Unlocking Brain Complexity: Higuchi's Fractal Dimension as a Biomarker for Neurodegenerative Diseases and Follow-up

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The analysis of fractal dimension (FD) has, for over two decades, represented a valuable tool for the diagnosis and follow-up of neurodegenerative diseases, characterized by changes in synaptic function and a progressive decrease in brain activity. Early diagnosis and continuous monitoring of the disease progression represent current challenges to be addressed. When applied to electroencephalography (EEG), FD enables a quantitative characterization of nonlinear, non-stationary, and noisy (3N) signals, providing a more comprehensive description of signal complexity compared to linear and established analyses based on Power Spectral Density (PSD).

Physiologically, EEG signals typically show FD values between 1 and 2, where values closer to 1 indicate a smoother and less complex signal, whereas values closer to 2 indicate greater temporal irregularity and higher signal complexity. Among estimation methods, the Higuchi Fractal Dimension (HFD) stands out for its accuracy, computational efficiency, and robustness, proving effective even on short data segments. The method (Higuchi 1988) is based on computing the complexity of a time series directly in the time domain.

The discriminative capacity of Higuchi Fractal Dimension was explored across three predefined subject groups: neurologically unimpaired older adults (NOLD), individuals with Alzheimer's disease (AD) and individuals with Alzheimer's disease and further cognitive disease (AD+).
EEG signals were pre-processed through band pass filtering (1-48 Hz) to isolate physiological frequencies, along with re-referencing to reduce the noise associated with the reference electrode. Despite the effectiveness of HFD, the lack of a standardized criterion for selecting the parameter k_{max} still limits the definition of a single representative numerical value, one for each signal. Several studies addressed the issue of the best selection for this tuning parameter, but at our knowledge at present, there are no generalized or standardized methods to determine/assign a priori, k_{max}. Without a universally accepted criterion, the

arbitrary selection of k_{max} risks compromising the reproducibility and the clinical meaningfulness of the HFD metric.

To address this issue, the trend of the HFD-vs-k curve was analyzed, exploring the interval $k \in [2,128]$, where the upper limit of 128, in accordance with the Nyquist-Shannon theorem, corresponds to half of the EEG signal sampling rate (256 Hz).

The resulting curves were used as features for unsupervised machine learning algorithms. The aim of the study is to evaluate the ability of clustering and if doable classification algorithms to autonomously discriminate among the three clinical reference groups (NOLD, AD, AD+), thereby validating the Higuchi-curve based approach as a biomarker of the disease.