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Diagnosis of neurological diseases based on data mining and complex network

Caroline Lourenço Alves[1]
Instituto de Ciências Matemáticas e de Computação, ICMC
Universidade de São Paulo, USP, São Carlos, SP
Francisco Aparecido Rodrigues[2]
Instituto de Ciências Matemáticas e de Computação, ICMC
Universidade de São Paulo, USP, São Carlos, SP

Abstact. A data mining and knowledge discovery is in a field of research, with applications in different areas, as in medicine, its methods have proven very effective in performing automatic diagnostics, helping in making decisions by medical teams. In addition to the use of data mining, medical data can be represented by complex networks in order to include connections between its elements. For example, in the case of the brain, cortical regions can represent vertices in a graph and the connections can be defined through cortical activities. Thus, we can compare the brain structure of healthy patients with those of patients with mental disorder in order to defibe methods for diagnosis and to obtain knowledge about how the structure of the brain is related to behavioral and neurological changes. Here, we are interested in using data mining methods and complex networks to classify patients with four different types of mental desorders, that is, schizophrenia, autism, attention deficit / hyperactivity disorder, and progressive supranuclear paralysis.

Keywords. Articial Intelligence, Data Mining, Complex Networks, Neurological Diseases.

1 Introduction

1.1 Context of the study

Data mining methods have been widely used in the medical field in order to offer more accurate and automatic diagnoses of various diseases [1]. Among the main applications, we can cite the diagnosis by imaging, as in the oncological area (mainly breast cancer) [2–5]; in the neurophysiological area [6–8]; and heart disease [9, 10].

In addition to the use of data mining, complex network representation has been used successfully to characterize the structure of several biological systems [11], mainly the

[1]caroline.lourenco.alves@usp.br
[2]francisco@icmc.usp.br

brain [12]. The network area consists of the use of graphs to represent the structure of complex systems [13]. At the end of the 1990s, in order to represent and analyze the dynamics of different complex systems, the theory of complex networks [14, 15] was introduced, gaining importance since 1999 when the topology of the internet networks [16] and World Wide Web [15] were mapped [13].

1.2 Motivation

In neuroscience, the use of networks has allowed a better understanding of the organization of the brain [17]. Several neurological diseases have been studied from a network perspective and several studies have been carried out in an attempt to understand how behavioral changes are related to brain organization [18].

However, several neurological diseases haven't yet been studied in terms of networks and many of them are difficult to diagnose and are often confused with other diseases. This causes great social and mental harm to the patient, who often remain a long time being treated and misdiagnosed.

1.3 The aim of study

In this work, we are interested in the use of data mining methods and complex networks in order to classify patients according to four types of neurological diseases. Basically, we will consider data obtained by functional magnetic resonance imaging (fMRI) and represent a cortical structure of the brain of healthy patients and patients with brain disorder. From this representation, we extracted measurements of the networks, which represent the set of attributes of each patient, which constitutes an observation in the data set.

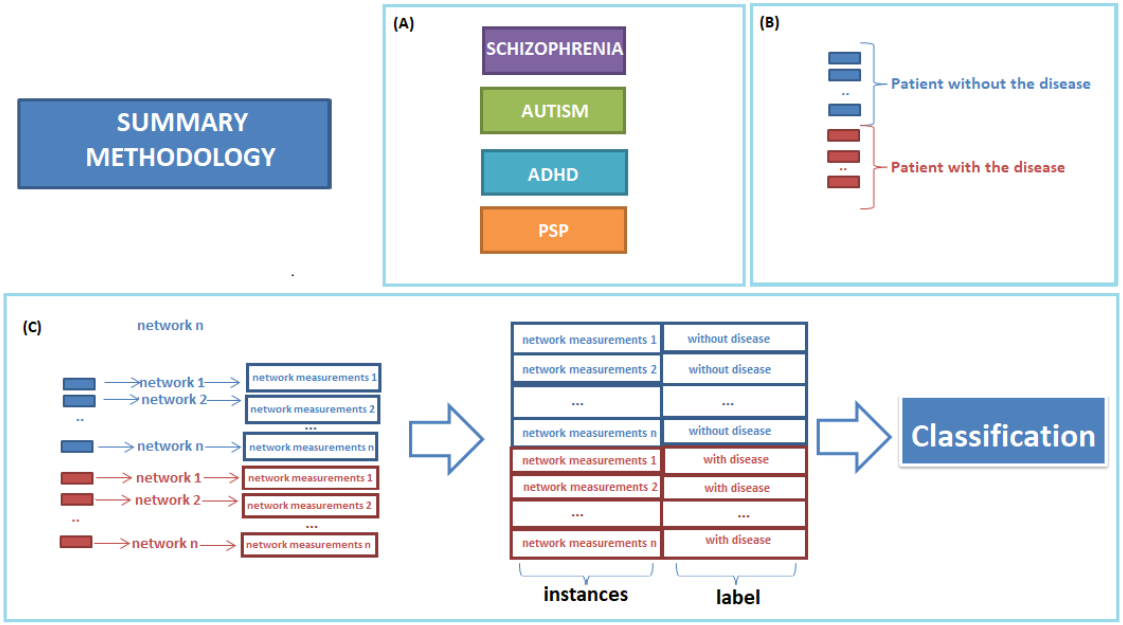
Furthermore, to achieve the aim of our research, we used various data mining algorithms, selection methods and normalization in order to create predictive models that best discriminate the two classes.

2 Methodology

As already mentioned 1, the aim of this study is to generate predictive models capable of discriminating two classes (of patients with certain mental illness and healthy people) in order to assist in the automatic diagnosis of metal diseases. In order to reach this objective, cortical networks of four databases related to the following neurological diseases were analyzed: (i) schizophrenia, (ii) autism, (iii) attention deficit / hyperactivity disorder and (iv) nuclear progressive paralysis. Each database contains networks of patients with one of these diseases and healthy people. For each network, some network measures were extracted, which served as attributes for predictive algorithms to discriminate the two classes (with or without the disease). These steps were diagrammatize in the figure 1.

In the following subsections we describe the methodology used for each database.

Figura 1: Schematization of the methodology used in the present work. Four bases, represented in (A) by four rectangles: purple, green, blue and orange, corresponding respectively to diseases: schizophrenia, autism, attention deficit / hyperactivity disorder (ADHD) and progressive nuclear paralysis (PSP) . Each of the bases contains matrices of connectivities, represented in(B) with rectangles, which in blue are those referring to the patients without the disease, and in red, to those referring to patients with the disease. For each of these matrices, they correspond to a network; and, for each network, a series of measures of networks were extracted that served as an instance for the classification, as can be seen in (C).



2.1 Schizophrenia database

2.1.1 Database

The database was extracted from [19][3] and obtained from the fMRI technique in two groups of volunteers: 20 healthy participants and 19 patients childhood-onset schizophrenia (COS), being their average age of 18.7 and they were recruited from the National Institutes of Health (NIH).

Participants were submitted to the MRI scanner operating at 1.5T General Electric Signa at the NHI clinical center in Bethesda, Maryland in the United States.

2.1.2 Methodology

We've extracted the following measures, as well as litetura in which the choice of them was based:

- The measures present in [19]: average of the degree distribution, shortest path, efficiency and clustering coefficient (which was calculated by the transitivity formula).
- The measures present in [13]: betweennees centrality, closeness centrality, k-core, assortatividade.
- The measures present in [20–28]: second moment of degree distribution, complexity, eigenvector centrality, diameter, entropy of the degree distribution, knn and pagerank.

These measures were extracted for each of the networks resulting in a file with 13 attributes corresponding to the measures and the class to which they belong (normal or with schizophrenia, COS). The classification was done in this file obtained with the following algorithms:Naive Bayes, KNN, decision trees, neural networks. The use of these was based on the classifiers used to classify data related to schizophrenia [28–32].

In order to make the predictive model more reliable, we used k-fold cross-validation with $k = 10$ based on some articles found [33–38] that employed this value in the case of predictive models applied to medical data. For each of these classifiers some parameters were used in the package *caret* in the statistical software R. In the case of the k-NN classifier, we used 'knn' [39] and the Euclidean distance metric [40]. For the decision tree algorithm, we used the CART methodology (Classification and Regression Trees) whose choice occurred based on articles that employed this type of algorithm to medical data [41–43]. In the case of neural networks, the backpropagation algorithm was used based on the literature [44, 45], with a learning rate of 0.25 (based on [46, 47]) and the method used for neural networks was *'nnet'* [39].

In addition to these classifiers, they were also combined by means of the stacking technique using a generalized linear model.

Then we use the selection and normalization methods to increase the performance of the classifiers.

[3]Available in https://www.nimh.nih.gov/labs-at-nimh/research-areas/clinics-and-labs/chp/research-articles.shtml

2.2 ASD database

2.2.1 Database

The database used in this section [4] (as well as the other bases of the following two sections) were extracted from the *UMCD* (*USC Multimodal Connectivity Database*), being part of the project *Human project Connectome*, which has several studies whose goal is to unravel the connection of the human brain using neuroimaging. The database in question consisted of 60 children and adolescents with ASD (52 men and 8 women) and 45 normal (38 men and 7 women) recruited by the Center for Autism Research and Treatment (CART) of the University of California-Los Angeles (UCLA).

2.2.2 Methodology

We used a methodology similar to the one in the previous section, differing in some points, since the connectivity matrices available for this base were weighted. As in [48], which used the same database, the matrix was binarized using a *threshold* ranging from 0.15 (which according to the article, was minimum correlation required to be statistically significant) at 0.34 with the lowest end of the interval based on the requirement that all graphs be fully connected. Thus, in order to verify if the thresholds interfered in the prediction of the disorder, the following values were chosen: 0.3, 0.4, 0.5 and 0.6, thus generating binary graphs, being 79 different graphs for each of the values. The network measurements were extracted through igraph using the Python programming language (because an algorithm that read all the matrices at once was elaborated in the Pyhton environment). The measures chosen were the average of the degree distribution, the second moment of the degree distribution, mean clustering coefficient, transitivity, assortative, mean of the shostest paths, complexity, betweenness centrality, eigenvector centrality, closeness centrality, pageRank, diameter and central dominance, based on the previous section and in [48, 49]. In this first stage, we select the threshold that best improved the performance of the classifiers. Then, we used the methods of selection and normalization.

2.3 ADHD database

2.3.1 Database

The database [5] used consists of 520 connectivity matrices obtained from two types of groups: those who have a ADHD (190 patients) and healthy control (330 people). In addition, patients with this disease were subdivided into three classes: ADHD-Inattentive (74 patients characterized by symptoms such as inattention and difficulty concentrating on activities that require attention), ADHD-Hyperactive/Impulsive (7 patients, whose symptoms are characterized as restlessness, impatience and mood instability) and ADHD-Combined (109 patients who presented both symptoms of the two previous types). However, all three class types were agglutinated into a single so-called ADHD, since the primary

[4] Extracted fromhttp://umcd.humanconnectomeproject.org

[5] Available in: http://umcd.humanconnectomeproject.org/umcd

purpose was to discriminate between patients with the disease and those who are developing.

2.3.2 Methodology

We used the same methodology of the database related to autism (previous subsection), since it is also extracted from the USC Multimodal Connectivity Database, being the matrices of connectivity with weight.

Thus, the connectivity matrices with weight were transformed into binary as in other studies using this database [50–54], for this, the z-score normalization was performed and the thresholding and binarization process was used with values of 0.3, 0.4, 0.5 and 0.6. As mentioned in [50], the values of choice to transform the graphs into binaries is very subjective, so we choose this range of values to evaluate which of them contribute to the better performance of the classifiers. Thus, at each of these values, a different binary matrix is generated and in each of them the same network measures used in the base related to autism are extracted.These measures are classified by the same machine learning algorithms used before and then we use the selection and normalization methods.

2.4 PSP database

2.4.1 Database

The database [6] contained connectivity matrices corresponding to each one of the patients that were evaluated in the University of California, San Francisco (UCSF). Being 20 of them diagnosed with PSP according to the criterion determined in [55] and 12 healthy and it was ensured that the movement of the head was less than 3mm of the maximum translation, 3 degrees of maximum relative rotation, with acceptable head movement levels [56].

2.4.2 Methodology

We used threshold and binarization values of 0.3 based on [57], after performing z-score normalization in each connectivity matrix (which was also done in the article cited above), resulting in binary matrices.Then, we perform the same methodology of the two previous bases.

3 Results and discussion

In the present work, four networks bases, whose composition was of networks of patients with some neurological disease and healthy, analyzed. For each of these diseases, some network measures were extracted, which served as attributes for predictive algorithms to discriminate the two classes (with or without the disease).

The table 1 containing the performance of the best classifiers obtained by each base, from it we can conclude that decision tree was common to the four bases, indicating that

[6] Available in:http:*umcd.humanconnectomeproject.org*

this is a good algorithm for this type of classification. On the other hand, the table 2 contain the subsets of attributes for the highest performance classifiers for each base, from it we can observe the only measure common to all bases was the eigenvector centrality. For the bases Autism and ADHD in which there was variation of the values of binarization and thresholding (0,3-0.4-0.5-0.6), in both the value that increased the performance of the classifiers was 0.6.

In relation to the Schizophrenia basis, in terms of accuracy, the classifier that obtained the best performance (whose value was 82%) was that resulting from the combination of classifiers k-NN, naive bayes and neural networks, a value higher than that of [13], whose accuracy for Baysian networks was 79%.

As for the Autism-related basis, in [58], using the same base, the highest AUC obtained was 0.77 (by the classifier Supporting Machine Machine), and the worst 0.57 (by decision tree with boosting technique). Comparing, although the classifiers are different, the higher AUC obtained (0.71) is very close to that of the article and because other measures have been used, it makes the model more reliable. In other article [49], the authors also used the same basis and the classifier Vector-Machine Support, which obtained 0.64 accuracy, 0.61 specificity and 0.88 sensitivity. Although the classifiers were different, in this work the decision tree algorithm obtained a higher accuracy and sensitivity than in this article.

With respect to the ADHD base, in [59] using the same base, the accuracy of 61% was obtained using the SVM classifier (the threshold value used was 0.25) whose performance was inferior to this study. In [60], the SVM classifier obtain 64.48% of accuracy, 84.71% of specificity and 30.66% of sensitivity, so the accuracy and speci fi city of some classifiers in the present work was superior to that obtained in this article. In [51], the average performance of the algorithms used by the authors was 63.75%, which is less than the accuracy obtained by some classifiers in the present work. Also, the maximum accuracy reached in the ADHD-200 competition was 61.04%, which value is also lower than the values obtained here

For the PSP database, in the literature, the articles found related to it, focused on the structural analysis of the network of PSP patients, trying to identify the regions that differ most from a patient network without the disease. In the present study, we focused on something new, in order to classify network measures in an attempt to distinguish the two classes (of patients with PSP and healthy patients) and to predict patients with PSP.

4 Conclusion

The performance of the machine learning algorithms obtained in the present work with the bases related with schizophrenia, autism and ADHD was better than the one obtained in the literature. In the case of the PSP related base, we focused on something new (because the the literature focused on the structural analysis of the network of PSP patients), in order to classify network measures in an attempt to predict patients with PSP. Futhermore, the commonm algorithm that obtained a good performance in the four bases was the decision tree and the complex network mesuare was eigenvector centrality.

The results suggest that the extraction of measures of networks, as well as their clas-

Tabela 1: Table containing the best performing classifiers for each base. We highlighted, in bold, the decision tree, the algorithm common to all bases.

Database	**Classifiers**	**Acur.**	κ**(Acur.)**	Sens.	Esp.	AUC
Schizophrenia	**KNN**	0.72	0.44	0.70	0.85	0.83
	DT	**0.72**	**0.45**	**0.65**	**0.75**	**0.70**
	KNN and DT	0.72	0.43	0.70	0.75	0.82
	KNN e NB	0.72	0.50	0.65	0.85	0.75
	NB e NN	0.75	0.50	0.65	0.80	0.75
	NB e NN	0.75	0.50	0.65	0.80	0.75
	KNN, NB and DT	0.82	0.65	0.60	0.70	0.67
Autism	**DT**	**0.68**	**0.34**	**0.96**	**0.37**	**0.67**
	KNN e DT	0.63	0.23	0.90	0.35	0.69
	KNN, NN e DT	0.61	0.81	0.90	0.37	0.70
	KNN, NB e DT	0.65	0.28	0.75	0.55	0.69
ADHD	**DT**	**0.62**	**0.02**	**0.07**	**0.93**	**0.54**
	NN	0.631	0.04	0.09	0.95	0.56
	KNN e NN	0.63	0.01	0.06	0.95	0.60
	KNN e DT	0.63	0	0	0.98	0.56
	DT e NB	0.64	0.05	0.09	0.96	0.57
	DT and NN	0.63	0.01	0.02	0.98	0.57
	NB e NN	0.65	0.1	0.06	0.96	0.56
	KNN, NN and NB	0.62	0.01	0.06	0.95	0.53
	NB, NN and DT	0.65	0.07	0.03	0.95	0.57
	KNN, NN, DT and NB	0.64	0.04	0.14	0.93	0.60
PSP	**DT**	**0.65**	**0.17**	**0.90**	**0.40**	**0.63**
	KNN e DT	0.65	0.27	0.84	0.29	0.61
	KNN, NN and DT	0.66	0.24	0.90	0.22	0.54
	NB, NN e DT	0.71	0.37	0.80	0.23	0.65
	k-NN, AD e NB	0.71	0.39	0.82	0.38	0.65

Tabela 2: Table containing the best performance classifier for each dataset and the subset of attributes that contributed to this. In addition, the binarization and thresholding value for each base and standardization method used.

Database	Attributes subsets	Standardization method	Threshold value	Classifiers
Schizophrenia	-average degree distribution - second moment of degree distribution -characteristic path length -transitivity -betweennees centrality -closeness centrality -eigenvector centrality -k-core -Assortativity coefficient -complexity	-	-	DT
Autism	-average degree distribution -second moment of degree distribution -average local clustering coefficient -transitivity -Assortativity coefficient -characteristic path length -complexity -betweenness centrality -eigenvector centrality -closeness centrality -pageRank -diÃmetro -central point dominance	-	0.6	KNN, NN e DT
ADHD	-characteristic path length -eigenvector centrality -closeness centrality -Assortativity coefficient -average local clustering coefficient	softmax scaling	0.6	KNN and NB
PSP	-average local clustering coefficient -transitivity -complexity -second moment of degree distribution -eigenvector centrality	-	0.3	KNN, DT e NB

sification according to their label can auxiliary in the diagnosis of these diseases, since nowadays it is based on subjective criteria.

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