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A framework for the automatic detection and characterization of brain malformations: Validation on the corpus callosum

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ABSTRACT

In this paper, we extend the one-class Support Vector Machine (SVM) and the regularized discriminative direction analysis to the Multiple Kernel (MK) framework, providing an effective analysis pipeline for the detection and characterization of brain malformations, in particular those affecting the corpus callosum.

The detection of the brain malformations is currently performed by visual inspection of MRI images, making the diagnostic process sensible to the operator experience and subjectiveness. The method we propose addresses these problems by automatically reproducing the neuroradiologist's approach. One-class SVMs are appropriate to cope with heterogeneous brain abnormalities that are considered outliers. The MK framework allows to efficiently combine the different geometric features that can be used to describe brain structures. Moreover, the regularized discriminative direction analysis is exploited to highlight the specific malformative patterns for each patient.

We performed two different experiments. Firstly, we tested the proposed method to detect the malformations of the corpus callosum on a 104 subject dataset. Results showed that the proposed pipeline can classify the subjects with an accuracy larger than 90% and that the discriminative direction analysis can highlight a wide range of malformative patterns (e.g., local, diffuse, and complex abnormalities). Secondly, we compared the diagnosis of four neuroradiologists on a dataset of 128 subjects. The diagnosis was performed both in blind condition and using the classifier and the discriminative direction outputs. Results showed that the use of the proposed pipeline as an assisted diagnosis tool improves the inter-subject variability of the diagnosis.

Finally, a graphical representation of the discriminative direction analysis was proposed to enhance the interpretability of the results and provide the neuroradiologist with a tool to fully and clearly characterize the patient malformations at single-subject level.

1. Introduction

Magnetic Resonance Imaging (MRI) is currently the gold standard technique to study the brain morphology in the medical practice. The detection of brain malformations is performed by trained neuroradiologists, who examine the images and evaluate the presence/absence and the shape of all brain structures. Multiple geometric features (i.e., size, architecture, curvature, thickness, density) are considered and visually inspected to detect possible alterations and malformative patterns. Such approach is useful but suffers from the limitation of being subjective and only qualitative. As a consequence, the diagnosis of subtle malformations is scarcely reproducible among different neuroradiologists and it is usually influenced by the overall clinical pattern of the subject, rather than by the structure shape alone.

Automatic classifiers, such as Support Vector Machine (SVM) (Schölkopf and Smola, 2001; Vapnik, 1998), can be used to support the diagnostic task, providing mathematical tools to describe and classify either the single structure or the whole brain, therefore improving the reproducibility of the diagnosis. In particular, the one-class SVM methods (Schölkopf et al., 2001; Tax and Duin, 2004) have been specifically designed for the outlier detection, i.e.,

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for the identification of objects which do not belong to a specific group. Moreover, Multiple Kernel (MK) methods (Gönen and Alpaydın, 2011) can efficiently combine features from different descriptor functions, hence including all the different aspects usually taken into account by neuroradiologists for a given brain structure. Therefore, SVM methods can be used to automatically reproduce the neuroradiologist's approach in the diagnosis of morphologic malformations of the brain. This can not only improve the intra-subject reproducibility of the diagnosis, but also the inter-subject agreement in the diagnosis, particularly in the borderline cases.

On the other hand, the main drawback of automatic classifiers is that they are usually developed as "black box" tools that provide the subject classification, but not a description or a list of the aspects that led to the choice. This hinders the diffusion of diagnosis support tools based on automatic classifiers, since the detected malformation should be presented for a validation and its characterization is expected in the medical report.

In Golland et al. (2005), Golland and colleagues introduced the concept of *discriminative direction* as the direction in the sample space that affects the output classifier, while introducing as little irrelevant changes as possible into the input vector. The discriminative direction tool can be used to highlight the features that caused the assignation of the subject to a specific group, giving the opportunity to not only detect but also describe the critical aspects in the abnormal structure. Moreover, a subsequent evolution, the *regularized discriminative direction* (Zhou et al., 2009), gives the opportunity to include also a prior knowledge in the analysis. In particular, Zhou and colleagues noticed that when deforming a shape along the original discriminative direction proposed in Golland et al. (2005), spurious shape differences may appear, as a solution may be mathematically acceptable, but not from a physiological point of view. The solution proposed in Zhou et al. (2009) allows to overcome this problem by introducing a physiological constraint directly derived from the training set.

In this work, we propose a fully automatic framework for the detection and characterization of brain malformations. The analysis pipeline exploits the one-class SVM methods embedded in a MK framework to reproduce the neuroradiologist's approach to the diagnosis problem. Moreover, we apply the regularized discriminative direction analysis to the one-class MK classifier to provide not only the subject classification, but also a description of the malformation. In particular, we verify the effectiveness of the proposed pipeline in the detection of malformations of the corpus callosum. Finally, we study the effectiveness of the proposed pipeline as an assisted diagnosis tool (ADT) comparing the inter-subject agreement rate between the blind-diagnosis and the diagnosis assisted by the classifier. This work expands the results presented in Peruzzo et al. (2014a), where only two-class SVMs and the original formulation of the discriminative direction analysis were applied to the problem and no study was performed to evaluate the impact of the proposed method on the diagnostic process. One-class SVMs are more suitable than standard SVMs to deal with heterogeneous brain abnormalities, as in our case-study. Only healthy subjects are used to estimate the SVM model, while patients are considered as general outliers, not necessarily associated to a particular class.

We focused our analysis on the corpus callosum (CC) that represents the largest commissural structure in the human brain, playing a fundamental role both in motor and cognitive functions. It has a well-defined shape on the midsagittal cerebral plane, appearing as a broad-arched structure, with a variable thickness along its major axis. It is frequently involved in several genetic conditions showing a wide range of malformative patterns (i.e., complete or partial agenesis, hypoplasia, thinning, thickening) Bodensteiner et al. (1994); Kendall (1983); Paul et al. (2007); Van Bon et al. (2008) associated with mental retardation and motor impairment. Alterations in the morphology of the CC can therefore represent a clue of more widespread brain derangement and their identification and quantification is of the utmost importance in the clinical practice.

2. Methods

2.1. Feature extraction

The CC feature extraction procedure was implemented on MRI T1-weighted structural images. Images were firstly preprocessed using the FMRIB Software Library (FSL) (Jenkinson et al., 2012). In particular, images were corrected for the magnetic field inhomogeneities, non-brain tissue was removed and the resulting brain images were rigidly registered to the MNI atlas. Finally, a segmentation operation was performed to obtain a probability map for the White Matter (WM) tissue. All preprocessing operations were performed using the default settings of the FSL algorithms.

The CC mask was extracted combining both anatomical T1-weighted images and WM maps using an automatic segmentation method proposed in Herron et al. (2012). Briefly, the method affinely moved the images to the MNI atlas and selected the three central sagittal slices where the CC was delineated. Each slice was independently analyzed and the final results were averaged. A searching ROI was defined in the middle of the brain, where the CC is located, and a cluster analysis was performed on the WM map to detect the CC. Several refinement steps were performed to eliminate the fornix (a WM tract running close to the ventral surface of the CC) and improve the contour using the T1 images. Finally, the CC mask was moved back to the native space using the inverse transformation.

Once the masked CC was obtained, it was further processed to extract the geometric features. Firstly, the perimeter was computed using a $b-spline$ model. Two well-known anatomical markers were subsequently defined on the perimeter and identified as the points with the highest perimeter curvature. The first marker is localized in the anterior part of the CC and it is called *rostrum vertex*, the second one is in the posterior part and it is called *splenium vertex*. The anatomical vertices naturally divide the perimeter into two sections, a superior and an inferior one. From them, the CC skeleton was derived as the line connecting the rostrum to the splenium and equidistant from the two perimeter sections. Following Herron et al. (2012), fifty uniformly distributed points were defined on the skeleton and the CC thickness was computed for each one. In particular, the CC thickness was defined as the minimum distance between the superior and the inferior perimeter section measured on a straight line passing through the considered point.

At the end of the image processing, the CC was characterized by its area, perimeter length and curvature, skeleton length and curvature, distance between rostrum and splenium, thickness profile (see Fig. 1 for a visual representation).

2.2. Multiple Kernel - Support Vector Machine

The basic idea of the kernel methods, such as SVM, is to project data which are not linearly separable in the sample space $\left(\mathbb{R}^d\right)$ to a higher dimensional space, called *feature space* $(\mathbb{F})$, where the classes become linearly separable (Schölkopf and Smola, 2001; Vapnik, 1998). In the classic SVM formulation, the classifier in the feature space is represented by a hyperplane and the decision function is $f(x) = \langle \vec{w}, \Phi(\vec{x}) \rangle + b$, where $\vec{w}$, b are the parameters describing the hyperplane, $\Phi(\cdot)$ is the mapping function and $\vec{x}$ is the sample we want to classify. Using the "kernel trick", the decision function can be derived in terms of kernel function, thus