“Modelling Neural Processing
Using Venn-Networks in
Physiological and Pathological
Scenarios”

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Schematic view of main contribution – Venn-networks

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"He who loves practice without theory is like the sailor who boards ship without a rudder and compass and never knows where he may cast".

Leonardo da Vinci 1452-1519
Dedication

To my two ‘true-angels’:

Mônica¹
Jane²

¹ My wife and greatest friend – always for and beside me.
² My mother and all-time supporter – always for and thinking of me.
Abstract

This investigation, of multidisciplinary interest, delves into how the structure and connectivity of the brain influences neural processing. This thesis addresses issues of modelling brain function and consequent changes due to neural disorders. It is carried out through computer simulations within a systemic framework. The work offers plausible explanations for selected neural processing by bringing together topics from neuroscience, medical imaging, artificial intelligence, and computing. In doing so, it also helps to reduce the gap between neurobiology and cognitive neuroscience. All of the above topics are presented in a coordinated manner, gradually transitioning from biological to artificial “worlds”. The employed formalism and holistic approach are aimed at systemic analyses of granularities compatible with data acquisition techniques.

The Venn-network, a novel neural network model proposed by the author, is introduced and exhaustively simulated. This new neural network architecture allows definition and use of multiple types of processing unit, multiple regions within the network structure, and several types of axonal fibres. Most interestingly, the internal activity of utilised networks resembles images produced by functional brain imaging.

A comprehensive computer simulator was developed for implementing the Venn-network model. This simulator was used to carry out experiments such as structural-functional equivalence, active-passive activations, modulation, ageing, and contralateral inhibition. Next, disrupting effects such as the ones produced by (1) multiple sclerosis plaques and (2) strokes, were applied in these simulations. Throughout these simulations, Venn-networks were trained to control flexions of (ten) virtual fingers to reproduce movements of a piano player performing a Mozart Sonata.

The Venn-network model proved to be an effective tool for predicting behaviour in both physiological and pathological scenarios. The correctness and robustness of all implemented Venn-networks was verified in the simulations carried out, as the functionality of all neural architectures conformed with the expected behaviour.

Potential applications of the research include: (i) to support prognoses in neurology (e.g. multiple sclerosis effects due to plaques growth and inference of damage due to strokes), (ii) as a test-bed for producing insights into neuromorphic systems, (iii) to interface between cognitive algorithms and front-end electronics of robots, (iv) as a brain interface for controlling prosthetics, and (v) to provide underlying models for checking hypotheses in medical imaging experiments.
Objectives

• To investigate neural processing using computational models and intelligent algorithms considering biologically plausible constraints;

• To investigate how changes in structure and connectivity of the simulated systems affect evoked processing in physiological and pathological scenarios; and

• To investigate if underlying models and algorithms developed can produce activations that resemble functional images while these algorithms produce expected results.
Contribution and statement of originality

This thesis contains material produced by independent scientific research pursued by the author during his post-graduate studies at Imperial College of Science, Technology and Medicine, London, United Kingdom.

To the best of his knowledge the ideas and results included in this work are original, and the major contributions offered by this work are:

A. Proposition of Venn-networks\(^3\) – a new artificial neural network that allows definition and use of multiple types of processing units (i.e. cortical columns), multiple regions within the network structure, and four types of axonal fibres.

B. Proposition of a computational model for simulation of the effects caused by multiple sclerosis plaques to single nervous pathways\(^4\). The model can also be used to investigate consequences (inference) of MS-plaques growth to neural processing.

C. Development of a computer simulator\(^5\) that implements Venn-networks which incorporate the model of multiple sclerosis plaque. The simulator allows concomitant simulations of ageing, modulation, strokes, and other aspects related to physiological and pathological scenarios of neural processing.

D. The models and simulator proposed were used to provide satisfactory explanation and forecasting of selected neural processing in physiological and pathological scenarios\(^6\). Furthermore, the internal activity of Venn-networks resembles images produced by current functional imaging methods.

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\(^3\) Annex A contains publications supporting the Venn-networks model and its simulations using the constructed simulator

\(^4\) Annex A also includes some publications supporting the multiple sclerosis model

\(^5\) The accompanying CD-ROM includes version 1.0 of the simulator and several demonstrations

\(^6\) In chapter 6 and chapter 7 of this thesis the constructed simulator is widely used to investigate various aspects of neural processing in physiological and pathological scenarios
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I would like to express thanks to friends listed in forename alphabetical order, for the encouragement and help given during my PhD. It may be the case that some already forget the reason why their name is here, however their help cannot be disregarded. They are: Adriana Maciel Buarque, Albaniza Pimentel, Alcina Taison, Ana Luzia da Silva, Dr André Massensini, Aladim Cordeiro, Alcyr Oliveira, Andrew Thorpe, Carlos Eduardo Thomaz, Dr Catti Llado, Celine Barros, Christiano de Matos, Dr Cristovam Buarque, Desirée Lamb, Fábio Nogueira, Dr Felipe França, Dr Fernando Marar, Fernando Sérgio Santiago, Hindemburg Santana, Hilary Glasman-Deal, Ivan Mouro Fernandes, Jane Maciel Buarque, Dr Janet De Wilde (thanks also for supporting the colour printing of this thesis), Jean-Pierre Gutzwiller, José Adolfo de Almeida Neto, José do Rego, José Mário Santos, José Orlando de Miranda Júnior, Josemir Lira Alves, Dr Julie Wilkinson, Karina Barroso, Dr Kátia Guimarães, Dr Katya Kozicki,
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Sincere acknowledgements to members of the staff and colleagues of previous three Universities where I have studied prior to Imperial, namely Catholic University of Pernambuco-UNICAP, State University of Pernambuco-UPE/FCAP and Federal University of Pernambuco-UFPE. In addition, thanks to fellow countrymen of the Brazilian Association of Researchers and PG Students in the UK (ABEP), and to all unnamed Brazilians that have preceded me in this endeavour; their advice was inestimable.

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Two British texts shall be treasured as they gave me pause for thoughts. Though of diverse origins, they graciously complement each other as they subsume the nature of this overseas experience of mine, which was plenty of discoveries leading to reflection (and vice-versa). The first piece was found inside the London underground during an unremembered trip: “Reality is all that one manages to discover”. The second piece is a line from William Shakespeare’s Midsummer Night’s Dream (vide poetic section). In many occasions – similarly to what Theseus says in the play – I vividly felt like having the poet’s pen in my hand shaping-up immaterial thoughts. Indeed the vicissitudes of this period abroad, the panoply of my discoveries, and the substantial amount of reflection throughout the past four years have immensely and irreversibly changed my reality. This high fire most certainly forged me into another person.

Above all, Thanks to God for this great opportunity, actually to study abroad was an old dream that came true. My doctoral studies in the UK shall be remembered as a pleasurable privilege. It is also pleasant to think of so many people, who helped this work. The names above refer to great people who made all the difference for me. The many and priceless scientific-cultural-personal acquisitions obtained in the green-England, exciting-London and fantastic-Imperial College can only be yield by one’s lifetime dedication paying forward all these teachings. I can only and humbly be grateful forever!
Poetic Section

**Actus Quintus** - Folio text (1623 A.D.)[^9]

from: *A Midsummer Night's Dream* by William Shakespeare

---

Hippolita: 'Tis strange my Theseus, y these louers speake of.
Hippolita: More strange then true. I never may believe
These anticke fables, nor these Fairy playes,
These lovers and mad men have such nothing knowne,
Such shadowy phantastes, that apprehend more
Then cold reason can comprehend.

The Lunaticke, the Louer, and the Poet,
Are of imagination all compact.
One sees more diuels then vaste hell can hold;
That is the mad man. The Louer, all as franticke,
Sees Helens beauty in a brow of Egypt.

The Poets eye in a fine frenzy rolling, doth glance
From heaven to earth, from earth to heaven.
And as imagination bodies forth the forms of things
Heathen, the Poets pen turnes them to shapes;
And gives to aire nothing, a local habitation,
And a name. Such tricks hath strong imagination,
That if it would but apprehend some ioy,
It comprehends some bringer of that ioy.

Or in the night, imagining some feare,
How easie is a bush suppos'd a Beare?

Hippolita: But all the storie of the night told ouer,
And all their minds transfigur'd so together,
More witnesseth than fantasies images,
And grows to something of great constancie;
But howsoever, strange, and admirable.


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Roadmap (or suggestion for a selective reading of this thesis)

Ideally all parts components of this thesis should be read in sequence. Below there are some suggestions for selective reading according to readers’ background.

- **Neurologists**
  - Introduction (Chapter 1)
  - Chapter 2
  - Chapter 3
  - Chapter 4
  - Chapter 5
  - Appendixes B, C and D
  - Chapter 6
  - Chapter 7
  - Conclusion (Chapter 8)

- **Other neuroscientists**
  - Introduction (Chapter 1)
  - Chapter 2
  - Chapter 3
  - Chapter 4
  - Chapter 5
  - Appendixes B, C and D
  - Chapter 6
  - Chapter 7
  - Conclusion (Chapter 8)

- **AI researchers**
  - Introduction (Chapter 1)
  - Chapter 2
  - Chapter 3
  - Chapter 4
  - Chapter 5
  - Appendixes B, C and D
  - Chapter 6
  - Chapter 7
  - Conclusion (Chapter 8)
### Symbols and operators (relating to contribution)

<table>
<thead>
<tr>
<th>Symbols</th>
<th>Meaning</th>
<th>Operators</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>( U )</td>
<td>Type of processing unit</td>
<td>( \sum_{k=1}^{M} )</td>
<td>Sum index ( k ) from 1 to ( M )</td>
</tr>
<tr>
<td>( P_U )</td>
<td>Processing unit</td>
<td>If and only if</td>
<td>Proportional to</td>
</tr>
<tr>
<td>( R_o )</td>
<td>Region of the cortical map</td>
<td>Or</td>
<td>In all</td>
</tr>
<tr>
<td>( S^c )</td>
<td>Stimulus source of cardinality ( c_S )</td>
<td>And</td>
<td>Contains</td>
</tr>
<tr>
<td>( E^c )</td>
<td>Effector of cardinality ( c_E )</td>
<td>( \text{avg}(x) )</td>
<td>Has (cardinality one to) many</td>
</tr>
<tr>
<td>( F^{o,ef} )</td>
<td>Axonal fibre cardinality ( c_O, c_T )</td>
<td>( \text{arg Max}(x) )</td>
<td>Has (cardinality one to) one</td>
</tr>
<tr>
<td>( \theta )</td>
<td>Threshold</td>
<td>( { } )</td>
<td>Angle and simple braces</td>
</tr>
<tr>
<td>( D_o )</td>
<td>Distance between columns</td>
<td>[ ]</td>
<td>Interval, or Cartesian pair</td>
</tr>
<tr>
<td>( D^c )</td>
<td>Square distance – component ( h )</td>
<td></td>
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<tr>
<td>( C_n )</td>
<td>Collaboration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( { X }(t) )</td>
<td>Variable ( X ) at timestamp ( t )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( { X }(t+1) )</td>
<td>Variable ( X ) at timestamp ( t+1 )</td>
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<tr>
<td>( R_o )</td>
<td>Winning unit of region ( R_o )</td>
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<tr>
<td>( c{ P_U } )</td>
<td>Collaboration for unit ( n )</td>
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<tr>
<td>( n_n )</td>
<td>Learning rate for afferents</td>
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<tr>
<td>( n_{n_1} )</td>
<td>Decrement learning rate afferents</td>
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<tr>
<td>( C_R )</td>
<td>Cooperation radius</td>
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<td></td>
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<tr>
<td>( n_e )</td>
<td>Learning rate for efferents</td>
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<td>( n_{n_1} )</td>
<td>Decrement learning rate efferents</td>
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<tr>
<td>( Err_n )</td>
<td>Error for unit ( n )</td>
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<tr>
<td>( O )</td>
<td>Network output</td>
<td></td>
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<tr>
<td>( h_j )</td>
<td>Activation of neuron index ( j )</td>
<td></td>
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<tr>
<td>( w_{jk} )</td>
<td>Synaptic weight index ( jk )</td>
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<td>( \mu_j )</td>
<td>Multiple sclerosis factor index ( j )</td>
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<tr>
<td>( \alpha )</td>
<td>Additive error (constant)</td>
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<tr>
<td>( t_j )</td>
<td>Transmission time for axon ( j )</td>
<td></td>
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<tr>
<td>( T_{win} )</td>
<td>Time window for target area</td>
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<tr>
<td>( T_{win} )</td>
<td>Linear constant to find ( T_{win} )</td>
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<tr>
<td>( d_{win} )</td>
<td>Internode transmission time</td>
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<tr>
<td>( h_j )</td>
<td>MS imposed delay to internode</td>
<td></td>
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<tr>
<td>( \hat{h}_j )</td>
<td>Exclude activation of neuron ( j )</td>
<td></td>
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<tr>
<td>( \hat{g}_j )</td>
<td>Stroke factor index ( j )</td>
<td></td>
<td></td>
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<tr>
<td>( \Xi )</td>
<td>Stroke affected areas</td>
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Chapter

1 Introduction

“I have striven not to laugh at human actions, not to weep at them, nor to hate them, but to understand them.” Baruch Spinoza 1632–1677: in Tractatus Politicus (1677).
1.1 Foreword

Understanding how a functioning brain produces a mind is one of the ultimate challenges posed to humankind. Assuming that this bold task is possible, it certainly will require a number of preceding steps: (i) understanding life formation itself and (ii) understanding the emergence of intelligence.

Even though science has been producing breakthroughs at incredible rates, one cannot be sure if the mind will ever be fully understood. At present physicists, biochemists and biologists are committed to this quest in their respective research fields. They are all aiming at understanding how, from sub-atomic particles, we may ended up having complex molecules and ultimately, life. Concomitant to this, some psychologists, neuroscientists and scientists studying artificial intelligence are dedicated to comprehend how life became intelligent, and how intelligence can self-sustain itself. Recent advances in genetics, especially after the conclusion of the ‘Human Genome project’ [NHGRI02], have contributed towards the pace of unveiling mysteries of life. All these scientific resolve leave researches on plausible intelligent computation a yet more appealing and challenging path.

But intelligence in itself is not an immaterial or intangible entity. It is grounded in the underlying mechanisms of the nervous systems of living creatures, no matter how simple or complex they are. This emergent phenomenon – magnificent in itself – seems yet to be accountable for the self-sustainability and non-monotonicity of life, and eventually, for (our) free-will. Thus, any advance in understanding of how life can exhibit intelligent behaviour requires insights in the “mechanics” of the nervous system.

This thesis is intended to be one more brick on this tortuous and long way ahead, towards the goal of explaining how biology can sustain intelligence (and then, vice-versa). The central idea investigated is how biologically inspired computation and a systemic framework for neural information processing can be an alternative to the traditional cumbersome mathematical or statistical approaches for tackling the problem. The author suggests that more flexible, adaptable and scalable models can be created if structural and dynamic features of the biological system are taken into consideration.

In addition to the contributed model and simulator, some philosophical considerations, reviews on neurobiology and current functional imaging methods, and a handful of simulations are presented. We expect that these “ingredients” may stimulate and inspire the reader in this fascinating and not uncomplicated subject.
1.2 Context and motivation of this thesis

The organisers of the world congress of **neuroinformatics** held in Vienna on September 2001 stated that understanding structure, function and development of the brain in **health and disease** represent one of the great scientific challenges of the 21st century [VIENNA01]. Many others before have also acknowledged the difficulty of these challenges to understanding brain function [Kandel00][Greenfield97]. Although many scientific communities are committed to this task, which produces synergistic cross-fertilisation, their non-coincident approaches and sometimes non-coincident objectives do not make the task any easier.

In order to restrict the limits of these challenges, we assumed that a working brain only produces two outcomes, which are observable: in the **macro-scale** – ‘behaviours’ and in the **micro-scale** – ‘functional images’. However, this simplification is not sufficient to help on understanding of how these two observable outcomes relate to the neurobiological substrate. This is surprising, considering the vast amount of scientific knowledge which is currently available.

In fact, all information about organisation and function of the brain (*vide* chapter 2), and functional imaging techniques that allow us to investigate a working brain (*vide* chapter 3) are not eloquent enough to explain the gap between sound neurobiological concepts and cognition (including behaviour). Similarly, the symptoms of some neurological diseases are not fully explained in terms of the effects of their physical causes. Consequently, we cannot foresee evolution of symptoms of these diseases based on evidence readily available in the patients’ brains. Hence, the challenges above can be rephrased as a question, not incidentally as motivation of this research: **how can one better understand neural computation if the available knowledge does not safely bridge what one sees to what one knows?**

A plausible answer to this question, which becomes part of the hypotheses adopted in this thesis, is to utilise ‘computer models’ based on sound neurobiology constraints. If carefully built, these models should be able to evaluate these hypotheses and be used in simulation of brain function. Fortunately, computers are now powerful enough to deliver the necessary help on such high goal. Moreover, neurally inspired models – *i.e.* connectionist systems – provide a useful start point for understanding how cognitive computation might be performed [McLeod98]. Hence, by combining the
ingredients shown in Figure 1, we produce a putative contribution to better understanding the functioning of the brain.

![Figure 1](image)

**Figure 1 – Research areas considered in this thesis**

1.3 The research hypotheses

This research hypothesises that:

a) structure and connectivity of the brain influence neural processing;

b) selected neural disorders can be explained and forecast in terms of changes to the normal physiology of the system; and

c) underlying principles used in some artificial models can produce emergent activations that resemble imagery of functional modalities of the brain.

1.4 Thesis and research

1.4.1 Organisation of this thesis

This thesis was conceived for readers interested in various aspects of the brain, and from various disciplines. Therefore, this thesis is organised in a way to represent gradual the transition between initial philosophical aspects towards a computational model to simulate functional aspects of the brain. The background is divided into three chapters addressing:

(i) the biological features of the brain – chapter 2,

(ii) the current method for acquiring functional data of the brain – chapter 3

(iii) the principles of artificial intelligence and connectionist systems that were utilised in the proposed model – chapter 4.
The contributed ideas of this thesis are presented as a theoretical model – chapter 5, and as an implemented computer simulator – appendix B. The simulator produced was intensively used to generate various simulations of physiological and pathological scenarios for testing the hypotheses. Due to the large number of simulations carried out, they were divided into two chapters. Chapters 6 and 7, respectively, include simulations of physiological and pathological scenarios (i.e. for testing correctness and robustness).

Within a systemic and analytical framework, this research was carried out through computer simulations. As such, the organisation of this thesis can be understood as the phases of a system engineering process: analysis, design, implementation and test. In Figure 2 see how the chapters of this thesis are grouped according this perspective.

![Figure 2](image)

**Figure 2** – Main parts of the thesis viewed as phases of the system engineering process

### 1.4.2 Approach and conduction of the research

The complex nervous system (described in the chapter 2) is the object of study of many disciplines. Rather than complying with existing particular disciplines in this work we started by analysing the nervous system using an interdisciplinary approach. The first obvious fact was the above mentioned two observed brain outcomes: ‘behaviour’ and ‘activations’ of the cortex. The cause-effect relation between them (discussed in chapter 3) implies that neural substrate dynamics is directly involved in their production. Thus, behaviour and activations are mere **effects** caused by the underlying neural activity. So, we decided to concentrate the research on the understanding of **causes**, i.e. how neural activity happens.

To avoid deducing neural activity from behaviour, we decided to use computational models as the metaphor for explaining the latter. The initial stages of the model involved identification of the building blocks of the system and the dynamics of their interactions. This process had to be holistic as the model should account for behaviour rather than only reproducing cortical activations. This means, for example, that ‘structure’ and ‘dynamics’ were conceptualised separately, but implemented (and processed) jointly, as shown in Figure 3.
Another constraint selected for the model was that the granularity level needed to be compatible with data available on neural activity, *i.e.* functional imaging data. After the extraction of the major features of the system, a formal model was devised considering that the model construction should follow the inverted order of the analysis, *i.e.* the model construction should happen from bottom to top. If this was correct and if the reverse-engineering was made right, the produced model should be as flexible as biological systems. This flexibility allows that *n* individual structures exhibit *m* specific dynamics (see idea illustrated in Figure 4), and ultimately, the model should express some emergent properties of the modelled system.

Following the computation implementation of the ideas included in the model, a series of simulations were carried out to validate the axioms utilised. To provide comparability among simulation results we decided to utilise one functional system and data set, and many scenarios of neurophysiology and neuropathology.
1.4.3 Expected results

The results of this exploratory investigation are expected to examine whether the theoretical and methodological approaches used are appropriate for helping the research problem (i.e. checking the validity of hypotheses). This means that the proposed model and approach should advance the understanding about the impact of brain structure on selected brain functions (and behaviour). Therefore, the simulation results of the artificial models utilised in this thesis are the putative metaphor for an explanation of the observable behaviour and activations of the cortex.

The proposed models should also be accountable for symptoms elicited in the case of selected diseases. Hence, the correctness and robustness of the models in simulations of ‘physiological’ as well as in ‘pathological’ scenarios should contribute to reducing the gap between micro and macro neural computation.

1.4.4 Notation, conventions and terminology

- Some terms less frequently used in the technical literature were selected to be explained, vide the Glossary section. Items included in the glossary are indicated by bold font.
- Cited references (in angle brackets) are composed of the surname of the first author plus the two last digits of the publication year.
- A few terms are used as synonyms, notably:
  - cerebral cortex – cortex;
  - cortical column – processing unit;
  - brain area – region;
  - axon – fibre;
  - synapse – connection weights;
  - experiment – a complete and self-contained set of computer simulations carried-out in this work (loosely it is equivalent to a simulation-set in most cases);
  - architecture – umbrella for structure and connectivity of any sort of network, sometimes as a generic term for Venn-network;
  - contra-lateral activation are referred to regions instead of effectors.

Finally, we encourage the reader to consult the sections: Summary of chapter and appendices, and Road map. This will improve the understanding as well as the efficacy of the reading of this thesis.
1.5 Philosophical and other issues out of the scope of this work

Given the intricacy of the areas involved in this work, we found it useful to explicitly include a list of philosophical and other topics that are not incorporated as part of this research. This decision is aimed to improve the understanding of the scope and objectives of this work, as well as highlights and limitations of the thesis. This decision does not imply a lack of importance or pertinence of any issues not addressed and listed below. Actually some of these issues are suggested as future work (see chapter 8).

A list with topics not intended to be addressed in this work is included below. The list is organised from a philosophical perspective up to practical issues:

- Evolution (i.e. acquired features of further generations [Premack03])
- The nature and nurture debate
- Brain development
- The mind-body problem (or psychoneural intimacy [Honderich88])
- Proposition of psychophysical laws10
- Free-will and Consciousness (or intentionality [Searle00])
- Definitions of intelligence
- Functional image analysis or model for any particular modality
- Clinical investigations in psychology and neurology

Also not considered central in the scope of this work are:

- the central question for the fathers of experimental psychology11: “How does stimulus lead to subjective experience?” [Gardner00], i.e. this work does not aim to explain how neural processes generate a mind.
- the role of genetics as the ‘white-paper’ that shapes up not only anatomy but also physiology (i.e. the functionality) of live systems. This means that the known genetically controlled mechanisms of deciding topology, connectivity, and features of the processing units of the nervous system are taken for granted throughout this thesis.
- the reasons why a system that is imminently physical (and interact with an outside physical world) may not be deterministically influenced by it.

---

10 If some neurological event is sufficient condition for the occurrence of psychological event then it should exist a psychological law to facilitate predictions of psychological events given neurological events [Honderich88]
11 Weber, Fechner, Helmholtz, and Wund are considered the fathers of experimental psychology [Gardner00].
1.6 Summary of chapters and appendixes

This thesis is organised into eight (self-contained) chapters and six appendixes. Each of these parts is summarised in the paragraphs below. Readers should use the provided Roadmap section to read selected parts of the thesis. Sections of this thesis such as Abstract, Objectives, Contribution, in addition to the various indexes should also assist the reading of this document. Finally, this work has also an accompanying CD-ROM, which content is as well subsumed below:

Chapter 1: has introduced the context, the motivation and the research hypotheses. It described the organisation of the thesis, the approach adopted in the research, the expected benefits and notation utilised in this dissertation. The chapter described the scope of the research and also included a list of issues that were not addressed during the course of the study.

Chapter 2: briefly looks at the central nervous system (CNS) with the objective of collecting facts that are going to be used as axioms in the computational model adopted in this thesis. There is a top-down review of previous research carried out on the CNS in relation to aspects of anatomy, histology, connectivity, physiology, and one example of a functional system is looked at (i.e. voluntary motor control). The chapter focuses on the cerebral cortex and brain organisation, as well as on the understanding of the main mechanisms of neurocommunication. The chapter concludes by reviewing the main features of ‘normal’ ageing processes in the CNS, together with the main characteristics of neurological common illnesses such as multiple sclerosis (MS) and strokes.

Chapter 3: includes a review of various methods of acquiring functional data from the CNS. Functional principles of each method are described in relation to their potential and limitations. Radiological methods reviewed include computer tomography (CT), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Electromagnetic recordings reviewed include electroencephalography (EEG) and magnetoencephalography (MEG). Finally, magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) are also described. The chapter concludes by discussing the advantages of multiple modalities, and additional methods that can help in the understanding and acquiring of functional data.
Chapter 4: this chapter begins by introducing some of the features of algorithms that use artificial intelligence, specifically focusing on the abilities of artificial neural networks (ANN) techniques. Fundamental issues of ANNs such as type of neurons, network structure, and learning strategies are then discussed. Special attention is given to ‘error-correction’ and ‘competitive’ types of learning. Selected topologies of ANNs are briefly analysed namely, self-organising maps, counterpropagation and instar-outstar.

Chapter 5: describes Venn-networks that are novel neural network introduced in this thesis and used for testing the research hypotheses. Starting with a general discussion about usage of computational models to understand brain function, this chapter highlights several aspects of the putative neural network which enable a better understanding of certain aspects of brain function – especially when modelling disorders such as multiple sclerosis and strokes. The chapter concludes by laying down some directions for the computer implementation of Venn-networks; and offering directions for aspects and properties to be simulated.

Chapter 6: presents the five (self-contained) simulation-sets used to investigate the properties of healthy biological systems: (i) structural-functional equivalence; (ii) active-passive activations; (iii) ageing; (iv) modulation (including thresholding, and inhibitory/excitatory signalling); and (v) contra-lateral inhibition. Each set of simulations presented contains several graphic illustrations of training, output performance of virtual effectors and typical activations elicited by the cortical map. A brief motivation for the experiment, descriptions of data used, network structure and simulation, and comments upon results are presented. Together, these simulations show how flexible GVNS is and prove the correctness of the Venn-network when processing physiological scenarios.

Chapter 7: presents the five (self-contained) simulation-sets used to investigate the properties of diseased biological systems: (i) multiple sclerosis; (ii) cerebral stroke; (iii) multiple sclerosis (re-learning); (iv) strokes (re-learning); and (v) activation lateralisation. Similarly to chapter 6, each set of simulations presented contains several graphical illustrations of training, output performance of virtual effectors, and typical activations elicited by the cortical map. A brief motivation for the experiment, descriptions of data used, network structure and simulation, and comments upon results are also provided. Together, these simulations show how versatile GVNS is and prove the robustness of the Venn-network when processing pathological scenarios.
Chapter 8: presents the overall conclusion of the work. Next, an overall discussion of the results touches more philosophical aspects of the work (recall that partial conclusions and discussion about each experiment are included in chapters 6 and 7). The chapter short-lists the enormous possibilities for future works that are grouped into three, so-called, “avenues” – namely, (i) refinements upon the models proposed, (ii) calibrations utilising the proposed model, and (iii) further computer simulations using the proposed models. Finally, the chapter concludes with a list of questions offered for motivating new researches that may continue along the line of research pursued in this thesis.

Appendixes:

- Appendix A contains a list of abstracts of the author’s publications that were published during the course of the research.

- Appendix B comments upon the GVNS (i.e. generalised Venn-network simulator), which is a comprehensive neural network simulator developed by the author to illustrate the ideas proposed in this thesis. It includes a brief description of the simulator and highlights its use-cases, internal structure, “behaviour”, operation, key-concepts, parameterisation, input-output files, user interface, and screen snapshots of the simulator.

- Appendix C has comments upon the pathology-like generator that is a small computer auxiliary application to the GVNS, which produces pathology-like data specifically for simulations of multiple sclerosis plaques and strokes of the cortex. The appendix includes a brief description of the pathology generator, and explains briefly the process of data generation for the selected diseases, *i.e.*, MS and strokes.

- Appendix D describes data used to train and test the simulation model. It also explains how Mozart’s piano composition – *Sonata Facile* – was encoded into the numerical computer files that are used to train the artificial neural networks. This appendix also includes the complete set of data used for training and testing all of the topologies in the thesis.

- Appendix E describes the content of the CD-ROM accompanying this thesis. It includes some technical information about the medium and recording process, minimum computer requirements for browsing and running the demonstrations, and some instructions and applications for starting-up the CD-ROM and applications included.

- Appendix F contains a description and results of initial simulations carried out with the MS-plaque model, mostly extracted from [Buarque01a].
**Accompanying CD-ROM:** The CD-ROM is included as complementary material produced to illustrate some of the concepts, ideas and simulations included in the main thesis. The CD contains eight distinct types of information, namely:

- The GVNS software with some brief documentation;
- Ten demonstrations (demos) of the Venn-simulator performing various tasks;
- Abstracts and charts of various experiments carried out during the course of the research;
- A complete set of the data generated in Chapter 6 (encompassing all five experiments);
- A complete set of the data generated in Chapter 7 (encompassing all five experiments);
- Input data used for trainings of all topologies appearing in the thesis
- Pathology generator software with brief documentation
- Pre-emptive answers about potential problems executing the simulations, author contacts and some selected introductory sections of the thesis.
Chapter

2 Issues of Neuroscience and Neurology

2.1 Introduction

Throughout recorded history understanding the “production” mechanisms of human thoughts, body functions and behaviour has always been a challenge to scholars and scientists [Greenfield97]. As long as 500 B.C., ancient Greeks such as Hippocrates and Plato wondered about these and realised that the brain is responsible for the behaviour of both humans and other animals [Levitan97]. Following that, many theories have been proposed to explain the intriguing phenomena of a functioning brain. With hindsight, initial ideas were as audacious as they are now known to be absurd, e.g. phrenology. Nonetheless, most of these initiatives have not effectively advanced boundaries of knowledge a great deal; at least they kept alive the interest on the subject.

The succession of scientific advances and discoveries related to the brain and nervous system were very slow and of low profile for over two millennia. It was only in the late 18th Century that Galvani discovered electrical properties of muscle and nerves (inaugurating electrophysiology), and in the early 19th Century, Ramon & Cajal discovered that the nervous tissue is composed of neurons (leading to the neuron-doctrine) [Kandel00]. From this point in time, interest in the brain has only grown, and so did the relevance of research works.

Modern research on brain and nervous system has generally involved breaking down the complexity of the functions of this system into their more evident aspects namely: anatomy, physiology, behaviour, pathology, formation, development, evolution, and cognition. By doing this, the complexity of the task is greatly reduced. However, these aspects are often interdependent, interact and even interfere with each other. \textit{<this is used as a conjecture for the proposed model: attempts to tackle neural computation should include an integrative approach of its constituent aspects>.}

The nervous system is an astonishing creation of nature and is largely responsible for the survival and adaptation of humans (and other animals) to their natural environment. Per Brodal describes the nervous systems in his seminal book [Brodal98] as a complicated highly organised network for communication and information processing. \textit{<this is used as a conjecture for the proposed model: brain structure is related to its evoked properties>.

The nervous system is divided in two major structures or sub-systems [Leeson85]:

\footnote{12 “Neuron doctrine – the principle that individual neurons are the elementary signalling elements of the nervous system” [Kandel00]}

Chapter 2 – Issues of Neuroscience and Neurology

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1) Central Nervous System (CNS), consists of brain and spinal cord
2) Peripheral Nervous System (PNS), connects the CNS to the rest of the body

Although both of these quite intricate systems perform very different functions, they are complementary and communicate with each other extensively. The CNS – one of the most complex systems in existence – is composed of a large number of anatomical and functional units. Most of these are extremely interconnected and interdependent to one another. Because the CNS mostly encompasses the domain of this work, this chapter is dedicated to comment upon it.

This chapter includes background issues about anatomy, physiology, functional system (i.e. motor system), and an introduction to some pathologies of the CNS. An understanding of the fundamental concepts discussed below is necessary in order to tackle the goals of this thesis and as inspiration for realistic models of brain function.

### 2.2 Anatomy and histology of the nervous system

The CNS is divided into two anatomical parts: the brain and the spinal cord. The brain, which is the most important, can be further dived into (i) the cerebrum, (ii) the cerebellum, and (iii) the brain stem. All of these and other components are illustrated in Figure 5 and Figure 6.  

- The spinal cord, which is a 40-45 cm long with approximately the same thickness as the little finger, lies inside the vertebral canal.
- The brain stem, the rostral continuation of the spinal cord. From its caudal portion, the brain stem is subdivided as follows: the medulla oblongata, the pons, the mesencephalon and the diencephalon.
- The cerebellum, or “little brain”, has two hemispheres. It is located in the base of the skull and dorsal to the brain stem, with which it is connected.
- The cerebrum is an egg-shaped structure filling most of the cranial cavity. It has two almost completely disconnected halves, the cerebral hemispheres, where the cortex (i.e. grey matter) is located. Each hemisphere can be topologically divided in four lobes: frontal, parietal, temporal and occipital.
- The cortex is a thin layered tissue, all folded that envelops the two cerebral hemispheres. The cortex can also be divided into areas that do not match with the lobes. Normally the functional activity is the criterion used for its classification, e.g. sensory and motor cortices [Brodal98] [Wilson99].
Figure 5 – Annotated visualisation of computer reconstruction of the human brain displaying sulci, giri, lobes and major anatomical structures; picture extracted from [Sundsten94]
Figure 6 – Annotated visualisation of computer reconstruction of the human brain displaying ventricles, corpus callosum, and other important subcortical structures; picture extracted from [Sundsten94]
From a histological perspective, the CNS is composed of two types of tissue, the (i) neuronal and (ii) glial tissues; together they make the ‘nervous tissue’.

- The neurons, or nerve cells, are responsible for all the processing (stimulation or inhibition to other neurons) existing in the nervous system. The human brain is made up of approximately one hundred billion neurons, most of them interconnected up to 40,000 others via connections called synapses [Rolls97]. At variable spike frequency and potentials, these connections can transmit and receive the signals processed by other neuron. Kasabov [Kasabov96] also mentions the substantial range of neurons in existence: over 50 different types in the cerebellum alone. Despite such impressive figures, this does not reasonably explain the complex behaviour responsible for the exceptional flexibility and computing power of the brain <this is used as an axiom for the proposed model: models should include many types of processing units>.

- The glial cells are accountable for supporting the nerve tissue. There are four types of neuroglia: (a) astrocytes, (b) oligodendrocytes (composing the macroglia), (c) the microglia, and (d) the ependymal cells [Shepherd94]:
  - Astrocytes are involved in the structural support in the CNS, they may also exchange substances with the neurons, maintain extracellular ionic concentrations, degrade some neurotransmitters, remove neuronal debris, and compose a diffusion barrier (part of ‘blood brain barrier’) [Leeson85]; the latter is argued [Shepherd94].
  - Oligodendrocytes are responsible for the myelin formation, which insulates some of the nerve fibres, the axons. Smaller axons are generally unmyelinated while longer ones tend to be myelinated [Leeson85]. The problems resulting from damage to the nerve cells’ sheathing is addressed further in chapters 5 and 7.
  - The microglia are phagocytes and are intimately related with brain protection and respond rapidly to nerve injury [Banati98].
  - Ependymal cells form the lining of the interior cavities (ventricular systems) existing in the brain and spinal cord [Brodal98].

---

13 The term nerve fibre refers to both axon and dendrites together.
2.3 Connectivity in the CNS: pathways and type of fibres

The various components of the nervous system and regions of the cortex presented before communicate with each other in an extremely organized manner. Bundles of nerve fibres comprise pathways that are punctually originated and target specific regions, and can be identified in almost the same locations in different individuals [Amaral00]. These pathways are mostly composed of myelinated axons when implementing the necessary short as well as long-range connections. According to their physical characteristics, pathways are grouped into three types: commissural fibres, u-fibres, afferents and efferents. This section is aimed to briefly describe them.

2.3.1 Commissural fibres

The two hemispheres of the brain are highly connected one to another. Homologous areas have (inhibitory) long-range fibres crossing to the contra-lateral side mostly via the corpus callosum [Brodal98][Bianki85]. A partial removal of the hemispheres, in Figure 7, shows the trunk of the corpus callosum featuring (transversely oriented) calosal (or commissural) fibres. Laterally, the fibres of the corpus callosum radiate towards the various lobes of the hemispheres [Williams97].

According to a number of researchers, the commissural fibres can be bisected in some severe cases of epilepsy [Gazzaniga00a][Saper00]. Which shows that the cerebral hemispheres can operate independently from each other <this is used as axioms for the proposed model: cortical regions operate independently; and axons interlink them>.

![Figure 7](image)

**Figure 7** – Commisural fibres of human brain (see legend on the right); picture extracted from [Williams97]
2.3.2 U-fibres

Comprising the subcortical myelinated fibres, the brain has another type of short and long-range of fibres interconnecting regions of the same hemispheres – association tracts. Short-range association tracts connect adjacent gyri and are called u-fibres [Diamond85], the other association tracts link non-adjacent gyri within the same hemisphere. In Figure 8 both of these modalities of fibres can be seen; legends (1) and (2) depict examples of long and short range association fibres respectively.

Figure 8 – Association (u-) fibres of human brain; picture extracted from [Williams97]

2.3.3 Afferent and efferent fibres

Legends 1-7 of Figure 9 illustrate the fibres that connect the cortex to subcortical structures, e.g. thalamus, medulla. Often, these structures relay signals back to cortex.

Figure 9 – Ascending/descending fibres of human brain; picture extracted from [Williams97]

All these pathways comprise a highly intertwined network of fibres \(<this is used as an axiom for the proposed model: fibres should connect components widely/freely>\).
2.4 Physiology of the nervous system

The range of tasks processed by the CNS is very diverse. The tasks can vary from simple reaction to sensory stimuli to very complicated tasks such as action planning and verbal communication. The CNS controls the majority of these functions, either directly or indirectly. As such, the complexity and importance of the nervous systems grows markedly as the animal “climbs” on the ladder of evolution.

Various approaches have been adopted to analyse the CNS and its functionality. On the one hand, computational neuroscientists generally consider different levels of abstraction for their investigations, namely sub-cellular, cellular, network and behavioural levels. On the other hand, neurobiologists adopt other criteria [Gay95]:

(i) architectonics – observing the distinct structures (cytoarchitectonics and myeloarchitectonics or histochemical and non-histochemical), e.g. Brodmann areas\textsuperscript{14};
(ii) connectivity – focusing on patterns of input/output for groups of neurons;
(iii) topographical mappings (either anatomical or physiological areas);
(iv) behavioural studies – observation of diseases;
(v) impairments; or
(vi) any combination of the above

The physiological functions of the anatomical areas mentioned in the previous section are briefly described as follows [Wilson99][Gilman92][Kandel00]:

- The spinal cord, apart from the simple but important local information processing, the spine mediates the communication of the PNS and the brain via the brain stem.
- The brain stem is responsible for the functions necessary for survival (\textit{i.e.} breathing, digestion, heart rate, and blood pressure) and for arousal (\textit{i.e.} being awake and alert). The brain stem includes the following structures: mid-brain, pons and medulla oblongata.
- The cerebellum, together with other structures of the brain, is intimately involved with the execution and co-ordination of movements.
- The cerebral hemispheres perform the higher cognitive functions and constitute, ultimately, the apex of the whole nervous system.

\textsuperscript{14} Brodmann produced the most utilised classification of the human cortex into areas according to its cytoarchitectonics [Brodmann09], refer also to the diagram in the beginning of chapter 3.
2.5 Example of a functional system: voluntary motor control

2.5.1 Overview

The CNS encompasses many functional (sub-)systems that vary in complexity, functionality and internal organisation. This thesis does not aim to discuss these systems in detail, but it does need a focal point of reference for computer simulations (as described in chapters 6 and 7). Moreover, this necessity forced us to select one, out of many existing sub-systems of the CNS. The motor system is an obvious candidate because of its hierarchical organisation, evident elicited 'outputs' and abundant knowledge available. Notice that rather than trying to model the entire motor system, we aimed at the voluntary motor control. This portion of the motor system provided inspiration and was used to develop and test our ideas on modelling neural processing.

The motor system comprises the set of structures of CNS that control the skeletal muscles (i.e. voluntary movements), which contrasts to the somatic motor system that controls glands and smooth muscles. This interrelated and complex subsystem of the nervous system has several components mediating, initiating and controlling the execution of voluntary movements. Peripheral motor neurons and central motor pathways comprise the structures used to mediate the movement commands, which are initiated and corrected on the motor cortex, cerebellum and basal ganglia.

Movements of the body, limbs and extremities – the resulting actions of the motor system, can be analysed in many different ways. From a muscular perspective they are isometric or isotonic contractions. Regarding the degree of conscious control of the movement, they can be voluntary or involuntary. And finally, movements can also be analysed based on the velocity of their execution, which can range from ballistic (so fast that once initiated cannot be stopped) to very slow ones. Per Brodal argues that the degree of variation in the conscious motor control is related to the participation of the cortex [Brodal98]. This means that the more voluntary the movement, the greater the participation of the cortex and lesser involvement of sub-cortical structures <this is used as an axiom for future models: motor control presupposes hierarchy of regions>.

Although not formally part of the motor system, sensory feedback is of great importance for learning, execution and improvement on the performance of the movements. Thus, visual and mechanic cues from exteroceptors and proprioceptors were also obvious candidates as integrants in a model of the motor system <this is used as an axiom for the proposed model: motor control presupposes feedback>. 
2.5.2 CNS components involved in voluntary sensory-motor control

Apart from most reflexes\textsuperscript{15} that are mediated in the spine or in the lower parts of the CNS, even simple voluntary movements may involve many components of the CNS and several portions of the cortex for its perception and execution. This subsection includes a brief description of the components and cortical regions involved in sensory motor control in humans [Brodal98]:

- **Peripheral motor neurons** (or lower motor neurons) – are somatotopically located in the spine and their axons link to skeletal muscles. They are the final stage of signal propagation that originates in the CNS. The motoneurons use \textit{acetylcholine} as their \textit{neurotransmitter} and are of two types (\textit{alfa} and \textit{gamma}). Motoneurons vary greatly in their sizes and firing rates, which influence their functional usage, e.g. smaller \textit{alfa}-motoneurons have lower firing rate. Thus, they can fire for longer periods and as a result of that are used in movements that do not require force. Muscle cells connected to the same motoneuron function together at the same time the associated neuron fires. The force requirement determines the number of these muscular units to be recruited.

- **Basal Ganglia** – are intercalated in a loop between the thalamus and the cerebral cortex. Diseases of the basal ganglia generally interfere with the execution of movements. Because these structures only indirectly control movements they are not of direct interest for the present work.

- **Cerebellum** – is another structure indirectly involved in the execution of movements. Like the basal ganglia, the \textit{cerebellum} is intercalated in a neural loop between cortical motor areas and central motor pathways. Receiving massive proprioceptive information, this important structure chiefly contributes with performance enhancement of movement correctness. Because the \textit{cerebellum} only indirectly controls movements, it is also not of much interest for the present work.

- **Motor areas** directly control voluntary movement; Figure 10 illustrates their precise location in the cortex. These areas are \textit{primary motor area}, \textit{supplementary motor area} and \textit{premotor area}; see described below:

\textsuperscript{15} Reflexes are simpler (motor) actions than can be “resolved” as sensory-motor loops closed at the spine. \textit{Sign of Babinski} and knee-jerk are examples of reflexes, and also prove of the existence of various levels of control in the CNS.
- Primary motor area (or area MI) – is located at Brodmann area 4 and receives afferents from SI\textsuperscript{16}, SII\textsuperscript{17}, thalamus (specifically the ventrolateral nucleus – VL) and cerebellum via VL. The firing frequency of neurons of this area is related to the force of muscular contraction exerted for the excitation of motoneurons, at the same time they inhibit antagonistic muscles. Part of the pyramidal tract originates in the MI. This area has the ability to directly control voluntary movements <this is used as axioms for the proposed model: motor control presupposes specificity of regional function; activity of the cell population defines force to be applied in the movement execution>.

- Supplementary motor area (or SMA) – is located in front of the MI (medial on both hemispheres). It sends fibres to spinal cord, reticular formation and MI. Thus, it influences motor control, both directly and indirectly. Activity in this area is recorded especially in complex tasks. Animal damage studies show that impairment of SMA troubles movement dexterity and coordination [Brodal98].

- Premotor area (or PMA) – is located at Brodmann area 6 and receives afferents from the frontal lobe. It is strongly connected to the reticular formation, the red nucleus, the basal ganglia and indirectly the cerebellum. Animal damage studies show that impairment of this area produce consequences for visual coordination and planning of movement [Krakauer00].

In Figure 10 notice the hierarchical organisation of the motor system, namely, frontal lobe projecting to PMA and SMA, and these areas then projecting to MI. The homunculus displayed in Figure 11 has complementary indication of sensory and motor functions localisation in the motor and sensory “strips” of the cortex; the colour schema of figure legends agrees. Although movements can be elicited from almost every part of the CNS, only in some specific areas of the cortex the activation threshold is low enough to accommodate the motor control (Brodmann 4 and 6). This suggests that cytoarchitectonics is decisive for function localisation in the brain <this is used as an axiom for the proposed model: processing units should include type specificities>.

\textsuperscript{16} SI is the somatosensory cortex.
\textsuperscript{17} SII is the second somatosensory cortex.
Figure 10 – Cortical areas that control movement; picture modified from [Driesen02]

Figure 11 – Sensory and motor homunculus; picture modified from [Amaral00a]
2.5.3 Central motor pathways

The fact that many structural components of the motor system utilise distinct tracts to send or receive signals to the muscles does not mean that there is no interaction and cooperation between them. On the contrary, although not yet completely understood, the mechanism of selection among the motor tracts considers aspects such as the nature of the movement to be performed, e.g. sequential, non-periodic etc. It also considers features such as the expected velocity and strength, and expected performance. Altogether this will define the type of control exerted, neuronal populations and routes to be used to generate and transduce signals towards the muscles.

The main central motor pathways in humans are described below. Their intertwined conformation makes difficult the identification of their individual functions, and much of the available data come from animal experiments, thus containing an inherent degree of imprecision. The list below includes a brief description of the tracts, their main function and some characteristics [Brodal98]:

- The pyramidal tract (or corticospinal tract) – is the most important amongst all the motor tracts, it connects neurons adjacent to the central sulcus in the cortex directly to the spinal cord and the cranial nerves nuclei. Most of the fibres cross to the other side of the body, resulting in the contra-lateral sensory-motor control (see this in Figure 12). The thickness of the fibres of this tract varies greatly, however the majority is thin, and the conduction speeds are between 5-30m/sec. This is the only pathway that connects the cortex directly to the spinal cord, and its function is chiefly related to voluntary movements this is used as an axiom for the proposed model: pyramidal tract directly controls voluntary movement.

- The corticoreticulospinal tract – is the tract involved in the control of the body posture, i.e. maintaining the body in the upright position. The reticular formation is an important source of descending nerve fibres to the spinal cord. It receives inputs from many other areas centres in the CNS involved with movement smoothing and balance control namely, the cerebellum and the vestibular nuclei.

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18 Anterior areas to the central sulcus: Brodmann areas 4 (MI), and area 6 (SMA and PMA).
19 Posterior areas to the central sulcus: Brodmann areas 3, 1, 2 (SI and SII) and parts of the parietal cortex - Brodmann area 5.
• The **Rubrospinal tract** – anatomical studies among species have found smaller ratios of *rubrospinal* to *corticospinal* fibres as the complexity of animals increase. This may suggest a diminishing importance of the *rubrospinal tract* in humans [Brodal98]. The existence of red nucleus connections to the cerebellum also suggests some participation in the modulation on more elaborated physical movements.

![Figure 12](image)

*Figure 12 – Human pyramidal tract controlling finger flexion; picture modified from [Amaral00a]*

• The **tectospinal tract** – this pathway is mainly involved in the coordinated movements of the head and eyes together. It connects some structures of the mesencephalon to superior parts of the spinal cord.
• The vestibulospinal tracts – are a pair of pathways, lateral and medial, that are mainly related to maintenance of balance and body posture. Both tracts connect the vestibular nuclei to the spinal cord in various distinct portions. As opposed to the reticulospinal tract, the influence of the cortex on the modulation of movements via this tract is small. Therefore, the nature of the posture adjustments mediated by this tract tends to be more automatic, although some voluntary control is also possible.

• Monoaminergic pathways from brainstem to spinal cord – are a scattered group of cells, the nucleus locus coeruleus and the raphe nuclei, send monoaminergic20 descending fibres to the spinal cord. These tracts are unlikely to control directly body movements, but are deeply involved in the modification on the excitability of motor neurons. They also can increase the pain threshold of the nociceptors. Therefore, the monoaminergic pathways can modify the performance of the execution of the movements <this is used as an axiom for the proposed model: modulation can happen via confluent pathways>.

2.6 Cerebral cortex

The human cerebral cortex is by far the most evolved living tissue. It is responsible for all higher cognitive functions, as other simpler tasks are looked after by lower components of the CNS. Although the latter maybe classified as simple, they are important as to life supporting activities such as breathing and heart beating. However, the complexities of the tasks dealt with by the cortex encourage much more investigations on functioning and organisation of this important component of the CNS. This section aims to study organisation and principles of functioning of the cortex.

2.6.1 Layers of the cerebral cortex

The cortex is highly convoluted, 4-6 mm thick, six-layered tissue. Each layer contains different cell types, fibres and has a distinctive connectivity. From the external part of the brain to the inside, the layers are: (I) molecular layer – where there are no cells, but axons and dendrites to interconnect cell bodies laying beneath; (II) external granule cell layer – containing small spherical cells; (III) external pyramidal cell layer –

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20 Serotonin is an important monoamine, which can alter the neuronal excitability <to be used as an axiom for the proposed model: modulation can happen via changes in the excitability of processing units>.
includes small pyramidal neurons; (IV) internal granule cell layer containing small spherical cells; (V) internal pyramidal cell layer – containing pyramidal cells that are bigger than the ones in layer three; (VI) polymorphic layer – various cell types that border grey and white matters [Amaral00].

Figure 13 shows three different staining methods, each of them highlighting distinct aspects of the six layers of the same part of the cortex. The Golgi method (on the left) reveals cell bodies of neurons and their dendrites; the Nissl method (in the centre) shows cell bodies and only proximal dendrites; and finally the Weigert method (on the right) reveals myelinated axon distributions [Amaral00].

![Figure 13](image)

**Figure 13** – Cortical layers in three different staining methods: (a) Golgi, (b) Nissl, and (c) Weigert; picture modified from [Amaral00 – from [Heimer94]]

In addition of presenting variations in the cytoarchitectonics among layers, the cortex also exhibits variations of thickness, pattern of connectivity and types of fibres used. Because of these differences, there are also differences in the functionality of each layer. Apparently, input, output and cross-talk with neighbouring cortical areas are well organised in the cortex that has these tasks compartmented among layers [Calvin95] [Calvin98]. For example, feed-forward fibres in the visual system originate in layer III and terminate mainly in layer IV of target areas; whereas feedback connections
originate from layer V and VI and terminate in layer I, II and VI [Amaral00]. To corroborate the idea of functional specialization within the layers of the cortex, observe the direction of fibres of layer I in the Weigert staining of Figure 13. The horizontal direction adopted by fibres in this layer suggests that information is mainly exchanged between adjacent cortical areas. In contrast, fibres of other layers present vertical fibres suggesting that information leaves (or arrives) the cortex via the white matter towards more distant regions of the CNS.<this is used as an axiom for the proposed model: same location of the cortex can simultaneously receive inputs, send outputs, and connect to neighbouring>.

2.6.2 Cortical columns

Although of unequivocal importance and participating in every single function of the nervous system, a single neuron – because of the simplicity of its operation – cannot perform complex functions. Rather than operating alone, neurons combine to form minicolumns that are perpendicularly disposed in relation to the cortical surface (i.e. involving cells of various layers). These minicolumns connect to their neighbours forming the cortical columns, which are understood to be the basic units of information processing. From these columns, when motivated by external or internal stimuli, specific neurons are recruited to form neuronal assemblies; chapter 4 has more on this issue. For example, if these assemblies are in the area MI they can elicit finger flexions.

2.7 Neurocommunication

2.7.1 Interaction between nerve cells

To process physiological complex tasks, biological systems require their constituent cells to communicate with each other. In the CNS, this communication is normally carried out in a collaborative manner, and evolution has provided the nerve cells with elaborate mechanisms to perform their functions. In neurocommunications, the existing mechanisms are of an electrical and chemical nature [Whitfield84]. Nevertheless the latter is predominant in almost all of the body’s biological systems, in the nervous system both communication mechanisms are equally omnipresent. These mechanisms interact in a very efficient and effective manner. Figure 14 shows the communication pathway between two neurons. Note the direction of traffic taken by the signal (i.e. nerve impulse). Figure 15 presents a magnification of synaptic buttons.
illustrated in Figure 14. These structures house the **neurotransmitters** that can be either inhibitory or excitatory and are responsible for the chemical signalling between neurons.

![Figure 14](image1)

**Figure 14** – Direction of impulse progression between two neurons; picture modified from [IPIB02]

![Figure 15](image2)

**Figure 15** – Schematic view of a synaptic button; picture modified from [Driesen02]

### 2.7.2 Passive electrochemical properties of nerve cells

As in other cells, the neuronal membrane is susceptible to changes in potential electrical energy. A brief explanation for this phenomenon is the selective permeability of the cellular membrane (wall) to specific ions. This selectivity induces these ions to pass through existing channels in the cell membrane and accumulate either inside or outside the cell. This diffusion process is counteracted by the electrical work associated
with the electrical charges of the ions. See below the Nernst equation. In which the membrane potential for a given temperature is proportional to the product of a constant and the logarithm of the concentration gradient for the ionic solution, in this case concentration of K⁺ (Potassium). This equation was derived from the balance of the forces of diffusion and electrical work [Kingsley96], and can be used to predict the equilibrium potential (Nernst Potential) of simple selective membranes to one single ion, as described by Equation 1.

\[ V_m = \frac{RT}{FZ} \ln \left( \frac{[K^+]_{out}}{[K^+]_{in}} \right) \]

\text{Equation 1 – Nernst equation}

The equation presented above considers the concentration gradient of just one ion, which is not realistic as real physiological systems involve many other ions. Therefore, other ion concentrations present in the real case have to be taken into account. Below, one finds the Goldman-Hodgkin-Katz (GHK) constant field equation, also known as Goldman equation. This equation can measure the membrane potential expressed in mV of a multi-ionic system. The GHK, Equation 2, is a generalisation of the Nernst equation for the neuronal environment where, as well as K⁺, other ions such as Na⁺ (Sodium) and Cl⁻ (Chlorine) are relevant in determining the membrane potential.

\[ V_m = \frac{RT}{F} \ln \left( \frac{P_{K^+}[K^+]_{out} + P_{Na^+}[Na^+]_{out} + P_{Cl^-}[Cl^-]_{out}}{P_{K^+}[K^+]_{in} + P_{Na^+}[Na^+]_{in} + P_{Cl^-}[Cl^-]_{in}} \right) \]

\text{Equation 2 – Goldman-Hodgkin-Katz (GHK) constant field equation}

Considering the information above and according to the given conditions of the ionic diffusion along the cell membrane it is trivial to deduce that local electrical
currents can be generated between areas of different potential. Ohm’s law governs the relations between these current and electrical potentials, see Equation 3.

\[
E = I \cdot R
\]

- \(E\) electrical potential (in Volts)
- \(I\) electrical current (in Amperes)
- \(R\) resistance to current flow (in Ohms)

Equation 3 – Ohm’s law

In addition to offering resistance to current flow, cellular membranes also have another property related to the accumulation of electric charge. This property is called capacitance and means that the membrane can behave similarly to an electric capacitor. The electric charges are accumulated for small periods before the current flows according to Ohm’s law. However, this phenomenon is of a non-linear nature with regard to the incoming stimuli. Thus, it is an extremely important for information processing of neurons.

The final topic of this subsection refers to two constants existing on the cell membranes, namely time (\(\pi\)) and space (\(\lambda\)) constants. Both constants are independent from the applied stimulus (here, electric current), and are solely dependent on the membrane features; they can be seen in Equation 4 and Equation 5. Figure 16 describes how stimulated membranes respond symmetrically either in time or space (left and right portions of the figure, respectively) to changes of 63%, i.e. \((1-1/e)\) or 37% of the initial steady-state potential where \(e\) is a constant equal to 2.718.

The time constant (\(\pi\)) represents the delays of the membrane to hyper or hypopolarisation, whereas the space constant (\(\lambda\)) represents the amplitude loss in the signal from the peak value when the distance from the signal source increases.

\[
\pi = R_m C_m
\]

Equation 4 – Time constant of cellular membranes

\[
\lambda = \sqrt{\frac{R_m}{R_d}}
\]

Equation 5 – Space constant of cellular membranes
In the previous sections, the properties of the cellular membrane were of a passive nature, i.e. the ionic diffusion throughout the cell wall was assumed to be constant. However, the permeability of the cell membrane to some ions can change over time, mostly driven by variations in membrane potential. This finding on the membranes provides interesting and useful active properties, which were mathematically formalised for the first time by Hodgkin and Huxley in the 1950’s [Hodgkin52].

The changes in membrane permeability in relation to selected ions are only possible due to the existence of special kinds of ion channels in the cell wall that are different to the ones previously referred to in sub-section 2.7.2. The generic name of these channels, voltage-gated channels (VGC), is inspired by their functional nature. Physiologically, voltage-gated channels participate in the generation of two very important electrical signals. Both signals are intimately related to the functioning of the nervous system, which relate to their ‘action potential’ and ‘postsynaptic potential’.

The action potential (AP) is defined as a rapid change in the cell membrane potential triggered by an incoming electrical stimulus. For this phenomenon to happen, two kinds of voltage-gated channels acting with remarkable co-ordination. The VGCs involved in the action potential are the Sodium (Na⁺) and Potassium (K⁺) channels. An ‘action potential’ starts when the incoming stimulus positively polarises the membrane...
(depolarising phase) by inducing the Sodium channels to allow these ions to enter rapidly into the cytoplasm. As a result, the cell membrane leaves its rest potential to reach a peak of activation in just a few milliseconds.

Meanwhile, the Potassium VGCs start to counteract this process, by releasing Potassium ions from the cellular body. In comparison to the Sodium VGCs, the Potassium channels are simpler and slower in performing their function. This can explain why the occurrence of the sharp depolarisation peak during the beginning of an action potential is possible. On the other hand, Sodium channels have a more complex behaviour and rapidly reach their saturation level. As a result, Sodium ions stop entering the cell shortly after the initial stimulus. As oppose to that, the Potassium channels stay open longer. The consequence of this is that Potassium ions (positive charges) are released for longer periods from inside of the cytoplasm; contributing this time, unopposed, to a quick return of the membrane to its resting state. Figure 17 show the changes in the membrane potential resulting from the VGCs openings and closures. This curve can vary slightly among different kinds of neurons, but the overall shape remains the same. The non-linear dynamics of neurons is now greatly understood [WilsonH99].

![Figure 17 – Changes in the membrane potential during an action potential](image)

The subtitles of the figure, notated by Roman numbers, refer to the four distinct moments when the ion channels are stochastically assumed to be ‘open’ or ‘closed’. The moments are: (I) Resting state – the Sodium and Potassium channels are closed; (II) Depolarisation – only the sodium channels are open; (III) Re-polarisation – the Sodium channels become inactive, blocking ions from entering the cell whilst Potassium
channels are open; (IV) **After re-polarisation** – the Potassium channels remain open longer before returning to the resting state. The arrow featured in Figure 17 marks the moment when stimulation has occurred.

The start-up of an action potential is highly dependent on an external (electrical) stimulation. However, there are periods which are referred as ‘absolutely refractory’, when the cell does not respond to any stimulus. While in some other periods another action potential is unlikely, or at least will demand a supra-stimulation. The physical properties of the VGCs and ion flux may explain this complex behaviour.

In order to illustrate quantitative assessment of the functioning of VGCs, we conclude this section by providing some key values. The necessary time for VGCs to open and close can be considered zero (*i.e.* less than 10μsec), *i.e.* a channel can only be considered either open or closed [Kingsley96]. The resting state fluctuates at the potential of –70 mV, where all VGCs stay closed most of the time. A single opened channel allows passing only about 10^7 ions per second (the current generated is as small as 2 pA). During an action potential, the Na⁺ channels stay open for 1 msec, while K⁺ channels delays 5 msec to reach every other state [Whitfield84].

### 2.7.4 Potential propagation

Although resulting from the collective behaviour of a vast number of ion channels of different kinds, the action potentials are a highly localised phenomenon. They occur in small regions of the cell membrane during a given lapse of time. The actual length of these action loci are only approximately 1-2 millimetres [Changeux93]. However, the great utility of these phenomena derives from their possibility to be propagated through out an entire axon, *i.e.* originating at the hillock (at the cell body) until the synaptic terminations. As a result, another cell can receive signals for further local processing.

Before describing upon the mechanisms of potential propagation within the nerve fibres, it is important to notice the existence of two types of axons regarding the propagation of signals: myelinated and unmyelinated axons. The main difference between the two is the presence or absence of a lipoprotein coating, *i.e.* the myelin. This protection envelops part of the CNS nerve fibres, and is organised into a set of extremely thin layers one on the top of the other. Functionally, myelin sheathing (1) speeds up transmission of the potentials, while it saves in the axon diameter for producing equivalent results, and (2) avoids ectopic discharges or excitation within the white matter of the CNS (*this is used as an axon for the proposed model: presence or absence of insulation affects neurocommunications*).
In unmyelinated axons, the impulse propagates as a “wave” of modulation along the cellular membrane, as can be seen in Figure 18. This illustrates that the electrical balance of charges is achieved when the ions permeate through the membrane.

As a result, the balance of charges may happen towards areas of the axon, in favour of, or against of, the direction of impulse propagation. However, the region that lies behind the action potential is refractory to diffusion because of the inactivation of the Na⁺ channels. In light of this, it is possible to understand why evolution has created (or evolved) a mechanism such as the refractory periods within the membranes. The most probable reason of this is to force the potentials to flow along the axon in one sense, but not allowing them in reverse. Another interesting aspect to be observed in Figure 18 is the practical implication of the space constant ($\lambda$) commented in 2.7.2; it affects the area ahead of the action potential locus (threshold area), represented by dotted arrows. For example, faster propagation speeds happens as the axon becomes thicker (i.e. as $R_m$ increases).

The other type of axon, regarding the signal propagation in the membrane, is the myelinated axon. These types of axons are of significant interest to this work because they are targets for the ‘MS-plaques’ in the white matter of the CNS. The myelin sheathing endows this type of axons with a “cheaper” and faster way to transmit signal between distinct regions of the brain [Kingsley96].

Figure 19 denotes the important aspects of axon myelination such as (i) limited number of loci (Ranvier nodules) where local currents can leave the axon leading to
more transmission efficiency; (ii) a much further range of internodes left ready for depolarisation; and (iii) finally the saltatory manner (skipping internodal gaps) that the action potential occurs.

![Diagram of impulse propagation along a myelinated axon](image)

**Figure 19** – Impulse propagation along a myelinated axon

### 2.8 Neurology

The CNS is subject to many types of disorders that can be grouped into classes according to their intrinsic nature, namely vascular diseases (i.e. strokes), neoplastic diseases (i.e. tumours), degenerative diseases, inflammatory diseases, and infectious diseases [Johnson95]. Moreover, the CNS as any other alive tissue is also subject of normal (e.g. ageing) and abnormal processes of decaying (e.g. infarction or strokes). This section describes some processes utilised in this thesis to test the correctness and robustness of the computational model presented and simulated in chapters 6 and 7.

#### 2.8.1 Multiple sclerosis

Multiple sclerosis (MS) is a serious chronic demyelinating disease of the CNS. Pathologically, MS is characterised by disseminated inflammatory lesions to the myelin sheathing of nerve fibres, i.e. the ‘MS-plaques’ [Compston98]. Figure 20 shows a schematic comparison between one normally myelinated axon and another suffering a mild demyelination process. In the same figure one can also observe the nodes of Ranvier (i.e. the gaps in the sheaths), as commented and pointed out in Figure 19. These features of the axons are of absolute importance in the saltatory action-potential transmission along the axon [Shepherd94].
Although possible, myelin re-formation is a slow process not always observed in affected areas [Leeson85]. A direct result of the demyelination processes of axons is a loss or reduction of signal amplitude and velocity between any two communicating areas within the nervous system. Further consequences of this are bad synchronisation, de-coupling and other communication related problems among communicating cortical areas. 

Regarding the MS aetiology, according to some clinical evidence, many researchers are converging towards disturbances of the immune system, although the pathogenesis of MS is not yet fully understood [Esiri97]. Some other possible acknowledged causes that may give rise to the condition are viral infection, genetic inheritance and environmental factors [Raine97]. The autoimmune process gradually removes the sheathing of the myelinated axons. This means that any part of the electrical insulation of the axons within the white matter of the CNS – i.e. axons having myelin sheathing – can cause disruption of the function of the nervous system.

Advanced cases of multiple sclerosis can severely disable patients. The MS symptoms can vary from simple weakening of specific muscular groups to some psychological and behavioural changes. Confirmed and anecdotal evidences indicate that MS cases occur more frequently in patients who are: Caucasian female [Whitaker97]; geographically, in colder areas of higher latitude/temperate regions [IMSSF00]; 20-30 years old at onset of disease.

Presently, MS disease is diagnosed into four different clinical classes. The four classes are (1) relapsing-remitting MS, where there is a partial or total recovery after exacerbation or relapses – this is the most common form of MS; (2) secondary-...
progressive is relapsing-remitting, which later becomes steadily progressive – attacks and partial recoveries may continue to occur; (3) primary-progressive is a form of MS with progressive course from onset – the symptoms generally do not remit and only a few patients experience this form of MS; (4) progressive-relapsing, where there is a progressive course from the outset characterised by acute attacks – this class is also rare. This inexpressive classification normally drives all the therapeutic measures to be taken in due course. Other criteria for MS diagnose are Schumacher’s criterion, Poser committee, Fazekas criteria [Raine97, NMSS00, Compston98].

Multiple Sclerosis disease has a ‘hallmark’, the MS-plaques. These plaques are ubiquitous on various cerebral pathways of MS patients. These sclerotic plaques are attributed to the decay in the myelin sheathing of groups of myelinated axons from distinct regions within the CNS. From a physical perspective, one can assume that these inflammatory processes are solely communication problems of different areas that need to ‘converse’ through a given path. This reductionism is made possible by abstractions of all the unsolved medical aspects of MS, especially those concerning etiology and therapy.

Figure 21 shows the two possible (normal) modalities of myelination processes existing in the nervous systems, which are produced by Schwann cells and oligodendrocytes. In the CNS, one single oligodendrocyte process form a network of axonal insulation for portions of axons of many neurons at the same time\textsuperscript{22}.

\textbf{Figure 21} – Different modalities of myelination: (left) Schwann cells in the PNS, (right) oligodendrocytes in the CNS; picture modified from [Driesen02]

\textsuperscript{22} One might argue that MS-plaques could acquire their shapes partly influenced by the branching pattern of oligodendrocytes, which highly contrasts with what happens in the PNS.
Figure 22 shows the (extremely thin) myelin layers (one on the top of the other) that are sheathing an axon (only seen partially in the bottom-left part of the figure). Notice in the figure that there are more than 30 layers enveloping the axon.

Because of the discussions of the topics seen in the previous sections, it is possible to deduce that the demyelinating processes present in MS causes a reduction in the quality of the membrane insulation of the axon. Consequently, the transmission speed of the longitudinal current on the axon is markedly slower (refer to the time and space constants on Equation 4, Equation 5 and Figure 16).

If the demyelination process carries on (i.e. destroying the myelin), the membrane is forced to behave similarly to an unmyelinated nerve fibre. In extreme cases demyelination can totally block the communication between two cortical regions. This phenomenon brings out all the inconveniences of unmyelinated axons, i.e. slowness of signal propagation leading to complete decoupling of areas.
Figure 23 shows an MRI of the brain featuring a vast periventricular demyelination in both hemispheres; note the variations in shape, coloration (i.e. intensity of damage), location and orientation of the plaques. These variable aspects of the MS-plaques, namely the individual non-uniformity of symptoms and the symptoms’ temporal irregularities (regarding exacerbation and remittance) produce no distinctive patterns among patients and represent major challenges for any research on computational models for MS.<this is used as a motivation for proposing a MS-plaque model: necessity of relating MS-plaques and their elicited impact>.

Throughout history, some persistent diseases have challenged scientists and medicine. However, time has proved that human persistence and inventiveness usually succeeds finding a solution either to prevent or relieve the sequels of these diseases. Multiple sclerosis, described by the French Doctor Jean Charcot, is known since 1868. It remains one of these diseases labelled as treatable, but yet not curable. The reduced efficacy of the conventional therapeutic methods and the non-existence of any kind of prognosis from clinicians only worsen the psychological consequences that accompany every MS case. A major goal of research on MS is to identify more precise indicators of prognosis or prediction mechanisms on the disease activity [NMSS00]<this is used as an addition motivation for proposing an MS-plaque model: necessity of assisting prognosis in MS due to plaque size increase>.

2.8.2 Stroke

Stroke is the brain disorder we selected to be investigated concomitant with multiple sclerosis. This cerebrovascular accident is characterised by either occlusive or haemorrhagic lesions of blood vessels that supply the brain with oxygen and nutrients. A continuous and abundant blood supply is a mandatory condition for a healthy and fully functional nervous system. When a steady blood supply is not provided – even for small lapses of time – this leads to infarction<sup>23</sup> and consequent (invaluable) functional losses. Sometimes the blood supply is only reduced causing a temporary ischemia that may not result in brain tissue loss.

Causes of strokes are very diverse. Occlusive strokes are due to atherosclerosis and thrombosis and most haemorrhagic strokes are linked to hypertension or aneurysms [Brust00]. The consequences of a stroke are highly dependent on the location the problem happens; unfortunately, there are no areas free from this severe problem.

<sup>23</sup> Infarction here means nerve cells death.
Figure 24 shows an acute infarction in the left pre-central gyrus. The "bright signal" is due to the presence of excess water, which has a prolonged relaxation time [Johnson95].

![MRI of the brain presenting stroke lesion](image)

**Figure 24** – MRI of the brain presenting stroke lesion; picture extracted from [Johnson95]

As with research in multiple sclerosis, it would be helpful to develop a means to computationally predict brain damage due to stroke *<this is used as a motivation for proposing a stroke model: necessity of evaluating brain damage after strokes>.*

### 2.8.3 Ageing

Although ageing processes are present in every living organism, it is not known exactly, why they happen or which factors trigger them. Most likely cells are genetically set to have a fixed life span according to the combination type and organism specie. Even though many theories have been proposed to describe the ageing processes, scarce longitudinal studies prevent a more conclusive explanation [Price00].

Similarly to research in multiple sclerosis and stroke, it is necessary for physicians to have a means to predict computationally consequences of normal ageing processes in neural processing *<this is used as a motivation for proposing a ageing model: necessity of evaluating neural processing subject to ageing processes>.*

Longevity studies result in the production of longevity curve for humans as it is presented in Figure 25; note how human longevity has improved over the years due to various factors.
Figure 25 – Trends in human longevity from early 19th Century until 1980s [adapted from Strehler 1975] *apud* [Price00] Legend: A to B – improved housing, sanitation, antiseptics; B to C – public health, hygiene, immunization; C to D – antibiotics, improved medical practice, nutrition, health education; and D to F – biomedical advances. E and F are male and female survival.

Figure 26 shows an MRI scan of an octogenarian healthy female. This image shows clearly signs of ageing process, which has substantially reduced the overall brain volume and cortical area.

Figure 26 – MRI of the brain presenting normal ageing; picture extracted from [Johnson95]

2.9 Closing remarks

Flexibility, robustness and adaptability are just a few of the many features observed in the overwhelming “machine” that is the nervous system. More extensive information regarding neurobiology, and brain dynamics can be found in [Shepherd94][Leeson85][Broda98][Kandel00][Greenfield97][Rolls97].
In addition to the overview of the organisation of the central nervous system described in this chapter, we have identified and listed some important motivational and axiomatic facts to be used in the computational models to be proposed for neural computation (including multiple sclerosis, stroke and ageing models):

**Motivational:**
- necessity of relating MS-plaques and their elicited impact
- necessity of assisting prognosis in MS due to plaque size increase
- necessity of evaluating brain damage after stokes
- necessity of evaluating neural processing subject to ageing processes

**Axiomatic:**
- models should include many types of processing units with consequent specificities
- models should include many distinct processing regions that operate independently
- cortical regions can simultaneously receive inputs, send outputs, and connect to neighbouring
- models should include pathways of various kinds to interlink regions (and other components) in a wide and free manner
- motor control presupposes hierarchy of regions
- motor control presupposes feedback
- motor control presupposes specificity of regional functionality
- force to be applied in the movement should be defined by the activity of the cell population in the various regions
- voluntary motor control is directly controlled by one region (i.e. pyramidal tract)
- modulation can happen via confluent pathways
- presence or absence of insulation affects neurocommunications

The detailed descriptions of the proposed models, their implementation and extensive simulations are presented in chapter 5, appendix B, and chapters 6 and 7, respectively.
Chapter 3  
Acquiring functional data from the Central Nervous System

3.1 Introduction

Throughout its history, medicine always used physical observation to help diagnosing and then formulating therapeutics for healing patients. As technology evolved, the observation methods became increasingly more accurate and “revealing”. In addition, to helping in diagnosing diseases, technological advances in instrumentation devices were also applied to understand the “intricacies” of biological systems. The nervous system, with its idiosyncratic complexity, would not be left out.

This chapter aims to review various imaging methods used to “see” inside the human head; a special emphasis is placed on functional methods. A pragmatic approach is taken in order to find out principles, advantages and pitfalls of functional methods currently available. Throughout this chapter, information such as temporal, spatial and functional abilities for every method studied is commented upon. Ultimately, the information gathered here will be used to define granularity levels and features to be adopted in further developments of this research work.

3.2 Functional imaging of the CNS

Although only confirmed many decades later, as early as in 1890 Sherrington proposed a relationship between stimulation and local increase in cerebral blood flow [Matthews01]. Even though scientists were aware of this fact, until a few decades ago, information about functioning human brains was very limited. Obviously, neither post-mortem exams nor behavioural observations could tell much about the dynamic characteristics of the brain. Thus, for many years the academic community had to be content with low-key techniques for studying brain function. Examples of such techniques are direct cortical stimulation of conscious-patients during neurological surgery (e.g. Wilder Penfield in the 1930s [Clarke96]), and post-lesion studies on patients who suffered brain damage of various sorts. This lack of experimental results kept the understanding about brain function at a disappointing pace for a long time. Fortunately, some breakthroughs, namely PET and fMRI (refer to further sections), were to change all that.

Neuroscientists and neurologists are now exhaustively using recent scanning methods to investigate and diagnose diseases of the CNS. The aspect to be emphasised is that the newest methods are acquiring information about the CNS without both (i) intervention (i.e. opening the skull) and (ii) presenting a danger to patients and subjects.
Although of moderate risk, the latter happened in earlier methods, e.g. PET. Moreover, some of these recent methods offer the unprecedented possibility to identify and register physiology rather than just anatomy. For example, this allows researchers to relate the cytoarchitectonics of the brain (mentioned in chapter 2) to function localisation. Figure 27 illustrates the instigating idea of relating anatomy to physiology.

![Comparison between Brodmann areas (anatomy) on the left with functional areas (physiology) on the right; picture extracted from [Duban02]](image)

Temporal correlation between (a) stimulation and cognitive tasks to (b) observation of brain activated areas is fundamental to the idea conveyed in the figure above. However, this inference cannot be precise as there is no assured causal relation of a leading to b <this is used as a motivation for the proposed model: functional imaging methods would benefit of models that directly test cause-relation hypotheses>.

![Functional data acquisition along time: spatial and activation information are preserved](image)
Figure 28 conveys the complimentary ideas of spatio-temporal information digitally acquired data from a functioning brain.

Be it for (i) mapping functions in the brain, (ii) understanding the functioning of the brain, or (iii) supporting neurologist decision, acquiring functional information is no longer a conceivable alternative. Although encompassing many cliques with widely distinct interests, research groups interested in brain function have profoundly incorporated functional (imaging) methods into their armoury.

To orderly review the currently available functional methods, the sections to follow are organised based on the technology involved in acquisition of the information namely, radiological, electromagnetic and magnetic resonance.

3.3 Radiological methods

3.3.1 Computed Tomography

Computer tomography (CT) is an imaging technique in which the contrast of the imaged parts relies on the different absorption rates of x-rays\(^{24}\) by distinct tissues of the body. The image formation is generated as a set of parallel slices (\textit{i.e. \textit{tomes}}) – transversally oriented, as normally preferred on CT scans of the brain. X-ray detectors then arranged in a circumference (inside the scanner) collect attenuation readings from multiple angles [Johnson95]. A computerized algorithm reconstructs slices, which produces a 3-D volume of the scanned brain of the subject [Clarke96].

Clinical uses of CT range from tumour detection, confirmation of vascular damage and degenerative disease evaluation. CT is also used for diagnosing multiple sclerosis (MS), Alzheimer’s disease, Parkinson’s disease etc. Although ionizing radiation is utilised, the risk to health is judged not to be high. However, [Miller97] has reported worrying lesions enlargements (of MS plaques) when some contrast media were used to image multiple sclerosis.

Although CT has better accuracy than traditional X-rays, it has poor spatial resolution and limited contrast of grey and white matter. Therefore, CT use is restricted to structural acquisition. Hence, a combination with other imaging methods is mandatory for any functional information to be generated. Figure 29 shows an example of a CT transversal image; in the figure one can see two hemispheres, the ventricles, the cortical gyri (faintly) and a large lesion on the right hemisphere.

\(^{24}\) X-rays can also be referred as Roentgen ray. They were named after the German Physicist Wilhelm Conrad Roentgen – who in 1895 discovered x-rays, by accident.
3.3.2 Positron Emission Tomography

Positron emission tomography (PET) is an imaging method that uses positron emitting radioisotopes, such as $^{15}$O – Oxygen, integrated into pharmaceuticals of known biological function to detect inner aspects \textit{in vivo} (\textit{i.e.} of a living being).

The underlining physics of PET detection is quite simple: when positrons collide with electrons, they annihilate rapidly emitting two photons in opposite directions, which are spatially identified by a set of detectors displayed conveniently \cite{Brodal98} (like x-ray detection in CT). The detected accumulation of labelled tracers in some areas may indicate modification of oxygen, glucose metabolism, or dopamine transporter concentration \cite{Johnson95}. By this means, PET can also detect change in the regional cerebral blood flow (rCBF) in consequence of metabolic responses to local neuronal activity. Subtraction of images is the technique employed to infer the activation in the brain related to stimulation. Researchers have been using PET for many different applications, most of them to map brain function. Clinically, PET is also used to study modification of rCBF due to disease.

Relatively low resolution, high costs and limitations in frequent use due to the radiation effects of the contrast media (\textit{i.e.} labelled chemicals) are the drawbacks apparent to PET imaging in clinical basis \cite{Miller97}. Some research groups point out that PET is valuable because of its sensitivity and selectivity in imaging molecular interactions in the living body \cite{RPMS02}. In fact, PET scans allow neuroscientists and
neurologists to visually examine the cerebral dynamic behaviour of various areas simultaneously. However, there are references in the literature about the increasing difficulty in using PET to analyze higher cognitive processes other than simple-task localization [Clarke96]. Figure 30 shows an example of a PET transversal image; in the figure, one can see activation in both hemispheres where different colours areas are associated to levels of activation of the brain.

![Figure 30 - Example of transversal PET scan of the brain; picture extracted from [Johnson95]](image)

3.3.3 Single Photon Emission Computed Tomography

Single Photon Emission Computed Tomography (SPECT) also uses radioisotopes for scanning the inner structure and dynamics of the body. Examples of common radioisotopes used in SPECT are xenon-133, iodine-123 and technetium-99m [Sapper00]. The utilized pharmaceuticals (labelled with the radioisotopes), as with PET, can be injected, ingested or inhaled by the subjects. The image acquisition in SPECT relies on the detection of Gamma radiation (Gamma rays) originated from the inside of the scanned subjects’ body using a special device, the Gamma camera [MIRG02].

In comparison with PET, SPECT has simpler medical protocols, less complex acquisition equipment and long-lived radiopharmaceuticals. As a result, SPECT is a more affordable and available technique for clinical usage. Nevertheless, PET has a better spatial resolution and sensitivity. Even though PET and SPECT have been used successfully in some neuropathology applications, neither of these imaging methods has a role in the diagnosis of Multiple Sclerosis [Miller97].
Variations of SPECT have been developed, namely Dynamic SPECT. In this method, images are acquired in very fast intervals allowing more accurate visualization of selected metabolic processes (according to the tracer utilised). Nonetheless, high spatial resolution images require another, modality such as MRI, to improve localization.

Figure 31 shows a transversal SPECT image also representing (with different colours) the various levels of activation within the brain associated with a given stimulus; note the hotspots (white blurs) in the posterior area and how spatial resolution is smaller than PET (in Figure 30).

![Figure 31 – Example of transversal SPECT scan of the brain; picture extracted from [MIRG02]](image)

3.4 Electromagnetic recordings

3.4.1 Electroencephalography

Electroencephalography (EEG) is a recording method of the electrical activity of the superficial layer of cells in the brain. In EEG the activity (either excitatory or inhibitory) of large assemblies of neurons can be measured because the normal metabolism of the nervous systems involves ionic transport through the membrane of the nerve cells. This ionic mobility produces measurable electromagnetic signals as changes in electrical potential. Healthy persons exhibit low voltage and fast activity when they are awake (i.e. beta waves or alpha waves); modifications of these patterns may indicate diseases.

The recording process in EEG is far from being topologically precise since relatively few electrodes (typically 64-128) placed on the subjects’ scalp acquire the
signals. Nevertheless, temporal resolution can be as small as few milliseconds. This remarkable feature allows acquisition of temporal data about neural activity on a scale not possible by virtually any other method.

Even though EEG is not strictly an imaging technique, the evoked potentials (recorded in millivolts) can generate pictorial geodesic representations of the active areas within the cerebral cortex. In this technique, the gaps between electrodes are filled (i.e. coloured) with interpolated values calculated from the neighbouring values; see an example of that in Figure 32.

![Figure 32](image)

**Figure 32** – Pictorial representation of brain activation based on EEG recordings; picture extracted from [Mayer94]

Similar to other methods already described, dynamic aspects of brain activation can easily be perceived using EEG. Recording EEG over short periods is usually enough to generate useful sequences of “images” representing brain activation.

In Neurology, clinical applications of EEG have been observed for diagnostics and research since its introduction in 1930 [Brodal98]. Currently, EEG is used to diagnose epilepsy, detection of epileptic foci (injured regions of the brain that give rise to the electrical storm that is epilepsy), as well as to determine brain death. Over the past 20 years, recordings of the evoked potentials have been used for making diagnoses and as an adjunct in MS therapeutics [Nuwer97].

EEG is an important clinical tool because (i) subjects cannot interfere (much) with the EEG results; (ii) there is a large reproducibility of results; (iii) there is no restriction on continued re-use on the same subject (i.e., non-harmful); (iv) normally the equipment
is inexpensive, and (v) it has the ability to detect silent lesions. On the other hand, some limitations partially restrict usage of EEG: poor spatial resolution; and the inability to acquire data on deeper activation in the brain.

### 3.4.2 Magnetoencephalography

Magnetoencephalography (MEG) measures the minute magnetic fields generated by electric current flow in the brain. In MEG, the recording apparatus is called SQUID (acronym for superconducting quantum interference device), which has to be very sensitive since there is a large difference of magnitude between the magnetic fields of the various evoked potentials of interest within the brain (approximately $10^{-12}$ T) and the Earth (approximately $10^{-4}$ T). Because of that, costly installations are required, which is a problem for MEG to become a widespread functional imaging technique.

MEG is a natural complementary method to EEG because both modalities are sensitive to tangential and radial currents respectively [Clarke96][Beisteiner98]. The reason for this is simple as each method focuses solely on one aspect of electromagnetic fields (which are orthogonal between themselves). Similarly to EEG, MEG has great temporal resolution. However, the spatial resolution degrades as deeper areas are recorded. The explanation for that comes from the inverse square law, whereby the field reduces rapidly with distance.

In MEG, the spatial resolution is much better (in the order of 1-2 mm) than that of EEG. This may be explained because of the radial selectivity of the method that excels on the vast number of existing fissures on the cerebral cortex. This anatomical fact facilitates detection of magnetic dipoles on these areas, which contrasts to EEG as discussed earlier [Clarke96]. Moreover, MEG suffers no “blurring” due to the widely varying electrical resistance of different tissues as the signal is acquired (this is a great problem in EEG) [Bach98].

Therefore, MEG is a strong candidate for medical studies and assessments as it can provide valuable spatio-temporal information. The specialized literature has registered vastly increasing numbers of MEG clinical applications in association with other imaging methods such as EEG, SPECT and PET [Beisteiner98].

### 3.5 Magnetic resonance

#### 3.5.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is another class of medical imaging method we review in this work. MRI is based on the physical phenomenon of nuclear magnetic reso
resonance (NMR), which was first measured by E. M. Purcell in 1946. This phenomenon refers to the magnetic moment and spins of nuclei with an odd number of nucleons [Savoy97]. In other words, every atom with an odd number of protons or neutrons in its nucleus will have a characteristic precession rate when subjected to an external magnetic field. The resonance frequencies of these nuclei are directly proportional to the magnetic field applied. Resonance frequencies are given by the Larmor equation (see Equation 6) [Webb98].

\[ \omega = \gamma \times B_0 \]

Equation 6 – The Larmor equation

In the equation above, \( \gamma \) – the gyromagnetic ratio, varies according to the mass number of each individual atomic component. For example: hydrogen (\(^1\)H) has \( \gamma \) equal to 42.6 MHz/T. This means that at 0.5 Gauss (i.e. 0.0005 T = the earth’s magnetic field), 1.5T and 3.0T, the Larmor frequency for \(^1\)H is 0.002MHz, 64 MHz and 128 MHz, respectively [Matthews97].

As opposed to some clinical MRI scanners that used resistive or permanent magnets, the most recent scanners use superconducting magnets to produce the necessary large magnetic field (\( B_o \)) to achieve good signal to noise ratio (SNR). Many reasons exist for the selection of the latter such as more homogeneity of the generated fields, ease of serial production of the scanners and their reliability.

In addition to this large magnetic field \( B_o \), a perpendicular RF (i.e. radio frequency) pulse is used to force the flip of all the precessing nuclei up to a 90° angle (or greater). This second field, referred to as \( B_1 \), is considerably smaller than \( B_o \) (\( B_1 \ll B_o \)). The reason for using this second magnetic field is smart yet simple: it slightly disturbs the direction of the axis of the precessing nuclei. Of course this will only last while \( B_1 \) is still on, which happens during brief periods (pulses) given by \( \tau \) in Equation 7. Overall, whenever \( B_1 \) is switched off all the precessing nuclei re-align parallel to \( B_o \). Figure 33 schematically displays the magnetization angle just described, the three spatial axes of precession, three nucleon orbits, and the orientation of the magnetic fields \( B_1 \) and \( B_o \).

\[ \theta = \gamma \times B_1 \times \tau \]

Equation 7 – Flip angle equation (RF – pulse)
The time necessary for the various nuclei to return to their previous precessional angle (i.e. relaxation time) varies greatly for different atoms. In MRI, these time differences are used to contrast different tissues. There are two ways to measure the relaxation time, namely $T_1$ and $T_2$. The first, also called spin-lattice, is the rate of energy (or nuclear spin) transferred to the surrounding environment (the lattice), in other words the realignment with $B_0$. The second, or spin-spin, is the rate of spin dephasing.

Matthews [Matthews97] comments that as the signal detected by the RF coil, then $T_2$ expresses the rate at which detectable signal is lost. $T_1$ and $T_2$ are strongly related but cannot be assumed interchangeable because not every process leading to $T_2$ relaxation will exhibit $T_1$ relaxation either [Henning98]. De Wilde [DeWilde-J98] mentions that $T_2$ is always less than $T_1$ (five to ten times less, approximately). In addition to $T_1$ and $T_2$, other parameters such as repetition time\(^{25}\) (TR), and echo delay time\(^{26}\) (TE) are involved in image contrast. Combinations of these parameters produce different results and are referred differently: short TR and TE results in $T_1$ weighting ($T_1^*$); long TR and TE results in $T_2$ weighting ($T_2^*$); long TR, short TE results in ‘proton’ weighting etc [Matthews97]. In addition to combinations of the parameters just mentioned there are many different combinations of pulse sequences (RF) that can be set accordingly to the experimental needs; this flexibility produce the necessary contrast enhancement.

\(^{25}\) TR – interval between RF pulses
\(^{26}\) TE – delay between RF pulse and start of signal detection
Examples of these sequences are inverse recovery pulse sequence (IR), spin echo, fluid attenuated inverse recovery (FLAIR) etc.

To conclude the explanation of the underlying physics of MRI, it is important to understand how the vortex signal is (i) spatially encoded during acquisition and later (ii) decoded for analysis. Each one of the three dimensions (i.e. axes $x, y$ and $z$) is processed in a complete different manner: the first dimension can be characterised by linear changes in the strength of $B_0$, along the axis of choice that will be only resonant with equivalent RF applied frequencies, which is known as a slice selection. Following slice selection, the next two dimensions can be encoded or decoded using frequency and phase. This means that the positional detection along the second axis of choice is obtained by varying the frequency; and the position along the third axis is given by phase shifts in the resonant signal (as encoded after the RF pulse and before the echo). The intensities of the resonating signal are calculated using two-dimensional Fourier transform [Webb88] [Matthews97] [Henning98] [DeWilde-J98].

Some problems, such as the time consuming phase-encoding, which necessitates many repetitions until all the 2D data is acquired, are being imaginatively countered by the use of some pulse sequences such as EPI (echo planar imaging). In EPI, one of the fastest sequences available, the slices (e.g. any plane parallel to $x$-$y$ in Figure 33) are acquired using a single excitation pulse in the interval of just one $T_2^*$ decay; before each frequency encoding change, the phase encoding is rapidly “blipped” [Matthews97] [Henning98].

The complete imaging process using magnetic resonance comprises several steps that can be broadly grouped into four steps: image acquisition, volume reconstruction, data filtering, and image analysis (that applies mainly to fMRI). So far, the first two have been commented upon. Data filtering and image analysis mostly use basic statistics techniques for filtering the signal in order to detect and correct problems such motion of the head, and obtain global intensity normalization. In the case of fMRI, the image analysis also includes steps to obtain and generate an image mask, cluster detection and threshold definition (for functional information).

Currently, clinical neurology relies very much on MRI, which is one of the most important diagnostic tools for brain diseases, mainly due to its non-invasive characteristics, good spatial resolution and outstanding ability to differentiate white from grey matter in the brain [Clarke96]. Figure 34 displays a high-resolution MRI scan.
MRI usage in neurological disorders such as MS, in which diagnosis is essentially clinical, is of invaluable importance for early diagnosis, especially when the hardware used has sufficient spatial resolution to localise newly formed plaques. Miller [Miller97] reports that 95% of MS-definite patients present abnormalities (in the white matter) revealed by MRI brain scans of these patients. Various pulse-sequences are used either for diagnosis or for therapeutic treatment of MS, namely T2 weighted spin-echo, gadolinium enhanced27, FLAIR etc [Filippi97].

### 3.5.2 Functional Magnetic Resonance Imaging (fMRI)

FMRI is a further advance in traditional MRI modality, relying on the same physical phenomena described in the previous sub-section. In addition to conventional MRI abilities, this other modality of medical imaging is able to capture some of the aspects of the cerebral dynamics, i.e. the detection of activated regions.

Jezzard [Jezzard98] mentions the existence of three possible candidates to be used for mapping neuronal activity, namely blood volume imaging, blood flow imaging and blood oxygenation imaging. All three imaging techniques rely on metabolically produced reactions that indicate neuronal activity. The latter is undoubtedly the most widely used in functional images of the brain (acquired with NMR).

27 gadolinium diethylenetriaminepentaacetic acid is a contrast agent that enhances detection of specific features in brain MRI.
Functional MRI image relies on the discovery, in 1990 (i.e. 100 years after Sherrington’s proposal), that the MR signal is correlated to blood oxygenation. This phenomenon is referred as blood oxygenation level dependant signal response (BOLD). Physiologically, this means that cerebral activated regions demand more oxygen to function than other non-activated regions. In fMRI, activation detection relies on this fact and the (opposed) magnetic properties of oxygenated or deoxygenated blood\textsuperscript{28} [Bandetini95].

The fMRI image generation involves two types of data: (i) high-spatial resolution structural volume and (ii) low-spatial resolution images acquired rapidly (e.g. fast EPI sequences). After some intensive statistical processing, the latter data set is superimposed on the former. There are many ways to perform these statistical operations; they all aim to correlate the candidate activation areas with the stimuli presented. Savoy [Savoy97a] gives examples of some statistical tests normally used, such as non-parametric Kolmogorov-Smirnov (KS) test and principal component analysis. These methods transcend the scope of this work, but the interested reader can find a comprehensive introduction to various related aspects at [FMRIB02]. Figure 35 displays a high-resolution fMRI scan. The coloured area indicates activation in the motor cortex, here displayed on a 3-D high-resolution structural data.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{motor_cortex_fMRI}
\caption{Example of fMRI of the motor cortex, overlaid upon standard high resolution data set (task: finger opposition at 2Hz. p <0.05); picture extracted from [FMRIB02a]}
\end{figure}

\textsuperscript{28} Oxyhaemoglobin is diamagnetic and conversely deoxyhaemoglobin is paramagnetic
3.6 Multiple modalities

Integrating modalities is a means of overcoming some of the limitations of a particular functional imaging technique. In other words, two (or more) modalities are synergistic combined to maximise advantages and to minimise each modality’s limitation. Thus, their data are co-registered to successfully produce better information for the experimenters. The literature indicates many successful combinations of such integration, e.g. MEG and EEG, fMRI and MEG, and even fMRI and MEG+EEG [George01] [Beisteiner98].

Figure 36 presents a comprehensive comparison of various modalities of brain mapping methods that can be utilised either in vivo or in vitro. This figure is useful to illustrate how various modalities could eventually complement each other’s shortcomings. It suggests the appropriate granularity that various techniques should be used at.

![Figure 36 – Spatial and temporal sensitivities of brain mapping methods [Matthews01 – from [Cohen94]]](image)

The major problem arising when utilising (i.e. analysing) multi-modal images is the risk of wrongly attributing spatial and temporal dynamic features. However, many techniques have been developed to deal with this problem and are already widely available [FMRIB02b] [Jezzard01]. Atlases of the brain are also another mean to consistently register the functional information acquired from the brain, e.g. **Talairach and Tournoux space** [Jenkinson01].
3.7 Additional help on acquiring functional information about the brain

In addition to the methods reviewed above, others can be of great value on understanding and acquiring functional data of the CNS. Examples of these other methods are magnetic resonance spectroscopy imaging (MRSI), transcranial magnetic stimulation (TMS), and near infrared spectroscopy (NIR). MRSI is a variation in the MRI modality that allows imaging of concentration of biochemical compounds in the various regions of the brain [Matthews01a]. TMS is a non-invasive and non-harmful controllable means to stimulate brain areas allowing circuit identification [Bohning01]. NIR is also a non-invasive and non-harmful means that is able to measure attenuation of light by various tissues of a functioning brain [Delpi01].

3.8 Closing remarks

Based on Figure 36 one notices the preponderant position of fMRI among all other modalities; functional MRI occupies a substantial and central area of the spatio-temporal spectrum [Matthews01]. Despite its relatively poor temporal resolution, fMRI is the one single non-invasive functional method that offers the best trade-offs for investigations centred at cortical columns and up-wards (i.e. larger structures). This fact may explain why this modality is so extensively used on its own, as well as in multiple modal studies.

Current clinical MRI scanners use typical magnetic field strengths as high as 1.0 - 3.0T. The observed trend in that respect for the near future is the use of even higher magnetic field strengths, since this directly improves the spatial resolution. Scanners of 8T (i.e. sub-millimetre spatial resolution) and interventional MRI are already available for restricted clinical use. Despite the restricted spatial resolution of current high-resolution MRI scanners, it is adequate for clinical use and brain activation detection. The temporal resolution, however, still imposes severe constraints on some applications. At present limiting factors are the hardware utilised, pulse sequences, and the physiological response delay itself (using BOLD). Among these three, the latter is very

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29 The non-invasiveness of fMRI permits much better use of the potential human subjects.
30 Interventional MRI is a special type of scanner that allows the physicians to perform a medical intervention while the images are being acquired. Generally these scanners have a lower resolution when compared to others used for diagnosis [Henning98]
31 MRI is likely to have its resolution improved in the near future, with the introduction of scanners with even faster gradient.
32 Pulse sequences are likely to undergo improvements and new ones are also likely to be created in the near future.
unlikely to be superseded for applications in need of millisecond temporal resolution. Notice that most cognitive processes do occur below 1000 msec, while significant detectable changes in the haemodynamics using current fMRI occurs 2000 msec from the original stimulation or action [Savoy97] [Rees00] <this is used as an axiom for the proposed model: delay and relaxation of cortical activations are features to be considered>.
Chapter

4 Artificial Intelligence, Artificial Neural Networks, and Computational Neuroscience

“We used to have lots of questions to which there were no answers. Now with the computer there are lots of answers to which we haven’t thought up the questions”. Peter Ustinov

4.1 AI and Artificial Neural Networks

In recent years, many computational methods have been created to address the complexity of real world problems. Some of the most flexible of these algorithms are from the field of artificial intelligence (AI) – a major branch of computer science. Actually, problems dealt with by AI techniques are of a wide range and are generally difficult [Rich91]. Besides flexibility, the main characteristics of algorithms of the “umbrella” term – AI – are their ability to learn and store knowledge. Moreover, knowledge acquired by these algorithms allows generalisations, which (i) extrapolate the situations used for their training and (ii) most of the time can be used for improvements in performance. These features are unprecedented in other computational implementations. Therefore, AI algorithms ‘trained’ within one context are theoretically able to effectively process in other contexts, data that may have not been ‘seen’ before. Generalisation ability (i.e. the ability to learn) and flexibility of AI are probably the reasons why these algorithms are so widely and successfully used.

Artificial intelligence generally deals with modelling human intelligence [Kasabov96] and its applications. To achieve this, AI includes various paradigms and techniques; the main ones are ‘symbolic’ and ‘sub-symbolic’. The first paradigm is oriented by Newell and Simon’s theory of physical symbols (symbols and rules) [Newell72], and the second paradigm is inspired by neural computation. Smolenski coined the term sub-symbolic [Smolenski90], by that he meant that intelligent behaviour is computed on a level between neuron and symbol [Kasabov96]. Both paradigms diverge about the level at which information should be stored and processed. According to them, the real world could have its representations varying from symbols (one-to-one mapping regarding storage) to a completely distributed representation of features of the information. However, there are attempts to integrate both approaches [Garcez02].

Artificial neural networks (ANNs) also referred to as connectionist models, is a prominent sub-field of AI and representative of the sub-symbolic paradigm. Artificial neural network methods are inspired by the nervous system, and represent some of the most important techniques for modelling and solving real world problems. Haykin describes them as massively parallel-distributed processors that acquire knowledge through learning and store it in a distributed manner (i.e. synaptic values) [Haykin99]. The learning algorithms and distributed manner that the acquired knowledge is stored in the ANN confers to systems that use this technique features such as nonlinearity,
adaptability, robustness, and generalisation ability (flexibility). This set of characteristics is highly necessary to tackle complex tasks. Hence, artificial neural network methods represent nowadays one of the most important sets of techniques for modelling and solving real world problems [Haykin99].

Moreover, as highlighted by Philippe De Wilde [DeWilde-P97], another interesting feature of ANNs is their ability to relate (non-trivially) microscopic to macroscopic phenomena. This feature allows emergence in ANN systems, which is a particularly important concept for the present work and can be observed extensively in the simulations contained in chapters 6 and 7.

This thesis adopts ANNs for all data processing (i.e. simulations). The main reasons for this decision, in addition to the commented advantages of this approach are: (i) ANNs do not exhibit the symbol grounding problem of the symbolic approach, and above all (ii) ANNs are themselves inspired by the CNS (i.e. the domain of study of this thesis). The latter implies that modelling ‘tool’ and modelled ‘system’ intrinsically have many similarities namely, internal organisation based on neurons, spread representation of data (i.e. synapses) and parallel distributed processing.

4.2 Inside artificial neural networks

Artificial neural networks can be analysed and classified by many different criteria, such as: type of artificial neuron used, network structure, learning strategy etc. An additional classification parameter can also be the recall strategy or algorithm used [Kasabov96]. However, for brevity in this chapter we restrict our comments to ANN concepts that are relevant to this work. Specifically, we focus on topics regarding constitution, operation and application of connectionist models.

To guide this brief analysis we also utilise some of the aspects that Rumelhart refers to in his seminal book [Rumelhart86] as of major importance for parallel-distributed processing [Rumelhart86a]: (i) processing units, (ii) state of activations, (iii) output functions, (iv) pattern of connectivity, (v) propagation rules, (vi) activation rules, (vii) learning rules, and (viii) operational environments.

The emergence phenomenon can be understood as what happen in animals, whose behaviours mediated by the CNS are much more complex (in time and space) than the behaviours of its constituent neurons [Holland98].

Symbol grounding is a computational problem, which demands that concepts are defined in a first language and in real world experience and knowledge [Harnad90]. Because it is out of the scope of this thesis, we avoid commenting further on the requirements (and implication) of ‘symbol grounding’ for consciousness, as for example, in acquisition of meaning of words where there is a necessity for a “head” (or brain) where concepts are grounded upon [Harnad03].
4.2.1 Processing unit (i.e. artificial neuron)

Analogous to the brain, all kinds of ANNs are composed of basic processing units (or building blocks), *i.e.* artificial neurons. Also as in the brain, these units can individually be of various types, which consequently elicit different functionalities. The pioneers McCulloch and Pitts mathematically proposed the first artificial neuron in 1943 [McCulloch43]. Named after them, this neuron is often referred to as MCP in short, yet simple, it is able to compute linear pattern separation between two classes. Fundamentally, MCP neurons consist of two functional sub-units as displayed in Figure 37 in the two halves of the schematic neuron. The first, computes the weighted-sum of all inputs; which is equivalent to the incoming axons and corresponding synapses of a real neuron \( x_i * w_i \). The other functional unit applies a threshold function (or activation function) to the just calculated sum in order to decide on the activation (or not) of the neuron. In MCP neurons the activation function is extremely simple, *i.e.* +1 for \( \Sigma \geq 0 \), or -1 for \( \Sigma < 0 \) (*vide* (a) in Figure 38). This is loosely equivalent to the natural mechanisms that define spikes in a real neuron. Also note the existence of a threshold term (\( \theta \)) that is used to set the input operational ranges that the neuron will react to.

![Figure 37 - McCulloch-Pitts neuron – schematic view](image)

It was only in 1958, 15 years after the MCP neuron’s inception, that the first working version of McCulloch and Pitts’s idea for using artificial neurons for logic computation was presented, *i.e.* Rosenblatt’s ‘perceptron’ [Rosenblatt58]. The perceptron was used firstly for optical character recognition, and overcame the limitations of MCP neurons. This meant that perceptrons could classify data into more than two two-classes \(^{35}\) [Principe00]. Furthermore, the perceptron algorithm was the first that was able to learn from data using a simple learning rule. In this first learning

\(^{35}\) The ‘perceptron’ – multiple \( D \) inputs fully connected to a multiple single layer of \( M \) MCP neurons – was able to classify the inputs in \( M \) classes, so that each MCP of the (single layer) topology is able to linearly discriminate data of a \( D \)-dimensional space [Principe00].
algorithm, quantised differences between actual and desired responses of the system are used to adapt ‘synaptic’ values, i.e. the weight vector. The output value computed by an MCP (and other more complex) neurons are given by Equation 8.

\[ y = \left( f \left( \sum_{i=1}^{n} \omega_i \cdot x_i \right) - \theta \right) \]

Equation 8 – Output computed by an artificial neuron (e.g. MCP)

Although flexible and powerful, the perceptron and other initial attempts to use neural inspired computation to tackle real world problems proved very limited: Minsky and Papert showed that classifications using ‘perceptrons’ could only deal with linearly separable classes [Minsky69]. This was a severe blow to connectionism, and certainly, an immense constraint if one needs to address complex problems. Consequently, not much could be done with these tools for modelling neural processing and cognition.

All artificial (processing) units hitherto have in common simple activation function \( f(\Sigma) \) such as shown in (a) and (b) of Figure 38. This is a limiting factor if one needs to address complex classification problems, which are ubiquitous in neural computation. To remedy that, artificial neural networks started to adopt a non-linear activation function in their processing units [Principe00], e.g. (c) and (d) in Figure 38, i.e. \( 1/(1+\exp(-\alpha \Sigma)) \) and \( (1-\exp(-\Sigma))/(1+\exp(-\Sigma)) \), respectively. Moreover, these differentiable functions were used to derive the gradient descent algorithm [Widrow60].

Figure 38 – Common ‘activation functions’ of artificial neurons, from top-left, clockwise: (a) step, (b) Piecewise-linear, (c) logistic function, and (d) hyperbolic tangent
Following the lead of MCP, other artificial neurons were introduced, namely RAM/SLAM nodes [Aleksander66], oscillatory neurons [Borisyuk91], probabilistic RAM [Aleksander89][Taylor89], fuzzy neurons [Yamakawa90].

4.2.2 Artificial network structures

Although the type of neuron (just commented on) is a very important factor for the function of neural networks, this section comments upon two more factors that also deserve attention: the ‘layout’ and ‘connectivity’ of artificial neural networks.

There are many structural arrangements where neurons can be placed and interconnected. Every one of these (different) topologies provides their networks with distinct features, abilities and behaviour. For example, artificial neurons can comprise of ‘single or multiple’ layers of units. Neuronal arrangements and connectivity can also admit feedback loops when processing information, thus, they are referred to as a ‘recurrent network’. Furthermore, network structures can be ‘hybrid’, i.e. combining more than one of the concepts above.

Based on the results of simulations in chapters 6 and 7, we learn that different layouts in which processing units are arranged and interconnected are highly important for the emergence of some specific neural processing. Actually, the adaptability to construct (and rearrange) networks freely has a highly positive impact on the applications of these methods. In this work, we use the term ‘network structure’ to refer to both the topological arrangement and the pattern of connectivity of processing units (i.e. neurons) of examined artificial neural networks.

4.2.3 Learning strategies (i.e. learning paradigms)

Learning strategies are the overall manner in which groups of networked artificial neurons acquire knowledge, this can vary greatly among topologies. Haykin [Haykin99] proposes a distinction between paradigms and rules of learning. The latter as just instantiations (i.e. algorithm bounded) of the former which are mostly philosophical (i.e. functioning principles). The most commonly considered paradigms are (i) supervised-learning, (ii) reinforcement learning, and (iii) unsupervised learning:

- The supervised-learning paradigm is widely used and presupposes an external supervisor ‘teaching’ the network what it should learn, e.g. error back-propagation of multi-layer perceptrons\(^{36}\) (MLP) [Rumelhart86b].

\(^{36}\) The idea behind MLP networks was first proposed by Paul Werbos in 1974 [Werbos74].
• **Reinforcement learning** resembles supervised-learning, with the difference that the learning process occurs on a ‘trial-and-error’ basis with the participation of an external “critic” evaluating the appropriateness of the results [Barto83]. Some authors consider reinforcement learning as a special case of supervised-learning.

• **Unsupervised learning** is the process in which learning occurs in the absence of “teachers” or “critics”. This means that all knowledge is extracted from intrinsic information from training data in a self-organised way, e.g. Kohonen’s ‘self-organising maps’ (SOM) [Kohonen90] – see also sub-section 4.3.1. SOM algorithms perform dimensional reduction in the data input space. As the nervous system is a very noisy environment [Milton96], these algorithms lead to the tractability of some neural processing via computational methods.

Recently, a significant number of researchers are involved in a new approach to learning in artificial neural networks as proposed by [MacKey92], namely the Bayesian approach. This method considers a ‘probability distribution function’ over the weight space, regarding beliefs for the considered weights [Bishop95]. Other topologies, referred to as constructive networks, even include new nodes (neurons) to achieve better results when learning (e.g. cascade-correlation [Fahlman90]). However, none of these have a plausible neurobiological appeal. The interested reader can find more information about neural topologies in [Jain96].

### 4.2.4 Learning rules

Similarly to synapses in the brain, weights in artificial neural networks are the place where information is effectively stored, and learning rules are responsible for the update of these weights. By using learning rules, ANN algorithms are able to learn from data; hence, the great importance of them in neural network models.

In the literature, one can find a vast number of references to learning rules (or algorithms) of various types. Didactically, Haykin groups these rules into five major classes [Haykin99]: (i) error correction learning, (ii) competitive learning, (iii) Hebbian learning, (iv) Boltzmann learning, and (v) Thorndike’s law of effect. Next, the first two of these rules are commented upon in more detail because of their use in chapter 5 (i.e. the theoretic part of this thesis). The origin of these rules is very diverse, namely, ‘error correction’ is originated in signal processing, ‘competitive learning’ and ‘Hebbian learning’ are rooted in biology, ‘Boltzmann learning’ is inspired from ideas of...
thermodynamics, and Thorndike’s law of effect is an heuristic about animal behaviour.\(^{37}\)

O’Reilly states that mixing Hebbian rules and error correction seems to be a good idea, as they might complement each other [O’Reilly00], see subsection 4.3.

### 4.2.4.1 Error correction (Delta rule)

Inspired by Rosenblatt’s ideas, in 1960, Widrow and Hoff proposed the learning rule displayed in Equation 9 [Widrow60]. This learning rule, also known as delta rule, carries out update an values of the weights that are proportional to the error and activation of the neuron [Principe00]. This means that differences (or errors) between elicited and expected “behaviours” of the neuron are fed back to the neuron by the delta rule, which uses this information for updating weights accordingly.

\[
\omega_j(t_{k+1}) = \omega_j(t_k) + \eta \cdot e(t_k) \cdot y(t_k)
\]

\(^{37}\) Thorndike suggests that in animal behaviour, the greater the satisfaction or discomfort, the greater the strengthening or weakening of the bond to the action recur (or not) [Thorndike11].

As can be deduced by the reader, the operation of this rule necessitates data with examples of correct (or expected) behaviour, at least during training of the neural network topologies. This idea is biologically sound as some types of behaviour, notably in the motor system, involve error feedback and improve with rehearsal [Ghez00].

### 4.2.4.2 Competitive learning rule

Some problems and data domains do not offer the possibility of additional “help” being given by the learning algorithm. As mentioned for unsupervised learning, the learning task in this paradigm is entirely driven by the information encapsulated in the training data. There are four principles that subsume ‘self-organisation’ as it happens in biological and artificial neural networks [von der Malsburg90]:

- Modification of synaptic weights tends to self-amplify [Hebb49];
- Limited resources induce competition among synapses, with growth of the fittest and reduction of others;
• Following competition, modification in synaptic weights tends to cooperate with the production of desired outcomes;
• Redundancy in input patterns is the reason why networks manage to learn in a self-organised manner [Barlow89] [Barlow99].

Competitive learning rules are smart yet simple ways to overcome the absence of supervision during training, in addition to implementing self-organisation plausibly. Unlike LMS, competitive learning rules do not require a ‘desired target’ to operate on. This is an advantage when information for training is not available, e.g. communication between some cortical areas that do not evoke any observable behaviour.

There are many ways to implement competition in artificial networks, didactically, these algorithms can be grouped into two competition classes: ‘soft’ and ‘hard’ [Principe00]. This classification takes into consideration how “runner-up” processing units are treated after a given input pattern (i.e. stimulation). The set of runner-ups only includes units that are near the only “winner”-processing unit of the competition: ‘winner-takes-all’ and ‘soft-competition’. The former, a harder form of competition, implies that only the winner unit receives all the synaptic modification. The latter allows the existence of activation bubbles, in the shape of a Mexican hat that are produced by the activity of neighbourhood units formed due to the lateral inhibition of processing units surrounding the winner. In this case, after stimulation more than one processing unit has their weights updated by a competitive rule. See some examples of the rules commented before in Equation 10. Generally, the weight update is inversely proportional to the distance from the epicentre of activation.

\[
\Delta \omega = \eta \cdot y \cdot x \\
\Delta \omega = \eta \cdot (y \cdot x - y^2 \cdot w) \\
\Delta \omega = \eta \cdot (y \cdot x - y \cdot w)
\]

**Equation 10** – Competitive rules: (top) Hebb’s, (mid) Oja’s, and (bottom) Instar rule (Outstar, swap x,y)

The notable point of Hebb’s and other competitive rules is that global order can be obtained by means of local processing of the locality of the weights that they work with, which avoids undesirable global searches, as pointed out by Alan Turing [Turing52].

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38 There are various ways to calculate the distance of a unit \( x_i \) to the winner \( x_j \); an example would be the Euclidean distance, which is calculated as follows: \( d(x_i, x_j) = \sqrt{\sum(x_{ik} - x_{jk})^2} \).
4.3 Selected topologies of soft competition ANN

Soft competition is ubiquitous in the nervous system. Moreover, many important biologically computed functions such as the specialisation of resources, some forms of representation, and access to information are performed using soft competition (i.e. no global control) [Principe00]. Three ANN topologies, relevant to the contribution of this thesis, are briefly commented on next.

4.3.1 Kohonen’s SOM [Kohonen82,90]

Self-organising maps are artificial neural networks that perform a dimensional reduction of input data while mapping from a continuous input space $D$ to a discrete output space $N$, while preserving the topological features of the inputs [Principe00]. The network is composed of a single-layer and weight vectors. The latter represents complete connections of an output neuron $j$ to all inputs. An illustration to help understand the function of SOMs, is that these maps are analogous to an elastic surface that covers the input vector’s space [Kasabov96].

The map formation occurs interactively when the neighbourhood of units surrounding the competition winner have their weights updated. The competitive rule used for training approximates the weight vectors toward the stimulation presented. The competition occurs in the output layer, which can be of dimension greater than two. Figure 39 displays a schematic view of a two-dimensional self-organising map of $D$ inputs and $J$ neurons in the competitive layer.

![Figure 39 – Kohonen network (2-D output)](image)

Kohonen states that the initial map formation plays an important role in the future of the network performance [Kohonen90].
4.3.2 Hecht-Nielsen’s Counterpropagation [Hecht-Nielsen87,88]

This hybrid network includes two layers that utilise distinct paradigms, namely unsupervised learning (i.e. competitive) in the first processing layer, and supervised learning (in the output layer), each one trained independently (see Figure 39). The rationale is that the competitive layer in a “winner-takes-all” manner clusters the input spaces, whereas the supervised layer fine-tunes the key encoding carried out previously. This network trains fast and the competitive layer exhibits meaning itself [Kasabov96].

![Figure 40 – Counterpropagation network](image)

4.3.3 Grossberg’s Instar-Outstar [Grossberg74,97]

This three-layered network performs associations between scalar inputs to vector outputs for pattern recall. It is very similar to ‘counterpropagation’, with the difference that normalisation is carried out by the input layer as in the present one [Principe00]. In other words, ‘instars’ are neurons fed by a set of inputs through synaptic weights, while ‘outstars’ are neurons driving a set of weights [Medler98].

![Figure 41 – Instar-Outstar network](image)
4.4 Closing remarks

The understanding of how the brain works is the goal shared by two disciplines namely, neuroscience and cognitive sciences [Churchland00]. Cognitive neuroscience is a cross fertilisation between the two and studies mental activity. It integrates diverse methods such as (i) single cell activities in healthy animals, (ii) correlation studies between pattern of firing and higher cognitive processes, (iii) analysis of behaviour of patients with lesions, (iv) medical imaging and (v) computing [Kandel00c]. Finally, a further branching field, computational neuroscience is concerned with modelling of specific brain systems [DeSchutter00]. Some authors prefer to assume that computational neuroscience is the theoretical study of the brain to uncover various constituent aspects of the nervous system, ultimately, of the mind [Trappenberg02].

This thesis relates to modelling portions of the nervous system that can be observable by functional imaging methods. Based on chapter 3, this requirement implies that areas candidate to be modelled have to be at least a few millimetres. This contrasts with the few microns that are offered by current computational neuroscience models, which consider (for the sake of plausibility) only a few neurons. Obviously decisions towards a larger model involve necessarily a “price” to pay, as there is a fine-balance to be observed between ‘accuracy’ and ‘utility’ of results. In other words, modelling small neural circuits can be more realistic [Calabrese00] but may be also of low utility as far as medical imaging is concerned. The contrary is also true, i.e. large artificial neural networks may not be very realistic but can be beneficial [Hasselmo00]. Theoretically, there are certain applications that could benefit from models of large networks, namely, (i) to help on prognoses in neurology and (ii) to provide an underlying substrate for checking hypotheses in medical imaging experiments.

The advantages of artificial neural networks commented in this chapter were found sufficient for the selection of these models (i.e. the connectionist paradigm) to be used for addressing the objectives and hypotheses of this research work defined in chapter 1. However, many of the features identified as necessary for a suitable model to tackle the objectives (recall the axioms identified and formulated in chapter 2 and 3) are not readily and entirely available in one single existing model of neural networks. This motivated us to, in the next chapter, investigate new alternatives that may offer all the necessary (and previously) identified features that are expected to be present as part of a more general and flexible computational (connectionist) model.
Chapter

5 Venn-Networks: a framework for brain function and neural computation

“Probable impossibilities are to be preferred to improbable possibilities”. Aristotle 384–322 BC: Poetics
5.1 Understanding brain function and neural computation

5.1.1 Using computer models to understand brain function

Current medical imaging techniques and other experimental methods for investigating the brain provide spatio-temporal resolutions which are not imaginable a few years ago (refer to Chapter 3). Comparable advances are ubiquitous in all other areas of neuroscience (refer to Chapter 2). This means that the cumulative knowledge about the nervous system has never been so extensive. In light of this, one might question: are computational models necessary for understanding the brain? However, one should not disregard (in a broad discussion such as understanding brain function) the astounding advances in computer science and artificial intelligence; especially connectionist systems with their remarkable abilities to mimic neural processing (refer to Chapter 4) and brain disease [Stein98].

This first section of this chapter aims to address the question above. It also aims to discuss a suitable approach to the problem and the necessary requirements of a framework for understanding brain function in relation to the techniques and knowledge readily available. The remaining sections introduce and comment upon Venn-networks, which is a new kind of artificial neural network we developed to address some of the existing limitations of connectionist systems when investigating brain function. Together with other auxiliary models of brain disorder, Venn-networks have the potential to help further investigations combining functional imaging methods to realistic underlying biological facts.

The bold question posed in the first paragraph above, about the utility of models for understanding brain function, can be seen as a stricter version of another question asked by James MacClelland in the foreword of O’Reilly and Munakata’s book [O’Reilly00]. He discusses the necessity of computer models for studying cognition. Although the scope of the two questions is not necessarily the same, their answers share most of the arguments put forward. Initially, we follow the lead argument in agreement with MacClelland who states that – among other things – models:

(i) have the ability to acquire emergent properties of the modelled system;
(ii) help to abstract unnecessary details of the problem, and
(iii) can be used to check correctness of a theory.

In relation to the problem of understanding brain function via experimental methods, we strongly defend the need of using underlying computational models – also because of the ill-posed nature of observations as a means to correlate cognition to
brain function. By ill-posed, we refer to the generally large number of possible solutions when one tackles the “inverse problem”\textsuperscript{39}.

In addition, other potential advantages of using a computer model are:

(i) the experimenter has more control over experiments carried out, specifically the pace of the simulation, and the \textit{granularity}\textsuperscript{40} and portion of the problem selected to be simulated

(ii) the possibility of using artificial data as well as real data (the first reduces problems of short sized data samples), and

(iii) the ability to tackle complex systems and scale them up without many of the oversimplifications common in mathematical models.

Obviously any kind of model – including computational ones – involve abstractions of some sort, hence their imprecision. This problem is particularly exacerbated when attempting to model a system as complex as the brain.

\subsection*{5.1.2 Algorithmic approaches for understanding neural computation}

Another important aspect to be considered is the approach to utilise when producing algorithms to understand neural computation. Henning states that there are two main approaches namely \textit{model-driven} and \textit{data-driven algorithms} [Hennig98]. The first paradigm focuses on the functionality of the systems and the second considers only the existing data about the problem considering the system that generated them.

\textit{Model-driven algorithms} make initial assumptions about the behaviour and structure of the modelled system, which later are incorporated into the processing. Generally, the greater the number of features considered, the better are the results of the model. Although these algorithms often acquire the most prominent and emergent behaviours, nevertheless it is unlikely that they will ever incorporate all expected behaviours of the modelled systems.

\textit{Data-driven algorithms}, conversely, do not make initial assumptions about the modelled system. As a result, they are sometimes easier to implement and quicker to simulate. Overall this approach is a good way to understand relatively easy problems, but this is not the case of neural processing. In addition to the already mentioned consequences of tackling the inverse problem, the other major criticism to this paradigm is that some useful information – often available about the systems – is simply ignored.

\textsuperscript{39} The inverse problem is a mathematical metaphor to indicate impossibility for deciding causation

\textsuperscript{40} Granularity is a term to express level of abstraction when defining a model
5.2 Venn-networks as a framework of brain investigation

5.2.1 Venn-networks rationale – name origin and initial assumptions

Since the beginning of twentieth century, neuroanatomists and neurophysiologists have discovered that the constitution of the brain is complex and diverse [Kandel00a]. Surprisingly, connectionist systems very often do not explore and use such inspiring diversity. Actually, it is fairly common for artificial neural systems to have only one type of neuron and for all its processing units to be fully connected to each other.

We disagree with this exaggerated simplification, as we hypothesise that brain structure is an important aspect of its own emergent computation. As a result we propose a new type of neural network that readily admits definition of various types of processing units, at the same time these diverse units can be grouped together in regions (each with specific properties and connectivity). The preliminary sketches of the system used two dimensional maps containing different regions drawn on them. These sketches resemble Venn-diagrams, and because of this resemblance, the novel neural network was named after John Venn [Venn80] – inventor of Venn-diagrams. Venn’s formalism can also convey the overlap of features of the new system.

5.2.2 Venn-network lemma – flexibility, adaptability, and scalability

Every intelligent system, irrespective of its algorithmic approach, construction paradigm and design path can be analysed regarding its flexibility, adaptability and scalability. Obtaining a good balance between these three aspects is paramount if one seeks interesting results. Ultimately these three aspects inform how suitable the system is for dealing with a multitude of tasks and potential modifications (in complexity) of these tasks. In neural systems, (i) flexibility concerns the extent to which the system’s structure is alterable; (ii) adaptability relates to how effective the reactions of the system are towards changes in environmental conditions (i.e. how good the learning process is); and (iii) scalability deals with computational resource consumption due to increase in the complexity of the executed task. Thus, together with informed decisions about approach in sub-section 5.1.2, these three aspects were major priorities when creating the novel type of neural network proposed in this thesis, i.e. Venn-networks.

In light of this, Venn-networks are considered to be flexible to freely accept many types of processing units, at the same time they allow a non-trivial connectivity, and in addition to a sound learning algorithm, they are highly adaptable and scalable.
5.2.3 Venn-network structure – components

5.2.3.1 Processing units: cortical columns

The notion of one type of processing unit in an entire model completely contradicts cytological evidence found in the brain. Cytoarchitectonic differences in the neocortex were suggested as early as 1909 by Brodmann [Amaral00]. Indeed, electrical and chemical differences among neurons result in distinct signal encoding, and ultimately, in distinct behaviours of the system [Kandel00b][Levitan97]. In Venn-networks the set of attributes defining such functional differences is referred to as a unit type. We assume one unique type $UT$ per individual processing unit $PU$, see formal specification of that in Equation 11. The Symbols and operators section contains all mathematical notation used in the equations of this chapter.

$$
UT_n \in \{\text{unit type}\} \mid n = 0,1,\ldots
$$

$$
PU_n \in \{\text{processing units}\} \mid n = 0,1,\ldots
$$

$$
PU_n \rightarrow UT_n
$$

Equation 11 – Uniqueness of unit type ($UT$) for each processing unit ($PU$) of a Venn-network

The unitary correspondence between processing units (PU) and cortical columns is another main assumption in Venn-networks. Recall from chapter 2 that individual neurons, despite their vital role to neural processing, should be considered part of a column for producing perceivable functions. Figure 42 shows PUs placed on a 2D map.

![Figure 42](image)

Figure 42 – Schematic view of processing units (PUs) arranged in a two dimensional map
5.2.3.2 Processing regions: cortical areas

The existence of different types of processing units, which are base components of Venn-networks, suggests that units akin could implicitly define regions on the processing map. By akin we understand three concepts: (i) processing units are of the same type, (ii) PUs are topographically neighbours, and (iii) PUs have similar connectivity patterns. Venn-networks incorporate the principle of uniqueness of unit type, but only for processing units comprising same regions of the map. Equation 12 formalises ‘unit type’ ($PU$) uniqueness per processing regions ($R$). Figure 43 illustrates various regions arranged onto a 2D map.

$$
R_s \in \{\text{cortical regions}\} \ | s = 0,1, \ldots \\
R_s \rightleftharpoons PU_s \\
R_s \Rightarrow PU_s \& UT \ (PU_s) = m \\
R_s \Leftarrow UT_s
$$

Equation 12 – Uniqueness of unit type in one region of a Venn-network

![Diagram](image)

Figure 43 – Example of multiple processing regions ($R_s$) and their types ($UT_s$) of a Venn-network

The explicitly localised results within processing regions in the cortex can be observed by various functional imaging methods as synergistic activations when a subject is performing cognitive tasks [Kandel00a]. Based on the axioms above it is...
possible that different regions comprise of processing elements of the same type. However, the opposite is not true. In other words, one region cannot have processing units of more than one type. This feature allows interesting properties to be investigated – especially in physiological scenarios, e.g. see fourth experiment of chapter 6. It is another evident reason for the name selection of this model, i.e. Venn-networks.

5.2.3.3 **Stimuli sources and Effectors**

The various regions within the brain can either ‘emit’ or ‘receive’ (i.e. be origin or target) of signals that are transiting throughout the nervous system. These two contrasting roles are not necessarily fixed or mutually exclusive. Indeed, most cerebral regions can be the origin of some stimulation as well as the target of other signals (see explanation about layered organisation of the cortex in chapter 2). In this respect, it is important to consider that the whole body processes neurological information too. Thus, nearly all parts of an organism can also initiate or can be destination of signals.

Considering that visceral organs, muscles, **proprioceptors** and **exteroceptors** are spread all over the organism, and the interactions between the body’s components, and the nervous system becomes of unprecedented complexity. This fact should prevent every diligent neural modeller from abstracting neural-somatic interaction, but surprisingly this is often not the case (i.e. many modellers do abstract this important detail). One should bear in mind that this interaction happens in parallel, as the brain is the highest-level element for co-ordination and consolidation of all bodily signals. An analogy between the nervous system and a telephone network may help to clarify the parallel, punctual and mediated nature of such interaction. In this analogy the cortex is viewed as the telephone switchboard and body parts are viewed as callers, the latter, able to call or be called by others members of the system.

Venn-networks assume that originators and targets of neural communications are mandatory components that can be freely defined in the network structure when necessary; **stimuli sources** ($S_p$) and **effectors** ($E_q$) are the terms used to refer to these components. Furthermore, as observed in biological systems, Venn-networks incorporate the notion that such components can have different **cardinalities** to reflect

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41 Venn-diagrams can illustrate the overlap of concepts such as unit type and region: Let's assume that $R_1$ and $R_2$ are regions; $PU_1$ and $PU_2$ are processing units; $UT_1$ and $UT_2$ are unit types. By definition we assume: $R_1 \cap R_2$ is null, $PU_1$ is different of $PU_2$, and $UT_1$ is also different of $UT_2$. Using Equation 11 and Equation 12 it is valid to say that $R_1$ or $R_2$ can be composed of $PU_1$ and $PU_2$ if these units have either types $UT_1$ or $UT_2$. On the other hand it is not valid to say that $R_1$ or $R_2$ can be composed of $PU_1$ and $PU_2$ if these units have types $UT_1$ and $UT_2$, respectively.
differences in size and importance. With cardinality specified in Equation 13, stimuli sources and effectors will always be present in the network structure of Venn-networks.

\[
\begin{align*}
S_p^\delta &\in \{\text{stimuli sources}\} & p = 1,2, \ldots \\
E_q^\delta &\in \{\text{effectors}\} & q = 0,1, \ldots \\
\text{cS} &\text{= cardinality}_{\text{stimuli}} & \text{cS} > 0 \\
\text{cE} &\text{= cardinality}_{\text{effectors}} & \text{cE} > 0
\end{align*}
\]

\textbf{Equation 13} – Minimum cardinality of Stimuli source and Effectors of Venn-networks

5.2.3.4 Axonal connections: fibre types

We have discussed components of Venn-networks, where neural communications initiate and terminate. In this section, we present Venn-network component to simulate the transmission of neuronal signals, i.e. fibres.

Neurocommunications in Venn-networks admit highly parallel and non-trivial connectivity. This complex task is achieved by a collection of bundles of fibres connecting freely pairs of various components of Venn-networks in the following manner: (i) stimuli sources-region, (ii) regions-region, (iii) region-effector, and (iv) effector-region. These bundles of fibres (i.e. axons) are based on anatomical knowledge about the system to be modelled and are composed by fibres that completely connect\(^{42}\) all elements of the two components involved. Each fibre of the bundle (i.e. pathway) is assumed as passive medium that conducts signals between origin and target component.

According to the components they connect, fibres in Venn-networks can be of four functional types, namely: (i) fibres connecting stimulus \(S_p\) and region \(R_o\), (ii) fibres connecting region \(R_{o1}\) and region \(R_{o2}\), (iii) fibres connecting region \(R_o\) and effector \(E_q\), and (iv) fibres connecting effector \(E_q\) and region \(R_o\) (see definition in Equation 14).

\[
\begin{align*}
\mathbf{F}_r^{\text{cO}} &\in \{\text{fibres}\} | r = 0,1, \ldots \\
\text{O} &\text{= signal } \_\text{origin} \\
\text{T} &\text{= signal } \_\text{target} \\
\mathbf{F}_r^{\text{cO}} &\subset [0,7][0,7] - \{\langle S_p, R_o \rangle, \langle R_{o1}, R_{o2} \rangle, \langle R_o, E_q \rangle, \langle E_q, R_o \rangle\} \\
\text{cO} &\text{= cardinality } \_\text{origin} | \text{cO} \geq 0 \\
\text{cT} &\text{= cardinality } \_\text{target} | \text{cT} \geq 0
\end{align*}
\]

\textbf{Equation 14} – Generic two-part composition of fibres

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\(^{42}\) full-connection means that all elements of origin are connected to all elements of target

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Another fibre classification considers the order in the abstract processing cycle assumed in Venn-networks. In this classification fibres are: afferents (from stimuli), u-fibres type 1 (after afferents), efferents (towards effectors), efferent-feedback (from effectors), and u-fibres type 2 (just after efferent-feedback); see Figure 44 to Figure 48. In all these figures the direction of information flow adopted is from ‘top’ to ‘bottom’.

Afferent fibres

![Figure 44 – Schematic view of afferent fibres, i.e. fibres that reach PUs from stimuli sources](image)

U-fibres or commissural fibres type 1 (i.e. just after afferents)

![Figure 45 – Schematic view of u-fibres type 1, i.e. fibres that interconnect PUs (after afferents)](image)
Efferent fibres

Figure 46 – Schematic view of efferent fibres, i.e. fibres that leave PUs towards effectors

Efferent feedback fibres

Figure 47 – Schematic view of efferent-feedback fibres, i.e. fibres that reach PUs back from effectors
U-fibres or commissural fibres type 2 (i.e. just after efferents-feedback)

Figure 48 – Schematic view of u-fibres type 2, i.e. fibres that interconnect PUs (after efferent-feedback)

Venn-network: structure overview

Figure 49 – Schematic view of all components of Venn-networks put together
5.2.4 Venn-network dynamics – functioning

5.2.4.1 Signal transmission

As opposed to many connectionist systems but in consistent with biological evidence [Whitfield84], we assume that fibre delay is a feature which is not to be abstracted. This means that transmission time of axons is not considered to be negligible information, as in other connectionist systems. Thus, in Venn-networks bundles of fibres have specific associated delays. This feature allows interesting properties to be investigated – especially in pathological scenarios – as we will show in chapter 7. In this way, myelinated, un-myelinated, and demyelinated fibres can all be used in Venn-networks by only addition of distinct overall transmission delays (see chapter 2 – types of propagation of potential). Thus, the model still copes with cases when specific fibre delays cannot be estimated by simply assuming no fibre-delay.

5.2.4.2 Processing unit activation

In Venn networks one processing unit (PU) abstracts the behaviour of populations of biological neurons within the same location, i.e. the cortical column. Thus, respecting region boundaries and unit features, activation of PU – shown in Equation 15 – is an independent activation function summation (\( f \) is logistic function) upon all \( N \) incoming signals – both excitatory (\( \text{Exc} \)) and inhibitory (\( \text{Inh} \)) – directed towards the \( PU_n \), where \( \text{Exc} \) and \( \text{Inh} \) are weighted (synaptic) signals from other PUs; \( \Theta \) is a threshold value.

\[
PU_n(t_t) = f \left( \sum_{i}^{2^{J}} PU_n^{\text{Exc}}(t_t)^{i} - \sum_{i}^{2^{J}} PU_n^{\text{Inh}}(t_t)^{i} \right) - \Theta
\]

Equation 15 – Calculation of threshold activation of processing unit (PU)

5.2.4.3 Abstract processing cycle

Even though PUs are entirely randomly selected for calculation purposes explained in Equation 15, an abstract closed processing cycle for Venn-networks is assumed. This cycle (displayed in Figure 50) follows an intuitive sequence of five steps in which:

(1st) afferent signals arrive to the computed map from areas external to the model;
(2nd) cortical map “reacts” to that stimulation;

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\( \text{Exc} \) and \( \text{Inh} \) refer to excitatory and inhibitory signals, respectively.

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\( \Theta \) is a threshold value.

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This cycle does not imply sequential processing for the brain as a whole, but an enormous number of causal cycles happening in parallel for its constituent processing units.
(3rd) efferent signals are issued to effectors;
(4th) signals from effectors are feedback to the map; and finally
(5th) cortical map “reacts” again to the fed back stimulation.

![Abstract processing cycle adopted in Venn-networks computation](image)

We refer to this processing cycle as “abstract” because it only fulfils computational needs of implementation. In other words, it neither directly interferes with the evoked computation of the network, nor has necessarily to start at step 1. In each of the five steps of the cycle there is a complete recalculation of activation of all processing units of the cortical map which are randomly selected and updated according to Equation 15. It is evident that, if no signals arrive for a particular processing unit, its instantaneous activation is not likely to change. An exception to that is when considering in the simulation non-zero added random noise and relaxation.

Every step of the processing cycle is in close agreement with the type of fibres defined in sub-section 5.2.3.4. Every type of fibre defined is computed separately in each of the steps of the processing cycle, namely: afferent fibres are computed in step 1 of the processing cycle; u-fibres type 1, in step 2; efferents fibres, in step 3; efferent-feedback, in step 4; and u-fibres type 2 are computed in step 5 of the cycle.

### 5.2.4.4 Processing cycle step 1: afferent fibre processing

The first step of neural computation in Venn-networks starts abstractly with afferent signals arriving from areas external to the model, e.g. frontal lobe, eyes, ears.
etc. Following that, if the network is engaged in learning tasks, a self-organising process such as suggested by von der Malsberg and Barlow mentioned in Chapter 4 (see also [Haykin99]) happens for all processing units within all participating regions of the map provided they are destination of those incoming signals. This self-organising process is mainly responsible for the map formation within regions. Also, respecting regional boundaries it occurs in three sequential and distinct activities, namely, (i) competition, (ii) collaboration, and (iii) weight adaptation of afferent fibres.

5.2.4.4.1 Competition (within regions)

The competitive activity of the self-organising process is inspired by the well-known biological process of lateral inhibition. This activity happens in all regions receiving stimulation. Each stimulated region has the most excited of their cell group elected as the competition winner for that particular stimulation. In Venn-networks, the winning unit has a central role in further activities of afferent fibre processing. Equation 16 contains the formalisation of the competition process carried out for every region comprising Venn-network maps; \( \text{arg} \) gives the unit location instead of activation.

\[
PU_{R_i}(t_i) = \text{arg}\max\left\{PU_n(t_i)\right\}, \text{ for all } PU_n \text{ in } R_i
\]

Equation 16 – Competition among processing units of one region – max activation is winner

5.2.4.4.2 Collaboration (among units of same regions)

After the selection of the winning processing unit for each region, i.e. as described above, all processing units within the boundaries of every region collaborate with each other. Collaboration is also neurally inspired (refer to Hebbian learning). It is assumed that collaboration between cells is directly proportional to how topographically close they are in respect to the previously selected winner. Closeness to winner is a concept that computationally can be implemented in various ways. In the Venn-network implementation we offer two possibilities: one ‘linear’ and the other ‘Gaussian’, as described in Equation 17 (legends \( w \) and \( h \) are width and height components of distance).

In Venn-networks clear regional boundaries are considered as another mandatory condition for collaboration because connectivity among different regions (regardless of neighbourhood) are not likely to be similar. Based upon this, the processing unit at distance \( D_i \) from the winner is more likely to collaborate (or will collaborate more) than the PU at \( D_i \) distance, as illustrated in Figure 51. Also, despite \( D_2 < D_1 \), processing unit
at $D_1$ distance to the winner is likely to collaborate in its region rather than PU at $D_2$ distance to the winner. This is only because PU at $D_2$ distance to the winner lies outside the region at hand indicated by the dotted line.

\[
D_n = \left\{ \begin{array}{ll}
\infty & (5) \\
\sqrt{D_R^2 + D_R^2} & (b)
\end{array} \right.,
\quad D_n = \exp \left( \frac{\infty}{CR_n [l_i]} \right), \quad \frac{(x)^2}{D_R^2 + D_R^2} \right.
\]

\[CR_R [l_i] \]

**Equation 17** – Two manner of calculating column distances to the winner: ($D_1$) linear and ($D_2$) Gaussian

![Figure 51](image)

**Figure 51** – Schematic view of various column distances in and out a given cortical Venn-region

In addition to the distance from the competition winner, the collaboration process in a Venn-network also obeys a proportionality defined by a neighbourhood parameter, *i.e.* cooperation radius ($CR$). This additional parameter serves to help on the global map formation described by Kohonen [Kohonen01] (here the map formation is of regional circumscription). This parameter shrinks monotonically during the learning process as the map is being formed. Neighbourhoods here are squared and, because the map is not toroidal, there is some border effect (*i.e.* possible irregular formation). Equation 18 shows the formalisation of the collaboration process $C$ as proportional to the distance between a given processing unit and the winning unit of each region.

\[
C \left( PU_s, \{ l_i \} \right) = D_{PU_s, PU_{s'} \{ l_i \}} \text{ for } \forall i \quad PU_s \text{ in } R_s
\]

**Equation 18** – Collaboration among processing units of one region is proportional of distance to winner
5.2.4.3 Learning (weight updates)

Following the computation of collaborations between processing units, the final activity of afferent fibre processing in Venn-networks is synaptic updating (if network is on learning mode). This activity is the one in which the network effectively incorporates the stimuli representation. Equation 19 shows how weights of afferent fibres are strengthened based on learning rate $n_a$ and collaboration factors $C$. There is also a linear reduction of learning rate by the parameter decrement of learning rate $n_{na}$.

$$F^{S\rightarrow R}_{r}(t_{a}) = F^{S\rightarrow R}_{r}(t_{a}) \left[1 + \left(\frac{n_{a}}{n_{na}T_{l}}\right)C(PU_{n}(t_{a}))\right]$$

Equation 19 – Weight update rule for afferent fibres

At the end of this step of the processing cycle, activations can already be seen on the map (chapters 6 and 7 have examples of that). Due to the incremental nature of the learning process described above, many training epochs are required for the production of clearly visible activations.

5.2.4.5 Processing cycle step 2: u-fibres (type 1) processing

Immediately after afferent fibres computation i.e. after these have conveyed their “messages” to the processing units on the map, the second step of the (abstract) processing cycle of Venn-networks is the computation of type 1 u-fibres. These fibres perform interregional connections that can either be of ‘excitatory’ or ‘inhibitory’ nature (i.e. activity type of u-fibre). They can connect adjacent regions as well as form long-range connections like commissural fibres in the human nervous system [Brodal98].

The rule in Equation 20 implies that u-fibres have a powerful ability to excite or inhibit target regions that they are connected to (see emergent behaviours in chapter 7).

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$44$ Process encompasses two distinct actions depending on what the network is performing. It can be either learning new input representations of the problem or solely reproducing already known ones.

$45$ Type 1 u-fibres refers to fibres that are originated from regions targeted by afferent fibres.
5.2.4.6 Processing cycle step 3: efferent fibres processing

Subsequent to u-fibre computation, efferent fibres are handled next in the Venn-networks processing cycle. This step is another important part in the overall functioning of Venn-networks and is the one in which the network effectively processes suitable output behaviour. If the network is in the learning mode, Equation 21 shows how weights of efferent fibres are strengthened (i.e. weight updating) based upon gradient descent of output evoked errors [Widrow 60], which is controlled by learning rate \( n_e \).

Here, there is again a linear reduction of learning rate by the parameter decrement of learning rate \( n_{ne} \).

\[
F^e_r E^e_i(t_{in}) = F^e_r E^e_i(t_r) - \frac{n_e}{n_{ne} \cdot \alpha} \left[ \text{Err}_e(t_r) \right] \left[ PU^e_i(t_r) \right]
\]

Equation 21 – Weight update rule for efferent fibres

5.2.4.7 Processing cycle step 4: efferent-feedback fibres processing

Efferent-feedback fibres are computed when signals are back-propagated to the map from effectors. This step happens in a similar way to the self-organising step 1 of the processing cycle of Venn-networks. Likewise, this self-organising process is responsible for more map formation within regions and happens in three sequential and distinct activities, namely, (i) competition, (ii) collaboration, and (iii) weight adaptation of efferent-feedback fibres (refer to sub-section 5.2.4.4, i.e. Processing cycle step 1: afferent fibre processing). The concepts and formulae apply integrally to the efferent-feedback fibres, and this time the only adjustment to be done regards the orientation of signals originated at effectors and targeting the various regions of the map.

5.2.4.8 Processing cycle step 5: u-fibres (type 2) processing

The final step of the abstract Venn-networks processing cycle is analogous to the processing of u-fibres of type 1. The only difference is that it happens just after efferent-feedback fibres have conveyed their feedback from the effectors. Accordingly, u-fibres work absolutely in the same manner as Type 1. Hence, Equation 20 also holds for these fibres. Notice that type 2 u-fibres are also very powerful, perform interregional connections (of adjacent regions and far apart ones), and can be excitatory or inhibitory. After this final step, the processing cycle initiates again indefinitely.

46 Process here again encompasses two distinct actions depending on what the network is realising. It can be either learning new suitable outputs for the problem or solely issuing already known ones.

47 Type 2 u-fibres refers to fibres that are originated on regions targeted by efferent-feedback fibres.
5.2.5 Venn-network dynamics – additional features

5.2.5.1 Added random noise and relaxation

The processing units introduced previously all have a deterministic behaviour. This means that same inputs generate similar activations on the map if weights are not updated. Computationally this is correct, but it does not reflect the fluctuating (i.e. noisy) nature of biological systems that may reflect modulation by input from the environment [Levitan97].

To be in agreement with these phenomena we have devised a small algorithm that adds random noise to whatever activation the processing unit exhibit at timestamp t, as well as this same algorithm subtracts random values from the unit activation’s (PU) mimicking what would be equivalent to normal relaxation of columns in biological systems. The reader should refer to appendix B for the computer interface and parameters devised, and refer to the examples showing usage of this algorithm in the simulations of chapter 6 and chapter 7, where one can observe comparisons of using or not added noise and relaxation.

5.2.5.2 Externally stimulation on effectors and stimuli sources

The processing cycle discussed before does not rule out the possibility of external stimulation of various components of Venn-network. By external stimulation we mean exactly what would be the equivalent action in biological systems to TMS, electrode stimulation or even simple mechanical stimulation of skin. Venn-networks accept that any eventual stimulation, regardless of its source, is a signal to be processed. Although external, these additional “signals” are added as input to the next step of the processing cycle. For example, if stimulation is realised on effectors, the step (of the processing cycle) that handles it is the feedback send to the map, i.e. the processing of efferent-feedback fibres. Analogously, this occurs whether the stimulation is exerted on stimuli sources and the step (of the processing cycle) that handles it is the processing of afferent fibres.

In light of this need we have equipped the computational implementation of Venn-networks with apparatus to externally stimulate effectors and stimuli sources. Refer to Appendix B for the computer interface and parameter available. Included in chapter 6 one can see an example with elicited results of such external stimulation in the simulation “active-passive activations”.

5.3 Further challenges in understanding neural computation: illnesses, disorders, and decays

5.3.1 Introduction

The physiology and emergent behaviours of a healthy nervous system are very hard to understand, but these are made even more complex when we consider various forms of neurological decay, illness and brain disorder. Ageing and pathologies of the nervous system may generate highly distinct symptoms from one another, as they are of various sorts, severities and aetiologies. These should be considered in relation to the various CNS disorders discussed in chapter 2, which are classified according to their intrinsic nature, namely vascular diseases (strokes), neoplastic diseases (tumours), degenerative diseases, and inflammatory or infectious diseases [Johnson95]. Being the main “processor”, a dysfunctional CNS will produce significant adverse consequences in the function of the body. Moreover, there are the – not few – psychosomatic diseases\textsuperscript{48}, psychological problems, \textit{i.e.} disorders of the mind\textsuperscript{49}, and ageing processes.

It is far out of the scope of the present work to discuss advanced medical or psychological issues of neuropathology, psychosomatic diseases, and psychological illnesses. However, these pose a very relevant question to the research in relation to how brain diseases affect neural processing. There are a number of ways in which this question may be approached. To be consistent with the approach to analyse the brain in a systematic manner, a brain disorder – seen from an engineering standpoint – is as a system operating under “new” (generally adverse) conditions. In other words, the challenge of understanding neural computation in pathological scenarios is not so distinctly different from the computation in physiological scenarios; provided that the main features of the disease are also incorporated into the general model.

To test the robustness of Venn-networks as a framework for understanding neural computation – this time in pathological scenarios – we decided that some brain diseases should be conjointly investigated. Two brain diseases were selected for this purpose, namely ‘multiple sclerosis’ and ‘strokes’ in the brain. The rationale for this selection was to have one disease that affects \textit{neurons}, \textit{i.e.} the generator of neural information, and another disease affecting \textit{axons}, \textit{i.e.} the carrier of the signal across the “system”.

\textsuperscript{48} Illnesses where psychological factors interfere with physiological bodily aspects [Davis98]

\textsuperscript{49} By referring to physiological and psychological problems as distinct ones we do not imply that body and mind are necessarily of different physical nature (\textit{i.e.} two entities). Likewise, we do not go into discussions of their borders. Being clearly two different concepts is enough for the case at hand and for us to avoid delving into the old philosophical debate of the body-mind problem (see [Armstrong98]).
5.3.2 Multiple sclerosis

5.3.2.1 Overview

As presented in chapter 2, multiple sclerosis (MS) is one of the many degenerative diseases that affects the nervous system. It is a gradual and in many cases non-monotonic process that removes the sheathing of the myelinated axons. This condition is characterised by disseminated inflammatory lesions to the myelin sheathing of nerve fibres, i.e. the MS-plaques [Raine97]. Regarding pathogenesis, although not fully understood, some clinical evidence points out that MS aetiology are due to disturbances of the immune system [Esiri97]. Other possible causes that may give rise to the disease include prior viral infection, genetic inheritance and environmental factors [Raine97]. This thesis does not address the unsolved medical aspects of MS, especially those concerning therapy.

MS-plaques are ‘hallmarks’ of the multiple sclerosis disease and are ubiquitous in various nervous pathways of MS patients [Compston98]. This means that any part of the electrical insulation of the axons within the nervous system can be disrupted. The direct result of MS-plaques action is either loss or reduction in the signal amplitude and velocity between any two communicating areas within the nervous system. Further consequences include bad synchronisation, de-coupling of cortical areas and other communication related problems. These nodes are of absolute importance in the saltatory economical action-potential transmission along the axon [Shepherd94], as described in the comparison of myelinated and non-myelinated axons in Chapter 2. Although myelin re-formation is possible, it happens as a slow process [Leeson85].

From an engineering perspective, one can assume that these inflammatory processes are the sole cause of communication problems between different cortical areas that need to ‘converse’ through a given nervous path. These demyelinating processes cause a reduction in the quality of the membrane insulation of the axon. Consequently, the transmission speed of the longitudinal current on the axon is significantly reduced. If the demyelination process continues, the physical properties of membrane may change drastically and irreversibly. This adverse phenomenon brings about all the functional inefficiencies of unmyelinated axons, i.e. slowness of signal propagation leading to a possible decoupling of the two areas. In extreme cases, inflammation and demyelination can even totally block the communication between the two previously communicating cortical regions.
5.3.2.2 MS plaque model

Based upon the description of the MS disease in section 5.3.2.1, it is reasonable to assume that for the purpose of computation of the effects of the MS disease may be simplified to the action of various assembles of plaques throughout specific parts of the nervous system. To model MS plaque effects, we present a computer algorithm that incorporates into neural inspired networks some of the biological features observed in the axon membrane affected by multiple sclerosis [Buarque00, Buarque01a].

Early computer models of demyelination such as the work by Koles [Koles72] just addressed single nervous fibres, which is an oversimplification of the problem. The proposed model aims to improve understanding of the anomalous and complex communication behaviours presented by a nervous pathway connecting two distinct cortical regions, when affected by MS-plaques.

The first aspect devised in the proposed model for MS-plaques was to include into a multi-layer neural network the physiological transmission delays observed when an action potential propagates in a healthy axon. It is important to highlight that most of the widely used artificial neural networks, including MLP, assume an ideal axonal propagation, i.e. signal propagation without delays. In most situations this assumption can be adopted with no further consequences; however, in more realistic models this simplification should not be made because delays are precisely the aspect disrupted when MS-plaques impinge and damage long-range pathways.

Amongst all considered biological features, two are of great importance for tackling the current problem, namely (a) the local dynamics of the internodes interaction, and (b) the nature in which the axon sheathing is organised. Interestingly, the inclusion of these two features into the model enables a reduction in the complexity and the volume of computation required. Both refer to the kind of activity in a myelinated axon membrane. We assumed they are constituted imminently of local interactions that occur in the vicinity of the Ranvier nodes with signal transmission orientated towards the synaptic terminations. This means that the model considers the activation of only one node as the main cause of triggering activation along the internodal region of the consecutive Ranvier node. Computationally, this also means that the propagation of the action potentials along a single axon can be processed in a discrete and sequential manner. The second feature mentioned above also allowed discrete and sequential simulations by varying the membrane insulation effectiveness.
In other words, the model allows transversal axonal resistances to be simulated in either binary or in a more complex manner.

In reality, when sclerotic plaques affect axons, the myelin layers of the affected internode of the fibre are likely to be removed all at once. The MS-plaque model can simulate either partial or total damage to the layers, i.e. homogeneous and inhomogeneous damage to the myelin among different parts of the axonal insulation.

Figure 52 presents a schematic view of long-range connections between two cortical areas that are subject to MS-plaques. The areas affected by MS lesions (indicated by grey ellipses) have distinct degrees of impact on slowing down the signal propagation, i.e. different inflammation epicentres indicated by radiuses $r$. Each of these radiuses indicates homogeneous density of damage to the pathway sheathing. The other symbols used in the figure are: $h_n$ – processing units that originate affected axons, $o_n$ – processing units that are target of affected axons, and $w_{jk}$ – synaptic values of the various connections.

![Figure 52](image)

The consequences of delays caused by MS-plaques to the output units of the network ($O$) are expressed by Equation 22; $\varepsilon$ is additive error. This equation represents the network output (i.e. activations of processing units of the target area) computed as the forward path of the multi-layer perceptron architecture – proposed in 1986 by Rumelhart, Hinton and William in the famous book, “The PDP” [Rumelhart86].
Equation 23 specifies a criterion to exclude axons that ‘fail’ to deliver their signals within an expected arbitrary time-window. In this criterion, the failing axons have their contributing signals discarded from the overall summation when the corresponding transmission time $t_j$ is greater than the time window defined and measured in the target area. This time window is variable, and was considered in the simulations to be linearly proportional ($\tau = 1$) to the ‘normal’ transmission time of the average of all axons of the pathway i.e. $\text{avg}(t_j)$, see Equation 24. Recall that a complete description of all symbols use below can be found in the Symbols and operators section.

\[
O = \sum_{k=1}^{M} \sum_{j=1}^{H} h_{kj} \cdot W_{jk} \cdot \mu_j + \varepsilon
\]

**Equation 22** – Network output considering eventual delays due to MS-plaques

\[
\begin{align*}
\text{if} & \quad t_j \leq T_{\text{window}} \\
\text{then} & \quad \mu_j = +1, \\
\text{otherwise} & \quad \mu_j = 0.
\end{align*}
\]

**Equation 23** – Rule governing if an axon is or is not to be considered for current computation

\[
T_{\text{window}} = \left\lfloor \text{avg}(t_j) \cdot \tau \right\rfloor, \tau \geq 0
\]

**Equation 24** – Calculation of the time-window for the entire nervous fibre

Finally, Equation 25 shows how the transmission time of a particular axon is calculated. Where $t_{\text{node}}$ is the transmission time for one internode, and $d_{\text{node}}$ is the additional delay imposed, to it by MS-Plaque lesions.

\[
t_j = \left( \sum_{n \in \partial i} t_{\text{node}} \cdot d_{\text{node}} \right)
\]

**Equation 25** – Calculation of the transmission time of a particular axon
The assumptions described above are believed to accommodate the most important physiological impacts present in the MS disease which result in a gradual slowing of evoked expected ‘behaviour’. Also, the way the model was conceived contributes towards low computational complexity and a high plausibility.

The proposed MS-plaque model also caters for plaque growth. This means that the model can be used to foresee the adverse effects of MS plaques when they expand to neighbouring internodes of already affected ones either transversally to the nerve or along the fibre. Because of the inflammatory process triggered by the plaque lesions [Raine97], the model assumes that the size increase of the plaques occurs mainly around the vicinity of affected parts of nerve fibres rather than to other more distant lesions.

5.3.2.3 Preliminary simulations of MS-plaque model

The various results produced in early simulations of this model can be seen in Appendix F, which also shows how modelled MS-plaques can exhibit some of the features observed in biological systems affected by MS.

Among the parameters varied in the early simulations of the MS-plaque model (again see Appendix F), it was found that the number of affected axons was consistently the most influential factor causing transmission delays. This feature surpassed all the other ones investigated, namely the number of internodes affected and the severity of individual attacks on internodes. Thus, transversal damage to the pathway is more devastating to neurocommunications than longitudinal destruction to myelin. This could lead to the conclusion that MS-plaque layouts can be in certain cases a more relevant feature than their own size [Buarque01a].

5.3.2.4 MS-plaque model within Venn-networks

Although in Venn-networks the computation of MS-plaque effects is simplified, two fundamental principles of the MS disease are considered. Both of temporal nature, they are (i) temporal evolution of lesions (obtained via different ‘processing phases’ of Venn-networks) and (ii) increase of axonal conduction time due to MS lesions (given by the MS model that is applied to all four types of fibres defined in Venn-networks). Thus, temporal features of Venn-network allow that evolving damage caused by MS-plaques to a pathway alters the conduction time of constituent axons affected. This means that some axons will not be able to convey their “messages” forward if ‘axon-delay’ is greater than ‘fibre-delay’ plus ‘specific allowance’. The two latter are parameters input per fibre and the former considers the MS-plaque load for the axon.
5.3.3 Strokes

5.3.3.1 Modelling stroke effects

The approach adopted towards modelling strokes50 utilises the same intuition used in the MS-plaque model concerning the network structure. However, the difference is that this time the damage is applied directly to neurons of the network. Similarly to the MS-plaque model, there is still the notion of severity of damage – indicated by $\Xi$, but now as a result of regional damage density (see Figure 53). Other symbols in the figure are: $h_n$ – processing units that are origin of affected axons, $o_n$ – processing units that are target of affected axons and $w_{jk}$ – synaptic values of the various connections.

![Schematic view of a patch of the nervous tissue affected by stroke](image)

Figure 53 – Schematic view of a patch of the nervous tissue affected by stroke

The output produced by a network ($O$) with neurons being “deleted” by a stroke is given by Equation 26. The first term of the equation accounts for normal neural activity, whereas the second term, disregards activity not produced because of neuronal death; $\varepsilon$ is additive error. Although not all ischemic areas lead to infarction, the current model does make this assumption. Thus, it doesn’t admit tissue recovery after ischemia.

$$O = \sum_{i=1}^{M} \sum_{j=1}^{H} \hat{h}_j \cdot w_{jk} - \sum_{k=1}^{M} \sum_{j=1}^{H} \hat{h}_j \cdot w_{jk} + \Xi$$

Equation 26 – Network output considering eventual effects due to neuronal knock-out

---

50 More information about strokes can be read in chapter 2.
Equation 27 and Equation 28 govern which neurons are considered in the computation in relation to their position in the lesion.

\[
\hat{h}_i = h_i \cdot \xi_j
\]

Equation 27 – Neurons removed due to a stroke factor ($\xi$) as can be read in Equation 28

\[
\begin{align*}
\text{if} \{ h_i \in \Xi \} & \text{ then } \xi_j = 0, \\
\text{otherwise, } \xi_j = 1.
\end{align*}
\]

Equation 28 – Rule governing if a neuron should or should not to be computed

At the moment, the computational implementation of Venn-networks only accepts user-generated input in relation to the location and quality of lesions. However, the model only accepts this information from automatic routines produced by non-invasive imaging methods on human subjects. We believe that interface routines can be built and effectively input data into the computational models. The data should include features about localization of lesions within the nervous system and the magnitude of these lesions. This assumption is supported by several works featuring computational routines that perform segmentation of neurological lesions [Atkins98] [Pineiro00] [Kaus01].

5.3.4 Ageing

5.3.4.1 Simple model of neurological ageing

The scope of this work allows us to abstract causes of neurological ageing as well as pathologies such as Alzheimer disease or deterioration of neurotransmitter system [Li1999]. On the other hand, it requests some algorithmic explanation to infer impact of ageing-like processes onto Venn-networks. To produce a suitable algorithm, we assume that non-pathologic ageing symptoms are caused by natural cell death, and therefore our model uses continuous functions to govern death of nerve cells over time in the Venn-networks (refer to the ‘longevity curves for humans’ in chapter 2).

The approach selected was to use the most recent longevity curve as an inverted objective function for the algorithm. The precision obtained is directly dependent on how good ageing processes are “captured” by such functions. Here any of the functions shown in Figure 54 are suitable candidates, because we only want to prove the principle.
The algorithm for including ageing into Venn-networks has two main steps, firstly, calculation of cell death at a timestamp \( t_i \) and secondly, selection of which are the cells effectively to die. The first step is carried out based on calculations using any of the functions presented above in order to generate parameter values to control quantitatively cell deaths. The second step of the algorithm utilises a pseudo-random number generator to decide, among the cells still alive at just before \( t_i \), which ones are going to die. The first step above is governed by the cell death rate assumed. The second step is automatically computed afterwards during simulations. Figure 55 displays deaths of nerve cells that consequently will not send any signal (see axons marked as black stars) to pos-synaptic neurons, similarly to what happen in the stroke model. However, in the stroke model neuron deaths are more likely to occur scattered.
5.4 Using Venn-networks for investigations on brain function

5.4.1 The need for a simulator

The set of models described above enables some theoretical issues of neural processing associated or not with pathologies and ageing to be examined using computer simulations. The flexibility and computing power of these models can only be assessed if Venn-networks are implemented as a computer program and then exhaustively simulated. This decision resulted in the construction of a comprehensive simulator for Venn-networks. The associated aims with this were to:

(i) produce a tool that could validate the theory behind the novel neural network, and

(ii) use this tool on investigations for better understanding brain function.

5.4.2 Outline of the Generalised Venn-Networks Simulator (GVNS)

The simulator developed incorporated all of the features presented above in order to deal with more than one type of processing unit, more than one region, and various types of fibres that can freely interconnect stimuli sources, effectors and regions etc. In addition, the simulator construction aimed to provide some other facilities to make the simulation task more effective (and uncomplicated to perform). Among the major facilities incorporated in the GVNS were:

- User friendly interface
- Flexible parameterisation (differentiating structure, simulation & input data)
- User full-control over learning, simulation of disorders and task termination
- On-screen display of activations and behaviours elicited by the network
- Built-in statistical tool to assess network performance (based on output error)
- Possibility of including time-dependent events
- Ability to execute in various operating system platforms
- Easy maintenance and extendibility for new functionalities

5.4.3 Directions for simulations using the Venn-network simulator

Brain function and cognition include many problems of various fields and of diverse complexities. To avoid drifting or producing a disarticulated work we decide to:

- Restrict the scope of simulations to one biological system
- Fix input data and vary as much as possible the structures simulated
- Compare physiological and pathological scenarios whenever possible
- Focus on finding general properties rather than specific results
5.5 Closing remarks

We described some aspects of Venn-networks that make them different from other competitive neural architectures (i.e. Kohonen’s SOM, Hecht-Nielsen’s Counterpropagation etc), thus, and which contribute to their innovativeness:

- Venn-networks have (by definition) one extra constraint in their competitive layer, i.e. the regions. This makes them closer to biological neural networks, and for instance distinguishable from SOM.
- Instead of considering (i) index of winner of competition or (ii) synaptic weight of competitive layer as the utilised output computation, Venn-networks display the inner product evoked by the competitive layer as both (1) “snapshot” of instantaneous activation (thus with aggregated meaning) and (2) input for the output supervised layer.
- The processing units have a continuous output produced by a non-linear activation function. This is different for the “winner-takes-all” (i.e. binary activations) as seen, for example, in counterpropagation. Because of this, map formation is non-trivial and meaningful. Moreover, as in Counterpropagation networks (see chapter 4) the learning of Venn-networks is also very fast [Principe00].

Finally, for more information about the rationale and design decisions included in this chapter refer to:

- Chapter 2, recall all axioms identified there and review issues about motor system and voluntary control of movement
- Appendix B, for description of the computer implementation of the Venn-network simulator (i.e. GVNS)
- Appendix D, for the input data used in all simulations to follow, and
- Chapters 6 and 7, for all simulations carried out in this thesis. Chapter 6 presents five simulation-sets of neural ‘physiological’ scenarios, and chapter 7 contains other five simulations of neural ‘pathological’ scenarios. Notice that some of the latter simulations (i.e. of chapter 7) refer to diseased “versions” of former simulations presented in chapter 6.
- Annex E contains an interesting “bird’s view” of all simulations carried-out in this thesis; see section Simulations organisation and composition.
Chapter

6 Simulation of physiological scenarios: correctness

“Nothing is too wonderful to be true, if it be consistent with the laws of nature, and in such things as these, experiment is the test of such consistency”. Michael Faraday 1791–1867: diary, 19 March 1849.
6.1 Introduction

The objective of this chapter is to illustrate that Venn-networks process correctly selected physiological scenarios given the need to test the ideas introduced in chapter 5. At this point, the reader should be familiar with the GVNS simulator, i.e. the computer implementation of Venn-networks (appendix B), and the data-set utilised in all simulations (appendix D).

A brief example of how empirical data relates to regular output behaviour of the simulator is presented in Figure 56. The top part of this figure shows a single line of ten numbers, which are digital representations of finger flexion positions of a piano player during a Mozart sonata. In the bottom part of the same figure two output screens of the Venn-network simulator display the elicited flexion of finger of both (virtual) hands. The interested reader can observe that the empirical data, selected for this example, is the pattern number 15 of the data set used for training and testing Venn-networks throughout this thesis – see appendix D for further details.

Empirical data:

| 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |

Elicited output:

![Figure 56](image_url)

Figure 56 – Empirical pattern number 15 and its normal\(^{51}\) elicited finger flexion for both (virtual) hands

\(^{51}\) The term “normal” is used here to designate simulations of neural networks with no neurological decay, illness or brain disorder, i.e. an example of behaviour of a healthy nervous system. On the other
Instead of attempting to solve specific tasks using Venn-networks, the selected approach was to organise this (and the next) chapter in a way that all simulations relate to important properties that are likely to exist in healthy biological systems. This means that each simulation carried out in this thesis is part of a set; ‘simulation-sets’ are not only examples of successful processing of Venn-networks but also, of their flexibility. Jointly, all properties simulated here are the verification of Venn-networks correctness.

All simulation-sets included and described in this thesis are self-contained within each of their sections. To ease reading and whenever possible, their descriptions will follow the same internal organisation – corresponding to sub-sections in the text. The sub-sections are organised to comprise the six most relevant aspects to be reported about investigations, namely:

1. motivation, i.e. description of tested property;
2. network structure used;
3. simulation configuration;
4. input data utilised and simulation execution;
5. results;
6. discussion upon results obtained.

Each simulation-set receives one name, which designates a group of various independent computer simulations addressing the same particular issue or property. Likewise, each independent simulation (components of the simulation-set) also receives a unique designation to simplify its identification. Although independent, each individual simulation is only marginally different from the other components of the set, as they are conceived as factorial combinations of the architectural and experimental parameters investigated. Throughout the text simulation-set and simulation names are always referred appropriately to distinguish between collective and individual properties, respectively. Finally, observe that individual simulations very often are repeated for result comparisons. This is also reflected in their nomenclature, e.g. ‘Sim2603A2’ means the ‘2nd’ repetition of simulation ‘A’ of simulation-set ‘2603’.

In chapter 7 the same empirical data can elicit finger flexion very different from the ones observed here. This will be explained by the special aspects simulated there.
6.2 Simulation-set 1: Structural-functional Equivalence

6.2.1 Motivation

In various studies carried out with monkeys during mid-1980s, Merzenich showed the existence of changes in the topographic organisation of somatosensory cortical areas – those changes due to lesion studies and task trainings [Merzenich82, 83]. He and his colleagues have then shown that cortical maps of inter and intra-species are dynamically and continuously formed through competition among neighbouring cortical areas. One could also conclude from their experiments that distinct arrangements of cortical areas can perform similar functions, i.e. they are functionally equivalent. It is important to make the distinction here between equivalence and neural plasticity. The later being the process of neural reorganisation (shown by Merzenich’s work) as opposed to the former that solely concerns to the equivalent computing power of distinct neural structures52.

In light of these arguments, we suggest that structural-functional equivalence is a property that must exist in plausible artificial neural architectures. The first set of simulations was carried out to demonstrate that Venn-networks maybe used to model this property. These simulations should show that even with different structural arrangements the same number of processing units is able to:

(i) learn a complex task through examples; and
(ii) be able to achieve similar results despite different layouts.

6.2.2 Network structure

This section involves two simulation-sets, namely Sim2603 and Sim2703. Respectively, these simulation-sets address the two motivation topics of this section.

As with all simulations in this thesis, the component simulations of Sim2603 and Sim2703 were entirely carried out using the GVNS, the Generalised Venn-Network Simulator. As suggested before appendix B contains an extensive description of the simulator, which reading will allow the reader to better understand the graphical results presented, and terms used to describe network structure and simulation configuration.

52 The concept of equivalence here shall not be confused with the idea supported by Karl Lashley – the theory of equipotentiality. This theory refers to the ability of any intact cortical area to perform functions of others [Clarke96].
To demonstrate equivalence we arbitrarily selected a Venn-network composed of 1,000 cortical columns (i.e. processing units) arranged in a map of 50 x 20 (respectively width and height). In Sim2603 all these units are part of a unique area or cortical region – the only one defined for this particular simulation-set. In Sim2703 the 50 x 20 cortical map was evenly partitioned into five different cortical regions. Figure 57 shows that only one cortical region was defined for Sim2603, as opposed to the five regions defined for Sim2703 that are presented in Figure 58.

Figure 57 – Network architecture defined and used for all simulations of set Sim2603 (mono-region)

The top portions of Figure 57 and Figure 58 contain the stimuli sources defined for both simulation-sets. They are indicated by $S_n$ – where $n$ is the order of each stimulus source. Bottom portions of the two figures contain the effectors defined for both simulation-sets. The notation $E_n$ indicates that – where $n$ is the order of each effector target. The lines connecting stimuli and effectors to the map are indications of
axon bundles, i.e. entire pathways. Each of these pathways has as many axons as the cardinality of stimuli or effector times the number of units connected by them in target or source region(s). For example: in Sim2603 (seen in Figure 57) the number of afferent connexions (i.e. incoming axons on mid-top of the figure) is 5 times 1,000, equal 5,000. The number of efferent connections (i.e. outgoing axons on mid-bottom of the figure) is 1,000 times 5 also equal 5,000. Breaking down these values: 5 is the cardinality of stimuli and effectors and 1,000 is the number of processing units in the map.

In Sim2703 (structure seen in Figure 58) the total number of afferent and efferent axons is equal to 1,000 each. The calculation to reach this value is proceeded in the same manner explained before. But here the cardinality of each stimulus and effector now is reduced to 1. Sub-section 6.2.4 explains this in more detail. The important point to notice is that although Sim2603 and Sim2703 have a different total number of axons either incoming or coming out of the map, both architectures have the same number of

Figure 58 – Network architecture defined and used for all simulations of set Sim2703 (multi-region)
cortical columns, stimuli sources and effectors. These were kept constant because of the motivation to prove that Venn-network implements structural-functional equivalence.

In both Sim2603 and Sim2703 only one type of processing unit was used. This decision was taken regardless of the regional boundaries defined that could suggest otherwise. Figure 59 and Figure 60 illustrate cross-section views of cortical columns of simulation-sets Sim2603 and Sim2703, respectively. This time instead of indicating region boundaries they contain the type of processing units used in each set of simulations. The same (unique) unit type was used in both simulation-sets. By comparing these two figures with Figure 57 and Figure 58, it is evident the ‘disagreement’ of boundaries between cortical regions and unit type defined for both sets of simulations. The ability to allow network definitions to be flexible like that is a useful feature incorporated into Venn-networks. More examples to this will be found in other simulations later. For the moment this structural decision was taken to preserve the validity of structural-functional equivalence.

![Network Architecture - Sim2603](image)

**Figure 59** – Unit type defined and used for all simulations of set Sim2603 (mono-region)
6.2.3 Simulation configuration

The two network structures (Sim2603 and sim2703) featured above were trained to perform the finger flexion task under identical parametrical configurations. Amid all existing parameters to control the execution of simulation, afferent learning rate and efferent learning rate were the only ones selected to change as they produced the greatest impact on output performance of Venn-networks [Buarque01b]. In a factorial varied manner and for all simulation devised here, the selected parameters assume one out of two possible values randomly selected. Thus simulation-sets Sim2603 and Sim2703 comprise a total of four different simulations each, which are referred to as A, B, C and D. Every simulation was repeated three times for greater accuracy, and outputs were averaged among these three repetitions. Details of values assumed by each parameter can be found in Table 1. All other existing parameters for the current

---

53 Two values for each of the two selected parameters gives $2^2$ that is equal to four simulations
Simulations were kept constant to their default values, *e.g.* decrement of afferent learning rate, and decrement of efferent learning rate, whose values can also be seen in Table 1.

<table>
<thead>
<tr>
<th>Simulations (both sets)</th>
<th>Afferent learning rate</th>
<th>Efferent learning rate</th>
<th>Decrement afferent learning rate</th>
<th>Decrement efferent learning rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1</td>
<td>0.05</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>0.1</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>C</td>
<td>0.05</td>
<td>0.1</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>D</td>
<td>0.05</td>
<td>0.05</td>
<td>0.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 1 – Parameters (varied in factorial manner) used for both simulation-sets Sim2603 and Sim2703

Simulations A to D were devised having 3 processing phases each (see Figure 61), the first phase aimed at cortical map formation (*i.e.* training of afferent connections); the second, for training of efferent connections; and the third for performance test.

![Figure 61 – Configuration window for simulation Sim2603C (similar to Sim2703C)](image)
Figure 61 shows other values assumed by major parameters along each one of the three processing phases (i.e. the columns of table in the figure). Some of these parameters may not have been utilised depending on the action defined for each processing phase. The GVNS produces one window such as Figure 61 for every simulation, but not all of these are shown from this point of the thesis. Instead, more objective comments are to be added directly upon relevant parameters investigated (plus values used) and the rationale behind every selection.

Another common window produced by GVNS to all simulations is the indication of modulatory effects acting on the cortical map. Figure 62 shows an example of such an output for simulation Sim2703A. The small white ellipsoids in the figure inform that maximum modulatory effect is exerted on cortical columns of the map. In Figure 62 all columns are featuring maximal modularity because no modulatory effects are being investigated this time. Similarly to the simulation configuration windows, from now on windows with modulatory maps will only be included when relevant.

![Modulation effect map for simulation Sim2703A](image)

The stopping criterion selected for training during all simulations of this section was a maximum average (output) error of 0.05%. This means that network training continued until this threshold was reached. Recall from annex B that output error is calculated at the end of every training epoch by averaging the error evoked in all its effectors. The last parameter different from its default value was threshold activity of processing units, which was set to -0.2. This was necessary in order to filter minor fluctuation observable in the map, similarly to biological systems [Levitan97]. This decision again does not interfere with our search for structural equivalence within Venn-networks, as all simulations in this section utilised the same value.
6.2.4 Input data and simulation execution

Similarly to most simulations throughout this thesis, trainings and testings of simulation-sets Sim2603 and Sim2703 utilise data obtained by translating into numeric values an arbitrary initial portion of the Sonata Facile composed by Mozart [Mozart51]. More details on how the digital files encode finger position of the piano player can be found in Appendix D, which read is strongly recommended before any progression to further parts of this work.

Processing phases 0 and 1 of simulations A to D from simulation-sets Sim2603 and Sim2703 (in all three repetitions) utilised for training the initial 333 patterns of the file left hand finger position – also referred as ‘usual training file’. And processing phase 2 (i.e. performance testing) utilised the final 111 patterns of the file left hand finger position – also referred as ‘usual testing file’. The overall cardinality of both training and testing patterns is 5 (i.e. virtual fingers mimicking a human hand). It is also crucial to remember that all output performances were calculated based only on unseen testing patterns used in processing phase 2. This makes it more difficult for trainings to converge, but doubtless highlights the generalisation ability of Venn-networks.

Regarding the data set the main difference between Sim2603 and Sim2703 is not the information inside files (derived from the same source), but the way it was presented to the two architectures. Sim2603 has one single stimulus source of cardinality 5 whereas Sim2703 has 5 stimuli sources each one with cardinality 1. As the data set for training and testing has cardinality 5, it could be fed directly to Sim2603 without problems. However, to be presented to Sim2703 every pattern of the data set (equivalent to rows in a spreadsheet) had to be separated into five independent values. In this way, each of these values is presented simultaneously to every one of the five stimuli sources of this group of simulations. Both arrangements of data input can hypothetically be found in biological systems where bunch of axons originating from say one same area of the CNS travel together for a certain distance and then either enervates the same target region, or they branch in the arrival connecting contiguous target regions.

After setting up the architectural and control parameters in the GVNS, the 24 simulations54 were carried out sequentially by presenting the training and testing data in the way mentioned above. The simulator then produced its various graphical windows as well as performance evaluation files; details about this can be found in appendix B.

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54 Total of simulation is given as 2 sets comprising 4 simulations, each one repeated three times.
6.2.5 Results

All simulations of sets Sim2603 and Sim2703 have two very distinct stages in their life cycles. These two stages – namely training and testing – correspond to the processing phases 0 together with 1, and phase 2 alone. The only formal difference between them is the existence or not of the computation of synaptic updates (i.e. weights of afferent and efferent connections). Even though all patterns presented to stimuli sources of the networks invariably produce an output; synapses are only recalculated during training phases. This sub-section analyses results evoked by both stages for all simulations, as they were considered equally important for the results.

Regarding training (first of the two mentioned stages) it was found that:

- In Table 2, both layouts of Sim2603 and Sim2703 present a very steady learning curve no matter which parametrical choice was investigated. This means that the average output error observed in the effectors of all simulations decreased smoothly as more training epochs are completed. Most importantly, this means that Venn-networks are able to efficiently learn fairly complex tasks (the first initial motivation of this experiment), i.e. learning converges.

- Another finding related to learning is that simulations of the set Sim2703 invariably require more epochs to achieve the stopping criterion established. This may be explained by the fact that Sim2703 has less synergistic effects among processing units, as all axons going to and coming out of the map connect independent cortical regions (i.e. distinct portions of the map).

- The variability of results produced across repetitions of the same simulation proved to be very small. This is an interesting feature of Venn-networks as they prove themselves to be also reliable when learning the same task.

All findings above can be graphically observed in Table 2 and Table 3. Both tables contain graphics illustrating average output error versus epochs of training for all four simulations components of sets Sim2603 and Sim2703. Each graphic has three data lines corresponding to the repetitions carried out in the simulations.

Following the training phase, the next step was to analyse the output performance of the two architectures and their parameter selection by using unseen patterns (vide annex D). As stated before, this will be the common practice for performance evaluation of Venn-networks.
Table 2 – Output error evolving throughout training epochs of simulation 2603 A, B, C and D
Table 3 – Output error evolving throughout training epochs of simulation 2703 A, B, C and D
Regarding performance test (using the same unseen data file) it was found that:

- Sim2603 has almost all its component simulations performing worse than the threshold defined as the stopping criterion for trainings (considering individual output error). The opposite fact is observed for nearly all simulations comprising set Sim2703.

- Output error of simulations of set Sim2603 present a great variability per effector (i.e. virtual finger – see examples in Table 6). This was in contradiction to the results from the simulations from set Sim2703 above.

- Finger 4 is the subject of greatest output errors in both sets of simulations. The remainder of fingers have their overall output errors varying less wildly in Sim2703 than Sim2603.

- Simulations Sim2603C and Sim2703C produce the smaller errors respectively in the mono and multi-region architecture, respectively. Consequently the parameters of these topologies and calculated synaptic values are to be used again in further parts of this work.

All findings above can be fully observed in the graphics presented in Figure 63 and Figure 64. These two graphics are also important because they are used as base line for many pathology experiments described next chapter.

To illustrate the dynamical differences of the two architectures just simulated, mono- and multi-regions, as presented in Figure 65 and Figure 66, respectively. Notice the five peaks of activations in the multi-region map of Sim2703, as opposed to a unique peak dominating the landscape of Sim2603. These graphics also show how the rest of the processing units of the two maps still present small activity.

Based on these results we conclude that Venn-networks incorporate the structural-functional equivalence property sought, as they are able to learn (complex) tasks regardless of variations in parameters and structure of networks of same dimensions.

### 6.2.6 Discussion

The results above trigger the discussion of why nature would have preferred multi-region maps instead of a unique large assembly. We speculate that on top of obvious economy of resources, multi-regions are also more consistent performance-wise. The trade-off offered is their greater convergence time and partial loss in the synergistic effect among processing units. Nevertheless, the latter may produce undesirable effects such as the ‘swaps’ of function (i.e. mistaken learning) observed among fingers 2 and 5, seen in Figure 63.
Figure 63 – Average output error per finger across simulations of Sim2603

Figure 64 – Average output error per finger across simulations of Sim2703
Figure 65 – Typical activation for simulations Sim2603 (Mono-region topology)

Figure 66 – Typical activation for simulations Sim2703 (Multi-region topology)
6.3 Simulation-set 2: Active-Passive activity

6.3.1 Motivation

In the simulations described in Section 6.2 we saw that (motor) commands ‘issued’ by Venn-networks are passed on to virtual fingers, which perform accurately almost all of them. However, an important physiological issue was not included, i.e. the presence of direct feedback signals sent from proprioceptors of effectors towards the cortex – sensory feedback. This type of signal has a completely separate neural circuitry that allows it to be functionally independent from other nervous pathways. Generally speaking sensory feedbacks are extremely important to biological systems, which extensively use them for various purposes, e.g. voluntary and involuntary movement control [Pearson00]. Although feedback in neural systems has a much wider scope, the simulations described in this section focus on sensory feedback. In particular, the objectives were: (i) to investigate this other existing property of biological systems, i.e. the independence of descending and feedback signals; and

(ii) to check if Venn-networks are able to implement this property while executing (satisfactorily) the assigned tasks.

6.3.2 Network structure

In order to investigate the possibility of Venn-networks implementing independent pathways starting and returning to the simulated cortical map, a more complex network structure than the used in the previous simulation was needed. Figure 67 shows the devised network architecture defined and used for all simulations of the current section – Sim1905 and Sim2005. It features one pair of stimuli sources, one pair of effectors, and four cortical regions of equal size 10 x 15 columns (width and height). The structure also features three different types of fibres namely afferent, efferent, and efferent-feedback (efferent-FB). The efferent-FB fibre – this section’s object of investigation – is responsible for the feedback transmission of sensory signals. Each of these fibres comprise two sets of distinct bundles of axons, as networks control fingers of two virtual hands. Only one type of cortical unit is used, see Figure 68.

6.3.3 Simulation configuration

Four distinct processing phases were used here. These phases aimed to train afferent fibre, efferent fibres, efferent feedback, respectively and the last one aimed to test network performance on unseen patterns. Unless stated otherwise, repetition number was reduced to two (because of the small variability observed so far).
Values for the three learning rates were randomly selected and varied in a two-step factorial manner for the eight networks utilised here, the used values are in Table 4. Other parameters different from default were: decrement of afferent, efferent and efferent-FB – set respectively to 0.7, 0.9, and 0.3; neighbouring – set to 1.0 for afferent and efferent-FB; and cooperation radius – set to 1.0 for afferent and 0.5 for efferent-FB.

<table>
<thead>
<tr>
<th>Simulations Sim1905</th>
<th>Afferent learning rate</th>
<th>Efferent learning rate</th>
<th>EfferentFB learning rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>C</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>D</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>E</td>
<td>0.2</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>F</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>G</td>
<td>0.2</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>H</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 4 – Parameters used for simulation-set Sim1905
6.3.4 Input data and simulation execution

For training processing phases 0, 1 and 2 of all simulations components of Sim1905 utilised the initial 333 (or 75% of) patterns of the files with finger position of left and right hands. And the testing phase (i.e. processing phase 3) utilised the final 111 (or 25% of) patterns of the files with finger position of left and right hands. The cardinality of both training and testing patterns was 5 for all phases. The stopping criteria for all four phases were: fixed number of epochs (equal to 5) for phases 0 and 1, output error lower or equal to 0.01 for phase 2, and single epoch for test phase.

Following trainings of all simulations component of Sim1905, a new set of simulations was carried out, i.e. Sim2005. These new simulations used the same parameters and synaptic values of Sim1905; in other words they do not involve training. Actually the only difference between Sim1905 and Sim2005 is that on the latter some external stimulation was applied. Three different situations were investigated namely, stimulation on (1) on stimuli sources, (2) null stimulation on stimuli sources, and (3)
solely directly stimulation on effectors. The objective of that is to induce active and passive flexions of the virtual fingers.

6.3.5 Results

Training of all simulations component of Sim1905 converged within 13 epochs as can be seen by the learning curves of the eight graphics shown in Table 5. Each graphic has two curves representing results of each simulation repetition. There were no substantial variations across simulations and their repetitions, which indicates that the parameters used had little impact on training.

The output performances on unseen patterns for the simulations Sim1905 are shown in Figure 69 and Figure 70, for left and right hands respectively. The figures show that the right hand ended up better trained than the left hand. Again, a ‘swap’ was observed to occur for Sim1905D that performed badly for the right hand and well for the left hand. Finger 4 was observed to be the most difficult to train in both hands. Variation of finger average performance across simulations was not large.

Finally, the external stimulations devised for Sim2005, three situations of Table 6, produced cortical activations observable in Table 7. Table 8 and Table 9 show cortical map activations evoked by networks of simulations A-D and E-H, in situations 1 and 3. Compare the absence of activations on motor areas in situation 3 (marked as red ellipsis) during effector stimulation, i.e. passive flexion, to activations in motor and sensory areas during stimuli sources stimulation (see blue ellipses), i.e. active flexion.

6.3.6 Discussion

The observed activations in both sensory and motor areas – situation 1 (when external stimulations are carried out on stimuli sources) suggests that sensory feedback is a consequence of descending motor command. Additionally, the observed activations present in sensory areas but not present in motor areas – situation 3 (when stimulations are directly carried out on network effectors) demonstrates that sensory feedback can also be triggered independently from efferent signals. Together these two observations indicate that Venn-networks (because of the existence feed-back fibres) are able to implement this property of biological systems while are still able of executing specifically assigned tasks. Functional imaging techniques are now able to record the effects of this property in action [Zaman01a,01b]. We claim that the ability to implement independent pathways is crucial for neural processing.
### Table 5 - Output error evolving throughout training epochs of simulation 1905A-H

<table>
<thead>
<tr>
<th>Sim1905 A, B, C and D</th>
<th>Sim1905 E, F, G and H</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Epochs of training; (y) Output average error.  
**Legend:** ● Repetition 1  ■ Repetition 2
Figure 69 – Average output error of left effector (virtual hand) throughout Sim1905 simulations

Figure 70 – Average output error of right effector (virtual hand) throughout Sim1905 simulations
Table 6 – Three situations of virtual pair of hands used to show active and passive feedback

Table 7 – Top view of typical cortical activations evoked by (both) hands in each of the three situations devised above. The blue ellipse shows motor and sensory activations due to active finger flexion, whereas the red ellipse shows only activations in the sensory area due to passive finger flexion.
### Table 8 – Cortical activations resulting of two different hand positions (situations 1 and 3) of Sim2005 A-D demonstrating active and passive types of feedback on their best repetitions

<table>
<thead>
<tr>
<th>Sim</th>
<th>Active feedback (situation 1)</th>
<th>Passive feedback (situation 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim105A2</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Sim105B1</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>Sim105C2</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>Sim105D2</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Map width; (y) Map height; (z) Activation of specific cortical columns
Modelling Neural Processing Using Venn-Networks in Physiological and Pathological Scenarios – PhD Thesis
Chapter 6 – Simulation of physiological scenarios: correctness

<table>
<thead>
<tr>
<th>Sim</th>
<th>Active feedback (situation 1)</th>
<th>Passive feedback (situation 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim005E1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Sim005E2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Sim005H1</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Axes: (x) Map width; (y) Map height; (z) Activation of specific cortical columns

Table 9 – Cortical activations resulting of two different hand positions (situations 1 and 3) of Sim2005 E-H demonstrating active and passive types of feedback on their best repetitions.
6.4 Simulation-set 3: Ageing

6.4.1 Motivation

A ubiquitous fact in biological systems is their functional decline due to ageing processes. These processes are not uncomplicated and often affect various granularities and constituent parts of the system. Ranging from sub-cellular to macroscopic changes, alterations (chiefly performance decline) are gradually more evident over time as the organism “grows old”. The nervous system, unfortunately, is not immune to this very undesirable decay that results in idiosyncratic reduction of memory power, intellectual and physical abilities, as well as neuroendocrine alterations (e.g. affecting the mood and sleeping patterns) [Price00][Rechtschaffen00].

Although not aiming to model ageing processes as a whole, the objective of the present experiment is to investigate if Venn-networks are able to implement brain function degradations similarly to what happens in ageing processes. The unpretentious paradigm selected here relates loss of computing power in simulated networks to (nerve) cell death, as Price [Price00] affirms that this fact is a common feature always present in ageing processes.

6.4.2 Network structure

Investigations of ageing in this section are divided into two sets Sim2905A and Sim2905B. The first set considers that cell death happens uniformly distributed over the cortical map, and the second set assumes a more localised loss of nerve cells. Both sets use the same network structure utilised in the previous experiment (see section 6.3); that is four regions and one pair of: stimuli sources, effectors, bundles of afferent, efferent, and efferent-feedback (see Figure 67). Synaptic values used here are unique and also were borrowed from the best performing network of Sim1905, i.e. Sim1905G repetition 2. Hence, there is no training involved in the current set of simulations. The rationale for this decision is justifiable by the fact that we want to measure output performances of networks submitted to ageing processes on top of well-trained and “known” topologies.

6.4.3 Simulation configuration

In the simulation of both sets utilised here, four processing phases were used for evaluating output performances. Throughout all simulations the only parameter modified per processing phase was cell death rate. The values considered for this parameter in each processing phase were: 0.0, 0.079, 0.15, and 0.20. These values
correspond to the normalised-to-one decimal logarithmic function $\log(n+1)$ applied on the ad hoc selected series: 0, 20%, 40% and 60%.

To increase accuracy of results and minimise effects of race condition the number of repetitions carried out per simulation was fixed at five. The selection of this high value is partially due to the randomness of the generation process that governs neuronal death in all simulations.

6.4.4 Input data and simulation execution

The input data for all processing phases of every simulation (i.e. all repetitions of Sim2905A and Sim2905B) are the same 111 patterns, corresponding to the final patterns of the files with finger position of left and right hands (see Appendix D).

Once parameters and input data were set, five repetitions of Sim2905A were carried out using the GVNS for all four processing phases. Following that, a special parameterisation was made in the GVNS to make it possible that repetitions of Sim2905B had death of nerve cells to be restricted to specific parts of the cortical map.

6.4.5 Results

Table 10 shows average output performances of all five repetitions of Sim2905A. The left column of this table shows additive error per left and right finger – L(n) and R(n), and on the right column it displays output error per unit of time T(n). There is great variability of impact of cell death across repetitions and fingers. However, within each repetition cumulative cell death leads to consistent reduction of output performance per finger. Table 11 displays: (i) snapshots of cortical activations, (ii) indication of cell death, and (iii) evoked finger flexions. All these, result of one (same) pattern being presented to the network at each one of the four processing phases. Finally, Table 12 shows different combinations offered by the GVNS to set cell death.

6.4.6 Discussion

Randomness of cell death generation prevented further comparisons across repetitions. The slightly uneven variability of impact on performance among fingers is due to use of mono-region for controlling each hand as discussed in Section 6.2.6.

The overall discrepancy of performance between hands found here is coherent with previous experiments on Section 6.3, and indicate unequal difficulties of tasks being performed by the two virtual hands. This provides more definite corroboration that Venn-networks present graceful degradation of performance due to network decay; which is also a fact present in the brain [McLeod98].
<table>
<thead>
<tr>
<th>Repetition</th>
<th>Additive error - per finger L(n) or R(n)</th>
<th>Output error - per unit of time T(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition 1</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Repetition 2</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>Repetition 3</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>Repetition 4</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>Repetition 5</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
</tbody>
</table>

Table 10 – Output error of all five repetitions of simulation Sim2905A, both per fingers L(n) - left column, and per time T(n) - right column.
### Table 11 – Cortical activations resulting of a same pattern presented to the network at four different moments in time (processing phases), dead cells map and finger flexions

<table>
<thead>
<tr>
<th></th>
<th>Sim2905 – typical pattern</th>
<th>Simulator screens (dead cells and hands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Screen" /></td>
</tr>
<tr>
<td>1</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Screen" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Screen" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Screen" /></td>
</tr>
</tbody>
</table>
Table 12 – Examples of localised cell deaths caused by ageing: 20% columns affected

The table above displays a wide range of selection that can be made for defining which regions or even areas are going to be affected by ageing processes. The possibilities currently available in the GVNS are: (1) selective of areas, (2) exclusive of areas (all map), and (3) partially exclusive of areas. The latter only differs to the second by considering areas (regions) that are currently being utilised (defined) for processing, whereas in the second modality the whole map (except selected areas) is “candidate” for ageing. Note the additional possibility to mix diverse regions, e.g. left-motor. In this example some maps resemble the area selected for ageing, e.g. sensor-selective and motor-partially exclusive. However, this only occurred because the number of groups of regions is limited to two, which would not be the case in a more complex topology. All modalities shown in the example used the same cell death parameter of 20%.
6.5 Simulation-set 4: Modulation

6.5.1 Motivation

Another interesting property of the nervous system is its functional non-monotonocity. This means that same circuitry and inputs can evoke distinct “results” depending on some extrinsic factors that in this work we call modulatory mechanisms. These processes vary greatly in the way they are neurally implemented and are vital for complex behaviours, motivational and attentional processes [Amaral00].

We claim that any general modelling tool of brain function should incorporate at least one type of modulatory mechanism to be worth considering.

Currently, Venn-networks (i.e. GVNS) have two distinct modulatory mechanisms implemented, namely, thresholding and inhibitory/excitatory signalling. The first mechanism emulates cell populations that have distinct operational features and the second, emulates incoming neurotransmitter-specific pathways. Sim3105 and Sim0106 are the two blocks of simulations that form this section’s simulation-set, and respectively address the two mentioned mechanisms. Because of their dissimilarities these blocks are described and commented upon into 6.5.2 and 6.5.3. Overall, this section aims to investigate the effectiveness of these mechanisms equipping Venn-nets.

6.5.2 Modulatory mechanism 1: thresholding

6.5.2.1 Network structure

The network structure used here in the first block of simulations, i.e. Sim3105, is exactly the same used back in simulation-set 2 of section 6.3. That is: one pair of stimuli sources, one pair of effectors, and four identical cortical regions of size 10 x 15 columns – width and height, three different types of group of fibres namely afferent, efferent, and efferent-feedback; refer to Figure 67 in sub-section 6.3.2. However, the type of units utilised in Sim3105 is not restricted to one as before. Here, two distinct types of processing units are used to realise the first modulatory mechanism. Figure 71 shows “motor” regions of Sim3105 having different unit type from the rest of the map.

6.5.2.2 Simulation configuration

Threshold was the only parameter modified and only one processing phase was used for testing various threshold values for motor regions of one network (best synaptic values trained of Sim1905, i.e. repetition G2) on unseen patterns. No more than one repetition was necessary as no training and random processes were carried here.
6.5.2.3 Input data and simulation execution

The input data for test phases of all simulations of Sim3105 are the same 111 patterns, corresponding to the final patterns of the files with finger position of left and right hands (see appendix D). As already mentioned the only differences across simulations of Sim3105 are punctual small changes to the threshold values of motor regions, which have consequent output performances compared.

6.5.2.4 Results

From left to right, the blue vertical columns in Figure 72 indicate output error produced by simulations of Sim3105. The tested threshold values (red area in the figure) were calculated as additions/subtractions to the baseline threshold value, i.e. 0.2. This value was used in the trainings of the original network. The percentage values utilised for producing the candidate thresholds were: -80%, -50%, -40%, -30%, -20%, -10%, 0%, +10%, +20%, +30%, +40%, +50%, +80%, and 0% (this time with the network
using random weights). The resulting values of thresholds for simulations were then, respectively: 0.04, 0.1, 0.12, 0.14, 0.16, 0.18, 0.2 (the threshold base line), 0.22, 0.24, 0.26, 0.28, 0.3, 0.36, and 0.2 (untrained network). In the figure, the black solid line is a polynomial regression curve adjusting all output errors observed.

Table 13 shows resulting activations for four different threshold values together with evoked finger flexion when the same pattern is presented to the network.

![Figure 72](image)

**Figure 72** – Polynomial regression and output error evoked by Sim3105 as result of variations of the threshold used for the motor units; the two darker columns (centre and right) indicate output error of fully trained and non-trained (i.e. random weights) networks, both using the same threshold of 0.2

### 6.5.2.5 Discussion

Regardless of the signal of the alterations made to the originally trained threshold, a brief analysis on the results shown in Figure 72 reveals that the error produced by the network increases almost symmetrically. Another important observation is that the threshold baseline is *not* the optimal point regarding network performance. Although numerically very close to this point, the error produced by the baseline threshold is greater than other small positive changes to the threshold. This may indicate that: (i) the original training process did not adjust optimally the network synaptic values in relation to the threshold, or if so, (ii) that this particular network could have been better trained. Either way is sufficient to suggest that thresholding is an efficient way to interfere in the network performance. In this experiment some values tested even improved the output performance, e.g. threshold equal +20%.
Table 13 – Cortical activations resulting of same pattern presentation to Sim3105 utilising different thresholds for motor areas, and evoked movements of virtual fingers
6.5.3 Modulatory mechanism 2: inhibitory/excitatory signalling

6.5.3.1 Network structure

A different network structure is used in this second block of simulations. Simulations Sim0106 use four stimuli sources, three effectors, and four identical cortical regions of identical sizes equal to 15 x 8 columns – width and height, three different types of group of fibres namely afferent, efferent, and u-fibres; refer to Figure 73 for details about network connectivity. All processing units of Sim0106 are of the same one type as can be seen in Figure 74. Notice that region 0 and region 1 both receive u-fibres from region 3, which in the present experiment act as modulatory structures (black lines in Figure 73). Hence, they are the second modulation mechanism in Venn-networks. Here, modulation is effectively realised in two ways by the defined u-fibres 0 and 1 that send inhibitory or excitatory signals according to their pre-set type.

Figure 73 – Network architecture defined and used for all simulations of set Sim0106
6.5.3.2 Simulation configuration

Three processing phases were used here to respectively train afferent fibre, train efferent fibres, and test network performance on unseen patterns. However, the training task itself is of minor importance here because the objective of this experiment was solely to observe differences in outputs produced by effectors performing the same task under different modulatory effects. As a result, the training parameters were selected entirely upon previous observations when training other networks. The values of training parameters used, other than defaults, were: learning rate of afferent and efferent fibres, both set to 0.1; decrement of afferent and efferent fibres, respectively – set to 0.8, and 0.9; neighbouring – set to 1.0; and cooperation radius – set to 0.6.

6.5.3.3 Input data and simulation execution

The training data were the 333 initial patterns of the file with finger position of left hand (see Appendix D), presented simultaneously to the three first stimuli sources.
After training, the testing data were the 111 final patterns of the file with finger position of left hand, also presented simultaneously to the three first stimuli sources. During testing these simulations have two experimental conditions (Sim0106A and Sim0106B) defined by the kind of data presented to the fourth stimulus source. Which received a dummy set of 0s (zeros) or 1s (ones) in each condition, representing respectively a forced minimal or maximal activation in region 3. This induces a minimal or maximal inhibitory and excitatory signal to be sent via u-fibres 0 and 1, respectively.

6.5.3.4 Results

Table 14 and Table 15 show a comparison of results obtained in the two experimental conditions (Sim0106A and Sim0106B). The two tables present output error evoked by the three effectors respectively: (i) during training phases of effector fibres and (ii) grouped by fingers when of testing phases on unseen patterns.

Table 14 – Output error of effectors (avg. of three repetitions) evolving throughout training epochs of Sim0106

Table 15 – Output error of effectors (avg. of three repetitions) grouped by fingers
Table 16 displays examples of the two experimental conditions for the same input pattern together with the evoked behaviour of hands controlled by regions 0, 1, and 2.

<table>
<thead>
<tr>
<th>(1)</th>
<th>Sim0106 – typical activation</th>
<th>Simulator screens (finger positions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim0106A2, gating value = 0</td>
<td>![Image of typical activation 1]</td>
<td></td>
</tr>
<tr>
<td>Sim0106B1, gating value = 1</td>
<td>![Image of typical activation 2]</td>
<td></td>
</tr>
</tbody>
</table>

Table 16 – Cortical activations resulting of a same pattern been presented to Sim0106. Region 3 is gating, via u-Fibres, regions 0 and 1; the column to the right shows movements of virtual fingers evoked by regions 0, 1, and 2, which are inhibited(I), excited(E) and not-gated(N) by region 3, respectively.

6.5.3.5 Discussion

The charts of the three tables presented in this section – Table 14, Table 15 and Table 16 – clearly display how the two experimental conditions investigated have affected learning and performance of simulations Sim0106. We observed that when “modulation” is switched-off all three effectors produced equivalent expected results. However, when “modulation” is switched-on, distinct learning curves (case of training) and error performance bars (case of testing) are produced. Although differences between effects of inhibitory and excitatory modulations produced are coherent among themselves, more work is necessary to make overall modulation results to be coherent in relation to the baseline.
6.6 Simulation-set 5: Contra-lateral inhibition

6.6.1 Motivation

Anatomical and physiological evidences indicate that some regions of neo-cortex inhibit others via long-range fibres through the corpus callosum [Brodal98]. This produces an intricate tread of nervous pathways as well as a complex functional dynamics. In this final experiment investigating physiological scenarios with Venn-networks we reproduce this peculiar mechanism of the nervous system. To illustrate this property we assembled a fairly complex (computational) network that resembles the (biological) simplified circuitry of voluntary control of finger flexion in both hands. The aim was to observe expected movements and the production of contra-lateral inhibition.

6.6.2 Network structure

The complex network structure selected for this experiment – Sim1506 – can be seen in Figure 75, it includes all four types of fibres available in Venn-networks.
Sim1506 utilise eight regions of identical size – 30 x 30 columns – divided into two “hemispheres”; regions numbered 0, 1, 4 and 5 lie on the right hemisphere, the other four region numbers lie on the left hemisphere. Each of these two portions of the cortical map contains four regions. Throughout this experiment they perform various types of functions namely, motor control (regions 0 and 3), sensory processing (regions 4 and 7), inhibited-motor control (regions 1 and 2) and inhibited-sensory processing (regions 5 and 6). The network structure also has a non-trivial connectivity. Each of the two stimuli sources send afferents to one pair of regions (i.e. motor control and inhibited-motor control). Each of the two effectors receives efferent fibres from motor region, and simultaneously send feedback signals to one pair of regions (i.e. sensory processing and inhibited-sensory processing). Finally, four u-fibres perform the contra-lateral inhibitory function of left-to-right and right-to-left regions. Figure 76 displays the single type of processing units utilised in this experiment.

![Figure 76 – Unit type defined and used for all simulations of set Sim1506](image)
6.6.3 Simulation configuration

This experiment has four distinct processing phases. These phases aimed to: train respectively afferent fibre, efferent fibres, efferent feedback, and the fourth aimed to test network performance on unseen patterns. Just two repetitions were carried out per simulation. Two parameters were selected ad hoc and varied in a two-step factorial manner for training the four networks utilised here. These parameters have their values indicated in Table 17. Other parameters different from default values were: decrement of afferent, efferent and efferent-FB – set respectively to 0.8, 0.9, and 0.8; neighbouring – set to 1.0 for afferent and efferent-FB; and cooperation radius – set to 0.6 for afferent and efferent-FB. Learning rate values for efferent-FB were the same used for afferents.

<table>
<thead>
<tr>
<th>Simulations</th>
<th>Sim1905</th>
<th>Afferent learning rate</th>
<th>Efferent learning rate</th>
<th>EfferentFB learning rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1</td>
<td>0.05</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.05</td>
<td>0.1</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Table 17 – Parameters used for simulation-set Sim1506

6.6.4 Input data and simulation execution

Processing (training) phases 0, 1 and 2 utilised the initial 333 patterns of the files with finger position of left and right hands. And the testing phase (i.e. processing phase 3) utilised the final 111 patterns of the same files just mentioned. The cardinality of both training and testing patterns was 5 for all phases – corresponding to the five fingers of the virtual hand. The stopping criteria for all four phases were: fixed number of epochs was equal to 8 for phases 0 and 1, was equal to 2 for phase 2, and single epoch for test phase. Following simulations component of Sim1506, some of these were repeated using same parameters but with the noise/relaxation module of GVNS switched-on.

6.6.5 Results

As shown in Table 18, output training error produced by simulations Sim1506 were observed to decrease smoothly in all four simulations reaching negligible values after eight epochs of training. The performance on unseen values produced by Sim1506 in shown in Figure 77 and Figure 78; Sim1506C1 was the repetition that has presented best performance. Figure 79 and Figure 80 illustrate network activities when processing a typical input, i.e. the activations are resulting from the same stimulus. The only difference is that in the second network random noise and relaxation are being utilised.
<table>
<thead>
<tr>
<th>Simulation</th>
<th>Output error vs. epochs of trainings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim1506A</td>
<td><img src="image" alt="Graph for Sim1506A" /></td>
</tr>
<tr>
<td>Sim1506B</td>
<td><img src="image" alt="Graph for Sim1506B" /></td>
</tr>
<tr>
<td>Sim1506C</td>
<td><img src="image" alt="Graph for Sim1506C" /></td>
</tr>
<tr>
<td>Sim1506D</td>
<td><img src="image" alt="Graph for Sim1506D" /></td>
</tr>
</tbody>
</table>

**Legend**
- [ ] Rep1
- [ ] Rep2

Table 18 – Output error evolving throughout training epochs of Sim1506, simulations A, B, C and D
Figure 77 – Average output error of left fingers across all repetitions of Sim1506

Figure 78 – Average output error of right fingers across all repetitions of Sim1506
Figure 79 – Typical activation of simulations Sim1606 presenting activations of four contra-lateral inhibitory regions

Figure 80 – Typical activation of simulations Sim1606 presenting activations of four contra-lateral inhibitory regions (as above), this time including background noise during processing
6.6.6 Discussion

Sim1506 (of this section) involves training of two virtual hands using a pair of motor regions – one for each hand. Apart from the significant differences of having more processing units (7200), regions (eight) and fibres (14 pathways), this experiment elicits results that resemble a great deal previous simpler experimental results for just one hand (the left) produced in the first part of simulation-set 1 (i.e. Sim2603). This suggests that even in more complex configurations Venn-networks produce synaptic values that are coherent among similar task, with same training patterns, and overall experimental situations.

In other past experiments involving two virtual hands presented before, e.g. Sim1905 (in section 6.3) and Sim3105 (in section 6.5), as well as in this one there is an asymmetry between performances of hands. The right hand ended-up better trained than the left hand (observed previously). As the same data set is used in all experiments, we believe that uneven tasks among hands in the data set are the cause of this fact. Swapping input files corroborates this belief as elicited performance results are inverted.

The facts commented above (see results sub-section of Simulation-set 2 (6.3.5)) again indicate that Venn-networks are able to control non-trivial behaviour in an equivalent manner either in simple or complex configurations. However, the current experiment help us to extend this conclusion by adding to it that this control happens even if other (many) internal tasks are also being processed – e.g. four regions contralaterally inhibited. This is an important finding and feature of Venn-networks as in the nervous system many tasks are processed in parallel.

Following the first time, noise and relaxation were simulated using previous simulations carried out in here (i.e. Sim1506). The difference can be observed between in Figure 79 and Figure 80. This is an interesting resource of the GVNS that certainly makes any simulated cortical map much more realistic, as real neurons do fluctuate even when not engaged in any particular task of receiving stimulation [Levitan97].

Finally, although not clearly observable in the results from the activations presented in Figure 79 and Figure 80, the ‘u-fibres’ included in simulations Sim1506 are indeed sending inhibitory signals to contralateral regions. These inhibitory signals are obviously preventing the visualisation of any activity in the target regions of the u-fibres. This issue is explored in the next chapter when in some new simulations – this time of neurological disorders – signals sent via commissural fibres are affected.
Chapter

7 Simulation of pathological scenarios\textsuperscript{55}: robustness

“Illness is not something a person has; it’s another way of being”. Jonathan Miller 1934\textendash\textendash 2010 in The body in question (1978).

\textsuperscript{55} The simulation-sets (i.e. experiments) included in this chapter refer to some simulations previously carried out in chapter 6 with certain lesions added to them.
7.1 Simulation-set 6: multiple sclerosis (MS)

7.1.1 Motivation

As described in chapter 2, MS patients report weaknesses and slowness of their voluntary movements. Also in chapter 2, we studied the underlining mechanisms of neurocommunication and disruptions caused by multiple sclerosis that may produce these symptoms. However, MS-plaques can affect non-monotonically various types of fibres of distinct cardinalities, as well as presenting various layouts. Thus, one needs to know the impact of MS lesions in such diverse scenarios. By using the MS-plaque model built in Venn-networks, we aim to offer many simulation results on this problem.

7.1.2 Generated MS-plaques

In order to evaluate systematically the impact of MS-plaques in the output performance of various different networks, we utilised the pathology generator (see appendix C) to produce a large and diverse set of artificial MS-plaque lesions. The generation of the plaques considered four variable aspects, namely, (i) generation regime, (ii) number of axons affected, (iii) damage layout, and (iv) damage to axons:

- Generation regime (SZ or SV) is concerned with the type of “growth” of the plaques, where SZ represents growth in ‘size’ (i.e. more axons affected in larger plaques), and SV represents growth in ‘severity’ of lesions (i.e. instead of new axons, larger plaques aggravate previously affected ones);
- Number of axons affected (‘Mild’ or ‘Hard’) concerns with the overall number of axons affected by MS-plaques, ‘Mild’ means 20% of the axons and ‘Hard’ means 40% of the axons.
- Damage layout (‘Grouped’ or ‘Scattered’) is concerned with lesions outline.
- Damage to axons (‘Tiny’ or ‘Vast’) concerns with the overall damage to the neurocommunication ability of axons, ‘Tiny’ means from 25% to 50% of damage and ‘Vast’ means from 50% to 100% damage to axons;

In total, 64 artificial plaques were generated, as 16 plaques were increased by 20%, 40%, and 60% according to the two generation regimes (i.e. SZ or SV). Table 19 and Table 20 display all plaques generated that have cardinality fixed and equal to five (i.e. five axons per fibre). Note the colour scheme adopted; ‘white’ means no damage, and a gradient from ‘green’ to ‘blue’ indicates gradual worsening of signal conductivity.

---

56 Names of plaques used reflect the factorial combination of parameters underlined above. They varied into 2 steps for generation regime, class of affected axons, plaque layouts, and class of damages.
Table 19 – Multiple sclerosis lesions generated as factorial combination of parameters: tiny lesions
<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Original</th>
<th>20% size increase</th>
<th>40% size increase</th>
<th>60% size increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV-Mild-SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV-Hard-GV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV-Hard-SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ-Mild-GV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ-Mild-SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ-Hard-GV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SZ-Hard-SV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20 - Multiple sclerosis lesions generated as factorial combination of parameters: vast lesions
Apart from varying the MS-plaque features, in this experiment we also applied the lesions to different group of fibres namely, afferents and efferents. This decision was motivated to produce comparative information about the MS impact in respect to different types of fibre. Therefore, all MS-plaques presented in Table 19 and Table 20, were utilised during simulations of this experiment. Figure 81 shows examples of the same MS-plaque – SV_Hard_GV, affecting separately afferent and efferent fibres. In both pictures the target region of the map (indicated by a red square delimiting the target region) coincides with the entire cortical map of a fully-connected network.

![Figure 81 – Example of same MS-plaque of cardinality equal to five affecting (top) afferent and (bottom) efferent fibres](image)

7.1.3 Architecture and simulation

This experiment is composed of two simulation-sets namely, Sim2404 and Sim2504. The former utilises the same network structure of Sim2603 (i.e. the first part of simulation-set 1 of chapter 6), and the latter utilises the network structure of Sim2703 (i.e. the second part of experiment 1 of chapter 6). This means that Sim2404 adopts a unique cortical region, whereas Sim2504 adopts five non-overlapping regions (for other details, check chapter 6). Therefore, with respect to structure the present experiment only differs from the previously mentioned two (i.e. Sim2603 and Sim2703) by considering that the plaques are applied to afferent or efferent fibres of architectures.
The simulations of the present experiment were carried-out by presenting the usual testing file to the best performing trained networks of first and second parts of simulation-set 1 of chapter 6 – i.e. Sim2603C2 and Sim2703C2, respectively. In other words, there is no training involved in the current experiment. As a result of that, all changes observed in the outputs (i.e. effectors) of Sim2404 and Sim2504 can be directly considered as consequences of the various MS-plaques, which are independently simulated either in the afferent or efferent fibres. By doing so, we are able to compare the impact that each plaque has upon the network performance as well as trends for classes of plaques, e.g. grouped or scattered, Tiny or Vast, and Mild or Hard.

Two different fibre allowances were considered, one for each group of simulations regarding damage to axons (i.e. ‘Tiny’ and ‘Vast’). The two constants selected were calculated as the average of the maximum and minimum percentage range considered for damage to axons. As the ranges were respectively 25% to 50% for the ‘Tiny’ group and 50% to 100% for the ‘Vast’ group, fibre allowances considered for all simulations were 37.5% for the ‘Tiny’ and 75% for the ‘Vast’ “flavours” of damage. To reduce the complexity of this experiment, all simulations considered that the ‘fibre delays’ were equal to zero. Normally, these values should be as calculated by the signal propagation equations described in chapter 2.

7.1.4 Results and Discussion

7.1.4.1 Mono-region (Sim2404)

Simulations of multiple sclerosis affecting afferent and efferent fibres connected to mono-regions evoked quite different results, which are all displayed in Table 21 and Table 22. Individual graphics contain output errors evoked by each of the five virtual fingers under the effect of the indicated MS-plaque either in afferent or efferent fibres. The results displayed also indicate errors evoked by the networks in various stages of “growth” for the same plaque. Tables are organised by ‘Tiny’ or ‘Vast’ type of damage.

Overall, the impact of artificially generated MS-plaques is greater if these plaques affect efferent connections. The impact over virtual fingers also varies greatly, but individual finger performances were training dependant (see absolute and cumulative frequency studies in Appendix ‘D’). As the plaques have their sizes or severities increased, they systematically induced larger error. However, there were some intriguing exceptions (e.g. SV_Mild_SV); although rare, in such cases some plaque growths improved performance this maybe due to the disregarding of “bad” signals.
<table>
<thead>
<tr>
<th>Tiny</th>
<th>Lesions located at <strong>afferent</strong> axons</th>
<th>Lesions located at <strong>efferent</strong> axons</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GT</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Mild-ST</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-GT</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-ST</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-GT</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-ST</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-GT</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-ST</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Fingers; (y) %Error

**Legend:**
- Original plaque
- Increase 20%
- Increase 40%
- Increase 60%

Table 21 – Output error of progressive MS-plaques at afferent/efferents on Sim2603C: damage Tiny
<table>
<thead>
<tr>
<th>Vast</th>
<th>Lesions located at <em>afferent</em> axons</th>
<th>Lesions located at <em>efferent</em> axons</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GV</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Mild-SV</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-GV</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-SV</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-GV</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-SV</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-GV</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-SV</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Fingers, (y) % Error  
**Legend:**  
- Original plaque  
- Increase 20%  
- Increase 40%  
- Increase 60%

Table 22 – Output error of progressive MS-plaques at afferent/efferents on Sim2603C: damage Vast
7.1.4.2 Multiple-region (Sim2504)

In the second half of this experiment we investigated the impact of the same MS-plaques affecting afferent and efferent fibres now connected to a network containing multiple-regions. Figure 82 shows examples of a same MS-plaque (i.e. SV_Hard_GT) affecting simultaneously and separately the five afferent axons that connect each region; the equivalent example for efferent is not shown. This time the target regions of the map (indicated by a red square delimiting the target region) are more clearly distinguishable.

![Figure 82 - Example of MS-plaques of cardinality 1 affecting different afferent fibres](image)

Similarly to the first part of this experiment, afferent and efferent fibres connected to multiple-regions evoked quite different results, which are displayed in Table 23 and Table 24. The organisation of the tables is similar to the first part of the experiment.

Here, the impact of the same MS-plaques is also greater if these plaques affect efferent connections. Although training dependent, individual finger performances are more homogeneous among fibre types. Increase in size and severity of plaques, usually induced larger error. Overall, we found more localisable damage in these architectures.
<table>
<thead>
<tr>
<th>Tiny</th>
<th>Lesions located at afferent axons</th>
<th>Lesions located at efferent axons</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GT</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Mild-ST</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-GT</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-ST</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-GT</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-ST</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-GT</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-ST</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

Axes: (x) Fingers, (y) % Error

Legend: Original plaque, Increase 20%, Increase 40%, Increase 60%

Table 23 – Output error of progressive MS-plaques at afferent/efferents on Sim2703C: damage Tiny
Vast | Lesions located at *afferent* axons | Lesions located at *efferent* axons
---|---|---
AD-P-Mild-GV | ![Graph](image1) | ![Graph](image2) |
AD-P-Mild-SV | ![Graph](image3) | ![Graph](image4) |
AD-Hard-GV | ![Graph](image5) | ![Graph](image6) |
AD-Hard-SV | ![Graph](image7) | ![Graph](image8) |
SZ-P-Mild-GV | ![Graph](image9) | ![Graph](image10) |
SZ-P-Mild-SV | ![Graph](image11) | ![Graph](image12) |
SZ-Hard-GV | ![Graph](image13) | ![Graph](image14) |
SZ-Hard-SV | ![Graph](image15) | ![Graph](image16) |

Axes: (x) Fingers, (y) %Error

Legend: | Original plaque | Increase 20% | Increase 40% | Increase 60%

Table 24 – Output error of progressive MS-plaques at afferent/efferents on Sim2703C: damage Vast
7.2 Simulation-set 7: stroke

7.2.1 Motivation

In chapter 2 we learnt about the devastating consequences of strokes for neural processing. Similarly to MS-plaques, seen in the experiment before, strokes can happen in many varied ways promoting cortical map reorganization [Reggia96]. Thus, one also needs to know the impact of this type of lesions in diverse scenarios. By using Venn-networks, we aim to offer simulation results to help with future inferences.

7.2.2 Generated stroke lesions

In order to evaluate systematically the impact of strokes on the output performance of various different networks, we utilised the pathology generator (see appendix C) to produce a large and diverse set of artificial stroke lesions. For this experiment, the generation of strokes considered four variable aspects, namely, (i) range of affected processing units, (ii) location of stroke areas on the cortical map, (iii) grouping-layout and (iv) roundness-layout of damage. The names of lesions refer to:

- Range of units affected was decided ad hoc to assume 5%, 15%, 25%, and 35% of all processing units comprising the cortical map.
- Location of the lesion on the map (i.e. stroke-seeding) could be ‘Centred’ or ‘Off-centred’.
- Grouping-layout of damage could be ‘Grouped’ or ‘Scattered’; and
- Roundness-layout of damage could be ‘Round’ or ‘Elliptic’.

In total 128 artificial stroke lesions were generated, as 32 basic strokes were increased in size by 10%, 20%, and 30% according to the combination of aspects described above. Table 25 to Table 28 display all strokes generated on a map of fixed dimensions equal to 50 x 20 processing units. The meaning of the three letter stroke-acronym is as follows: the first letter gives ‘grouping’, the second letter gives ‘roundness’, and third letter gives ‘location’. E.g., ‘GRC’ means that the artificial stroke lesion is grouped, rounded and centred. The colour scheme adopted is ‘white’ and ‘black’ for operational and non-operation processing units (i.e. dead cells). This means that differently from MS, stroke only admits a binary state for processing units.

Notice that stroke generation does not respect boundaries of regions. As a result, most likely stroke lesions affect more than one region at the same time.

---

57 Resulting of the factorial combination of parameters commented above into four ranges of units affected, and two steps for location, grouping, and roundness.
<table>
<thead>
<tr>
<th>Column</th>
<th>Original stroke</th>
<th>10% size increase</th>
<th>20% size increase</th>
<th>30% size increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>GRO</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>GUC</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>GRO</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
<tr>
<td>SRC</td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
</tr>
<tr>
<td>SUC</td>
<td><img src="image25" alt="Image" /></td>
<td><img src="image26" alt="Image" /></td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image29" alt="Image" /></td>
<td><img src="image30" alt="Image" /></td>
<td><img src="image31" alt="Image" /></td>
<td><img src="image32" alt="Image" /></td>
</tr>
</tbody>
</table>

Table 25 – Stroke lesions generated as factorial combination of parameters: 5% columns affected
<table>
<thead>
<tr>
<th></th>
<th>Original stroke</th>
<th>10% size increase</th>
<th>20% size increase</th>
<th>30% size increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>GRO</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>GEC</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>GEO</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
<tr>
<td>SRC</td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image21.png" alt="Image" /></td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td><img src="image24.png" alt="Image" /></td>
</tr>
<tr>
<td>SEC</td>
<td><img src="image25.png" alt="Image" /></td>
<td><img src="image26.png" alt="Image" /></td>
<td><img src="image27.png" alt="Image" /></td>
<td><img src="image28.png" alt="Image" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image29.png" alt="Image" /></td>
<td><img src="image30.png" alt="Image" /></td>
<td><img src="image31.png" alt="Image" /></td>
<td><img src="image32.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Table 26 – Stroke lesions generated as factorial combination of parameters: 15% columns affected
Table 27 – Stroke lesions generated as factorial combination of parameters: 25% columns affected
Table 28 – Stroke lesions generated as factorial combination of parameters: 35% columns affected

<table>
<thead>
<tr>
<th></th>
<th>Original stroke</th>
<th>10% size increase</th>
<th>20% size increase</th>
<th>30% size increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>GRO</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>GEC</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>GEO</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
<tr>
<td>SRC</td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
</tr>
<tr>
<td>SEC</td>
<td><img src="image25" alt="Image" /></td>
<td><img src="image26" alt="Image" /></td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
</tr>
<tr>
<td>SLO</td>
<td><img src="image29" alt="Image" /></td>
<td><img src="image30" alt="Image" /></td>
<td><img src="image31" alt="Image" /></td>
<td><img src="image32" alt="Image" /></td>
</tr>
</tbody>
</table>
7.2.3 Architecture and simulation

This experiment is composed of two simulation-sets namely, Sim0104 and Sim0204. The former utilises the same network structure of Sim2603 (i.e. the first part of simulation-set 1 of chapter 6), and the latter utilises the network structure of Sim2703 (i.e. the second part of experiment 1 of chapter 6). This means that Sim0104 adopts a unique cortical region, whereas Sim0204 adopts five non-overlapping regions (for other details, check chapter 6). Therefore, with respect to structure the present experiment only differs from the previously mentioned two (i.e. Sim2603 and Sim2703) by considering that stroke lesions are applied to processing units of the architectures.

The simulations of the present experiment were carried out by presenting the usual testing file to the best performing trained networks of first and second parts of simulation-set 1 of chapter 6 – i.e. Sim2603C2 and Sim2703C2, respectively. In other words there is no training involved in the current experiment. As a result of that, all changes observed in the outputs (i.e. effectors) of Sim0104 and Sim0204 can be directly considered as consequences of the various stroke lesions that are simulated. This allows comparisons of impacts that stroke “classes” have upon network performance as well as comparing robustness of mono and multiple-region types of maps.

7.2.4 Results and Discussion

Stroke lesions when affecting mono and multiple-regions evoked quite different results, which are displayed in Table 29 to Table 32. Each table contains simulations of stroke lesions at a different range of units affected, i.e. 5%, 15%, 25%, and 35% of the total of processing units of the maps. The columns on the left contain simulations of stroke affecting a mono-region map, and columns on the right contain simulations of stroke affecting a multiple-region map. Each individual graphic presents output error per fingers (of the left hand) and includes progressive stroke lesions (i.e. growth of the same lesion) at 10%, 20% and 30% size increase.

Overall and depending on lesion features, we observed that multiple-region networks present a more localisable damaging effect (in respect to a particular effector), if compared to mono-region ones. We also observed in some cases, an intriguing fact, performance improvements when worsening of small lesions occurs, e.g. fingers 1 and 2 of lesion GRO of mono-region, and GEO of multiple-regions both in Table 29. This may be due to ‘loss’ of “counter-productive” units or linked to training effects as shown by cumulative frequency studies in Appendix ‘D’. Finally, we confirmed the high-dependency on area of stroke occurrence for evoked damage, even in multiple-regions.
### Table 29 – Output error of progressive stroke lesions affecting mono/multi region nets: 5% initial size
### Table 30 – Output error of progressive stroke lesions affecting mono/multi region nets: 15% initial size

<table>
<thead>
<tr>
<th>15%</th>
<th>Sim0104 – Mono-region (based on Sim2603C learning)</th>
<th>Sim0204 – Multi-region (based on Sim2703C learning)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1" alt="GRC Graph" /></td>
<td><img src="image2" alt="GRC Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="GRO Graph" /></td>
<td><img src="image4" alt="GRO Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="GEC Graph" /></td>
<td><img src="image6" alt="GEC Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image7" alt="GEO Graph" /></td>
<td><img src="image8" alt="GEO Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image9" alt="SRC Graph" /></td>
<td><img src="image10" alt="SRC Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image11" alt="SRO Graph" /></td>
<td><img src="image12" alt="SRO Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image13" alt="SEC Graph" /></td>
<td><img src="image14" alt="SEC Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image15" alt="SEO Graph" /></td>
<td><img src="image16" alt="SEO Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Fingers, (y) % Error

**Legend:** [Original stroke] [Increase 10%] [Increase 20%] [Increase 30%]
### Table 31 – Output error of progressive stroke lesions affecting mono/multi region nets: 25% initial size

<table>
<thead>
<tr>
<th>(25%)</th>
<th>Sim0104 – Mono-region</th>
<th>Sim0204 – Multi-region</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td>![Graph GRC]</td>
<td>![Graph GRC]</td>
</tr>
<tr>
<td>GRO</td>
<td>![Graph GRO]</td>
<td>![Graph GRO]</td>
</tr>
<tr>
<td>GEC</td>
<td>![Graph GEC]</td>
<td>![Graph GEC]</td>
</tr>
<tr>
<td>GEO</td>
<td>![Graph GEO]</td>
<td>![Graph GEO]</td>
</tr>
<tr>
<td>SRC</td>
<td>![Graph SRC]</td>
<td>![Graph SRC]</td>
</tr>
<tr>
<td>SRO</td>
<td>![Graph SRO]</td>
<td>![Graph SRO]</td>
</tr>
<tr>
<td>SEC</td>
<td>![Graph SEC]</td>
<td>![Graph SEC]</td>
</tr>
<tr>
<td>SEO</td>
<td>![Graph SEO]</td>
<td>![Graph SEO]</td>
</tr>
</tbody>
</table>

**Axes:** (x) Fingers; (y) % Error. **Legend:** Original stroke, Increase 10%, Increase 20%, Increase 30%.
Table 32 – Output error of progressive stroke lesions affecting mono/multi region nets: 35% initial size
To illustrate the cortical activity of mono and multiple-region Venn-networks affected by large strokes of the same proportion \((i.e. \text{stroke-layout SEO35})\), see Figure 83 and Figure 84, respectively. In the two figures one can observe the (i) different type of instantaneous activation evoked \((i.e. \text{notably peaks})\), and (ii) the fact that although large, the stroke did not disrupt much the epicentre of activity of the considered regions.

![Figure 83](image1.png)  
**Figure 83** – Typical activations for simulations Sim0104C (mono-region topology) under the effects of a stroke lesion (layout SEO35)

![Figure 84](image2.png)  
**Figure 84** – Typical activations for simulations Sim0204C (multi-region topology) under the effects of a stroke lesion (layout SEO35)
7.3 Simulation-set 8: multiple sclerosis (re-learning)

7.3.1 Motivation

This experiment aims to complement the simulation-set 6, by considering learning after the MS-plaques onset. Hence, one would like to know if there is convergence of further learning (after disease) and consequences to performance.

7.3.2 Architecture and simulation

This experiment is composed of two simulation-sets namely, Sim1006 and Sim1106. Similarly to Simulation-set 6, the former utilises the same network structure of Sim2603 (i.e. the first part of simulation-set 1 of chapter 6), and the latter utilises the network structure of Sim2703 (i.e. the second part of experiment 1 of chapter 6).

The simulations of this experiment involved two re-training of all the networks utilised. There were three processing phases; phases 0 and 1 (i.e. afferent and efferent training) used the usual training file and processing phase 2 (i.e. testing phase) used the usual testing file. The following parameters were utilised to train afferent and efferent fibres: (i) afferents: training epochs 5, afferent learning rate 0.05, decrement afferent learning rate 0.6 and cooperation radius 0.8; (ii) efferents: training epochs 6, efferent learning rate 0.1, and decrement efferent learning rate 0.9.

All MS-plaques presented in Table 19 and Table 20 are utilised to inflict damage to afferent and efferent fibres of the two architectures. Fibre allowances were considered in the same manner as in simulation-set 6, i.e. 37.5% and 75% for the ‘Tiny’ and ‘Vast’ “flavours” of damage, respectively; and ‘fibre delays’ were equal to zero.

7.3.3 Results and Discussion

The next eight pages present a number of graphics containing two types of information about re-learning in networks with MS-plaques affecting afferents and efferents fibres: (i) output error evolving throughout re-training epochs and (ii) output error after relearning. Table 33 to Table 36 refer to Sim1006 (i.e. mono) and Table 37 to Table 40 refer to Sim1106 (i.e. multiple-region). Results are averaged over 2 repetitions.

Regarding the learning processes, there was no observable pattern amid any existing grouping criteria namely, fibre type, number of regions, or MS-plaque layout. Although most learning curves decreased along relearning epochs, this was very gradual. Further analysis revealed that output error on unseen patterns has increased. This suggests overfitting, and poor re-learn abilities when axons are affected by multiple sclerosis.
Tiny | Lesions located at afferent axons (re-learn based on Sim2603C) | Lesions located at efferent axons (re-learn based on Sim2703C)
--- | --- | ---
SV-Mild-GT | ![Graph](image1) | ![Graph](image2)
SV-Mild-ST | ![Graph](image3) | ![Graph](image4)
SV-Hard-GT | ![Graph](image5) | ![Graph](image6)
SV-Hard-ST | ![Graph](image7) | ![Graph](image8)
SZ-Mild-GT | ![Graph](image9) | ![Graph](image10)
SZ-Mild-ST | ![Graph](image11) | ![Graph](image12)
SZ-Hard-GT | ![Graph](image13) | ![Graph](image14)
SZ-Hard-ST | ![Graph](image15) | ![Graph](image16)

**Axes:** (x) Epochs of re-training; (y) Output average error. **Legend:** ◆ Repetition 1  ■ Repetition 2

Table 33 – Output error evolving throughout re-training epochs of Sim1006: damage Tiny
Tiny

Lesions located at \textit{afferent} axons

Lesions located at \textit{efferent} axons

Table 34 – Output error of Sim1006 after relearning with MS-plaques at afferents/efferents: damage Tiny
Vast

Lesions located at afferent axons (re-learn based on Sim2603C) | Lesions located at efferent axons (re-learn based on Sim2703C)

<table>
<thead>
<tr>
<th>Simulations</th>
<th>Damage</th>
<th>Epochs</th>
<th>Output Average Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.000-0.002-0.004-0.006</td>
</tr>
<tr>
<td>SV-Mild-SV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.000-0.002-0.004-0.006</td>
</tr>
<tr>
<td>SV-Hard-GV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.005-0.010-0.015-0.020</td>
</tr>
<tr>
<td>SV-Hard-SV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.035-0.040-0.045-0.050</td>
</tr>
<tr>
<td>SZ-Mild-GV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.000-0.002-0.004-0.006</td>
</tr>
<tr>
<td>SZ-Mild-SV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.000-0.002-0.004-0.006</td>
</tr>
<tr>
<td>SZ-Hard-GV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.005-0.010-0.015-0.020</td>
</tr>
<tr>
<td>SZ-Hard-SV</td>
<td></td>
<td>1-2-3-4-5-6</td>
<td>0.035-0.040-0.045-0.050</td>
</tr>
</tbody>
</table>

Legend: Repetition 1 | Repetition 2

Table 35 - Output error evolving re-training epochs of Sim1006: damage Vast

 Axes: (x) Epochs of re-training; (y) Output average error.
Vast Lesions located at afferent axons Lesions located at efferent axons

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Afferent Lesions</th>
<th>Efferent Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GV</td>
<td><img src="image1" alt="Graph Afferent" /></td>
<td><img src="image2" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SV-Mild-SV</td>
<td><img src="image3" alt="Graph Afferent" /></td>
<td><img src="image4" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SV-Hard-GV</td>
<td><img src="image5" alt="Graph Afferent" /></td>
<td><img src="image6" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SV-Hard-SV</td>
<td><img src="image7" alt="Graph Afferent" /></td>
<td><img src="image8" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SZ-Mild-GV</td>
<td><img src="image9" alt="Graph Afferent" /></td>
<td><img src="image10" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SZ-Mild-SV</td>
<td><img src="image11" alt="Graph Afferent" /></td>
<td><img src="image12" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SZ-Hard-GV</td>
<td><img src="image13" alt="Graph Afferent" /></td>
<td><img src="image14" alt="Graph Efferent" /></td>
</tr>
<tr>
<td>SZ-Hard-SV</td>
<td><img src="image15" alt="Graph Afferent" /></td>
<td><img src="image16" alt="Graph Efferent" /></td>
</tr>
</tbody>
</table>

Axes: (x) Fingers, (y) %Error. Legend: □ Average among two repetitions (original size of MS-Plaques utilised)

Table 36 – Output error of Sim1006 after relearning with MS-plaques at afferents/efferents: damage Vast
<table>
<thead>
<tr>
<th>Tiny</th>
<th>Lesions located at afferent axons</th>
<th>Lesions located at efferent axons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(re-learn based on Sim2603C)</td>
<td>(re-learn based on Sim2703C)</td>
</tr>
<tr>
<td>SV-Mild-GT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Mild-ST</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-GT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-ST</td>
<td><img src="image" alt="Graph" /></td>
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</tr>
<tr>
<td>SZ-Mild-GT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-ST</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-GT</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-ST</td>
<td><img src="image" alt="Graph" /></td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:**
- (x) Epochs of re-training
- (y) Output average error

**Legend:**
- Repetition 1
- Repetition 2

Table 37 – Output error evolving throughout re-training epochs of Sim1106: damage Tiny

---

**Modelling Neural Processing Using Venn-Networks in Physiological and Pathological Scenarios – PhD Thesis**

Chapter 7 – Simulation of pathological scenarios: robustness

Page: 218
Tiny

Lesions located at afferent axons | Lesions located at efferent axons

| SV-Mild-GT | 0.2 | 0.15 | 0.1 | 0.05 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SV-Mild-ST | 0.2 | 0.15 | 0.1 | 0.05 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SV-Hard-GT | 0.2 | 0.15 | 0.1 | 0.05 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SV-Hard-ST | 0.2 | 0.15 | 0.1 | 0.05 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SZ-Mild-GT | 0.02 | 0.04 | 0.06 | 0.02 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SZ-Mild-ST | 0.02 | 0.04 | 0.06 | 0.02 | 0.0 |
| 1 | 2 | 3 | 4 | 5 |
| SZ-Hard-GT | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| 1 | 2 | 3 | 4 | 5 |
| SZ-Hard-ST | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 |
| 1 | 2 | 3 | 4 | 5 |

Axes: (x) Fingers; (y) % Error. Legend: Average among two repetitions (original size of MS-Plaques utilised)

Table 38 – Output error of Sim1106 after relearning with MS-plaques at afferents/efferents: damage Tiny
<table>
<thead>
<tr>
<th>Vast</th>
<th>Lesions located at <strong>afferent</strong> axons (re-learn based on Sim2603C)</th>
<th>Lesions located at <strong>efferent</strong> axons (re-learn based on Sim2703C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>AV</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image17" alt="Graph" /></td>
<td><img src="image18" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image19" alt="Graph" /></td>
<td><img src="image20" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image21" alt="Graph" /></td>
<td><img src="image22" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image23" alt="Graph" /></td>
<td><img src="image24" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image25" alt="Graph" /></td>
<td><img src="image26" alt="Graph" /></td>
</tr>
<tr>
<td>SV</td>
<td><img src="image27" alt="Graph" /></td>
<td><img src="image28" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Epochs of re-training; (y) Output average error. **Legend:** ◆ Repetition 1 ■ Repetition 2

Table 39 – Output error evolving throughout re-training epochs of Sim1106: damage Vast

---

Corresponding data in the text.
<table>
<thead>
<tr>
<th>Damage</th>
<th>Lesions located at <strong>afferent</strong> axons</th>
<th>Lesions located at <strong>efferent</strong> axons</th>
</tr>
</thead>
<tbody>
<tr>
<td>SV-Mild-GV</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Mild-SV</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-GV</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>SV-Hard-SV</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-GV</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Mild-SV</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-GV</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SZ-Hard-SV</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Fingers; (y) %Error. **Legend:** Average among two repetitions (original size of MS-Plaques utilised)

Table 40 – Output error of Sim1106 after relearning with MS-plaques at afferents/efferents: damage *Vast*
7.4 Simulation-set 9: stroke (re-learning)

7.4.1 Motivation

This experiment aims to complement the simulation-set 7, by considering learning after the stroke onset. Hence, one would like to know if there is convergence of the subsequent learning process (following disorder) and what happens to performance.

7.4.2 Architecture and simulation

This experiment is composed of two simulation-sets namely, Sim2205 and Sim2305. Similarly to Simulation-set 7, the former utilises the same network structure of Sim2603 (i.e. the first part of simulation-set 1 of chapter 6), and the latter utilises the network structure of Sim2703 (i.e. the second part of experiment 1 of chapter 6).

The simulations of this experiment involved two re-training of all networks utilised. There processing phases 0 and 1 (i.e. afferent and efferent training) used the usual training file and processing phase 2 (i.e. testing phase) used the usual testing file. The following parameters were utilised to train afferent and efferent fibres: (i) afferents: training epochs 5, afferent learning rate 0.05, decrement afferent learning rate 0.6 and cooperation radius 0.8; (ii) efferents: training epochs 6, efferent learning rate 0.1, and decrement efferent learning rate 0.9. All stroke lesions in Table 25 to Table 28 represent “deleted” processing units of the maps of the two mentioned architectures.

7.4.3 Results and Discussion

The next three pages present a number of graphics containing two types of information about re-learning of networks with strokes affecting their cortical maps: (i) output error evolving throughout re-training epochs and (ii) output error after relearning. Table 41 and Table 42 refer to re-learning of Sim2205 and Sim2305, at 5% and 35% stroke size. Regarding the learning processes, there was no observable pattern amid any stroke generation criteria namely, range of affected processing units, location of stroke areas on the cortical map, grouping-layout of damage, and roundness-layout of damage. Most learning curves decreased smoothly along relearning epochs.

Table 43 compares performances on unseen patterns averaged over 2 repetitions. Interestingly enough, re-learning results were sometimes better for some fingers if the damage was 35%; and both of them were worse than if all synaptic weights were reset and learning process started upon a ‘tabula-rasa’. An explanation could be that because stroke-lesions disrupt the “rationale” set by the initial learning, a relearning (i.e. rewiring synapses) would not be effective as training from the start (refer to chapter 6).
<table>
<thead>
<tr>
<th></th>
<th>Sim2205 – Mono-region (re-learn based on Sim2203C)</th>
<th>Sim2305 – Multi-region (re-learn based on Sim2703C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRC</strong></td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td><strong>GRO</strong></td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td><strong>GEC</strong></td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td><strong>GEO</strong></td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td><strong>SRC</strong></td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td><strong>SRO</strong></td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td><strong>SEC</strong></td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td><strong>SEO</strong></td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Epochs of re-training; (y) Output average error.  
**Legend:** 🟡 Repetition 1 🟢 Repetition 2

Table 41 – Output error evolving throughout re-training epochs of Sim2205 and Sim2305: 5% stroke size.
### Table 42 – Output error evolving throughout re-training epochs of Sim2205 ; Sim2305: 35% stroke size

<table>
<thead>
<tr>
<th>35%</th>
<th>Sim2205 – Mono-region (re-learn based on Sim2603C)</th>
<th>Sim2305 – Multi-region (re-learn based on Sim2703C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td>GRO</td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
<tr>
<td>GEC</td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
</tr>
<tr>
<td>GEO</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
</tr>
<tr>
<td>SRC</td>
<td><img src="image9.png" alt="Graph" /></td>
<td><img src="image10.png" alt="Graph" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image11.png" alt="Graph" /></td>
<td><img src="image12.png" alt="Graph" /></td>
</tr>
<tr>
<td>SRO</td>
<td><img src="image13.png" alt="Graph" /></td>
<td><img src="image14.png" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td><img src="image15.png" alt="Graph" /></td>
<td><img src="image16.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Axes:** (x) Epochs of re-training; (y) Output average error.  
**Legend:**  
- Repetition 1  
- Repetition 2
Table 43 – Output error of stroke lesions (5%;35%) affecting mono/multi region nets following relearning

<table>
<thead>
<tr>
<th>Region</th>
<th>5% Error</th>
<th>35% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Axes: (x) Fingers; (y) % Error. Legend: Stroke size 5% Stroke size 35%
To illustrate the cortical activity of mono and multiple-region Venn-networks affected by large strokes of the same proportion (i.e. stroke-layout SEO35), see Figure 85 and Figure 86, respectively. In the two figures one can observe the (i) different type of instantaneous activation evoked (i.e. one and five peaks), and (ii) the tiny changes in the landscape after re-learning following stroke onset.

**Figure 85** – Typical activations for simulations Sim02205C (mono-region topology) under the effects of a stroke lesion (layout SEO35) and after relearning

**Figure 86** – Typical activations for simulations Sim2305C (multiple-region topology) under the effects of a stroke lesion (layout SEO35) and after relearning
7.5 Simulation-set 10: contra-lateral activation

7.5.1 Motivation

In the simulation-set 5 of chapter 6, we observed how commissural fibres (implemented as u-fibres in Venn-Networks) have produced inhibitory effects on contra-lateral regions. This inhibitory effect almost totally suppresses activity of regions target by these fibres. As multiple sclerosis reduces the transcallosal conduction time [Boroojerdi98] we decided to simulate a simplified version of the motor system (only voluntary control with sensory feedback) to observe theoretical contra-lateral activation (in-respect to the region controlling the movement). Analogously to this rationale, we also investigate what would be the impact of *stroke-lesions* in these pathological scenarios.

7.5.2 Architecture and simulation

This experiment is divided into two sets of simulations: Sim1706A and Sim1706B. The former investigates contra-lateral activations due to stroke-lesions and the latter investigates contra-lateral activations due to MS-plaques.

Both groups of simulations utilise eight regions of identical size – 30 x 30 columns – divided into two “hemispheres”; regions numbered 0, 1, 4 and 5 lie on the right hemisphere, the other four region numbers (*i.e.* 2, 3, 6 and 7) lie on the left hemisphere. This is basically the same structure adopted in simulation-set 5 of chapter 6; the non-trivial connectivity of the network as well as illustration of the region map can be seen in that part of the thesis.

This final experiment only utilised already trained Venn-networks as the objective was to identify activation patterns rather than learning on its right in such scenarios. The network weights utilised were of Sim1506C1, because it was the best performing network of that simulation-set (*i.e.* experiment 5 of chapter 6). Therefore, we have one single processing phase here, where we aimed to test network behaviour on unseen patterns. The usual testing file was used for the only existing processing phase (*i.e.* final 111 patterns of data presented in appendix D). Recall that (i) the cardinality of both effectors utilised (*i.e.* two virtual hands) was 5 and (ii) there were only two areas of motor control (*i.e.* one region for all fingers of each hand) amid all regions defined. This means that the five fingers of both virtual hand a single landscape of activation controlling them all. However less-realistic, this could be extended to a region per finger as it was shown in the first experiment of chapter 6.
7.5.3 Contra-lateral activation due to stroke

In order to pursue the investigation of contra-lateral activation due to stroke lesions, we utilised the pathology generator (see appendix C) to produce three artificial stroke lesions (see Figure 87). The generation process was non-exhaustive and parameters were: 5% of processing units affected; the stroke lesion ‘grouping-layout’ and ‘roundness-layout’ were respectively grouped and round. The only parameter varied was the off-centred plaque location. Note seeding values, i.e. centre position of lesions, which are here indicated by ‘width’ x ‘height’ of maps with sizes normalised to 1: 
(i) stroke lesion 1: ‘motor-left’ – seeding 0.125x0.25; (ii) stroke lesion 2: ‘sensory-right’ – seeding 0.875x0.75; and (iii) stroke lesion 3: ‘motor-sensory left’ – seeding 0.125x0.5;

![Figure 87](image)

Figure 87 – Example of 5% of stroke lesions in respect to the cortical map which are affecting: (top) motor-left, (middle) sensory-right, and (bottom) motor and sensory left

Figure 88, Figure 89 and Figure 90 are examples of instantaneous activations of the whole map of a same network subject to the stroke-lesions described above.
**Figure 88** – Typical activations of Sim1706A1 displaying switch of activation to a contra-lateral region following stroke lesion on the motor-left region (this simulation was also carried out on top of Sim1606C1 and includes background noise).

**Figure 89** – Typical activations of Sim1706A2 displaying switch of activation to a contra-lateral region following stroke lesion on the sensory-right region (this simulation was also carried out on top of Sim1606C1 and includes background noise).
Figure 90 – Typical activations of Sim1706A3 displaying switch of activation to a contra-lateral region following stroke lesion on both motor and sensory left regions (this simulation was also carried out on top of Sim1606C1 and includes background noise)
7.5.4 Contra-lateral activation due to multiple sclerosis

Similarly to the stroke investigation described in 7.5.3, we utilised the pathology generator (see appendix C) to produce four artificial MS-plaque in order to investigate contra-lateral activation due to MS-plaques. The generated MS-plaques were utilised to inflict damage to neurocommunication of a 30x30 transcallosal fibre-like (see example of one of them in Figure 91). The generation process of the MS-plaques was non-exhaustive and some parameters were fixed namely: ‘grouping-layout’, ‘roundness-layout’, ‘seeding’. Their values were: grouped, round, and 0.5x0.5, respectively. The four plaques generated differ in two ways: (i) number of axons affected and (ii) damage to axons. Two steps of ‘damage to axons’ were used namely: ‘Tiny’ meaning from 25% to 50% and ‘Vast’ meaning from 50% to 100% of damage to the neurocommunication ability of the commissural fibre. Fibre allowance were 0.625 and 0.25, respectively; the ‘number of axons’ also had two steps, namely: 5% and 10% of the number of axons affected by MS-plaques within the commissural fibre.

Figure 91 – Example of ‘tiny’ MS-plaques affecting 5% of the 30x30 commissural fibre (top) connecting region-2 of simulation 1706B (bottom)

Figure 92 to Figure 95 are examples of instantaneous evoked activations of the whole cortical map for a same network subject to the four MS-plaques described above.
Figure 92 – Typical activations of Sim1706B1 displaying switch of activation to a contra-lateral region following MS-lesion onto left-to-right commissural fibres of the left motor region (this simulation was carried out using previous Sim1606C1).

Figure 93 – Typical activations of Sim1706B2 displaying switch of activation to a contra-lateral region following MS-lesion onto left-to-right commissural fibres of the left motor region (this simulation was carried out using previous Sim1606C1).
**Figure 94** – Typical activations of Sim1706B3 displaying switch of activation to a contra-lateral region following MS-lesion onto left-to-right commissural fibres of the left motor region (this simulation was carried out using previous Sim1606C1)

**Figure 95** – Typical activations of Sim1706B4 displaying switch of activation to a contra-lateral region following MS-lesion onto left-to-right commissural fibres of the left motor region (this simulation was carried out using previous Sim1606C1)
7.5.5 Results and Discussion

This experiment (in its two parts) shows that Venn-networks can be used as a paradigm to explain some facts observed in neural processing. Notice that some lesions simulated in the stroke experiment (Sim1706), were not within the circumscription of the same regions. This shows the flexibility of Venn-networks and also exemplifies their names. I.e. two superimposed regional boundaries: processing and damage regions.

In both investigated scenarios (i.e. ‘stroke’ and ‘MS’) we found that the ‘abnormal’ peaks evoked in the contra-lateral regions seems to be proportional in area to the damage inflicted. And in the multiple sclerosis case, damages are also correlated with the intensity (or severity) of the MS-plaques.

The production of the abnormal patterns of activation mentioned above was only possible because of some internal features incorporated in Venn-networks. Although resembling each other, the activations in both scenarios are produced by complete different mechanisms. Obviously, all activations are highly dependent on the structure of the network simulated. The particular connectivity utilised here (i.e. same as in experiment 5 of chapter 6) helps to illustrate potential use of Venn-network in neurology. In the stroke simulations the observed activations were due to the ability of Venn-networks of (i) accepting localised damage to selected processing units and still staying functional as a whole, and (ii) the use of inhibitory fibres (that in this case will not send inhibitory signals). As a result, the simulations of stroke do present abnormal contra-lateral shifts of activation, as inhibitory signals of contra-lateral regions are not sent because of the destruction of the processing units responsible for their generation in the opposite side of the cortical map. In the ‘MS” simulations, activations are also due to the ability of Venn-networks of (i) accepting localised damage to selected fibres that may or may not stay functional, and (ii) the use of inhibitory fibres (that will not send inhibitory signals as well). As a result, the various simulations of MS also present abnormal contra-lateral shifts of activation. However, the inhibitory signals of contra-lateral regions are not sent because of damage to the insulation of axons (see MS-plaque model in chapter 5). Although processing units responsible for the generation of inhibitory signals are intact, the signals still do not reach the opposite side of the cortex.

We conclude this chapter with an example of how Venn-networks, operating within relatively non-complex configurations, can evoke images that resemble functional methods of medical imaging, compare Figure 96 to a top view of it displayed
in Figure 97. Both contain a contra-lateral ‘abnormal’ peak due to MS-plaque affecting the transcallosal fibre of the motor-left (to right) region.

![Figure 96](image1.png)

**Figure 96** – Typical activations of Sim1’706B4 displaying switch of activation to a contra-lateral region following MS-lesion onto left-to-right commissural fibres of the left motor region (this simulation was carried out using previous Sim1606C1 and includes background noise)

![Figure 97](image2.png)

**Figure 97** – Top view of the data presented on the figure above. The right mid-top faint activations are due to MS-lesions on the contra-lateral region, nevertheless neurons in that region are still active. Finally notice the strong resemblance of this graphic to images obtained with functional magnetic resonance.
Chapter

8 Conclusion

"So many words, so much to do, so little done, such things to be". Alfred, Lord Tennyson 1809–1892: In memoriam A. H. H. (1850).
8.1 Overall conclusion and discussion

The objectives of this thesis were to investigate how changes in structure and connectivity impact on results evoked by simulated systems. The term ‘result’ used here encompasses two simultaneous occurrences in both biological and artificial neural networks: (i) elicited behaviour and (ii) evoked observable activations of neural activity.

The strategy adopted during the course of the research was to create a computational intelligent model that uses artificial neural networks for producing simulations of selected cognitive processes. The model proposed considers biologically plausible constraints and was implemented as a simulator that was extensively used to carry out simulations of both pathological and physiological scenarios. Specific results and discussions included in chapter 6 and 7 help to understand some aspects of neural processing.

In spite of the difficulty of modelling any brain function, by utilising the contributed models and computer simulator, we showed that:

A. Venn-neural networks can be ‘trained’ to evoke expected behaviour of complex tasks. The learning tasks of all ten experiments described in the chapters 6 and 7 have converged without requiring any ad hoc programmed routines or extremely complex architectures.

B. At the same time all simulated tasks were satisfactorily learnt and executed by Venn-networks, the internal activity of these architectures evoked observable activations that resembled functional images (i.e. spatially and temporally localisable kernels of neural activity correlated to the task performed).

C. Venn-networks are robust for training and execution of some motor tasks with respect to a range of disrupting factors of various kinds namely, neural disorders (e.g. multiple sclerosis and strokes), background noise, and ageing processes.

D. The neural structure in Venn-networks does influence neural processing simulations, even though some structural differences may not be of critical
importance or cannot be easily observable in healthy and some unhealthy conditions. This was proved when simulations of physiological scenarios of networks trained to perform some tasks revealed different observable neural activation in induced pathological situations on that same task, e.g., *vide* simulation-set 5 (in chapter 6) and simulation-set 10 (in chapter 7).

E. Although more evident and of penalising consequences in lesions studies, functional localisation was demonstrated by Venn-networks to be economic concerning consumption of computational resources: ‘space’ and ‘time’. *E.g.* refer to simulation-set 1 (in chapter 6).

F. Even though evaluating the computational power of the model is not the focus of this thesis, further simulations utilising other data sets would help towards an improved better understanding of the limits and abilities of Venn-networks. In the ‘Future work’ section (i.e. section 8.2) we suggest some improvements to Venn-networks, especially by using multiple-layers in the cortical map. This would equip the model to tackle better more complex classification problems than the auto-encoder ones already simulated. Note that Venn-network model, as proposed here, can already tackle multi-function control (i.e. be trained with different data sets concurrently) [Buarque01c].

In addition to the conclusions above (section 8.1), confirming the hypothesis that architecture (i.e. network structure and connectivity) influences neural processing, the results also show that some observable activations of the cortex can only happen if there is an underlying pre-set order in the circuitry. Thus, structure is an active participant of the produced computation. Because of observations such as these, some researchers such as Gen Matsumoto’s group at Riken [RIKEN02] are trying to understand the brain by reconstructing it as a non-von Neumann processor (i.e. ‘memory-based’) rather than a ‘processor-based’ device (as is the case of conventional computers). This approach implies that structure should provide the means for algorithm acquisition and execution. In Venn-networks, this ‘algebra’ is embedded in the user-defined architecture. Analogously, in biological systems, genetics may play the role of a guardian (for future
generations) of a reliable substrate for correct and robust neural computation (see also proposed questions in section 8.2.4).

Even though there is some variability in the micro and macro neural structures, evolution has guaranteed a great deal of architectural uniformity in individuals of the same species. The levels of intra-species “hard-wiring” are greatly pre-established, which contrasts with what happens interspecies. This observation can be drawn from anatomical interspecies comparisons of nervous systems. In other words, most interregional (and inter-hemispheric) connections are not produced at random; rather they are genetically programmed [Redies00] [Strittmatter00] [Polleux00]. To understand how the brain wiring is produced, scientists often use axon markers to identify cell-autonomous mechanisms in axon guidance, *i.e.* neurochemicals targeting [Leighton01]. In fact, humans exhibit the highest level of organisation and complexity of brain connectivity. This is also corroborated by preliminary interspecies comparison of *semaphorin* levels [Walsh01], which were observed in the *animal* and *human genome projects*\(^{58}\). Thus, we argue that ‘structure’ and ‘connectivity’, very likely, play a crucial role in the high neural computational abilities of humans. Moreover, between the two, we think that connectivity may well be more relevant than local features because of the relative homogeneity of the former [Valiant94].

In addition to the knowledge gained in this work about architectures evoking physiological neural processing, it is important to notice the view adopted here that illnesses are solely “new” operational modes (or expressions\(^{59}\)) of the brain. One might extend this concept and hypothesise that both normal and altered states of *mind* could also be consequent emergent changes of the neural circuitry. Explaining mechanisms or causes of these eventual changes seem to be another interesting research topic.

Finally, the approach adopted in this thesis seems to be in line with the approach taken by other researchers such as:

(i) **Christopher Frith**, who suggests that when the weights (*i.e.* synapses) in one module of the system are adjusted, this should not alter the functioning other modules [Frith97]; and

(ii) **Stephen Wolfram**, who suggests that simple units can implement complex computations when conveniently arranged [Wolfram02].

\(^{58}\) The human genome project is a trans-national endeavour to understanding gene expression, the connection between sequence variations and phenotype, large-scale protein-protein interactions, and a host of other global analyses of human biology [NHGR02]

\(^{59}\) Brain-operative expression is a term used at Riken laboratory [RIKEN02]
All this suggests other investigations focusing on ‘why’, ‘how’ and at ‘which level’ these architectural arrangements are more likely to occur. We conclude this discussion by offering provisional answers to these questions. Actually, these answers are conjectures about possible reasons that ‘nature’ might have used, on which to base its various evolutionary “decisions”. The provisional answers provided are:

• (why?) to strike a balance between correctness and robustness using criterion such energy efficiency or resource consumption;

• (how?) by means of self-organisation, as physical laws are likely to be omnipresent and uniformly acting upon all units of the system;

• (which level?) towards lower levels of organisation. As it is more logical a decision in favour of simplicity (as a key to complexity), because self-organising processes are more likely to be successful if they tackle simpler units.
8.2 Future work

Despite of all the abilities and advantages offered by the model developed in this thesis, we have identified several possible improvement points that could be incorporated into the model. In order to enhance the understanding of them, we have classified all them into three classes – or “avenues” – of improvement (each class refers to actions to be performed in respect of the model). These three “avenues” of improvements are (i) to refine the model; (ii) to calibrate the model; and (iii) to carry out new simulations using the existing model.

Figure 98 illustrates these classes, note that each class encompasses the research fields of this work as described in chapter 1 (refer to first figure of chapter 1) namely, artificial neural network, functional medical imaging, and neuroscience/neurology.

8.2.1 Improvement “Avenue” 1 – Refinements upon the proposed models

The improvements identified as refinements are primarily concerned with computational modifications upon the existing algorithms of the simulator (GVNS) and development of new routines. Overall, both these tasks aim to include new functionalities and concepts that are not currently incorporated into the existing models described in this thesis.

8.2.1.1 Venn-networks

New models of computation (per level of abstraction, see Table 44)

- a) Venn-networks interacting with other Venn-networks (Macro)
- b) Venn-networks containing multiple-layers in the cortical map (Intermediary)
- c) Other types of processing units, regional geometries, and fibres (Micro)
Table 44 – Innovative models of computation at various levels of abstraction
New data features

a) Incorporate concepts of neurotransmitters in all fibres (e.g. longitudinal or performance studies could be carried out using neurotransmitter depletion)

b) Diffusion model for oxygenated blood – non-trivial capillary distribution underlining the cortical map. (e.g. non-trivial dilation of capillaries could interfere with cortical column competition)

c) Haemodynamic function as attributable feature per region (e.g. different relaxations and physiological activation delays could help fMRI inference)

Features and parameters to implement (per component of the model)

a) Resilience and latency (effector and stimulus source)

b) Delays, density and off-sets (all fibre types)

c) Refractory period and operation frequency (processing unit)

d) Metabolic differences across regions (region)

e) Overlap of regions

New routines

fMRI inference routine – a routine that could produce a sequence of images that resemble in detail what would be seen by an external observer using functional imaging devices, e.g. an fMRI scanner. The input data could be taken directly from activations of cortical maps of Venn-networks. This routine could also be equipped with spatial and temporal transformations to better represent voxel activities. The similarity between generated fMRI maps and real functional images would also benefit from parameterised colour schema for activations, voxel size, and selected types of sequences.

Seeding routine – a short routine that could be parameterised by the user to induce map formation into specific areas of the cortical map of Venn-network regions. This would be useful for calibrations of models in respect to real data.

TMS stimulation routine – a routine similar to current stimulation of ‘stimuli sources’ and ‘effectors’ that could be used to directly stimulate processing units (i.e. artificial cortical columns) of Venn-networks. This routine could be used analogously with TMS in experiments with biological networks.

Routine for alterations of regional boundaries – a routine for changes of regional boundaries due to as chemicals, trauma, or development. This might allow simulations of developmental disorders, e.g. autism and some language impairment [Mareschal01].

Routine for simulating axon growth – used for simulation of axon growth in investigations of developmental problems from early stages of network formation.
8.2.1.2 MS-plaque model

Other features not included in the MS-model might be considered for further improvements in the accuracy of simulations:

- Ectopic action potentials (i.e. spuriously generated signals);
- Ephatic action potentials (i.e. axonal ‘cross-talk’);
- Temperature effects in the conductivity of the axon.

We also find valuable to consider that the MS-plaque model should incorporate the synergistic influence to neurocommunication of multiple trains of neuronal spikes for each stimulus.

8.2.1.3 Ageing model

- Include other (more realistic) functions for ageing processes
- Consider other dynamics for neuronal death
- Consider non-cellular factors associated with ageing processes

8.2.2 Improvement “Avenue” 2 – Calibrations utilising the proposed models

This thesis did not aim to find or fit its models to specific functional data of the brain. However, some data from in vivo functional experiments could be cross-validated using the Venn-networks. This calibration process could be used, for example, for: disambiguate initial hypotheses.

Another possibility after calibrating the model to a particular subject would be to use it as a prediction tool for prognoses in neurology. To achieve this objective, instead of using data generated by the pathology generator (see appendix C), real data from neurological diseases could be used. Some illustrative possibilities of use would be to foresee multiple sclerosis effects due to plaques growth, inference of damage due to strokes and impact due ageing processes.

In all cases of calibration above, we anticipate a non-trivial necessity of pre-processing input data (towards the Venn-networks). Some of the data manipulation envisaged includes (i) adaptations of geometrical information about the cortex (including structural and functional) to the planar layout of Venn-networks, (ii) temporal correlation of stimuli and elicited behaviour, and (iii) some form of normalisation of activation as well as “seeding” the peaks of activation of the functional information prior to map formation in the Venn-networks.
8.2.3 **Improvement “Avenue” 3 – Further simulations using the proposed models**

The final class for future work using the simulator includes many options and features that were not used in any of the simulations carried out so far. Therefore, this “avenue” is concerned with the execution of more experiments *in silico* to take advantage of this unexplored potential of the GVNS. Two are the sub-sections included here: (i) a list of features and parameters not simulated, and (ii) a list including suggestions of for new experiments to be carried out.

### 8.2.3.1 Features and parameters not simulated (per model component)
- Relaxation (processing unit);

### 8.2.3.2 New experiments
- Finger sequence processing (or “the skilled typing”) [McClelland86]
- PMA involvement on planning of movements
- Acceleration considered in effector movements
- Variable opposing forces
- Gravitational effects in movements
- Keyboard position of fingers (as well as correct finger flexions)
- Collaboration among neighbour fingers
- Gradual migration of “responsibility” between two regions controlling movement [Brodal98]
- Receptive fields change due to modulation
- SMA involvement on learning of complex movements
- Different activation patterns between learning and mental rehearsal of sequences [Krakauer00]
- Contralateral weakness due to sectioning of corticospinal axons from MI and pre-motor areas [Krakauer00]
- Trans-section of commissural fibres
- Use of inhibited contralateral areas in acting as supramotor areas in the arm alternated swing
- Use of inhibited contralateral areas for activating fingers ipso-lateral fingers and then stimulate only these areas. Desirably ipso-lateral movements should be evoked in case of diseases.
- Attentional perspective of task control (via modulation)
8.2.4 Proposed questions

During the course of this work, a number of new questions were identified; the most instigating ones are listed below\(^60\). We hope these ‘inquisitive’ contributions inspire others to continue from where this thesis ends.

- Is there an algebra\(^61\) for neural computation? If so, is this algebra unique to each individual?

- If so, what are the mechanisms that define this algebra? (e.g. nature or nurture?)

- Are neural algebras inheritable? If so, where is the boundary between genetic information on network structure and genetic information on neural computational mechanisms? Is this boundary static?

- How are new algebras acquired and grounded in the processing neural circuitry?

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\(^60\) Gary Markus [Markus01] has interesting views related to some of these questions

\(^61\) The term algebra used here is concerned with the existential notion of ‘operands’ and ‘operations’ defined over these operands.
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“What’s in a name? That we call a rose. By any other name
would smell as sweet.” William Shakespeare 1564–1616:
Romeo and Juliet (1595).
Antagonistic muscles – some skeletal muscles that function in pairs of contrary functions, *i.e.* while one flexes the antagonistic extends and *vice-versa.*

Beat – music velocity unit; one swing of the pendulum or balance of a timepiece.

Cardinality – quantity (but not order) of a given concept. In this work it is closely related to number of elements (*e.g.* fibres or units) comprising Venn-networks.

Co-registration – basic requirement for multimodality functional imaging in which spatial relationships between methods involved have to be established [George01].

Dia-/paramagnetic – refers to the quality of some substances to present or not magnetic properties.

Ectopic – referring to the outside part of something.

Electric capacitor – component of electrical circuits, which is intended to store electric potential for a variable lapse of time.

Emergence – phenomenon in which the evoked behaviour or sum of parts of a system is greater than its constituent parts [Holland98].

Equivalence – ability of producing same results from different computations.

Exteroceptors – special type of sensory receptors in the body that respond to stimuli from the outside of the body, *e.g.* the ones located in the eyes and skin.

Phrenology – introduced by Franz Joseph Gall in 1790, this school suggested that mind and mental faculties were located in specific areas of the brain surface [Clarke96].

Graceful degradation – quality of systems that remain operational (at some extent) even after severe problem(s) happened to them.

GUI – acronym for Graphic User Interface that is the set of screens shown to users for interactions with the automated system.

GVNS – acronym for Generalised Venn-Network Simulator, which is the piece of software produced by the author that implements the main ideas of this work.

Hebbian learning – Donald Hebb’s theory, which states that connections between coactive neurons, should be strengthened [O’Reilly00].

Holism – completeness of systems before their constituent parts.

Homunculus – pictorial man-like representation of cortical areas requested for performing specific motor and sensory tasks.

Isometric (muscular contraction) – when the muscular and external forces are equivalent.
Isotonic (muscular contraction) – when the muscular force is greater than the external opposing force to the movement.

Lateral inhibition – the process of interaction between adjoining cells in which there is inhibition of surrounding cells by an active one [Levitan97].

Neuroinformatics – is an emerging field that combines approaches of neuroscience, informatics and several other disciplines in order to develop and apply new sophisticated tools and theoretical concepts that will be essential for substantial advances in brain research [Organisers of the world congress of neuroinformatics – Vienna, 2001].

Neurotransmitter – chemical substances that allow signals to pass selectively from one neuron to another.

Nociceptors – special type of sensory receptors, specialised in pain perception, e.g. the ones located in the skin.

Nucleons – number of protons and neutrons in the atomic nuclei.

Overfitting – jargon of artificial neural networks, this term refers to the loss of generalisation ability of artificial networks. This normally happens if a neural network is over trained. Some direct consequences of that are: (i) bad performance on responding to patterns that were not seen before, as opposed to a (ii) good performance of the network while processing already known input patterns (i.e. patterns that were seen during training).

Precession – type of circular movement that is angular in relation to an axis performed by a body, e.g. some atomic nuclei precess when submitted to a magnetic field used in medical scanners.

Proprioceptors – special type of sensory receptors in the body that respond to stimuli from the inside of the body, e.g. the ones located in the joints and skeletal muscles.

Race condition – potential problem in algorithm execution that may arise due to some randomness of the processing program or system. It conveys the idea that expected results may not happen all the time because of particular instantaneous conditions of hardware or software.

Sensory receptors – biological structures where the sensory impulses are originated; they transduce stimuli into action potentials.

Sign of Babinski – or inverted plantar reflex (of foot) in central pareses, is an abnormal plantar reflex observed as a dorsiflexion (upward movement) of the big toe when a pointed instrument is moved along the sole of the foot (heel-to-toes). This indicates reduced cerebral activity (or none), i.e. arc-reflex is being closed at the spinal cord [Brodal98].

Silent lesions – physiologic changes not accompanied by physical sign or symptoms.

SNR – the ratio of the signal power to the noise power (used in medical imaging).
Talairach and Tournoux space – a commonly used atlas based on a single post-mortem brain; 3D coordinates then refer to eight landmark points [Jenkinson01].

Tesla (T) – international unit of magnetic flux density (magnetic field strength) \(1 \text{T} = 10^4 \text{ Gauss}\), named after Nikola Tesla (1856-1943).

Tempo – the rate of speed of a musical piece or passage indicated by one of a series of directions (as largo, presto, or allegro) and often by an exact metronome marking.

Tome – (from Greek) a slice [Johnson95].

Toroidal – of, relating to, or shaped like a torus or toroid: doughnut-shaped [Merriam-Webster on-line dictionary, http://www.m-w.com]

Training epoch – one complete presentation of the entire set of training patterns.

UML – acronym for Unified Modelling Language, which is a special notation to plan and document computer systems [Jacobson99] [Boock99] [Rumbaugh99].

Venn diagrams – Venn-diagrams were introduced by John Venn in 1880 [Venn80]. In brief, the \(v\)-Venn diagram is a collection of \(v\) finitely-intersecting closed curves in the plane, such that each of the \(2^v\) sets \(X_1 \cap X_2 \cap \ldots \cap X_v\) where each \(X_i\) is the open interior or exterior of the \(i\)-th curve, is a non-empty connected region [Bultena98]. The weight of a region is the number of curves that contain it. A region of weight \(j\) is a \(j\)-region. A more general concept, independent families (IFs), was proposed by Grünbaum [Grünbaum75]. IFs are defined as a collection of closed curves drawn in the plane, where the \(X_i\) intersections are also nonempty but not necessarily finitely-intersecting. See Figure 99 for an illustration of a three curve Venn-diagram. In the Venn-network context, for example, these three regions could be equivalent to: (A) target cortical region, (B) cytoarchitectonic region (i.e. same type of processing unit), and (C) region of a stroke lesion.

Figure 99 – Example of a 3-region Venn-diagram
**Voxel** – is the volume element of images, with spatial extension of \((\Delta x, \Delta y, \Delta z)\), it is complimentary to pixel that applies to planar images \((\Delta x, \Delta y)\).

**Figure 100** – Terminology used in medicine to reference positioning
Appendixes

“Ideas won’t keep. Something must be done about them”.

Appendix A – Scientific publications
A.1 Explanation

Throughout the present work the author has participated of an extensive range of scientific meetings and conferences. In addition to that some preliminary results of this work were submitted and accepted for publication. In this appendix the reader will find abstracts of the published work directly derived from the present piece of research.

A.2 Published work during PhD progress (only abstract of publications)

A.2.1 Multiple Sclerosis plaques on nervous pathways: A computational model using Neural Networks [Buarque01a]

[Journal paper]

This work presents a computational model of Multiple Sclerosis (MS) plaques affecting the normal axon transmission in nervous pathways. Some biological features observed in the axon membrane are considered, namely the local dynamics of the internode interaction, and the nature in which the axon sheathing is organised within and among internodes. The idea behind the model is to utilize an artificial feed-forward neural network composed of threshold units, representing two areas of the nervous system connected by long-range myelinated axons, i.e. a nervous pathway. This pathway is then subjected to the effects of artificially generated MS-plaques. The resulting delays in the signal propagation are made possible by changes in the conduction regime of the internodes, whose insulation was affected by the MS-plaques. The reductions in velocity conduction were then utilised to discard some axons, which were considered to be failing in the delivery of their signals within a varying time window, this measured in the target area.

Finally, the consequences of plaques growth were investigated. The model at hand did not consider temperature or ectopic stimulation and assumed only single spikes in the network for each stimulus. The computer simulations revealed that (a) transversal damages to the pathway are generally more devastating to neurocommunications than longitudinal destruction to the myelin, and (b) increases on the plaques size (i.e. plaques growth) cause the pathway to be just less efficient.

Keywords: Multiple Sclerosis, MS-Plaques, Neural Networks, Computer Simulations
A.2.2 Flexion of Virtual Fingers Controlled by Artificial Neural Networks

[Buarque01b]

{Paper and Oral presentation}

This work presents simulations of a recently proposed neuro-inspired architecture of artificial neural networks - Venn networks. Here distinct topologies of this model are trained to control flexions of virtual fingers, where ten finger reproduce movements of a piano player performing a Mozart Sonata. In a factorial manner parameter combinations of 32 topologies were tested and compared. The network performances on unseen patterns were evaluated, commented upon and some conclusions are drawn for further utilization of this type of network.

Keywords: Neural networks; Venn networks; control; simulations of movements; pyramidal pathway; fine movement control; volitive movement control.
A.2.3 Multi-function control using Venn Networks [Buarque01c]

Abstract and Poster presentation

In this work a recently introduced computational neuro-inspired model - Venn Networks - is used to control two independent functions that resemble finger and hand movements of a piano player performing a Mozart Sonata. Following comments upon the model and algorithms utilised, simulation results of virtual hands and fingers are presented and discussed.

In previous simulation works analogous artificial neural networks and algorithms proved themselves successful in controlling one single function, e.g. movements of virtual fingers. In addition to that, the architecture also acquired the topographical representation of inputs as observable voxel-like activations, such as the ones produced by fMRI scans of the brain. Now, we included an additional function to be controlled by the model, namely movement of virtual hands. Thus, the objective of the present work is to investigate how the system performs when it has to tackle two different objective functions.

Although the model at hand incorporates the feed-forward and feedback control loops present in voluntary movements, it does not include the mechanisms of movement initiation and sequence acquisition. However, it is still an important contribution on probing the capabilities of the Venn networks.

The neural architecture utilised here acquires the non-linear associations between inputs and outputs by using a 2-dimensional map composed of threshold units that mimic biological cortical columns. These processing elements compete locally among each other after receiving afferents from other cortical regions that are not included in the model. They also send efferents to both types of effectors being simulated, i.e. fingers and hands. Initially the map is trained in an unsupervised manner using Kohonen’s ideas of self organizing maps. Following the map formation, the efferent connection weights are trained in a supervised manner using the Least-Mean-Square algorithm.

The simulations are organised in two distinct groups. The first, considering the correct sequence of the music, whereas in the second, the sequence of music movements were shuffled. After the training of the network, the output performance was measured by counting misplaced or incomplete finger and hand movements of unseen input patterns.
A.2.4 Simulation of fMRI images - 2D Map controlling finger flexions

(Poster session – 2001 Autumn School in Neuroscience – Oxford/UK)

Simulation of fMRI images - 2D Map controlling finger flexions

Voluntary flexion of fingers: the cortico-spinal tract controls volitive movements of fingers in an almost uncontrolled manner. This kind of movement is goal-directed and repetition improves the execution performance. Feedback and feed-forward mechanisms play an important role in the accuracy of the movement.

Venn-network is a neuro-inspired computational architecture that acquires the non-linear associations between inputs and outputs by utilizing a 2-dimensional map composed of threshold units that mimic biological cortical columns. The processing elements of the map compete locally among each other after receiving afficients from other cortical regions. They also send afficients to the effector being simulated. The processing has two parts: (a) map formation and (b) effenter training. In brief, the map is trained in an unsupervised manner using Kohonen's self-organizing map. Next, the weights of the affenter connections are trained in a supervised manner using Local-Mean-Square algorithm.

Ideas: in this work an external process was included and was used to serve the main cortico-like processing grid. This additional grid, the fMRI map, incorporates the known physiological delay of the functional imaging method, and a non-linear hemodynamic curve.

Simulations: mono-energic Venn-networks with 400 processing units were used to control flexions of 10 virtual fingers performing piano music. Normalized vectors of numerical values were then presented for network training. These values were encoded based on a Moseur matrix and referred to fixation positions of the pianist's fingers. The network performance was calculated considering the number of correct finger flexions per test pattern (assessed by the test).

The Results: (a) the simulations show that it is possible to generate streams of fMRI-like images of a cortical model where it is controlling a cognitive-like function; (b) although of a cortical nature, the transition function between fMRI snapshots can be customisable. Additionally, the hemodynamic response, image sampling and cortex fMRI ratio, g; a, and λ, respectively, can also be configured. The authors believe that an intelligent algorithm to acquire the transition function can be conceived.
A.2.5 Modelling axonal delays caused by Multiple Sclerosis Plaques [Buarque00]

{Abstract and Oral presentation}

In this work, a computational model of Multiple Sclerosis (MS) plaques affecting the axonal transmission is proposed and its simulation results are presented and discussed.

MS-plaques are ‘hallmarks’ of the Multiple Sclerosis disease and are ubiquitous on various cerebral pathways of MS patients. These sclerotic plaques are the decay in the myelin sheathing of the myelinated axons from distinct regions within the CNS. From an engineering perspective, one can assume that these inflammatory processes are solely communication problems between different areas that need to ‘converse’ through a given path. This approach abstracts all the unsolved medical aspects of MS, especially those concerning aetiology and therapy.

This work was started motivated by the need to understand the MS-plaque impairment mechanisms on a smaller scale of neural communication leading to the anomalous and complex communication behaviour when a cerebral pathway connecting two distinct cortical regions is affected by MS-plaques.

The model considers some of the biological features observed in the axon membrane, namely (1) the local dynamics of the internode interaction, and (2) the nature in which the axon sheathing is organised. Then, this was incorporated into artificial neural networks, which are composed of layers of threshold units – artificial neurons. The model proposed here utilises a neural network arranged in distinct sub-nets (layers), representing two cortical areas connected by a number of myelinated axons. A set of synaptic parameters was produced by training the network on a non-linear input-output relation. The effects of the MS-plaques on the nerve fibres were obtained by varying the influence (i.e. resistance) of the insulation of the internodes of a subset of those axons (that are subject to the generated MS-plaques) within the pathway. Finally, conduction velocity changes, due to the MS-plaque effects, were observed using a varying time window in the target cortical area.

The simulations were organised in three distinct groups, starting with comparisons between the discrepancies of control and abnormal predicted values. The second group of simulations involves the same kind of comparison, as well as a varying time-window on the target cortical area for including or excluding delayed signals. The latter simulation presented here, different from the previous two, analyses the impact on the signal transmission delays. This simulation presents increases of their severity of internode damage.

It was found that the number of affected axons was consistently the most influential factor causing transmission delays. This surpassed all the other investigated features, namely the number of internodes affected and the severity of individual attacks on internodes. In other words, transversal damage to the pathway is more devastating to neurocommunications than longitudinal destruction to the myelin, so that plaques layout can be a more relevant feature than their size.

Keywords: Multiple Sclerosis, MS-Plaques, Neural Networks, Computer Simulations;
A.2.6 Modelling the effects of MS-Plaques growth

{Poster presentation - 2000 Autumn School in Neuroscience – Oxford/UK}

Modelling the effects of MS-Plaques growth

MS-Plaques: MS-plaques are hallmark of the Multiple Sclerosis disease and affect the conduction velocity of the axons of various pathways within the CNS.

Myelin decay: the inflammatory process present in the sclerotic plaques causes the decay of the myelin layers on the axons insulation.

Plaques growth: MS-plaques usually present a very irregular pattern of growth. Consequently, the effect caused in the neural communication of small neural populations is of a complex nature and thus difficult to assess. The picture to the right shows how the processes of a single oligodendrocyte form a network of normal axonal insulation.

The Computer model: considers the local dynamics of the intramembranous interaction and the way in which the axon sheathing is organized. An artificial neural network composed of layers of threshold units is used to represent two cortical areas connected by a number of myelinated axons. The effects of the MS-plaques on the nerve fibres were examined by varying the insulation of the internodes of a subset of those axons that are subject to the generated MS-plaques. The conduction velocity changes were observed using a varying time window in the target cortical area.

\[ \Delta = \{ \sum w_i x_i \}^2 \]

\[ \mu = \frac{1}{t + T_{conv}} \]

\[ r = \{ \sum t_{euc} d_{euc} \} \]

The Simulation: the impact on the signal transmission delays are analysed when plaque severity(i.e. damage to the internodes) increases. Below, the two figures show the same plaques in its initial configuration and after a 10% increase on the severity of the damage to the internodes.

The Results: the chart below shows that, although progressively shifted to the right, the squared errors observed on the target cortical region of the different stimulated plaques, are very similar. This means that plaques with their severity increased cause the pathway to be just as efficient for the same stimuli.
Appendix B – The generalised Venn-network simulator (GVNS)
B.1 – Introduction

In order to simulate Venn-networks and other ideas introduced in this thesis, their implementation as computational programs was necessary. The generalised Venn-network simulator or GVNS is the name given to the computer routines that have implemented these ideas altogether. At this point it is assumed that the reader is already familiar with the theory and algorithms proposed and utilised here.

This appendix contains a comprehensive yet brief description of the simulator including various aspects of its implementation as well as snapshots of most of the screens. To help the comprehension of this very extensive piece of software we selected documentation techniques largely used in software engineering [Pressman00], specifically structured and object-oriented analysis, the latter chiefly from UML [Jackobson99] [Boock99] [Rumbaugh99]. The sections to follow address the most important aspects of the produced system: use-cases, structure, behaviour and operation.

B.2 – Selected path for tackling neural computation via simulation

The available computational technology is another aspect that should be considered. Although Alan Turing\(^\text{62}\) has proved that the same computation can be achieved regardless of the complexity of the machinery (hardware and software) they execute upon [Turing35], this does not mean that technological aspects should be disregarded altogether; especially on a complex problem such as modelling neural processes. Likewise, the notion that there are more suitable methodologies for system analysis also holds. Actually, we advocate that if a methodology for system analysis (and also a computer programming language) includes concepts that are identifiable in the modelled system, modelling itself is greatly simplified. In this respect, Unified Modelling Language (UML) [Jackobson99] [Boock99] [Rumbaugh99], together with object oriented programming languages (OO) represent an excellent combination to be used for modelling and implementing brain function, respectively.

There are two main reasons to support the selection of these modelling tools: (i) UML models problems in a unified manner as opposed to separate ‘function’ and ‘data’ of other methodologies of analysis; and (ii) OO languages, in their axioms, incorporate many concepts present in the brain such as information encapsulation, function-
overriding, and hierarchical conceptualisations. Furthermore, combining UML and OO certainly simplifies the extendibility of any piece of software implemented. The reason is the facility to reuse code, which is an aspect provided by the property of inheritance of the classes hierarchy of the latter.

Based on the information provided so far (including of previous chapters) we have selected a combination of approaches that are proposed to be a flexible, realistic, and feasible framework to understand brain function while tackling neural computation. They selection is to use:

- Computational model-driven algorithms
- Connectionist systems (ANN)
- Top-down design, with bottom-up implementation
- Unified Modelling Language for software design (UML)
- Object oriented programming language for software development (OO)

The first two items provide an interesting mid-position between two opposing views, *i.e.* ‘nativism’ and ‘constructivism’ [Karmiloff-Smith96].

### B.3 – Description and highlights of the Venn-network simulator

In brief the GVNS can be described as a powerful computational tool to simulate two-dimensional patches of cortex in physiological and pathological scenarios.

There are five aspects of the simulator that should be highlighted because they enable the end-user to investigate artificial neural networks of non-trivial connectivity as well as the non-homogeneous composition of processing units. The GVNS highlights are:

- The various types processing units, multi-processing regions, multi-fibre type, and multi-input/output sources. Jointly these characteristics allow investigations of fairly complex artificial topologies of the network.
- The incorporation of the concept of processing phases permits simulations to utilise non-monotonic sets of learning parameters, and allows investigations of time-variable aspects such as ageing and modulation.
- The ability to deal with lesions similar to multiple sclerosis plaques and strokes grants the experimenter a great deal of flexibility in investigating the functional impact and evolution of these diseases.
- The internal calculation of output statistics greatly simplifies data analysis.
And the ability to produce highly configurable streams of snapshots (that resemble functional images) is a bonus that can be used in clinical studies.

B.4 – Use-cases of the Venn-network simulator

The generalised Venn-network simulator incorporates six main use-cases. Figure 101 shows these usage scenarios from the end-user’s perspective.

![Figure 101 – High-level use-case diagram of the Venn-network simulator](image)

Below the reader can find a brief description of each one of the GVNS use-cases:

- **Input architecture parameters**: this use-case allows the end-user to create and graphically visualise the static structural features of the simulated network.
- **Input simulation parameters**: this other use-case allows the end-user to specify and inspect the way in which simulations are set to be carried-out over a period of time.
- **Input pathology-like data**: this use-case aims to input and also graphically visualise any disease-like data that eventually will be utilised in some types of simulations. Diseases which are possible to be simulated in this version of the simulator are MS (plaque lesions) and/or stroke-like effects.
- **Train, test and stimulate network topologies**: this one allows the user to carry-out training and testing upon any topology that has been created.
considering (i) simulation parameters, (ii) pathology-like data (iii) training and test patterns, and (iv) external stimulations.

- Observe pathological and physiological results: after network training and testing, when untrained data is presented to the network, the simulator can also be used to produce graphical results. Note that re-run of simulations is also possible because synaptic values can be saved on permanent media.

- Obtain statistics of simulations: finally the end-user can use the simulator to calculate performance and error statistics of training, testing and simulations of behaviour – this can be in any combination of network topology and simulation set-up.

Further details such as parameters used and operations defined per use-case will be provided in the following sections.

B.5 – Internal structure of the Venn-network simulator

The Venn-network simulator was designed as an assembly of interdependent modules (i.e. classes) that communicate which each other to produce the desired results (i.e. use-cases). Figure 102 contains classes comprising the internal static structure of the simulator, plus the external subsystem that generates disease-like data. The indicated cardinalities (relationship between classes) define the actual existence of their instances.

![Figure 102 – Constituent classes of the Venn-network simulator](image-url)
To improve readability in the figure above all data exchanged between modules and their collaboration relation was omitted. Another simplification was the abstraction of any references to physical data repositories, as well as references to system dynamics. This information will be given in further sections.

Below, the most important classes of the GVNS are briefly explained:

- **Main**: this class controls most of the functions of the simulator, namely, learning algorithms, processing of pathologies, and routines such as ageing, modulation, and generation of random noise/relaxation. It also carries-out all calculations of performance and errors, as well as managing the user interface.

- **Architecture**: this auxiliary class displays graphically all the details of the topological design of the simulated networks. It selectively displays types of processing unit types, region boundaries, and the various types of fibres.

- **Simulation**: this other auxiliary class displays the list of parameters selected for simulations. To help user visualisation all information is grouped into processing phases, where the most relevant or unusual parameters are highlighted accordingly.

- **Map**: by means of variations in the colour of the units that compose the cortical map (there is a colour scale besides the map), this class displays a stream of snapshots of the simulated cortex-like patches. This class is instantiated twice in the simulator; the first instantiation indicates cortical activity and the second illustrates various modulatory effects actuating on the cortex.

- **MS-plaque**: this class displays transversal cuts of fibres affected by multiple sclerosis. Variations in colour illustrate the severity of the damage imposed by the plaques to the various axons that are components of the affected fibre. Additionally, there is an indication of which region of the cortex is connected to the diseased fibre.

- **Hand**: this class graphically illustrates the evoked behaviour of hand-like effectors when stimulations are carried out. Finger flexions are indicated by the reduction in size of the rectangles that symbolise fingers of the virtual hand. The number of instantiations of this class (i.e. hands) as well as the number of fingers is defined prior to simulations.
• **Keyboard**: this class also graphically produces an illustration of evoked behaviour resulting from simulations. Here, lateral movements of virtual hands are indicated on a featured keyboard. Evoked keystrokes are represented as numbers on top of the keys, with different colours for each hand. Instantiations of this class are also defined in advance.

• **Stimulation**: this class was introduced to perform various external stimulations into the various networks simulated. In the present version of the simulator it works in two different ways generating external: (i) input afferent patterns or (ii) efferent feedbacks such as sensory feedbacks. The only difference of these two kinds of stimulations to the normal ones is that they are externally controlled by the experimenter and can be produced at any time on top of all other signals being processed by the net.

### B.6 – Behaviour of the Venn-network simulator

Another important aspect of understanding how the simulator work is to learn the sequence of actions and reactions between the user and the system over a period of time. In Figure 103 the most relevant of these interactions can be seen (time is indicated downwards, along the vertical dotted lines); optional classes are indicated by asterisks.

![Sequence diagram of the Venn-network simulator](image)

**Figure 103** – Sequence diagram of the Venn-network simulator
Operation and Key-Concepts of the Venn-Network Simulator

The operation of the simulator is intuitive and simple. All interactions between the end-user and the application utilise visual interfaces as can be seen in Section B.11. All data used during simulations can also be entered primarily via script files stored on permanent media (e.g. a computer’s hard-disk).

In addition to the already discussed user and system interaction, the execution of the simulator involves some key-concepts that have to be fully understood. Below is a brief description of the five most important key-concepts, namely processing phases, action-to-proceed, training/testing epochs, stopping criteria, and grouping/granularity of results (i.e. output statistics).

- **Processing phase** is the way we included in the simulator the principle of developmental stages (or life cycle) of the networks. It is the upper most division of one simulation race (i.e. a single simulation execution). This concept allows the occurrence of great functional and parametrical changes during one simulation race. The user prior to simulation initiation should indicate the desired number of processing phases. For trivial technological reasons (i.e. high consumption of computer main memory), the current version of the GVNS has up to ten processing phases.

- **Action-to-proceed** is the means selected to include in the simulator the notion of distinct tasks to be performed in each processing phase of one simulation. As a design decision every processing phase has one and only one action associated with it. The actions defined in the current version of the simulator are: training afferents, training efferents (including two sub-modalities), training efferent feedback, testing, and resting. The first three titles indicate that they deal with selective training of fibres including u-fibres. The testing action does not involve training as the simulator uses previously stored values for all synapses (or just after trainings). Finally, the resting action is functionally similar to testing, with the difference that no pattern is presented to the network – except: (i) sensory feedbacks and (ii) some external stimulation.

- **Epoch** of training and testing is the term used to describe one complete presentation of all the patterns used either for training or testing of the network being simulated. This is a well known concept in the artificial neural networks literature that was incorporated into the simulation...
function. Typically, training and testing of artificial neural networks involve several epochs. In GVNS, many epochs are allowed to happen in each action-to-proceed, and consequently in each processing phase. Again, because of restrictions of computer main memory, epoch value is limited to a few hundreds.

- **Stopping criterion** is what objectively terminates training or testing phases. The GVNS implements two stopping criteria, namely (i) maximum number of training or testing epochs, and (ii) minimum average error in the effectors. It is the user’s responsibility to specify which of these two criteria should be considered in each processing phase. At the end of every epoch the system checks if the indicated value is reached – whatever the selected criteria. If this has happened that particular phase is then terminated.

- **Grouping and granularity of results** are concepts used in the GVNS that respectively define (i) the type and (ii) the summarisation of output files containing statistics of the evoked behaviour produced by the network. Results can be grouped into four distinct manners that are: none, output, epoch or both (both means output and epochs at the same time). Regarding granularity the results can be generated in two manners namely individual or average. The adequate selection of these two options is very important for analyses of results as they govern the production of several files that contain all the history and statistical data of evoked behaviour (refer to Figure 104). Appropriately selected, these files are then generated along side processing phases per each effector defined in the network.

### B.8 – Parameterisation of the Venn-network simulator

The GVNS accepts a large number of parameters to produce its expected results (i.e. use-cases, see Figure 101). The present implementation of the simulator was designed to receive its parameterisation from three distinct sources; these sources were devised according to their functionality. This section aims to briefly comment upon them.

The sources of parameters mentioned before correspond to three physical files, where similar parameters are grouped together: *cardinality, architecture* and *simulation*. This design decision allows different simulations to be carried out by simply changing
one of the files; this helps the user to reuse parameter files across different simulations. For example, two distinct simulations can share the same net architecture thus the user only needs to prepare simulation files and vice-versa.

Lists of these three groups of parameters will follow including their components and features. Notice that although they have already been defined and input, not all of the features below are considered during processing. The section future work in the concluding chapter of this thesis contains more information about this issue.

The cardinality source (i.e. parameter-file #1) contains information about the dimension of the network, and the number of each component utilised. It also includes the file and simulation names. The latter prefixes all the screens and, input and output files used during one simulation. The full list of cardinality parameters is below:

- Cortex width;
- Cortex height;
- Number of unit types;
- Number of regions;
- Number of u-Fibres;
- Number of afferents;
- Number of efferents;
- Number of efferent feedbacks;
- Number of stimuli;
- Number of effectors;
- Number of processing phases;
- Number of plaque assemblies;
- Number of stimulus sets;
- Simulation name;
- Log file name;
- Cardinality file name;
- Network file name;
- Simulation file name;

The architecture source (i.e. parameter-file #2) contains information about the structure of the network, i.e. what are the features of the structural components used to make-up the simulated neural network. Notice that the number of a component defined in the cardinality file implies an equivalent number of feature definitions for that.
component in the architecture file. For example if the number of regions specified in the cardinality file is two, this requires that the features of two regions have to be entirely defined in the architecture file. The list of architecture parameters accompanied by their features (terms inside brackets) can be seen below:

- Unit Types (Threshold; Activation function; Operation frequency; Refractory period);
- Regions (Initial width, Initial height, Final width, Final height, Unit type);
- U-Fibre fibres (Origin region, Target region, Activity type, Density, Delay);
- Afferent fibres (Stimulus source, Target region, Density, Off-set, Delay);
- Efferent fibres (Target effector, Origin region, Density, Off-set, Delay);
- Efferent-feedback fibres (Origin effector, Target region, Density, Off-set, Delay);
- Stimulus sources (Cardinality, Latency, Resilience);
- Target Effector (Cardinality, Threshold, Function, Latency, Resilience)

The last parameter source, i.e. simulation, contains all the non-structural information necessary for the simulations to be carried out. It must also be in agreement with the parameters informed in the cardinality file. Notice that all the parameters listed below have to be given for each processing phase specified in the cardinality file. In the case where more than one multiple sclerosis plaque and stimulus set are specified in the cardinality file they too have to have information provided according to their specific cardinality. The list of simulation parameters (per processing phase) is:

- Output observation (Effector breaks and granularity; Cortex sample rate);
- Network function (Cell death rate; Axon growth rate; Noise rate; Relaxation rate);
- Afferent learning (Learning rate; Decrement of learning rate; Cooperation radius; Neighbouring function);
- Efferent learning (Learning rate; Decrement of learning rate);
- Pathology-1 (Stroke file name);
- Pathology-2 (Affected fibre type and order; Ms-plaque file name; Fibre allowance);
- Stimulation (Stimulus order; Train/test file name);
- Processing action (Action identification; Number of epoch/Error; Number of Patterns/Time);
B.9 – Input/Output data of the Venn-network simulator

In Figure 104, all files that comprise the permanent data set of the simulator can be seen. They are all grouped according to their access type and function. Input files are on the left and output files are on the right. Other functional groups (dotted boxes) include parameters, fibres, train/test and pathology data, windows, log, history and statistics.

![Figure 104 – Input/Output diagram of the Venn-network simulator](image)

B.10 – Technology utilised in the Venn-network simulator

Over 18,000 lines of code entirely written in the computer programming language Java™ 2 constitute the current version of the GVNS. The integrated development environment utilised for producing the simulator was JBuilder™ 4 Professional from Borland®. All classes of the simulator were compiled and executed under the virtual machine Java HotSpot™ version 1.3.0-C from Sun Microsystems® Inc, and the basic software platform (i.e. operating system) was the Windows XP Professional™ produced by Microsoft Corporation®.

The present design of this generalised version of the Venn-network simulator was inspired by previous experiments carried out using a prototype written in the spring of 2001. However, all results reported in this thesis were produced with the newly constructed (version 1.0) of the GVNS.
B.11 – User Interface of the Venn-network simulator

The user interface of the simulator greatly utilises graphical resources available in the software platform selected for this system implementation. Because of that user-simulator interaction is extremely effective, as can be inferred from figures to follow.

The initial and main window of the simulator is shown in Figure 105. This window contains all cardinality parameters and file names used for the simulation session. As soon as the program starts default data is retrieved from disk. Then, the user can (i) inform a new set of parameter files to be read, (ii) make changes to all parameters on display, or (iii) simply accept the default parameters. By using this window the user can select the processing mode, processed module, control the display appearance of other windows in further processing steps, and decide on various other aspects of the simulator. Note that all parameters are conveniently grouped by function to easy operation.

![Figure 105 – Main window of the Venn-network simulator](image-url)
At the top right of this window there are fields utilised to keep the user informed about tasks currently being processed during a given simulation. Underneath those there is the selector for the module to process. Next, there are selectors to indicate which windows are to be displayed during the further steps of processing, and other control options for simulator function. By default most of these fields are initially set-on (i.e. selected), thus there is no need for changes unless for special situations. An example of one special situation is when the user chooses to utilise already trained synapses (of fibres) for retraining. In this case the user should simply deselect the parameter reset synapses. In the bottom half of this window there are cardinality, file name parameters and action buttons.

The user should always pay special attention when providing parameters to the system via the main window. The reason is that after accepting all parameters, by using the first button on the left, it will not be possible to make any further changes to them. If such a need arises a new simulation session will have to be initiated.

Following the set-up of all parameters and control options plus the acceptance of the network structure, the main window is reformatted and becomes the action control window. Figure 106 shows an example of how an action control window appears, whilst one simulation is being carried out. The reader may notice that some buttons are not available to the user (this is indicated when the buttons titles are faded). The buttons status (available or not) changes according to the stages of processing; it was implemented in this manner to avoid unwanted operating mistakes.

The user can finalise applications at any time by pressing the exit application button. In this case the application will not generate any of the output files originally expected, except the log. When the simulation reaches the end of all its defined

![Figure 106 – Action control window of the Venn-network simulator](image-url)
processing phases it has three possible outcomes: (i) the user may not want any files to be saved to disk (then, they should press the exit application button); (ii) the user may want output files to be saved to disk (then, they should press the terminate button); or (iii) the user may want to restart the simulation session (by pressing the return main button).

Figure 107 – Log window of the Venn-network simulator
All actions taken by the user and all operations carried out by the simulator are automatically recorded in the system log. The log also contains a written record of all parameters and options utilised during a simulation session.

Throughout processing log entries are displayed to the user in a window also called a log. Figure 107 displays a hardcopy of a log screen featuring some of the initial recordings of one simulation. After every simulation a hard copy of all information contained in the log window is transferred to permanent media. As with every other file generated by the GVNS, the log file name is prefixed by the simulation name provided in the main window. A typical log file contains hundreds of lines such as the following:

- Headings (various information including simulator version);
- Simulator boundaries (architecture and simulation hardwired assumptions);
- Current simulation information:
  - Race name;
  - Start date and time;
  - Processing mode and module;
  - Windows to be displayed;
  - Processing options set;
  - Cardinalities considered;
  - File names considered;
  - Architecture parameters (i.e. all network features read from file);
  - Cross-check of architecture parameters;
  - Simulation parameters (i.e. all simulation features read from file);
  - Cross-check of simulation parameters;
- Internal structures initialised (almost one hundred of internal arrays);
- All necessary fibres (i.e. synapses) read/randomised;
- Train/test patterns input;
- Pathology-like data input;
- Initialisation of threads;
- Processing phases:
  - Simulation action and parameters utilised (some recalculated);
  - Windows displayed to user;
  - Average output error;
  - Eventual file reading (vary according to simulation proceeded);
  - Finish condition (plus other messages).
Once all parametrical information is input into the simulator, it reacts by presenting to the user windows similar to Figure 108 and Figure 109, i.e. network topology windows. These windows contain graphical representations of the main components selected by the user to be considered during a simulation session. Altogether, these components constitute the structure of the network to be simulated. According to experimental needs, network architecture can assume very different layouts across simulations; hence the need for having this type of visual aid.

The components featured in the topology window are unit types (i.e. cortical columns), regions, stimuli sources, target effectors, and four types of fibres. The different fibres are indicated by lines of distinct colours, namely afferent fibres – green, efferent fibres – blue, efferent-feedback fibres – red, and u-fibre fibres – black.

Figure 108 – Example of a network topology window ready for simulation (featuring: regions)
In the bottom of the network topology window there is a set of check boxes to control feature display, e.g. unit type and region. This facility is useful when the user needs to observe particular topological aspects, especially in complex architectures. For example, Figure 108 and Figure 109 are two views of the same network topology; the apparent great difference is due to distinct aspects being shown. In the first figure, the different colours of the ellipsoids (i.e. processing units) indicate the boundaries of the four defined regions. Whereas in the second figure the outlined ellipsoids – coloured blue and green, indicate the unit type composition of each of the regions.

To sum up these two figures represent one topology where regions 0, 1, and 2 are composed of the same type of processing units (i.e. type 0), which is different from region 3 that is composed of processing unit type 1.

Figure 109 - Example of a network topology window ready for simulation (featuring: processing units)
In the example provided in Figure 108 and Figure 109 the reader can also observe that the network topology has three stimulus sources (black squares on top), and three single afferent connections originating from each of these stimuli and connecting to regions 0, 1, and 2, respectively. It also has a single u-fibre connecting regions 0 to 1; three single efferent fibres connecting regions 0, 1, and 2 to effectors 0, 1, and 2 respectively (white squares in the bottom). Finally, one unique efferent-feedback fibre connects effector 0 to region 3. Although not indicated in this example and just to remind the reader, more than one fibre (of the same kind) can start or arrive at one stimulus, region or effector.

Topology windows are very rich in information provided and that is why they have a great deal of different legends to represent the various components that are displayed. However, as any other featured component, the legends can be deselected by the user to improve visualisation.

Another important information window prompted to the user before the effective start of a simulation is the simulation configuration window. Similarly to the network topology window this one also provides a visual summary of the parameters as defined for the current simulation. In the case of this window the information displayed is about the non-structural aspects of the simulation.

In Figure 110, there is an example of a simulation configuration window. It shows that two processing phases are defined (represented by vertical columns) for this particular simulation. As has been stated before, up to ten processing phases are allowed in the current version of the simulator. The window has all the different parameters arranged in the rows of a spreadsheet-like chart. They are grouped into three categories of information: (i) granularity and grouping of results; (ii) simulation main parameters; and (iii) pathology simulated. Yellow, green and blue squares indicate these groups.

The motivation to have simulation configuration windows is only for the user to quickly check which parameters are being used in the simulations, and what are their values. This information can be read out by simply observing the intersection of the columns and rows, i.e. processing phases and simulation parameters. To make visualisation of simulation parameters even easier, the colour red highlights unusual parameters. The important parameter action identification is also highlighted.

A check of Figure 110 reveals that the example simulation is composed of two processing phases, a training of afferents followed by a training of efferents (stop
criterion is minimum error). No output files are generated (controlled by effector breaks); and besides all other necessary training parameters, 333 training patterns are utilised in both processing phases. Finally, there are three MS-plaques simulated in each one of the two processing phases.

![Simulation Configuration Window](image)

**Figure 110** - Example of a simulation configuration window ready for simulation

Following the presentation to the user of the network topology window and the simulation configuration window, it is for the user to decide the initiation of the processing phases. To do that the user has only to press the button *initiate* in the action control window. The simulator then displays selectively five distinct groups of windows as subject to the user’s requirements as informed in the main window. These window groups are the cortex-like map, modulatory effects map, MS-plaques, effectors, and external stimulation windows. The former four groups of windows inform dynamically to the experimenter about particular aspects of the current simulation. The latter group of windows is used solely for inputting data.
The first and most important window pertaining to the second phase of the simulator processing is the cortex-like map. This window presents a map that includes all the defined processing units of the cortical map being simulated. The number of processing units and layout of this map is completely controlled by the parameter files as discussed before.

In Figure 111 cortical columns-like (i.e. processing units) have their colours varying from blue to red representing their instantaneous levels of activations. On the right hand side of the map, there is a scale to help the user to assess the various levels of activation amongst the patches of the map. Maximal and minimal activations are in that order, indicated by white and black.

To facilitate the understanding, the map presented below is in agreement with all parameters discussed previously in this appendix. That is why one can identify four vertical distinct groups of processing units in it, i.e. regions 0, 1, 2, and 3 of Figure 108. Note also that region 1 shows the inhibitory effects u-fibre 0 seen in Figure 109.
The second type of window presented to the user during simulations is the modulatory effect map. Similarly to cortex-like maps, this one has cortical columns-like in the same layout defined by main parameters. The difference is that it shows the instantaneous modulatory effects affecting processing at a given timestamp.

Figure 112 shows an example of a window with modulatory effects on the cortical map simulated. In the example, one can observe that all the cortical columns have the same modulation intensity, i.e. the maximum possible. However, special situations such as diseases or aging could alter this, and the modulation map would have their units presenting different colours accordingly. The colour scale presented on the right hand side of the map helps the user to assess what are the effects of instant modulation actuating upon the cortical map. The colour spectrum from blue up to green indicates cortical modulation; white and black represent minimal and maximal intensity, respectively.

Another important group of windows included in the GVNS is the one that feature the eventually simulated MS-plaques. Each MS-plaque assembly is featured in one specific window. These windows show graphically a transversal cut of axonal fibres affected by MS-plaques, plus the impairment intensity caused by these plaques along the axons that compose the fibre (i.e. cardinality). The target region of the affected fibre under study is also displayed relatively to the cortical map simulated. Each window provides a colour scale to help the user to gauge the intensity of the impairment within the axons of the nervous fibre. Similarly to the modulatory effect window, blue up to green is the spectrum selected to indicate increase of impairment; white and black also represent minimal and maximal intensity.
In Figure 113 there are examples of three distinct windows containing multiple sclerosis plaques-like that are in agreement with parameters discussed earlier in this appendix.

![Example of three distinct windows](image)

**Figure 113** - Example of three distinct windows displaying simulated MS-plaques: impairing effects onto the axons of fibre (plaque 0), and target region of the affected fibre in the cortical map (plaques 1 and 2)

An **Effector window** is another important element that helps the visualisation of all processing carried out during simulations. Effectors by definition can have a wide variety of behaviours and layouts (including configurable cardinality). They are intended to be output visual devices to graphically display commands that are dispatched to them. Although the GVNS includes more types of effector throughout this work, virtual hands are the only effector layout used for illustrating behaviour controlled by the simulator, when simulating various topologies. Figure 114 exemplifies the finger position of the (virtual) hands during the execution of a given motor command.

![Example of two distinct effectors](image)

**Figure 114** - Example of two distinct effectors illustrating graphically the flexion position of fingers of two virtual hands
The fifth and final group of windows comprising the simulator is the external stimulation window. In the current version of the GVNS, there are two different windows in that group: (i) external stimulation of sources and (ii) external stimulation of effectors. These two windows can be seen in Figure 115 and Figure 116, respectively. In both windows there are two pieces of information required, namely (i) the order of stimulus or effector (depending on which case) and (ii) the values to be sent to each of the elements that comprise the stimulus sources or effectors. This, according to the type of window at hand, i.e. for external stimulation by stimulus sources or effector.

**Figure 115** – Example of external stimulation windows of stimulus source

**Figure 116** – Example of external stimulation windows of stimulus source

Attached to this thesis is a CD-ROM containing various demonstrations and other examples of various parts of the GVNS, this, for a more hands-on contact with the simulator.
Appendix C – The pathology-like generator
C.1 – Introduction

Simulation of pathologies requires vast amounts of data for its execution. Moreover, it is desirable that this data should encompass the most prominent features of the pathologies investigated. In neurology, the problem is even worse due to the non-trivial process of data acquisition, the anatomical and individual variability, and the great diversity of symptoms in most neural pathologies.

A generator of pathology lesion like-data was devised and implemented to overcome the problem of scarce and hard to obtain data. The major requirement for such an application is that it should be able to produce disease data that resembles in detail the damaging effects produced by the original illnesses. This is required especially for the two neurological conditions studied in this thesis: (i) multiple sclerosis and (ii) stroke of the cortex. In order to achieve that, the configuration of the pathology generator has to be highly flexible and should be easy for the experimenter to parameterise.

After the completion of all the programming, the application was tested and the results fully satisfied all the sought after requirements. The aim of this appendix is to briefly comment on the pathology generator created and the data it produces.

The pathology-like generator created is a small yet versatile computer program devised to be an auxiliary tool to the generalised Venn-network simulator, sharing the same software technology for both development and execution. The generator works as a computer file producer. It transforms a user defined set of parameters into data arrays of data, which are saved as files in permanent media. Later these files are read by the GVNS and interpreted as features of neurological diseases such as multiple sclerosis and strokes, i.e. disorders that affect axons and neurons respectively.

C.2 – Multiple Sclerosis data generation

As explained earlier the most evident feature of multiple sclerosis is the occurrence of sclerotic plaques in the white mater of the nervous system. The pathology generator produces – according to parameters – numerical files with normalised pseudo-random values corresponding to axon damage caused by the “parameterised” plaques.

The parameters required by the generator can be seen on the left hand side of Figure 117. They are: name of MS-plaque files, cardinality of nervous fibre (i.e.
number of axons per fibre); estimated percentage of affected axons; damage range to be considered per axon during generation process (i.e. max and min); layout of MS-plaque lesions within the fibre (i.e. grouped or scattered); plaque modalities of growth (i.e. in size or severity) and their relative percentage; and number of instances for a plaque to grow.

The range of values acceptable for each parameter is always given between brackets besides the parameter name on the generator interface, see Figure 117. Unless stated otherwise numerical parameters are normalised to 1.0, and are treated by the program as percentage of the field given relative to the maximum value possible for it. For example, 0.4 as axons affected actually means 40% of all axons component of the fibre.

In addition to the physical files containing generated lesion-values, the application also produces windows with graphical illustrations of the generated plaque damage of fibres; a ribbon shape is the means used to convey this information as it simplifies visualisation. A colour scheme is also utilised to indicate the severity of the lesion caused by the plaques to the fibre. Colour changes from green to blue (consult legend) imply degradation in axonal transmission; white and black mean normal and completely blocked axons, respectively.

Figure 117 – User interface of the pathology-like data generator: MS parameters enabled
Figure 118 contains two windows featuring examples of *grouped* and *scattered* layouts of lesions to fibres of cardinality five, *i.e.* comprising five axons. By consulting the colour scale in both figures, one can observe that two out of five axons present damage of distinct severities. Hence, neurocommunication for these fibres will be different from the original levels before the lesions.

Another generation regime for the lesions – *grouped* – assumes the centre of the ‘ribbon’ (*i.e.* nervous fibre) as the locus for the most severe damages that fades out towards the extremities. These lesions are generated in a random manner yet obeying the max/min parameters specified by the experimenter. Finally, the *scattered* regime of lesion generation is similar to grouped one, with the difference being the randomly selecting locations for lesions amongst any previously healthy axons of the fibre.

Another interesting and useful feature of the pathology generator is its ability to produce multiple sclerosis plaque-like data of a progressive nature. In other words, the generator can produce the same MS-plaque layout with progressive damaging effect to axons. This feature is extremely useful when the experimenter needs to use the GVNS for simulations of future symptoms evoked by the worsening of the disease.
The generator currently incorporates two actual regimes of ‘worsening’ sclerotic-like plaque sizes, and consequently increasing their impairing effects. To this process of augmenting plaque damaging effects we refer here as plaque growth, or growth regime. The two growth regimes devised are severity and size growth. Respectively, they are implemented in the pathology generator, either by (i) increasing the severity imposed by each micro-lesion or (ii) by generating new lesions to other axons (previously healthy) of the same fibre. Figure 119 and Figure 120 show three windows with graphical data of the same layout of multiple sclerosis plaque in three different evolution stages for severity and size growth, respectively. From top to bottom, changes towards the blue (legend) indicate gradual degradation of the fibre conductivity.

Figure 119 – Example of aggravation in the severity of lesions produced by the same MS-plaques (top-down) of a fibre with cardinality equal to ten.
Figure 120 – Example of aggravation in the size (number) of lesions produced by the same MS-plaques (top-down) of a fibre with cardinality equal to ten.

Another layout of MS-lesion that can be generated by this computer application is what we refer here as *commissural MS-plaques*. The idea just explained remains the same for this new modality with the difference that instead of a one-dimensional ribbon of axons, the “bunch” of axons can assume a 2-dimensional layout. The colour scheme is absolutely the same as before and the cardinality maximum values can be as large as the size of the cortical map.
Figure 121 shows four distinct layouts of commissural MS-plaques (again transversal sections) as a result of the parameters given to the pathology generator routine included in Table 45.

<table>
<thead>
<tr>
<th>Plaque name</th>
<th>% affected axons</th>
<th>Type of damage</th>
<th>Grid size (WxH)</th>
<th>Seed location</th>
<th>Spread control</th>
<th>Grouped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comm10</td>
<td>10%</td>
<td>Vast</td>
<td>30 x 60</td>
<td>0.25 x 0.5</td>
<td>1.5 x 0.5</td>
<td>No</td>
</tr>
<tr>
<td>Comm20</td>
<td>20%</td>
<td>Vast</td>
<td>30 x 60</td>
<td>0.25 x 0.75</td>
<td>0.5 x 1.5</td>
<td>No</td>
</tr>
<tr>
<td>Comm30</td>
<td>30%</td>
<td>Tiny</td>
<td>30 x 30</td>
<td>0.5 x 0.5</td>
<td>0.3 x 1.7</td>
<td>Yes</td>
</tr>
<tr>
<td>Comm50</td>
<td>50%</td>
<td>Tiny</td>
<td>80 x 100</td>
<td>0.75 x 0.5</td>
<td>1.7 x 0.3</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 45 – Parameters used for generating the four commissural plaques of Figure 121

Figure 121 – Example of four distinct layouts of commissural MS-plaques (their names are in top green bar)
C.3 – Stroke data generation

The second type of data produced by the pathology generator is neuron death, which is caused by strokes in the cortex. Similar to the MS-plaque generation, user provided parameters instruct the application to produce numerical files composed of arrays of lesion-like values. These output files contain indications of stroke areas as well as healthy patches of the cortex. Subsequently, these files are utilised by the GVNS for simulations of stroke impact on network functionality.

The generator allows the user to control three aspects of stroke lesion production, namely size, location and layout. The size of stroke lesions is given (by the user) as a proportion of the map-size, which later is simulated in the GVNS. The location of stroke lesions can be randomly selected within the cortical map or ‘seeded’ (i.e. directly specified) by the user. Finally, the layout of stroke lesions can be manually informed by the user as grouped or scattered, and distorted or not along axes x and y (i.e. width and height, respectively).

On the right hand side of Figure 122, the parameters required for generating stroke-like lesions can be seen. They are: cortex cardinality (i.e. number of cortical columns of the map); estimated percentage of affected columns; layout of stroke lesions on the cortex; and lesions growth/instance parameters.

![Figure 122 – User interface of the pathology-like data generator: stroke parameters enabled](image-url)
In Figure 123 two distinct centred lesions are displayed. Black dots are areas affected by the strokes, whereas healthy cortex is indicated by white dots. Although affecting the same number of cortical columns, the lesion to the left was produced in a grouped manner whereas the other is slightly scattered. In Figure 124 there are two examples of how the location of similar lesion (number of affected cortical columns) can be selected freely by the user. Moreover, in Figure 125 there are two additional examples of how the overall shape of lesions can also be controlled by the user and distorted along axes $x$ and $y$ in both figures respectively.

![Figure 123](image1.png)  
**Figure 123** – Example of grouped (left) and scattered (right) layouts of lesions to a patch of cortex

![Figure 124](image2.png)  
**Figure 124** – Example of parameterised ‘seeded’ locus of lesions to a patch of cortex

![Figure 125](image3.png)  
**Figure 125** – Example of parameterised geometry of lesions to a patch of cortex
All features of lesion generation presented before can be combined. This flexibility allows the user to generate data that quite reasonably matches real data.

Finally – also parametrically controlled – there is another very interesting and useful ability of the generator regarding stroke lesions generation. That is to produce a series of strokes with their size increased in an orderly manner. This means that an original stroke lesion can have its size gradually increased (or decreased – theoretically), whereas its location and overall layout are preserved. The files corresponding to these lesions can then be used by the GVNS to simulate impact on network functionality. Figure 126 presents an example a ‘growing’ stroke lesion. Note the increase in size of the area affected by the strokes relative to the rest of the cortex.

**Figure 126** – Example of aggravation in the severity of lesions (top-down) considering the same original stroke on a patch of the cortex
Appendix D – Training and testing data
D.1 Data quest

An artificial neural network is a computational approach to data processing that learns the features of its application domain from available representative examples. Being an ANN itself Venn-nets are no exceptions. In order to carry out training as the ones presented on some simulations of this thesis, a comprehensive and suitable data set had also to be used. The often selected option in situations such as this is to use known benchmark data. However, given the peculiarities of the simulations of this work a more specific yet laborious alternative was taken. The decision was towards seeking data more closely connected to the nature and objectives of this investigation.

Obviously the choice for the right data set was a very important decision to make, as it would have direct impact on all simulations to be carried out. Therefore, prior to any quest for data to match the purposes of this work we established a number of pre-conditions. They would help not only to select the appropriate data set but would guarantee that all features required from data by all simulations were not missed out during the decision process. The list of considered pre-conditions is enclosed below:

- **Non-linearity** – data should be highly non-linear and non-monotonic to offer a realistic challenge to the neural model proposed
- **Connection to human cognitive tasks** – data should be linked or show similitude to cognitive tasks so that symbolic manipulations might be tried
- **Sizeable number of patterns** – the number of patterns available should not be small to avoid offering restrictions during trainings of networks
- **Implicit order** – an implicit notion of order among patterns is also desirable
- **Implicit cardinality with in each pattern** – patterns should also offer a non-trivial cardinality (i.e. one) in order to allow more complex simulations
- **Extensibility** – new patterns should be effortlessly obtainable for eventual further experiments

This strict criterion for data selection ruled out most of the data sets readily available. However, the requirements above do not represent any sort of problem in music. Pentagrams of musical instruments are precisely the sought extensible set of ordered patterns of largely non-linear motor instructions. Following this line, our data quest was reduced to what musical instrument to select. Albeit most instruments could be appropriate, piano was the selected one mainly because of (i) the balanced use of the player’s hands and (ii) discrete strokes of each finger.
D.2 Original data and numerical encoding of finger movements

As explained before piano music was the selected source of data for training the networks in this work. The issue remaining was which piece of music to use. Because of its character yet simplicity Mozart’s *Sonata Facile* [Koehler51] was the one chosen.

An arbitrary initial portion of the sonata originated 444 training patterns that were produced by encoding the former into numeric values. Percentual usage and cumulative frequencies for finger movements are shown in Figure 127 and Table 46, respectively.

![Figure 127 – Percentual usage of fingers in each pattern within the considered portion of the music](image)

Each pattern produced contains distinct numeric information about flexion of all ten fingers of the piano player in a given time (regardless of their position on the keyboard). In other words, the encoding mechanism relates keystrokes within timestamp (t) to normalized numerical values. The convention used was 0.0; 0.5; and 1.0 to represent respectively: (a) no finger flexion, (b) the same finger flexed after a brief release of a keyboard key and (c) sustained finger flexion on a key. So far only three discrete values are used; in future experiments normalised values between [0, 1] could be used to encode strength of finger flexion. This would be relevant should “real music” is expected. Figure 128 is an example of how the initial portion of the original data [Koehler51] relates to the produced patterns. Red-ticks, *i.e.* time \( t(n) \) is 1/8 of a beat (according to tempo); \( F_1 \) to \( F_{10} \) are flexion values from left to right hand little fingers.

The credits for ‘translating’ music notation into the numeric representations devised by the author are due to Flavio Fröhlich.

![Figure 128 – Example of the encoding process carried out for the three first patterns produced](image)
<table>
<thead>
<tr>
<th>Finger</th>
<th>Left hand</th>
<th>Right hand</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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<td><img src="image7" alt="Graph" /></td>
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<td><img src="image17" alt="Graph" /></td>
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<td>10</td>
<td><img src="image19" alt="Graph" /></td>
<td><img src="image20" alt="Graph" /></td>
</tr>
</tbody>
</table>

Table 46 – Cumulative frequencies per finger of all 444 data patterns used for training and testing neural networks of this thesis
D.3 Produced data after encoding of finger movements

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<th>Pattern 111+t</th>
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<td>99</td>
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</tbody>
</table>

Table 47 – Initial 222 patterns produced based on Mozart’s Sonata Facile
The tables above and below contain all 444 patterns produced after the encoding before.

<table>
<thead>
<tr>
<th>t</th>
<th>Pattern 222+ν</th>
<th>Pattern 333+ν</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

Table 48 – Final 222 patterns produced based on Mozart’s Sonata Facile
Appendix E – Accompanying CD-ROM content
E.1 Introduction

Three aspect of the present thesis strongly suggested that an additional large capacity medium were to be appended to the written text, namely (i) the diversity of simulations included, (ii) the extraordinary amount of data produced by all simulations, and last but not least (iii) the great flexibility and resources of the GVNS. The latter, to be freely used by interested readers. These aspects were not disregarded, and an accompanying CD-ROM was produced.

The objectives of this laborious initiative was to entitle readers to run by themselves some demos of simulations carried out in this work, examine all data utilised and produced by the simulator, and even adventure to attempt new simulations of their own.

E.2 Technical information about the CD-ROM and the recording process

The media selected was a 74 minutes recordable compact disk (CD-R) because of its large capacity of 650Mb, low cost, long durability and vast compatibility across computer platforms. For future reference, below is included some technical information regarding the CD production:

- Software utilised: Roxio Easy CD Creator™ Version 5.1.0.99s1 copyright ©1995-2001 Roxio Corporation
- Hardware used: CD-RW Memorex driver 24X10X40X
- File system: ISO9660 (considering 30 characters for long file names)
- Physical format of the CD: CDROM XA
- Recording process: single session closed with CD at the end of the recording, with automatic verification of file system after recording
- Bonus for users of Windows™ by Microsoft Corporation®: autorun feature for configured disk-drivers

E.3 Content of the Accompanying CD-ROM

The CD-ROM produced to accompany this thesis is organised in several directories comprising all software and data judged worth for an interested user. In addition to that an easy to use hypertext structure (i.e. homepage structured files) was utilised for helping the user to browse the disk content, which is summarised below.

The present CD features eight distinct kinds of information, namely:
• The complete version 1.0 of the GVNS software (including documentation)
  o Introduction and organisation
  o Operation, Parameterisation and I/O files
  o Snapshots of screens and Description

• Ten demonstration of the Venn-simulator performing various tasks similar to the ones included in Chapters 6 and Chapter 7:
  o Introduction, objectives and contents
  o Mono-region (learning Mozart's Sonata Facile)
  o Multi-region (learning Mozart's Sonata Facile)
  o Sensory Feed-back
  o Modulation
  o Ageing
  o Contra-lateral inhibition
  o Stroke affecting motor region
  o MS affecting sensory region
  o Ipso-lateral activations due to Stroke
  o Ipso-lateral activations due to MS

• Abstract and charts of various experiments carried out in the work
  o Introduction, objectives & contents
  o Graphs produced by all simulations

• Complete set of data generated in chapter 6 (Physiological Scenario)
  o Equivalence
  o Active/Passive
  o Modulation
  o Ageing
  o Contra-lateral inhibition

• Complete set of data generated in chapter 7 (Pathological Scenario)
  o Multiple Sclerosis (MS)
  o Stroke
  o MS re-learning
  o Stroke re-learning
  o Contra-lateral activation switch

• Input data used for trainings of all topologies of the thesis
  o Introduction & data manipulation
• Mozart's *Sonata Facile* - Produced patterns
  • Other files (including version of Mozart’s *Sonata Facile*)

• Pathology generator software including brief documentation
  • Demonstration version of the generator
  • Generated Multiple Sclerosis lesions
  • Generated Stroke lesions

• Extra
  • Some selected parts of this thesis
  • Questions, Problems, and Contacts

E.4 Computer requirements for running the software produced

• For browsing the CD-ROM
  • Any internet browser, but hypertext was optimised to Microsoft®
    Internet Explorer™ and Windows™ operating system

• For running demonstrations
  • Java 2
  • 512Mb main memory

E.5 Operation of the accompanying CD-ROM

The start-up of the CD is very simple as it includes an *autobahn* feature (for Windows platforms only). Thus, it will automatically open its main page in the computer's default browser. Users of other computer platforms have to browse the CD, and before starting, they have to select the file *index.htm* in the root directory.

The layout of the hypertext (*i.e.*, html files) was kept very simple. Hence, once the main page is displayed all the content of the CD-ROM should be selectable (*e.g.*, double-clicking the desired hyperlink or figures). To return to the main page use the browser buttons.

If the reader wants to run the demos, the sought html links and batch file of interest (*i.e.*, file names initiating as *_RunDemo*) will promptly start the simulations.

Notice that a complete copy of all the simulator's classes is also included.

Finally, for further actions and problems consult the section (on the CD): *Questions, Problems, and Contacts*, which contains additional useful information.
The GVNS is very prolific regarding the output generated for each simulation. In addition to that this thesis includes ten non trivial simulation sets each of which contains two parts. The obvious outcome of that – partly seen in the previous chapters – is a large number of graphs and data tables. The unseen part is all physical files upon which all analyses were carried out. These files are included in the accompanying CD-ROM as part of the directory structure explained before. However, one needs to have a clear overview of the organisation of the simulations in order to better understand the rationale used in it. Table 49 and Table 50 address these issues.

### Table 49 – Internal organisation of initial four simulation sets and rationale of their composition

<table>
<thead>
<tr>
<th>Simulation heading</th>
<th>Simulation name</th>
<th>Chapter in the thesis</th>
<th>Simulations' composition</th>
<th>Repetitions</th>
<th>Base simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalence</td>
<td>Sim2603</td>
<td>Chapter 6</td>
<td>A, B, C, D</td>
<td>Three reps each</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Sim2703</td>
<td>Chapter 6</td>
<td>A, B, C, D</td>
<td>Three reps each</td>
<td>None</td>
</tr>
<tr>
<td>Stroke</td>
<td>Sim0104</td>
<td>Chapter 7</td>
<td>GRC, GRO, GEC, GEO, SRC, SRO, SEC, SEO,</td>
<td>Single reps for: 5%,15%, 25% &amp; 35% affected units</td>
<td>Sim2603</td>
</tr>
<tr>
<td></td>
<td>Sim0204</td>
<td>Chapter 7</td>
<td>GRC, GRO, GEC, GEO, SRC, SRO, SEC, SEO,</td>
<td>Single reps for: 5%, 15%, 25% &amp; 35% affected units</td>
<td>Sim2703</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Sim2404</td>
<td>Chapter 7</td>
<td>a) Ms-plaques at Afferents: SV5Hard (GT, GV, ST, SV) SZ5Hard (GT, GV, ST, SV) SV5Mild (GT, GV, ST, SV) SZ5Mild (GT, GV, ST, SV) b) Ms-plaques at Efferents: SV5Hard (GT, GV, ST, SV) SZ5Hard (GT, GV, ST, SV) SV5Mild (GT, GV, ST, SV) SZ5Mild (GT, GV, ST, SV)</td>
<td>Single reps for plaque sizes: Original, 20% increase, 40% increase, 60% increase</td>
<td>Sim2603</td>
</tr>
<tr>
<td></td>
<td>Sim2504</td>
<td>Chapter 7</td>
<td>a) Ms-plaques at Afferents: SV5Hard (GT, GV, ST, SV) SZ5Hard (GT, GV, ST, SV) SV5Mild (GT, GV, ST, SV) SZ5Mild (GT, GV, ST, SV) b) Ms-plaques at Efferents: SV5Hard (GT, GV, ST, SV) SZ5Hard (GT, GV, ST, SV) SV5Mild (GT, GV, ST, SV) SZ5Mild (GT, GV, ST, SV)</td>
<td>Single reps for plaque sizes: Original, 20% increase, 40% increase, 60% increase</td>
<td>Sim2703</td>
</tr>
<tr>
<td>Active Passive</td>
<td>Sim1905</td>
<td>Chapter 6</td>
<td>A, B, C, D, E, F, G, H</td>
<td>Double reps each</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Sim2005</td>
<td>Chapter 6</td>
<td>A, B, C, D, E, F, G, H</td>
<td>Two single reps. each (one active, the other passive)</td>
<td>Sim1905</td>
</tr>
<tr>
<td>Simulation heading</td>
<td>Simulation name</td>
<td>Chapter in the thesis</td>
<td>Simulation compositions</td>
<td>Repetitions</td>
<td>Base simulation</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td>-------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Stroke (relearning)</td>
<td>Sim2205</td>
<td>Chapter7</td>
<td>GRC, GRO, GEC, GEO, SRC, SRO, SEC, SEO,</td>
<td>2 double reps: for 5% &amp; 35% affected units</td>
<td>Sim2603</td>
</tr>
<tr>
<td></td>
<td>Sim2305</td>
<td>Chapter7</td>
<td>GRC, GRO, GEC, GEO, SRC, SRO, SEC, SEO,</td>
<td>2 double reps: for 5% &amp; 35% affected units</td>
<td>Sim2703</td>
</tr>
<tr>
<td>Ageing</td>
<td>Sim2905A</td>
<td>Chapter6</td>
<td>1, 2, 3, 4, 5,</td>
<td>Single reps for cell death rate: 0.0%, 0.079%, 0.15%, 0.2%</td>
<td>Sim1905</td>
</tr>
<tr>
<td></td>
<td>Sim2905B</td>
<td>Chapter6</td>
<td>Motor, sensor, Left, Right, Mixed</td>
<td>Single reps for: Selective, Exclusive, Part-exclusive</td>
<td>Sim1905</td>
</tr>
<tr>
<td>Modulation</td>
<td>Sim3105</td>
<td>Chapter6</td>
<td>0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12</td>
<td>Single reps each</td>
<td>Sim1905</td>
</tr>
<tr>
<td></td>
<td>Sim0106</td>
<td>Chapter6</td>
<td>A and B</td>
<td>Three reps each for: modulation On, Off</td>
<td>None</td>
</tr>
</tbody>
</table>
| Multiple Sclerosis (relearning) | Sim1006        | Chapter7              | a) Ms-plaques at Afferents: \(\text{SV5Hard (GT, GV, ST, SV)}\), \(\text{SZ5Hard (GT, GV, ST, SV)}\), \(\text{SV5Mild (GT, GV, ST, SV)}\), \(\text{SZ5Mild (GT, GV, ST, SV)}\) 
b) Ms-plaques at Efferents: \(\text{SV5Hard (GT, GV, ST, SV)}\), \(\text{SZ5Hard (GT, GV, ST, SV)}\), \(\text{SV5Mild (GT, GV, ST, SV)}\), \(\text{SZ5Mild (GT, GV, ST, SV)}\) | Double reps for plaque of original sizes | Sim2603 |
|                    | Sim1106        | Chapter7              | a) Ms-plaques at Afferents: \(\text{SV5Hard (GT, GV, ST, SV)}\), \(\text{SZ5Hard (GT, GV, ST, SV)}\), \(\text{SV5Mild (GT, GV, ST, SV)}\), \(\text{SZ5Mild (GT, GV, ST, SV)}\) 
b) Ms-plaques at Efferents: \(\text{SV5Hard (GT, GV, ST, SV)}\), \(\text{SZ5Hard (GT, GV, ST, SV)}\), \(\text{SV5Mild (GT, GV, ST, SV)}\), \(\text{SZ5Mild (GT, GV, ST, SV)}\) | Double reps for plaque of original sizes | Sim2703 |
| Contra-Lateral Inhibition | Sim1506        | Chapter6              | A, B, C, D            | Double reps each | None |
| Function contra lateral side switch | Sim1606        | Chapter6              | Single example         | Also single repetition | Sim1506 |
|                    | Sim1706A       | Chapter7              | (Stroke) Noise, No-Noise for: Motor left, Sensory right & Mono-Sensory left | Single rep each | Sim1506 |
|                    | Sim1706B       | Chapter7              | (MS commissural plaques) Noise, No-Noise for: a) 5% Affected: TINY, VAST b) 10% Affected: TINY, VAST | Single rep each | Sim1506 |

Table 50 – Internal organisation of final four simulation sets and rationale of their composition
### E.7 Rationale for names of output files

This final section of the appendices aims to clarify what is the content and the internal organisation of all output files, automatically generated by the GVNS at the end of every simulation. Even though all names given to output physical files are very intuitive, one might need a formal means to disambiguate names and internal content of output files; Table 51 addresses this necessity.

<table>
<thead>
<tr>
<th>File name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>&lt;Sim_name&gt;_log.txt</code></td>
<td>Output file that keeps a record of all operations performed by the simulator and the user. Internal structure varies depending on each simulation.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;_cardinality.txt</code></td>
<td>Input file (parameter) that informs the simulator values of structures component cardinalities of every simulation. Fixed internal structure.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;_network.txt</code></td>
<td>Input file (parameter) that informs the simulator values of structural features of simulated networks. Internal structure can vary, but is keyword set.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;_simulation.txt</code></td>
<td>Input file (parameter) that informs the simulator values of dynamical features of simulation itself. Internal structure can vary, but is also keyword set.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;-Afferent&lt;n&gt;_IN.txt</code> &lt;Sim_name&gt;-Afferent&lt;n&gt;_OUT.txt</td>
<td>Input/Output files that keep synaptic values for afferent connections of stimulus order &lt;n&gt;.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;-Efferent&lt;n&gt;_IN.txt</code> &lt;Sim_name&gt;-Efferent&lt;n&gt;_OUT.txt</td>
<td>Input/Output files that keep synaptic values for efferent connections of effector order &lt;n&gt;.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;-EfferentFeedback&lt;n&gt;_IN.txt</code> &lt;Sim_name&gt;-EfferentFeedback&lt;n&gt;_OUT.txt</td>
<td>Input/Output files that keep synaptic values for efferent feedback connections of effector order &lt;n&gt;.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;-uFibre&lt;n&gt;_IN.txt</code> &lt;Sim_name&gt;-uFibre&lt;n&gt;_OUT.txt</td>
<td>Input/Output files that keep synaptic values between regions connected by u-Fibre order &lt;n&gt;.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;_CortexSnapshot-USER-&lt;t&gt;_OUT.txt</code></td>
<td>Output files that keep instantaneous 2D snapshots of the cortical map activity of time &lt;t&gt;. The generation of these files can happen at any time and can be controlled by USER or SYSTEM.</td>
</tr>
<tr>
<td><code>&lt;Sim_name&gt;-PHASE&lt;p&gt;-EffectorBehaviour-Effector&lt;e&gt;_OUT.txt</code></td>
<td>Output files that keep output behaviour of effector order &lt;e&gt; at the end of processing phase &lt;p&gt;. Each epoch of training produces a block of data inside the file. Rows of these blocks are calculated outputs for input patterns presented to the network and columns are individual components of the effector &lt;e&gt;.</td>
</tr>
</tbody>
</table>

To continue…
Table 51 - Rationale for output file names and brief description of their content

To conclude, notice below three final remarks about output file names:

- Output effector files are generated separated per processing phases and per effectors (with the exception of files SUMEffectorEpoch)
- The generation directory of all output files is the same of the Java classes of the simulator
- The internal code used for all files generated by the GVNS is the ASCII standard (i.e. txt files also known as “DOS” files).
Appendix F – Initial simulations of MS-plaque model
(adapted from [Buarque01a])
F.1 Introduction

In early simulations of the MS-plaque model [Buarque01a] two preliminary steps were performed, namely (a) generation of some lesion-like data set and (b) generation of synaptic-like information for the simulated pathway. The first data set was generated to mimic the delays on the signal propagation when simulating affected nervous pathways. The second data set generated was used to depict an arbitrary non-linear relationship of distinct cerebral regions, when they communicate one with each other via long-range myelinated pathways. The former (i.e. plaque artificial lesions) was produced by a computer program that, according to parameters, generated ‘tailored’ plaques. The latter (i.e. synaptic values) were obtained by training a simple Multi-Layer Perceptron (MLP) network, with the back propagation algorithm [Rumelhart86].

These initial simulations of the MS-model were organised in three distinct groups. In the first group, comparisons between the discrepancies of control and abnormal predicted values were proceeded. The second group involved the same kind of comparison, as well as a varying a time-window on the target cortical area for including or excluding delayed signals. The latter group of simulations, different from the previously described two, analyses delays on signal transmission when the MS-lesions considered present increases in their severity. Chapter 7 of this thesis includes simulations that consider multiple sclerosis plaques that “growth” dimension-wise.

F.2 Data

F.2.1 Lesion-like data

In order to simulate the delays on the signal propagation in a single affected nervous pathway, some numerical values representing MS-plaque lesions were necessary. This data set was achieved as various matrices each one containing information about the conductivity of the simulated pathway, i.e. incorporating specific MS-plaque layouts. Each element of these lesion-like matrices symbolizes the internodes of all axons constituting the pathway. In other words the lines and columns of these artificially created MS-plaques represent the axons and the internodes of a given pathway, some of which, defective in function.

The plaque load configuration was generated by a fully parameterised program constructed to produce MS lesion-like of various kinds. The most important parameters of this routine are (i) the percentile of axons affected; (ii) the percentile of internodes affected within a single axon; (iii) the severity of the demyelination; (iv) the spatial
distribution pattern of the plaques; and (v) the uniformity of the plaques within the pathway, assuming two possible values: uniform or non-uniform. Notice that all these parameters can be deduced from currently available medical imaging methods.

Three spatial configurations were devised for the generation of initial plaques namely, (a) spatially grouped, (b) moderately grouped, or (c) randomly scattered. Figure 129 contains examples of these distinct kinds of generation regimes. In the figure, darker shades of the grey scale represent more severe lesions.

A total of 24 distinct plaques, eight in each generation regime, were utilised in all three simulations to follow. The investigated features in the generated plaque loads were varied in a two-step factorial design, as seen in Table 52. Severity, axons and internodes affected refer to the percentage of the absolute values calculated on an axon that is – in this initial simulation – 300 mm long, has 25 myelin layers, and has internodes of 1.5 mm long. All plaque loads generated most likely affect differently the physiology of the long-range pathway and consequently the transmission time. Thus, the abnormal values observed in the target cortical area are result of distinct configurations of these MS-plaques. Figure 129 (a), (b) and (c) are respectively top views of plaque loads 7, 16 and 18 of table.

<table>
<thead>
<tr>
<th>Plaque load</th>
<th>Generation regime</th>
<th>Severity</th>
<th>Axons affected</th>
<th>Internodes affected</th>
<th>Lesions produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S-grouped</td>
<td>70%</td>
<td>25%</td>
<td>25%</td>
<td>1250</td>
</tr>
<tr>
<td>2</td>
<td>S-grouped</td>
<td>70%</td>
<td>25%</td>
<td>50%</td>
<td>2500</td>
</tr>
<tr>
<td>3</td>
<td>S-grouped</td>
<td>70%</td>
<td>50%</td>
<td>25%</td>
<td>2500</td>
</tr>
<tr>
<td>4</td>
<td>S-grouped</td>
<td>70%</td>
<td>50%</td>
<td>50%</td>
<td>5000</td>
</tr>
<tr>
<td>5</td>
<td>S-grouped</td>
<td>35%</td>
<td>25%</td>
<td>25%</td>
<td>1250</td>
</tr>
<tr>
<td>6</td>
<td>S-grouped</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
<td>2500</td>
</tr>
<tr>
<td>7</td>
<td>S-grouped</td>
<td>35%</td>
<td>50%</td>
<td>25%</td>
<td>2500</td>
</tr>
<tr>
<td>8</td>
<td>S-grouped</td>
<td>35%</td>
<td>50%</td>
<td>50%</td>
<td>5000</td>
</tr>
<tr>
<td>9</td>
<td>M-grouped</td>
<td>70%</td>
<td>25%</td>
<td>25%</td>
<td>1244</td>
</tr>
<tr>
<td>10</td>
<td>M-grouped</td>
<td>70%</td>
<td>25%</td>
<td>50%</td>
<td>2485</td>
</tr>
<tr>
<td>11</td>
<td>M-grouped</td>
<td>70%</td>
<td>50%</td>
<td>25%</td>
<td>2490</td>
</tr>
<tr>
<td>12</td>
<td>M-grouped</td>
<td>70%</td>
<td>50%</td>
<td>50%</td>
<td>4973</td>
</tr>
<tr>
<td>13</td>
<td>M-grouped</td>
<td>35%</td>
<td>25%</td>
<td>25%</td>
<td>1312</td>
</tr>
<tr>
<td>14</td>
<td>M-grouped</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
<td>2487</td>
</tr>
<tr>
<td>15</td>
<td>M-grouped</td>
<td>35%</td>
<td>50%</td>
<td>25%</td>
<td>2169</td>
</tr>
<tr>
<td>16</td>
<td>M-grouped</td>
<td>35%</td>
<td>50%</td>
<td>50%</td>
<td>4978</td>
</tr>
<tr>
<td>17</td>
<td>Scattered</td>
<td>70%</td>
<td>25%</td>
<td>25%</td>
<td>1245</td>
</tr>
<tr>
<td>18</td>
<td>Scattered</td>
<td>70%</td>
<td>25%</td>
<td>50%</td>
<td>2496</td>
</tr>
<tr>
<td>19</td>
<td>Scattered</td>
<td>70%</td>
<td>50%</td>
<td>25%</td>
<td>2497</td>
</tr>
<tr>
<td>20</td>
<td>Scattered</td>
<td>70%</td>
<td>50%</td>
<td>50%</td>
<td>4974</td>
</tr>
<tr>
<td>21</td>
<td>Scattered</td>
<td>35%</td>
<td>25%</td>
<td>25%</td>
<td>1145</td>
</tr>
<tr>
<td>22</td>
<td>Scattered</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
<td>2488</td>
</tr>
<tr>
<td>23</td>
<td>Scattered</td>
<td>35%</td>
<td>50%</td>
<td>25%</td>
<td>2485</td>
</tr>
<tr>
<td>24</td>
<td>Scattered</td>
<td>35%</td>
<td>50%</td>
<td>50%</td>
<td>4982</td>
</tr>
</tbody>
</table>

Table 52 – Parameters utilized for lesions generation of initial simulation of MS-plaque model
Figure 129 – Top view of generated MS-plaque layouts: (a) spatially-grouped (b) moderately-grouped (c) scattered
F.2.2 Synaptic-like data

To produce a realistic environment for the MS-plaque simulation, the simulated pathway required artificial axons and their associated synapses. To produce this data, an MLP neural network was used and trained. The weights of this network function then as the non-linear mechanism of two hypothetical communicating cerebral regions.

The routine that generates this data set was executed only once, as the non-linear relation learnt by the network and the synaptic-like data did not change for the purpose of these simulations. As a consequence of that, the network output should be always the same unless external factors cause disruption to its functioning. And this is exactly what happens when the MS-plaque data is applied to part of its axons. Later on this appendix, observable disruptions to neurocommunications are measured and compared.

The selected network topology for all simulations in this section was kept as simple as two input cortical areas, connected via 100 ‘myelinated’ axons to a third area ‘distant’ from the others. Each axon has the same physical characteristics specified before.

F.3 Simulations (of this early part of the MS-plaque)

F.3.1 Simulation 1: control versus MS-plaques

The common practice among all simulations here was to compare the network output when control data were used (i.e. no plaques), to predictive values produced by the network when plaque-like data were utilised (i.e. MS-plaque model).

In the particular case of this first group of simulations the aim was to observe the discrepancies between control and abnormal predicted values. Note that inputs to all topologies tested here were the same, and the output results for the normal case were used as the baseline.

Figure 130 shows the square errors between control and abnormal outputs for all testing patterns. The thick solid line represents control results and the other lines represent output errors for the various tested MS-plaques, i.e. the averages among various groups of features investigated. Note that the number of affected axons, internodes, and the severity of the plaques are the grouping criteria used for plotting the graphic rather than the overall regime of generation. The chart also shows that there are no other natural candidates for explaining output discrepancies other than (a) the absolute number of damaged internodes, (b) percentages of internodes affected and (c) average severity of the plaques. Among all these factors no one seems to be as
influential as the percentage of affected axons. To observe this, refer to the sub-title of the same figure; specifically when the percentage of affected axons assumes the tested value of 50%. Conversely, the graph also shows that when this feature assumes the other possible value tested, i.e. 25%, the output errors fall to the lowest level possible.

![Figure 130 – Output error under various MS-plaque configurations](image)

F.3.2 Simulation 2: control versus MS-plaques (varying time-window)

This group of simulations involves the same kind of comparison presented before, i.e. comparison between control and abnormal output of the network. However, on this occasion a time-window was used on the target cortical area for including or excluding axons that have their signals delayed more than expected.

The objective of the present set-up is to investigate how the output values produced by the MS-plaque model change when the generated plaques are simulated using a variable time window to monitor the number of axons that fail to deliver their signal to the target area.

One conclusion that arises is – given extra time to the pathway – it may be possible that some failing axons can achieve their mission, which is of delivering signals to the output (i.e. target cortical area). Consequently, the output error is likely to be reduced.
The two graphics presented in Figure 131 show how additional processing time can reduce the number of failing axons (top) and the output square error to all the plaques simulated (bottom). In other words, the two graphics show how the simulated pathway behaves when MS-plaques damage it, hence requiring more time to transmit the original signal in case of greater damages.

Figure 131 – Number of failing axons (top) and output square error (bottom) per time-windows
F.3.3 Simulation 3: MS-plaque growth

The last group of simulations – different from previous two – analyses the impact in the signal transmission (i.e. delays) when MS-plaques present increases in their size. The embedded idea here is of predicting impacts on neurocommunications of progressive growth of MS-plaques. Ultimately, this progression is responsible for most of the observable clinical effects characteristic of the disease. This simulation also incorporates notions of varying time-window and network outputs comparisons.

Before discussing the results a new concept needs to be looked at, that is plaque growth regime. The need for defining growth regimes for the plaque arose when the algorithm that calculates the ‘new’ plaque load was to be implemented. The problem was then how to implement changes to the plaques so they were characterised as having increased their damaging features on the myelin.

Three distinct methods had been devised for the MS plaques to evolve. The first method of plaque ‘growth’ was (i) to modifying the severity of individual damages to the internodes leading to decreases in the axonal overall transmission speed; a second growth regime was (ii) to consider new internodes of the same already affected axons to be become also affected (longitudinal growth). This means that, healthy internodes of affected axons that are located within the vicinity of a pre-existing plaque, they are likely to present damage. The last devised growth regime uses the same principle just explained, but this time it was applied to (iii) neighbour axons (i.e. leading to a transversal growth of plaques). Although not necessarily the most plausible of the three devised growth regimes for the MS-plaques, the first method was selected to illustrate the idea of having plaque load evolving through time because of its localistic implication (i.e. an appealing approach if medical imaging are to be used for extracting lesion-loads). Examples of other growth regimes can be seen in chapter 7.

Figure 132 presents three top views of plaque load 16, under different stages of evolution, growth-wise. Darker colours in the three figures indicate increases – of 10%, 20%, and 30%, respectively – of damages impinged to myelin of original plaques. Compare these to the initial layout presented in Figure 129(b), i.e. the same plaque load.

The simulation results for all plaque loads and three stages of growth investigated (10 %, 20 %, and 30 % of size increase) show that the number of failing axons and the output square error exhibit a clear progressive tendency to be zeroed when more time is allowed for the pathway to process. Note that advanced stages of plaque growth only require more time for convergence of the model, i.e. axons to deliver their signals.
Figure 132 – Top view of plaque load 16 at 10% (top), 20% (mid) and 30% (bottom) of increased 'damage' to neurocommunications
Figure 133 shows how this phenomenon can be observed as the number of failing axons decreases with time, but this reduction is slightly retarded for larger plaques. So does the output square error, which can be seen in Figure 134.

Physiologically this effect is an illustration of what happens with MS patients, when they are performing – for example – some motor tasks. These patients most likely have their movements slowed down, but stay able to perform them almost until advanced stages of their diseases. Of course, such observations are patient dependent as MS symptoms are highly depending on individual lesions load. Another example of plaques slowing down neurocommunications, which is ubiquitous in MS patients, is a clinical symptom called double vision. Diplopia is a result of inflammatory processes of the optic nerve causing asymmetric conduction delays in the two visual pathways.

![Figure 133](image)

**Figure 133** – Number of failing axons (average of all patterns, three growth stages, and plaque load 16)

![Figure 134](image)

**Figure 134** – Output square error (average of all patterns, three growth stages, and plaque load 16)
Final note from the author

This work was not possible without examples and primarily inspirations given by:

Fernando\(^{63}\) (in memoriam)

Nazinha\(^{64}\) (in memoriam)

The early classical thinkers\(^{65}\)

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\(^{63}\) My father and paradigm of how a good human being should be; he was the first to show me by his own example the importance of sociability, resourcefulness, and altruism.

\(^{64}\) My grandmother and other paradigm; she also showed me for the first time by her personal example qualities such as endurance, faith, and thankfulness.

\(^{65}\) The ‘Greeks’ were inspirational to me throughout my green years, and of course they have ignited this “revolution” so called science by simply wondering about “mysteries”, interconnections and “reasons” of nature, ultimately, of God.
“Understanding and modelling nature is one of the ultimate aspirations of man in order to prove his superiority above other beings and elements. One could say that science is the most secure path to achieving this archetypal dream. Our work has the aim to be one more brick along the long way ahead”

Fernando Buarque, 3rd November of 1999.