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A fuzzy rule-based approach via MATLAB for the CDR instrument for staging the severity of dementia☆

Wallaci P. Valentino [a], Michele C. Valentino [b], Douglas Azevedo [*,b], Natáli V.O. Bento-Torres [c]

[a] Instituto de Ciências da Saúde - Universidade Federal do Pará - Av. Generalíssimo Deodoro, 01, Umarizal, Belém, 66050160, PA, Brasil
[b] Av. Alberto Carazzai, 1640, Departamento Acadêmico de Matemática, Universidade Tecnológica Federal do Paraná, Campus Cornélio Procópio, 86300000, PR-Brasil
[c] Universidade Federal do Pará, Faculdade de Fisioterapia e Terapia Ocupacional, Inst. de Ciências da Saúde. Av. Bernardo Sayao, Belém 01 Guamá 66075110, PA, Brasil

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ABSTRACT

Background: The CDR scale is a standard qualitative staging instrument that has been widely applied for assessing the severity of dementia which is based on information elicited through a semi-structured interview standardized in an assessment protocol. Despite clinical skills to elicit appropriate information are required, subjectivity still lies in the administration of the protocol and scoring process of the CDR. In this paper we propose a fuzzy rule-based CDR instrument to stage dementia based on the usual CDR, aiming to cover the subjectivities of the scoring process in the usual CDR which are directly related to the scoring system. This is effectively achieved by the F-CDR, our proposed expert system, which allows assigning scores continuously throughout the interval [0,3].

Results: In order to test the performance of our fuzzy model, we compare the outputs FCDR obtained from of F-CDR approach to the outputs U-CDR obtained by a usual application of the CDR via the same inputs for both. The dataset provided by ADNI, composed of more than eleven thousand CDR tests, including the inputs and outputs (U-CDR), is the source for comparisons.

Methods: The fuzzy rule-based model for the CDR that we propose in this paper is a fuzzy inference system (FIS) constructed in MATLAB with the aid of the Fuzzy Logic Designer app. The FIS was constructed based on the CDR and the specialist's indications and tested on real data provided by ADNI.

Conclusion: The high accuracy of matches between U-CDR and F-CDR via the same inputs over random samples selected from the ADNI dataset suggests that the fuzzy approach to the CDR instrument here proposed is suitable to extend the scoring process of the usual CDR since the fuzzy approach allows the possibility of scoring continuously in the interval [0,3].

1. Introduction

Dementia is a syndrome associated with an ongoing decline of brain functioning and it is characterized by a significant decline social, occupational, and domestic functions [1,2]. In other words, it is not a specific disease but is rather a general term for the impaired ability to remember, think or make decisions that interfere with doing everyday activities. Certainly, is not part of normal aging however dementia mostly affects older adults and Alzheimer's disease (AD) is the leading subtype of dementia.

According to Alzheimer's Disease International [3], in 2020 there were over 50 million people worldwide living with dementia. This number will almost double every 20 years, reaching 82 million in 2030 and 152 million in 2050. Furthermore, as pointed out by the 2020 World Alzheimer Report [4], the most up-to-date global estimate, published in the 2015 World Alzheimer Report, indicates that the economic impact of the global costs of dementia worldwide exceeded US$818 billion. The annual cost today is over US$1trillion alongside with a forecast to

☆ Alzheimer's Disease Neuroimaging Initiative Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

* Corresponding author.
E-mail addresses: wallacipvalentino@gmail.com (W.P. Valentino), valentino@utfpr.edu.br (M.C. Valentino), douglasa@utfpr.edu.br (D. Azevedo), natalivalim@ufpa.br (N.V.O. Bento-Torres).

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double by 2030 and continues to rise.

Early and precise diagnosis of dementia can be managed to slow down its progression. However, due to the multifactorial nature of dementia, early diagnosis is a challenge that still needs to be overcome [5]. As highlighted in [6], the diagnosis of dementia should be an outcome obtained after a rigorous clinical assessment, including, but not limited to, patient's clinical history, neurological evaluation, laboratory tests, and imaging exams.

Among many tools used to evaluate an individual's cognitive impairment and identify possible dementia cases the clinical dementia rating (CDR) is a standard well-recognized instrument to rate the severity of the manifestation of dementia. Precisely, it is a clinical instrument developed to evaluate cognitive and functional domains (Memory, Orientation, Judgment/Problem solving, Community affairs, Home/Hobbies, and Personal Care) affected by dementia. It attributes scores to each domain and establishes a global score by a rating system adapted by Morris, 1993 [7]. This evaluation tool is utilized at a worldwide level for recognition and staging cases of dementia. CDR's expected outputs can be described by five scores possibilities (inputs) : Healthy (0), Questionable (0.5), Mild (1), Moderate (2) and Severe (3) [7,8].

Just like other clinical instruments, CDR also presents limitations in detecting early dementia. Since mild impreciseness of the inputs can lead to distortion of the final score, a particular downside of the CDR in this sense is that it relies upon the interpretation of a specialist for the scoring process about the collected and observed data during neurological evaluation.

Computer-aided decision support systems using artificial intelligence, machine learning and fuzzy logic can be explored to deal with the subjectivities of problems. In particular, they have been successfully applied to a wide variety of decision-making or classification problems in the area of medical diagnosis [9–17].

To handle with uncertain and imprecise knowledge in real applications, in 1965 Lotfi Zadeh presented the fuzzy set theory [18]. The term fuzzy logic was introduced along with the emergence of fuzzy set theory and it has been employed to handle the concept of partial truth, where the true value may range between completely true and completely false. An important area of application of fuzzy sets and fuzzy logic is the fuzzy rule-based system, which has become a powerful method to deal with a wide range of problems dealing with uncertainty, imprecision, and non-linearity. New techniques, which have advantages for performing fuzzy systems design and optimization when compared to conventional optimization techniques, were recently presented in [19–21] A fuzzy rule-based systems is also known as fuzzy inference system or simply fuzzy system. It is commonly used for identification, classification and regression tasks and it finds its foundations on the fuzzy set theory, which aims at representing the knowledge of human experts in a set of fuzzy IF-THEN rules, which can facilitate resolutions of problems. Some recent works with focus on biomedical applications [22–24], investiment projects [25] and robotics [26], ratify the importance of this class of system.

As the problem of recognizing and staging cases of dementia has many subjectivities, in this research we focus on obtaining a system based on fuzzy rules to assist specialists in this task. More specifically, we present a fuzzy rule-based model composed of six input variables from the CDR inputs from which dementia staging is provided as output.

Objectively, the main purpose of this work is to propose an extension of the usual CDR approach by means of a fuzzy rule-based approach aiming to reduce the natural impreciseness of the usual process of staging dementia. In the process, we ratify the well-known fact that fuzzy logic is well applied to such problems.

A core difference between the usual CDR application and the fuzzy approach proposed herein, which we will call from now on by F-CDR, is that the last one provides to the user a wilder range for scoring the inputs compared to that fixed scoring system of the usual CDR (U-CDR). Precisely, the F-CDR provides to the user a gradual transition between one subclass and another, which incorporates the situation of subjectivity regarding the score of an entry/input. For instance, 1.6 is a score allowed in the F-CDR as input whereas in the U-CDR it would not be possible, since in this case the scoring possibilities are fixed: 0, 0.5, 1, 2, 3. Therefore, this feature plays an important role when subjective observations determine what inputs are used to infer about staging the severity of dementia. This feature makes the F-CDR approach more robust in the sense that small variations in the inputs do not lead to extreme variations in the final result. This feature helps to overcome the impreciseness that may arise from the specialist scoring in the U-CDR.

The paper is hereinafter organized as follows. In Section 2, an overview of the basic aspects of fuzzy set theory and fuzzy classification systems is presented. Also, we give the background about the dataset used to verify the robustness of our fuzzy

In Section 3 we present the main contribution of this paper, a fuzzy rule-based system approach to stage the severity of dementia. There we ratify the robustness of our fuzzy-approach to the staging of dementia by comparing the rating results obtained by usual applications of the CDR staging instrument with the use of the fuzzy system proposed herein. This is done using data provided by Alzheimer's Disease Neuroimaging Initiative (ADNI) database[1]. Henceforth, we use the abbreviations U-CDR (meaning usual CDR) e F-CDR (meaning fuzzy CDR) in the context indicated above.

Finally, in Section 4 we present the conclusions.

An appendix section was included at the end. There, the random samples extracted from the ADNI dataset as well the results obtained from an application of the fuzzy model here proposed to these samples are presented in Appendix A, and more details about the membership functions and the rule base that are used in the application of this paper can be found in Appendix B.

1.1. Related works and problem statement

Classification of dementia stage and especially identifying Alzheimer's disease (AD) with computational aid have been the focus of several research works. In [27], for instance, a review of methods used in dementia research is presented and a brief introduction to some recently proposed algorithms is subsequently discussed. The presentation is centered on the fact that it is possible to develop computerized methods that can be a great help to clinicians to discover hidden patterns in the data since patient data in clinical research often includes large amounts of structured information. Fuzzy logic and data-driven approaches to classify dementia and AD have been usually applied to situations dealing with electroencephalography (EEG), magnetoencephalography (MEG), or Magnetic resonance imaging (MRI). Recently, for instance, [28] developed an approach based on the decomposition of the signals by means of discrete wavelet transform in the four neurophysiological frequency bands. The classification is done via Fuzzy logic-based algorithms. There, the investigation aimed to identify patterns or differences among the electroencephalography signals from AD and Mild Cognitive Impairment (MCI) patients and healthy control subjects, and that these patterns or features could be employed to aid in the classification of different dementia stages. Their proposed methodology differentiates MCI and AD patients from Health Control (HC) subjects with an accuracy of 82.6 and 86.9%, respectively. In [29] epoch-based entropy (a measure of signal complexity) and bump modeling (a measure of synchrony) are features that are shown to be sufficient for efficient discrimination between subjective cognitive impairment (SCI) patients, MCI patients, possible AD patients, and patients with other pathologies. Classification is done via multi-class probabilistic SVM classifiers with an accuracy of 91.6% for discriminating SCI patients from possible AD patients and 81.8% to 88.8% for the 3-class classification of SCI, possible AD, and other patients. In [30] a computer-aided system was implemented also on MRI data from the ADNI database to diagnose AD using optimal deep neural network. The design of a CAD system to estimate

[1] adni.loni.usc.edu

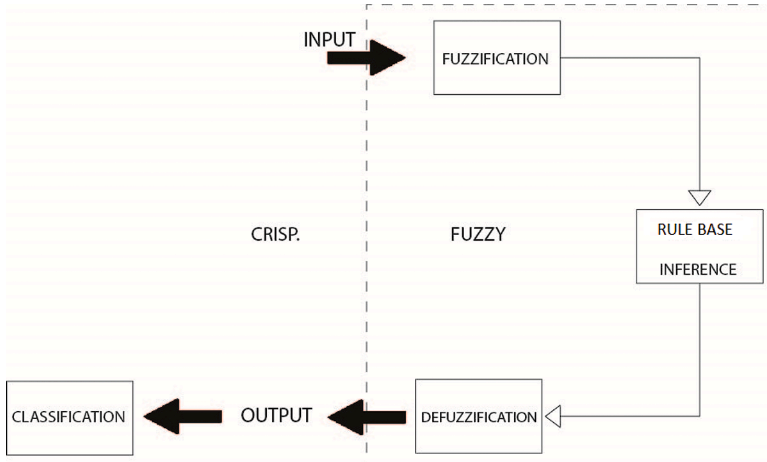

Fig. 1. The structure of a fuzzy rule-based classifier.

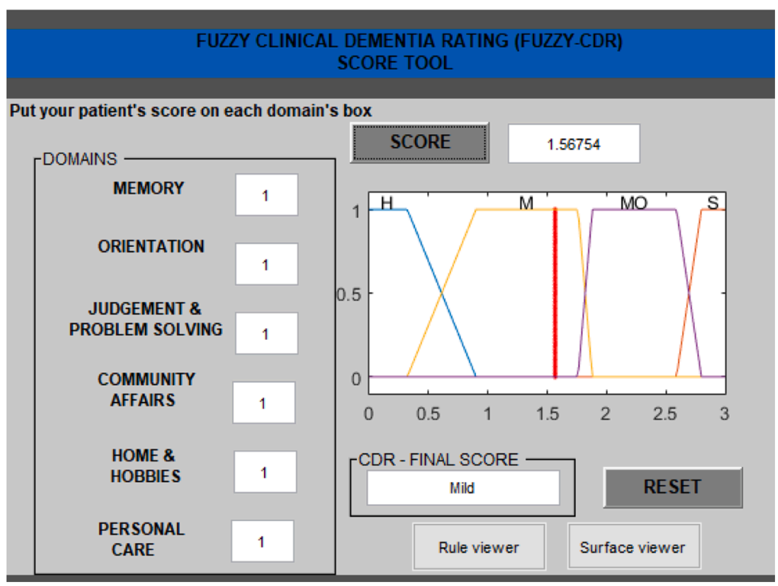

Fig. 2. Graphical user interface of F-CDR.

the classification performance on the grey matter of structural 3D MRI for AD was the main achievement of the paper. The accuracy of their method for AD/HC, AD/MCI, and MCI/HC are 96.43%, 94.64% and 91.07%, respectively. Also, in [31] convolutional neural network-based Alzheimer's disease classification from magnetic resonance brain images. This is done via a mathematical model based on transfer learning is used in which a convolutional neural network architecture trained on ImageNet dataset is used as a feature extractor for the classification task. The approach was tested on data collected from Alzheimer's Disease Neuroimaging Initiative (ADNI) database. In their setting, an accuracy of the classification is 95.73% was achieved. In [32], it is presented an expert system with fuzzy inference system (FIS) to classify the brain MRI images into AD, MCI, and HC subjects. In order to achieve this goal, brain MRI images from OASIS (the Open Access Series of Imaging Studies) were considered. The brain images were preprocessed and segmented to extract the hippocampus volume, which is the key biomarker of AD diagnosis considered and also is used as the input to the FIS. The classification measures of the FIS proposed there for brain MRI images for axial, coronal, and sagittal brain MRI projection achieved an accuracy of 86.53%, 84.13% and 82.12%.

Due to the importance of cognitive assessment scales when dealing with dementia, cognitive impairment screening instruments play a fundamental role [33,34]. Detecting possible cognitive impairment is the first step in determining whether or not a patient needs further evaluation, such as the exams covered in the works above, and the CDR is surely a prominent tool for this purpose.

As we have indicated, our main interest in this paper is to propose an alternative approach to the CDR staging instrument via a fuzzy logic aiming to deal with possible impreciseness that comes from the subjectivities of the scoring process of the usual CDR and this is precisely our goal in this work: using CDR data provided ADNI and the experience of a specialist we have constructed a simple rule-based fuzzy classifier that extends the CDR by allowing a continuous scoring throughout the interval [0,3]. The main interest in this approach is based on the fact that "continuous scoring" is a feature that is suitable the encompass possible uncertainty of the scoring process. As it is shown in Section 3, our proposed methodology differentiates Mild (MCI), Moderate (MoCI), and Severe (SCI) cases with an accuracy of 98,8%, 94,7%, and 97,8%, respectively. The tests were performed on random samples of data collected from Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Our results indicate that the approach is a promising possible extension for the CDR staging instrument which is also of great utility in tracking changes within and between stages of dementia severity.

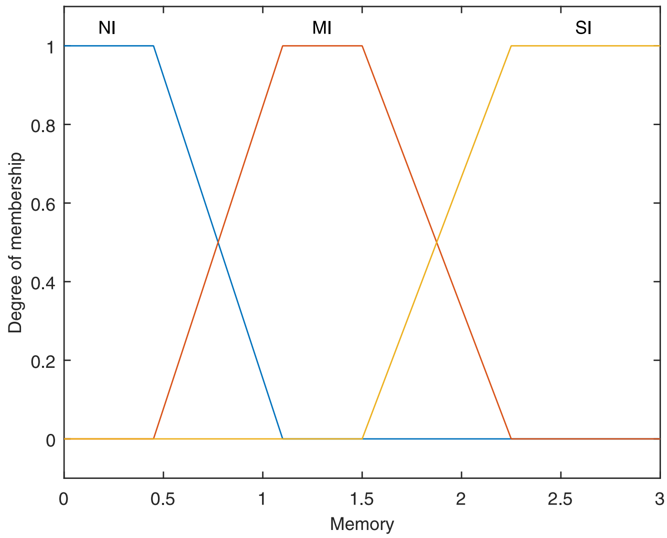

Fig. 3. Fuzzy sets No Impairment (NI), Mild Impairment (MI) and Severe Impairment (SI) for the input variable Memory.

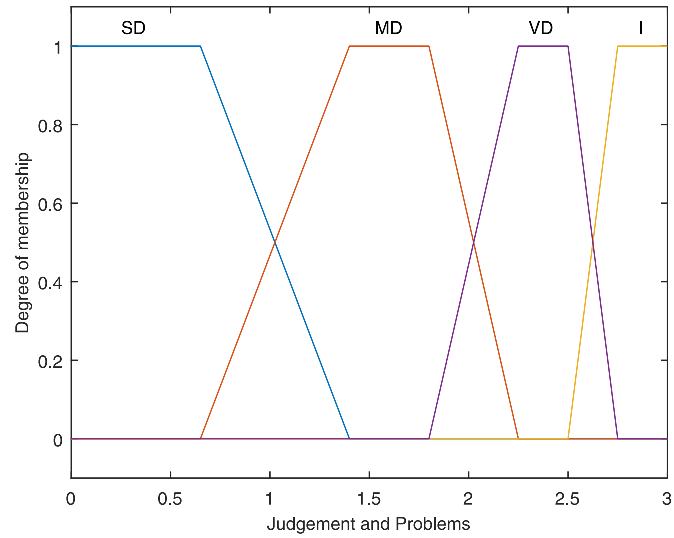

Fig. 5. Fuzzy sets Some Difficulty (SD), Moderate Difficulty (MD), Severe difficulty (S) and Inept (I) for the input variable Judgement and Problems.

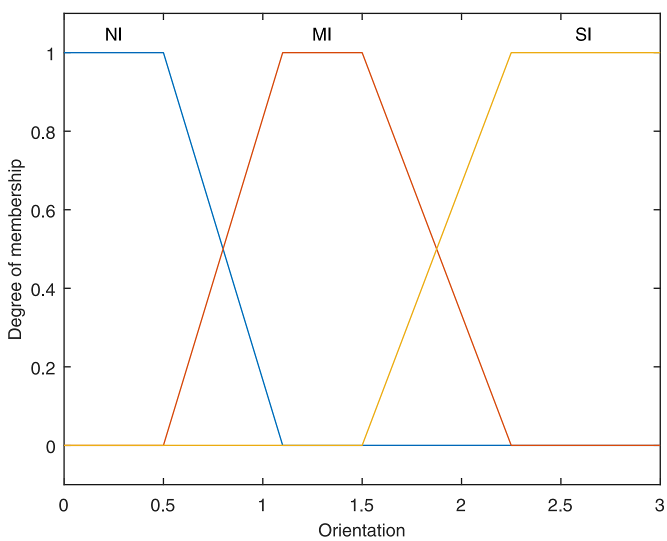

Fig. 4. Fuzzy sets No Impairment (NI), Mild Impairment (MI) and Severe Impairment (SI) for the input variable Orientation.

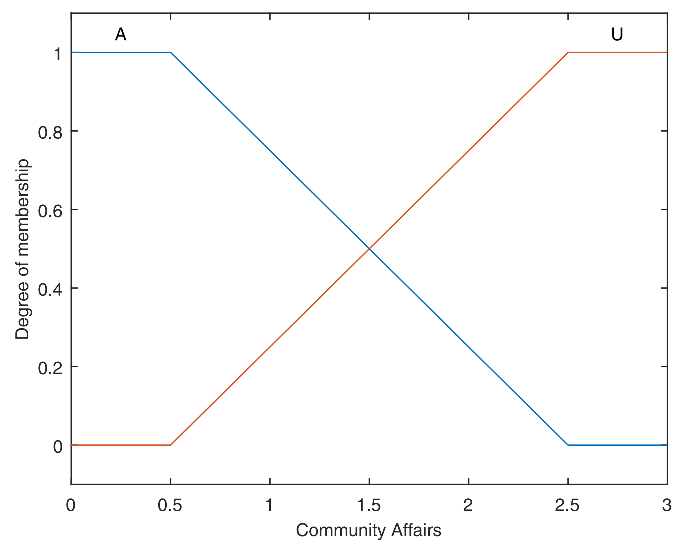

Fig. 6. Fuzzy sets Able (A) and Unable (U) for the input variable Community Affairs.

2. Material and methods

The underlying theory and computational support of the fuzzy set theory that we apply in this work as well as the dataset that we use to evaluate the robustness of our proposed system are presented in the following subsections.

2.1. Fuzzy sets and fuzzy classification systems

In the classical set theory, an element belongs or not to a given set. However, the fuzzy set theory allows a gradual assessment of the membership of elements in a set, that is, each element of the set is mapped to a value between 0 and 1 by a membership function. In this sense, an element can belong to a set partially and for this reason fuzzy sets may be seen as a generalization of the classical concept of sets (also called crisp sets), since the indicator functions of classical sets only take values 0 or 1. Thus, the fuzzy set theory can be used in a wide range of applications in which information is incomplete or imprecise.

A fuzzy rule-based system is an extension of the classical rule-based system, where fuzzy sets and fuzzy logic are used to model the interactions and relationships between its variables. A particular case of such a system is the fuzzy classification system, which is the process of grouping variables having the same characteristics into a fuzzy set. In the traditional classification method, each variable is a member of a class or not, whereas in the fuzzy classification a variable can belong to several classes concurrently with respect to a pertinence function, which determines how much the input variable is pertinent to each fuzzy set considered. Fig. 1 displays the structure of a fuzzy classification system, which is composed of five steps: fuzzification, rule base, fuzzy inference, defuzzification, and classification. Note that, before applying these steps we first need to determine which inputs and outputs (linguistic variables) are essential for the system.

Next, in order to clarify the present discussion, we introduce some basic aspects of the above-mentioned steps described in Fig. 1.

Fuzzification: Fuzzification is the process of determining the membership functions for all linguistic labels of the linguistic variables. Since the inputs and outputs of the system are expressed in linguistic terms, then it allows rules to be applied in a simple manner to express a complex system.

Rule Base: In this step, the mapping of inputs to outputs can be

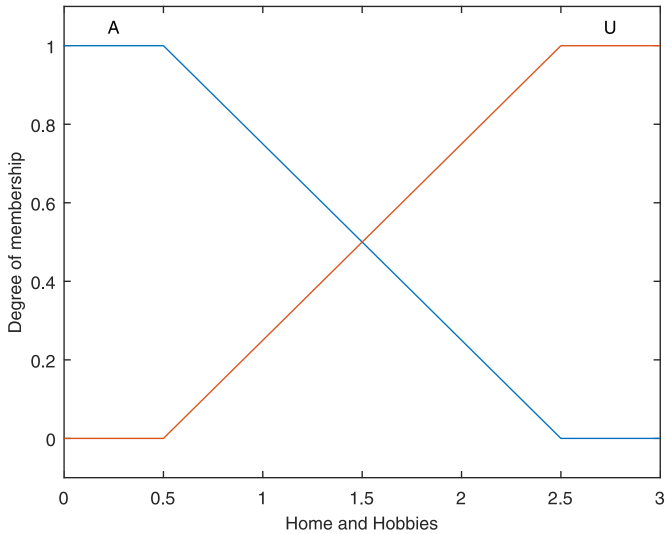

Fig. 7. Fuzzy sets Able (A) and Unable (U) for the input variable Home and Hobbies.

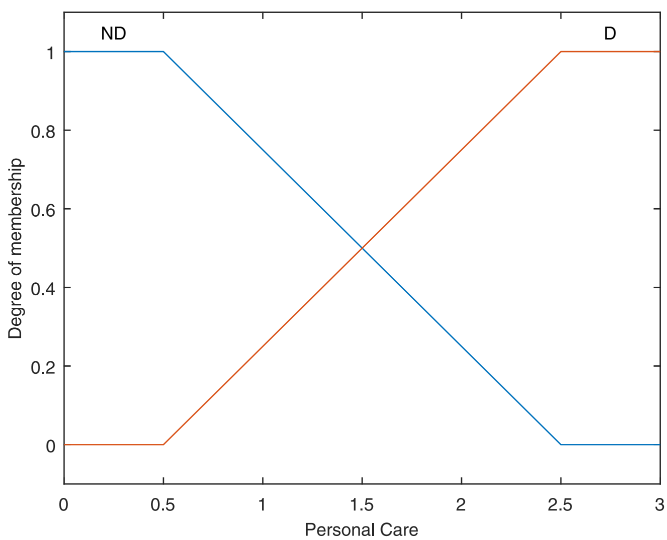

Fig. 8. Fuzzy sets Not Dependent and Dependent for the input variable Personal Care.

expressed as a set of rules of the form:

R_1: IF x_1 is A_{11} and x_2 is A_{12} and... x_n is A_{1n}
THEN y is D_{11}
R_2: IF x_1 is A_{21} and x_2 is A_{22} and... x_n is A_{2n}
THEN y is D_{21}
⋮
R_r: IF x_1 is A_{r1} and x_2 is A_{r2} and... x_n is A_{rn}
THEN y is D_{r1} where r is the number of rules, $x_1, x_2, \ldots, x_n$ are the input variables, A_{11}, A_{12},..., A_{1n} are the fuzzy sets, y is the output variable and D_{11}, D_{21},..., D_{r1} are the output fuzzy labels. The production of the rules is a crucial step that should be intermediated by a specialist accordingly to the setting to which the fuzzy approach is being applied. A specialist judgment and experience can be used to define the degree of membership function for a variable. Alternatively, rules can also be produced from data or other techniques, such as Neural Networks [35].

Fuzzy Inference: The inference method employed relies on its classification. In our context, Mamdani inference method is the appropriate one, since it returns a number as the output after defuzzification. Alongside Mamdani [36], Takagi-Sugeno [37] is the most used class of fuzzy inference.

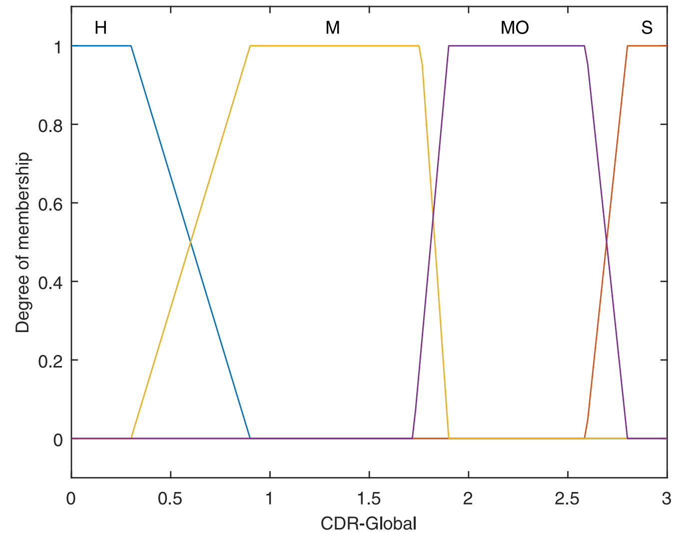

Fig. 9. Fuzzy Sets Healthy (H), Mild (M), Moderate (MO) and Severe (S) for the output variable F-CDR.

The main idea behind this step is to apply fuzzy logic to make inferences from linguistic variables from a fuzzy associative matrix to output the system's response to the given inputs [38]. Here, the Mamdani min-max approach was adopted for the inference mechanism.

Defuzzification: The defuzzification is the process that maps a fuzzy set to a crisp set. There are three defuzzifiers: the center-average defuzzifier, maximum defuzzifier and center-of-gravity defuzzifier [39]. Here we explore the center-of-gravity defuzzifier. Besides being widely applicated, using the center-of-gravity defuzzifier in a fuzzy system is a reasonable and optimal method in the sense of mean squares as shown in [40].

2.2. Matlab: fuzzy logic toolbox and GUIs

The model proposed in this work is based on Mamdani's inference method and it was developed in the FIS (Fuzzy Inference System) editor of the Fuzzy Logic Toolbox, which is a tool of the MATLAB software.

The interactiveness between the user and the model is intermediate by a graphical (user-friendly) interface built with the Matlab GUIs (Graphical user interfaces or apps). See Fig. 2.

The Matlab files and instructions to run the programs are available at the Mendley data repository https://data.mendeley.com/datasets/hm4vp824pz/4.

2.3. Specialists and dataset

Throughout the paper, two of the authors, namely, Wallaci Pimentel Valentino and Professor Natáli Valim Oliver Bento-Torres are referred to as specialists. Both have a background in Health Science and, in particular, Professor Natali has a Ph.D. in Neuroscience and Cell Biology and she has experience plications of the U-CDR.

The robustness of our model was tested on data provided by Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) that has a repository of neurology clinical evaluation of patients, which include CDR results.

The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

We use this database, which is composed of the inputs of the CDR and the outputs of U-CDR, to show that the fuzzy approach that we propose

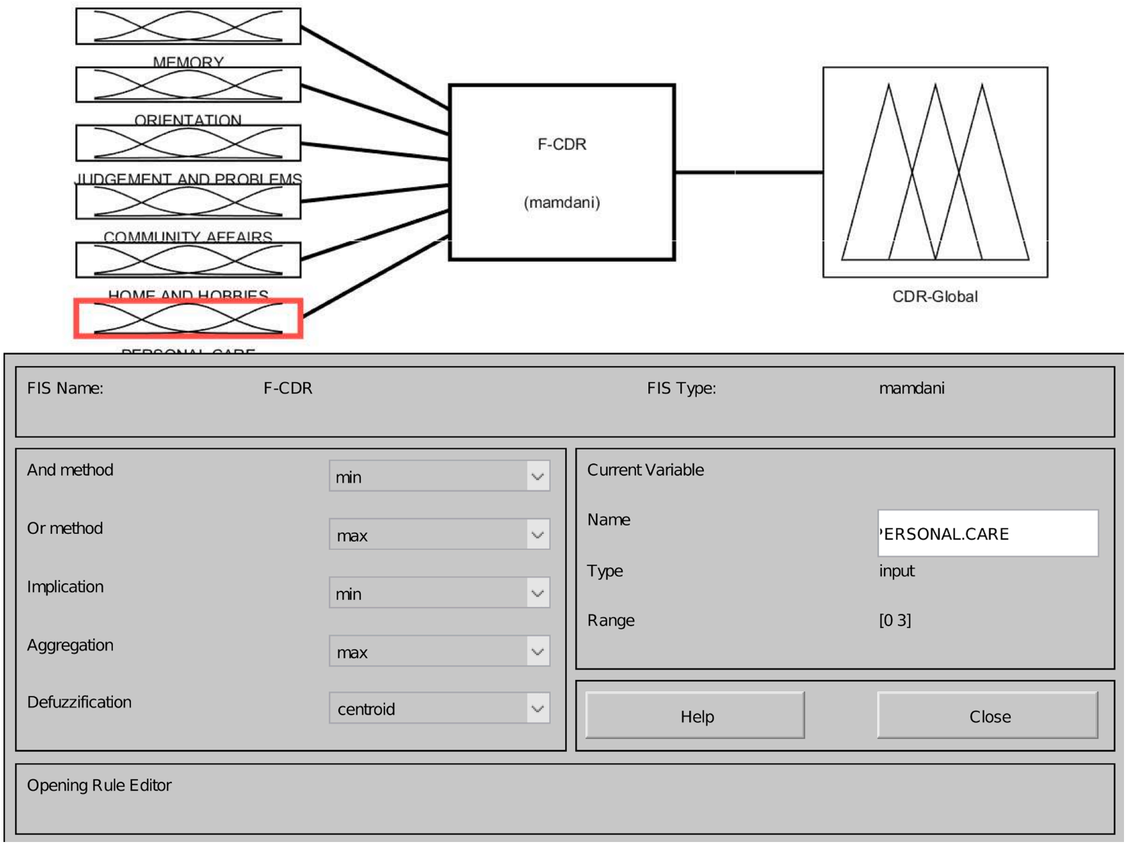

Fig. 10. Fuzzy inference system block diagram and constructed FIS system characteristics.

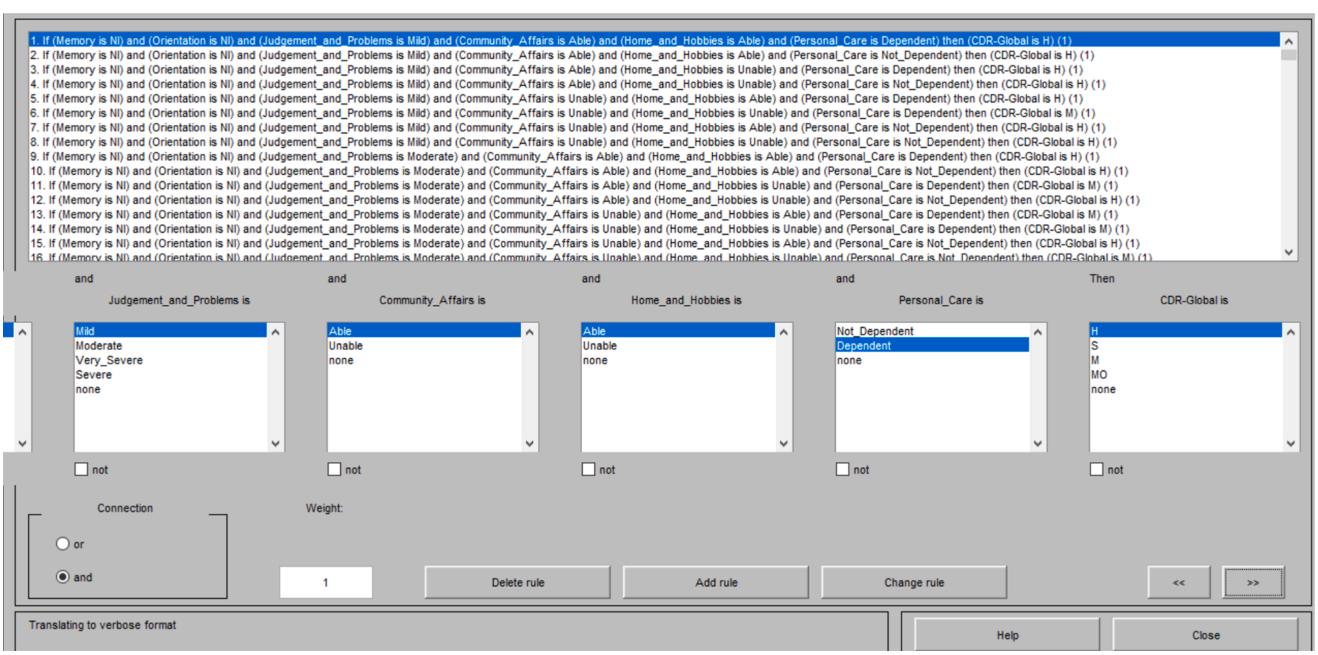

Fig. 11. Rule Base.

herein (F-CDR) provides outputs matching closely to those of the U-CDR and, by that, endorse the fact that the fuzzy logic applied to this context allows the user to score in a wider range and still obtain trustworthy staging of dementia.

Since the dataset is large (composed of 11.957 clinical evaluations) we extracted random samples aiming at a margin of error of 10% and a confidence level of 95%. The size of the samples were calculated with aid of the well know formula of sample size, with standard of deviation equal to 0.5. Precisely,

$$n = \frac{N\frac{Z^2 p(1-p)}{e^2}}{(N-1) + \frac{Z^2 p(1-p)}{e^2}},$$

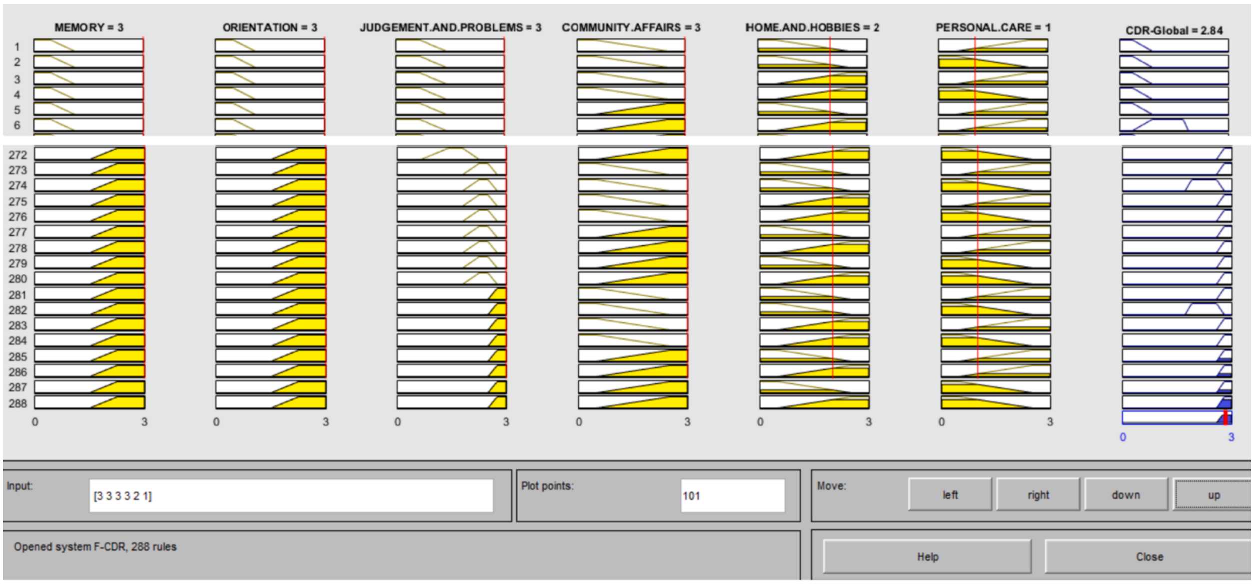

Fig. 12. Rule Viewer.

Table 1
Classification.

IF	F-CDR
OUT ≤ 0.32	Healthy
$0.32 < \text{OUT} < 0.9$	Questionable
$0.9 \leq \text{OUT} < 1.82$	Mild
OUT $= 1.82$	Mild and Moderate
$1.82 < \text{OUT} < 2.695$	Moderate
OUT $= 2.695$	Moderate and Severe
OUT > 2.695	Severe

where N is the total size of the population, Z is critical value of the normal distribution at the required confidence level, p is the sample proportion. It was taken as $p = 0.5$ in order to obtain the largest possible sample size; ℓ is the margin of error. For instance, the formula above applied for $N = 11957$, $p = 0.5$, $Z = 1.96$ which is the z value for 95% and $\ell = 0.1$ give us the sample size $n = 95.28 \approx 96$. Then, we used the `randperm(n,k)` function of Matlab with two parameters n and k to select the rows of each table. The Matlab function `randperm(n,k)` returns a row vector containing k unique integers selected randomly from 1 to n. In particular, we have used the Matlab comand `randperm(11957,96)` to random select 96 integers from 1 to 11957.

To sum up the role of the dataset in this work, we can say that the ætrainingg of the classifier F-CDR was done in the process of its construction relying on the specialist's experience whereas the testing was done afterward, using random samples of the dataset in order to compare the outputs of U-CDR and F-CDR.

3. Discussion and results

In this section we propose a fuzzy rule-based approach to diagnose dementia based on the CDR Staging Instrument. We call this by F-CDR model and it plays a central role in the achievements of this paper.

The linguistic variables, their fuzzification, and the set of rules that we use in this section were chosen based fundamentally on the specialists' experience, aiming to cover the U-CDR entries for each domain.

The U-CDR analyzes the dementia staging based on six input variables, Memory, Orientation, Judgment/Problem Solving, Community Affairs, Home/Hobbies, and Personal Care, which can take values 0, 0.5, 1, 2 or 3. In the F-CDR model that we propose, based on the specialist's indications, the same six input variables that are used in the U-CDR are considered, however, now each of them can assume any value in the interval [0,3].

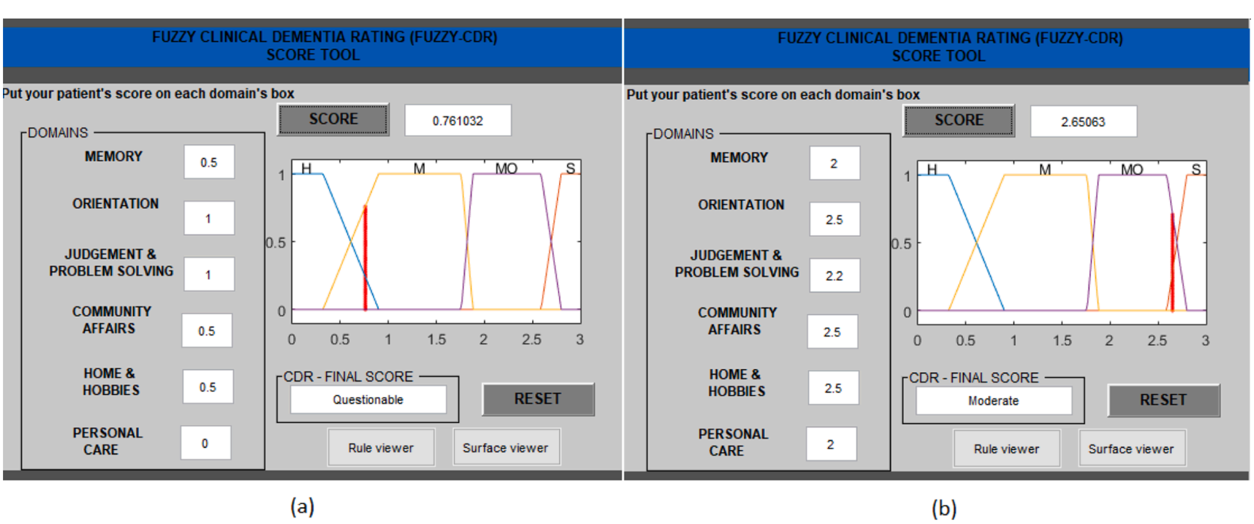

Fig. 13. F-CDR for the inputs (a) $(0.5, 1, 1, 0.5, 0.5, 0)$ and (b) $(2, 2.5, 2.2, 2.5, 2.5, 2)$.

Table A1
First comparison.

	I1	I2	I3	I4	I5	I6	U-CDR	F-CDR
1	0	0	0	0	0	0	H	H
2	0.5	0.5	0.5	0.5	0.5	0	Q	Q
3	0	0	0	0	0	0	H	H
4	0	0	0	0	0	0	H	H
5	0.5	0	0.5	0	0	0	Q	Q
6	0	0	0	0	0	0	H	H
7	0.5	0	0	0	0	0	Q	Q
8	0.5	0	0	0	0	0	Q	Q
9	0	0	0	0	0	0	H	H
10	2	1	0.5	1	1	0	M	M
11	0.5	0	0.5	0.5	0.5	0	Q	Q
12	0.5	0.5	0.5	0	0	0	Q	Q
13	1	1	0.5	0.5	0.5	0	**Q**	**M**
14	0.5	0	0	0	0	0	Q	Q
15	0.5	0	0.5	0	0	0	Q	Q
16	0	0	0	0	0	0	H	H
17	1	0.5	0.5	1	0.5	0	Q	Q
18	0.5	1	1	0.5	0	0	Q	Q
19	0.5	0.5	0	0	0.5	0	Q	Q
20	0.5	0	0.5	0	0	0	Q	Q
21	1	0.5	1	1	0.5	0	Q	Q
22	0	0	0	0	0	0	H	H
23	0	0	0	0	0	0	H	H
24	0	0	0	0	0	0	H	H
25	0	0	0.5	0	0	0	H	H
26	0	0	0	0	0	0	H	H
27	0	0	0	0	0	0	H	H
28	1	1	1	1	1	0	M	M
29	0	0	0	0	0	0	H	H
30	0	0	0	0	0	0	H	H
31	0.5	0.5	0	0	0	0	Q	Q
32	0	0	0	0	0	0	H	H
33	0.5	0	0.5	0	0	0	Q	Q
34	0.5	0	0	0	0	0	Q	Q
35	0.5	0	0	0	0	0	Q	Q
36	0	0	0	0	0	0	H	H
37	0.5	0	0.5	0.5	0.5	0	Q	Q
38	0.5	0	0	0	0	0	Q	Q
39	0.5	0	0	0	0	0	Q	Q
40	0	0	0	0	0	0	H	H
41	1	0	0.5	0.5	0.5	0	Q	Q
42	0	0	0	0	0	0	H	H
43	0.5	0.5	0.5	0	0.5	0	Q	Q
44	0.5	0	0	0	0	0	Q	Q
45	0	0	0	0	0	0	H	H
46	0.5	1	1	0.5	0.5	0	Q	Q
47	0	0	0	0	0	0	H	H
48	0.5	0	0	0	0.5	0	Q	Q
49	0.5	0	0.5	0	0	0	Q	Q
50	0	0	0	0	0	0	H	H
51	1	0.5	1	1	1	0	M	M
52	0.5	0	0.5	0	0.5	0	Q	Q
53	0	0	0	0	0	0	H	H
54	0.5	1	1	0.5	0.5	0	Q	Q
55	0	0	0	0	0	0	H	H
56	1	1	1	1	0.5	0	M	M
57	1	0.5	0.5	0.5	1	0	Q	Q
58	0.5	0	0	0	0	0	Q	Q
59	0	0	0	0	0	0	H	H
60	0.5	0.5	0.5	0.5	0.5	0	Q	Q
61	0	0	0	0	0	0	H	H
62	0.5	0	0	0	0	0	Q	Q
63	0	0	0.5	0	0	0	H	H
64	1	0.5	0.5	0.5	0.5	0	Q	Q
65	0	0	0	0	0	0	H	H
66	0.5	0.5	0.5	0.5	0	0	Q	Q
67	0.5	0	0	0	0	0	Q	Q
68	0.5	0.5	0.5	0.5	0.5	0	Q	Q
69	0	0	0	0	0	0	H	H
70	0.5	0	0	0	0	0	Q	Q
71	0.5	0	0.5	0.5	0.5	0	Q	Q
72	1	1	1	1	1	0	M	M
73	0.5	0.5	0.5	0	0	0	Q	Q
74	0.5	0	0	0	0	0	Q	Q
75	0.5	0	0.5	0	0	0	Q	Q
76	1	0.5	1	1	0.5	0	Q	Q
77	0	0	0	0	0	0	H	H
78	0	0	0	0	0	0	H	H
79	0	0	0	0	0	0	H	H
80	0	0	0	0	0	0	H	H
81	0	0	0	0	0	0	H	H
82	1	1	1	1	1	0	M	M
83	0.5	0	0.5	0	0	0	Q	Q
84	0.5	0	0	0	0	1	Q	Q
85	0	0	0	0	0	0	H	H
86	0	0	0	0	0	0	H	H
87	1	1	0.5	0.5	1	0	**Q**	**M**
88	0.5	0.5	0.5	0.5	0	0	Q	Q
89	0.5	0	0	0	0	0	Q	Q
90	0.5	0.5	1	0.5	0.5	0	Q	Q
92	0.5	0	0.5	0	0.5	0	Q	Q
93	0	0	0	0	0	0	H	H
94	0.5	1	1	0.5	1	0	M	M
95	0.5	0	0	0	0	0	Q	Q
96	2	2	1	1	1	1	M	M

The input variables are represented by fuzzy sets, as shown in Figs. 3-8, where NI, MI, SI, SD, MD, VD, I, A, U, ND, and D mean No Impairment, Mild Impairment, Severe Impairment, Some Difficulty, Moderate Difficulty, Very Difficulty, Inept, Able, Unable, Not Dependent and Dependent, respectively.

The output variable F-CDR is represented by four fuzzy sets, namely Healthy (H), Mild (M), Moderate (MO), and Severe (S), as showed in Fig. 9. The output Questionable, which is considered in the U-CDR, was not taken into account in variable F-CDR since it can be understood as an output that can be obtained from the transition range between the Healthy and Mild sets. See Fig. 9, for F-CDR greater than 0.32 and less than 0.9. The use of trapezoidal fuzzy sets is justified in our setting since, besides providing a simple algorithm of arithmetic operations, as well as easy and intuitive interpretation, we also understand that for our problem it makes sense to consider that the fuzzy sets are described by subintervals of the interval [0,3]. The vertices of the trapezoids were chosen based on the U-CDR scores, according to the specialist's indications. For example, for the output variable shown in Fig. 9, the idea is to keep the value 0.5 in the transition range of sets H and M, because in the U-CDR this score means questionable, that is, it is neither Healthy nor Mild.

Based on the descriptions of the input and output variables, 288 rules were constructed by selecting an item in each input and output variable and one connection (AND), which is performed by a min operation (Fig. 11). More details about the membership functions and the rule base can be found in Appendix B.

The system was developed using Matlab's Fuzzy Toolbox (Fig. 10). The Rule Viewer presented in Fig. 12 shows in detail the computation for inputs 3, 3, 3, 3, 2, and 1, which are displayed on the topmost part above each column. The first six columns of plots show the IF part of each rule and the seventh column of plots shows the THEN part of each rule. For each rule, the last plot in the seventh column is obtained aggregating the variables presented in the first six columns, which depend upon the input values of the system, by the minimum t-norm which takes into account only the lowest membership during the aggregation process. In the next step, all membership functions of the seventh column are aggregated by the maximum operator to provide one single fuzzy set. So the aggregation of the fuzzy sets is defuzzified by the centroid method in order to resolve upon a single output value from the set. It returns the center of the area under the curve which is displayed as a bold vertical red line in this graph. See Fig. 12.

In order to make a comparison between the results obtained with the U-CDR and the F-CDR, we use the classification presented in Table 1. Here it is important to emphasize that, although the Questionable set is not a fuzzy set of the output in F-CDR, we assume that, if after

Table A2
Comparison for Mild cases.

	I1	I2	I3	I4	I5	I6	U-CDR	F-CDR
1	2	1	0.5	0.5	1	0	M	M
2	2	1	1	1	0.5	0	M	M
3	1	1	1	1	1	1	M	M
4	1	1	1	1	1	0	M	M
5	1	1	1	1	1	1	M	M
6	1	1	1	1	1	0	M	M
7	0.5	1	1	0	1	1	M	M
8	1	1	1	0.5	1	0	M	M
9	1	1	1	1	1	1	M	M
10	1	1	1	1	0	0	M	M
11	1	1	1	2	2	1	M	M
12	1	1	1	1	1	1	M	M
13	1	0.5	1	1	1	0	M	M
14	1	0.5	2	2	1	1	M	M
15	2	1	2	1	1	0	M	M
16	1	1	1	2	2	1	M	M
17	1	0.5	1	1	1	0	M	M
18	1	1	0.5	1	1	0	M	M
19	1	1	1	1	1	0	M	M
20	1	1	1	1	2	1	M	M
21	1	1	1	1	0.5	0	M	M
22	1	1	1	0.5	1	0	M	M
23	1	1	1	1	1	0	M	M
24	1	1	1	1	1	1	M	M
25	1	1	1	1	1	1	M	M
26	1	1	1	1	1	0	M	M
27	1	1	1	1	1	0	M	M
28	2	2	1	1	1	0	M	M
29	1	1	1	1	1	0	M	M
30	1	0.5	1	1	1	0	M	M
31	1	1	1	1	0.5	0	M	M
32	1	1	1	1	1	0	M	M
33	1	1	1	1	1	1	M	M
34	2	1	1	1	1	1	M	M
35	1	1	0.5	1	1	1	M	M
36	2	1	1	1	1	0	M	M
37	1	1	1	0.5	0.5	1	M	M
38	1	1	0.5	1	0.5	1	M	M
39	1	1	1	1	0.5	0	M	M
40	2	3	1	2	0.5	1	M	M
41	1	1	1	1	1	0	M	M
42	1	1	1	1	0	0	M	M
43	1	1	1	1	2	1	M	M
44	1	1	1	1	1	1	M	M
45	1	2	1	1	2	1	M	M
46	1	1	1	0.5	1	1	M	M
47	1	1	1	0.5	0.5	1	M	M
48	1	1	1	1	1	0	M	M
49	1	1	0.5	1	1	0	M	M
50	1	1	1	0.5	1	0	M	M
51	2	1	1	1	1	0	M	M
52	1	1	1	1	2	1	M	M
53	1	0.5	1	1	1	0	M	M
54	2	1	2	1	1	2	M	M
55	1	1	1	1	1	0	M	M
56	1	1	1	1	1	0	M	M
57	2	1	2	1	1	1	M	M
58	2	2	2	1	1	0	M	M
59	2	2	0.5	1	0	1	M	M
60	1	1	1	1	1	1	M	M
61	2	1	1	1	1	0	M	M
62	1	1	1	1	0.5	0	M	M
63	1	1	1	2	1	0	M	M
64	1	1	2	1	1	0	M	M
65	1	1	1	0.5	1	0	M	M
66	2	2	1	1	1	0	M	M
67	2	2	0.5	1	2	1	M	M
68	2	1	1	1	1	0	M	M
69	1	1	0.5	1	1	1	M	M
70	1	1	0.5	1	1	0	M	M
71	1	1	1	0.5	1	0	M	M
72	1	1	1	0.5	1	0	M	M
73	1	1	0.5	1	1	0	M	M
74	2	2	1	1	1	1	M	M
75	1	1	1	1	1	0	M	M
76	2	1	2	1	2	1	M	M
77	1	1	1	0.5	1	0	M	M
78	1	1	1	0.5	1	1	M	M
79	1	1	1	1	0.5	1	M	M
80	1	1	1	1	1	1	M	M
81	1	0.5	1	0.5	1	1	M	M
82	1	1	1	2	2	1	M	M
83	2	1	1	1	2	0	M	M
84	1	1	1	1	1	1	M	M
85	0.5	1	0.5	1	1	0	M	Q
86	1	1	1	0.5	1	0	M	M
87	1	1	1	1	1	1	M	M
88	2	2	1	1	2	0	M	M
89	1	1	1	1	1	0	M	M
90	2	2	1	2	1	1	M	M

defuzzification the numerical output provided by the model belongs to the transition range between Healthy and Mild, then the system presents Questionable as a classification. In other cases, the greater membership degree (output) is the one that is assigned, as we can see in Table 1. Fig. 13 shows the final score of F-CDR for two different inputs. The first one (0.5, 1, 1, 0.5, and 0) provides the numerical value 0.760132 for the output (see Fig. 13 (a)) and it is represented by the red line on the graph of the membership functions of the output variable. Since 0.760132 belongs to the transition range between the Healthy and Mild sets, the final score 'Questionable' was obtained. For the inputs (2, 2.5, 2.2, 2.5, 2.5, 2) the F-CDR provides the numerical value 2.65063 (see Fig. 13 (b)), and once again is represented by the red line on the graph of the membership functions of the output variable. It shows that the output belongs "more" to the Moderate set than the Severe one and therefore the F-CDR is Moderate.

For the sake of completeness, it is worth mentioning that the numerical values 1.82 and 2.695, which appear in Table 1, represent the intersections between the pairs Mild/Moderate fuzzy sets and Moderate/Severe fuzzy sets, respectively.

We proceed by presenting a comparison between the CDR results obtained from a usual specialist's application (U-CDR) and the results obtained from our fuzzy approach (F-CDR). That is, we compare the performance of our F-CDR model with that of U-CDR by showing that the outputs obtained via our fuzzy approach match closely to those of the U-CDR. This analysis comparing how close are the approaches U-CDR and F-CDR, were done with the use of the data indicated in Section 2.3.

Aiming a margin of error of 10% and confidence level of 95%, for the first analysis of our model, a sample composed of 96 cases was randomly selected from ADNI database which is composed of 11.957 clinical evaluations.

For this sample, using the same inputs, the F-CDR performed with 98,06% of matches to that of the U-CDR. See Table A.2 in Section Appendix A.

In this sample, there were no Moderate and Severe cases. Moreover, very few cases were Mild. So, in order to test and challenge the robustness of our fuzzy approach against these cases, we considered an isolated analysis for each of the cases with (U-CDR) output Severe, Moderate and Mild. To do so, we extracted from the dataset each of these cases isolatedly and then we selected a random sample, still keeping a margin of error of 10% and confidence level of 95%. This sample selection approach provided us with 45 cases of Severe, 75 cases of Moderate, and 90 cases of Mild. Following, an application of the F-CDR to the same inputs that generated such cases presented an accuracy of matches of 98,8% for the Mild cases, for Severe cases, there was a 97,8% of accuracy and 94,7% for Moderate cases. See Tables A.3–A.5 in Section Appendix A.

To close the section, we highlight the fact that our proposed

Table A3
Comparison for Moderate cases.

	I1	I2	I3	I4	I5	I6	U-CDR	F-CDR
1	2	2	2	2	1	1	MO	MO
2	1	2	2	2	3	1	MO	MO
3	2	2	2	2	3	1	MO	MO
4	2	1	2	2	2	1	MO	MO
5	2	2	1	2	2	1	MO	MO
6	2	2	3	2	2	1	MO	MO
7	2	2	3	2	2	2	MO	MO
8	2	2	1	2	2	1	MO	MO
9	2	3	2	2	2	1	MO	MO
10	2	2	2	2	2	2	MO	MO
11	2	2	2	2	2	1	MO	MO
12	2	2	1	2	2	3	MO	MO
13	2	3	2	2	3	2	MO	MO
14	2	2	1	2	2	1	MO	MO
15	3	3	2	2	2	2	MO	MO
16	3	3	2	2	3	2	MO	MO
17	3	2	2	2	2	2	MO	MO
18	2	2	1	2	2	3	MO	MO
19	2	2	2	2	3	2	MO	MO
20	2	1	1	2	2	2	MO	M
21	2	2	2	2	2	1	MO	MO
22	2	2	3	2	2	2	MO	MO
23	2	2	2	3	3	2	MO	MO
24	1	2	2	2	3	3	MO	MO
25	2	2	1	2	2	1	MO	MO
26	2	2	2	2	1	1	MO	MO
27	3	2	2	2	2	1	MO	MO
28	2	2	1	2	2	3	MO	MO
29	3	2	2	2	2	3	MO	MO
30	2	3	2	2	3	2	MO	MO
31	2	2	2	2	2	0	MO	MO
32	2	2	2	2	1	1	MO	MO
33	2	2	1	2	3	2	MO	MO
34	2	2	2	2	2	1	MO	MO
35	2	2	1	2	2	0	MO	MO
36	3	2	2	2	2	2	MO	MO
37	2	1	2	2	2	2	**MO**	**M**
38	2	2	1	2	2	1	MO	MO
39	3	2	2	1	1	2	MO	MO
40	2	2	2	2	2	2	MO	MO
41	2	2	1	2	2	0	MO	MO
42	3	2	3	2	2	2	MO	MO
43	2	2	2	2	2	2	MO	MO
44	2	2	2	2	2	2	MO	MO
45	3	3	2	2	2	2	MO	MO
46	1	1	1	2	2	2	MO	M
47	2	2	3	2	2	1	MO	MO
48	2	2	1	2	2	3	MO	MO
49	2	3	2	1	2	1	MO	MO
50	2	2	2	2	2	2	MO	MO
51	2	2	1	2	2	1	MO	MO
52	2	2	2	2	3	2	MO	MO
53	2	2	3	3	2	0	MO	MO
54	2	2	2	2	2	1	MO	MO
55	2	2	1	2	2	0	MO	MO
56	3	3	0.5	2	2	2	MO	MO
57	2	2	1	3	3	2	MO	MO
58	2	2	1	2	2	1	MO	MO
59	2	2	2	2	2	1	MO	MO
60	1	1	1	2	2	2	**MO**	**M**
61	2	2	2	3	3	2	MO	MO
62	2	2	1	2	2	1	MO	MO
63	3	2	3	2	2	2	MO	MO
64	2	3	2	2	2	2	MO	MO
65	2	2	1	2	2	0	MO	MO
66	2	2	1	2	2	0	MO	MO
67	2	2	1	2	2	1	MO	MO
68	2	2	2	2	3	2	MO	MO
69	2	2	2	2	2	1	MO	MO
70	2	2	2	1	2	1	MO	MO
71	2	2	1	2	2	2	MO	MO
72	2	2	2	2	2	1	MO	MO
73	2	2	1	2	2	0	MO	MO
74	2	2	1	2	2	1	MO	MO
75	1	1	2	2	2	2	MO	MO

Table A4
Comparison for Severe cases.

	I1	I2	I3	I4	I5	I6	U-CDR	F-CDR
1	2	3	3	2	3	3	S	S
2	3	3	3	3	3	3	S	S
3	3	3	3	2	3	3	S	S
4	3	3	3	2	3	3	S	S
5	3	3	3	3	3	3	S	S
6	3	3	3	2	3	2	S	S
7	3	3	3	2	3	2	S	S
8	3	3	3	3	2	2	S	S
9	3	3	3	2	3	2	S	S
10	3	3	2	2	3	3	S	S
11	3	3	3	3	3	2	S	S
12	3	3	3	2	2	3	S	S
13	3	2	3	3	3	3	S	S
14	3	3	3	3	3	2	S	S
15	3	3	2	2	3	1	**S**	**MO**
16	3	3	3	3	3	3	S	S
17	2	2	3	2	3	3	S	S
18	3	3	3	3	3	3	S	S
19	3	3	3	3	3	3	S	S
20	3	3	3	3	3	3	S	S
21	3	3	3	3	3	3	S	S
22	3	3	3	3	3	3	S	S
23	3	3	3	2	3	3	S	S
24	3	3	2	3	3	3	S	S
25	3	3	3	2	3	2	S	S
26	3	2	2	3	3	3	S	S
27	3	3	3	2	3	3	S	S
28	3	3	3	2	3	2	S	S
29	2	2	3	2	3	3	S	S
30	3	2	3	2	3	3	S	S
31	3	3	3	2	3	2	S	S
32	3	3	3	2	3	1	S	S
33	3	3	3	3	2	2	S	S
34	3	3	3	3	3	2	S	S
35	3	3	3	2	3	2	S	S
36	3	3	3	2	3	2	S	S
37	3	3	3	2	3	2	S	S
38	3	3	3	2	3	3	S	S
39	3	3	3	2	3	3	S	S
40	3	3	3	2	2	3	S	S
41	2	2	3	3	3	1	S	S
42	2	3	3	3	3	2	S	S
43	3	3	3	2	3	1	S	S
44	3	3	3	2	3	3	S	S
45	3	3	3	2	3	1	S	S

approach F-CDR to the U-CDR allows to stage dementia into several categories at the same time, but with different membership degrees. This situation is represented by the vertical red line on the graph of the membership functions of the output variable in the created graphical interface. See Fig. 13.

4. Conclusions

The CDR is a commonly used scale to stage dementia severity. However, since subjective observations determine what score is used in each entry to infer about the severity of dementia, the fuzzy logic finds a suitable situation to be applied. This is ratified by the fact that the usual scoring of the entries in the CDR is fixed (0, 0.5, 1, 2, 3) and the fuzzy model herein proposed allows scoring entries continuously which makes the F-CDR more suitable to work through subjectivities of the scoring process.

The tests against data provided by ADNI showed that the F-CDR approach herein proposed performs with high accuracy, matching closely to those of the U-CDR. This indicates that the F-CDR can be understood as a generalization of the usual approach, since it encompasses the possibility of scoring the input variables continuously throughout the interval [0,3], taking into account the inherent subjectivities of the scoring process of the U-CDR.

Summing up, in this paper, we have proposed a way to approach the CDR instrument as a clinical decision support system based on fuzzy logic. In the future, we intend to compare the performance of this fuzzy approach with other computer decision-support such as, for instance, machine learning, which will certainly contribute towards the construction of a more accurate dementia staging instrument.

Authors contributions

The contributions of each author are listed below

Wallaci P. Valentino: conceptualization and design, data gathering and analysis, software development and drafting the manuscript.

Michele C. Valentino: conceptualization and design, data analysis, software development and drafting the manuscript.

Douglas Azevedo: conceptualization and design, data analysis, drafting and formating the manuscript.

Natáli V. O. Bento-Torres: conceptualization and design, data analysis.

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Appendix A. Tables of comparison between the results obtained with the U-CDR and F-CDR

This section is reserved for the presentation of the tables that were used as random samples in the fuzzy approach to the CDR staging instrument that we introduced and discussed in this paper.

Each table represents a random sample from the ADNI dataset which means that each line represents the process of staging dementia of a patient. Precisely, in each line, the columns I1 to I6 are the score inputs, that is, Memory, Orientation, Judgment/Problem solving, Community affairs, Home/Hobbies and Personal Care, respectively, and while column U-CDR is the output obtained from a usual application of the CDR over the inputs and the column F-CDR is the output returned from the fuzzy model herein proposed, via the same inputs. As it is shown in the tables, the fuzzy approach performs over the input data with high accuracy, matching closely the outputs U-CDR. This indicates that the fuzzy model we propose is suitable to extend the scoring process for a 'continuous scoring process' which allows the specialist to assign any number in the interval [0,2] during the evaluation process for staging dementia. We understand that this feature encompasses an alternative to deal with the uncertainties during the scoring process and implies more truthful staging dementia compared to the usual approach of the CDR.

Appendix B. Membership functions and rule base

In order to facilitate the reproduction of the model presented in this work, in this section we present the membership functions and rule base in details.

```

%Membership Functions

%Memory
a = addvar(a, 'input','Memory',[0 3]);
a = addmf(a,'input',1,'NI','trapmf',[0 0 0.45 1.1]);
a = addmf(a, 'input', 1, 'MI', 'trapmf', [0.45 1.1 1.5 2.25]);
a = addmf(a, 'input', 1, 'SI', 'trapmf', [1.5 2.25 3 3]);

%Orientation
a = addvar(a,'input','Orientation',[0 3]);
a = addmf(a,'input',2,'NI','trapmf',[0 0 0.5 1.1]);
a = addmf(a,'input',2,'MI','trapmf',[0.5 1.1 1.5 2.25]);
a = addmf(a,'input',2,'SI','trapmf',[1.5 2.25 3 3]);

%Judgement_and_Problems
a = addvar(a,'input','Judgement-and-Problems',[0 3]);
a = addmf(a,'input',3,'SD','trapmf',[0 0 0.65 1.4]);
a = addmf(a,'input',3,'MD','trapmf',[0.65 1.4 1.8 2.25]);
a = addmf(a,'input',3,'VD','trapmf',[1.8 2.25 2.5 2.75]);
```

```
a = addmf(a,'input',3,'I','trapmf',[2.5 2.75 3 3]);

%Community_Affairs
a = addvar(a,'input','Community_Affairs',[0 3]);
a = addmf(a,'input',4,'A','trapmf',[0 0 0.5 2.5]);
a = addmf(a,'input',4,'U','trapmf',[0.5 2.5 3 3]);

%Home_and_Hobbies
a = addvar(a,'input','Home_and_Hobbies',[0 3]);
a = addmf(a,'input',5,'A','trapmf',[0 0 0.5 2.5]);
a = addmf(a,'input',5,'U','trapmf',[0.5 2.5 3 3]);

%Personal_Care
a = addvar(a,'input','Personal_Care',[0 3]);
a = addmf(a,'input',6,'ND','trapmf',[0 0 0.5 2.5]);
a = addmf(a,'input',6,'D','trapmf',[0.5 2.5 3 3]);

%GlobalCDR
a = addvar(a,'output','Global-CDR',[0 3]);
a = addmf(a,'output',1,'H','trapmf',[0 0 0.32 0.9]);
a = addmf(a,'output',1,'S','trapmf',[2.59 2.8 3 3]);
a = addmf(a,'output',1,'M','trapmf',[0.32 0.9 1.76 1.88]);
a = addmf(a,'output',1,'MO','trapmf',[1.76 1.88 2.59 2.8]);


% Rule Base
%I1 I2 I3 I4 I5 I6 F-CDR Weight Connection
regras=[1 1 1 1 1 2 1 1 1;1 1 1 1 1 1 1 1 1;1 1 1 1 2 2 1 1 1;
1 1 1 1 2 1 1 1 1;1 1 1 2 1 2 1 1 1;1 1 1 2 2 2 3 1 1;
1 1 1 2 1 1 1 1 1;1 1 1 2 2 1 1 1 1;1 1 2 1 1 2 1 1 1;
1 1 2 1 1 1 1 1 1;1 1 2 1 2 2 3 1 1;1 1 2 1 2 1 1 1 1;
1 1 2 2 1 2 3 1 1;1 1 2 2 2 2 3 1 1;1 1 2 2 1 1 1 1 1;
1 1 2 2 2 1 3 1 1;1 1 4 1 1 2 1 1 1;1 1 4 1 1 1 1 1 1;
1 1 4 1 2 2 4 1 1;1 1 4 1 2 1 1 1 1;1 1 4 2 1 2 4 1 1;
1 1 4 2 2 2 2 1 1;1 1 4 2 1 1 1 1 1;1 1 4 2 2 1 4 1 1;
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1 1 3 1 2 1 1 1 1;1 1 3 2 1 2 4 1 1;1 1 3 2 2 2 2 1 1;
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1 3 4 2 2 1 2 1 1;3 3 1 1 2 4 1 1;3 3 1 1 1 1 1 1;
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