

# Performance Evaluation and Fusion of Methods for Early Detection of Alzheimer Disease

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## Abstract

*The number of people that develop Alzheimer's Disease (AD) is rapidly rising, while the initial diagnosis and care of AD patients typically falls on non-specialist and still taking up to 3-5 years before being referred to specialists. An urgent need thus exists to develop methods to extract accurate and robust biomarkers from low-cost and non intrusive modalities such as electroencephalograms (EEGs). Contributions of this paper are three-fold. First we review 8 promising methods for early diagnosis of AD and undertake a performance evaluation using ROC analysis. We find that fractal dimension ( $AUC = 0.989$ ), zero crossing interval ( $AUC = 0.980$ ) and spectrum analysis of power alpha/theta ratio ( $Pwr_{\alpha,\theta}$ ) ( $AUC = 0.975$ ) perform best. with all three having sensitivity and specificity higher than 94%. We plot ROC curve with 95% confidence contours because of the small size of our data set (17 AD and 24 NOLD). Second, we investigate a fusion approach to combine these methods, using a logistic regression model, into one single more accurate biomarker ( $AUC = 1.0$ ). Thirdly, to help support the distribution and use of these methods for early detection and care of AD, we developed them as web-services, integrated into online tools available from the BIOPATTERN project portal ([www.biopattern.org](http://www.biopattern.org)).*

## 1. Introduction

Worldwide, the number of people that develop Alzheimer's Disease (AD) is rapidly rising. In 2000 there were, in the US, 4.5 million persons with AD with this number likely to increase to 13.2 million by 2050 [17]. Figures

for Europe are also alarming, the number of prevalent patients with dementia in 2000 was 7.1 million and likely to rise, based on the population projections of the United Nations, to about 16.2 million within the next 50 years [32]. This is creating considerable financial burden on the health and social services [26] and making the clinical and economic benefits of early diagnosis an important issue [25]. In the long term, the real cost [7] and economic impact [4][31] of such disease is rather difficult to assess.

The initial diagnosis and care of AD patients typically falls on non-specialist, e.g. General Practitioners (GPs) at a surgery, before they are referred to specialists (e.g. in geriatric neurology) for further tests, and could take up to 3-5 years [8][27].

An urgent need is therefore required to develop methods to extract accurate and robust biomarkers from, low-cost and non intrusive, electroencephalograms (EEGs). There is also a need develop computer tools that can, easily and accurately, help early diagnosis within an acceptable time frame.

Biomarkers are found useful in many aspects of AD research. First, they are used as index to distinguish Normal Old (NOLD) persons from patients with Mild Cognitive Impairment (MCI) or probable AD [5]. Second, they are used monitor the progression of the disease in serial EEG studies [30]. Finally, they are used to assess the effectiveness of drug treatments in clinical trials [6]. In our research we focus on EEG-based biomarkers but it is worth mentioning that recent research aim to exploit multiple modalities [14][9].

The aims of our research, presented in this paper, are threefold: 1) to review promising methods for early diagnosis of AD and undertake a performance evaluation using

ROC analysis, 2) to investigate a fusion approach to combine these methods into one single biomarker, and 3) to help support the distribution and use of these methods with on-line tools developed as web-services for early detection and care of AD [15].

The remainder of the paper is organized as follows. In Section 2, we review the methods used in the evaluation study. In Section 3, we describe the EEG data set. Results are presented in Section 4. Finally, in Section 5, we conclude the paper.

## 2. Methods

In this paper, we restrict the evaluation to the following methods: spectrum analysis with power ratio ( $Pwr_{\alpha,\theta}$ ), fractal dimension (FD), zero-crossing interval (ZCI), central tendency measure (CTM), HjorthIndex a measure combining activity, mobility and complexity, sample entropy [2], Kolmogorov complexity [24], Tsallis entropy (TsaEnt) [34].

Power spectrum analysis is the reference method used for research in AD [29][28][10]. We filter each EEG channel to extract frequency bands, typically delta ( $\delta$ , 2-4Hz), theta ( $\theta$ , 4-8Hz) and alpha ( $\alpha$ , 8-13Hz), and beta ( $\beta$ , 13-30Hz). The power ratio,  $Pwr_{\alpha,\theta}$ , is then calculated as:

$$Pwr_{\alpha,\theta} = \frac{Power_{\alpha}}{Power_{\alpha} + Power_{\theta}} \quad (1)$$

Sophisticated nonlinear signal processing techniques now exist that can be used to handle problems associated with, for example, non-linearity and non-stationarity [22]. A good review of method for AD can be found in [23]. We use FD and ZCI that were the basis of previous work [19][18].

CTM has also been used for early detection of AD [3]. The method allows to quantify the variability seen in the second order difference plot and is computed by selecting a circular region of radius  $r$ , around the origin, and then counting the number of points falling within the radius, over the total number of points. CTM is defined as:

$$CTM = \frac{\sum_{i=1}^{n-2} \delta(d_i)}{n-2} \quad (2)$$

$$\delta(d_i) = \begin{cases} 1 & \text{if } ([x_{21}]^2 + [x_{10}]^2)^{0.5} < r \\ 0 & \text{otherwise} \end{cases}$$

where  $x_{21} = [x_{i+2} - x_{i+1}]$  and  $x_{10} = [x_{i+1} - x_i]$ . For sample entropy we use the same setting as in [2] with  $m = 1$  and  $r = 0.25$  times the standard deviation of the EEG channel. Finally, we use a Hjorth-based index [12] using parameters activity, mobility and complexity [20] defined as:

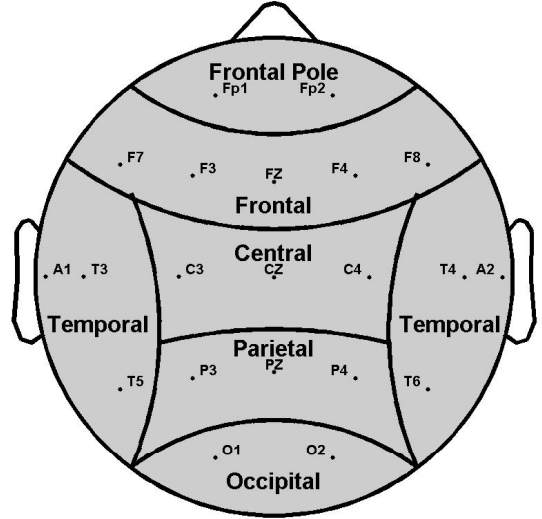


Figure 1. Electrodes and brain regions

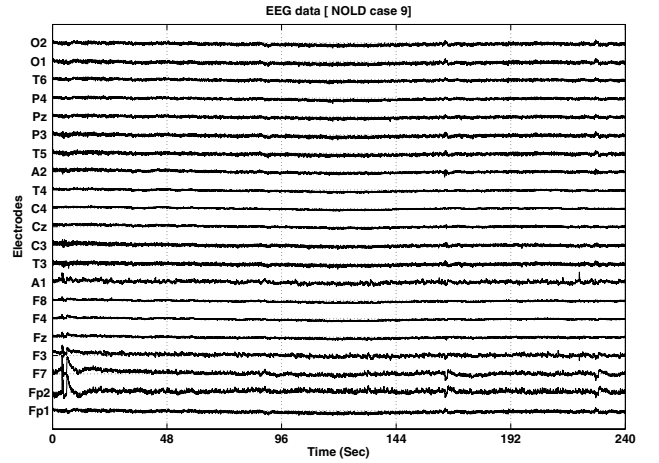


Figure 2. Example of EEG trace

$$Activity(x(t)) = VAR(x(t)) \quad (3)$$

$$Mobility(x(t)) = \sqrt{\frac{Activity(\frac{dx(t)}{dt})}{Activity(x(t))}} \quad (4)$$

$$Complexity(x(t)) = \frac{Mobility(\frac{dx(t)}{dt})}{Mobility(x(t))} \quad (5)$$

$$HjorthIndex = 2 * Complexity + \frac{100}{2 * Mobility} \quad (6)$$

where both mobility and complexity are averaged over all channels.

### 3. Data

We have used the data set recorded at Derriford hospital (Plymouth, Devon, U.K.) used as evaluation data set in other recent studies [18][11][13]. It consists of 17 AD cases (9 men and 8 women, age mean = 77.6 years, std = 10) and 24 age-matched normal old (NOLD) cases (10 men and 14 women, age mean = 69.4 years, std = 11.5). EEG were recorded from 21 scalp loci of the international 10-20 system with electrodes Fp1, Fp2, F7, F3, Fz, F4, F8, A1, T3, C3, Cz, C4, T4, A2, T5, P3, Pz, P4, T6, O1, O2 (See Figure 1). Each EEG is 4 minutes long (See Figure 2) and was left as raw as possible which would be the case for portable EEG machine at a GP surgery, with only bandpass filtering (0.5–50Hz IIR Chebyshev Type II filter) to remove DC and high frequency noise such as main sector.

### 4. Results

Results presented in this section are for each individual method and combined one using a fusion approach.

#### 4.1 Evaluation

We use each method to calculate biomarkers per individual channel, then average them over all channels to obtain one single biomarker. With the results of all EEGs, we change the decision threshold and count True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) cases. We then calculate the sensitivity, calculated as the ratio of TP over TP+FN, the specificity, as the ratio of TN over TN+FP, and the accuracy (ratio of TP+TN over TP+TN+FP+FN). We also plot ROC curve for each method and calculate the Area Under the Curve (AUC) using the trapezoid rule and Standard Error (SE) [16]. Performance results are shown in Table 1. We can clearly see that some methods are providing very high accuracy (such as FD, ZCI and  $Pwr_{\alpha,\theta}$ ) with both sensitivity and specificity better than 90% while others are not as robust.

As the size of our data set is relatively small ( $N = 41$ ), we prefer to plot the ROC curves showing the method's true performance with 95% confidence contours as shown in Figure 3(a) for FD, Figure 3(b) for ZCI and Figure 3(c) for  $Pwr_{\alpha,\theta}$ .

#### 4.2 Fusion approach

We investigated a fusion approach in which the outcome of each method are combined into one biomarker using a logistic regression model [21] of the form:

$$y(X) = \frac{1}{1 + e^{-\left(\beta_0 + \sum_{i=1}^N \beta_i x_i\right)}} \quad (7)$$

where  $\beta_0$  is the bias,  $\beta_i$  are the regression coefficients, and  $x_i$  the values of each method. The overall performance, using the fusion approach, is improved to a 100.0% accuracy (sensitivity of 100% and specificity of 100%). This shows the potential of combining multiple methods to obtain a more accurate early detection of AD rather than using individual method. The logistic regression model gives also indication on each method's discriminative power from a statistical point of view. Notice that this improvement is relative to the small number of cases ( $N = 41$ ) and such performance could decrease for larger data sets. Using the biomarker value of each method however, we can compare them on a case-to-case basis and help to assess which case was missed (i.e. False Negative) and thus further investigate.

### 5. Conclusion

In this paper we presented an evaluation study of promising methods for extracting biomarkers used for early detection of Alzheimer Disease (AD). The evaluation was carried out on data set with 17 AD and 24 NOLD. We presented the performance results with each method's sensitivity, specificity, accuracy, AUC and SE. Due to the small sample size, ROC curves are plotted with the 95% confidence intervals are shown as contours.

To improve the diagnosis, we investigated a fusion approach, using each method biomarker as one feature of a logistic regression model. The final outcome was shown to improve the overall diagnosis accuracy (with the fusion outcome becoming perfect, i.e. AUC of 1.0). Moreover, such fusion approach provides insights on each method's discriminative power and allow to assess specific individual case missed by certain method. Ultimately, we can design an optimized classifier with only the best few methods. In this study they were found to be: FD, ZCI and  $Pwr_{\alpha,\theta}$ .

The methods described in this paper have been developed in MATLAB. Work is in progress to port them in JAVA to further support online tools and services [15].

Future work will investigate the effects of artifacts removal and extend this evaluation to brain regions and frequency bands (delta, theta, alpha, beta, gamma, etc.), adding more methods like Lempel-Ziv complexity (LZ) [3], multiscale entropy (MSEnt) [1], and from information theory with LZW-based compression [33]. To further improve the clinical significance of our current evaluation, we will look at larger multi center data set [5] and possibly initiate EEG data collection from patients of different ethnic groups (e.g. from the Asia-Pacific region).

**Table 1. Performance results for all methods**

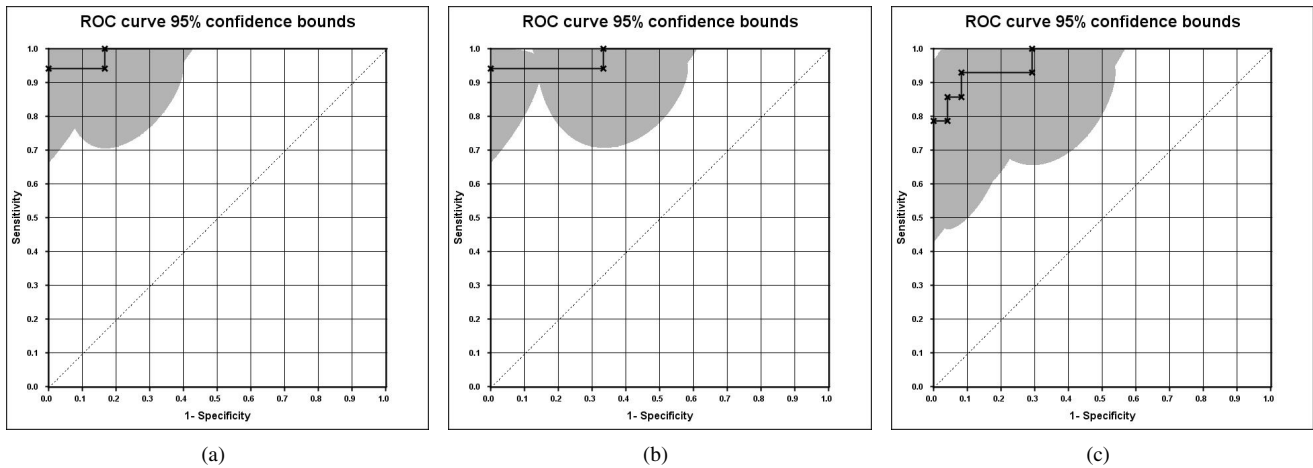
	Sen.	Spec.	Acc.	AUC	SE
$Pwr_{\alpha,\theta}$	94.12 %	91.67 %	92.68 %	0.975	0.027
ZCI	94.12 %	100.00 %	97.56 %	0.980	0.024
FD	94.12 %	100.00 %	97.56 %	0.989	0.018
CTM	47.06 %	79.17 %	65.85 %	0.605	0.091
Hjorth	64.71 %	66.67 %	65.85 %	0.620	0.091
SamEnt	29.42 %	79.17 %	63.41 %	0.561	0.092
KolEnt	82.35 %	50.00 %	63.41 %	0.577	0.092
TsaEnt	41.17 %	79.17 %	63.41 %	0.604	0.091
Fusion	100.0 %	100.0 %	100.0 %	1.000	

## 6. Acknowledgments

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**Figure 3. ROC curve for (a) FD, (b) ZCI and (c)  $Pwr_{\alpha,\theta}$  method**

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