# Combination of Tsallis Entropy and Higutchi Fractal Dimension for Quantifying Changes in EEG signals in Alzheimer's Disease

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***Abstract*—Alzheimer's Disease (AD) is one of the challenges of modern medicine since no cure has been found yet, the scientific community still does not fully understand the pathogenesis behind it, and any interventions found can delay the progress for only a limited amount of time. Over the years, research has shifted from curing the disease to understanding the mechanisms behind it as well as finding tools that will speed up diagnosis many years before its clinical manifestation, when the decline begins. One of the many promising tools that have been explored towards that direction is the electroencephalogram (EEG), which holds many different measures that can be used as biomarkers for early diagnosis and differentiation from other neurodegenerative disorders by exploiting various bio-informatics techniques. Literature has presented a high correlation between EEG signals and structural abnormalities in AD. However, there is no analysis that can provide a clear result that binds the two and leads to early diagnosis, and very few studies have explored early stages of AD, such as Mild Cognitive Impairment. Moreover, most of the approaches applied do not adopt a multimodal methodology that combines different analysis methods. To that end, the present work proposes the combination of Tsallis Entropy and Higuchi Fractal Dimension, in a common framework for either the entire EEG or on each frequency separately, to examine the performance in Mild Cognitive Impairment (MCI) and AD subjects.**

***Keywords- Alzheimer's Disease; Mild Cognitive Impairment, EEG; Tsallis Entropy; Higuchi Fractal Dimension.***

## I. INTRODUCTION

As stated by the International Alzheimer's Association [1], Alzheimer's Disease (AD) is the most common form of dementia. With 60% to 80% of dementia cases being diagnosed as AD, which practically means that one out of ten people over 65 has AD, it is one of the most severe diseases that affect mainly elderly people and is expected to affect roughly 131 million people by 2050. Although medicine and technology breakthroughs follow one after another, the mortality of AD keeps rising. From 2000 to 2014, an increase of 89% has been observed. To that end, an enormous amount of resources have been employed not only to postpone the progression of AD (which is still currently the only successful course of action) but to understand and thoroughly analyse the processes responsible for the brain degradation. As depicted in Figure 1, brain degradation originating from AD has severe effects both in terms of quality and volume.

As research has failed so far to grasp a cure for AD and solutions available only target symptoms and not the cause of the disease [2], effort has shifted towards better understating of the initial mechanisms that cause cognitive decline that could lead to an early diagnosis, especially at Mild Cognitive Impairment (MCI) level, which is considered a precursor stage of AD [3]. An early diagnosis may contribute not only to develop more effective interventions that could delay the progress or even inhibit it entirely but could also prevent some of the symptoms to evolve when dealt with at an early stage.

Towards the direction of early diagnosis, a handful of different methodologies have been proposed, some of which are invasive (i.e., blood) and dangerous (i.e., Cerebrospinal Fluid – CSF), others are expensive (i.e., Magnetic Resonance Imaging – MRI, Single-Photon Emission Computed Tomography – SPECT, or Positron Emission Tomography - PET), and with some still eluding significant results [4]. In contrast with these, a non-invasive, low-cost and with high resolution in terms of brain activity tool is the electroencephalogram (EEG).

### *A. EEG and AD*

With research going back a few decades [5][6], many studies have been focused on researching the use of EEG in AD, revealing certain commonly agreed features and some other somewhat controversial [7]. The most interesting features that are commonly agreed upon in the literature regarding EEG and AD can be summarized as follows [8]-[11]: a) Overall retardation of specific rhythms, in particular, the observations so far present an increase in delta (0.1 - 4 Hz) and theta (4 – 8 Hz) activities and decrease in alpha (8 – 13 Hz) and beta (13 – 30 Hz) activities. Earliest changes are an increase in theta and a decrease in beta activities, followed by a decrease in alpha, while delta increases later during the progress of the disease. This is supported by the fact that patients with severe dementia exhibit a decrease in alpha and an increase in delta activity, whereas patients with mild dementia show a decrease in beta and an increase in theta activity, b) decreased complexity, and c) decreased coherence in general and among different brain regions. From a topographic perspective, observations indicate that slow activity is prominent in the left temporal area of AD

 ISBN: 978-1-61208-717-7 

patients, whereas differences between pre-senile patients and healthy controls are detected in the right posterior temporal area. Most significant differences between senile patients and the controls are found in the midfrontal and anterior frontal lobes bilaterally.

When evaluating complexity, significant effort has been focused on non-linear dynamics [12], under the assumption that EEG signals are generated by nonlinear deterministic processes with nonlinear coupling interactions between neurons. Studies employing such measures have found that AD patients have reduced values of the correlation dimension (D2) in the occipital EEG compared with those of healthy subjects, and with probable AD subjects [13]-[16]. In addition, it has been highlighted that AD patients exhibit reduced spatiotemporal brain activity in comparison with that in healthy controls [17], and in some cases, the former subjects are characterized by specific patterns of dysfunction in dementia [18].

Investing in the analysis of EEG complexity, a lot of novel biomarkers have been extracted from non-linear approaches (e.g., entropies, fractality, lacunarity) towards providing the necessary methods for accurate and early diagnosis of AD. This study is focused on two of them that hold promising potential and intends to combine them into a single biomarker for the intended purpose.

The manuscript is structured as follows: Section I summarizes the related work on the subjects discussed, whereas Section II presents the methodology designed to address the identified challenges. Section III describes in detail the dataset selected, and finally Section IV concludes this work with some initial findings.

## II. METHODOLOGY

There are a lot of different complexity measures that have been employed in EEG signal analysis for many diseases including AD [19][20]. Two of them that have been found to hold much potential when used individually [21] are the Tsallis Entropy and the Higuchi Fractal Dimension.

### A. Tsallis Entropy

The Tsallis Entropy (TE) [22] has been widely used in the analysis of EEG signals for over two decades now [23], with work on AD starting somewhere in between [24]. In multiple occasions, TE has been introduced as a possible biomarker for differentiating AD from Healthy and even MCI subjects [21][25][26].

Given a discrete set of probabilities {pi} with the condition $\sum$pi =1, and q any real number, then the Tsallis Entropy is defined as:

$$\mathrm{TE}_q = \frac{(\sum_{i=1}^{k} p_i - p_i^q)}{(q-1)} \quad (1)$$

### B. Higuchi Fractal Dimension

The Fractal Dimension (FD) as a nonlinear approach for analyzing EEG signal complexity in AD was introduced around the same time as the introduction of the TE [27]. By using it as an index of irregularity of a time series, thus evaluating time series with non-periodic and turbulent behavior [28], FD becomes a very suitable tool for EEG waveforms. Specifically in AD, FD has been found significantly lower in AD subjects when compared with healthy individuals [14][29][30]. As the basic FD can be quite processing-intense, the Higuchi Fractal Dimension (HFD) [31] has been introduced as a fast and efficient computational method that is able to successfully and accurately estimate the dimension also for segments shorter than 250 ms, thus enabling the study of brief EEG events and the identification of behavioral variations with a good temporal resolution [32][33].

For a $N$-sample EEG data sequence (1), (2), . . . , $x(N)$, the data is first divided into a $k$-length sub data set as:

$$x_k^m : \quad x(m), x(m+k), x(m+2k), \ldots, x(m+[\frac{N-m}{k}]k) \quad (2)$$

where [ ] is Gauss' notation, $k$ is constant, and $m$=1,2,…,$k$. The length ($k$) for each sub data set is then computed as:

$$L_m(k) = \left\{ [\sum_{i=1}^{[(N-m)/k]} |x(m+ik) - x(m+(i-1)k|] \cdot (\frac{N-1}{[(N-m)/k] \cdot k}) \right\} \quad (3)$$

The mean of Lm(k) is then computed to find the HFD for the data as:

$$< \mathrm{L_m(k)} >= \frac{1}{K} \sum_{M=1}^{K} L_m(k) \quad (4)$$

In order to calculate the HFD, a least-squares linear best-fitting procedure as the angular coefficient of the linear regression of the log-log graph of $<L_m(k)> \sim k^{-HFD}$ is applied.

### C. Complexity Measures Combination

As both of these measures have been tried individually in the analysis of EEG signals for AD diagnosis and are presenting rather promising results (sensitivity and specificity more than 90% when comparing only AD and normal subjects), the purpose of this study is to present an approach that will also focus on MCI stage, exploring not only the effect of these complexity measures individually but

also combine them in formulating a new biomarker that is based on both for the indented purposes, as similarly suggested by [34] for depression. By employing Support Vector Machine algorithms after extracting features from applying TE and HFD on both the entire EEG bandwidth and each channel separately, we hypothesize that it will lead to enhanced performance in diagnosing and differentiating normal, MCI, and probable AD subjects.

As most of the literature suggests changes of EEG signals on the frontal and temporal brain regions, initially only specific channels have been examined, namely Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, and T4. Since it is suggested that both MCI and AD have a different effect on the four main rhythms (delta, theta, alpha, and beta), these are also evaluated separately to identify any distinguished alterations on the proposed metrics.

The analysis of the EEG signals was performed using Python language and various open source libraries with the main ones being MNE (Minimum Norm Estimates) [35] and SciPy.

## III. DATASET

This study is currently performed on EEG samples collected from a 10-20 electrode system placement [34], over 100 subjects (30 healthy, 16 probable AD, and 54 MCI) from an EEG setup with 21 electrodes, and in particular a NIHON KOHDEN Neurofax JE-921A, digitized and analysed with Neurofax EEG-1200.

Based on the available signals, the study aims to explore the potential of diagnosing and differentiating AD, starting from the initial stages of MCI.

All of the subjects were examined and diagnosed by experts at the Greek Association of AD and Related Disorders. A battery of neuro-psychometric tests has also been provided to evaluate future findings better.

The EEG signals were collected following the 10-20 placement system (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, A1, A2) [36] at 500Hz. The input impedance was set to $Z < 10k\Omega$. The protocol used for the acquisition of the EEG signals refers to resting stage and lasts for 10 minutes with 5 minutes eyes closed and 5 minutes eyes open. An one minute window was used during eyes closed for the analysis of the EEG signals.

Low and high band pass filters have been applied to remove any artifacts prior to analysis, including a filter on 50Hz for noise from electrical equipment, whereas specific zone band filters were applied to retrieve the different EEG rhythms.

Finally, for calculating Tsallis Entropy, the probability density function was found and normalised for every examined signal.

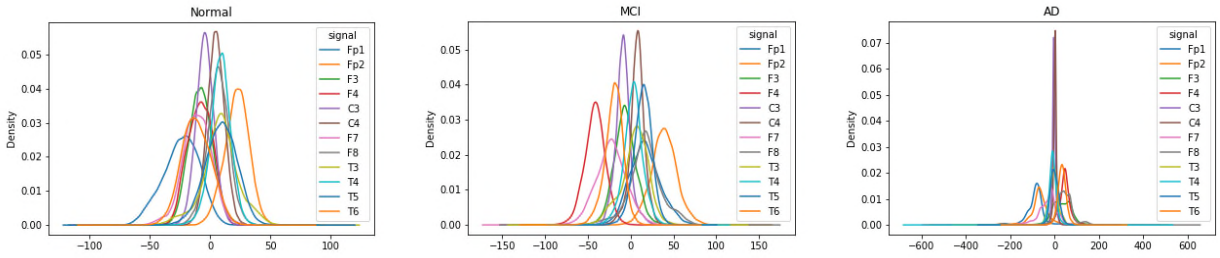


Figure 1. Whole EEG probability density functions: (a) Normal, (b) MCI and (c) probable AD subjects.

## IV. DISCUSSION & CONCLUSION

Initial findings of a first uniform sample from all three groups/classes (Healthy/Normal, MCI and probable AD) indicate significant changes between Healthy Vs. (probable) AD, and MCI Vs. AD, but only mild ones between Healthy Vs. MCI, even from the fundamental comparison of the Probability Density Functions (PDF), as can be observed in Figure 1.

By calculating the TE and HFD for each electrode and the different basic bands, for all three classes we have so far identified that it is extremely difficult for TEq and HFD (with the configuration parameters explored) individually to provide valuable insight for the differentiation between Normal/Healthy, MCI and AD subjects (Figures 2 and 3). Nevertheless, certain characteristics are in line with the literature, and thus more elaborated research is required.

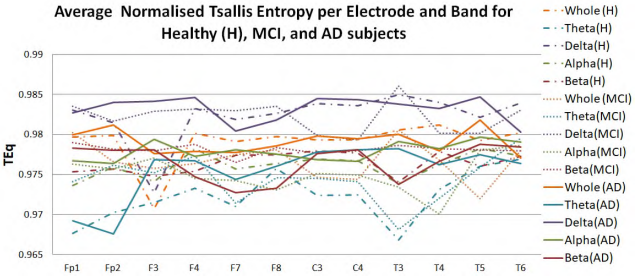


Figure 2. EEG Tsallis Entropy

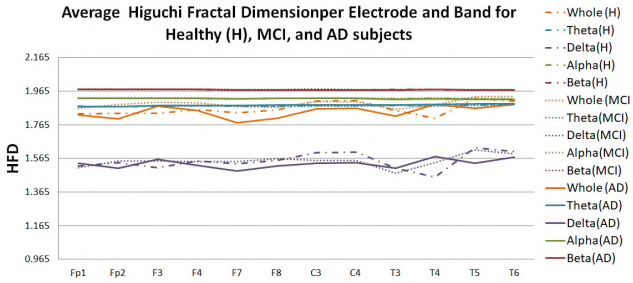


Figure 3. EEG Higuchi Fractal Dimension

 ISBN: 978-1-61208-717-7

As the presented work is an ongoing research endeavour, current and future steps involve the complete analysis of the subjects' pool with SVM and the extraction of the proper features (electrodes and bands) for maximising the accuracy of the suggested methodology.

Additional analysis of the signals is required in order to be able to provide more clear results, as well as applying additional machine learning algorithms towards evaluating the fusion of TE and HFD in a common biomarker for early diagnosis of both MCI and AD. Currently, a set of 8 subjects from each class have been used to train the models and its accuracy is being evaluated to the remaining subjects. To further enhance the reach of the analysis, the presented work will also be used for evaluating signals from a 256 electrodes set up that has many additional capabilities [14].

## ACKNOWLEDGMENT

This study is co-financed by the European Union and Greek national funds through the National Strategic Reference Framework (NSRF) 2014-2020, under the call Researchers' Support with Emphasis on Young Researchers "EΔBM34". We would also like to show our gratitude to the Greek Association of Alzheimer's Disease and Related Disorders (Alzheimer Hellas) [37] for providing us with the EEG samples and the neuro-psychometric tests.

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 ISBN: 978-1-61208-717-7 