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# Evaluation of morphometric descriptors of deep brain structures for the automatic classification of patients with Alzheimer’s disease, mild cognitive impairment and elderly controls

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## 1 Introduction

Our participation in the MICCAI 2014 CADDementia challenge aims at evaluating the performance of morphometric descriptors in multi-class classification tasks for the prediction of Alzheimer’s disease and Mild Cognitive Impairment from structural Magnetic Resonance Images (MRIs).

We used the method for the construction of population-specific atlases that is described in [6, 5]. The method takes as input a set of segmented brain structures, which take the form of the union of labelled 3D surface meshes, called shape complexes. The method estimates an anatomical model, called template, which is representative of the shape complexes within a group of subjects. The variability in shape within the group is captured by 3D space deformations of the ambient space, which warps the anatomical model to the anatomical shape complex of each subject. The method estimates the anatomical model together with the deformation parameters.

The method requires to use the same set of homologous structures for all subjects. We choose a subset of 12 deep brain structures that were segmented from MRIs: caudate nucleus, putamen, pallidum, thalamus, hippocampus and amygdala of each hemisphere. We do not include the lateral ventricles because of a large variability in the segmentation of the horns of the ventricles, which could have masked other patterns of shape variability in the statistical analysis. We do not include the cortical surface because of the subject-specific gyrification.

Deformation parameters are seen as a multi-variate descriptor, which encodes the differences in shape between each subject’s anatomical configuration and the anatomical model. This descriptor encodes different patterns such as the shift of the caudate nucleus due to the ventricular enlargement and the hippocampal atrophy, for instance. The residual shape, namely the difference between the

deformed template and the subject’s shape complex, is considered as noise. The combination of the two terms gives the likelihood of a given anatomical shape complex, which will be used in classification.

We use a sub-set of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database to build the anatomical models. We build three anatomical models considering a group of Cognitively Normal (CN) subjects, subjects with Mild Cognitive Impairment (MCI) and patients with Alzheimer’s disease (AD). Once the models are built, we test any new subject by registering each model to the shape complex of this subject and computing its likelihood. We then classify according to the maximum likelihood. We test our classifiers on another sub-set of the ADNI database and the CADDementia database.

The method is fully automatic. The atlas construction method uses the concept of varifolds [3] for mesh comparison and therefore does not require specific mesh pre-processing. The method is indeed robust with respect to changes in topology between meshes, small holes, spikes, irregular sampling and inconsistency in normal orientations. We do not perform quality control of the segmentations as small errors in the position of the boundaries are likely to be averaged out in this kind of shape analysis. The use of smooth 3D deformations also acts as low-pass filter which smoothes out irregularities in the boundaries of the structures. Few important failures in segmentations are likely to be considered as outliers in the statistical analysis. We use the implementation of the method in the software Deformetrica, which is freely available at [www.deformetrica.org](http://www.deformetrica.org).

Building the anatomical models took 3 days, 15 hours on average (with a parallelization on 40 threads). Registering the anatomical models to test subjects took 10 hours and 20 minutes on average, with a standard deviation of about 1 hour and 30 minutes. The computations were made on a computer cluster which is composed of two types of machines. The first one (with 32 computing nodes) is running on an Intel®Xeon®Processor X5650 (2x6 Cores, 2.66 GHz) and 12x4GB 1333MHz DDR3 Memory and the second one (with 2 computing nodes) is running on an Octo-processor Intel®Xeon®Processor X7550 (8x2x8 Cores, 2 GHz) and 128x2GB 1066MHz DDR3 Memory.

## 2 Material and Methods

### 2.1 Data sets

We use the baseline images from the ADNI database to build the statistical models. We choose the same set of 509 subjects as the ones selected in [4], decomposed into 162 cognitively normal controls (CN), 210 patients with Mild Cognitive Impairment (MCI) and 137 patients diagnosed with Alzheimer’s disease (AD) at baseline. We split the data set into a training set of 50 CN, 50 MCI and 50 AD, the rest being our test set.

We perform the same pre-processing to all ADNI and CADDementia data. The atlas construction is performed only on the training sub-set of the ADNI data. Classification are performed on the test set of the ADNI data and the CADDementia data.

## 2.2 Data pre-processing

The data pre-processing consists of the following steps:

- We run FreeSurfer<sup>1</sup> on the T1 MRI data [7] with default parameters. The output is volumetric segmentation of various structures. At this stage, we exclude from the ADNI dataset, 2 subjects for which the FreeSurfer pipeline failed.
- We run a marching cube algorithm (as implemented in FreeSurfer) to reconstruct 3D triangular meshes from the volumetric segmentation of the 12 selected structures on the RAS coordinate system (Right, Anterior, Superior). We do not perform any other processing on the meshes, although they have holes, spikes and irregular meshing.
- We register all images to the image of a control young adult from the ADNI training data set (126\_S\_0405\_S14635\_I38828) using FSL software<sup>2</sup> [9]. We use rigid and scaling transformation with 7 degrees of freedom. The transformations are then applied to the meshes. The transformed meshes are the inputs given to the software Deformetrica.

Additionally, we build a naive prototype initialization for the anatomical models to give as input of Deformetrica. We build this prototype by mapping a sphere to each structure of the reference subject with very smooth parameters. The corresponding initial anatomical model is shown in Fig. 1-left.

## 2.3 Atlas construction on ADNI training data

We use the Deformetrica software to build the anatomical models and estimate the deformation parameters. The method minimizes the following criterion (see [5] for details):

$$E(\mathbf{X}_0, \mathbf{c}, \boldsymbol{\alpha}_0, \dots, \boldsymbol{\alpha}_N) = \sum_{i=1}^N \left\{ \sum_{k=1}^{12} \frac{1}{2\sigma_k^2} \|\phi^{\boldsymbol{\alpha}_i}(\mathbf{X}_{0,k}) - S_k^i\|_W^2 + \boldsymbol{\alpha}_i^T \mathbf{K}_V \boldsymbol{\alpha}_i \right\} \quad (1)$$

where

- $\mathbf{X}_0 = \{\mathbf{X}_{0,k}\}_{k=1,\dots,12}$  denotes the position of the vertices of the anatomical model with 12 components, one for each anatomical structure,
- $\mathbf{c}$  denotes a set of control points which are supposed to move to the most variable parts of the anatomical model,
- $\{\boldsymbol{\alpha}_i\}_{i=1,\dots,N}$  denotes momentum vectors attached to the control points which parameterize the deformations of the anatomical model to each subject's anatomical configuration (among  $N$  the number of subjects),
- $S_k^i$  denotes the mesh of the  $k$ -th structure of the  $i$ -th subject,

<sup>1</sup> <http://surfer.nmr.mgh.harvard.edu>

<sup>2</sup> <http://fsl.fmrib.ox.ac.uk>

- $\{\phi^{\alpha_i}\}_{i=1,\dots,N}$  denotes the smooth 3D deformation from the anatomical model to the  $i$ -th subject,
- $\|\cdot\|_W$  denotes the varifold norm,
- $\sigma_k^2$  denotes the variance of the noise of the  $k$ -th structure in the space of varifolds,
- $\mathbf{K}_V$  is the deformation kernel matrix, so that  $\alpha_i^T \mathbf{K}_V \alpha_i$  measures the squared norm of the initial velocity of the deformation

We choose the following parameters, using the rationale detailed in [5]:

- deformation kernel width:  $\sigma_V = 10$  mm,
- varifold kernel width:  $\sigma_W = 5$  mm,
- variance of noise:  $\sigma_k^2 = 16$  for all structures,
- template kernel width  $0.5\sigma_V$ ,

other parameters being the ones by default in Deformetrica.

## 2.4 Classification of ADNI test data and CADDementia data

Any test image is transformed into a set of sub-cortical structures after the pre-processing steps explained in 2.2. We then register each atlas to this subject’s shape complex. The registration is performed by minimizing the following criterion, which is essentially (1) for  $N = 1$  and keeping fixed the atlas parameters: the template shape  $\mathbf{X}_0$  and the control points  $\mathbf{c}$ :

$$E(\alpha) = \sum_{k=1}^{12} \frac{1}{2\sigma_k^2} \|\phi^\alpha(\mathbf{X}_{0,k}) - S_k\|_W^2 + \alpha^T \mathbf{K}_V \alpha, \quad (2)$$

where the  $S_k$ ’s denotes the test subject shapes.

The value of the criterion  $E$  at convergence is an approximation of the log-likelihood of the test data [1, 2]. In order to take into account the covariance of the deformation parameters, we replace the matrix  $\mathbf{K}_V$  by the inverse of the regularized empirical covariance matrix of the momentum vectors  $\alpha_i$ . This corrected value of the criterion is used in classification.

## 3 Results

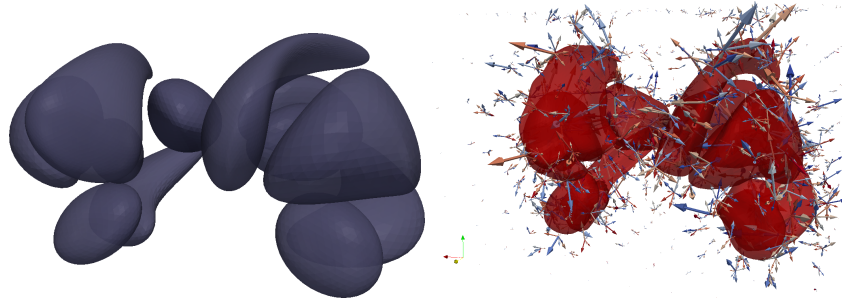
### 3.1 Results on the ADNI data

In Fig. 2, the 3 estimated template shape complexes are shown. The template of the MCI class falls in-between the template of the CN and AD classes. These shapes show the shift of the caudate nucleus toward the lateral parts of the brain due to a larger and larger ventricular enlargement. We notice also a greater and greater atrophy of the hippocampus.

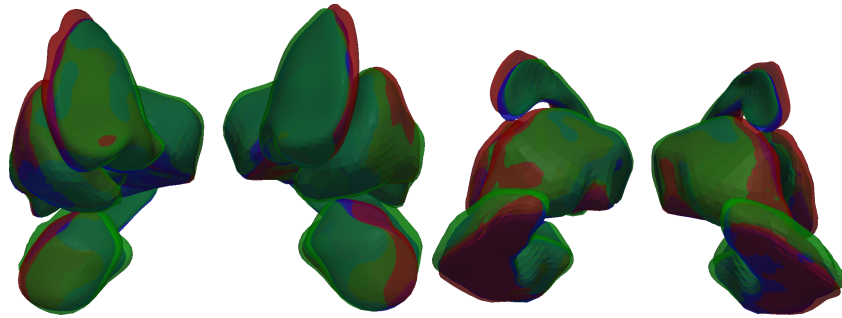
The confusion matrix of the classification performed on the test sub-set of the ADNI database is shown in Table 1. The accuracy, assuming the probability of 1/3 for each class, is 51% (i.e.  $\frac{1}{3} \sum_{k=1}^3 n_{k,k}/n_k$  where  $n_k = \sum_{i=1}^3 n_{i,k}$  is the

total number of samples of the class  $k$ ). We notice that our classifier tends to empty the MCI class, and to classify MCI subjects as either CN or AD with equal probability. This may be explained by the fact that our descriptors of MCI subjects overlap the descriptors of CN and AD classes, as if there is a continuum between the three classes. In other words, our classifier does not detect shape patterns that are specific to MCI subjects. This conclusion is corroborated by the visualization of the 3 template shapes complexes in Fig. 2.

The ROC curves of pairwise classification are shown in Fig. 3. As expected, the AD versus CN classification has overall better performance than classification of AD or CN against MCI.



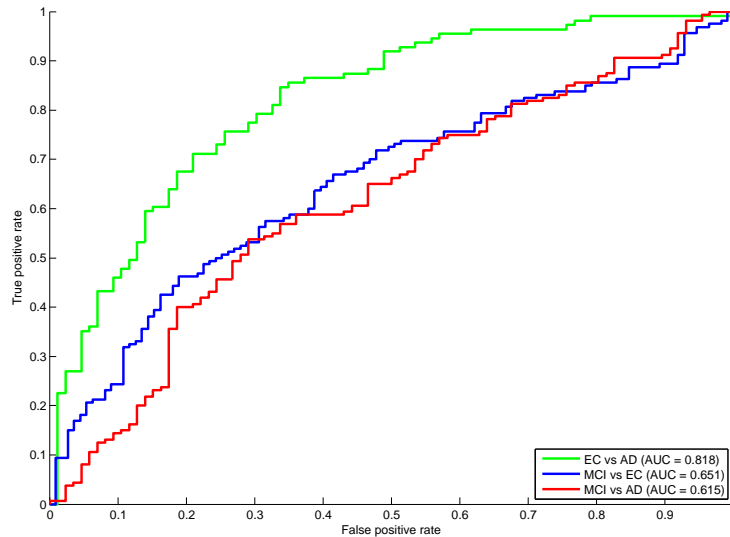
**Fig. 1.** Initial prototype given as input of Deformetrica (left) and an instance of estimated atlas given as output (right); template shapes are representative of the group and momenta arrows parameterize template-to-subject deformations.



**Fig. 2.** Superimposition of the 3 template shapes for the CN, MCI and AD classes in green, blue and red respectively. Anterior view (left) and posterior view (right)

|                    |     | True class |     |    |
|--------------------|-----|------------|-----|----|
|                    |     | AD         | MCI | CN |
| Hypothesized class | AD  | 66         | 83  | 28 |
|                    | MCI | 6          | 13  | 5  |
|                    | CN  | 14         | 64  | 78 |

**Table 1.** Confusion matrix on ADNI test data set.



**Fig. 3.** ROC curves of pairwise classification on the ADNI database.

### 3.2 Results on the CADDementia training data

We test our classifier on the 30 subjects of the training database of CADDementia. Table 2 shows the confusion matrix using the thresholds that maximize the accuracy of the classifier on the ADNI data set, for which the accuracy is 50%. These two thresholds determine the position of the boundaries between the three classes. The optimization of these two thresholds on the given 30 subjects of the CADDementia database yields the confusion matrix in Table 3 and an accuracy of 73%. Differences in optimum thresholds between the two databases may come from differences in patients, differences in age distribution, differences in clinical practice for the diagnosis of mild cognitive impairment and dementia. Optimizing the thresholds on only 30 subjects is also not ideal, as they might not generalize well to the rest of the data set. For these reasons, we decided to submit two predictions for each subject: one using the thresholds estimated from

the ADNI data set and the other one using the thresholds estimated from the CADDementia training data set.

|                    |     | True class |     |    |
|--------------------|-----|------------|-----|----|
|                    |     | AD         | MCI | CN |
| Hypothesized class | AD  | 4          | 3   | 0  |
|                    | MCI | 3          | 0   | 1  |
|                    | CN  | 2          | 6   | 11 |

**Table 2.** Confusion matrix for the classification of the CADDementia training set, using the thresholds that are optimum for the ADNI data set.

|                    |     | True class |     |    |
|--------------------|-----|------------|-----|----|
|                    |     | AD         | MCI | CN |
| Hypothesized class | AD  | 9          | 5   | 2  |
|                    | MCI | 0          | 4   | 1  |
|                    | CN  | 0          | 0   | 9  |

**Table 3.** Confusion matrix for the classification of the CADDementia training set after optimizing the thresholds for this data set.

## 4 Discussion and conclusion

This work evaluates the performance of the Deformetrica software in classification tasks. The software computes shape descriptors for anatomical shape complex of sub-cortical structures that are known to be markers of disease progression. The approach is essentially multi-variate and combine different shape patterns such as the effect of hippocampal atrophy and ventricular enlargement on the shape of the sub-cortical structures. Our results suggest that the method does not find shape features that are characteristic of MCI subjects. The method tends to position the anatomy of MCI subjects, as an intermediate stage of disease progression. This fact may come from the method itself, which does not capture characteristics of such non-demented subjects. It may also come from the heterogeneity of the MCI group.

Our goal was to use the software Deformetrica “out of the box” as a test case, whereas several improvements could be made such as the estimation of the covariance of deformation parameters and noise variance during the training phase along the lines of [1, 8]. We could have determined also the best thresholds using cross-validation on the ADNI database. Correction for age and sex could also have improved classification performance.

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<sup>3</sup> <http://www.loni.ucla.edu/ADNI>



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. ADNI investigators include (complete listing available at [http://www.loni.ucla.edu/ADNI/Collaboration/ADNI\\_Author\\_ship\\_list.pdf](http://www.loni.ucla.edu/ADNI/Collaboration/ADNI_Author_ship_list.pdf)).

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