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ONLINE TOOLS AND SERVICES FOR EARLY DIAGNOSIS AND CARE FOR ALZHEIMERS DISEASE

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Abstract: Currently a need exists for an efficient low-cost screening tool that can be used by clinicians for the early diagnosis of Alzheimer's Disease (AD) based on human electroencephalogram (EEG). In this paper, we present such tool (web services and demonstrator) we have developed which incorporates a number of promising non-linear analysis methods for early diagnosis and care of AD. The tool's functionalities include database query, import/export EEG, computation of biomarkers and visualization. We illustrate how it can be used to evaluate the performance of five methods for early detection of AD: zero crossing intervals (ZCI), fractal dimension (FD), central tendency measure (CTM), Hjorth index and sample entropy (SamEnt).

The availability of such tool is important as it would provide a platform to compare and benchmark data sets and analysis methods used in AD research, giving access to data and analysis tools in a seamless and secure manner over the internet. It is envisaged that the tool can potentially be used as a low-cost screening tool at General practitioners (GPs) with its success to contribute towards future developments of web-based decision support system (DSS) for brain diseases. The tool is available from the BIOPATTERN portal (www.biopattern.org).

Keywords: Web services, Alzheimers disease (AD), dementia, early detection, electroencephalogram (EEG), biomarker, zero crossing interval (ZCI), fractal dimension (FD), Hjorth parameters, mutual information (MI), sample entropy (SamEnt), receiver operating characteristic (ROC).

INTRODUCTION

The number of people that develop Alzheimer's Disease (AD) is rapidly rising and will create a considerable financial burden on the health and social services worldwide [1]. The availability of new drugs that may slow or even halt the disease progression makes accurate early diagnosis a crucial issue.

At present, the initial diagnosis and care of AD patients typically falls on non-specialist General Practitioners (GPs) before they are referred to specialists for further tests, which could take up to 3-5 years [2][3]. There is therefore, an urgent need for developing methods to extract robust biomarkers from biosignals such as electroencephalograms (EEGs) and develop tools that can easily and accurately help early diagnosis within an acceptable time frame. Such tools should support both non-specialists and specialists in their decision making if the disease is to be detected in the early stages.

In this paper, we present web services and a demonstrator platform developed for generic biosignal analysis and aimed to demonstrate their application for patient-specific diagnosis and care of AD. By making use of recent advancements in information and communication technologies (ICTs), we are using web services (WS), now also called rich internet application (RIA), to provide seamless data access, handling and analysis over the internet. It is believed to be the way forward in eHealth to support individualized health care. End-users such as GPs, clinicians and specialists at surgeries, memory clinics and hospitals will be able to securely connect to online medical services to upload data, perform some specialized analysis and retrieve the results to support their diagnosis and decision making.

The rest of the paper is organized as follows. First, we describe the demonstrator and functionalities of the web services. We also provide a step-by-step description on its usage. We then illustrate its use with a small evaluation of methods carried out on one data set of the Plymouth EEG database. Finally, we conclude the paper.

DEMONSTRATOR WITH WEB SERVICES

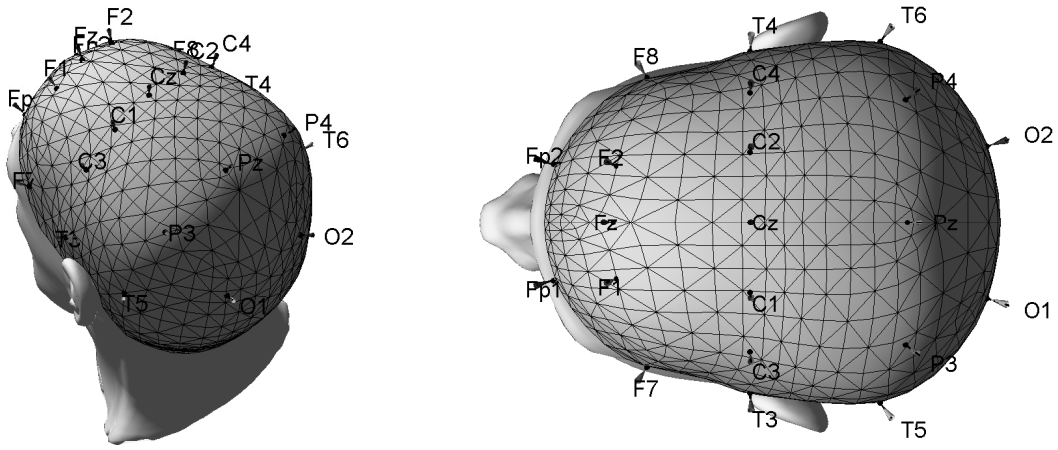
In this section we present the web services developed as independent online applications before being integrated into the online demonstrator on the BIOPATTERN Grid portal [4].

Functionalities

The functionalities of the demonstrator include database query, EEG import/export, EEG analysis and visualization.

Database query - The user can query the data available on the system. Note that only information related to the data files are provided which the final access depends on the login credentials of the user. Currently the database contains data from multiple centers including Plymouth,

Fig. 1: Online demonstrator - screen shoot



(a) (b)

Fig. 2: Head model with electrodes placement

Romania and Italy (See [5] for more details).

The current system can retrieve EEG files from a database using a unique identification code coded with the center ID (Plymouth = 1, Rome = 2, EUoB = 3), disease status (Probable Alzheimer Disease, AD = 1, Mild Cognitive Impairments, MCI = 2, Mix dementia, MIX = 3, Normal Old, NOLD = 4), and file number). For example the first AD case of Plymouth has the ID #1101. The identifier can be easily modified to include more advanced data management and security requirements [4].

EEG import / export - The demonstrator can import and export EEG files in the following formats: files recorded from Micromed EEG system, priority format from BIOSIG Inc., European Data Format (EDF) [6] and ASCII format (.txt).

EEG analysis - The main function of the analysis web service is to compute biomarkers or indices based on information extracted from the EEGs. These markers can help and support clinicians in their diagnosis of AD. At present, the analysis methods included for EEG analysis

are: zero-crossing intervals (ZCI) [7], fractal dimension (FD) [7], central tendency measure (CTM) [8], Hjorth index based on Hjorth descriptors [9], sample entropy (SamEnt) [10], and mutual information (MI) [11]. Other information about the EEG signal such as mean, standard deviation, skewness and kurtosis are also provided. To conduct an analysis, the user needs to select the analysis method and the specific brain regions to investigate. For example, one can use FD to analyze the EEGs in the frontal regions (specified by electrodes F1, Fz, F2, F7 and F8).

Visualization - The system can plot the EEG trace with functionalities to scroll along the time axis (forward and backward) and zoom in/out (See Figure 1). EEG traces can be displayed in different type of montages. After the EEG analysis is performed, results are presented in tabulated text and graphical forms such as canonogram, bar graph, or colour map. Canonograms, as shown in Figure 3, are topview representation of the scalp with colour-coded electrode positions (a colour scale associated to each marker value is given on the right side). bar graph can be used to represent results for each electrode as shown in Figure 4. Color maps can be used for cross channel biomarkers. For example, using MI we obtained results as shown in Figure 5(a) for AD patients and Figure 5(b) for NOLD subjects. Looking at these plots clinicians can draw conclusions on regional brain activities based on the similarities between different channels.

Usage in 5 steps

A simple and user-friendly 5-steps procedure to use the system was adopted. A screenshoot of the current demonstrator is shown in Figure 1.

Step 1 - The user selects an EEG file from the EEG database query using the unique ID. EEG data format is transparent to the user. The user can also upload EEG files (only currently supported formats) onto the demonstrator system. EEG data is stored locally and automatically deleted after the analysis session. Additional information from the EEG file header can also be shown to the user while keeping the data anonymized.

Step 2 - The user selects all channels or one specific electrode (e.g. P3 and O1 as in [8] [12]). Electrode labels are detected from the current EEG data file in use.

Step 3 - EEG analysis is typically based on brain regions. To facilitate this, the user can select all the electrodes (global) or specific region such as: anterior (Fp1, Fp2, F7, F3, Fz, F4, F8, C3, CZ, C4), posterior (C3, CZ, C4, T5, P3, Pz, P4, T6, O1, O2), perifrontal (Fp1-Fp2), frontal (F8, F4, FZ, F3, F7), temporal (T3, T4, T5, T6, F7, F8), parietal (T5, P3, P4, T6, Pz) or occipital (O1, O2). In such case, the resulting biomarker will be an average of the electrodes' biomarker within the region.

Step 4 - EEG analysis often focus on frequency bands of interest. The user can select original or filtered signals (δ: 2-4 Hz, θ: 4-8 Hz, α: 8-13 Hz, β: 13-30 Hz, γ: 30-40 Hz). Future versions of the demonstrator will allow adjustable frequencies to match the setup used in other studies [13].

Step 5 - The user selects the method to compute biomarkers. To begin the analysis, the user then clicks on the "Create Biomarker" button. The results are then presented as tabulated text, whereby the user can visualize using the canonogram, bar graph and colour map options.

PERFORMANCE EVALUATION EXAMPLE

To illustrate the use of the demonstrator, we have carried out a small performance evaluation of the EEG analysis methods on one data set from Plymouth EEG database. We describe the EEG data, methods, procedure and results.

EEG Data

The data was collected at Derriford Hospital (Plymouth, U.K.) and was used in previous studies [14][7]. It consists of 17 AD patients (9 men and 8 women, age mean = 77.6, Std. = 10 years) and 24 normal old patients (10 men and 14 women, age mean = 69.4, Std. = 11.5 years). Each recording is 4 minutes long with various states (awake, drowsy and alert) and periods of eyes closed and open. They were obtained using a traditional 10-20 system with common reference montage. The 21 channels are: FP1, FP2, F7, F3, Fz, F4, F8, A1, T3, C3, Cz, C4, T4, A2, T5, P3, Pz, P4, T6, O1, O2 (See Figure 2). The data was sampled at 256 Hz and down-sampled to 128 Hz for storage reasons [7]. Each patient went through psychometric tests, including Mini Mental State Examination (MMSE) [15] at a specialist memory clinic prior to referral to the hospital.

Methods

This study is focused on the following methods, which have been implemented and tested on the demonstrator: ZCI, FD, CTM, Hjorth index and SamEnt.

Procedure

To evaluate the performance of the methods using the demonstrator, the chosen analysis method is applied to the EEG of each file in the data set. The output of each analysis is then a marker or index i.e. FD index, Hjorth index, representing the state of the subject's condition. For example, a FD index of 0.5 would suggest that the subject has more severe AD compared to a FD index of 0.8. These outputs can then be used to calculate performance indicators such as sensitivity (SEN), specificity (SPE), accuracy (ACC) which are typically used in performance evaluation. The receiver operating characteristics (ROC) can also be plotted and the Area Under the ROC curve (AUC) computed. For a small data set, additional confidence bounds can also be calculated for specific points of the ROC curve using the method described in [16].

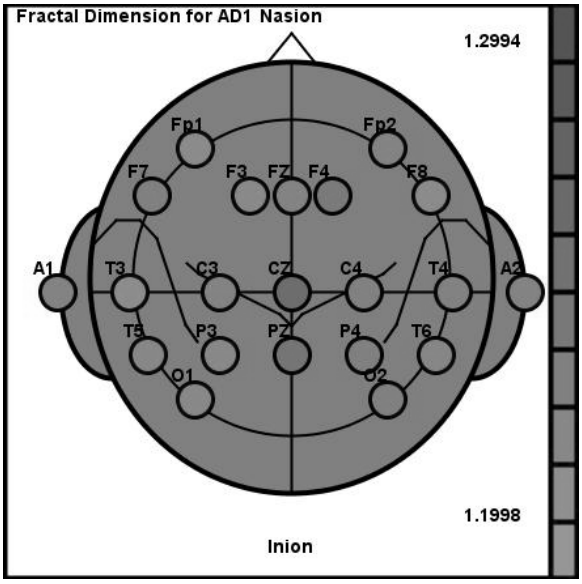


Fig. 3: Canonogram visualization

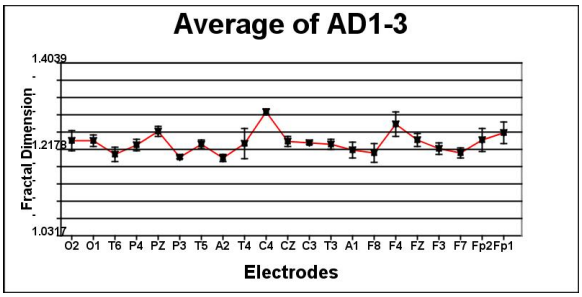
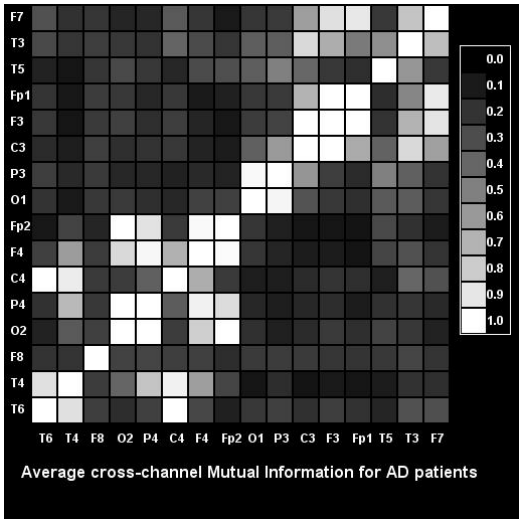
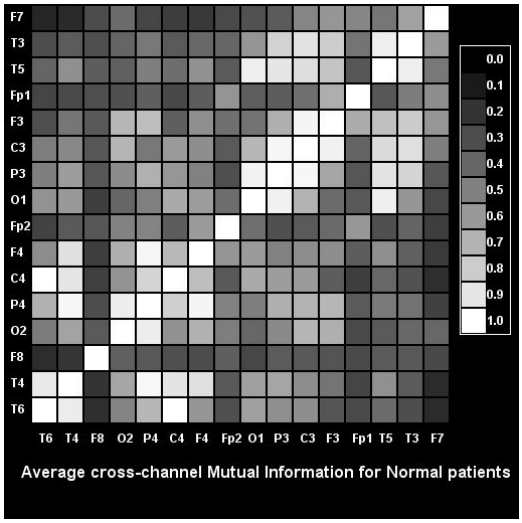


Fig. 4: Bar graph plot of average FD for AD patients



(a)



(b)

Fig. 5: Colour map of cross mutual information (CMI) for (a) AD patients and (b) NOLD patients

Results

Due to space constraints, only the results for FD and ZCI analysis are presented. Figure 6(a) and Figure 6(b) show FD biomarkers for normal old patients and AD patients, respectively. The mean value is 0.7613 (Std. = 0.0636) for NOLD patients and 0.4657 (Std. = 0.1298) for AD patients. Results for the ZCI method are shown in Figure 7(a) for NOLD patients (Mean = 0.6794, Std. = 0.0293) and in Figure 7(b) for AD patients (Mean = 0.5684, Std. = 0.0465). Results were used to create ROC curves showing the true performance of each method. Figure 8(a) and Figure 8(b) show the ROC curve with additional 95% confidence bounds for FD and ZCI methods, respectively.

CONCLUSIONS

In this paper, we presented the web services and demonstrator system developed for early diagnosis and care of AD. Such a system is important as it provides researchers and clinicians with seamless access to a large data sets and analysis tools. These can very effectively support AD research for in particular for diagnosis and care. The current functionalities include data query/import/export, analysis and visualization. A small evaluation study was conducted to illustrate the use of the web services for performance evaluation and comparison of methods. Results are used to compute well-known performance indicators (Sensitivity, specificity and accuracy) as well as ROC curves. The development of the demonstrator is ongoing and current efforts are focused on adding more algorithms such as synchronization likelihood (SL) [17] and multiscale entropy (MSE) [12]. The demonstrator is accessible from the web-services section of the BIOPATTERN Grid portal.

ACKNOWLEDGMENTS

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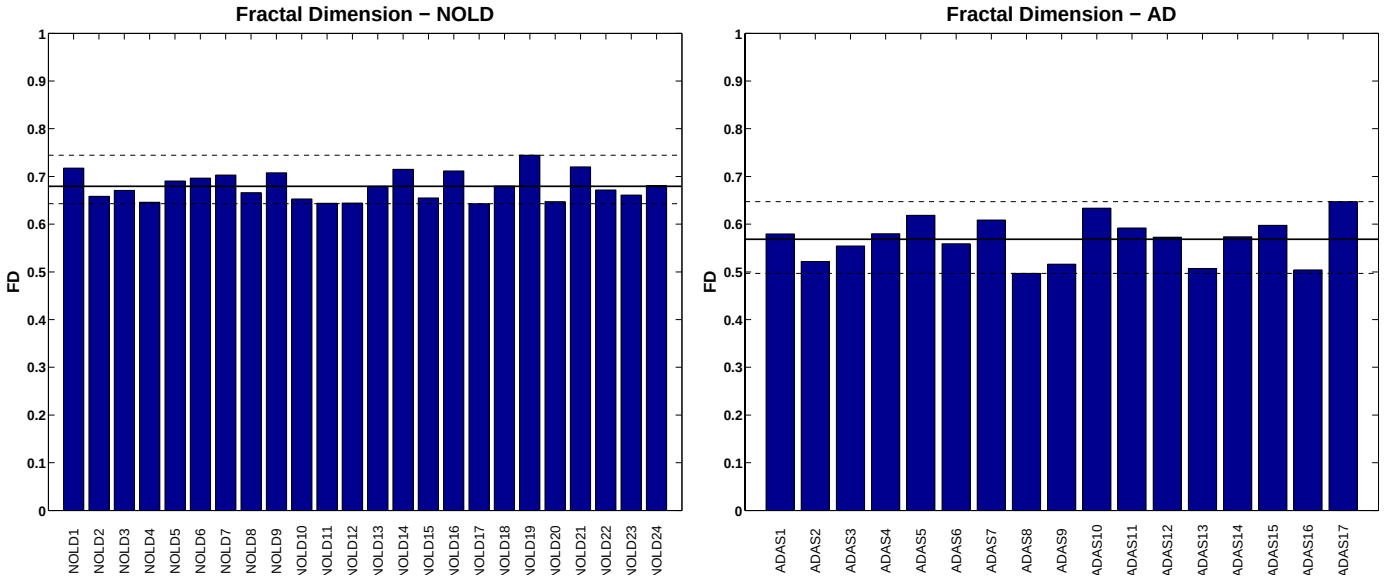
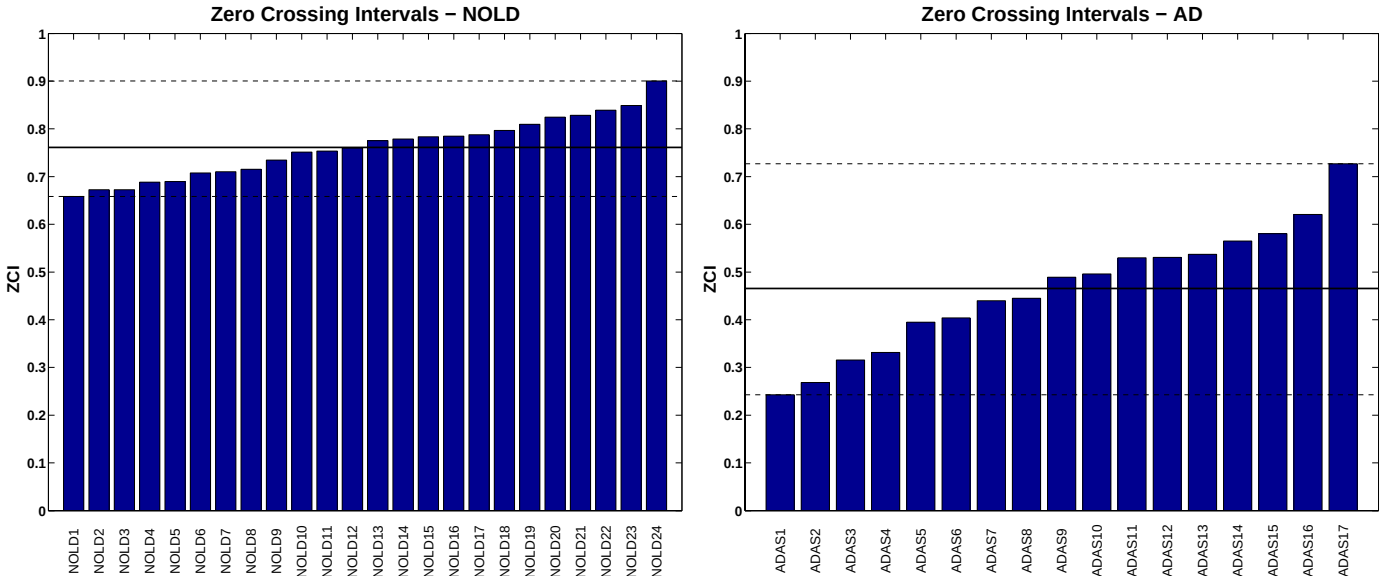


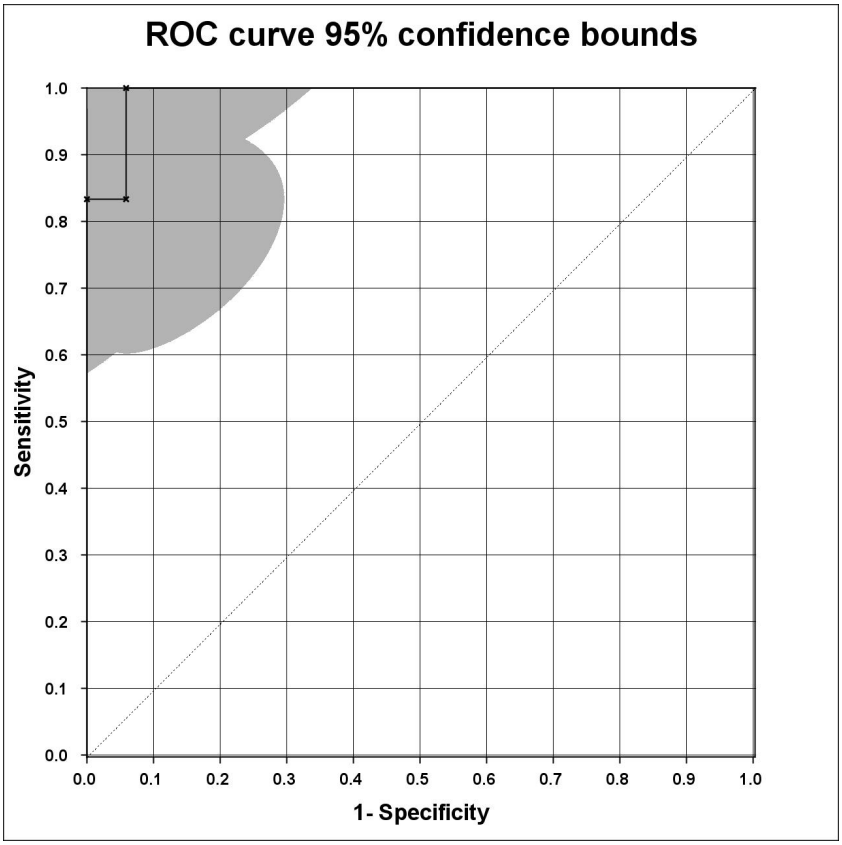
(a) (b)

Fig. 6: FD biomakers for (a) NOLD patients and (b) AD patients

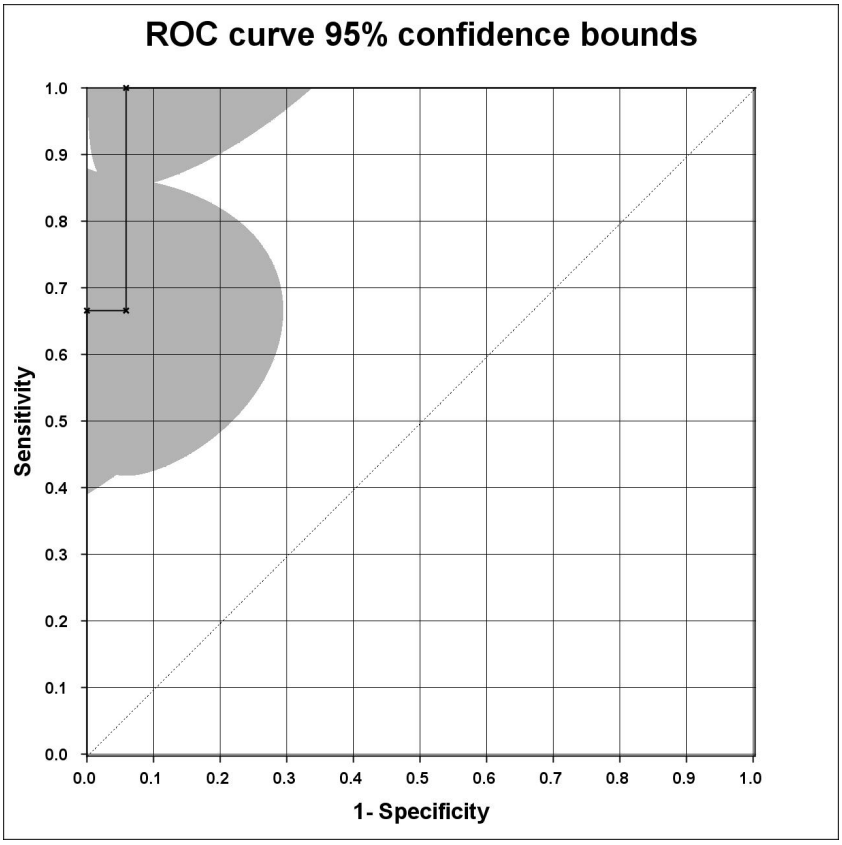


(a) (b)

Fig. 7: ZCI biomakers for (a) NOLD patients and (b) AD patients



(a)



(b)

Fig. 8: 95% confidence for the ROC curve for (a) FD and (b) ZCI