Multi-granular Computing Can Predict Prodromal Alzheimer's Disease Indications in Normal Subjects

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Abstract. The processes of neurodegeneration related to Alzheimer's disease (AD) begin several decades before the first symptoms. We have used multi-granular computing (MGC) to classify cognitive data from BIOCARD study that have been started over 20 years ago with 354 normal subjects. Patients were evaluated every year by a team of neuropsychologists and neurologists and classified as normal, with MCI (mild cognitive impairments), or with dementia. As the decision attribute, we have used CDRSUM (Clinical Dementia Rating Sum of Boxes) as a more quantitative measure than the above classification. Based on 150 stable subjects with different stages of AD, and on the group of 40 AD, we have found sets of different granules that classify cognitive attributes with *CDRSUM* as the disease stage. By applying these rules to normal ($CDRSUM = 0$) 21 subjects we have predicted that one subject might get mild dementia ($CDRSUM > 4.5$), one very mild dementia ($CDRSUM > 2.25$), four might get very mild dementia or questionable impairment and one other might get questionable impairment ($CDRSUM > 0.75$). AI methods can find, invisible for neuropsychologists, patterns in cognitive attributes of normal subjects that might indicate their pre-dementia stage, also in longitudinal testing.

Keywords: Granular Computing · Rough Set · Rules · Cognition · Genotype

1 Introduction

The prevalence of Alzheimer's Disease (AD) related dementia is fast increasing due to our aging population, and it may reach 139 million in 2050. There is no cure for AD, as during the first clinical symptoms and neurological diagnosis many parts of the

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brain are already affected without the possibility to recover. As the neurodegenerations begin two to three decades before observed symptoms, the best chance to fight AD is to estimate the beginning period of the AD-related brain changes. The BIOCARD* study was initiated in 1995 by NIH with 354 normal individuals interrupted in 2005 and continued from 2009 as Johns Hopkins (JHU) study. At JHU, patients have yearly cognitive and clinical visits that measured a total of over 500 attributes with 96 cognitive parameters [1, 2]. Albert et al. [2] have successfully predicted conversion from normal to MCI (Mild Cognitive Impairment) due to AD, 5 years after baseline, for 224 subjects by using the following parameters: CSF: beta-amyloid and p-tau, MRI hippocampal and entorhinal cortex volumes, cognitive tests scores, and APOE genotype. But our approach is different, as we have performed classification by using granular computing (GC) [3] connecting cognitive test results with genetic data (related to the apolipoprotein E ApoE genotype) and AD-related clinical symptoms in the group of different subjects from normal to AD. We took this group as our Model for the supervised training of different granules that are related to various stages of the disease, from normal subjects to MCI (Mild Cognitive Impairment) and to subjects with AD-related dementia.

In the next step, we applied these granules to individual, normal subjects to predict in every single tested subject, the possibility of the beginning of the neurodegeneration (AD-related symptoms). To **validate our method**, we have also applied it to the early stages in patients that were diagnosed with AD if we can predict their future AD stage (the preclinical classification of all potential patients).

Our GC method implemented with a rough set (RS) gave better classifications than such ML methods as Random Forest, Decision Tables, Bayes classifier, and Tree ensembles for Parkinson's disease patients [4], see review for more comparisons [5].

2 Methods

It is a continuation of our previous study [6] therefore methods are similar, but in this part, we are using MGC (Multi GC) in addition to analysis of the longitudinal changes in our subjects. We have analyzed predominantly cognitive and in addition to genotype (*APEO*) attributes of several different groups of subjects. The first group consists of 150 subjects with 40 normal subjects, 70 MCI (Mild Cognitive Impairment), and 40 subjects with dementias (AD). It was chosen this way as in the whole population of 354 normal subjects followed from 1995, only 40 subjects became demented. Therefore, we have added 40 normal subjects and 70 MCI as they are in between AD and normal subjects. The second group was 40 AD subjects, and the last group was 21 subjects, clinically classified as normal. We have estimated stages of the disease based on *CDRSUM* values (see abstract) as (0.0) – normal; (0.5–4.0) – questionable cognitive impairment; (0.5–2.5) – questionable impairment; (3.0–4.0) – very mild dementia; (4.5–9.0) – mild dementia [7]. We have used the same attributes as before [6]: Logical Memory Immediate (*LOGMEM1A*), Logical Memory Delayed (*LOGMEM2A*), Trail Making, Part A (*TrailA)* and B (*TrailB),* Digit Symbol Substitution Test (*DSST*), Verbal Fluency Test (*FCORR*), Rey Figure Recall (*REYRECAL*), Paired Associate Immediate (*PAIRED1*), Paired Associate Delayed (*PAIRED2*), Boston Naming Test (*BOSTON*), and new California Verbal Learning Test (*CVLT*). In addition, we have registered *APOE* genotype;

individuals who are *ApoE4* carriers vs. non-carriers (digitized as 1 vs. 0). Based on our classification, we have estimated Clinical Dementia Rating Sum of Boxes (*CDRSUM)*, compared with *CDRSUM* obtained by neurologists, and determined the predicted stage of an individual patient.

2.1 Rough Set Implementation of GC

Our data mining granular computing (GC) analysis was implemented by rough set theory (RST) discovered by Zdzislaw Pawlak [8], whose solutions of the vague concept of boundaries were approximated by sharp sets of the upper and lower approximations (Pawlak 1991). More details in our previous paper [9]

We have used Rough Set Exploration System RSES 2.2 as a toolset for analyzing data with rough set methods [10, 11].

3 Results

3.1 Statistics

We have performed statistical analysis for all 15 attributes, and we found that 7 attributes had stat. Sig. Difference of means: FCORR, REYRECAL, PAIRED1, PAIRED2, BOSTON, CVLT, CDRSUM. We analyzed different groups of subjects: normal (GroupN), a mixture of normal MCI, AD (Groupl), and AD (Group2).

3.2 Rules from the General Model (Group1)

In this study, by using MGC, we reduced the number of attributes from 14 that were used before [6] to the following five: *APOE, FCORR, DDST, TrailB,* and the decision attribute was *CDRSUM*. The APOE genotype; individuals who have *ApoE4* is an important genetic factor, which influences the probability of AD. One of the early predictors of AD is poor language performance, quantified by the *FCORR* test. Another early indication is difficulties in reasoning that may be estimated by the *DDST* test. Slowing processing speed is also observed as an early AD indicator that can be quantified by *TrailB* tests.

We put all data in the decision table as in [6], and with RSES help, after discretization, we found that because large data set and a small number of parameters, the decision attribute has 7 ranges (related to a very precise classification): “(-Inf,0.25)”, “(0.25,0.75)”, “(0.75,1.25)”, “(1.25,2.25)”, “(2.25,3.25)”, “(3.25,4.25)”, “(4.25,Inf)”. After generalization, there were 82 rules, below are some examples:

$$(APOE = 0)\&\left(DSST ='' (66.5, Inf)''\right) => \left(CDRSUM ='' (-Inf, 0.25)''[4]\right) 4 \quad (1)$$

$$\begin{aligned}&(APOE = 1)\&\left(TRAILB ='' (128.5, Inf)''\right)\&\left(FCORR ='' (6.5, 10.5)''\right) => \\ &(CDSUM ='' (4.25, Inf)'' [2])\, 2\end{aligned} \quad (2)$$

One significant attribute in the genetic *APOE* genotype, and in these approximate rules lack of *ApoE4* carriers ($APOE = 0$) related to health (Eq. 1), where ($APOE = 1$) increases the probability of AD (Eq. 2). The *DSST* - digit symbol substitution test is related to associative learning, and higher numbers are better (Eq. 1). In contrast to *TrailB* higher value means slow execution that is bad (Eq. 2) and language fluency problems (low value of *FCORR*) are the main factors that such patients have indications of mild dementia (*CDRSUM* is larger than 4.25) (Eq. 2).

By applying all 82 rules to the healthy patients (GroupN) with clinically confirmed $CDRSUM = 0$, we found one patient with *CDRSUM* significantly larger than 0 in the following classification:

$$(Pat = 164087)\&(APOE = 1))\&\big(DSST ='' (46.5, 49.5)''\big)\&\big(FCORR ='' (10.5, 13.5)''\big)\& (TRAILB ='' (72.5, 128.5)'' => (CDRSUM ='' (2.25, 3.25)''$$

(3)

The Eq. 3 indicates based on 4 condition attributes that patient *164087* might have. *CDRSUM* = *"(2.25,3.25)"* suggests very mild dementia [7].

In the next step of the MGC method, we have increased the number of attributes to seven: *APOE, BOSTON, FCORR, DDST, TrailB,* and *REYRECAL,* with *CDRSUM* as the decision attribute. We added the Boston naming test (*BOSTON*) forgetting the names of objects, and problems related to a visual memory of the complex figure (*REYRECAL*). After discretization with RSES help, the decision attribute has 3 ranges: "(-Inf,0.75)", "(0.75,1.25)", and "(1.25, Inf)". We have obtained 104 rules from Group1 patients and applied them to GroupN normal subjects, and got the following classifications, e.g.:

$$(Pat = 164087)\&(APOE = 1))\&\big(FCORR ='' (10.5, 13.5)''\big))\&(REYRCAL ='' (15.75, 25.25)'')''\big)\&\big(TRAILB ='' (75.0, 114.5)''\big)\&(DSST ='' (47.5, 53.5)''\big)\&\big(BOSTON ='' (25.5, 26.5)''\big) => (CDRSUM ='' (2.0,\ 3.25)$$

(4)

In this example the same patient $Pat = 164087$ with more condition attributes in Eq. 4 in comparison to Eq. 3 gives almost identical results for *CDRSUM*, as the main factors are related to bad speech fluency (*FCORR*) and the *APOE* genome. Comparing with 14 attributes from our previous work [6] actual results are at least partly overlapping:

$$(Pat = 164087)\&\big(LOGMEM\,1A = ''(-Inf, 15.5)''\big)\&\big(LOGMEM\,2A = ''(-Inf, 16.5)''\big)\& \big(TRAILA = ''(35.5, Inf)''\big)\&\big(TRAILB = ''(74.5, 153.0)''\big)\&\big(FCORR ='' (-Inf, 16.5)''\big)\& \big(REYRECAL = ''(15.75, 25.25)''\big)\&\big(PAIRD2 ='' (-Inf, 6.5)''\big)\&\big(age = ''(-Inf, 76.5)''\big)\& (APOE = 1) => (CDRSUM = ''(2.25, Inf)''$$

(5)

3.3 Granular Computing for Reference of Group2 Patients

In this part with our model is based on AD patients (Group2), we have reduced the number of attributes from 14 [6] to five: *APOE, DDST, FCORR, TrailB,* and the decision attribute was *CDRSUM*. After discretization (RSES) we obtained e.g.

$$(APOE = 1)\&\big(FCORR ='' (-Inf\,, 15.5)''\big) => \big(CDRSUM ='' (3.25, Inf)''[6]\big)\,6 \tag{6}$$

We applied the above rules from Group2 to predict the *CDRSUM* of GroupN:

$$(Pat = 164087)\&(APOE = 1))\&\big(DSST ='' (45.0, 56.0)''\big)\&\big(FCORR ='' (-Inf\,, 15.5)''\big)\& (TRAILB ='' (-Inf\,, 128.5)'' => (CDRSUM ='' (3.25,\ Inf)'' \tag{7}$$

Equation 7 confirms the previous classifications (Eq. 5) but now is based on AD patients.

If we add to all our original [6] classifications, an attribute related to the verbal learning and memory test *CVLT* (California Verbal Learning Test), we obtained the following classification:

$$Pat = 164087)\&\big(TRAILA = ''(-Inf\,, 73.5)''\big)\&\big(TRAILB ='' (52.5, Inf)''\big))\&(FCOR = ''(-Inf\,, 17.0)'')\&(PAIRD1 ='' (14.5, Inf)'')\&(PAIRD2 ='' (-Inf\,, 5.5)''))\&(BOSTON = ''(-Inf\,, 27.5)'')\&\big(CVLT = ''(33.5, Inf)''\big)\&(APOE = 1) => (CDRSUM ='' (5.75, 6.5)'' \tag{8}$$

In our previous work [6] patient *Pat = 164087* was classified with 9 attributes (after reduction of non-significant ones) that resulted in an estimation of his/her *CDRSUM* between 4.5 and 6, which means that this patient might have mild dementia [6]. We have repeated the same subject classification using an additional attribute *CVLT* as a more universal test of verbal learning and memory (now 10 attributes). The result is in Eq. 8 that not only confirm our previous results [6], but also gives a narrower *CDRSUM* range between 5.75 and 6.5 which means mild dementia [6] for a clinically normal patient. The doctor's estimation of *CDRSUM* was *0.*

3.4 GC Classification for Longitudinal Reference of Early Stages in AD Patients

We have applied GC to the psychophysical data to estimate *CDRSUM* in subjects in their normal, Impaired Not MCI, MCI, and dementia stages as determined by the diagnostic data (neurological diagnosis).

There are four different patients tested clinically every year (time in months from the beginning of their participation). The only times when changes in their symptoms have occurred are in Table 1. **These results validate our method.** Our predictions have higher values than clinical, fluctuate as clinical, and predict dementia.

In summary, we have demonstrated that our method gives similar results to neurological diagnostic and functional evaluation tests. In many cases, as shown above, is more sensitive and it gave predictive values in some cases. These findings are very important for our future clinical applications.

Table 1. Clinical and GC patients state estimations from normal to dementia

Pat#	Time (month)	CDRSUM Clinical	CDRSUM Predicted
653735	146	0 -*ImpNotMCI*	1.25–3.75
	157	0.5 - *MCI*	1.25–3.75
	169	1 - *MCI*	1.25–3.75
	182	4 - dementia	> 5.75
921569	143	0.5 - *MCI*	1.25–3.75
	217	5 - dementia	> 5.75
411007	149	1 – *MCI*	1.25–3.75
	213	1-*ImpNotMCI*	3.75–5.75
	224	1- dementia	3.75–5.75
703257	96	1 - *MCI*	1.25–3.75
	108	2 - *MCI*	3.75–5.75
	120	1.5 - *MCI*	1.25–3.75
	131	5 - dementia	3.75–5.75

4 Discussion

As Alzheimer's disease has a long (20–30 years) prodromal phase, during which individual compensatory processes may develop differently between subjects. Therefore, our aim was **to detect the beginning of compensatory changes reflective of underlying neurodegeneration,** as it might give a chance to prevent dementia. We have developed a novel tool to monitor ongoing progression in normal subjects more easily and accurately by looking into patterns of cognitive attributes' values and comparing them with our two groups of patients (Group1: general and Group2: AD).

We have studied these patterns with a multi-granular computing (MGC) method and by comparing different sets of attributes (granules) to find possible patterns in normal subjects (n = 21) that might have similarities to granules observed in AD patients.

In this study, we have changed our classifications by removing/adding attributes. As in the previous study [6] we have always used 14 attributes, in this part we have changed from 5 to 7, or even to 15 attributes, and compared classification results. The other new and important part was the interpretability of obtained rules.

Also, rules can be created with different granularity and algorithms that might give different classifications. Therefore, we were looking for classifications that are complete e.g., they give similar results with different sets of rules.

Groupl1 has given us subtle rules that determine the beginning of possible symptoms. These new granules gave us rules supporting our previous classifications like for 5 attributes or gave some new but consistent rules for 7 or 14 attributes.

In the next step, we used a more advanced model – Group2 that gave rules based on AD patients. Thanks to the AD group, we could get higher values of the *CRDSUM* that gave us classifications of the possible subjects with very mild or mild dementia.

Using only 5 attributes, we obtained a new classification confirming our previous findings for *Pat* = *164087* (compare eqs. 4 and 6). Both equations suggest that the patient might have at least very might dementia or maybe even mild dementia. Medium dementia was earlier confirmed for *Pat* = *164087* in 14 attributes classifications [6]. To confirm our previous [6] result, we performed classifications with 15 attributes (Eq. 8) that gave us confirmation of our actual (eq. 7) and previous [6] results and better precision in the estimation of patient's mild dementia. An advantage of the multi-granular computations is spectrum of new rules, and classifications with smaller numbers of attributes that were easier to understand and interpret. This approach might be important for clinicians if they want to estimate a patient's state in a simple and fast but approximate way (small number of tests). Depending on obtained results doctors might perform the following tests to get more precise classifications. This MGC approach follows the functioning of the visual brain [12] where object recognition starts from light spot classification (retina, LGN), through edge orientations (V1) to faces in higher cortical areas (IT). As we learn to recognize new objects, we expand our models (here Group1 and 2) that give advantages of better and faster classifications (descending brain pathways) [12]. We have used previously this approach to discover the concept of Parkinson's disease [13].

As it is the first, to our knowledge, work that estimates singular complex patterns of the individual patient's symptoms, our rules are taken from one population and applied to different subjects, so they are not certain. Therefore, the next step is to find different methods (e.g., tests in the clinic) for their confirmation.

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