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Nonlinear Analysis of the Change Points between A and B phases during the Cyclic Alternating Pattern under Normal Sleep.

Chouvarda I, *Member, IEEE*, Mendez MO, *Member, IEEE*, Alba A, *Member, IEEE*, Bianchi AM *Member, IEEE*, Grassi A, Arce-Santana E, Rosso V, Terzano MG and Parrino L

Abstract— **This study analyzes the nonlinear properties of the EEG at transition points of the sequences that build the Cyclic Alternating Pattern (CAP). CAP is a sleep phenomenon built up by consecutive sequences of activations and non-activations observed during the sleep time. The sleep condition can be evaluated from the patterns formed by these sequences. Eleven recordings from healthy and good sleepers were included in this study. We investigated the complexity properties of the signal at the onset and offset of the activations. The results show that EEG signals present significant differences ($p<0.05$) between activations and non-activations in the Sample Entropy and Tsallis Entropy indices. These indices could be useful in the development of automatic methods for detecting the onset and offset of the activations, leading to significant savings of the physician's time by simplifying the manual inspection task.**

I. Introduction

The Cyclic Alternating Pattern (CAP) is a sleep phenomenon that conveys fundamental information about the sleep process [1]. CAP is built up by "repeated spontaneous sequences of transient episodes (phase A) deviating from the background rhythm of the ongoing EEG with intervals that separate the repetitive elements (phase B)" [1-2]. Previous studies have shown that the main role of CAP is to create, consolidate and disrupt the sleep macrostructure [3]. The CAP behavior is a useful index to assess the sleep condition. This behavior is called CAP rate, and is computed by counting the total duration of phases A and dividing it by the total sleep time. This index presents a main characteristic: it is low during good sleep and high during disrupted sleep, which is produced by pathological events such as sleep apnea and insomnia [4]. Although CAP evaluation is a useful tool, its assessment is a tedious task requiring various hours to evaluate only one sleep recording. In addition, the CAP scorers need months of training before they are able to analyze a sleep recording. Due to all those difficulties, CAP scoring is unpractical in clinics, thus the development of automatic algorithms is one of the most viable ways to expand the application of CAP analysis.

As commented previously the CAP contains activations phases, named Phases A, which are divided in three subtypes: a) A1 composed by strong delta waves (0.5-4 Hz), b) A2 with rapid EEG oscillations observed in 20 % - 50 % of the total activation time and c) A3 also with rapid activities, especially beta (16-30 Hz), observed in more than 50% of the total activation time. Each phase A subtype has different characteristics, in terms of EEG synchrony, different role and distribution within the sleep cycle.

Many studies have tried to analyze the phase A characteristics with different approaches obtaining indices such as power, complexity, and spectral components. Most studies have used those indices to develop algorithms for automatic CAP detection [5-6]. These automatic methods produce usable results, however, most of the studies fail in correctly locating the onset and offset of the phases A. Those errors affect CAP rate evaluation since the CAP rate definition depends of the Phase A durations. Thus the main goals for accurate CAP rate evaluation are an adequate localization of the activations, and accurate assessment of their durations. These problems are not simple to solve since the statistical properties of the EEG signal vary significantly through the sleep cycles.

The aim of the current study is to assess the onset and offset of the phases A at the different sleep stages through complexity measures.

II. Methods

A. Protocol

11 healthy adult subjects (5 male and 6 female, aged between 25 and 45 years, mean age 32.7 yrs, and weight between 58 and 75 kg, mean weight 66 kg) were used in the study. The subjects did not present any primary medical or psychiatric disorder and did not intake drugs affecting the central nervous system. The sleep recordings acquired at the Parma University Sleep Disorders Center. Each night recording lasted approximately 8 hours, and included EEG leads (F4, F3, C4, C3, A1, A2), EMG, EOG and ECG derivations. Sleep scoring was performed by experts, following standard rules [1]. The macrostructure was defined according to R & K rules. The analysis was done in one channel, C3 or C4 (C3 by default, or C4 when C3 was not available). The EEG was acquired with a sampling

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I. Chouvarda is at the Lab of Medical Informatics, Aristotle University of Thessaloniki, Greece (+302310999281; fax: +302310999263; e-mail: ioannach@auth.gr).

V. Rosso, L. Parrino, A. Grassi, and M. Terzano are at Sleep Disorders Centre, Department of Neurology, University of Parma, Parma, Italy (e-mail: mterzano@unipr.it).

M. Mendez, A. Alba and E. Arce-Santana are at the Facultad de Ciencias, Diagonal Sur S/N, Zona Universitaria, San Luis Potosi, S.L.P., Mexico (email: mmendez@fc.uaslp.mx, fac@fc.uaslp.mx, arce@fciencias.uaslp.mx).

A.M. Bianchi are at the Biomedical Engineering Department, Politecnico di Milano, Italy (annamaria.bianchi@polimi.it, sergio.cerutti@biomed.polimi.it).

frequency of 100 Hz and was bandpass-filtered from 0.05-Hz to 40 Hz.

For each Phase A annotated in the EEG, a window (s_k) with the first seconds of the phase A was compared with a window before s_k (s_{k-1}) and a window before s_{k-1} (s_{k-2}). s_k lies completely within the Phase A, while s_{k-1} and s_{k-2} belong to the background. The same procedure was applied to the end part of the phase A, where s_k denotes the last seconds of the phase A, s_{k+1} represents a window after s_k and s_{k+2} a window after s_{k+1}. In this study the windows had duration of 2s, which is justified by the fact that the minimum duration of the Phases A is 2s. Figure 1 shows a description of the segments used for the analysis. The Phases A were grouped by subtype and sleep stage. A total of 3963 phases A were analyzed and defined as follows:

- Sub1 –S1-S2 stands for Phase A subtype 1 during sleep stages 1 and 2.
- Sub2 –S1-S2 stands for Phase A subtype 2 during sleep stages 1 and 2.
- Sub3 –S1-S2 stands for Phase A subtype 3 during sleep stages 1 and 2.
- Sub4 –S3-S4 stands for Phase A subtype 1 during sleep stages 3 and 4.

The total number of phases A per group was: Sub1 = 828, Sub2 = 793, Sub3 = 659 and Sub4 = 1683.

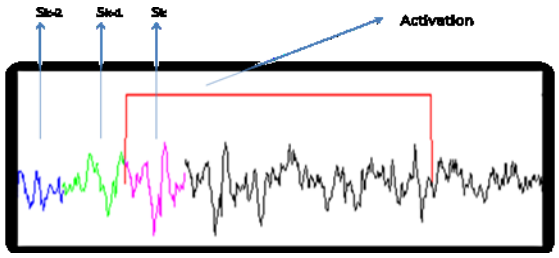

Figure 1. Example of a typical phase A, subtype 2 during sleep stage 2. S_k represents the first 2 seconds of the activation, and S_{k-1} and S_{k-2} represent the background close the initial point of the phase A.

B. Mathematical Methods

1) Lempel-Ziv Complexity (LZC)

The Lempel-Ziv complexity measure *c(k)* is defined as the minimum quantity of information needed to define a string with *k* symbols. The LZC quantifies the rate of new patterns arising with the temporal evolution of the string. The time series is coded into symbolic sequences, i.e. *010101* in the binary case or *0112021* in the ternary case. In this work we adopted both the binary LZC2 and the ternary LZC3 coding procedure. *c(k)* is a counter which defines the number of new elements that are added into an alphabet *v,* in which each element is composed by the combination of *0* or *1* in the case of binary sequences.

The EEG signal *f(n)*, where *n* is the sample number, was coded to binary and ternary sequences *h(n)* following the rules, respectively:

a) 1 if $f(n+1) > f(n)$, 0 if $f(n+1) <= f(n)$

b) 1 if $f(n+1) > f(n)$, 0 if $f(n+1) < f(n)$, 2 if $f(n+1) = f(n)$

Please note that $f(n+1)$ is considerate greater that $f(n)$, if $f(n+1)$ exceeds $f(n)$ by at least with a 5 % of the standard deviation computed from the window in study.

2) Sample Entropy

Sample Entropy (SE) is a measure of the regularity of a time series, being thus informative about the underlying complexity in the processes giving rise to it [Richman2000]. The quantification of regularity is based on the logarithmic likelihood that the patterns of the data that are close for *m* observations remain close on next incremental comparisons with a longer pattern. A greater likelihood of remaining close produces smaller values. Larger SE values indicate greater independence, less predictability, hence greater complexity in the data.

Let us consider a timeseries y(i)=[$x(i), x(i+1),\ldots,x(N)$], of length N. We define two sub-sequences $y_m(i)$ and $y_m(j)$ of the form $y_m(i)=[x(i), x(i+1),\ldots,x(i+(m-1))]$. The probability that the two sub-sequences match for *m* points ($B^m(r)$) and the probability of match for *m+1* points ($A^{m+1}(r)$), where *r* is the tolerance for accepting matches, give the SE, defined as the average over multiple templates of the log ratio of A/B:

$$SampEn\ (m,r) = \left| -\ln\left(\frac{A^{m+1}(r)}{B^{m}(r)}\right)\right| \qquad (1)$$

In this case, SE was calculated in overlapping windows of 2 sec, with 1 sec overlap, with m=2 and r=0.25.

3) Fractal Dimension

Fractal Dimension (FD) was computed in windows of 2 sec, with 1 sec overlap, according with Higuchi's method [Higuchi1988], based on the calculation of $L_m(k)$ for a time series *X*, as expressed in equation (2):

$$L_m(k) = \frac{1}{k}\cdot\left[\left(\sum_{i=1}^{\left\lfloor\frac{N-m}{k}\right\rfloor}\left|X(m+i\cdot k)-X(m+(i-1)\cdot k)\right|\right)\cdot\frac{N-1}{\left\lfloor\frac{N-m}{k}\right\rfloor\cdot k}\right] \qquad (2)$$

$L_m(k)$ represents the normalized sum of absolute differences in ordinates of pairs of points, with distance *k,* (with initial point *m*), and *N* is the total number of samples of the time series *X*.

The average of the *k* values $L_m(k)$ for *m=1, 2,..., k* is calculated as *L(k),* and the value of fractal dimension is calculated by a least-squares linear best-fitting procedure, as the angular coefficient of the linear regression of the log-log graph of *L(k)* vs *k,* with $k = 1, 2, \ldots, k_{max}$. Here, the value $k_{max}=8$ has been chosen, as in [2].

4) Tsallis Entropy

The probability distribution p_f of the EEG signal *f(n)* is calculated in *N* bins [8]. Tsallis Entropy (TE) is then defined as

$$Ts(q) = \frac{\sum_{j=1}^{N} \left(p_f(j) - p_f(j)^q \right)}{q-1} \quad (3)$$

where q can be a positive number. In the limit when $q \to 1$, TE corresponds to the Shannon entropy. The extremum of $Ts(q)$ in case of a uniform distribution $p_f(j)=1/N$ is:

$$TsExt\ (q) = \frac{N^{1-q} - 1}{1-q} \quad (4)$$

The normalized Tsallis Entropy is then the ratio of the two, i.e.

$$TsNorm\ (q) = \frac{Ts(q)}{TsExt\ (q)} = \frac{\sum_{j=1}^{N} \left(p_f(j) - p_f(j)^q \right)}{1 - N^{1-q}} \quad (5)$$

Here, two values of q are considered, $q=0.5$ and $q=3$, reflecting a focus on rare and frequent events, as TS1 and TS2, respectively.

B. Statistical Test

For each group (Sub1 to Sub4) three windows were available (s_k, s_{k-1}, s_{k-2} or s_k, s_{k+1}, s_{k+2}). The Kruskal-Wallis (KW) statistical test was used to compare among windows in each group. A p-value of 5% was used to define statistical significance. While KW was used to reject the global null hypothesis, a multiple comparison procedure was also employed to determine which means differ significantly in a pairwise manner. Bonferroni correction was used for multiple comparisons.

III. Results

Table I shows the mean and standard deviation of the computed measures for the different subtypes of Phases A at the onset and offset. Most of the measures (LZ indices, SampEn, FD, TS1 and TS2) present statistical differences (p-value < 0.05) in all the subgroups (Sub1-Sub4) between s_k and s_{k-2}, s_k and s_{k-1} but not between s_{k-1} and s_{k-2}. For the offset, LZ indices, SampEn, FD, TS1 and TS2 present statistical differences (p-value < 0.05) in all the subgroups (Sub1-Sub4) between s_k and s_{k+2}, s_k and s_{k+1}, but not between s_{k+1} and s_{k+2}.

Figure 2 shows the boxplots of the SampEn measure windows for Sub1 during the onset and offset segments of the activations. The LZ2 index shows smaller values (p-value < 0.05) during the activation window than during the background windows, which means a reduced complexity.

IV. Discussion

EEG signal properties at the onset and offset of the cyclic alternating pattern components were analyzed. Our main observations were a) at the onset, the TD1 and SampEn are the main properties to differentiate the background from the phase A and b) differences at the offset between the phase A and background are less clear.

It is very common to find an increment in the EEG amplitude at the onset of the Phases A. Thus this could means that most of the Phases A begin with an episode of high EEG synchronization.

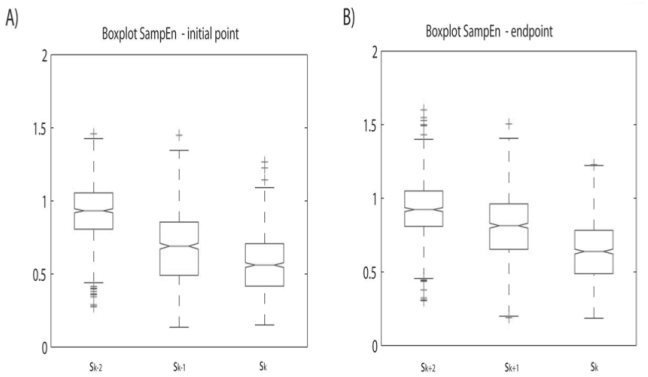

Figure 2. The distributions of SampEn per window during starting (A) and ending (B) cases.

Presently, a quantitative definition of Phases A does not exist, thus, a clear characterization of the phase A and its different subtypes is needed. Some studies have studied the phases A subtypes using different features [5-6] such as frequency content and variance; however, these studies do not focus on the onset and offset of the phase A subtypes. Only Ferri et. al. have studied this issue via spectral analysis, where they concluded that the spectral components of phases A and background are different. In addition, Ioanna et. al. complexity features have been employed, and different levels of complexity were found with activation type and sleep stage.

The reduced number of patients is the main limitation in this study. It is important to analyze large databases to obtain a better generalization. Furthermore, only healthy subjects were analyzed, therefore, a necessary extension is the exploration of the activation properties in pathologic cases such as insomnia and sleep apnea.

V. Conclusion

Clear changes with respect to the EEG background are observed in the onset and offset points of the Phase A activations in CAP sequences, and these changes can be characterized by means of complexity measures, such as the Lempel-Ziv index. This suggests that neural synchronization could be the major mechanism in the generation of the CAP phenomenon. This study constitutes a step towards developing an automatic CAP detection procedure.

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Table I. Mean and standard deviation of the measurements at the change points of Phases A

Starting points

	Sub1-S1-S2			Sub2-S1-S2			Sub3-S1-S2			Sub1-S3-S4		
Index	s_{k-2}	s_{k-1}	s_k	s_{k-2}	s_{k-1}	s_k	s_{k-2}	s_{k-1}	s_k	s_{k-2}	s_{k-1}	s_k
LZ2 #w	23.33±1.9	23.26±2	21.89±2.01 *&	23.49±2	23.62±2.1	22.27±2.1 *&	23.87±2	23.99±2	23.10±2 *&	21.35±2	21.37±2	19.69±2 #*&
LZ2 ind	0.90±0.07	0.89±0.08	0.84±0.08 *&	0.90±0.08	0.91±0.08	0.85±0.08 *&	0.92±0.08	0.92±0.08	0.89±0.08 *&	0.82±0.09	0.82±0.09	0.76±0.10 #*&
LZ3 #w	25.89±2.3	25.93±2.4	25.88±2.7	26.04±2.4	26.3±0.08	26.3±0.08 +	26.41±2.4	26.55±2.3	26.32±2.7	31.87±2.6	32.00±2.5	31.35±2.7 #*&
LZ3 ind	0.63±0.06	0.63±0.06	0.63±0.07	0.63±0.06	0.64±0.06	0.64±0.07 +	0.64±0.06	0.64±0.06	0.64±0.07	0.77±0.07	0.77±0.06	0.76±0.07 #*&
SampEn	0.92±0.19	0.68±0.25	0.57±0.19 +*&	0.94±0.22	0.65±0.25	0.60±0.22 +*&	0.79±0.26	0.75±0.28	0.81±0.29 +&	0.65±0.21	0.53±0.20	0.45±0.17 #+*&
FD	1.42±0.09	1.36±0.09	1.31±0.08 +*&	1.43±0.10	1.36±0.09	1.33±0.09 +*&	1.44±0.11	1.41±0.11	1.42±0.13 +*	1.29±0.08	1.25±0.08	1.23±0.08 #+*&
TS1	0.35±0.068	0.45±0.08	0.53±0.06 +*&	0.34±0.07	0.45±0.08	0.53±0.07 +*&	0.34±0.07	0.42±0.09	0.48±0.10 +*&	0.46±0.07	0.51±0.06	0.55±0.06 #+*&
TS2	0.49±0.00	0.49±0.00	0.57±0.19 *&	0.493±0.0	0.496±0.0	0.498±0.0 +*&	0.493±0.0	0.495±0.0	0.496±0.0 +*&	0.497±0.0	0.497±0.0	0.498±0.0 #*&

Ending points

	Sub1-S1-S2			Sub2-S1-S2			Sub3-S1-S2			Sub1-S3-S4		
Index	s_{k+2}	s_{k+1}	s_k	s_{k+2}	s_{k+1}	s_k	s_{k+2}	s_{k+1}	s_k	s_{k+2}	s_{k+1}	s_k
LZ2 ind	0.90±0.08	0.91±0.08	0.86±0.08 *&	0.91±0.08	0.92±0.07	0.88±0.08 *&	0.94±0.07	0.94±0.07	0.92±0.07 *&	0.84±0.08	0.85±0.08	0.81±0.09 #*&
LZ3 #w	26.13±2.58	26.36±2.4	26.11±2.5	26.52±2.3	26.47±2.3	26.08±2.4 *&	26.82±2.2	26.82±2.2	26.16±2.1 *&	25.66±2.4	25.75±2.5	25.68±2.5 #
LZ3 ind	0.63±0.06	0.64±0.06	0.63±0.06	0.64±0.06	0.64±0.06	0.63±0.06 *&	0.65±0.05	0.65±0.05	0.63±0.05 *&	0.62±0.06	0.62±0.06	0.62±0.06 #
SampEn	0.92±0.18	0.80±0.21	0.64±0.20 +*&	0.97±0.18	0.89±0.22	0.81±0.23 +*&	1.06±0.21	1.06±0.23	1.10±0.26 *&	0.64±0.20	0.58±0.19	0.48±0.17 #+*&
FD	1.41±0.09	1.39±0.09	1.34±0.08 +*&	1.43±0.09	1.42±0.10	1.40±0.10 *&	1.47±0.11	1.48±0.12	1.50±0.13 *&	1.30±0.08	1.29±0.08	1.26±0.08 #+*&
TS1	0.33±0.068	0.38±0.08	0.47±0.08 +*&	0.31±0.06	0.35±0.07	0.41±0.08 +*&	0.30±0.07	0.32±0.07	0.34±0.07 +*&	0.43±0.08	0.46±0.08	0.51±0.07 #+*&
TS2	0.493±0.0	0.494±0.0	0.497±0.0 +*&	0.491±0.0	0.493±0.0	0.495±0.0 +*&	0.490±0.0	0.491±0.0	0.493±0.0 +*&	0.496±0.0	0.497±0.0	0.498±0.0 #+*&

Sub1 –S1-S2 means phase A subtype 1 during sleep stages 1 and 2, Sub2 –S1-S2 is phase A subtype 2 during sleep stages 1 and 2, Sub3 –S1-S2 stands for phase A subtype 3 during sleep stages 1 and 2, Sub4 –S3-S4 means phase A subtype 1 during sleep stages 3 and 4. LZ2 #w is the number of words found by the Lempel-Ziv algorithm in a binary string. LZ3 #w is the number of words found by the Lempel-Ziv algorithm in a ternary string. + symbol means statistical difference between s_{k+1} and s_{k+2}, * symbol represents statistical difference between s_k and s_{k+2} and & symbol is for statistical deference between s_k and s_{k+1}. p-value was 5%. # symbol denotes that activation type 1 (during s_k)presents statistical differences (p-*value*=0.01)between the sleep stages 1-2 and 3-4. Please note that a std equal to 0.0 or 0.00 a mean value lower than 0.005.