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Dispersion Entropy for the Analysis of Resting-state MEG Regularity in Alzheimer's Disease

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***Abstract*— Alzheimer's disease (AD) is a progressive degenerative brain disorder affecting memory, thinking, behaviour and emotion. It is the most common form of dementia and a big social problem in western societies. The analysis of brain activity may help to diagnose this disease. Changes in entropy methods have been reported useful in research studies to characterize AD. We have recently proposed dispersion entropy (DisEn) as a very fast and powerful tool to quantify the irregularity of time series. The aim of this paper is to evaluate the ability of DisEn, in comparison with fuzzy entropy (FuzEn), sample entropy (SampEn), and permutation entropy (PerEn), to discriminate 36 AD patients from 26 elderly control subjects using resting-state magnetoencephalogram (MEG) signals. The results obtained by DisEn, FuzEn, and SampEn, unlike PerEn, show that the AD patients' signals are more regular than controls' time series. The *p*-values obtained by DisEn, FuzEn, SampEn, and PerEn based methods demonstrate the superiority of DisEn over PerEn, SampEn, and PerEn. Moreover, the computation time for the newly proposed DisEn-based method is noticeably less than for the FuzEn, SampEn, and PerEn based approaches.**

I. Introduction

Alzheimer's disease (AD), the most common type of dementia, is a neurodegenerative disorder characterized by cognitive deficits, disorders of daily activities, and behavioural disturbances [1] [2]. AD is clinically defined as a slowly progressive impairment of mental functions whose course lasts several years before the death. AD usually starts by destroying neurons responsible for storing and retrieving memories. Next, it affects the brain areas involved in language and reasoning. Finally, other brain areas are atrophied [1] [3].

Changes in electrophysiological time series, such as magnetoencephalogram (MEG) and electroencephalogram (EEG), have been broadly used to characterize AD in the recent years [4]–[8]. MEG is a non-invasive technique allowing to record the magnetic fields generated by the brain neuronal activity. Both the MEG and EEG signals have high temporal resolution. MEG signals do not depend on any reference point and they are less affected by extra-cerebral tissues than EEGs [9]. Changes in MEG and EEG can be detected by nonlinear dynamical techniques such as fractal dimension, Lempel-Ziv complexity, and entropy methods [7] [10] [11].

Entropy is a powerful and widely-used measure to quantify the irregularity or uncertainty of a time series [12]. Given a distribution $\mathbf{s}$ with N states $s_1, s_2, ..., s_N$, the entropy of the distribution is $-\sum_{k=1}^{N} Pr\{s_k\}\log(Pr\{s_k\})$, where $Pr\{s_k\}$ is the probability that $\mathbf{s}$ is in the state $\{s_k\}$. In fact, entropy is a feature of the probability distribution Pr. When all states are equally likely, the maximum entropy is achieved. In contrast, if one state is certain and the others are impossible, the minimum entropy occurs [13]. Based on the previous concept, several methods, such as sample entropy (SampEn) [12] and permutation entropy (PerEn) [14] have been introduced.

SampEn denotes the negative natural logarithm of the conditional probability that a time series of length N, having repeated itself within a tolerance r for m sample points, will also repeat for $m + 1$ sample points [12]. Details of the method can be found in [12]. SampEn has been extensively used to calculate the irregularity of time series [15]. SampEn was employed for characterizing EEG signals in AD, although the differences between AD patients and controls were not significant in the majority of channels [16].

Another well-known irregularity measure is PerEn [14]. This entropy is based on the permutation patterns or the order relations of the amplitude values of a time series. For more information about its algorithm, please refer to [14]. PerEn has received much attention in recent years because of being conceptually simple, computationally fast, and structurally robust [17]. PerEn and SampEn have various uses in biomedical signal processing study, such as epilepsy and cognitive neuroscience [15] [17].

One of the most important shortcomings of the SampEn is that it ignores the magnitude of the distance between two composite delay vectors that is larger than a defined threshold [12]. To alleviate this problem, fuzzy entropy (FuzEn) was proposed to consider every distance between two composite delay vectors [18]. Details of the FuzEn algorithm can be found in [18]. FuzEn, which is based on the fuzzy theory and SampEn, is more stable and reliable than SampEn, especially for short signals. However, FuzEn and SampEn, though powerful, are not fast enough for some real-time applications and PerEn fails to account for the equal amplitude values of

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embedding vectors and the differences between amplitude values [19].

To overcome the aforementioned shortcomings, we have very recently proposed a new, fast, and powerful measure, termed dispersion entropy (DisEn) [20]. We gained insight into the dependency of DisEn on a number of straightforward signal processing concepts via a set of synthetic time series. We also used the DisEn method for three real publicly-available datasets. The results using both synthetic and real-valued time series demonstrated the DisEn method significantly outperforms PerEn. The results showed that DisEn is sensitive to changes in frequency, simultaneous amplitude and frequency, noise power, and noise bandwidth. Furthermore, the running time of DisEn was considerably less than that of both the SampEn and PerEn [20].

In this paper, we employ DisEn, FuzEn, SampEn, and PerEn to investigate the MEG background activity in patients with AD and in control subjects with the objective of comparing DisEn with the already established entropy metrics.

II. Materials

A. Subject Groups

We considered 36 AD patients and 26 age-matched controls (CON). All 62 subjects gave their informed agreement for the research, which was approved by the local ethics committee. Diagnoses were confirmed with thorough tests. To screen the cognitive status, the mini-mental state examination (MMSE) was utilized. The 36 AD patients (12 men and 24 women; age = 74.06 ± 6.95 years, mean $\pm$ standard deviation (SD); MMSE score = 18.06 ± 3.36, mean $\pm$ SD) met the criteria for probable AD according to the guidelines of the NINCDS-ADRDA [21]. The CON group was formed by 26 subjects (9 men and 17 women; age = 71.77 ± 6.38 years, mean $\pm$ SD; MMSE score = 28.88 ± 1.18 (mean $\pm$ SD)). The difference in age between two groups was not significant (p-value = 0.1911, student's t-test) [4].

B. MEG Recordings

Resting state MEG recordings were obtained with a 148-channel whole-head magnetometer (MAGNES 2500 WH, 4D Neuroimaging) in a magnetically shielded room at the MEG Centre Dr. Perez-Modrego (Spain). The subjects lied on a hospital bed in a relaxed state with eyes closed. They were asked to avoid sleeping and not to move head and eyes. For each participant, five minutes of MEG resting state activity were recorded at a sampling frequency (f_s) of 169.54Hz. The signals were divided into segments of 10s (1695 samples) and visually inspected using an automated thresholding procedure to discard segments significantly contaminated with artifacts. The effect of cardiac artifact was reduced from the recordings using a constrained blind source separation procedure [22]. Finally, a bandpass FIR filter with cut-offs at 1.5Hz and 40Hz was employed for the data.

III. Dispersion Entropy

Assume we have a univariate time series of length N: $\mathbf{x} = \{x_1, x_2, ..., x_N\}$. The algorithm of DisEn includes four main steps:

1) First, $x_j (j = 1, 2, ..., N)$ are mapped to c classes with integer indices from 1 to c. To this end, there are a number of linear and nonlinear approaches. Although a linear mapping algorithm is the fastest one, when maximum or minimum values are noticeably larger or smaller than the mean/median value of the signal, the majority of x_i are assigned to only few classes. Thus, the normal cumulative distribution function (NCDF) is employed to map $\mathbf{x}$ into $\mathbf{y} = \{y_1, y_2, ..., y_N\}$ from 0 to 1. Then, we use a linear algorithm to assign each y_i to an integer from 1 to c. Note that, although this part is linear, the whole mapping approach is non-linear because of the use of the NCDF. To do so, for each member of the mapped signal, we use $z_j^c = \text{round}(c.y_j + 0.5)$, where z_j^c denotes the j^{th} member of the classified time series and rounding involves either increasing or decreasing a number to the next digit [20].

2) Time series $\mathbf{z}_i^{m,c}$ are made with embedding dimension m and time delay d according to $\mathbf{z}_i^{m,c} = \{z_i^c, z_{i+d}^c, +... + z_{i+(m-1)d}^c\}$, $i = 1, 2, ..., N - (m-1)d$ [12] [14] [20]. Each time series $\mathbf{z}_i^{m,c}$ is mapped to a dispersion pattern $\pi_{v_0 v_1 ... v_{m-1}}$ where $z_i^c = v_0$,$z_{i+d}^c = v_1$,..., $z_{i+(m-1)d}^c = v_{m-1}$. The number of possible dispersion patterns that can be assigned to each time series $\mathbf{z}_i^{m,c}$ is equal to c^m, since the signal has m members and each member can be one of the integers from 1 to c [20].

3) For each c^m potential dispersion patterns $\pi_{v_0 v_1 ... v_{m-1}}$, relative frequency is obtained as follows:

$$p(\pi_{v_0 v_1 ... v_{m-1}}) = \frac{Number\{i \,|i \leq N - (m-1)d, \mathbf{z}_i^{m,c} \text{ has type } \pi_{v_0 v_1 ... v_{m-1}}\}}{N - (m-1)d} \tag{1}$$

In fact, $p(\pi_{v_0 v_1 ... v_{m-1}})$ shows the number of dispersion patterns of $\pi_{v_0 v_1 ... v_{m-1}}$ that is assigned to $\mathbf{z}_i^{m,c}$, divided by the total number of embedded signals with embedding dimension m.

4) Finally, based on the Shannon's definition of entropy, the DisEn value with embedding dimension m, time delay d, and the number of classes c, is calculated as follows:

$$DisEn(\mathbf{x}, m, c, d) = -\sum_{\pi=1}^{c^m} p(\pi_{v_0 v_1 ... v_{m-1}}). \ln\left(p(\pi_{v_0 v_1 ... v_{m-1}})\right) \tag{2}$$

When all possible dispersion patterns have equal probability value, the highest value of DisEn is obtained, which has a value of $ln(c^m)$. In contrast, if there is only one $p(\pi_{v_0 v_1 ... v_{m-1}})$ different from zero, which demonstrates a completely regular/predictable time series, the smallest value of DisEn is obtained [20].

In the DisEn algorithm, it is needed to neither sort the amplitude values of each embedding vector nor calculate every distance between any two composite delay vectors with embedding dimensions m and $m+1$. This makes DisEn considerably faster than PerEn and SampEn. DisEn overcomes

the problem of equal values for embedding vectors obtained by the PerEn. Finally, DisEn is relatively insensitive to noise, because a small change in amplitude value will not vary the class label of the value [20].

IV. Results and Discussions

DisEn, FuzEn, SampEn, and PerEn were applied to all 148 MEG channels to quantify the signal irregularity. For each method, the box plot of the results averaged over all channels are shown in Fig. 1. For FuzEn, SampEn and DisEn, unlike PerEn, the AD patients' signals have smaller average of entropy values in comparison with controls' time series. This fact is in agreement with [5] [6] [8] [7]. In contrast, the PerEn-based results are very similar for both groups. A paired student's t-test was also used to assess the statistical differences between the DisEn/FuzEn/SampEn/PerEn values for AD patients versus controls. We adjusted the false discovery rate (FDR) independently for each entropy method. The adjusted p-values for DisEn, FuzEn, SampEn, and PerEn are about 0.014, 0.253, 0.31, and 0.95, respectively. As expected theoretically [18], FuzEn leads to lower adjusted p-values in comparison with SampEn and PerEn. The best method in terms of adjusted p-values is DisEn.

In this paper, the simulations have been carried out using a PC with Intel (R) Xeon (R) CPU, E5420, 2.5 GHz and 8-GB RAM by MATLAB R2010a. The computation time of the DisEn, FuzEn, SampEn, and PerEn for each channel is approximately 0.054 s, 0.298 s, 0.266 s, and 0.221 s, respectively. This shows the importance of DisEn for real-time applications.

In practical uses, the embedding dimension of PerEn, chosen based on [17] [23], is larger than the m for SampEn, FuzEn, and DisEn. This fact causes the computation time of PerEn is not significantly lower than that of SampEn and FuzEn. In this article, the parameters, chosen according to [12] [17] [20] [23], are as follows: I) the time delay for all approaches was 1, II) the embedding dimension for FuzEn, SampEn, DisEn, and PerEn respectively were 2, 2, 3, and 5, III) the tolerance r was 0.2 of the SD of each signal for SampEn and FuzEn, and IV) the number of classes for DisEn was 5.

For each channel, a paired student's t-test was also employed to evaluate the statistical differences between the DisEn/FuzEn/SampEn/PerEn values for AD patients versus controls. We adjusted the FDR independently for each entropy algorithm. The adjusted p-values obtained by DisEn, FuzEn, SampEn, and PerEn are respectively shown in Fig. 2(a)-(d) in a logarithmically scale. The adjusted p-values for DisEn, FuzEn, SampEn, and PerEn change from about 0.006 to 0.114, 0.098 to 0.86, 0.16 to 0.92, and 0.92 to 1, in that order. As expected theoretically [18], FuzEn leads to lower adjusted p-values in comparison with SampEn and PerEn. The best algorithm in terms of adjusted p-values is DisEn. Unlike PerEn, FuzEn, and SampEn, DisEn leads to significant differences for the majority of channels. This fact shows the superiority of the DisEn over the FuzEn, PerEn and SampEn methods in terms of adjusted p values in addition to computation time.

In future work, we will investigate the dependency between the threshold r for SmpEn/FuzEn and the number of classes c for DisEn. Moreover, we intend to consider different values of c and m for the DisEn method.

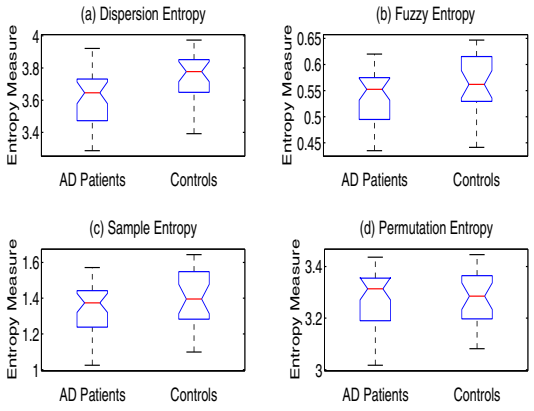


Fig. 1: Boxplots for the DisEn, FuzEn, SampEn, and PerEn for control subjects and AD patients.

V. Conclusions

We have investigated the irregularity of the resting-state MEG signals in controls and patients with AD by the use of DisEn as a new entropy measure, in comparison with FuzEn, SampEn and PerEn. The results have shown PerEn cannot discriminate the two groups. However, FuzEn, SampEn and DisEn based methods have shown the control subjects have more irregular MEG activity than AD patients. The smallest adjusted p-values for AD patients vs. controls have been achieved by the DisEn method and the computation time of the DisEn has been the lowest. Our results indicate that DisEn is a powerful and fast new entropy measure suitable for quantifying biomedical time series.

References

[1] J. Jeong, "Eeg dynamics in patients with alzheimer's disease," *Clinical neurophysiology*, vol. 115, no. 7, pp. 1490–1505, 2004.

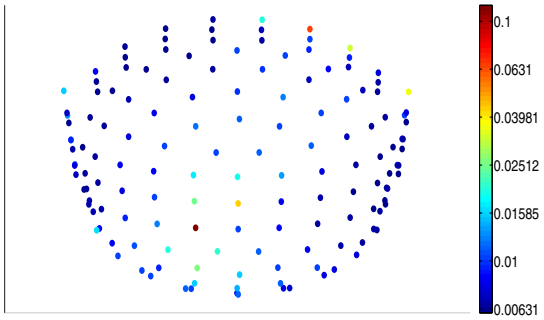
[2] A. Tsolaki, D. Kazis, I. Kompatsiaris, V. Kosmidou, and M. Tsolaki, "Electroencephalogram and alzheimers disease: Clinical and research approaches," *International Journal of Alzheimers Disease*, vol. 2014, 2014.

[3] S. Sanei and J. A. Chambers, *EEG signal processing*. John Wiley & Sons, 2007 (pp. 71).

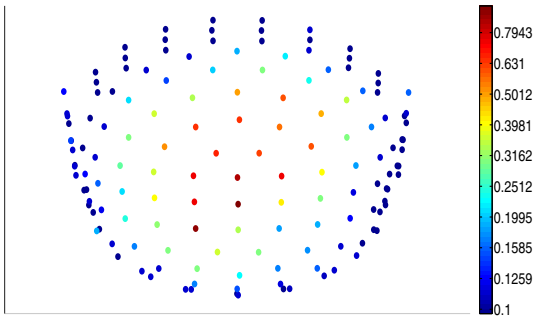
[4] J. Escudero, S. Sanei, D. Jarchi, D. Abásolo, and R. Hornero, "Regional coherence evaluation in mild cognitive impairment and alzheimer's disease based on adaptively extracted magnetoencephalogram rhythms," *Physiological measurement*, vol. 32, no. 8, pp. 1163–1180, 2011.

[5] F. C. Morabito, D. Labate, F. La Foresta, A. Bramanti, G. Morabito, and I. Palamara, "Multivariate multi-scale permutation entropy for complexity analysis of alzheimers disease eeg," *Entropy*, vol. 14, no. 7, pp. 1186–1202, 2012.

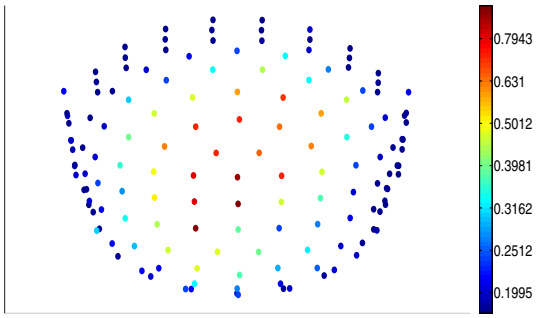
[6] H. Azami, K. Smith, A. Fernandez, and J. Escudero, "Evaluation of resting-state magnetoencephalogram complexity in alzheimer's disease with multivariate multiscale permutation and sample entropies," in *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*, pp. 7422–7425, IEEE, 2015.



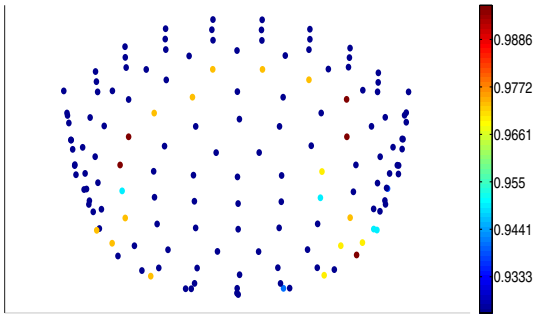
(a) Dispersion Entropy



(b) Fuzzy Entropy



(c) Sample Entropy



(d) Permutation Entropy

Fig. 2: FDR-adjusted p-values for the differences in dispesion entropy, fuzzy entropy, sample entropy, and permutation entropy at each channel between AD patients and controls.

[7] R. Hornero, D. Abásolo, J. Escudero, and C. Gómez, "Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with alzheimer's disease," *Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, vol. 367, no. 1887, pp. 317–336, 2009.

[8] D. Labate, F. La Foresta, G. Morabito, I. Palamara, and F. C. Morabito, "Entropic measures of eeg complexity in alzheimer's disease through a multivariate multiscale approach," *Sensors Journal, IEEE*, vol. 13, no. 9, pp. 3284–3292, 2013.

[9] M. Hämäläinen, R. Hari, R. J. Ilmoniemi, J. Knuutila, and O. V. Lounasmaa, "Magnetoencephalographytheory, instrumentation, and applications to noninvasive studies of the working human brain," *Reviews of modern Physics*, vol. 65, no. 2, pp. 413–505, 1993.

[10] R. Esteller, G. Vachtsevanos, J. Echauz, and B. Litt, "A comparison of waveform fractal dimension algorithms," *Circuits and Systems I: Fundamental Theory and Applications, IEEE Transactions on*, vol. 48, no. 2, pp. 177–183, 2001.

[11] M. Aboy, R. Hornero, D. Abásolo, and D. Álvarez, "Interpretation of the lempel-ziv complexity measure in the context of biomedical signal analysis," *Biomedical Engineering, IEEE Transactions on*, vol. 53, no. 11, pp. 2282–2288, 2006.

[12] J. S. Richman and J. R. Moorman, "Physiological time-series analysis using approximate entropy and sample entropy," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 278, no. 6, pp. H2039–H2049, 2000.

[13] R. Baddeley, *Information theory and the brain*. Cambridge University Press, 2008.

[14] C. Bandt and B. Pompe, "Permutation entropy: a natural complexity measure for time series," *Physical review letters*, vol. 88, no. 17, p. 174102, 2002.

[15] J. M. Yentes, N. Hunt, K. K. Schmid, J. P. Kaipust, D. McGrath, and N. Stergiou, "The appropriate use of approximate entropy and sample entropy with short data sets," *Annals of biomedical engineering*, vol. 41, no. 2, pp. 349–365, 2013.

[16] D. Abásolo, R. Hornero, P. Espino, D. Alvarez, and J. Poza, "Entropy analysis of the eeg background activity in alzheimer's disease patients," *Physiological measurement*, vol. 27, no. 3, pp. 241–253, 2006.

[17] M. Zanin, L. Zunino, O. A. Rosso, and D. Papo, "Permutation entropy and its main biomedical and econophysics applications: a review," *Entropy*, vol. 14, no. 8, pp. 1553–1577, 2012.

[18] W. Chen, Z. Wang, H. Xie, and W. Yu, "Characterization of surface emg signal based on fuzzy entropy," *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, vol. 15, no. 2, pp. 266–272, 2007.

[19] H. Azami and J. Escudero, "Amplitude-aware permutation entropy: Illustration in spike detection and signal segmentation," *Computer Methods and Programs in Biomedicine*, vol. 128, pp. 40–51, 2016.

[20] M. Rostaghi and H. Azami, "Dispersion entropy: A measure for time series analysis," *IEEE Signal Processing Letters*, vol. 23, no. 5, pp. 610–614, 2016.

[21] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of alzheimer's disease report of the nincds-adrda work group* under the auspices of department of health and human services task force on alzheimer's disease," *Neurology*, vol. 34, no. 7, pp. 939–939, 1984.

[22] J. Escudero, R. Hornero, D. Abásolo, and A. Fernández, "Quantitative evaluation of artifact removal in real magnetoencephalogram signals with blind source separation," *Annals of biomedical engineering*, vol. 39, no. 8, pp. 2274–2286, 2011.

[23] A. Kowalski, M. Martín, A. Plastino, and O. Rosso, "Bandt–pompe approach to the classical-quantum transition," *Physica D: Nonlinear Phenomena*, vol. 233, no. 1, pp. 21–31, 2007.