

A pipeline for the Analysis of Multilayer Brain Networks

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Abstract. The formalism of multilayer networks (MLN) makes possible to model and understand the multiple relationships between entities in a system. Indeed, this representation has found its way into a wide range of disciplines, particularly in the fields of neuroscience and neuroimaging. Human brain modelling made possible the identification of the basis for the construction of morphological, structural and functional brain connectivity networks.

In this work, we propose the design and implementation of a software pipeline for the construction and analysis of multilayer brain networks. This approach aims to identify groups of strongly connected nodes within the network and to evaluate the resulting communities. We examined 10 healthy subjects and 10 patients with multiple sclerosis. We analyzed the brain MLN by applying community detection algorithm that identified recurrent communities in patients with multiple sclerosis. To assess the structure of communities within the network, we calculate modularity indices for each subject. Finally, we confirm what has already been found in the literature, i.e. a high modularity in the brain networks of diseased subjects compared to those of healthy subjects. Future developments could involve aligning these networks to identify common patterns among multiple sclerosis patients and potentially identify subgroups of patients with similar neural characteristics.

Keywords: Multilayer Network · Brain Network · Community Detection · Modularity.

Introduction

In the last decades, network theory has undergone a profound evolution as an interdisciplinary field that combines methods and graph theories to study complex phenomena. Multilayer networks are an essential tool for understanding multiple interactions between elements of the same type, connected through edges

between the different layers or levels of a system. They are a mathematical extension [6] of traditional networks that find a place in a wide range of fields, from human and social sciences to computer science, from biology to medicine. Particularly, in the field of neuroscience and neuroimaging, multilayer networks summarise the concept of 'brain networks' to explain and model the structure and function of the brain. Starting from this concept, the intersection of network science and neuroscience has made it possible to understand precisely how multilayer networks facilitate this approach. In fact, the literature shows how multilayer modelling offers a unique opportunity to take into account the simultaneous existence of different types of relationships by including multiple network layers to explicitly represent the characteristics and functionality of the brain [5]. Specifically, we aim to bridge the gap in existing methodologies [18] [23] by offering a comprehensive approach integrating information from multiple layers of brain connectivity, including structural, morphological and functional aspects.

The origins and evolution of multilayer networks have been discussed extensively [14] [12], and each multilayer network model depends on how the layers and edges are implemented. In the simplest case, to describe a multilayer network one defines a set of entities as nodes, organised in different layers, whose edges connect nodes of the same layer (intra-layer) or of different layers (inter-layer). The human brain, on the other hand, is a complex system organised by a set of structural and functional relationships between its elements. It is represented as a graph that defines nodes as brain regions and edges as direct correlations between the various functionalities.

In this paper, we propose the design of a pipeline for the modelling and analysis of multilayer networks based on the functional and structural activity of the brain.

We used a public dataset provided by Jordi Casas et al. [4] on MRI images, from which we extracted 20 patients (10 healthy subjects and 10 multiple sclerosis patients). We using R programming [19, 19] to model brain connectivity matrices in a multilayer network. We also illustrate the difference between the two groups of patients (healthy and MS patients) by computing modularity and analysing the characteristics of recurrent communities associated with particular brain regions in patients with multiple sclerosis.

The rest of paper is organised as follows: In Section 1, we present background of a multilayer network, in particular the approach used in brain networks. In Section 2, we describe the proposed dataset and pipeline modelling techniques. In section 3, we discuss the data extracted from the analysis conducted on multilayer networks. We discuss the processed dataset and compare the results obtained. Finally, in the 4 section, we summarize and conclude the paper.

1 Background

In this section, we discuss the background of multilayer networks, outlining their main features and their strength in modelling complex systems.

Furthermore, we explore how this powerful paradigm has been adopted in the analysis of brain networks, highlighting the relationship between brain structure and function.

1.1 Definition of multilayer networks

Multilayer networks present an important architecture within network theory, involving the stratification of multiple layers of interconnections for understanding complex systems. In a multilayer network, each layer can represent a different connection or a different type of relationship between the elements of the system, allowing for a more accurate modelling of its structure and dynamics. Given a set of N nodes and L layers, a multilayer network is described as a quadruple $G = (N, L, V, E)$ where (V, E) is a graph $V \subseteq N \times L$ and $E \subseteq V \times V$ [13].

For definition, the set of nodes N represents the actors of the system, the set of layers L represent the interconnections and relationships of the system. Furthermore, entities of the graph may exist on different layers and assume different types of relationships. A distinction is made between intra-layer and inter-layer edges, the former connect nodes belonging to the same layer; inter-layer nodes, on the other hand, connect vertices of two distinct layers, as depicted in Fig. 1.

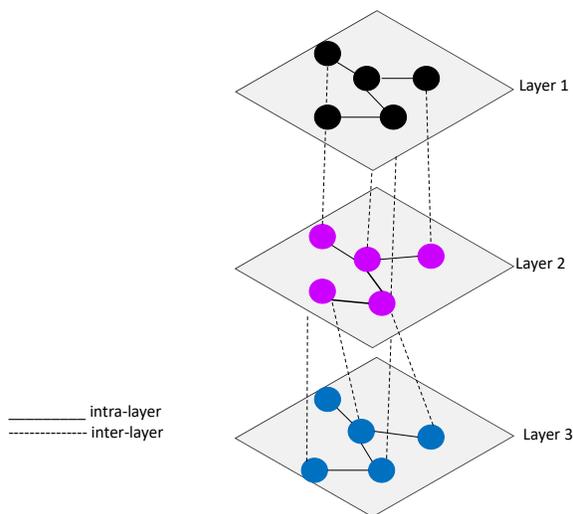


Fig. 1. Example of a multi-layer network. The figure illustrates the general model of a multilayer network, in which there is a set of nodes V , which can be connected to each other in pairs, either within the layers or across the layers themselves. Furthermore, the edges of a multilayer graph connecting nodes of the same layer are described as intra-layer (illustrated by the solid lines), and inter-layer connecting nodes of two different layers (illustrated by the dashed lines).

The definition of a multilayer network provides a more broad version, although the general model allows the specification of most systems that include the different interactions between entities; each layer may contain a complete set of nodes or a subset of them. Depending on the type of implementation and according to the network's conformation, it assumes different terminology, Kivela et al. [14] outline a general framework associating each type of network (Multiplex, Interconnected, Multilevel, Hypergraph) with each characteristic.

1.2 Brain Network Applications

The role that multilayer networks assume in the field of neuroscience and neuroimaging has become crucial, providing key insights into the possibility of modelling functional and structural connectivity between different areas of the human brain. In fact, based on the network concept, particularly multilayer networks, the human brain can be considered a complex network consisting of nodes that correspond to brain regions and edges that refer to structural or functional connections between these regions [16]. Multilayer brain network modelling approaches have been extensively employed to provide insights both into mechanisms of brain structure and function by investigating the topological characteristics of the network; but also into the diagnosis and treatment of brain diseases, as well as to deepen the understanding of cognitive and neurological processes (computational modelling). Specifically, the structural connectivity of the brain refers to the physical organisation of neural connections within the brain and their anatomical integrity and organisation [24]. Data are observed by means of diffusion tensor magnetic resonance imaging (DTI), which allows the direct mapping of neural fibres in the brain and the assessment of their integrity and organisation. This information is represented as multilayer networks, where each layer reflects a different connection mode, such as connectivity between cortical regions or connections between brain areas and white matter fibres [3].

Functional connectivity refers to patterns of synchronised neuronal activity between different brain regions during the performance of cognitive tasks or under resting conditions. This synchronisation can be measured using brain imaging techniques such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) [10]. Functional brain networks reveal the neural circuits involved in cognitive, emotional and behavioural processes [22]. From a diagnostic point of view, through the analysis of alterations in the structure and function of brain networks, it is possible to identify biomarkers for neurodegenerative diseases such as Alzheimer's [15], Parkinson's [26] or post-traumatic stress disorder [21].

Finally, brain networks are widely used in computational brain modelling to simulate cognitive and neurological processes. Through computational models based on multilayer networks, researchers can explore the complex dynamics of the brain and test hypotheses about its organisation and functioning [25]. This holistic approach provides a comprehensive view of the complexity of the brain. In fact, the different brain regions that constitute the nodes of the network, supplemented by the multiple layers that each respectively represent the brain

modalities already discussed, represent the right methodology for understanding complex neural processes.

2 Materials and methods

This section presents the developed pipelines.

2.1 Data source

The data were obtained from a public dataset made available by the authors (<https://github.com/ADaS-Lab/Multilayer-MRI/tree/main>). The dataset comprises: the adjacency matrices obtained from structural, morphological and functional MRI of 142 subject samples, from which we extracted 10 healthy subjects and 10 patients with relapsing-remitting multiple sclerosis (MS). Each network has 76 label nodes, specifying each of the 76 brain regions.

2.2 Construction and analysis of multilayer networks

The pipeline for modeling and analysis of multilayer networks includes 3 steps, as depicted in Fig 2 :

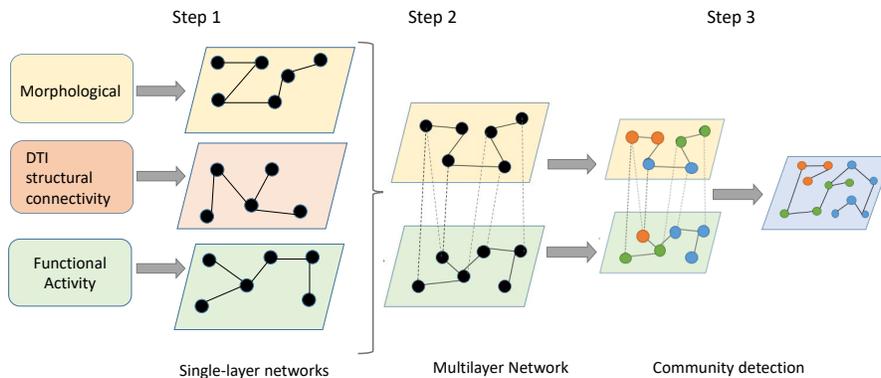


Fig. 2. Outline of workflow definition on pipeline development. Extraction of the functional, morphological and structural brain connectivity matrices and modeling of the individual network. Implementation of the multilayer network by combining the three of information, application of community detection algorithms to perform the analysis, and calculation of modularity indices to evaluate the structure of the network.

1. The first step consists of constructing the single-layer networks using the connectivity information extracted from the adjacency matrices. Functional matrices represent the connectivity of brain areas based on neuronal activity measured during the resting state of the brain (RS). Structural matrices reflect structural connectivity based on fractional anisotropy (FA) weighted connectivity, highlighting the directionality of nerve fibres and their structural integrity. Morphological matrices provide information on the morphological association of the grey matter (GM). From these matrices, the list of arcs (edge list) is extracted for each network, thus modelling single-layer networks. In this context, these are unweighted networks, so the edgelist consists of a row with two elements, the indication of the starting node and the ending node. For each subject, three monolayer networks were generated corresponding to structural connectivity by DTI, functional activity by rs-fMRI and morphological representation.
2. Multilayer network construction. The second phase consists in modelling the multilayer network by combining the three single-layer networks. The output is a multilayer network composed of layers representing morphology and functional activity, and DTI structural connectivity encoding the intra-layer connections of the network. The nodes of the cerebral networks are all constructed by 76 labels, representing the same object in each of the different layers and representing a particular brain region.
3. Analysis of multilayer network. The third step consists in the analysis of multilayer networks, through community extraction (to extract the set of densely connected nodes) and the calculation of modularity indices (evaluating the quality of the results). Community extraction for each network was performed by applying *infomap* [7] [8], a community detection algorithm for multilayer networks. It is based on the concept of finding optimal information structures within the network, interpreting links as information flows that seek to find a balance between the compression of the network structure and the discovery of distinct communities. Modularity, on the other hand, allows the evaluation of the resulting communities and provides an indication of the modular structure of the network: a higher value indicates a greater separation and distinction between communities, while a lower value suggests a more homogeneous network structure.

The code was run in R version 4.3.0.

3 Result and discussion

From the dataset, we extracted information from 20 subjects, 10 healthy and 10 relapsing-remitting multiple sclerosis patients. From the combination of functional, structural and morphological monolayer brain networks, we modeled a multilayer network for each patient. The characteristics of these networks are detailed in the tab 1 for MS patients, and in tab 2 for healthy subjects.

Table 1. The table describes the information for each MS patients network: the number of nodes and the number of edges belonging to each layer.

Brain MLN MS patients	Nodes	Edges	Layer
P1	1	68	291
	2	74	282
	3	43	274
P2	1	54	174
	2	34	147
	3	34	147
P3	1	67	306
	2	52	101
	3	29	109
P4	1	57	247
	2	63	121
	3	31	115
P5	1	56	188
	2	67	186
	3	39	163
P6	1	56	208
	2	63	168
	3	40	180
P7	1	73	495
	2	62	261
	3	54	285
P8	1	71	337
	2	73	419
	3	29	120
P9	1	138	525
	2	70	359
	3	47	322
P10	1	74	607
	2	74	535
	3	39	195

Table 2. The table describes the information for each Healthy Subject network: the number of nodes and the number of edges belonging to each layer.

Brain MLN Healthy Subject	Nodes	Edges	Layer
S1	1	75	209
	2	75	368
	3	40	840
S2	1	72	668
	2	75	368
	3	45	220
S3	1	70	449
	2	74	691
	3	38	255
S4	1	49	360
	2	73	297
	3	36	213
S5	1	72	834
	2	59	215
	3	36	181
S6	1	75	935
	2	71	477
	3	52	379
S7	1	72	500
	2	70	835
	3	56	314
S8	1	73	517
	2	50	249
	3	63	354
S9	1	62	396
	2	64	396
	3	56	292
S10	1	75	926
	2	72	510
	3	51	301

The analysis conducted on the modelled multilayer networks is based on the application of a community extraction algorithm. According to the literature, by performing a detailed evaluation of community detection algorithms, Infomap emerges as the only one that offers the optimal or near-optimal performance throughout [2]. In fact, it was observed that this algorithm revealed the presence of recurrent communities in MS patients, involved such as amygdala [20], brainstem and hippocampus [17]. In addition, we compared patients' brain networks with those of healthy subjects, revealing significant differences in modularity and network structure. In particular, we confirmed what is reported in the literature of greater modularity in the brain networks of patients with MS, for example Abdolizadeh et al. showed that subjects with MS had a higher modularity and a lower overall efficiency than the controls [1]. Studies reveal that already in single-layer functional connectivity networks there is greater modularity in MS patients than healthy subjects [9]. For example, Gamboa et al. found that the resting brain networks of MS patients showed a greater modularity of the network, ie a decrease in functional integration between distinct functional modules [11];

The following tables provide detailed information on the conducted analysis tab 3, tab 4. These tables offer a comprehensive description of the communities extracted using the applied algorithm, as well as the results of the modularity index analysis between the brain networks of patients with multiple sclerosis (MS) and those of healthy subjects.

We statistically examined the mean and variance of the modularity indices in the two groups to confirm the significance of the observed differences. Fig 3 and Fig 4 depict box plots illustrating the statistical analysis conducted on the modularity values in the two groups.

4 Conclusion

The success of network theory in the study of complex systems has highlighted the advantages of using multilayer networks to model the multiple relationships between entities in a complex system such as the brain.

In this paper, we have focused on the application of multilayer networks in the context of neuroscience, with the aim of understanding the structure and function of the human brain in a more detailed and accurate manner. The representation of the brain as a multilayer network allows the integration of information from different sources and acquisition modalities, such as structural and functional MRI images, to obtain a more complete and in-depth view of brain dynamics. Therefore, the main objective of this study was to construct a workflow based on the design of a pipeline to analyse a public dataset of relapsing-remitting multiple sclerosis patients and healthy subjects.

We have identified recurring nodes within communities extracted from multilayered brain networks of patients with multiple sclerosis, allowing us to observe the presence of similar neural structures among patients. This suggests that community detection is able to extract a significant region involved in multiple

Table 3. The table presents the number of communities identified in each brain multilayer network (MLN) for both MS patients and healthy patients. The rows represent the MLNs, with each cell indicating the number of communities detected within the respective MLN for both patient groups.

Brain MLN		Community Detection Results
M	N 1.	4
S	N 2.	2
	N 3.	9
P	N 4.	5
A	N 5.	6
T	N 6.	10
I	N 7.	7
E	N 8.	1
N	N 9.	8
T	N 10.	1
S	N 1.	5
	N 2.	3
	N 3.	2
	N 4.	7
	N 5.	9
	N 6.	1
	N 7.	2
	N 8.	10
	N 9.	4
	N 10.	2

Table 4. The table describes the values of the modularity indices calculated for healthy volunteers and MS patients.

Healthy Subjects	Multiple sclerosis patients
0.208	0.237
0.166	0.256
0.111	0.362
0.305	0.437
0.343	0.593
0.104	0.5790
0.117	0.479
0.454	0.134
0.184	0.376
0.114	0.114

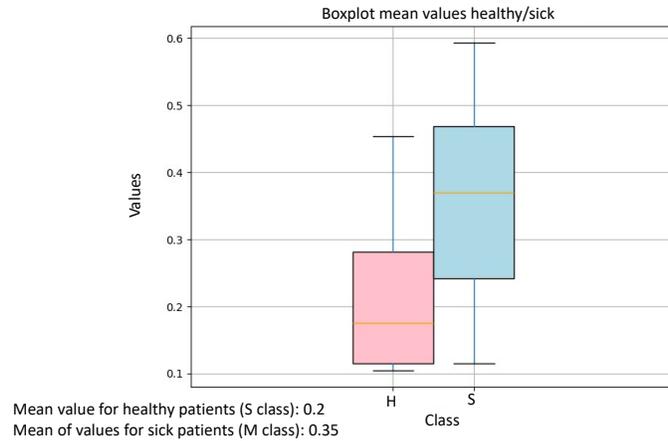


Fig. 3. Boxplot of the mean of the extracted modularity indices. Healthy subjects are shown in pink and MS patients in light blue.

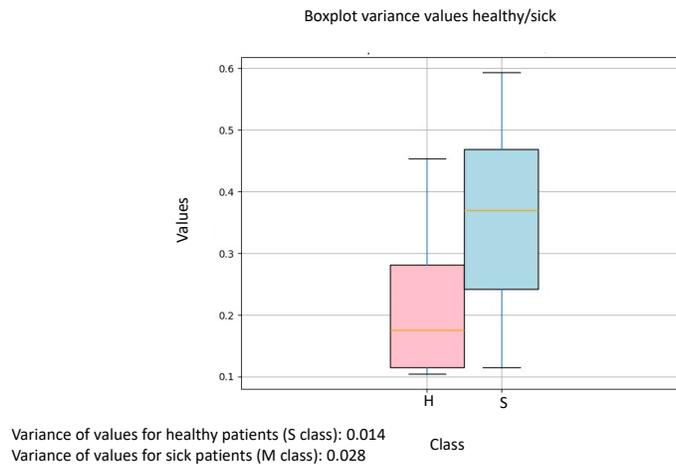


Fig. 4. Boxplot of the variance of the extracted modularity indices. Healthy subjects are shown in pink and MS patients in light blue.

sclerosis and that specific brain regions tend to be involved in a similar or related way in the pathogenesis of the disease. Moreover, the statistical analysis on the extracted modularity indices underscores the importance of modularity as a measure for understanding the structure of communities within networks, espe-

cially neural networks in pathological conditions, offering valuable insights into the development of analysis strategies needed to completely understand disease characteristics.

Future developments could involve aligning these networks to identify common patterns among multiple sclerosis patients and identify possible subgroups of patients with similar neural characteristics.

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