Permutation Entropy of the Electroencephalogram Background Activity in Alzheimer's Disease

Investigation into the Incidence of Repeated Values

Samantha Simons and Daniel Abásolo

Centre for Biomedical Engineering, Department of Mechanical Engineering Sciences, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, U.K.

Keywords: Alzheimer's Disease, Electroencephalogram, Non-Linear Analysis, Permutation Entropy.

Abstract: This pilot study applied Permutation Entropy (PE), a non-linear symbolic measure, and a novel modification (modPE), to investigate the regularity of electroencephalogram (EEG) signals from 11 Alzheimer's disease (AD) patients and 11 age-matched controls given input parameters n (embedding vector), τ (coarse graining) and *slide* (difference between the start of two concurrent embedding vectors). PE discriminated better than modPE with controls showing reduced regularity over AD patients. Increasing τ identified the greatest differences between EEG signals. Longer embedding vectors were also more able to identify differences. The greatest difference between groups was at Fp1 with $n,\tau,slide$ = 3,10,1 (p=0.0112 Kruskal Wallis with Bonferroni). Subject and epoch based leave-one-out cross validation was carried out with thresholding from Receiver Operating Characteristic Curves. The greatest ability to correctly identify AD patients and controls were 81.82% (Fp2 $n,\tau,slide$ = 7,4,4, PE and modPE, F7 $n,\tau,slide$ = 3,10,1, PE and modPE) and 90.91% (Fp1 $n,\tau,slide$ = 3,10,1, PE and modPE), respectively. The maximum accuracy (both groups correctly identified) was 81.82% seen at many electrode and input combinations. All are with subject based analysis. This suggests that PE can identify changes in EEG signals in AD, given appropriate variables. However, modPE makes little improvement over PE.

1 INTRODUCTION

Alzheimer's Disease (AD) is a neurological condition of complex aetiology producing progressive symptoms of memory and function loss caused by modification of amyloid β and hyperphosphorated tau in neurons, modifying information transition in the brain (Pieyani *et al*, 2011). The 'preclinical' phase of the disease, where the AD patient is undiagnosed, can be as long as 20 years (Reiman *et al*, 2012) due to the slow symptom onset and possible misdiagnosis, caused by the range of symptoms which can be presented (McKann *et al*, 2011). With the development of more effective treatments for AD and the increase in the number of patients suffering from this disease, the need for early, accurate diagnosis is imperative to ensure that treatments can be utilised effectively.

There is evidence that the progress of the disease can be detected through changes of brain signals measured with an electroencephalogram (EEG) (Dauwels, Vialatte and Cichocki, 2010). The disease must be highly progressed for visual identification from EEG signals but signal processing techniques may improve the ease at which changes due to AD can be seen in the early stages of the disease.

Non-linear signal processing has been shown to reliably identify changes in EEG signals in AD patients including the slowing of EEG signals and increased signal regularity and decreased signal complexity (e.g. Abásolo *et al*, 2006; Dauwels, Vialatte and Cichocki, 2010; Escudero *et al*, 2006). Permutation Entropy (PE) is a symbolic, non-linear method that calculates the complexity of a signal by identifying different patterns in it (Bandt and Pompe, 2002). However, information is lost about the magnitude of the patterns (Zanin *et al*, 2012) and so a number of modifications have been proposed to improve results when used with biological signals (Bian *et al*, 2012; Xiao-Feng and Yue, 2009).

In this pilot study PE and a novel modification of PE (modPE) are tested for investigating the

Simons S. and Abásolo D..
Permutation Entropy of the Electroencephalogram Background Activity in Alzheimer's Disease - Investigation into the Incidence of Repeated Values.
DOI: 10.5220/0004721000970103
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2014), pages 97-103
ISBN: 978-989-758-011-6

regularity of EEG signals of AD patients in comparison to age-matched controls. It is hypothesised that the modPE method will show clear differences between the two groups, while PE will show reduced differences between the two groups. Further, it is hypothesised that the AD patients will show an increased EEG regularity when compared to the control subjects.

The paper is arranged as follows. Section 2 introduces the test database and the methods used in this study. Section 3 contains results and a discussion is held in section 4. Section 5 contains the conclusion of this study.

2 METHODS

2.1 EEG Signals Database

This database has been described in a number of different studies (e.g. Escudero *et al*, 2009). The pertinent points are repeated here for completeness.

The sample group contained 22 subjects, 11 probable AD patients (6 men and 5 women, 72.5 ± 8.3 years, mean ± standard deviation (SD)), who had a Mini-Mental State Examination (MMSE) score of 13.1 ± 5.9 (mean ± SD) and 11 age-matched controls (4 women and 7 men, 72.8 ± 6.1 years, mean ± SD) with a MMSE score of 30 ± 0 (mean ± SD). The MMSE is a long established method of measuring the level of cognitive function of a patient (Folstein, Folstein and McHugh, 1975). Full ethical approval was obtained for the collection and use of this database.

Signals were recorded at 256Hz with a 12-bit analogue to digital converter using the international 10-20 electrode placement system (electrodes Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz and Pz) with subjects in an awake but resting state with closed eyes. In excess of 5 minutes of data were recorded from each subject.

This data was then reviewed by a clinician who selected 5 second epochs (1280 data points) with minimal electromyographic activity and no movement and electrooculographic artefacts. These epochs were copied for off-line analysis and were then further filtered using a Hamming window finite impulse band-pass filter with cut-off frequencies at 0.5 and 40Hz to remove DC components and residual noise. For each subject, 30.0 ± 12.5 (mean ± SD) epochs were collected. All epochs were tested with the methods described in this paper.

2.2 Permutation Entropy

PE is a symbolic dynamics non-linear method which has been shown to be robust to noise and can be applied to short time series (Bandt and Pompe, 2002). The method is as follows (Bandt and Pompe, 2002):

- Take the first embedding vector of the dataset n data points long, skipping τ data points between each data point selected to join the embedding vector. I.e. given time series $\{x(i),\ i = 1,2,\ldots\}$, *embedding vector* $= x(i),\ x(i+\tau),\ \ldots,\ x(i+(n-1)\tau)$.
- Assign the lowest data point in the embedding vector 0, the second lowest 1 and on until all data points in the embedding vector have been replaced with their ranking order.
- Collect a new embedding vector from the original dataset. The first data point is *slid* further along the original dataset from the first data point of the previous embedding vector. The subsequent data points of the embedding vector are found using the same pattern as the first embedding vector from its first data point. The movement of vectors along the dataset is shown in Figure 1.

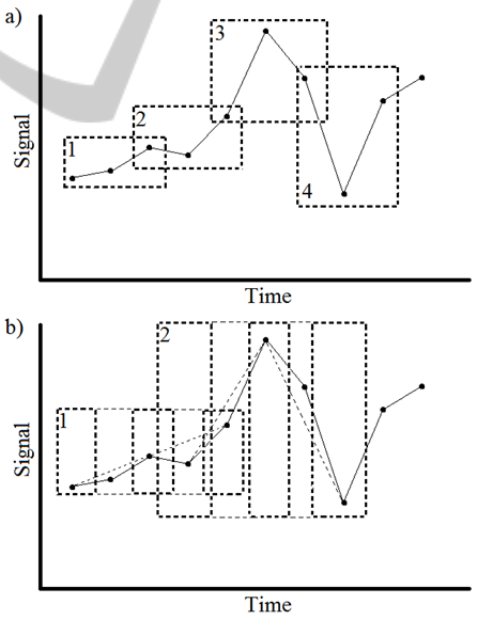

Figure 1: Two graphs showing how different combinations of $n,\tau,slide$ move along the same dataset with a) showing 3,1,2 and b) showing 3,2,4. In figure b) the dashed line between points indicate the pattern of the embedding vector created by τ=2.

- Again replace this with the ranking of the new vector as detailed in the previous point.
- Continue this until all possible embedding vectors

have been created and ranked. Then calculate the PE with equation 1.

$$PE(n,\tau,slide) = -\sum_{v=1}^{k} P_v \log_2 P_v \quad (1)$$

where k is the number of different sub-sequence ranked vectors and P_v is the fraction of the sub-sequence ranked vectors. Equation 1 is similar to Shannon's Entropy (Shannon, 1948). A less regular signal will have a greater range of embedding vectors and, therefore, a higher PE. Given the pattern recognition method in PE, where the ranking of each data point in order of assent is mapped back to their position in the original vector, {0.2 0.5 0.1 0.4 0.7} would create the ranking {1 3 0 2 4}.

The outcome of PE will be influenced by the choice of n, τ and *slide*. A greater value of n, the embedding dimension, will give a greater possible range of ranking vectors and, therefore a greater resolution. Bandt and Pompe (2002) recommended n=3 to 7 but $n!$ must be less than the length of the original time series. However, testing with epilepsy patients showed n=3 and 4 were too small to be of use (Cao *et al*, 2004). In this study this range will be adhered to along with testing of n=10 to identify if values greater than n=7 may also identify statistically significant differences between the two study groups.

Coarse-graining of the recorded EEG signal for creation of the sub-sequence vectors is carried out by τ. Initially Bandt and Pompe (2002) used τ=1 but it was identified that this may not be the optimum value for signal analysis (Cao *et al*, 2004). No studies have been completed to identify the most reliable range of τ and there is little consensus in the studies already completed using PE on the value(s) chosen for τ. The maximum τ seen in biological studies is 50, used to investigate EEGs of AD patients (Frantzidis *et al*, 2012) though this study produced results showing AD patients with more irregular EEGs, a finding inconsistent with the large body of other, already published results from similar studies. In this study, τ=1 to 4 was chosen with a further test of τ=10.

There is another variable that has not yet been investigated by previous work on PE. This is the movement of the sub-sequence vector along the original data set and will be denoted by *slide* in this paper. All previous papers have used *slide*=1 but this may not be the optimal choice of variable and could have a significant effect on the PE calculation given its interaction with the other two input variables. Therefore, this study looked at *slide*=1 to 4.

The combinations of n,τ,*slide* tested in this study are summarised in Table 1, chosen to investigate the influence of each input variable and variable combinations and to compare how low and high input variable combinations interact:

Table 1: Combinations of input variables tested.

n	τ	*slide*
3 to 7, 10	1	1
3	2 to 4, 10	1
3	1	2 to 4
7	4	1, 4

The results were normalised to allow for direct comparison between different variations in n, τ and *slide*. Equation 2 shows the normalisation procedure:

$$PE_n(n,\tau,slide) = \frac{PE(n,\tau,slide)}{\ln(n!)} \quad (2)$$

with $\ln(n!)$ the maximum number of ranking permutations given the length of the ranking vector. Note that the number of possible permutations is not dependent on τ or *slide* as these do not directly affect the theoretical maximum of possible permutations.

2.3 Modified Permutation Entropy

As previously mentioned, PE loses information which relates to the relative magnitude of the sub-sequence vector data points, including ignoring any repeated values, giving the first repeated value in the vector (the value to the left of the vector) a lower integer than subsequent repeats and so on until all repeats are accounted for (Bandt and Pompe, 2002). With biological datasets this can cause a significant loss of information due to the level of sampling applied in the data collection phase or the information needed being held in the signal amplitude (Bian *et al*, 2012).

A number of methods have been proposed to improve the PE algorithm when applied to biological datasets, Fine-grained PE (FGPE) (Xiao-Feng and Yue, 2009), Weighted permutation entropy (WPE) (Fadlallah *et al*, 2013) and index-modified PE (imPE- identified as mPE in the seminal paper) (Bian *et al*, 2012). FGPE adds a further argument to the sub-sequence ranking vector which relates mathematically to the specific values contained in the sub-sequence vector but maintains the PE method in all other aspects. WPE creates a multiplication factor of each logarithmic calculation which are created using amplitude information from each embedding vector. However, imPE allows for

repeated values to be given the same ranking value. The created ranking vector from imPE does not follow the same method as PE, unlike FGPE. The ranking of each data point in order of increasing value is not mapped back to their position in the original embedding vector, as in PE. Instead the ranking denotes the position of the data point in the embedding vector in an order that describes ascending value of each of those data points. The vector {0.2 0.5 0.1 0.4 0.7} described before with PE as pattern {1 3 0 2 4} would now be {2 0 3 1 4} with imPE. This is because as, when reordered, the lowest value 0.1 comes from the third position, denoted as two when starting from zero rather than one, the next lowest 0.2 is from position one, denoted zero in the ranking, and so on (Bian *et al*, 2012).

The method proposed in this paper, modPE, combines the ability to cope with repeated values within the embedding vector suggested by Bian *et al* (2012) with the ranking mapping used in the original PE method. The method will be described as PE though repeated values will retain the same ranking index, rather than being given differing ranking indexes. Retention of information pertaining to repetition of data points in an embedding vector of two or more instances with one or more values will be incorporated into the method. For example sub-sequence vector {0.2 0.5 0.1 0.2 0.7} will create the ranking {1 3 0 1 4}. Note position 2 is not recorded in the ranking vector as there are two 1's.

The variables for n, τ and *slide* will be the same as those tested for PE to allow for easy comparison. Again the results will also be normalised to allow for direct comparison by the method identified by equation 2, though the denominator for this method will be calculated differently due to the increased numbers of possible permutations. For modPE, this was calculated by summing the number of different combinations given different repeated values.

2.4 Statistical Analysis

Results given PE and modPE analysis from all epochs were averaged for each electrode from each subject. Normality of these average values was tested using Lilliefors test. Statistically significant differences were identified between the 11 AD patients and the 11 controls using Student's t test if the data were found to be normally distributed and Kruskal Wallis if not. Statistical significance was indicated with $p<0.05$ in both cases with a Bonferroni correction for the 16 electrodes. This correction leads to an uncorrected statistical significance of 0.0031.

Statistically significant combinations were further investigated using Receiver Operating Characteristic (ROC) curves (Fawcett, 2006) with a leave-one-out cross-validation procedure. Sensitivity is defined as the proportion of correctly identified AD patients and specificity is defined as the proportion of correctly identified controls, while accuracy identifies the total number of correctly identified AD and control subjects combined.

3 RESULTS

Controls have a higher PE and modPE value than AD patients, suggesting an increase of EEG regularity due to this form of dementia. At low n, τ and *slide* combinations, electrodes F7, T3 and T4 do not follow this trend. At n = 5 to 7 with τ and *slide* = 1 electrodes Fp1, Fp2, F7, F8, C4, T3, T4, T5 do not follow this trend though all these cases show a difference between values of less than 2%. At these values of n, increasing τ reduces the number of electrodes not following the trend but the modPE is less able to distinguish between the two groups, with almost all electrodes showing an increased modPE for patients as τ increases. With $n,\tau,slide$ = 10,1,1 electrodes T3, T4 and T5 show increased irregularity in AD patients. In total, 75.21% of calculations showed increased irregularity in controls over AD patients, but this was not equally distributed; some input parameters showed increased irregularity in EEG signals of AD patients in all electrodes and others increased regularity in EEG signals of AD patients in all electrodes. Results were found to be predominately normally distributed except for when τ=10. All electrodes showing statistically significant differences between the two groups are presented in Table 2.

With low values of n with *slide* and τ both equal to 1 both methods were unable to distinguish with statistical significance between the two test groups at any electrode. The ability to distinguish between the two groups increased as n increased. The choice of τ was found to be the most critical in distinguishing between the two test groups. *Slide* values had little effect on distinguishing between the two groups. However, a greater significance was seen between the two groups as *slide* increased though this did not reach statistical significance.

All statistically significant electrode combinations were then subjected to leave-one-out cross-validation analysis with the threshold identified through ROC plots. The results are also

Table 2: Statistical results for PE and modPE. Statistical significance calculated with Student's t Test is identified by S while statistical significance calculated with Kruskal Wallis is denoted KW. P values in this table have already been corrected with a Bonferroni correction. As such, statistical significance is denoted as $p<0.05$. Leave-one-out with subject based analysis is denoted SB and with epoch based analysis is denoted EB.

Electrode	*n,τ,slide*	Method	Normalised control (mean±SD)	Normalised AD (mean±SD)	Statistical method	*P with Bonferroni correction*	Leave-one-out method	Sensitivity (%)	Specificity (%)	Accuracy (%)
Fp1	3,10,1	PE	0.9957 ±0.0016	0.9886 ±0.0058	KW	0.0112	SB	72.73	90.91	81.82
							EB	60.93	69.55	65.04
		modPE	0.6588 ±0.0011	0.6541 ±0.0039	KW	0.0224	SB	72.73	90.91	81.82
							EB	61.52	71.47	66.26
Fp2	7,4,1	PE	0.7981 ±0.0071	0.7860 ±0.0082	S	0.0224	SB	63.64	81.82	72.73
							EB	76.61	69.86	73.56
	7,4,4	PE	0.6654 ±0.0020	0.6609 ±0.0033	S	0.0144	SB	63.64	81.82	72.73
							EB	67.54	73.05	70.03
F7	3,10,1	PE	0.9964 ±0.0023	0.9927 ±0.0034	KW	0.0368	SB	81.82	81.82	81.82
							EB	58.09	70.68	64.18
		modPE	0.6593 ±0.0015	0.6568 ±0.0023	KW	0.0368	SB	81.82	81.82	81.82
							EB	56.36	64.51	60.30

held in Table 2. For subject-based analysis, the greatest sensitivity of 81.82% was obtained at electrode F7 with *n,τ,slide* = 3,10,1 and the greatest specificity was 90.91% at electrode Fp1 with *n,τ,slide* = 3,10,1. In both cases this is the same for both PE and modPE. The greatest accuracy, 81.82%, was seen at a number of electrode and calculation combinations with subject based methods. Epoch based results were less sensitive to differences between the two groups, with a maximum sensitivity of 76.61% with Fp2 at *n,τ,slide* = 7,4,1, a maximum specificity of 73.05% with Fp2 at *n,τ,slide* = 7,4,4, and an accuracy of 73.56% with Fp2 at *n,τ,slide* = 7,4,1. This shows a significant ability to distinguish between controls and AD patients at this electrode.

4 DISCUSSION

In this study we tested PE and a novel version of PE, denoted modPE, to analyse the EEG signals of 11 AD patients and 11 age-matched controls. PE is a symbolic non-linear method and other symbolic non-linear methods, such as Lempel-Ziv Complexity, have been shown to discriminate between the EEG signals of AD patients and controls with statistical significance (Abásolo *et al*, 2006). While PE is not a new method, little research has been carried out into its behaviour with EEG signals from AD patients.

The increased signal irregularity of control subjects when compared to AD patients EEG signals supports the hypothesis stated in section 1 that controls show a less regular signal than AD patients. Morabito *et al* (2011; 2012) tested AD and MCI subjects using PE and multivariate multi-scale PE with n=3 and τ=1, also finding increased irregularity in control subject EEGs in comparison to AD patients. However, modPE did not perform significantly better than PE as hypothesised, a hypothesis which was based on the work by Bian *et al* (2012) where imPE was used with input parameters n,τ = 3-7,1 and 3,1-4 on R-R intervals from ECG signals rather than complete EEG signals.

The inability of small n ($n < 5$) to identify changes in signals caused by pathological changes in the brain was identified by Cao *et al* (2004) testing combinations of input parameters which included n=3-7 and τ=2,3 and 10. This is supported by our results, with low values of n unable to discriminate between control subjects and AD patients. Further, ranges of n outside those suggested by Bandt and Pompe (2002) can be utilised successfully with this method, shown by the support of the trend of reduced regularity in AD EEG signals seen with the lower values of n. These findings suggest that the differences in EEG signals between AD patients and controls only manifest themselves in larger patterns and similar smaller patterns are seen in both signal types.

The influence of τ was the greatest of all input variables on the ability of PE and modPE in distinguishing between the two groups. This input variable effectively coarse-grains the signal before calculating PE or modPE. It has been found that coarse-graining of signals can provide a greater understanding of those signals under investigation and in some cases has increased the ability to distinguish between differing groups such as AD

patients and controls (Escudero *et al*, 2006; Simons, Abásolo and Escudero, 2012a; 2012b). The ability of this method to improve understanding and discrimination and the link between coarse-graining and τ supports the findings of this study.

It was found in the range of *slide* variables tested in this study that this had no influence on the ability of the methods to distinguish between the two groups, though a trend was seen in the resulting *p* values that suggests that increasing *slide* may improve resolution for investigation of EEG signals. However, significantly increasing *slide* reduces the data investigated directly in the calculation of PE.

Given the findings of this pilot study, it is suggested that *n,τ,slide* = 3,10,1 is the optimum selection of parameters for discriminating between AD patients and controls. However, there may be another combination with higher *n* and *τ* values which has not been tested in this study which is more able to discriminate between the two groups.

The novel method of modPE was introduced to investigate the improvement over PE by retaining the information contained in the appearance of repeated values, identified as a key component of the changing R-R intervals from ECG signals investigated in the paper by Bian *et al* (2012) and vital to distinguish between the data from patients and healthy controls. This study does not confirm their findings, both as PE identified statistically significant differences in the EEG signals of AD patients and controls and that modPE, while also identifying statistically significant differences, did not provide a large increase in the ability of the methodology to distinguish between signals from healthy controls and patients.

This change in the abilities of the two methods to distinguish between the two groups is thought to be due to significant differences in the signal types analysed and, therefore, the appearance of repeated values. An ECG is more prone to repeatability than signals from other, more complex neuronal systems such as the EEG from the brain. This means that the probability of repeated values within a given pattern from an ECG trace is significantly higher than that from an EEG signal. Furthermore, the focus of a particular metric from a signal, such as the R-R interval, rather than the entirety of a signal further increases the possibility of repeated values.

While PE is currently undergoing wide ranging testing (e.g. Fadlallah *et al*, 2013; Li *et al*, 2013; Riedl, Müller and Wessel, 2013), there are few studies applying this method to AD diagnosis. The differences in signal regularity found by a majority of PE and modPE calculations with this dataset are comparable to those found with Multi Scale Entropy (Escudero *et al*, 2006), historically the most accurate method with this database.

Some limitations of this study should be mentioned. The small sample size of this dataset leads the findings of this work to be a pilot study. Furthermore, a greater range of input variables must be trialled to understand the optimum combination of input variables to discriminate between these two groups and other groups with similar pathologies such as Mild Cognitive Impairment (Albert *et al*, 2011). In addition, recent evidence suggests that the increased regularity observed in AD patients' EEGs with non-linear methods might be closely linked with the slowing found with traditional spectral techniques (Dauwels *et al*, 2011). Therefore, further research looking at possible correlations between different implementations of PE and spectral techniques is needed. One possible option might include synthetic signal analysis (Riedl, Müller and Wessel, 2013). In spite of these shortcomings, PE and modPE are able to distinguish changes in the EEG signal of AD patients with a range of input parameters.

5 CONCLUSIONS

This work has shown the application of PE and a novel modified version of PE to the analysis of EEG in AD patients in comparison to age-matched controls. The findings with PE corroborate other studies with this dataset and others with similar methods, in that control subject's EEGs were found to be more irregular than those of AD patients. The choices of input parameters were found to be a key component in identifying the changes in the signal. However, caution must be taken due to the small size of the dataset studied.

REFERENCES

Abásolo, D., Hornero, R., Gómez, C., García, M., Lopez, M., 2006 Analysis of EEG background activity in Alzheimer's disease patients with Lempel-Ziv complexity and central tendency measure. *Medical Engineering and Physics*, 28, pp. 315-322.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D.M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., Phelps, C. H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease:Recommendations from the National Institute on Aging-Alzheimer's Association

workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, pp. 270-279.

Bandt, C., Pompe, B., 2002. Permutation entropy- a natural complexity measure for time series. *Physical Review Letters*, 88(17), 174102.

Bian, C., Qin, C., Ma, Q. D. Y., Shen, Q., 2012. Modified permutation-entropy analysis of heartbeat dynamics. *Physical Review E*, 85, 021906.

Cao, Y., Tung, W., Gao, J. B., Protopopescu, V. A., Hively, L. M., 2004. Detecting dynamical changes in time series using the permutation entropy. *Physical Review E*, 70, 046217.

Dauwels, J., Srinivasan, K., Ramasubba Reddy, M., Musha, T., Vialatte, F.-B., Latchoumane, C., Jeong, J., Cichocki, A., 2011. Slowing and loss of complexity in Alzheimer's EEG: Two sides of the same coin?. *International Journal of Alzheimer's Disease*, 2011, 539621.

Dauwels, J., Vialatte, F., Cicjocki, A., 2010. Diagnosis of Alzheimer's disease from EEG signals: Where are we standing?. *Current Alzheimer's Research,* 7, pp. 487-505.

Escudero, J., Abásolo, D., Hornero, R., Espino, P., López, M., 2006. Analysis of electroencephalograms in Alzheimer's disease patients with multiscale entropy. *Physiological Measurement*, 27, pp. 1091-1106.

Fadlallah, B., Chen, B., Keil, A., Príncipe, J., 2013. Weighted-permutation entropy: A complexity measure for time series incorporating amplitude information. *Physical Review E*, 87, pp. 022911.

Fawcett, T., 2006. An introduction to ROC analysis. *Pattern Recognition Letters*, 27, pp. 861-874.

Folstein, M. F., Folstein, S. E., McHugh, P. R., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *American Journal of Physiology: Heart and Circulatory Physiology*, 12, pp. 189-198.

Frantzidis, C. A., Ladas, A., Diamantoudi, M. D., Semertzidou, A., Grigoriadou, E., Tsolaki, A., Liapi, D., Papadopoulou, A., Kounti, F., Vivas, A.B., Tsolaki, M., Pappas, C., Bamidis, P.D., 2012. What are the symbols of Alzheimer? A permutation entropy based symbolic analysis for the detection of early changes of the electroencephalographic complexity due to mild Alzheimer. In *Proceedings of the 12th International Conference on Bioinformatics*, IEEE.

Li, D., Liang, Z., Wang, Y., Hagihira, S., Sleigh, J. W., Li, X., 2013. Parameter selection in permutation entropy for an electroencephalographic measure of isoflurane anesthetic drug effect. *Journal of Clinical Monitoring and Computing*, 27, pp. 113-123.

McKann, G. M., Knopman, D. S.,. Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M.N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., Phelps, C. H., 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, 7, pp. 263-269.

Morabito, G., Bramanti, A., Labate, D., la Foresta, F., Morabito, F.C., 2011. Early detection of Alzheimer's onset with permutation entropy analysis of EEG. *Natural Intelligence: the INNS Magazine*, 1(1), pp. 30-32.

Morabito, F. C., Labate, D., la Foresta, F., Bramanti, A., Morabito, G., Palamara, I., 2012. Multivariate multi-scale permutation entropy for complexity analysis of Alzheimer's disease EEG. *Entropy*, 14, pp. 1186-1202.

Pievani, M., de Haan, W., Wu, T., Seeley, W. W., Frisoni, G. B., 2011. Functional network disruption in the degenerative dementias. *Lancet Neurology*, 10, pp. 829-843.

Reiman, E., Quiroz, Y., Fleisher, A., Chen, K., Velez-Pardo, C., Jimenez-Del-Rio, M., Fagan, A. M., Shah, A. R., Alvarez, S., Arbelaez, A., Giraldo, M., Acosta-Baena, N., Sperling, R. A., Dickerson, B., Stern, C E., Tirado, V., Munoz, C., Reiman, R. A., Huentelman, M. J., Alexander, G. E., Langbaum, J. B. S., Kosik, K. S., Tariot, K. P., Lopera, F., 2012. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin E280A kindred: a case control study. *Lancet Neurology*, 11, pp. 1048-1056.

Riedl, M., Müller, A., Wessel, N., 2013. Practical considerations of permutation entropy. *The European Physical Journal Special Topics*, 222, pp. 249-262.

Shannon, C. E., 1948. A mathematical theory of communication. *The Bell System Technical Journal*, 27, pp. 379-423.

Simons, S., Abásolo, D., Escudero, J., 2012a. Quadratic sample entropy and multiscale quadratic sample entropy of the electroencephalogram in Alzheimer's disease. In *Proceedings of the 5th International Conference on Medical Signals and Information Processing.*

Simons, S., Abásolo, D., Escudero, J., 2012b. Fuzzy entropy and multiscale fuzzy entropy of the electroencephalogram in Alzheimer's disease. In *Proceedings of the Young Researchers Futures Meeting-Neural Engineering*, Royal Academy of Engineering.

Xiao-Feng, L., Yue, W., 2009. Fine-grained permutation entropy as a measure of natural complexity for time series. *Chinese Physics B*, 18(7), pp. 2690-2695.

Zanin, M., Zunino, L., Rosso, O. A., Papo, D., 2012. Permutation entropy and its main biomedical and econophysics applications: A review. *Entropy*, 14, pp. 1553-1577.