Artificial Intelligent Systems Based on Supervised HUMANN for Differential Diagnosis of Cognitive Impairment: Towards a 4P-HCDS

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Abstract. Differential and early diagnosis of cognitive impairment (CI) continues being one of the crucial points to which clinical medicine faces at every level of attention, and a significant public health concern. This work proposes new CI diagnostic tools based on a data fusion scheme, artificial neural networks and ensemble systems. Concretely we have designed a supervised HUMANN [1] with capacity of missing data processing (HUMANN-S) and a HUMANN-S ensemble system. These intelligent diagnostic systems are inside EDEVITALZH, a clinical virtual environment to assist the diagnosis and prognosis of CI, Alzheimer's disease and other dementias. Our proposal is a personalized, predictive, preventive, and participatory-healthcare delivery system (4P-HCDS) and is an optimal solution for an e-health framework. We explore their ability presenting preliminary results on differential diagnosis of CI using neuropsychological tests from 267 consultations on 30 patients by the Alzheimer's Patient Association of Gran Canaria.

Keywords: Cognitive Impairment; Dementia; Diagnosis; Alzheimer's Disease; Missing Data; *k*-fold Cross-validation, Neural Network Ensemble; HUMANN.

1 Introduction

Many sociological studies point out the world's population ages rapidly, primarily in developed countries. In Spain, the percentage of elder age population is 16,66%, with a progressive increase of over-aging of 4,52% and with a rising tendency. The neurological disorders that cause gradual loss of cognitive function, are the diseases with more interest in the aging.

This special interest is caused by its high prevalence, 5-10% in older than 65 years and more than 25%-30% in the very old ones, [2][3], when it is assessed CI in the elderly as an early stage of dementia, and because of the important repercussions that

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originate, in the scope of the patient, in the familiar, social and sanitary spheres [4]. Therefore, the differential diagnosis, as well as the early one, of CI are fundamental and continue to be one of the crucial points to which clinical medicine faces at every level of attention.

Three types of CI evaluation are possible. The first uses an open form, another is semi structured, and the third evaluation is carried out using the application of a series of cognitive evaluation scales. Several neuropsychological tests [5] have been developed and used to evaluate different cognitive sections of a patient throughout the years. It is not a simple task to define a clear relationship between test results and specific symptoms or different levels of CI. Other important problems in the use of these scales are the absence of universal cut points, trans-cultural difficulties and the level of precision that seems to be similar with the use of short or long scales [6].

All these handicaps, the high uncertainty diagnosis [7], and the degree of the underdiagnosis which is so crucial and can reach 95% of the cases in some settings [8], highlight the need to develop new and alternative methods and instruments of diagnosis, making special emphasis on early and differential diagnosis, and causing its use in all the sanitary scopes, in the specialized and the primary attention care.

Especially computer-intensive algorithms based on “ensemble learning”-methods that generate many classifiers and aggregate their results, are being developed in the last years in regard of CI and Alzheimer´s disease (AD) classification using as input essentially EEG abnormalities associated with the analyzed pathology [9][2]. We have previously developed Counterpropagation based multi-net systems to diagnose neuro decline processes related to aging [10].

We propose new diagnostic tools based on a data fusion scheme using artificial neural networks and ensemble systems. Concretely we have designed two HUMANN-S based systems, where HUMANN-S is the supervised version of HUMANN architecture, with capacity of missing data processing. These systems are, a HUMANN-S diagnosis system, and a HUMANN-S ensemble system. HUMANN is a hierarchical, feed-forward modular neural network, with three operational modules, SOM, Tolerance, and Labelling [1]. The modular organization allows to develop a dynamic learning framework and provides the possibility to introduce specific behavior in each module. We used this capacity for designing HUMANN-S introducing a supervised labelling module, applying a perceptron-type neural network.

In this paper we explore the ability of a simple HUMANN-S and a HUMANN-S ensemble system, which was combined with simple and weight majority vote strategies. We present our preliminary results on differential diagnosis of CI using neuropsychological tests along with these systems. We also perform a comparative study between them. The inherent complexities of the information environment used and the scope of our work, are very appropriate scenes for using this approach.

Our proposed artificial intelligent systems are inside EDEVITALZH, which is a clinical virtual environment, focused on diagnosis and prognosis of CI, AD and other dementias. It is an environment based on Telemedicine which propitiates on line interactivity between physicians and their colleagues. EDEVITALZH will also allow that any patient with dementia, or any potential patient could have an appropriate medical attention, diagnosis and treatment, independently of existing specialized dementia centres where the patient is. Our proposal is a 4P-HCDS and is an optimal solution for an e-health framework.

The proposed systems in this paper has important advantages referring to other computational solutions based on artificial neural networks: HUMANN-S can handle in an efficient way the noise, it has a strong adaptive character, it has capacity for missing data processing and for the data fusion scheme. The importance of this proposal is in the fact that the specific application we investigate is itself a significant public health concern, and that it has widespread impact on long term geriatric care.

2 EDEVITALZH

EDEVITALZH [11] is a clinical virtual environment focused on diagnosis and prognosis of CI, AD and other dementias. This environment implements the Global Clinical Protocol for Dementias (GCPD), which reflects the specific data of interest channelled towards the diagnosis of theses neuropathologies. It will allow computerized medical records to be set up, creating a data base of the patients' medical records.

EDEVITALZH allows performing analysis of the CI evolution as well as predictive analysis with the possibility of providing pre-diagnosis. This makes possible to design proper and customized therapeutic strategies for each patient as well as the validation of these strategies. EDEVITALZH belongs to what we can call the 4P-HCDS. With the use of EDEVITALZH, the diagnostic work of the physician will be more accurate, agile, and patient dedicated, allowing time and resources optimization, while it is, in a parallel way, capable to work with different patients, in different geographical locations; patients which are able to be studied by other physicians.

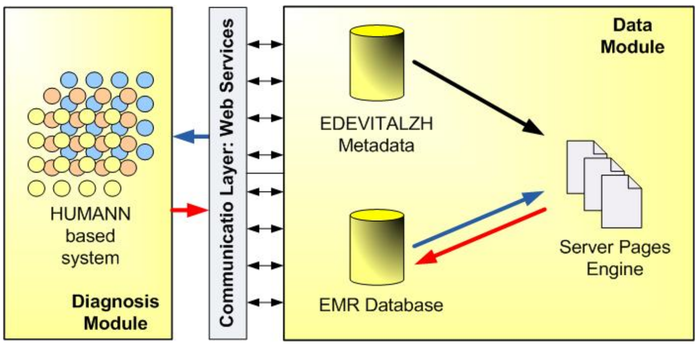

Fig. 1. EDEVITALZH Modular Architecture

EDEVITALZH has been implemented using a web application model. This allows that any computer can access the application using a web browser; and the information is centralized being always available for consultation from anywhere.

Based on a modular system concept, EDEVITALZH is made up of two first level blocks: 1) Data Module (Electronic Medical Records Database; Metadata; Server Pages Engine), and 2) Diagnosis Module (HUMANN-based system) [11]. Both modules communicate one another thanks to networking. This logical structural separation also allows a physical separation; different parts of the system can be located in different places. Furthermore, thanks to its modular character, its complexity and the cost of the system hardware and software are reduced –i.e., the same data module can operate with various diagnosis modules at the same time.

EDEVITALZH GUI (graphic user interface) also gives access and control of the HUMANN neural system, core of the intelligent system to aid the diagnosis. Both architecture modules will be connected one another using a communication layer based on Web Services, (Fig. 1) and data will be exchanged using standard XML. The area of development at a Research Level will allow the analysis and study of GCPD in depth, as well as the implementation of different configurations of HUMANN with the aim of producing precise and reliable diagnosis and obtain an optimum GCPD.

2.1 Diagnosis Systems

Two neural computing systems employing a simple-net and an ensemble approach [12] were used to approach the problem of CI differential diagnosis. The systems are based on modules that implement a supervised variant of HUMANN architecture (HUMANN-S) [1]. The first system is a HUMANN-S-based system an the second one is a HUMANN-S ensemble system, which was combined with simple and weighted majority vote strategies (SMVE/WMVE) [12].

2.1.1 Supervised HUMANN

The main part of both proposed systems is a supervised version of neural architecture HUMANN [1]. This neural network can implement the general approach of the classification process, which has three stages: a) feature extraction, b) template generation, c) discrimination (labelling), in a transparent and efficient way. Normally, and specifically in this application, step a), must be implemented by pre-processing modules that will be application-dependent. HUMANN is composed by three neural modules, SOM, Tolerance and Labelling, with a multilayer structure having different neurodynamics, connection topologies and learning laws.

The first neural module of HUMANN-S is a Kohonen´s Self-Organizing Map (SOM). This module implements a non-linear "projection" from an input space onto a two-dimensional array. This kind of neural structure is used because its main feature is the formation of topology-preserving feature maps and approximation of the input probability distribution, by means a self-organizing process which can produce feature´s detectors. For this application HUMANN-S has the capacity of missing data processing, which is implemented by means of a variant of the SOM architecture [13]. This variant prevents missing values from contributing when coming out or modifying weights. Even so, this way of approaching missing values is insufficient by itself, essentially when the proportion of missing values is excessive.

The second module is the Tolerance layer. It is the main module responsible for the robustness of HUMANN-S against noise. Its topology is a two-dimensional array which has the same dimension as the Kohonen layer and an interconnection scheme one to one with that previous layer. Its main objective is to compare the fitting between the input patterns and the Kohonen detectors. If the goodness of the fit is not sufficient the pattern is regarded as an outlier and is discarded. The weights of this layer are responsible for storing the mean of the fits between the inputs and the Kohonen detectors when these neurons are the winner ones. We are introducing a new concept called the “Tolerance margin”. The goodness of the representation of a pattern by a detector will be a function of the ratio of the euclidean distance between both of them and the Tolerance margin of the detector. This justifies its neurodynamic and it learning law [1].

The last module embodiment the supervised character of this neural network, is implemented by a perceptron type net [14] and perform the last stage of a classification process, the discrimination task. It receives the input values from the previous stage and has an output for each class to recognize. One of the most important advantages in this network is its tremendous speed. Possible trainings take place between 10 and 100 times faster than the conventional back-propagation networks, producing similar results. Increased speed is attributed to the simplification which occurs in the self-organizing stage. Simplification also allows this stage to use a simple classifier which produces proven convergence in linear problems, better generalization skills and a reduction in the consumption of computing resources [15].

2.1.2 HUMANN-S Ensemble System

Two strategies are needed to build an ensemble system, diversity and combination strategies. In our development we have used as diversity strategy, several HUMANN-S with data fusion scheme and lowest validation errors. The combination strategies used were the simple and the weighted majority voting, working with two schemes of HUMANN-S ensemble (SMVE/WMVE).

SMVE system uses the modules with the lowest validation errors and creates a simple majority voting process based on their outputs. Each module emits a vote, indicating whether it considers that said input belongs to a class or is unknown. A later module is responsible for the overall count, of considering whether the input belongs to one class or another, depending on whether most of the HUMANN-S modules consider it. Then the class with the maximum number of votes is selected as the ensemble output.

The WMVE system assigns different weights to the HUMANN-S modules, according to their performance, in order to avoid the possibility of certain classifiers to be better than the other ones. We assign heavy weights to the decisions of the more expert classifiers [12]. It is assigned a weight to each classifier in proportion to its estimated performance. We have used the single HUMANN-S validation error, as an estimate of that classifier's future performance. The combination of the outputs of several classifiers does not guarantee a superior performance to the best ensemble module, but it clearly reduces the risk of making a particularly poor selection [12].

3 Results and Discussion

The systems have been evaluated using a dataset that includes results from 267 clinical consultations on 30 patients during 2005 at the Alzheimer's Patient Association of Gran Canaria [16]. The data structure includes a patient identifier, results from 5 neuropsychological tests: Mini Mental Status Examination (MMSE), Functional Assessment Staging scale (FAST), Katz's index (Katz), Barthel's index (Bar) and the Lawton-Brody's index (L-B), and a diagnosis of CI as well as differential dementia. An important advantage in this data set is its homogeneity, each patient has scores from monthly tests, except the Mini Mental test, which is carried out twice a year.

Nevertheless, even though the majority of the patients were tested 12 times, there are some patients with missing data in their consultations. In effect, we are working with a dataset where a missing data feature is present, since not all of the patients are subject to the complete set of tests.

Table 1. Comparison between results for the validation sets of best module and ensembles

		HUMANN-S MSE+FAST	*SMVE / WMVE*
Sensitivity	*Mild CI*	88%	78%
	Moderate CI	85%	98%
	Severe CI	97%	100%
Specificity	*Mild CI*	82%	100%
	Moderate CI	90%	91%
	Severe CI	96%	99%
	Error	8.61%	4.12%

We obtain the error for the calculated training and validation sets by means of *k*-fold cross-validation (30 folds by leaving consultations of one-patient out) method for all of the HUMANN-S modules with different input subgroups. The best module using all validation data is the HUMANN-S with the MMSE and FAST tests inputs (HUMANN-S MMSE+FAST). The error reached in the validation set is 8.61%. Table 1 includes all the statistics for the validation sets. These results improve successfully, in a 0.38% the validation error, to the best Counterpropagation network obtained in our previous work [10], the same happened for the rest of the modules.

The 7 best modules stored by error using only the data with some available value to the input were used in the SMVE. They correspond to the following input combinations and errors: MMSE(5.73%), MMSE+FAST(8.61%), MMSE+FAST+Katz (10.11%), MMSE+FAST+Bar(10.11%), MMSE+L-B(10.49%), MMSE+FAST+L-B(11.99%) and MMSE+Bar(12.36%). The obtained system with this approach presents an error in the validation sets of 4.12% (see Table 1). These results successfully improve, by 4.04% the validation error when compared to the best one from the modules (HUMANN-S MMSE+FAST) applied on the total of all consultations. The drawback of this system is its computational requirements. Output computation of more than one module is required and combines the exit of theirs.

With WMVE we used also the 7 best HUMANN-S modules. The errors produced in the validation set are the same as in SMVE, and it rate error is also 4.12% (see Table 1). 4 of the 11 errors produced by both ensembles were misclassified by all of 7 modules, another 5 of them were misclassified by 6 modules and the remaining 2 cases were misclassified by 5 modules. HUMANN-S MMSE+FAST, the best module also for this 11 cases, failed to classify 7 of them; HUMANN-S MMSE failed on 9; HUMANN-S MMSE+FAST+Katz, HUMANN-S MMSE+FAST+Bar and HUMANN-S MMSE+L-B failed to classify 10 of them and the remaining modules failed on all of 11 cases. The Principal Component Analysis (PCA) of our data set [16] can help us to determine the difficulties of it classification. In Fig. 2. we show the errors of SMVE and WMVE inside PCA graphical projection.

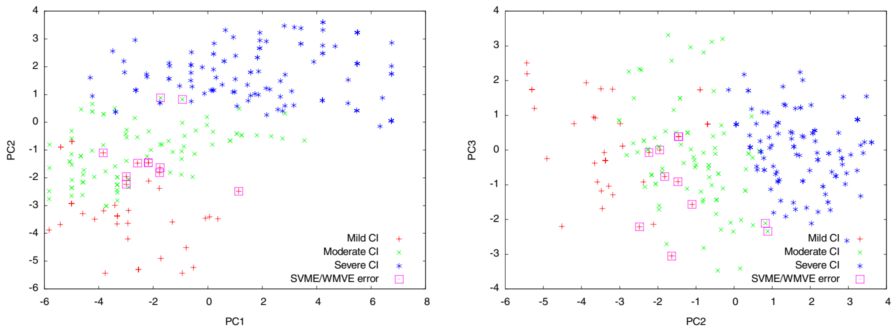

Fig. 2. Scores of first (PC1), second (PC2) and third (PC3) factors from PCA. Show patients with Mild CI (+), Moderate CI (x), Severe CI (*) and the SVME and WMVE errors (□).

4 Conclusions

Our work represents important advances on intelligent decision systems, medical informatics and on healthcare. We have presented intelligent diagnostic systems embodiment in a clinical virtual environment to assist the diagnosis and prognosis of CI, AD and other dementias, EDEVITALZH, Our proposal is a personalized, predictive, preventive, and participatory-healthcare delivery system (4P-HCDS) and is an optimal solution for an e-health framework.

We propose new CI diagnostic tools based on a data fusion scheme, artificial neural networks and ensemble systems. We have designed a supervised HUMANN with capacity of processing missing data which provides an important performance for this difficult application.

The use of this new instrument can help alleviate the degree of existing underdiagnosis, since it would be used in primary care centres. It also allows early detection of dementia which can be used to design appropriate therapeutic strategies which are practically effective in the early phase of the disease. In addition to this, the analysis conducted on the different modules which the system up, allows the best cognitive test for a correct diagnosis to be selected. Therefore the study of other possible tests could be extended to elaborate refined diagnosis protocols.

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