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Classification of preclinical markers in Alzheimer's disease via WiSARD classifier

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Abstract. Weightless Neural Networks (WNN) showed good results in various classification problems in different domains where a significant number of instances for each class was available. In this work, we present different WiSARD classifiers facing a quite difficult problem from both the clinical and the machine learning point of views: the classification of preclinical markers in Alzheimer's disease continuum patients. The four domain classes show overlapping molecular features and each has few instances (around 40). Together with improved class separation, the confirmation of the goodness of the results is given by a series of experiments that have compared the WiSARD classifiers to many state-of-the-art classifiers, even those ensembles, showing that the obtained results are very close to the top best models.

1 Introduction

Alzheimer's disease (AD) represents the principal neuronal dysfunction, and it is expected that ca. 75 million people will live with AD worldwide by 2030, causing a dramatic increase of the annual healthcare costs. The AD continuum from cognitively normal (CN) subjects begins with a Subjective Memory Decline (SMD), and via Mild Cognitive Impairment (MCI) reaches AD, with SMD timed 5-11 years, and MCI detected 1 to 5 years before reaching dementia. MCI subjects may not evolve into dementia as part of them revert to CN or do not progress to MCI, which is usually considered the first stage of dementia, including AD. An open question is whether subtle cognitive changes produce "molecular signs" before clinical manifestations appear.

Current state-of-the-art diagnostic tools analyze invasively biomatrices like cerebrospinal fluid (CSF), are costly like brain imaging, challenging (neuropsychological screening questionnaire) and often of restricted availability, while functional diagnostics requires noninvasivity and cost-effective tools to map the evolution of cognitive disorders.

Since about half a liter per day of CSF is drained from the brain into the blood, it can be considered a valuable biomatrix to investigate brain neurodegeneration.

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Presently, no robust and trustable blood-based biomarkers are available for diagnostic purposes. This opens several questions: Is this related to clinical heterogeneity of AD? Are biomarkers representative of a specific phenotype? Which is the acceptable prediction limit of a model based on blood biomarkers for the AD progression and diagnosis? We have used data from nuclear magnetic resonance (NMR)-based metabolomics of sera from CN, SMD, MCI and AD subjects to uncover preclinical markers characterizing the progression to AD [1]. Metabolomics investigates the disease molecular mechanisms and can distinguish phenotypical differences. Metabolites are downward products of transcriptome and proteome, and therefore they represent a more specific framework to understand complex biological outcomes.

Machine learning has been used to investigate Alzheimer's disease progression heterogeneity using data derived from postmortem brain samples [2]. In this paper, we investigated the CN-SMD-MCI-AD continuum by WNN aiming at uncovering molecular biomarkers useful to characterize the intermediate SMD and MCI stages to favor specific treatment at the onset of the pathology. Furthermore, the data were derived from NMR profiling of sera, pointing to a minimally invasive diagnostic approach.

2 The Alzheimer's disease data

Data were derived from ^{1}H-NMR spectra of serum samples acquired with a 600 MHz spectrometer and rearranged as a data matrix. Using the AMIX 3.9.15 software package (BrukerBioSpin GmbH, Rheinstetten, Germany), we performed an automatic data reduction to spectral integrated regions ("bins") of 0.04 ppm each, which represented the NMR features in columns for each observation (patient metabolic profile) in row. The obtained matrix consists of 170 instances (183 features for each) distributed in four unbalanced classes (see table 1).

In order to obtain significant data classification and extract useful clinical information, we face four different classification problems to discriminate:

- 1_2_3_4 – the four different patient metabolic profiles;
- 1_23_4 – CN, AD and all the intermediate profiles;
- 12_34 – "healthy" and "diseased" profiles;
- 123_4 – without and with AD.

In the next sections, the four different WiSARD classifiers [3], adopted and adapted to face these classification problems, will be introduced and results presented.

3 The WiSARD approach

WiSARD belongs to the class of WNNs, and it is based on a neural model which uses lookup tables to store the function computed by each neuron rather than

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ID	Classes	Instances
1	CN - Cognitive Normal	52
2	SMD - Subject Memory Decline	39
3	MCI - Mild Cognitive Impairment	39
4	AD - Alzheimer's Disease	40

Table 1: Classes and instances of the Alzheimer's disease dataset

storing it in weights of neuron connections [4]. WiSARD is characterised by a simple implementation and a fast learning phase due to one-way RAM access/lookup mechanism. WiSARD was originally conceived as a pattern recognition device mainly focusing on binary image processing [5] but showed good performance even in other different domains [6, 7, 8, 9]. In [3], it has been proved that WiSARD can be used as a multi-class classification method in machine learning domain for any data representation.

Dealing with four different classification problems (see section 2), we propose four different WiSARD classifier architectures: with four discriminators for 1_2_3_4, with three discriminators for 1_23_4 and with two discriminators for both 12_34 and 123_4. All of them work in the configuration of 16 bits and receive the set of features converted by a 2048 notch thermometer as input.

3.1 The classification process

Because of the small number of instances, for the experimental phase we gather the responses of the WiSARD classifiers using a cross validation based on the leave-one-out method and, moreover, those responses given by the systems on the remaining instances (discarded to balance the dataset). So, if the dataset consists of n instances, we generate n different training set with $n-1$ instances (see table 2). In this way, we have at least one instance for each class to be given as input to the WiSARD classifiers, in addition to the discarded ones. This ensure that the WiSARD classifiers are both trained with balanced classes and can classify all of the different instances of the intended classification problem. The same classification process has been carried out for the other classifiers reported in section 4.

	Instances per class				
Classification problem	1	2	3	4	Remaining instances
1_2_3_4	38	38	38	38	19
1_23_4	38	38		38	57
12_34	76		76		19
123_4	39			39	93

Table 2: Number of instances for each problem and for each class

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	1	2	3	4
1	33	7	11	1
2	13	16	8	2
3	9	6	18	6
4	3	4	8	25

	12	34
12	76	14
34	19	61

	123	4
123	121	9
4	13	27

	1	23	4
1	43	7	2
23	30	36	12
4	5	4	31

Table 3: Confusion matrices

4 Results

The results obtained by the WiSARD classifiers indicate that the four classes can hardly be distinguished (1_2_3_4 classification problem), while the separation between healthy and diseased patients with the rest (1_23_4 classification problem) is quite confused, as highlighted by the values reported in the light gray cells of table 3. A slightly better separation is obtained for 12_34 and 123_4. In fact, the percentage of misclassifications goes from 44% for 1_2_3_4 to 13% for 12_34, passing through 31% for 1_23_4 and the 19% for 123_4.

The results obtained by the WiSARD classifiers on classification problems 12_34 and 123_4 (see table 4) confirm that similarities exist between CN and SMI and between MCI and AD (12_34 classification problem), and for CN, SMI and MCI with AD (123_4 classification problem). This suggests that SMI and MCI classes oscillate between CN and AD most likely in ranges of specific molecular concentrations that should be quantified.

To evaluate the WiSARD classifiers performance from the machine learning point of view, we selected a number of state-of-the-art classifiers and compared the results. In addition, for a better comparison, among the chosen classifiers four ensemble classifiers have been included. The hyperparameters of the chosen classifiers have been set applying the Random Search method [10]. In order to choose an optimal configuration for each classifier, a grid of possible hyperparameters values has been set. Through different iterations (in our case 10 iterations, due to the number of classifiers involved in the comparison analysis), and with randomly generated hyperparameters values, we have chosen those classifier configurations that performed best. F-measure is the metric adopted to evaluate the classifiers performance.

Table 4 shows that Random Forest (RF) ranks first in two out of four classification problems, but it is followed very closely by the WiSARD classifiers. Score is calculated by adding the positions reached by the ranking in each classification problem.[1] One can notice that RF scored 9 while WiSARD 10 and the third method (Extra Trees Classifier) 13 confirming the good performance of the WiSARD classifiers.

As said before, all the results reported in table 4 relate with the information carried by this type of data (metabolic profiles).

[1] **Bold** - best results; *italic* - second best results; underline - third best results.

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		Approaches (F-measures – (Rank))				
Rank	Methods	1_2_3_4	12_34	123_4	1_23_4	Score
2	*WiSARD*	53.62 (4)	**80.44** (1)	81.36 (3)	*65.82* (2)	10
5	Logic Regression	53.88 (3)	71.57 (7)	76.78 (8)	63.80 (5)	23
9	Decision Tree	51.44 (5)	69.99 (9)	73.31 (10)	57.01 (9)	33
10	MultinomialNB	42.07 (11)	70.55 (8)	72.80 (11)	53.50 (10)	40
11	MLP	41.31 (12)	64.46 (12)	78.84 (5)	51.01 (12)	41
8	LDA	47.80 (9)	62.35 (13)	*81.60* (2)	61.03 (6)	30
12	KNC	43.94 (10)	67.46 (10)	70.62 (12)	52.70 (11)	43
6	GaussianNB	48.66 (8)	77.33 (3)	76.16 (9)	59.44 (7)	27
13	QDA	37.82 (13)	66.00 (11)	50.47 (13)	45.93 (13)	50
3	Extra-trees*	**57.88** (1)	76.88 (4)	80.71 (4)	64.95 (4)	13
6	AdaBoost*	49.01 (7)	75.87 (6)	78.50 (6)	58.61 (8)	27
4	Gradient Boosting*	50.08 (6)	*79.38* (2)	77.60 (7)	65.51 (3)	18
1	**Random Forest***	*54.18* (2)	76.35 (5)	**82.24** (1)	**66.20** (1)	9

Table 4: Results by approaches and by methods (*ensemble classifiers)

5 Conclusions and future works

The results presented in this work acknowledge that the intermediate stages SMD and MCI were less precisely classified. This is in line with the patients' heterogeneity indicated by clinical data, and rules out a "linear" molecular evolution of the pathology, pointing to the presence of overlapping "gray-zones" due to the reciprocal interference of the intermediate stages.

As a further development, pools of cascade classifiers will be developed to improve the system performance on the most difficult problems (1_2_3_4 and 1_23_4). Moreover, features selection methods will be adopted to understand whether the 183 features are all significant.

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