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Functional activity maps based on significance measures and Independent Component Analysis

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ABSTRACT

The use of functional imaging has been proven very helpful for the process of diagnosis of neurodegenerative diseases, such as Alzheimer's Disease (AD). In many cases, the analysis of these images is performed by manual reorientation and visual interpretation. Therefore, new statistical techniques to perform a more quantitative analysis are needed. In this work, a new statistical approximation to the analysis of functional images, based on significance measures and Independent Component Analysis (ICA) is presented. After the images preprocessing, voxels that allow better separation of the two classes are extracted, using significance measures such as the Mann–Whitney–Wilcoxon *U*-Test (MWW) and Relative Entropy (RE). After this feature selection step, the voxels vector is modelled by means of ICA, extracting a few independent components which will be used as an input to the classifier. Naive Bayes and Support Vector Machine (SVM) classifiers are used in this work. The proposed system has been applied to two different databases. A 96-subjects Single Photon Emission Computed Tomography (SPECT) database from the "Virgen de las Nieves" Hospital in Granada, Spain, and a 196-subjects Positron Emission Tomography (PET) database from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Values of accuracy up to 96.9% and 91.3% for SPECT and PET databases are achieved by the proposed system, which has yielded many benefits over methods proposed on recent works.

1. Introduction

Functional images, such as Positron Emitted Tomography (PET) or Single Photon Emitted Computed Tomography (SPECT), are very important in the process of diagnosis of neurodegenerative diseases. They allow clinicians to correctly interpret the presence of different functional patterns – like blood flow or glucose concentration – in several key regions of the brain, caused by neurological diseases such as Alzheimer's Disease (AD), where early diagnosis is of particular importance in the development of new treatments. However, the evaluation of these scans often relies on manual reorientation, visual reading and semiquantitative analysis. Therefore, Computer Aided Diagnosis (CAD) tools based on medical imaging are a very valuable help for physicians in the AD detection, providing an objective, operator-independent, consistent analysis of the images.

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.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: URL http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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A CAD system is a computer method and program that assists physicians in the diagnosis task using biomedical signals. It encompasses a set of signal processing methods implemented in a high-level language, i.e. Matlab, resulting in complete systems, such as Statistical Parametric Mapping (SPM) [1]. This is the most extended tool in the neuroimaging community, and refers to the construction and assessment of spatially extended statistical processes used to test hypotheses about functional imaging data. The CAD paradigm has been successfully applied to medical imaging in many works [1–5] to perform an exhaustive quantitative and qualitative analysis of these medical images. Even in the simplest approach, which uses the raw voxels as an input to the classifier (Voxels as Features, VAF [5]), a new strategy to avoid the small sample size problem [6] is desirable. This phenomenon occurs when the number of input features to the classifier is higher than the number of samples used to train this classifier. Techniques like image segmentation and definition of Regions of Interest (ROIs) [3,7–9] allows a CAD system to consider only brain zones which are significant for AD detection. Other techniques involve statistical measures that compute significance values for each voxels. Then, voxels are ranked and the most significative ones are selected. Statistical measures can be computed by the widely used Student's *t*-Test [1,2,5], Mann–Whitney–Wilcoxon *U*-Test [10,11] or Relative Entropy [12,13]. These methods have been proven very useful in applications ranging from cancer diagnosis [13] to segmentation of microscope images [12] or autoradiographic images [11]. Later, feature extraction algorithms like Independent Component Analysis (ICA) [14,15], Fisher Linear Discriminant Ratio (FDR) [16], Principal Component Analysis (PCA) [17–19] or Factor Analysis [2,20] have been used for extracting common features. In [15], a method for AD early diagnosis based on ICA analysis is proposed. The method has tested in the feature extraction step with excellent results, but some improvements can be applied to it. One voxel selection step by means of statistical significance has been added in order to select the most significant voxels in the brain and use them to extract the independent components. The second improvement relies in the estimation of the mixing matrix in the ICA step. While the method in [15] relies on creating an average image of the individual samples of each class (AD and CTRL) and then compute the mixing matrix, our method uses all the sample images and their class information to compute this matrix. This is possible thanks to the feature selection step, which reduces the number of voxels from over 500,000 to less than 20,000, enabling a faster computation, and hence, allowing us to include all the samples in the calculation of the mixing matrix. This leads to a more consistent estimation of the Independent Components.

In this work, a new combination of algorithms for voxel selection and feature extraction is proposed. Firstly, the most significative voxels in the task of separating classes are selected by using the significance values, computed using Student's *t*-Test, Mann–Whitney–Wilcoxon *U* test and Relative Entropy. To reduce the number of features, we extract independent components from the selected voxels using ICA. Then, these features are classified using a Bayesian or Support Vector Machine (SVM) classifier.

Processing of perfusion images is performed in three stages:

1 **Voxel selection**. Ranking of voxels by measures of difference between two classes and posterior selection of the first *N*, using Student's *t*-Test, Mann–Whitney–Wilcoxon (MWW) and Relative Entropy (RE) techniques.
2 **Feature extraction**. Extraction of *K* common features from the voxels selected in the previous step, using an ICA technique. These *K* features will be used as an input vector to the classifier.
3 **Classification** of the features vector in two different classes: Normal Controls (CTRL) and AD. We make use of two different classifiers: Naive Bayes and SVM.

A baseline method is also defined, and will be used along with the VAF approximation for comparing purposes. This method uses the selected voxels (obtained by the algorithms used in the voxel selection stage) as input features to the classifier, without using any feature extraction technique, and so, is called Selected Voxels As Features (SVAF).

2. Materials and methods

2.1. Datasets

To evaluate the performance of the proposed method, we use two different dataset of perfusion images: a database composed by 96 SPECT brain images from "Virgen de las Nieves" Hospital in Granada (Spain) and a set of 403 PET brain images from the ADNI initiative.

2.1.1. SPECT database

The database is built up of imaging studies of subjects following the protocol of an hospital-based service. First, the neurologist evaluated the cognitive function, and those patients with findings of memory loss or dementia were referred to the nuclear medicine department in the "Virgen de las Nieves" hospital (Granada, Spain), in order to acquire complementary screening information for diagnosis.[2] Experienced physicians evaluated the images visually. The images were assessed using 4 different labels: Control (CTRL) for subjects without scintigraphic abnormalities and mild perfusion deficit (AD1), moderate deficit (AD2) and severe deficit (AD3), to distinguish between different levels of presence of hypo-perfusion patterns compatible with AD. In total, the database consists of $n = 97$ subjects: 41 CTRL, 30 AD1, 22 AD2 and 4 AD3 (see Table 1 for demographic details). Since the patients are not pathologically confirmed, the subject's labels possesses some degree of uncertainty, as the pattern of hypo-perfusion may not reflect the underlying pathology of AD, nor the different classification of scans necessarily reflect the severity of the patients symptoms. However, when pathological information is available, visual assessments by experts have been shown to be very sensitive and specific labelling methods, in contrast to

[2] Clinical information is unfortunately not available for privacy reasons, but only demographic information.