New Approach for Clinical Decision Support System of Alzheimer’s Disease Diagnosis

Zouhour Maâtar
Electrical Engineering Department
Micro Electro Thermal Systems
National Engineering School of
Sfax Sfax-Tunisia

Chokri Abdelmoula
Electrical Engineering Department
Micro Electro Thermal Systems
National Engineering School of
Sfax Sfax-Tunisia

Mohamed Masmoudi
Electrical Engineering Department
Micro Electro Thermal Systems
National Engineering School of
Sfax Sfax-Tunisia

ABSTRACT
Alzheimer’s disease is a chronic dementia. It destroys gradually the memory and get worse over time. The diagnosis of AD is generally made very late. The great challenge is reaching an early and accurate diagnosis. In this case, a Clinical Decision Support System (CDSS) to help physicians diagnose AD and related disorders: mild cognitive impairment (MCI) and Dementia (D) is proposed. The originality of the idea is that many parameters are included such as cognitive test scores, neurological, biological, clinical and demographic data and this is in order to carry on the most accurate diagnosis for every subject. The Support Vector Machine showed that the proposed CDSS decision model achieves good performance.

General Terms
Support Vector Machine (SVM)

Keywords
Alzheimer’s disease (AD), Dementia, Clinical Decision Support System (CDSS), cognitive test

1. INTRODUCTION
Due to aging populations, dementia is one of the primary concerns of public health [1]. Dementia is a loss of brain whose frequency increases with age and its prevalence doubles approximately each five years from the age of 65. The report shows that between 60 and 69 years, 27.31% of people are demented. Also, between 80 and 89 years, 20.26% of people are demented [2]. Fig.1 shows the latest distribution of demented people by age range. Alzheimer’s disease is one of dementia types. It is degenerative, progressive and gradually destroys memory [1]. AD goes through different phases; the mild and the severe Alzheimer’s disease as it is shown in fig.2. While the evolution and duration varies from one individual to another, it can be seen that early cases tend to evolve more rapidly. AD represents 60-80% of all demented cases [2]. Today, about 46 million people worldwide are living with Alzheimer's disease and this number is expected to rise to 66 million by 2030 and even triple to 115 million in 2050. Every 67 seconds, one person in the world develops Alzheimer's disease. According to the review done by researchers of Alzheimer’s association, 66% of demented patients will have AD but just 10% of them will be diagnosed accurately.

In Tunisia, the number of studies determining the extent of dementia is very limited. Tunisia is not immune to this phenomenon. The estimation of demented people is 57,000 in 2015 [3]. This number will be multiplied by four in 2030. Early diagnosis of the AD is very essential to the rising number of patients with Alzheimer.

Clinical decision support systems (CDSS) are identified as a significant class of health information systems developed to enhance clinical decision making [4]. All the studies have shown that CDSS is able to minimize diagnostic error rates [5]. These systems are not aimed at substituting expert clinicians, but can provide them with a second opinion. The proposed CDSS is about to make the diagnosis of AD more easy, including a method to periodically refine its decision-making model using a new combination of several data. The concept of having such a system to support health care can have a significant impact on the information’s health quality systems designed to improve clinical decision making.

In this study, a new Clinical Decision Support System helping in the diagnosis of Alzheimer’s disease with an association of cognitive, neurological, clinical, demographic and biological data is proposed. Unlike, other systems in the literature gather with one type of data or a least two types. The article is organized as follows. The second section describes the related works. The proposed method and the database collection are explained in the third section. In the fourth section, results and discussion are included. Finally, in the last section the paper is concluded.

Fig 1: Distribution of demented people by age range
2. RELATED WORKS

Weakley et al. [6] used a combination of twenty-seven measures obtained from different neuropsychological tests. These tests include behavioral, cognitive and functional abilities. This system shows an accuracy of 82%. It was a predictive and robust model but unfortunately poor number of patients. A similar approach was applied to a higher number of patients but for only seven cognitive measures. It led to poor classification accuracy (59%). Battista et al [7] used a combination of 131 measures including MMSE test, clock drawing test, the Assessment Scale Cognitive behavior etc. The accuracy obtained is about 69%. Callahan et al. [8] proposed six types of tests such as the MMSE, the Blessed Dementia Rating Scale (BDRS) and the World List Recall. For a diagnosis of dementia, the sensitivity and specificity reached 88.7 % and 88 %. Tierney et al. [9] gives an idea of the possibility of using a battery of neuropsychological tests; the accuracy of this model was 89%.

A hybrid model combining Multicriteria Decision Aiding) (MCDA) and Bayesian Network (BN) has been proposed by [10] with a ranking model based on MCDA and BN for aiding the diagnosis of AD. Their model indicates which assessment patient items have the highest impact for determining the AD diagnosis.

There are several works that use neuroimaging data such as De Figueiredo et al. [11] showed a method of analyzing through computer tomography image (CT) data of the brain. Ramirez et al. [12] presented also a CAD system for the Alzheimer’s disease diagnosis based on single photon emission computed tomography (SPECT). The results revealed an accuracy of 95.87%. Daliri presented a computer aided diagnosis from brain MRI, the classification accuracy is about 96%. In this case many CADS are validated through the MRI imaging. There are also CADS that combine between two or more neuroimaging structures such as Polikar, Tilley et al. who proposed a study based on the association of various types of neuroimaging like PET, MRI and EEG [13], the accuracy is about 85.55%. D. Zhang et al. [14] proposed also a system of combining: MRI, PET and CSF for Alzheimer’s disease diagnosis. The classification accuracy is 93.2%.

3. MATERIALS AND METHODS

3.1 Database
The data base used in this study is obtained from the Neurology Department of the Sahloul Hospital in Sousse. This study lasted 3 years from January 2015 to December 2017. The study was approved by the ethical comity of the University Hospital of Sahloul. It included 304 distinct subjects, their age ranges from 47 to 93 years old. These patients were divided into three groups:

- The Normal Control (NC) group consisted of 153 subjects with an MMSE score of 30, without a neuropsychological history or pathologies that could affect cognitive functioning.
- The Mild Cognitive Impairment (MCI) group includes 15 cases. Their MMSE score varies between 19 and 23.
- The Alzheimer’s Disease (AD) group consisted of 136 patients, with an MMSE score ≤ 18/30

These three groups will serve as the three classes used in the classification process later on.

3.2 Methodology

3.2.1 Socio-demographic and clinical parameters
Sociodemographic data include several parameters that address many aspects such as geographic origin, habitat, gender, height, weight, Body Mass Index (BMI), primary caregiver, age at first visit, marital status, education, occupation, lifestyle such as smoking, family history mainly related to consanguinity and personal history such as high blood pressure (HTA) and diabetes. The age at which the disease begins and the mode of onset is sudden or progressive and the time to consult the disease are also cited as clinical evaluation parameters.

3.2.2 Neurological and biological data
Memory disorders that include recent and historical events, language disorders, apraxia, executive functions, walking, motor skills, psycho-behavioral disorders such as aggression,
agitation, hallucination, anxiety, depression and apathy. There is also extra-pyramidal syndrome, mood swings, attention disorders and loss of initiative.

### 3.2.3 Cognitive parameters
Validated, reliable and standardized neuropsychological tests, consistent with the country’s cultural norms and normative data scores were used in this study. This evaluation was conducted for the evaluation of executive functions, temporal-spatial orientation, verbal fluency, practical and gnosis functions, autonomy, episodic memory and psychiatric disorders. It included a mini-MMSE mental state test, a frontal assessment battery, a geriatric depression scale, a clock drawing test, a verbal fluency test, a five-word test and a scale of instrumental activities of daily living.

- Geriatric Depression Scale "GDS" 15 item
- Clock Test
- Verbal fluency test
- Frontal Efficiency Fast Battery (BREF)
- The Mini Mental State Examination (MMSE) in its Arabic translation
- The Dubois 5-word test
- IADL Personal Care Scale

#### 3.2.3.1 The Mini Mental State Examination (MMSE)
MMSE is a simple and quick test evaluating cognitive functions. It is a thirty-point questionnaire. MMSE is a familiar test exploring the temporo-spatial orientation, the attention and calculation, the registration, the language, the registration recall, the repetition and the visuo-constructive aptitudes. The MMSE score can be employed to classify the severity of cognitive impairment.

- No cognitive impairment: if MMSE score between 24 and 30
- Mild cognitive impairment: if MMSE score between 19 and 23
- Moderate cognitive impairment: if MMSE score between 10 and 19
- Severe cognitive impairment: if MMSE score ≤ 9

#### 3.2.3.2 The Dubois 5-word test
The test of Dubois is a test of serial verbal memory with indication to the recall and to the encoding. In the test, the subject is asked to repeat five words which do not resemble each other and belong to different categories during two trails and after a short period of time, with distracting elements, he is required to remind the five words. The recovery must be spontaneous. The test is normal for a total recall of 10 and is used to identify hippocampal amnesia syndrome in favor of AD, if certain words are forgotten without improvement after the indication.

#### 3.2.3.3 The Instrumental Activities of Daily Living Scale (IADLS)
Autonomy used to be controlled by Lawton's Physical Autonomy and Instrumental Activities of Daily Life (IADL), which included 14 elements. LDL less than 13/14, the patient is related to activities of daily living.

#### 3.2.3.4 Geriatric Depression Scale "GDS"
The Geriatric Depression Scale (GDS) is a questionnaire that relates to depressive symptomatology in the elderly. The 15-item questionnaire must be completed by the subject himself. Eventually, the questions can be read. It takes about 5 to 10 minutes to answer the 15 questions that relate to the person's feelings at the time of the interview or over the past week. If several successive evaluations are to be carried out, they must be spaced one week apart. The mood was assessed by the 15 item Geriatric Depression Scale "GDS" in Arabic version. A score ≥ 5 was in favor of depression.

#### 3.2.3.5 Clock Test
The clock test is used to evaluate visuo-constructive disorders. This involves asking the patient to draw a clock with a specific time (e. g. 10h10min). This test is rated on 7 points. The test is considered pathological if the score is under 7.

#### 3.2.3.6 Verbal fluency test
It is done by a verbal fluency test by asking the patient to name in one minute as many words as he can, these words correspond to a semantic (fruit) or phonemic (all words start with the letter S in Arabic) category. A semantic verbal fluency <15 and a phonemic fluency <10 are pathological.

#### 3.2.3.7 Frontal Efficiency Fast Battery (BREF)
The BREF is a cognitive and behavioral test for assessing frontal lobe function and identifying an executive dysfunction syndrome. It allows the following functions to be evaluated: Conceptual elaboration by testing similarities, mental flexibility, programming of motor acts by the gestural sequence of Luria, sensitivity to interference by testing conflicting instructions, inhibitor control by the Go-No Go test, environmental autonomy through the search for gripping behavior. Each item is rated from 0 to 3. The total score varies from 0 to 18. For subjects with a secondary school level or higher, a score of less than 16 is considered pathological, while for illiterate subjects and those with a primary school level the pathological threshold is 15.

#### 3.3 Proposed method
In the design of a Clinical Decision Support System (CDSS), the proposed method is about to diagnose Alzheimer’s disease. It is a multi-scale modeling. The first step is collecting an appropriate clinical dataset. The database includes the demographic information, neurological, cognitive and biological parameters. Then, the phase of pre-processing which consists on the choice of efficient parameters. The feature extraction is about to label each class C1 for the class of Normal Controls, C2 according to the MCI cases and C3 is for the Alzheimer’s disease patients. Finally, for the classification it consists on training the proposed system by several classifiers such as Support Vector Machine (SVM), k-nearest neighbors (KNN) and bagged tree to get the right decision in the end and verifying the ability of the proposed system to distinguish between Normal Controls (NC), MCI and Alzheimer’s Disease (AD) cases. The diagram in figure 3 shows the different steps of the system.
4. EXPERIMENTAL RESULTS

In the construction of the database, a neuro-radiologist, a radiologist and neurologist may check the data to distinguish between Normal Controls (NC), MCI and AD cases in order to create an efficient database.

4.1 Database description

4.1.1 Demographic and clinical information

Among the data base cases included, 59.2% were men with a sex ratio estimated at 1.45. The mean age of dementia was 71 years ± 9.7 with a peak frequency between 70 and 79 years. The patients were married in 58.1% of cases, widowed in 20.2% of cases and single in 21.7% of cases. Half of the study population was from urban areas (53.2%). In this population, 59.5% were illiterate, 24.4% had a primary education level, 11.3% had a high school education and 4.8% had a higher level of education. In contrast, the mean age of onset of Alzheimer disease and MCI patients was 70.79 years ± 8.93 with extremes ranging from 42 years to 89 years. A significant male predominance was noted. The average age of onset in the male and female gender was respectively 72.96 ± 8.49 and 69.36 ± 8.78 years. The start mode was progressive in 83.7% of cases and brutal in 16.3%. The average consultation time was 3 years with extremes of 1 and 5 years. Women consulted earlier (72.4 % female vs. 27.6 % male). The high level of education does not improve consultation times since 59.60% of patients who consulted within a period of <1 year were illiterate.

Table 1 represents the demographic and clinical characteristics of the patients in two groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dementia N=151</th>
<th>Controls N=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (Men/women)</td>
<td>0.98 (75/76)</td>
<td>1.04 (78/75)</td>
</tr>
<tr>
<td>Age mean ±SD</td>
<td>71.47 ±9.66</td>
<td>65.69 ±9.76</td>
</tr>
</tbody>
</table>

4.1.2 Cognitive information

The median MMSE was 14 ± 6 with extremes of 0 and 25. According to the MMSE score; 54.8% of patients had moderate impairment, 23.4% had mild impairment, and 21.8% had severe impairment. Table 2 presents the neuropsychological state of the participants. Due to NINCDS-ADRDA criteria, the specificity and sensitivity of Alzheimer’s diagnosis were 73% and 81% respectively.

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>14 ±6</td>
</tr>
<tr>
<td>5-words test</td>
<td>7</td>
</tr>
<tr>
<td>BREF test</td>
<td>8</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>7</td>
</tr>
<tr>
<td>IADL</td>
<td>4</td>
</tr>
<tr>
<td>GDS</td>
<td>2</td>
</tr>
</tbody>
</table>

4.1.3 Biological evaluation

Vitamin D (<10ug/L) and vitamin B12 deficiency, hyperglycemia, hypercholesterolemia and hypocalcemia were significantly more frequent in the AD group. Vitamin D regulates several brain phenomena such as proliferation, cellular differentiation and neurotransmitter metabolism. A vitamin D deficiency leads to memory and behavioral disorders.

4.2 Results

To evaluate the performance of such a classifier, the following metrics were used: [15]

The precision performance is an evaluation method to test the algorithm.

Precision = Number of TP / (Number of TP + Number of FP)

The Sensitivity measures the proportion of actual positive results that are correctly identified as such. In this case, the number of people with the disease who are classified as affected compared to the total number of people with the disease. Mathematically, sensitivity is defined as:
Sensitivity = Number of TP / (Number of TP + Number of FN)

Specificity measures the ability of the classifier to identify true negatives. In this case, it is the number of normal people who are classified as normal compared to the total number of normal people. Mathematically, specificity is defined as:

Specificity = Number of TN / (Number of TN + Number of FP)

- True positive (TP) = correctly identified
- False negative (FN) = incorrectly identified
- True negative (TN) = correctly rejected
- False negative (FN) = incorrectly rejected

Table 3 shows the performance of each classifier; Support Vector Machine (SVM), k-nearest neighbors (KNN) and bagged tree tested in the proposed clinical decision support system.

Table 3. Classification performance

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Precision</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNN</td>
<td>93.1 %</td>
<td>97 %</td>
<td>98.8 %</td>
</tr>
<tr>
<td>Decision Tree</td>
<td>98.4%</td>
<td>98.8%</td>
<td>99.2%</td>
</tr>
<tr>
<td>SVM</td>
<td>100 %</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The best classifier is the Support Vector Machine (SVM) classifier which shows best results of classification and high performance in terms of precision, sensitivity and specificity.

5. CONCLUSION

A lot of countries, even developed are moving to an aging society and AD is one of the brain dementia. Therefore, existing CDSS will become increasingly important in clinical practice. So this paper presents new system helping in the diagnosis of AD through the clinical database which combines the neuropsychological test scores, the demographic factors biological markers and neurological parameters. The choice of the classification with the Support Vector Machine (SVM) classifier shows best results. The door is still open for further research especially with the rapid advances in scanning and computer based technologies.

6. ACKNOWLEDGMENTS

The authors would like to express their thanks to all the staff of the neurologists in the Neurology Department of Sahlool University hospital for her support in providing the database and the help in the check of demented cases.

7. REFERENCES


