise and study the epileptogenetic zone is of great interest to neuroscientists. Spatio-temporal brain data (STBD) and especially EEG data is widely used to record changes of brain activity during seizures at a millisecond time scale. It allows us to obtain knowledge about frequency, time and space of the epileptogenetic events. When a subject experiences a seizure, he/she needs to undergo

recording of several EEGs. This implies inpatient or day-hospital care and, if epilepsy is diagnosed, the patient must undergo further several EEG recordings in order to assess the evolution of the disease and to monitor the effects of the treatment. Once the EEG has been recorded (which can last for minutes to days) a careful review of the entire recording is needed, in order to detect the presence of critical events and to come up with a diagnosis. In clinical practice, while reviewing the EEG, the neurologist manually scrolls through the EEG and visually detects seizures (ictal states) and seizure-free intervals (inter-ictal states), so that he/she can evaluate the events locally in space, electrode per electrode. The neurologist usually visualizes only 20 seconds at a glance, scrolling ahead till the end of the recording. Thus working with EEG data means handling “big data” and all the technologies that can support the neurologist in dealing with this huge amount of data, will certainly improve epileptic people’s quality of life as well as facilitate the neurologist’s work.

Furthermore, many results reported in the literature suggest that seizures are not completely random and unpredictable events, which means that they are part of a more complex network phenomenon, a sort of “epileptogenic process” that, for unknown reasons, arises, evolves, and finally results in a seizure. Based on such hypothesis, one should wonder *when*, *where* and *why* abnormalities in the electrical activity arise in the brain and *how* they evolve, recruiting other areas. So far, no tool has been developed in order to monitor such mechanisms which, if discovered and explored, would allow for a much deeper understanding of the pathology that could lead to novel therapeutic perspectives. The core of such a tool would be an algorithm, meant for the extraction of mathematical

descriptors from EEG signals, which would be able to follow the evolution of the dynamics of cerebral electrical activity and to identify the transition from the inter-ictal stage to the pre-critical stage, thus detecting possible impending seizures (early seizure detection).

Aiming at this purpose, in this study we proposed a spatial-temporal model to study the development of seizures, in order to: automatically mark the critical events on the recording; provide deep and novel diagnostic information about brain networks (off-line utility); and to provide a warning tool in case of high probability of an impending seizure (on-line utility). In already published studies [1], [2], we analysed spatial-temporal EEG signals based on ordinal measures of patterns through PE. There, long EEG recordings (minutes to hours before seizure onset) have been analysed in order to check whether the epileptogenic process in absence seizures actually corresponds to the model of a “jump” transition of the underlying dynamical system or a gradual transformation is detectable in advance. PE was used to convert real EEG signals into motifs neglecting amplitude of signals and excluding any dependence on the effect of the reference electrode.

In this paper, we analysed the dynamics of the epileptic events through the PE topographies by means of an evolving spatio-temporal data machine (eSTDM) based on neuromorphic, brain-like information processing principles. In particular, the methodology is based on the NeuCube framework [3]. This model utilises SNN as major processing modules. Data can be classified and the SNN cube (SNNc) analysed in term of connectivity and spiking activity generated during the learning process. This helps us to study and reveal spatio-temporal patterns retained in the data and to localise them in specific areas of the brain.

The paper is constructed in the following way: section II presents the problem and the data available; section III describes the NeuCube-based methodology used for the study; section IV reports the results and the conclusions; and section V proposes future work that we are currently undertaking.

II. EPILEPTIC EEG ANALYSIS WITH SNN

A. Absence Seizures

We based our study on Childhood Absence Epilepsy (CAE) data, a common idiopathic generalized epilepsy syndrome [4], [5]. CAE is usually present in children between age of 4 and 10 years, peaking at age 6-7 years. A strong genetic predisposition is evident, with occurrence more often in girls than in boys. The very frequent absences (several to hundreds a day) exert a negative impact on an otherwise normal child. Untreated children often exhibit learning and attention difficulties because of their alterations of consciousness. The pediatric neurologists main objective is to neutralize all absences as long as the side effects.

B. EEG data Description

Standard EEG recording from a patient, diagnosed with CAE, was used for training and testing. The patient was a young girl and her age was 9. The EEG was acquired using a 16-channel device (Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, P3, P4, O1, O2) according to the international 10/20 system with Cadwell Easy II (Cadwell Laboratories, Inc., Kennewick, WA). All channels were filtered with a pass

band of 0.53-25 Hz, and digitised at a rate of 200 Hz. In total, 8 paroxysms longer than 2 seconds were identified by a board-certified clinical neurophysiologist. In total, 15.8 minutes of electroencephalogram data were recorded. All data analysis was performed using MATLAB (The MathWorks, Inc., Natick, MA).

C. Permutation Entropy

The n -channels EEG recording was processed by means of sliding temporal windows. The EEG samples were buffered in 5 seconds non-overlapping windows (since the sampling rate is 200Hz, a window includes $N=1000$ EEG samples), then PE was estimated, channel by channel and window by window. Each EEG time window includes n time series, where n is the number of EEG channels. This window is stored in the computer as a nxN matrix. Within each window, a sample of PE per channel is computed and the n values are arranged in a $nx1$ PE vector, therefore, a nxN EEG matrix corresponds to a $nx1$ PE vector thus a compressed temporal representation of the original time series is produced. In order to calculate PE, each time series x was mapped into a m -dimensional space, with m being the embedding dimension and L being the time lag. Vectors X_t were constructed selecting m equally spaced samples from x , starting from time point t :

$$X_t = [x(t), x(t+L), \dots, x(t+(m-1)L)]^T \quad (1)$$

The values of X_t are reshaped in an increasing order, the time points are renamed yielding Xr_t , a reshaped version of X_t : $Xr_t = [x(t+(t_1-1)L), x(t+(t_2-1)L), \dots, x(t+(t_m-1)L)]^T$. Therefore, each vector X_t can be considered uniquely mapped onto a symbol vector $\pi = [t_1, t_2, \dots, t_m]$. The vector π is a sequence of time points, hence a symbol. The frequency of occurrence of each possible π is indicated as $p(\pi)$, which represents the frequency of occurrence of the specific vector π in the time series under analysis, normalized by $N-(m-1)L$ where N is the number of samples of the time series x . PE is finally computed as:

$$H(m) = - \sum_{i=1}^{m!} p(\pi_i) \ln(p(\pi_i)) \quad (2)$$

Where $\log$ is the natural logarithm and $m!$ is the number of the possible permutations. Since $H(m)$ can maximally reach $\ln(m!)$, PE is generally normalized as:

$$H_n(m) = \frac{\sum_{i=1}^{m!} p(\pi_i) \ln(p(\pi_i))}{\ln(m!)} \quad (3)$$

D. The NeuCube SNN Architecture

The eSTDM NeuCube was first introduced in [3], [6] and then developed in [7], [8]. It is a multi-modular computer systems designed to deal with large and fast spatio-/spectro-temporal data. It is inspired by the main biological principles that regulate learning and memory dynamics of spiking neurons that make up its network. A block diagram of the eSTDM NeuCube is depicted in Fig. 1. It consists of the following modules:

- Input information encoding module.
- Input mapping module.

- 3D SNN module (the SNNc).
- Output classification/regression module.
- Gene regulatory network (GRN) module (Optional).
- Parameter optimisation module.
- Visualisation and knowledge extraction module.

The input module transforms the raw data vectors into trains of spikes. The encoded STBD is then presented to the main module, the 3D SNNc, into certain areas of the cube that have the same 3D coordinates as the data source locations during collection.

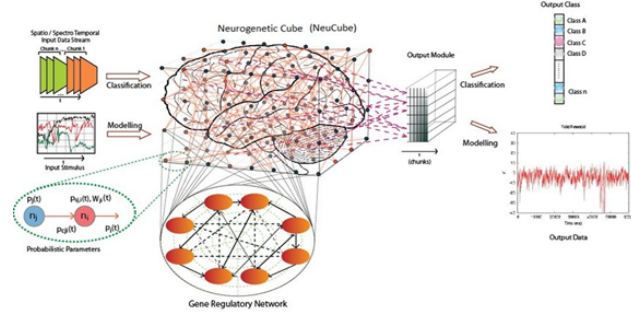


Fig. 1. A general NeuCube architecture of eSTDM for STBD modelling with its three main modules: input data encoding module; a 3D SNNc module; an output evolving classification module [3]. An optional Gene Regulatory Network (GRN) module can be incorporated if gene information is available. The spiking neurons can be implemented as the simple leaky integrate and fire model or probabilistic models (shown in the lower left section).

NeuCube has already demonstrated its ability to classify and extract new knowledge from both EEG [9]–[11] and functional magnetic resonance imaging (fMRI) [12] cognitive data and to other type of spatio-temporal data for personalised disease prognosis [13]. This paper contributes to the set of methods related to the NeuCube with the introduction of a new methodology for the analysis of spiking activity and connectivity of EEG data recorded from a CAE patient, using the information available from the PE features.

III. THE PROPOSED NEUCUBE METHODOLOGY FOR THE STUDY OF CAE PE DATA

The NeuCube-based methodology schematized in Fig. 2 consists of following procedures and parameters:

- 1) Every data vector was transformed into a spike train using the address event representation (AER) algorithm [14]–[16]. This is calculated as a bi-directional threshold (AER_{thr}), which is applied to the signal $x(t)$ as following:

$$AER_{thr} = \mu + s \sigma \quad (4)$$

where μ is the mean of the differential signal with respect to time, $x(t) = \{x_{t_2} - x_{t_1}, x_{t_3} - x_{t_2}, \dots, x_{t_n} - x_{t_{n-1}}\}$, calculated by using all samples; σ is its standard deviation; s is a scale parameter of σ . The AER_{thr} is used to generate two types of spike sequences, a positive spike train corresponding to the signal increment, which is

mapped to a specific input neuron in the SNNc; a negative spike train, corresponding to the signal decline, which is mapped into another input neuron of the SNNc that is placed in the same position as the positive one.

- 2) Then, the input spike sequences are presented to an evolving brain-mapped network of spiking neurons - the SNNc. Each of these neurons represented the centre coordinates of a 1 cm^3 area of a human brain template known as the Talairach Atlas [17]–[19]. Thus, the SNNc reflects the number of input variables, the Brodmann area associated with them and the size of the data available.
- 3) The neurons of the cube are initialised as a “small-world” (SW) connected networks and their initial connections weights are calculated as the product of a random number $[-0.1, +0.1]$ and the multiplicative inverse of the Euclidean distance $d(i, j)$ between a pre-synaptic i and a post-synaptic neuron j (calculated according to their (x, y, z) coordinates). 20% of these weights are randomly selected to be negative (inhibitory connections weights), while 80% are positive (excitatory connections weights). The $d(i, j)$ also depends on a distance threshold D_{thr} calculated as:

$$D_{thr} = \max(d(i, j)) p \quad (5)$$

where p is the SW connectivity parameter.

- 4) The neurons of the cube are modelled as leaky integrate and fire (LIF) neurons [20]. If an initial connection $c_{i,j}$ between two neurons is established, then, the action potential v_j of a neuron j increases according to the time and the order of the incoming spike S_i from neuron i . The v_j increases until a firing threshold Θ , then, it resets and an output spike S_j is emitted.

$$S_i = \begin{cases} 1 & v_j \geq \Theta \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

The membrane potential will keep to zero for the length of its refractory time (r). Between spikes, the membrane potential leaks according to the potential leak rate (l).

$$v_j(t) = \begin{cases} v_j(t-1) + w_j & r = 0 \\ v_j(t-1) - l & \text{otherwise} \end{cases} \quad (7)$$

- 5) The SNNc is trained in an unsupervised mode using the spike timing dependant plasticity (STDP) [21] learning rule. This Hebbian rule describes the connection between two neurons as stronger as their activation persists and repeats. This is implemented as following:

$$w_j(t) = \begin{cases} w_j(t-1) \pm \alpha / \Delta t & t_j \neq t_i \\ w_j(t-1) & t_j = t_i \end{cases} \quad (8)$$

where α is the STDP learning rate, Δ_t is the time elapsed since the last spike was emitted by neuron j . If a neuron i fires before a neuron j then, its weight

$w_{j,i}$ increases, otherwise, it decreases.

- 6) The output classifier is trained in a supervised mode using dynamic evolving SNN (deSNN) [22] algorithm, which combines the rank-order (RO) learning rule [23] and the STDP [21] rules. According to this algorithm, every trained sample is associated to an output neuron that is connected to every other neuron of the cube. In case of the NeuCube model, the inputs to the deSNN classifier are all neurons of the SNNc. Initially, the connection weights $w_{i,j}$ between the input neuron i and the output neuron j are all set to zero. Then, according to the rank-order (RO) learning rule, they are computed as following:

$$w_{i,j} = \text{mod}^{\text{order}(i,j)} \quad (9)$$

where mod is a modulation factor and $\text{order}(i,j)$ is the order of the first incoming spike.

The new connection weights will be modified according to the spike driven synaptic plasticity (SDSP) learning rule. Implemented as:

$$w_{i,j}(t) = \begin{cases} w_{i,j}(t-1) + \text{drift} & S_j(t) = 1 \\ w_{i,j}(t-1) - \text{drift} & S_j(t) = 0 \end{cases} \quad (10)$$

where drift is a parameter used to modify the connection weights and $S_i(t)$ represents the occurrence of the spikes arriving from neuron i at a time t after the first one was emitted.

- 7) The classification results are evaluated using repeated random sub-sampling validation (RRSV) or leave one out cross validation (LOOCV).
- 8) Steps (3) to (7) are repeated using different parameter values in order to optimize the classification output. The best performing model can then be recorded for further uses.
- 9) The trained SNNc is visualised, its connectivity and the dynamic spiking activity are analysed for a better understanding of the data and the brain processes that generated it including changes of brain functionality across conditions and subject groups.

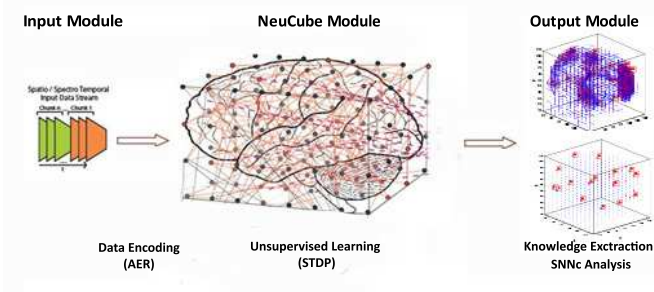


Fig. 2. A graphical representation of the NeuCube-based methodology used for PE data modelling and brain connectivity analysis.

IV. RESULTS AND DISCUSSION

For our experimental case study, data was first classified, to establish the effectiveness of the PEs as classification features.

Then, the SNNc was visualised and analysed in a step-wise mode to study the activity and connectivity generated during learning.

As shown in Fig. 3, the 187 PE vectors calculated from the 16-channel EEG data corresponded to 7 ictal (PE 2-5, 25, 34-41, 63-67, 95-99, 129-132 and 179-183) and 8 equivalent interictal states. This data was propagated through the cube generating a spiking activity according to the time and frequency of the encoded spike trains. Thus, a trained NeuCube represented a persons dynamic model of epileptic event progression over a short period of time.

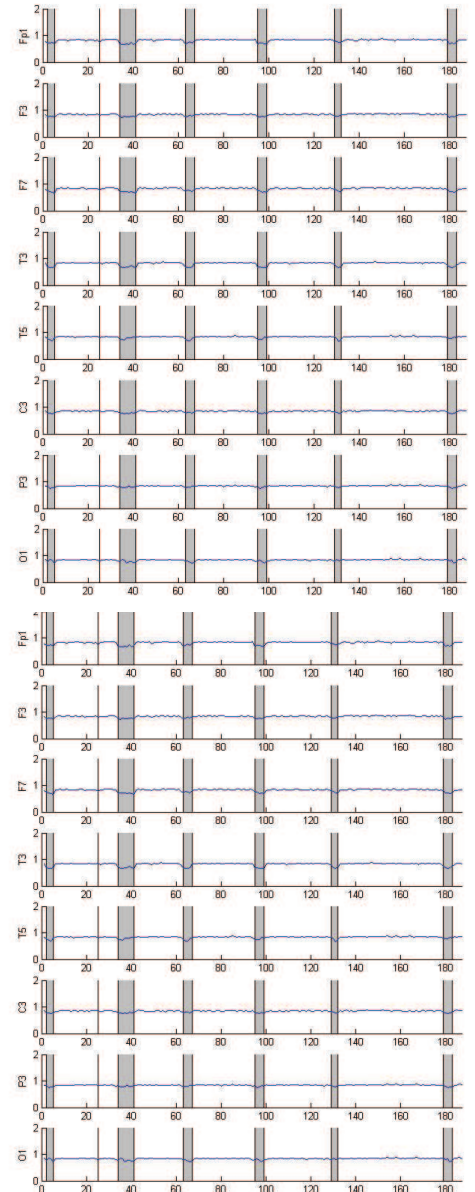


Fig. 3. Sequence of PE obtained from the 16-channel EEG data. In grey colour are the PE corresponding to the ictal state, while the other PE are associated to the interictal states.

A. Classification

For the classification experiments, the 187 PE levels were divided into the two respective classes. Excluding the samples containing just one of the PE topography, we obtained 6 samples for class 1 (ictal state) and 7 samples for class 2 (interictal state).

The encoded spike trains, obtained from the 187 PE vectors, were entered into a 3D grid of 1471 LIF neurons by entering them to the 16 corresponding brain-mapped input neurons. Data was first learnt in the SNNc in an unsupervised way and then classified *via* supervised learning method in a trained deSNN classifier. The classification results were evaluated using LOOCV and they are reported in table I.

TABLE I. NEUCUBE CLASSIFICATION RESULTS EXPRESSED AS ACCURACY PERCENT.

NeuCube Classification Results	
Ictal State	100
Interictal State	71
Overall Accuracy	86

The high classification accuracy (100% for class 1 and 71% for class 2) obtained *via* the NeuCube methodology proved the model ability to manifest this difference and also that the two classes were in fact two distinguishable groups when using PE values as features. Table II reports the NeuCube parameters used to obtain these results.

TABLE II. PARAMETER SETTING USED TO OBTAINED THE RESULTS REPORTED AS NEUCUBE CLASSIFICATION ACCURACY.

SNNc Parameter Setting		
Threshold of Firing: 0.5	Potential Leak Rate: 0.002	STDP: 0.5
Refractory Time: 2.5	SW distance: 0.15	AER Threshold 0.003
deSNN mod: 0.4	deSNN drift: 0.25	Time to Train: 1

These parameters were found after running a grid search in which 100 SNNc network configurations were evaluated regarding their test accuracy using RRSV (50% of the data was used for training and 50% for testing).

B. SNNc Analysis

In this case, the 187 PE sequences were used to train a NeuCube model in a step-wise manner. We looked for the first time at the dynamic of both spiking activity and connectivity during learning using the information available from the PE topographies. This threw more light on the functional changes in the brain provoked by the epileptic event and more importantly it helped to locate where these changes took place.

To analyse and visualise the cube activity, we have used again a 3D SNNc of 1471 brain-mapped spiking neurons. The data was learnt in the SNNc in an unsupervised way and then the SNNc activity was analysed and interpreted for a better understanding of the data and to identify differences between brain states.

Figure 4 show the NeuCube evolution over the 187 time points obtained during STDP learning. Table III reports the parameters settings used to obtain these results.

On the entire series of PE, we are interested in the spiking activity and connectivity generated by each of the 6 ictal states and the 7 relative interictal states. The first two sequences of

TABLE III. PARAMETERS SETTINGS USED FOR THE STEP-WISE SNNc ANALYSIS.

SNNc Analysis Parameter Setting		
Threshold of Firing: 0.5	Potential Leak Rate: 0.002	STDP: 1
Refractory Time: 2	Long Dist. Possibility: 0.01	Weight Threshold 0.08

PE topographies associated with a seizure (PE 2-5 and PE 25) do not show a particular change in terms of connectivity or spiking activity. The third series of PE related to an epileptic event (PE 34-41) represents the longest sequence of PE topographies. Here, the F4 electrode appears to be the focal point in term of enhanced connectivity. Also, new connections are formed in the (right) frontal polar area, electrode Fp2. The subsequent ictal state (PE 63-67) provokes the establishment of new connections in the right hemisphere especially in the anterior region of the frontal area, but also by the left hemisphere, at F7, F3 and FP1 positions. By the next sequence of ictal PE topographies (PE 95-99), the new connections have now consolidated and also new are formed by the (right) occipito-parietal area, channels O2 and P4. By the next ictal section (PE 129-132), most of the connections generated by the (right) frontal and occipito-parietal cortex and the (left) centro-temporal area keep consolidating, while the central regions are not affected. The last series of PEs associated with a seizure (PE 179-183), clearly show that most of the connections in the SNNc model are formed around the input neurons especially in the right frontal portion of the brain, while no connections are evolved in the central line at all.

Given a certain electrode and its PE level, we did not expect high PE to be linked to high degree of connections, we only expect PE to match the complexity degree of the electrical activity of the cerebral region covered by that electrode. PE levels can give us information that are local in space, depicting the topography over the scalp. It is a way to see which electrode showed similar PE levels, but we obtained information about brain connectivity only through our proposed NeuCube model.

Neurologists address the frontal-temporal regions as “critical” in absence seizure patients and this seems to be in line with our modelling results and in particular with the ictal states associated to the PE 67, 99, 132, 183.

V. CONCLUSION AND FUTURE WORK

The goal of the proposed study has been to develop a personalised model able to properly learn over time epileptic events in terms of space and time, so that the information can be dynamically visualised and analysed and possibly the epileptogenic event predicted.

Our results demonstrated that the methodology constitutes a valuable tool for epileptic EEG data analysis and understanding. However, more extensive evidence is needed to establish the feasibility of a purely data driven diagnosis method for CAE diagnosis. So far, our results are promising and NeuCube is planned to be used for molecular and genetic analysis of the disease and as a personalised model for the understanding of functional changes in the brain and for the prediction of epileptic events from new data.

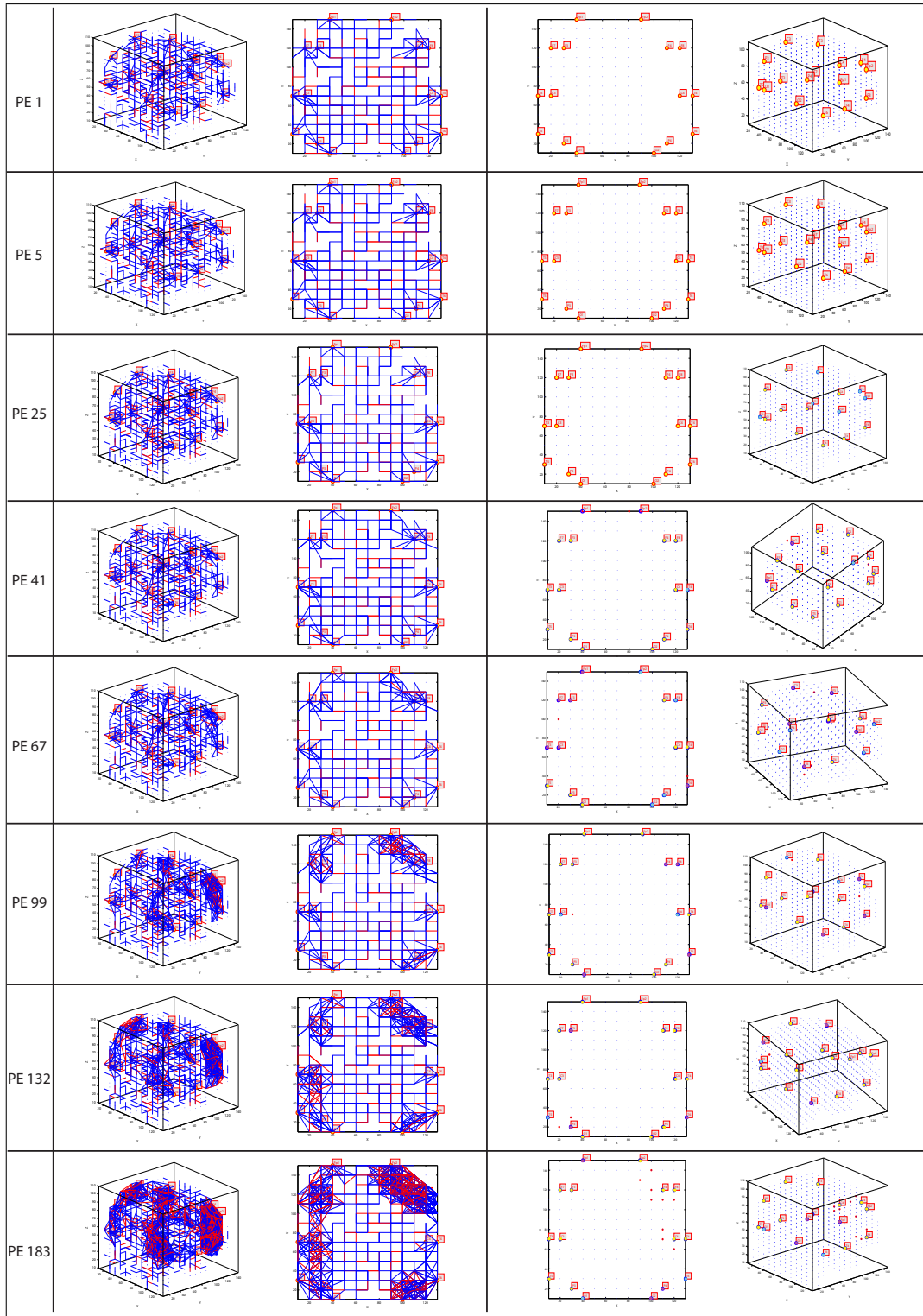


Fig. 4. Step-wise SNNc activity during STDP learning on the 187 PE topographies. The figure shows the evolution of connectivity of the 3D SNNc and its 2D plane. The top image presents the SNNc connectivity obtained from the first PE associated to the initial interictal state (PE 1). The subsequent SNNc images result from training the cube with one PE associated to the seven following ictal events (PE 5, 25, 41, 67, 99, 132 and 183). (left) Blue lines are positive connections (excitatory synapses), while red lines are negative connections (inhibitory synapses). The input neurons are identified by their labels corresponding to the 16 EEG channels. (right) The active spiking neurons are identified in red, while in blue the inactive neurons. Also, in magenta are the positive spiking input neurons and in cyan the negative spiking inputs. Yellow identifies the absence of a spike in the input neurons.

NEUROGENETIC NEUCUBE FOR THE ANALYSIS OF NEURORECEPTOR ACTIVITY RELATED TO CAE

A neurogenetic model of a neuron is proposed and studied in [24], [25]. It utilises information about how the main neuroreceptors, and the genes that expressed them, affect the spiking activities of a neuron. This model can be also optimised using a Gene/Protein Regulatory Network (GRN), controlling the dynamic interactions between genes/proteins over time, which affects the post synaptic potential of the network's neurons.

In this work, we used Hebbian learning rules to adapt the synapse amongst neurons, specifically the STDP as a way of competition for control of the timing of postsynaptic action potentials. However, the synapses adaptation can also be implemented through dynamic mechanisms involving the growth or decay of some neuroreceptors. They affect the spiking activity of a neuron such as *fast excitation*, *fast inhibition*, *slow excitation*, and *slow inhibition*. In turn, each neuroreceptor is affected by other neuroreceptors, therefore, the contribution of each neuroreceptor g_r to a neuron synapse in a time t might be computed as:

$$g_r(t) = g_r(t-1) + f(g_1(t-1), g_2(t-1), \dots, g_n(t-1)) \quad (11)$$

where $g_i(t-1)$ is the last state of an i th receptor, and the function f is the positive/negative contribution to g_r . Such that the synaptic weight g_{wij} between a neuron n_i and a neuron n_j is calculated as the difference of the sum of the excitatory receptor gains g_e and the sum of the inhibitory receptor gains g_h :

$$g_{wij} = \sum_{i=1}^n g_e - \sum_{i=1}^n g_h \quad (12)$$

This model, called Neurogenetic Neucube (NeuCube_{NG}), has been proposed in [26]. It can automatically balance the synaptic strengths making postsynaptic firing irregular but sensitive to presynaptic potentials such as the STDP like rules.

We plan to apply the NeuCube_{NG} to CAE data to study how the regulation of GABA-mediated inhibitory mechanisms, which are believed to be involved in the neural hypersynchronization responsible of type of epilepsy, can affect the post synaptic potential of a neuron [27]. This type of mechanisms are mediated by pharmacological treatments [28] and we believe the NeuCube_{NG} could be of great help for clinicians to analyse the possible changes in neural connectivity.

NEUCUBE FOR THE PREDICTION OF EPILEPTIC SEIZURES

NeuCube can be used also for dynamic predictive modelling based on neuromorphic learning. The acquisition of more CAE data and their comparison to healthy subjects can be used to create such model that learns the progression of the epileptic events of a person over time. The brain-like mapping of the cube can be used to study the specific characteristics of the epileptic events, the area of the brain where the event occurs and eventually to predict future epileptogenetic events based on the initial information.

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A.7 Neuroreceptors Dependent Plasticity (NRDP) Learning Rule for Spiking Neural Networks

The study presented in Chapter 11 resulted in a paper (Espinosa-Ramos, Capecci & Kasabov, 2015) that has been submitted to *Neural Networks Journal*. The submitted version of the full text of the paper is provided here.

Computational Neurogenetic Modelling Through Neuroreceptor Dependent Plasticity (NRDP) Based on Spiking Neural Networks

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Abstract

We introduce a new method for learning in spiking neural networks (SNN), based on the regulatory activity of Glutamate and GABA neurotransmitters and their main neuroreceptors: NMDA, AMPA, GABA_A, and GABA_B. The neuroreceptor-dependent plasticity (NRDP) model is implemented and demonstrated in a large-scale spiking neural network environment, NeuCube, for modelling EEG data from cognitive experiments. We show that the NRDP model can manifest the same behaviour as a SNN model based on the spike-timing-dependent plasticity (STDP). In addition, we show that the NRDP model can be used to study the behavior of a SNN model under different changes in the neuroreceptors. This makes it a promising tool for modelling EEG data, for instance, data obtained from subjects with Alzheimer's Disease or other cognitive impairment, and also for the development of novel models that utilise genetic information. We illustrate the method on original cognitive EEG data collected from 21 subjects. Through varying parameters of the neuroreceptors, we can study how changes of these parameters would affect the learning and memory ability of a subject. This can lead to new ways of early detection of Alzheimer's Disease or other cognitive impairments and better decisions for a more efficient treatment.

Keywords: Spiking neural networks, synaptic plasticity, Computational Neurogenetic Model, NeuCube, Hebbian rules.

1. Introduction

Over the last several decades, the increase in neurological disorders, especially cognitive impairment such as that arising from the early onset of Alzheimer's Disease (AD) [1], has created serious health problems with wider social consequences [2]. In response, the scientific community has focused considerable resources and effort on understanding the central nervous system and especially the mechanisms involved in learning and synaptic plasticity, since neurological decline initially affects these functions. New research and better techniques have resulted in a considerable amount of data being made available. However, a new problem has emerged: how to find a suitable technique in order to understand this information and make the best use of it.

In this context, the scientific contribution of information science, especially neuroinformatics, can play a pivotal role. Information science offers new computational techniques based on emulating the cognitive and learning functions of natural intelligent systems such as the human brain. However, many of the techniques already in use are not adequate, not only because the data preparation and filtering steps can take a considerable amount of processing time and cost, but also because they cannot represent the phenomena of study.

As a feasible paradigm, spiking neural network (SNN) constitute an important approach in neuroscience. They process and communicate information as real neurons do, raising the level of biological realism. Due to their more biologically realistic properties, they can be used to study the operation of neural circuits.

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SNN models rely on a learning mechanism known as synaptic plasticity for their computational power. Adjusting the synaptic weights can alter the flow of information through a neural network. When the strength of the incoming signal to a neuron is altered, the output signal will also change in strength.

A typical approach makes use of Hebbian learning [3], which is based on competition (*i.e.* between neurons' pre- and post-synaptic action potentials) such as *spike time dependent plasticity (STDP)* [4]. Other approaches are based on local competition (*i.e.* at a synaptic connection) through either synaptic current modifications, such as *transmitter-activated ion channels synapses* [5] and the *synaptic transmission model* [6], or dynamic mechanisms involving non-Hebbian rise and fall terms, *phenomenological model of dynamic synapses* [7] and *activity-dependent synaptic scaling* [8]. A computational model describing the input current of a neuron as a function of the excitatory and inhibitory conductance of glutamatergic and GABAergic synapses has been proposed [9]. In [10] the author proposed a computational neurogenetic model of a probabilistic spiking neuron that uses three probability parameters and calculates the neuron post-synaptic potential (PSP) as the contribution of four different types of synapses (fast excitatory, slow excitatory, fast inhibitory and slow inhibitory) that affect the connections between neurons as it was introduced first in [11, 12].

In this paper, we propose a new computational neurogenetic model - a neuroreceptor-dependent plasticity (NRDP) model. This is a simplified model that incorporates dynamic mechanisms responsible for modifying neuronal synaptic plasticity through biochemical processes. It is based on local synaptic competition between activity of excitatory and inhibitory neurotransmitters/neuroreceptors. The model was implemented in an evolving spatio-temporal data machine (the NeuCube [13]), which is based on SNN. This SNN allows to model EEG and other brain data, but more importantly, it allows us to study the impact of neuroreceptors on the process of learning of EEG data in the SNN model and to further interpret the findings for the study of brain conditions.

As a case study, we used electroencephalography (EEG) data to classify different EEG patterns and identify functional changes in the neural activity. Spatio-temporal brain data (STDB) and especially EEG can provide valuable information for the research and study of cognitive activity in the human cortex as well as the study of cognitive impairment. It is an affordable technique, easy to manage and carry, and it is not considered an aggressive method for the subjects being studied [14]. It has therefore been used extensively for the study of brain functional changes under different conditions, including neurological disease and drug treatments [15, 16, 17, 18].

Together with the NeuCube architecture, the proposed computational neurogenetic modelling with the use of the NRDP introduces a new set of techniques in the area of neuro- and bio-informatics. This will allow us to better study cognitive brain processes in order to understand how the changes in neurotransmitter levels affect learning and memory processes. By analysing the connectivity and spiking activity generated within this model, the NRDP model offers a means by which treatments could be assessed and neurological disorders diagnosed.

In the next section, we discuss the main mechanisms that regulate learning and neural plasticity in the central nervous system as a biological inspiration for the proposed NRDP learning rule, and introduce the proposed NRDP model. In section 3 we report our results and conclusions for the case study of EEG data using the NeuCube methodology. Finally, we discuss a future work on how to extend the methodology and to apply it on other brain data.

2. Axodendritic Chemical Synapses and the Neuroreceptor Dependent Plasticity Learning Model (NRDP)

Various different kinds of synapses between two neural cells are found in the central nervous system, although axodendritic chemical synapses are the most numerous [19]. Here, the axon of a neural cell (the pre-synaptic cell) enables communication with the other (the post-synaptic cell) through chemical transmissions [20].

At an axon's terminal, molecules called neurotransmitters arrive, carrying stimuli for the target cell; they are released in the synaptic cleft, where they bind to their corresponding receptors located in the dendritic membrane. Depending on the type of neurotransmitter released, they either depolarise the membrane (*i.e.* excitatory current) and propagate the signal, or hyperpolarise it (*i.e.* inhibitory current) and suppress the signal [21].

2.1. Neurotransmitters and Neuroreceptors Involved in the Mechanisms of Learning

There are many types of neurotransmitters released in a synaptic cleft. The main excitatory neurotransmitter in the central nervous system is glutamate, whilst the main inhibitory neurotransmitter is γ -aminobutyric acid (GABA) [22]. The most important neuroreceptors activated by glutamate are the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPA) and the N-methyl-D-aspartate receptor (NMDAR) [23]. The AMPA mediates

fast excitatory synaptic response [24], whilst NMDAR is a ligand-gated and voltage-dependent channel related to slow excitatory response [25]. The inhibitory neurotransmitter GABA activates two main classes of neuroreceptors, GABA type A (GABA_A) and GABA type B (GABA_B). They regulate a fast and a slow inhibition of the neural action potential respectively [26, 27, 28].

In the hippocampus, complex biochemical mechanisms mediate and process cognitive activities such as learning and memory through the regulation of synaptic plasticity [29]. Several of them occur in both pre- and post-synaptic cells [29]. Two phenomena involved in this process are known as long-term potentiation (LTP) and long-term depression (LTD). Memory formation and modelling synaptic plasticity in the mammalian brain is broadly thought to depend on this bidirectional activity [30, 31]. LTP is responsible for the transfer of information from short-term memory to long-term memory by means of long and persistent depolarisation of the post-synaptic cell's membrane (*i.e.* repetitive firing stimuli). This mechanism is able to increase synaptic transmission efficiency [32] and was studied by Hebb [3], who postulated the theory known today as Hebbian learning.

These cognitive mechanisms involve the release of a high number of glutamate neurotransmitters by the pre-synaptic cell, which in turn provoke the post-synaptic cell to activate enough receptors and increase their synthesis according to the demand [29]. There, the NMDAR allows the influx of a significant quantity of stimulatory Ca^{2+} into the cytoplasm [33]. In fact, the influx of these cations is believed to start LTP induction by generating a series of cascade events that are responsible for altering synaptic strength [31]. The NMDAR is a slow excitation neuroreceptor and its plasticity depends mainly on the fast excitation of the AMPAR [29]. In more details, glutamate neurotransmitters in the synaptic cleft bind to both the NMDAR and the AMPAR causing the opening of the latter channel. Subsequently, the influx of Na^+ in the post-synaptic membrane causes its depolarisation. If the depolarisation event is strong enough, it will provoke the removal of the Mg^{2+} ion, which obstructs the NMDAR voltage-dependent channel, enabling Na^+ and Ca^{2+} to enter the cell [31]. For this reason, NMDAR is a slow excitation receptor and its plasticity, which determines LTP formation, depends on these properties.

In a single synapse, different types of receptors can be found [5, 19]. In hippocampal neurons, NMDAR is broadly found to coexist with GABA_A [34]. However, GABA_B can also modulate synaptic plasticity through NMDAR regulation in both pre-synaptic cells, by inhibiting Ca^{2+} and therefore limiting GABA release, and in post-synaptic cells, by mainly co-operating with GABA_A in inhibiting NMDAR activation [35, 23, 28]. The localisation of both glutamate and GABA receptors in post-synaptic cells depends on neurotransmitters demand, as they are found to move rapidly from where they are synthesised to where they are required in the membrane according to neurotransmitters level [23]. The onset of glutamatergic post-synaptic currents suppresses inhibitory functions of GABA receptors and *vice versa*, inhibitory currents increase proportionally with excitatory activation [36, 37, 27]. The balance of these two forces modulates the period of the synaptic activity [38, 27, 25] and that is why the neuroreceptors are highly correlated and modulated [34, 25]. This dependency is defined as “cross-talk” [34, 28].

Hippocampal neuron mechanisms can be applied to many other neurons encountered in the brain, as they are considered representative of several types of synapses [23]. Studying hippocampal activity is of high relevance for the understanding of neurological disorders, as this region is also one of the first to be affected by the onset of mild cognitive impairment and AD. One hypothesis focuses on the constant activation of NMDAR in AD. High intracellular Ca^{2+} leads to mitochondrial dysfunction [39]. Consequently, the constant activation of this receptor leads to a chronic over-activity with an abnormally high synaptic glutamate level under resting condition, with a correspondingly low amount of neurotransmitters left to be released into synaptic cleft during neural activity [33], leading to cellular dysfunction and neural death over a period of time [39].

The study of neural plasticity and its biochemical counterpart is fundamental to the analysis and understanding of the brain's cognitive activity and consequently the information provided by the STBD collected. In this paper, we use the principles of axodentritic chemical synapses to enable synaptic plasticity in a spiking neural network (SNN) model through modelling the levels of neuroreceptors (next subsection). Such model is demonstrated on learning spatio-temporal EEG brain data and for the study of the effect of the neuroreceptors on the SNN model connectivity and therefore - on the brain functionality (next section).

2.2. The Neuroreceptor Dependent Plasticity Model (NRDP)

The NRDP model expresses mathematically the dynamic relationship between excitatory and inhibitory neuroreceptors, which results in learned connection weights between spiking neurons. This relationship generates a persistent

increase or decay in synaptic strength that influences the post-synaptic potential (action potential) and thus the spiking activity of the post-synaptic neuron. Here, we define the equations to calculate the synaptic strength between two neurons in a given time period as a function of four major neuroreceptor levels.

A connection C_{ij} between a neuron n_i and a neuron n_j is denoted by:

$$C_{ij} = \begin{cases} 1, & \text{connection;} \\ 0, & \text{no connection;} \end{cases} \quad (1)$$

The firing state $S_{i,j}$ of a connection C_{ij} (pre-synaptic spike) at a time t is defined as:

$$S_{ij}(t) = \begin{cases} 1, & \text{spike;} \\ 0, & \text{no spike;} \end{cases} \quad (2)$$

Now, let $M = \{A, N\}$ be the set of glutamate receptors where A and N are respectively the AMPAR and the NMDAR, and let $G = \{G_a, G_b\}$ be the set of GABA receptors where G_a and G_b are the GABA_A and the GABA_B respectively.

The activation of the inhibitory receptors is modelled so that the probability of activating receptor G_a is higher than the probability of activating receptor G_b :

$$P_{G_b} < P_{G_a}, P_{G_b} = 1 - P_{G_a} \quad (3)$$

Then, the inhibitory level of a G receptor in the synapse between n_i and n_j neurons is determined according to the following activation function:

$$G = \begin{cases} G_a, & \alpha < P_{G_a}; \\ G_b, & \text{otherwise;} \end{cases} \quad (4)$$

where P_{G_a} indicates the GABA_A activation probability, $\alpha = \text{unif}(0, 1)$ is a dimensionless random number with a uniform density probability.

The level of an inhibitory receptor activity with respect to time $G(t)$ is defined by

$$G(t) = \begin{cases} \max(\theta_{G^-}, G(t-1) - k_{G_l}), & S_{ij}(t) = 1; \\ \min(\theta_{G^+}, G(t-1) + k_{G_d}\Delta_t), & \text{otherwise;} \end{cases} \quad (5)$$

where: t is the training elapsed time, k_{G_l} and k_{G_d} are the losing and the gaining rate respectively; Δ_t is the elapsed time after n_i emitted the last spike to neuron n_j ; $\theta_{G^\pm}$ is the maximum and minimum threshold value for each G receptor respectively. The $\max$ and $\min$ functions are computed so that the receptor activation does not surpasses its threshold value. As far as the excitatory receptors are concerned, we made several assumptions to compute their values at a time t . If $S_{ij}(t) = 1$ then the level of A is defined by

$$A(t) = \min(\theta_{A^+}, A(t-1) + k_A) \quad (6)$$

where: t is the elapsed time; and k_A is the AMPAR gaining rate. If A reaches its maximum threshold value θ_{A^+} , then it maintains this value during a time window Δ_w , even if n_i has not emitted a spike. In this case the AMPAR is completely activated. On the other hand, if a connection C_{ij} lacks of a *stimulus* for a longer time than Δ_{w_t} , i.e. $A = \theta_{A^+}$ and $\Delta_{w_t} > \Delta_{w_t}$, then the inhibitory receptor will manifest a behaviour according to the Equation 7.

$$A(t) = \max(\theta_{A^-}, A(t-1) - k_G) \quad (7)$$

where: θ_{A^-} is the minimum level of AMPAR, and $k_G = f_G \cdot G$ is the gain of the inhibitory receptors over this receptor. Here, f_G is the rate that the inhibitory receptor level G affects AMPAR. This implies a decay on the synaptic weight due to a lack of sufficient *stimuli*, and therefore simulating the phenomenon of loss of memory.

Regarding the NMDAR, it is known that its activation often depends on the AMPAR, especially in mechanisms that involve memory formation in the hippocampus [23, 24, 25, 40]. Here, we propose a simplified model where the NMDAR is activated after the AMPAR reaches its maximum level. If $S_{ij}(t) = 1$ and $A = \theta_{A+}$ then:

$$N(t) = \min(\theta_{N+}, N(t-1) + k_N) \quad (8)$$

otherwise:

$$N(t) = \max(\theta_{N-}, N(t-1) - k_N) \quad (9)$$

where: θ_{N+} is the maximum and the minimum level of NMDAR; and k_N is the gaining rate for NMDAR.

Finally, the synaptic weight $W_{ij}(t)$ from neuron n_i to n_j at a time t is denoted by

$$W_{ij}(t) = N(t) + A(t) - G(t) \quad (10)$$

The postsynaptic potential or membrane potential $u(t)$ of a neuron n_j at the time t is calculated in the standard way for the leaky integrate-and-fire type spiking neurons:

$$u_j(t) = u(t-1) + \sum_{i=1}^m W_{ij}(t) S_{ij} \quad (11)$$

where m is the number of spiking neurons connected to the neuron n_j .

The membrane potential increases with every input spike at time t , until it reaches a threshold θ . Then, the neuron emits a spike and the membrane potential is reset to an initial state u_r as described in the Equation 12.

$$\text{if } u_j(t) \geq \theta \text{ then } u_j(t) = u_r \quad (12)$$

Afterwards, the dynamics described in the Equation 11 are interrupted during an absolute refractory time δ and restart the integration at time $t + \delta$ with the new initial condition u_r .

3. A Case Study of Cognitive EEG Data

We performed a modified Stenberg's Memory Scanning Test [41]. In this experiment, each subject was asked to sit comfortably and look at a screen. A fixation cross appeared for 3 seconds; after that, a "positive set" of three random letters was displayed for 5 seconds, to give the subjects enough time to memorise them. After a 3 seconds pause, when the screen turned blank, a single "test set" was presented that may, or may not, have been shown previously. Every subject was asked to decide if the test set was included in the positive set or not. The experiment was repeated increasing the number of elements in the positive set (from three to five and finally to seven letters).

3.1. EEG Data Collection

We collected EEG data from 21 healthy volunteers. Ethical approval 13/283 was granted by the Auckland University of Technology Ethics Committee. The subjects were aged between 28 and 50 years. They had all undertaken undergraduate university study as a minimum, had no history of cognitive impairment, and were all right handed. All measurements were taken in a quiet room with the participants seated in a dining chair and using a computer screen. Data was collected following two scenarios (a resting task and a cognitive task) using the Emotiv EPOC (<http://emotiv.com/>) device, a standard EEG system with 14 feature channel names based on the international 10-20 electrodes location system, which are AF3, F7, F3, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4 *plus* two references in the P3/P4 location. No filtering was applied to the data, neither on-line nor off-line, and the recordings were made at a sampling rate of 128 Hz per channel. Data was collected in one session. The length of each session was 30 s per scenario, chosen in accordance with the duration of the memory task.

The resting data was recorded with eyes closed in order to avoid disturbing artefacts (such as blinking of the eyes) and each subject was asked to avoid thinking or planning thoughts as much as possible.

For this study, only the last 15 s of the 30 s recorded were used to run the experiments in order to eliminate any possible noise related to the initial experimental settings. Also, one data point for every three was selected from the entire EEG sequence, obtaining one sample of 640 data points per 14-EEG channels per class and per subject. This information was considered enough for the algorithm to discriminate the resting scenario from the cognitive task. In total, we obtained 21 samples for class 1 (C1, resting) and another 21 samples for class 2 (C2, memory).

3.2. The NeuCube Architecture

NeuCube is a SNN architecture for mapping, learning and understanding of STBD. It was initially proposed in [13] and then further developed in [42, 43]. This architecture consists of the following functional modules: an input data encoding module, in which input data is encoded into trains of spikes that are then presented to the main module; the 3D spiking neural network cube (SNNc) module (the Cube), where time and space characteristics of the STBD are captured and learned in an unsupervised mode; and the output module for data classification (or regression) which applies supervised learning in a SNN classifier/regressor.

The process of creating a NeuCube model for the case study EEG data modelling can be summarised as follows:

- Using the input module, the available EEG data is transformed into spike sequences using the threshold-based algorithm (TBR_{Thr}), as this algorithm identifies just differences in consecutive EEG values.
- The spike trains are entered into a 3D brain-like SNN cube of 1471 leaky integrate-and-fire (LIF) neurons mapping the Talairach template [44]. The input variables (*i.e.* the 14 EEG channels) are mapped into spatially located spiking neurons in the SNN cube that correspond to the 3D spatial coordinates of the channels according to the 10-20 system. The synaptic connections were initialised using a small- world connectivity. Then we trained the SNN cube on the encoded EEG data, using the proposed NRDP as the unsupervised learning algorithm.
- In the output module, we use the deSNN [45] algorithm for supervised learning to classify the activated patterns in the SNN cube when the EEG data is entered again.

Previous implementations and experimentations with the NeuCube architecture used spike-time dependent plasticity (STDP) learning algorithm for the unsupervised learning in the SNN cube. Here we introduce the NRDP unsupervised learning rule in the SNN cube and the NeuCube system is now called NeuCube-NRDP. Parameters of the NeuCube-NRDP system were optimised for better classification results. A functional diagram of the NeuCube-NRDP is depicted in Figure 1.

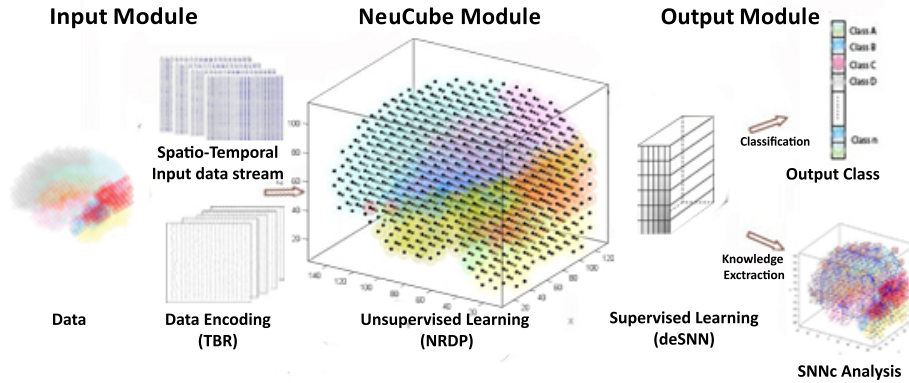


Figure 1: A general NeuCube-NRDP architecture.

3.3. Parameter Optimisation

As a starting point, we assumed that equivalent model behaviour can be achieved by using the NRDP or the STDP learning rules. Both NRDP and STDP learning rules, can automatically balance the synaptic strengths making post-synaptic firing sensitive to pre-synaptic potentials. In order to produce the same behaviour (spike sequences) when using either STDP and NRDP learning rules, we fitted the NRDP parameters by means the differential evolution (DE/rand/1/bin) algorithm [46] on a small recurrent SNN as shown in Figure 2.

The aim was to maximise the spike time coincidences between the spike trains produced by each neuron using the STDP rule with a learning rate $r = 0.01$, and then using the NRDP rule proposed with optimised parameters. These

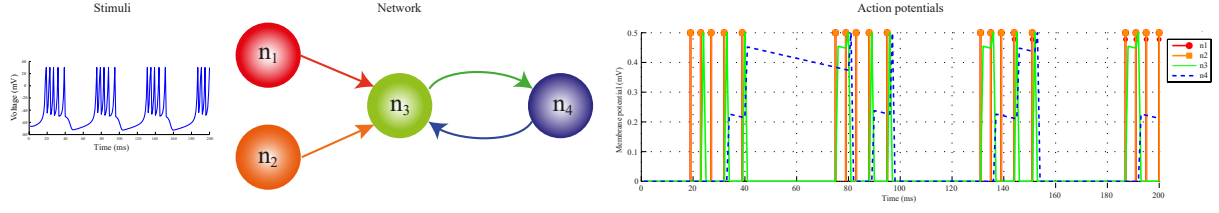


Figure 2: Spike trains generated after stimulating a recurrent spiking neural network with a periodic burst of spikes, and using the STDP or NRDP learning rules.

parameters are related to the maximum θ_+ and the gain k values for each neuroreceptor, the probability of GABA_A to be expressed P_{G_a} , and the inhibitory rate f_G . Each neuron on the SNN was a leaky integrate-and-fire neuron model that fired when the membrane potential reached a threshold value $th = 0.5$, using a leak value $lk = 0.02$ and a refractory time $t_r = 6$ ms. Table 1 shows the optimised NRDP parameters to produce the same spike trains when using the STDP rule.

Table 1: NRDP parameter settings that leads to same spiking activity as when using the STDP learning rule.

Neuroreceptor	Parameters	Values
AMPAR	θ_{A^+}	0.901680
	k_A	0.542872
NMDAR	θ_{N^+}	0.230013
	k_N	0.011660
GABA _A	$\theta_{G_a^+}$	0.755415
	k_{G_a}	0.385908
	P_{G_a}	0.7
GABA _B	$\theta_{G_b^+}$	0.795471
	k_{G_b}	0.110321
Inhibitory Rate	f_G	0.01

We can conclude that trough setting suitable parameters in a NeuCube-NRDP, we can achieve the same performance as in the NeuCube-STDP. In addition to that a NeuCube-NRDP can facilitate to study the effect of unusual modifications of neuroreceptors on the learning ability of an SNN model trained on brain data, making it possible to draw conclusions about the impact of these neuroreceptors on the connectivity and spiking activity of the brain as a source of the data.

In the next experiments the NeuCube-NRDP parameters were optimised by a grid search algorithm that evaluated the model based on the best classification accuracy result. The resulting best parameters were set as follows: the threshold TBR_{Thr} for encoding algorithm was set at 22.518; the small-world connectivity probability parameter p was set at 0.075; the spiking neurons threshold of firing Θ , the refractory time r and the potential leak rate l of the LIF neuron model were set at 0.306, 5 ms and 0.02 respectively; finally, the variables *mod* and *drift* of the deSNN classifier were set at 0.4 and 0.25 respectively.

After the optimisation procedure, we retained the best NeuCube-NRDP model to perform the final experiments. We used 50% of the data randomly selected for training and the remaining 50% for testing in a cross validation mode for 30 runs. We also performed two more experiments increasing the parameter θ_{A^+} (defining the maximum value for the AMPAR) by 10% and decreasing it by 10%. With the latter experiments we demonstrated the ability of the NeuCube-NRDP to model the effect of neuroreceptors on the connectivity of the learned SNN model from EEG data, therefore to offer some meaningful interpretations of the model in terms of brain learning and memory functions.

3.4. Results and Discussion

The NRDP model, along with the NeuCube architecture allowed us to analyse both the data and the brain-like processes that generated it, including the changes of its functionality across different conditions and groups of subjects. When we modified the excitatory and inhibitory levels, we were able to observe how the neuroreceptors affected the spiking activity and the connectivity of the SNNc, and therefore the classification results.

3.4.1. Classification

In Table 2, we report the classification accuracy results obtained by using the optimised parameter values and the modified θ_{A^+} values. We observe that optimised parameter values resulted in a good classification accuracy of 77%

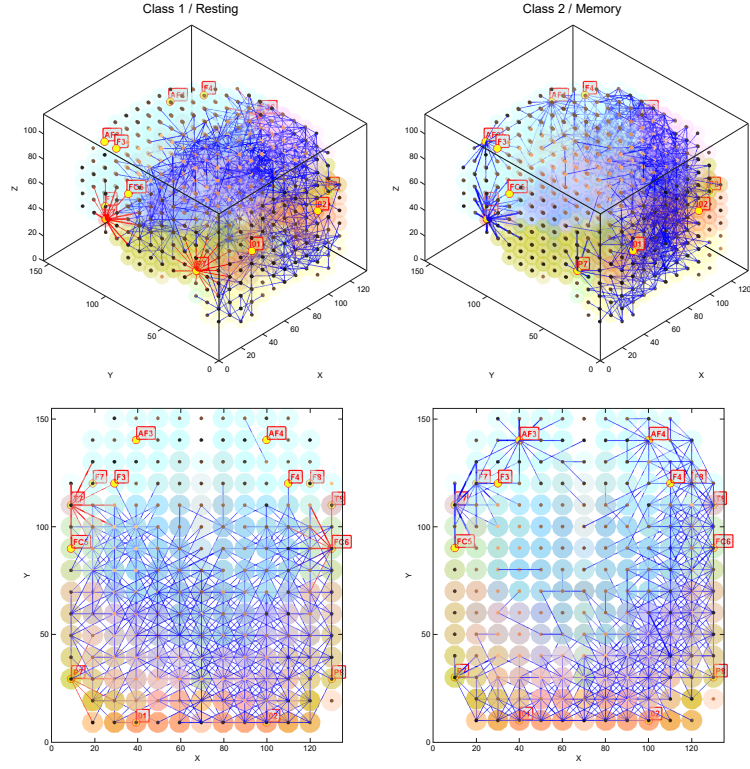
Table 2: Classification accuracy. The results are presented as classification accuracy percentage for class 1 (resting), class 2 (memory), and overall.

Parameters	Class 1	Class 2	Overall
Optimised	91%	64%	77 %
Optimised with $\theta_{A^+} + 10\%$	36%	73%	55 %
Optimised with $\theta_{A^+} - 10\%$	73%	36%	55 %

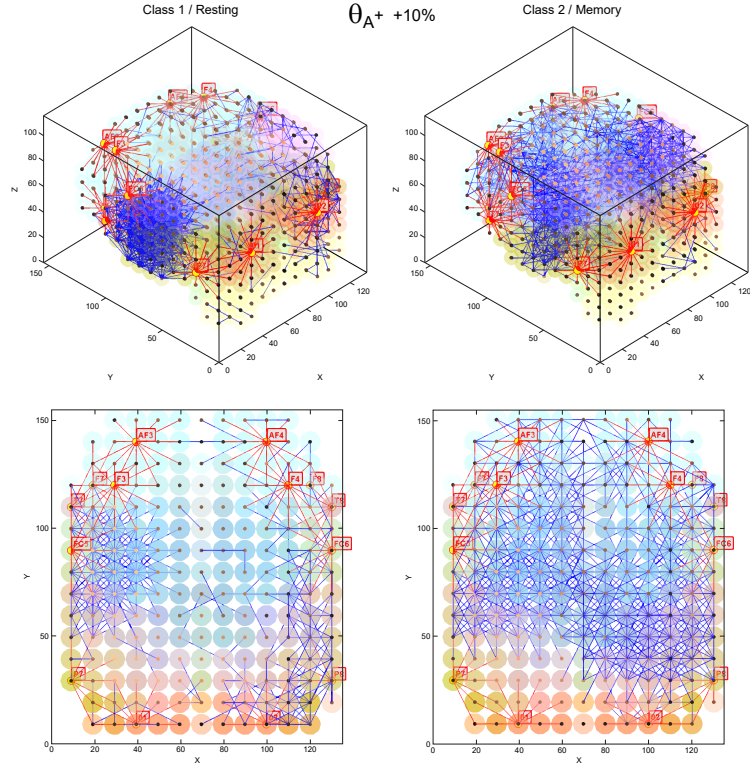
overall. Considering the short training period, the noisy nature of the data, its rather informal collection method, and the technical limitations of the EEG recording device, this result is satisfactory. Thus, the NRDP algorithm demonstrated its ability to properly distinguish between the resting and the memory tasks. However, modifying the maximum value of the AMPAR expression θ_{A^+} parameter affects the classification accuracy by both class and overall. After increasing θ_{A^+} value by 10% the classification accuracy for class 1 (the resting state) considerably decreased. This is because the increase of the excitation threshold would prevent subjects to get into a resting state. In contrast, decreasing the θ_{A^+} value by 10% makes the samples belonging to class 2 (the memory task) difficult to classify. A simple explanation is that a decrease in the excitation threshold does not support memory activity.

3.4.2. Analysis of the Connectivity of the SNNc in NeuCube-NRDP

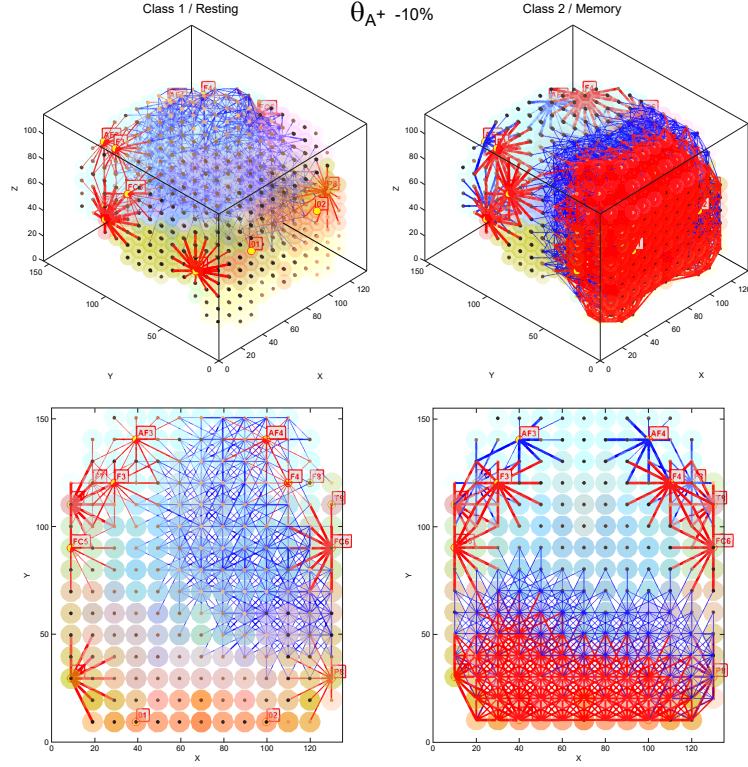
By visualising the connectivity of the training SNNc models in the experiment above (see Table 2), we can study how time-series EEG data is learned during unsupervised training, and to possibly extract new knowledge from it. We aim to understand how spiking activity and connectivity evolve during learning, for each of the two classes. Figure 3 shows the learning connectivity in 3D SNNc along with the corresponding 12 brain functional areas. Yellow-green denotes the temporal lobe; pink, the parietal lobe; light-blue, the frontal lobe; red, the fronto-temporal space; light-yellow, the posterior lobe; orange, the occipital lobe; green, the anterior lobe; blue, the sub-lobar region; grey, the limbic lobe; purple, the pons; blue-green, the midbrain; and brown, the medulla. Also, the 14 input neurons are highlighted and labeled in yellow according to their corresponding EEG channels. In figure, blue lines indicate the excitatory synapses and red lines the inhibitory synapses; the thickness of these lines indicates the strength of the activity between neurons.



(a) NeuCube-NRDP connectivity using optimised NRDP parameters.



(b) NeuCube-NRDP connectivity using optimised NRDP parameters with 10% higher AMPAR activation threshold θ_{A+} .



(c) NeuCube-NRDP connectivity using optimised NRDP parameters with 10% lower AMPAR activation threshold θ_{A+} .

Figure 3: NeuCube-NRDP connectivity obtained after training the SNNc with the EEG data recorded during either the resting task (class 1), or the memory task (class 2). The figures show the SNNc connectivity, both in a 3D and in a 2D view, together with the corresponding 12 brain functional areas. Connections in blue color are excitatory and in red - inhibitory.

We observe that modifying the threshold of the maximum value of AMPAR caused the SNNc to evolve different connectivity for both classes across the brain regions.

In Figure 3a we show the connectivity when the NeuCube was trained with optimised parameter settings. We observe that there is a significant difference between the SNNc connectivity generated by the two groups of subjects. The neural activity recorded during the resting task generated an equally distributed connectivity over the entire brain. Contrarily, the memory task evolved most of the connections in the (right) occipito-parietal cortex and centro-temporal area. These findings are consistent with those reported in the literature, as the parietal-temporal-occipital (PTO) area of the human brain is linked with the associative type of memory related to perception and execution processes [47].

Analysing the connectivity of the evolved NeuCube models may lead to new findings about the data and the brain processes that generated it. Each connection in the SNN cube represents a spatio-temporal causal relationship between the connected neurons that represent corresponding brain areas. When we increased the AMPAR threshold by 10% of its initial value (Figure 3b), we observed that the evolved connectivity in the 3D SNN cube differed between the two groups. Inhibitory connections increased for both classes. The resting task data generated increased connectivity in the temporal area of the left hemisphere, whilst the other areas decreased their connectivity. The memory task data showed increased inhibitory connections in the occipital area (especially by the electrodes O1 and O2), while excitatory connections increased in the right fronto-temporal area. In fact, over-expression of AMPAR was responsible for affecting the resting state data, as it increased the connectivity, making the classification task more difficult.

On the other hand, decreasing the AMPAR threshold by 10% of its initial value (Fig. 3c), resulted in increased inhibitory connections around the input neurons in the resting task data; and for excitatory connections to be generated by the fronto-temporal (right) area. The memory task data generated remarkably increased inhibitory connections in the occipital area. Thus, it is the increased activity of GABAergic synapses that affects the classification results; as inhibitory activity prevails over excitatory affecting the normal neural equilibrium. However, cognitive functions and

neural synchronisation are also mediated by GABA transmission, which is important for the correct evolution of the neural process [48].

4. Future Work

In this study, computational modelling of EEG data was achieved by implementing a proposed NRDP learning rule in the NeuCube architecture. Using this system, EEG and other brain data could be used to study the impact of neuroreceptor activity on the PSP of the neurons that form the SNN cube. Importantly, the evolved connectivity and spiking activity learned could be further interpreted and new knowledge about functional brain conditions could be revealed.

In future work, it would be useful to conduct more experiments using data sets related to the progression of neurodegenerative brain diseases, such as AD or vascular dementia.

In addition, future research could cover:

- Extension of the proposed methodology with the introduction of the probabilistic model of a neuron as proposed in [10];
- Extension of the proposed methodology with a gene regulatory network (GRN) module to study how gene expression data can be used to modify the SNNc neural activity (as explained below).

The expression of certain genes triggers mechanisms that are fundamental for the activities of the brain. When a gene is turned on in a neural cell, this is the starting engine of the various brain processes that determine its functions and development. Proteins influence the spiking activity of neural cells, which consequently is reflected in the collected STBD. Genetic parameters are extremely useful especially if we aim to develop a valid neurological computational model. To construct a biologically plausible computational model with the use of SNN, the inclusion of a GRN sub-model is of pivotal importance.

This approach has been taken by several researchers, who have demonstrated that modelling even just a single gene [11] or constructing a GRN [11] contributes to the optimisation of the results and to a better understanding of the phenomena of study. In [11] and [10] a neurogenetic model of a neuron is proposed and studied. The model utilises information about how the main neuroreceptors, and the genes that affect their expression related to the spiking activity of a neuron in terms of fast excitation, fast inhibition, slow excitation and slow inhibition. This model can be also optimised using a gene/protein regulatory network, controlling the dynamic interactions between genes and proteins over time, which affect the post synaptic potential of the neurons in the SNNc.

The NeuCube-NRDP model proposed here could be extended by adding genetic information, related to NMDAR in particular, in terms of a GRN. NMDAR plays a pivotal role in memory plasticity [30, 31] and it is well known that people affected by AD suffer from cognitive decline and disorientation as first symptoms [31]. In the human brain, the information transmitted by neurons is processed and consolidated in the hippocampus from short-term memory to long-term memory; hence this is one of the first regions to suffer damage as AD advances. The human brain has two hippocampi, which are part of the limbic system and located in the medial temporal lobes. One of the processes associated with the development of AD is the constant activation of the NMDAR. This event is thought to lead to an abnormal over-activity during neural processes [33] leading to cellular dysfunction and neural death over a period of time [39]. Moreover, these processes and related mechanisms are known to contribute to the effects of amyloid-beta, which is the major component of senile plaques, one of the typical features of AD formation and degeneration [49, 23, 33].

It is important to outline that NMDAR is a channel with a quaternary-structure (*i.e.* a three-dimensional or spatial structure of different proteins). Each of these proteins is encoded by a different gene [50]. The synthesis of this

neuroreceptor is only possible due to the simultaneous expression of these genes, as they are responsible for each unit that forms the macromolecule. To construct a GRN for the NMDAR, genes GRIN1, GRIN2A, GRIN2B, GRIN3A and GRIN3B could be used; since, in humans, the NMDAR principal sub-unit is NR1 (encoded by GRIN1 gene) [51]; NR2A and NR2B (encoded by GRIN2A and GRIN2B gene respectively) are found in glutamatergic synapses [23]; NR3A (encoded by GRIN3A gene) has been found in embryonic brain tissue and together with NR3B (gene GRIN3B) it has an inhibitory influence in NMDAR expression [52].

The NRDP model proposed here, implemented in the NeuCube architecture, constitutes only a preliminary step towards further development of new neurogenetic computational models, representing more closely biological neural networks in order to allow for a better understanding of brain cognition.

Acknowledgements

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Appendix C

Quantitative Measures

C.1 Quantitative Measures

Quantitative measures of the connectivity and spiking activity generated after unsupervised learning of the EEG signal (0-64 Hz) at t_0 and t_1 , as reported in the SNNc analysis presented in Chapter 7.2.5.

C.1.1 Spike Activity at t_0 and t_1

Fig. C.1 shows the spike activity generated after unsupervised training of the EEG signal (0-64 Hz) at t_0 and t_1 .

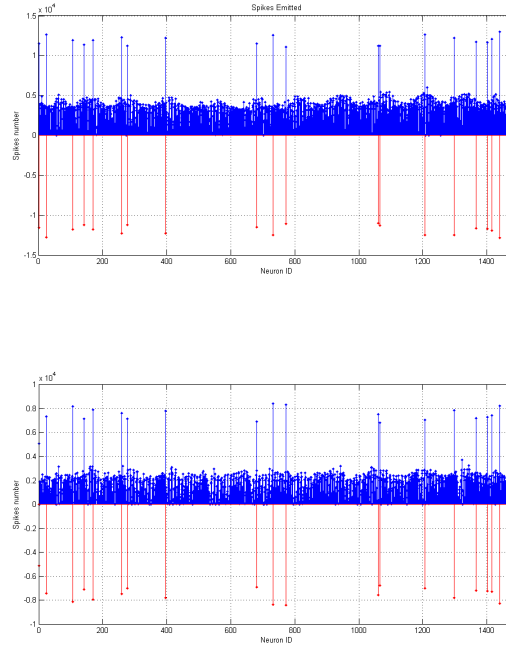


Figure C.1: The figure shows the spikes emitted after unsupervised training of the encoded EEG signal (0-64 Hz) recorded from a patient affected by AD at t_0 (top) and t_1 (bottom).

The quantitative measures of the spike activity generated after unsupervised training are reported in the following pages for t_0 and t_1 respectively.

NeuronsID	EncodedSpikes	GeneratedSpikes
T5	11548	11495
n2	0	3859
n3	0	3392
n4	0	2427
n5	0	0
n6	0	3819
n7	0	3970
n8	0	4023
n9	0	3606
n10	0	4855
n11	0	3820
n12	0	3974
n13	0	3656
n14	0	1610
n15	0	3407
n16	0	2975
n17	0	3381
n18	0	3757
n19	0	3598
n20	0	3419
n21	0	3527
n22	0	2385
n23	0	3584
T3	12742	12667
n25	0	2333
n26	0	3408
n27	0	3399
n28	0	3168
n29	0	3100
n30	0	3619
n31	0	3078
n32	0	3664
n33	0	3425
n34	0	3049
n35	0	3332
n36	0	573
n37	0	3048
n38	0	3140
n39	0	2886
n40	0	3660
n41	0	2608
n42	0	3258
n43	0	2713
n44	0	3320
n45	0	214
n46	0	2492
n47	0	3576
n48	0	3430
n49	0	3080
n50	0	3944
n51	0	3710
n52	0	470
n53	0	207
n54	0	4203
n55	0	4583
n56	0	1
n57	0	569
n58	0	3481
n59	0	1165
n60	0	4587
n61	0	4161

n62	0	5053
n63	0	3975
n64	0	0
n65	0	945
n66	0	3129
n67	0	1556
n68	0	3886
n69	0	3441
n70	0	4118
n71	0	4537
n72	0	2019
n73	0	549
n74	0	3307
n75	0	3298
n76	0	4023
n77	0	4131
n78	0	4502
n79	0	3351
n80	0	3502
n81	0	2876
n82	0	1960
n83	0	3856
n84	0	4223
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NeuronsID	EncodedSpikes	GeneratedSpikes
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n10	0	2128
n11	0	2500
n12	0	1891
n13	0	910
n14	0	184
n15	0	1883
n16	0	1841
n17	0	2003
n18	0	2014
n19	0	2079
n20	0	1376
n21	0	2301
n22	0	1689
n23	0	1798
T3	7426	7328
n25	0	1181
n26	0	1472
n27	0	2224
n28	0	2291
n29	0	1499
n30	0	1080
n31	0	910
n32	0	2104
n33	0	1248
n34	0	2250
n35	0	2238
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n37	0	1102
n38	0	1308
n39	0	961
n40	0	841
n41	0	1971
n42	0	1183
n43	0	1975
n44	0	2047
n45	0	636
n46	0	1859
n47	0	1875
n48	0	1844
n49	0	1991
n50	0	2106
n51	0	2011
n52	0	30
n53	0	33
n54	0	2541
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n57	0	0
n58	0	762
n59	0	1800
n60	0	2109
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n65	0	0
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n67	0	1290
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n70	0	2176
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n74	0	1160
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n77	0	1842
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n80	0	2039
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n1259	0	2446
n1260	0	2242
n1261	0	2112
n1262	0	2180
n1263	0	1982
n1264	0	1895
n1265	0	1262
n1266	0	1320
n1267	0	974
n1268	0	1876
n1269	0	2396
n1270	0	2362
n1271	0	2213
n1272	0	2021
n1273	0	2166
n1274	0	1956
n1275	0	548
n1276	0	821
n1277	0	2226
n1278	0	2267
n1279	0	2161
n1280	0	2416
n1281	0	2424
n1282	0	2373
n1283	0	2225
n1284	0	420
n1285	0	2217
n1286	0	2295
n1287	0	2264
n1288	0	2543
n1289	0	2195
n1290	0	2385
n1291	0	2121
n1292	0	2208
n1293	0	2300
n1294	0	2109
n1295	0	2388
n1296	0	2443
F4	7833	7865
n1298	0	2034
n1299	0	1938
n1300	0	2253
n1301	0	2616

n1302	0	2732
n1303	0	1889
n1304	0	2206
n1305	0	1957
n1306	0	2349
n1307	0	707
n1308	0	658
n1309	0	1822
n1310	0	385
n1311	0	471
n1312	0	525
n1313	0	1203
n1314	0	946
n1315	0	1471
n1316	0	0
n1317	0	350
n1318	0	1898
n1319	0	2022
n1320	0	2419
n1321	0	2882
n1322	0	3706
n1323	0	1246
n1324	0	1
n1325	0	754
n1326	0	1097
n1327	0	2645
n1328	0	2364
n1329	0	2320
n1330	0	2910
n1331	0	571
n1332	0	2035
n1333	0	606
n1334	0	2294
n1335	0	2295
n1336	0	2347
n1337	0	2214
n1338	0	1901
n1339	0	2548
n1340	0	1631
n1341	0	2219
n1342	0	1089
n1343	0	2929
n1344	0	3256
n1345	0	2907
n1346	0	2196
n1347	0	1820
n1348	0	1977
n1349	0	1926
n1350	0	627
n1351	0	2522
n1352	0	2419
n1353	0	2593
n1354	0	2470
n1355	0	2058
n1356	0	1616
n1357	0	1698
n1358	0	59
n1359	0	1791
n1360	0	2483
n1361	0	2492
n1362	0	2351
n1363	0	1992

n1364	0	2617
n1365	0	2391
C4	7194	7213
n1367	0	3639
n1368	0	2301
n1369	0	2235
n1370	0	2652
n1371	0	2400
n1372	0	2151
n1373	0	2286
n1374	0	1471
n1375	0	1788
n1376	0	951
n1377	0	978
n1378	0	2374
n1379	0	2570
n1380	0	2418
n1381	0	2220
n1382	0	2405
n1383	0	1688
n1384	0	1303
n1385	0	552
n1386	0	1375
n1387	0	2230
n1388	0	2253
n1389	0	2204
n1390	0	2354
n1391	0	2372
n1392	0	1628
n1393	0	977
n1394	0	2134
n1395	0	1593
n1396	0	2389
n1397	0	2351
n1398	0	2183
n1399	0	2524
n1400	0	2112
n1401	0	1954
F8	7270	7290
n1403	0	1548
n1404	0	2186
n1405	0	2128
n1406	0	1456
n1407	0	1493
n1408	0	1672
n1409	0	2339
n1410	0	562
n1411	0	1403
n1412	0	2076
n1413	0	1398
n1414	0	2348
n1415	0	2408
T6	7293	7415
n1417	0	1537
n1418	0	1790
n1419	0	615
n1420	0	1344
n1421	0	2616
n1422	0	1258
n1423	0	2243
n1424	0	1697
n1425	0	1

n1426	0	2799
n1427	0	1276
n1428	0	2825
n1429	0	1674
n1430	0	1271
n1431	0	1131
n1432	0	2647
n1433	0	2330
n1434	0	2519
n1435	0	1815
n1436	0	2154
n1437	0	1915
n1438	0	1289
n1439	0	2312
T4	8269	8231
n1441	0	2568
n1442	0	2250
n1443	0	739
n1444	0	1085
n1445	0	2238
n1446	0	1867
n1447	0	2421
n1448	0	2248
n1449	0	2354
n1450	0	1823
n1451	0	847
n1452	0	899
n1453	0	2281
n1454	0	2358
n1455	0	2199
n1456	0	1314
n1457	0	1948
n1458	0	1283
n1459	0	1800
n1460	0	1558
n1461	0	1916
n1462	0	1729
n1463	0	1095
n1464	0	1630
n1465	0	908
n1466	0	1681
n1467	0	1290
n1468	0	1967
n1469	0	682
n1470	0	1215
n1471	0	1573
n1472	0	7831
n1473	0	7587
n1474	0	7121
n1475	0	7483
n1476	0	8409
n1477	0	7833
n1478	0	7270
n1479	0	7426
n1480	0	8145
n1481	0	8377
n1482	0	7194
n1483	0	8269
n1484	0	5123
n1485	0	7955
n1486	0	6915
n1487	0	7023

n1488	0	7293
n1489	0	7033
n1490	0	6787

C.1.2 Activation Level at t_0 and t_1

Fig. C.2 shows the activation level of the neurons of the SNNc after unsupervised training of the EEG signal (0-64 Hz) at t_0 and t_1 .

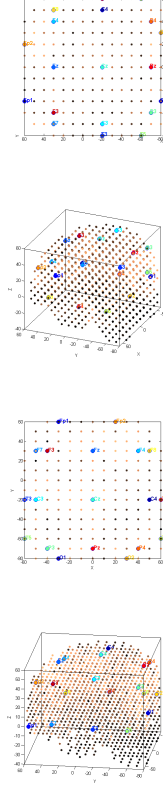


Figure C.2: The figure shows the activation level of the encoded EEG signal (0-64 Hz) recorded from a patient affected by AD at t_0 (top) and t_1 (bottom).

The quantitative measures of neurons activation level after unsupervised training are reported in the following pages for t_0 and t_1 respectively.

NeuronsID	ActivationLevel
T5	23043
n2	3859
n3	3392
n4	2427
n5	0
n6	3819
n7	3970
n8	4023
n9	3606
n10	4855
n11	3820
n12	3974
n13	3656
n14	1610
n15	3407
n16	2975
n17	3381
n18	3737
n19	3598
n20	3419
n21	3527
n22	2385
n23	3584
T3	25409
n25	2333
n26	3408
n27	3399
n28	3168
n29	3100
n30	3619
n31	3078
n32	3664
n33	3425
n34	3049
n35	3332
n36	573
n37	3048
n38	3140
n39	2886
n40	3660
n41	2608
n42	3258
n43	2713
n44	3320
n45	214
n46	2492
n47	3576
n48	3430
n49	3080
n50	3944
n51	3710
n52	470
n53	207
n54	4203
n55	4593
n56	1
n57	569
n58	3481
n59	1165
n60	4587
n61	4161

n62	5053
n63	3975
n64	0
n65	945
n66	3129
n67	1556
n68	3886
n69	3441
n70	4118
n71	4537
n72	2019
n73	549
n74	3307
n75	3298
n76	4023
n77	4131
n78	4502
n79	3351
n80	3302
n81	2876
n82	1960
n83	3856
n84	4223
n85	4002
n86	3401
n87	3009
n88	3483
n89	3205
n90	2547
n91	3129
n92	3463
n93	3528
n94	3315
n95	3448
n96	3598
n97	3856
n98	1129
n99	2279
n100	3153
n101	3460
n102	3553
n103	3586
n104	3484
n105	3283
C3	23728
n107	533
n108	3367
n109	3412
n110	3501
n111	3532
n112	3448
n113	3214
n114	3130
n115	2116
n116	971
n117	1334
n118	3151
n119	3697
n120	4073
n121	3710
n122	3572
n123	3661

n124	2236
n125	196
n126	685
n127	3259
n128	3497
n129	3966
n130	4376
n131	3723
n132	3544
n133	2512
n134	2565
n135	2851
n136	4210
n137	4021
n138	4567
n139	4034
n140	3584
n141	3483
F7	22584
n143	3587
n144	4465
n145	5715
n146	4021
n147	4274
n148	3744
n149	4220
n150	3159
n151	4711
n152	4358
n153	0
n154	526
n155	1851
n156	3503
n157	4060
n158	4025
n159	4536
n160	4186
n161	390
n162	1262
n163	3284
n164	4132
n165	4345
n166	3869
n167	4389
n168	4551
P3	23712
n170	568
n171	1220
n172	2425
n173	3280
n174	4531
n175	4351
n176	4496
n177	4440
n178	3367
n179	3726
n180	73
n181	1045
n182	903
n183	4045
n184	3651
n185	4564

n186	4319
n187	3781
n188	3576
n189	3647
n190	2315
n191	2627
n192	2501
n193	3624
n194	4109
n195	3843
n196	3152
n197	3349
n198	3130
n199	3191
n200	2550
n201	3600
n202	3918
n203	3801
n204	3768
n205	3338
n206	3167
n207	2950
n208	1918
n209	1667
n210	2705
n211	3260
n212	3551
n213	3498
n214	3625
n215	3087
n216	3406
n217	3517
n218	1772
n219	1325
n220	1659
n221	3419
n222	3448
n223	3670
n224	3448
n225	3680
n226	2679
n227	2063
n228	2018
n229	368
n230	1814
n231	2116
n232	3128
n233	3419
n234	3514
n235	3658
n236	3297
n237	3513
n238	1380
n239	2915
n240	3031
n241	4295
n242	3767
n243	3733
n244	3665
n245	3789
n246	3196
n247	938

n248	3864
n249	3813
n250	4720
n251	4581
n252	3586
n253	3989
n254	3618
n255	1919
n256	4658
n257	4572
n258	3884
n259	3614
F3	24586
n261	4383
n262	3712
n263	3205
n264	3579
n265	2863
n266	4448
n267	4038
n268	2782
n269	3042
n270	4190
n271	3851
n272	479
n273	33
n274	1228
n275	3878
n276	3620
O1	22493
n278	1593
n279	4524
n280	3798
n281	135
n282	1064
n283	2055
n284	3697
n285	3701
n286	4450
n287	5035
n288	4346
n289	1695
n290	634
n291	1060
n292	1976
n293	2871
n294	4208
n295	3875
n296	4303
n297	4389
n298	4014
n299	3438
n300	823
n301	926
n302	1318
n303	2186
n304	3086
n305	4203
n306	3813
n307	4326
n308	3974
n309	3868

n310	2799
n311	453
n312	895
n313	3074
n314	2901
n315	3834
n316	3913
n317	3780
n318	3880
n319	3470
n320	3227
n321	2879
n322	2827
n323	3263
n324	3527
n325	3487
n326	3891
n327	3229
n328	3127
n329	3393
n330	2677
n331	2956
n332	3420
n333	2914
n334	3799
n335	2123
n336	2809
n337	3369
n338	3352
n339	2123
n340	264
n341	2098
n342	2810
n343	2758
n344	3828
n345	3173
n346	3606
n347	3729
n348	3412
n349	2841
n350	247
n351	818
n352	1068
n353	2840
n354	3617
n355	3579
n356	3461
n357	3692
n358	3353
n359	3526
n360	3266
n361	915
n362	2207
n363	3074
n364	3574
n365	4161
n366	3319
n367	3733
n368	3480
n369	3359
n370	1753
n371	1208

n372	2338
n373	3897
n374	2736
n375	4044
n376	3755
n377	4047
n378	3453
n379	3617
n380	3183
n381	2611
n382	3841
n383	3497
n384	2168
n385	3802
n386	4297
n387	4659
n388	4134
n389	3969
n390	3663
n391	3405
n392	3707
n393	3938
n394	3857
n395	630
n396	2173
Fp1	24504
n398	4095
n399	2872
n400	1336
n401	457
n402	440
n403	2255
n404	1815
n405	2691
n406	4313
n407	4702
n408	4474
n409	418
n410	918
n411	2071
n412	1905
n413	3401
n414	3946
n415	3685
n416	4747
n417	4429
n418	3942
n419	626
n420	1325
n421	1706
n422	1590
n423	3526
n424	3924
n425	3971
n426	3723
n427	4618
n428	3692
n429	3197
n430	486
n431	1510
n432	2228
n433	2387

n434	3386
n435	3838
n436	3949
n437	3651
n438	3941
n439	2210
n440	3064
n441	0
n442	954
n443	1592
n444	2729
n445	3079
n446	3694
n447	3795
n448	3726
n449	3730
n450	2868
n451	3640
n452	426
n453	2578
n454	2357
n455	2958
n456	3589
n457	2627
n458	3613
n459	3341
n460	3367
n461	3437
n462	1338
n463	3322
n464	3388
n465	3050
n466	3338
n467	3370
n468	2733
n469	3249
n470	963
n471	1685
n472	2952
n473	2720
n474	3030
n475	3582
n476	3474
n477	3307
n478	3600
n479	2787
n480	951
n481	2375
n482	2646
n483	3161
n484	3386
n485	2834
n486	3072
n487	3553
n488	3273
n489	3274
n490	2348
n491	2925
n492	3497
n493	3324
n494	3561
n495	3451

n496	3430
n497	3143
n498	2003
n499	2310
n500	3280
n501	3345
n502	3718
n503	3289
n504	3480
n505	4170
n506	2508
n507	1340
n508	2982
n509	3080
n510	3233
n511	4095
n512	3647
n513	3486
n514	3764
n515	3118
n516	3071
n517	3686
n518	3478
n519	3468
n520	2808
n521	3145
n522	3192
n523	2180
n524	3149
n525	3679
n526	2830
n527	2957
n528	2735
n529	1936
n530	3483
n531	1739
n532	3037
n533	1137
n534	373
n535	2035
n536	1053
n537	3685
n538	3105
n539	4243
n540	3647
n541	3032
n542	295
n543	264
n544	2416
n545	2418
n546	3658
n547	3900
n548	3458
n549	3956
n550	3539
n551	3122
n552	51
n553	1356
n554	1610
n555	3022
n556	3031
n557	3677

n558	4417
n559	4165
n560	3594
n561	3694
n562	1308
n563	629
n564	739
n565	1763
n566	2809
n567	4035
n568	3269
n569	4230
n570	3874
n571	3939
n572	3619
n573	3573
n574	71
n575	1234
n576	2718
n577	2165
n578	3437
n579	3921
n580	3740
n581	4017
n582	3710
n583	2734
n584	868
n585	2149
n586	2742
n587	3132
n588	3480
n589	3686
n590	3387
n591	3572
n592	3070
n593	822
n594	1443
n595	2528
n596	2828
n597	3383
n598	3096
n599	2565
n600	3074
n601	3329
n602	3570
n603	2450
n604	2921
n605	3006
n606	3411
n607	3258
n608	3511
n609	3244
n610	3211
n611	2347
n612	3136
n613	3212
n614	2784
n615	3057
n616	2441
n617	3417
n618	3430
n619	1602

n620	2977
n621	3063
n622	3306
n623	3186
n624	2706
n625	3152
n626	3265
n627	1424
n628	2897
n629	3073
n630	3139
n631	2964
n632	3221
n633	3082
n634	3171
n635	3258
n636	2299
n637	3178
n638	3138
n639	3300
n640	4134
n641	3066
n642	3125
n643	3048
n644	941
n645	1919
n646	2539
n647	3082
n648	3320
n649	3146
n650	3495
n651	2984
n652	3184
n653	2834
n654	3040
n655	2772
n656	3364
n657	2276
n658	4035
n659	2936
n660	2350
n661	2579
n662	2582
n663	3050
n664	2804
n665	1725
n666	943
n667	1109
n668	3522
n669	3714
n670	3142
n671	4531
n672	4055
n673	1642
n674	793
n675	2559
n676	2942
n677	4406
n678	4031
n679	3623
n680	4055
Pz	23014

n682	1388
n683	2173
n684	3327
n685	3263
n686	4509
n687	3868
n688	3769
n689	3902
n690	4081
n691	3481
n692	1424
n693	1269
n694	2814
n695	3529
n696	4568
n697	4627
n698	4508
n699	3509
n700	3327
n701	3552
n702	6
n703	1632
n704	1849
n705	2682
n706	3452
n707	3312
n708	4151
n709	3702
n710	3520
n711	3125
n712	556
n713	1818
n714	2867
n715	3348
n716	3104
n717	3595
n718	3589
n719	3664
n720	3654
n721	3703
n722	1086
n723	851
n724	1336
n725	3023
n726	2622
n727	3358
n728	3479
n729	3566
n730	3465
Cz	25041
n732	2530
n733	3349
n734	3381
n735	2356
n736	3115
n737	3771
n738	3667
n739	3608
n740	2439
n741	2845
n742	3512
n743	3255

n744	3268
n745	3759
n746	3962
n747	3586
n748	2202
n749	1363
n750	3238
n751	3031
n752	3818
n753	2788
n754	3141
n755	3211
n756	1205
n757	3128
n758	3279
n759	2670
n760	3266
n761	3767
n762	3206
n763	3164
n764	2902
n765	1993
n766	1656
n767	3134
n768	1717
n769	4181
n770	3115
n771	3418
Fz	22217
n773	1333
n774	1997
n775	2743
n776	2879
n777	2975
n778	3222
n779	3456
n780	4382
n781	3739
n782	3851
n783	1345
n784	2259
n785	3516
n786	3729
n787	3986
n788	3190
n789	1369
n790	2369
n791	3060
n792	2353
n793	3990
n794	3677
n795	641
n796	1782
n797	2980
n798	3895
n799	4486
n800	4887
n801	3595
n802	2401
n803	582
n804	757
n805	3083

n806	1712
n807	4059
n808	4546
n809	4892
n810	4564
n811	4349
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NeuronsID	ActivationLevel
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n17	2003
n18	2014
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Appendix D

Ethical Approval

23 October 2013

Nikola Kasabov
Faculty of Design and Creative Technologies

Dear Nikola

Re Ethics Application: **13/283 NeuCube spiking neural network framework and genetic algorithm for on-line cognitive activity classification of EEG data.**

Thank you for providing evidence as requested, which satisfies the points raised by the AUT University Ethics Committee (AUTC).

Your ethics application has been approved for three years until 22 October 2016.

As part of the ethics approval process, you are required to submit the following to AUTC:

- A brief annual progress report using form EA2, which is available online through <http://www.aut.ac.nz/researchethics>. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 22 October 2016;
- A brief report on the status of the project using form EA3, which is available online through <http://www.aut.ac.nz/researchethics>. This report is to be submitted either when the approval expires on 22 October 2016 or on completion of the project.

It is a condition of approval that AUTC is notified of any adverse events or if the research does not commence. AUTC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,



Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Elisa Capecci ecapecci@aut.ac.nz

25 February 2015

Nikola Kasabov
Faculty of Design and Creative Technologies

Dear Nikola

Ethics Application: 13/283 NeuCube spiking neural network framework and genetic algorithm
for on-line cognitive activity classification of EEG data.

At their meeting of 23 February 2015, the Auckland University of Technology Ethics Committee (AUTEC) received the report on your ethics application. AUTEC noted your report and asked me to thank you.

When communicating with us about this application, we ask that you use the application number and study title to enable us to provide you with prompt service. Should you have any further enquiries regarding this matter, you are welcome to contact me by email at ethics@aut.ac.nz or by telephone on 921 9999 at extension 6038.

On behalf of AUTEC, I congratulate the researchers on the successful completion of the project.

Yours sincerely



Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

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