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A symbolic dynamics approach to Epileptic Chronnectomics: Employing strings to predict crisis onset

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ABSTRACT

Treating brain as a complex system is currently among the most popular approaches that are used to understand its function and explain encephalopathies. The networked epileptic brain has already been studied through various neuroimaging modalities based on estimates of functional connectivity. Here, we suggest that additional insights to epileptogenesis can be gained with an appropriate description on the network (re)organization dynamics as these are reflected in surface EEG measurements. Our approach commences with a pattern analytic step that turns a time series of connectivity patterns into a symbolic time series. The condensed dynamics are then analyzed by means of Markov chain modeling and a motif detection algorithm. Both descriptions yield novel dynamic characteristics that can capture the progression towards an epileptic crisis. Conceptually, our work adds to the emerging field of "chronnectomics". Empirically, the obtained results based on actual experimental data are very encouraging and deserve further consideration.

1. Introduction

Epilepsy is one of the most common neurological disorders of the human brain and affects people of all ages. It is characterized by sudden and unpredictable seizures that can cause other health problems as well [8]. The human brain is the source of human epilepsy, since all the electrical events that produce the symptoms occur in the brain. It has also been found that almost one in four patients with epilepsy cannot be controlled by any anti-epileptic drugs or surgery [15, 18]. Thus, it is essential to study epileptic data in order to warn patients that a seizure is about to occur and help them avoid potentially endangering situations. Moreover, individual patient-based detector training may be necessary to increase sensitivity and specificity [21].

The scientific community has continuously performed research towards improvement and development of automated seizure detection and prediction algorithms based on electroencephalographic (EEG) measurements, in order to characterize the transition from the pre-ictal or inter-ictal to the ictal state in quantitative terms. Measurements of brain electrical activity

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with EEG have long been one of the most valuable sources of information for epilepsy research and diagnosis [11], since they contain a large amount of rich information that is useful for detecting ongoing seizures. Most of these algorithms are based on linear and nonlinear time series analysis techniques of pre-seizure changes in the dynamics of either intracranial or scalp EEG recordings. However, the reported results are not always reliable [18] and all these studies strongly suggest that the information contained in EEG data relevant to seizure detection has not yet been fully exploited and thus, additional research and new approaches are needed.

In the last decade or so, many researchers have used complex network analysis to investigate the human brain function and especially the functional brain networks in epilepsy [20]. In this context, the brain is considered as a complex network [22] with the underlying dynamic substrate of this network being manifested in the form of signal correlations among distinct but functionally related brain areas. EEGs are spatio-temporal data, since electrodes are placed at specific locations on the scalp and monitor continuously the electrical activity of the brain. Usually, epilepsy-related EEG data are also recorded continuously and over long periods of time, even if the event of interest lasts only for very short periods (corresponding to a very small portion of the recorded data). The principal goal in the relevant research is to reliably detect the prodromal phase using brain signal analytics and consequently predict the upcoming seizure. In the context of complex systems, this corresponds to identifying self-organization tendencies that will eventually lead to a phase transition in the language of dynamical systems. For this reason, time-varying graphs have been introduced lately [9,10,13] as a promising methodology for encoding time-dependent inter-areal relationships such as those emerging in epilepsy. In the case of time-varying graphs (time-indexed networks), a time series of connectivity estimates is represented by an ordered sequence of graphs defined over a fixed number of nodes, with each graph corresponding to a connectivity snapshot of a patient's brain activity lasting for few seconds.

In this paper though, we go one step further by encoding epilepsy brain network dynamics in the form of a symbolic time series. We first design a codebook of k connectivity prototypes, that can represent the epileptic data in a parsimonious way and then assign each quasi-instantaneous connectivity pattern to the most similar code symbol (i.e. connectivity prototype) [5,6]. In this way, the derived symbolic time series corresponds to a predefined number of network organization prototypes and its evolution encapsulates the most important phase transitions of the underlying dynamical system. The proposed representation has been exploited in two, methodologically distinct, ways that are summarized below.

In the first approach, we adopt a modeling by means of finite state irreducible Markov chains [7] and we focus on the observed trajectories T_{ij} (meaning that the dynamical system reached state j from state i). We then estimate the entropy of these trajectories and form the matrix corresponding to all pairs among the utilized prototypes (states-symbols). As it will be shown in Section 3, the values of the trajectory entropy matrix are decreasing significantly before the seizure onset. Although seizure prediction is notoriously difficult to achieve, we assume that a fact like this could contribute to a possible epileptic seizure prediction. In the second approach, the well-known MoTeX-II tool [19] is used in order to perform motif extraction from the symbolic time series. As a result, MoTeX returns a list of detected motifs, which are then sorted alphabetically. Next the distribution of different time series segments on the derived motifs is compared with a 'baseline' distribution that corresponds to the whole symbolic time series. The empirical results show that the employed discrepancy measure increases dramatically before each epileptic crisis, and hence can serve as a sign in a suitable prediction algorithm.

Both approaches constitute novel methodological contributions to the emerging field of "chronnectomics" [2]. The recently term "chronnectome" is a concept that incorporates dynamic view of functional brain connectomics and the recurrence of particular connectivity patterns (in which two or more regions or sets of regions, all possibly evolving spatially in time, are coupled with connectivity strengths measured as explicit functions of time). Note that this is the first time that such a methodological perspective is exploited for the purposes of prediction in EEG epileptic data. Fig. 1 depicts the outline of the whole procedure.

2. Method

2.1. EEG recordings

Long-term video-EEG recordings were collected from patients with epilepsy in the Neurology Ward of the Cyprus Institute of Neurology and Genetics, as part of a diagnostic or a presurgical evaluation. The XLTEK scalp EEG recording system was used for this purpose. Twenty-one electrodes were placed according to the 10–20 international system (see electrode placement in Fig. 2a) with two additional anterotemporal electrodes. Moreover, another four electrodes were used to record the electrooculogram (EOG) and electrocardiographic (ECG) signals respectively. The data were recorded at a sampling rate of 200 Hz using a cephalic reference that was not part of the scalp derivations used to display the recorded channels. A bandpass filter 1–50 Hz was applied offline.

The data were converted to the bipolar montage, where pairs of electrodes placed in nearby locations of the scalp, taken in straight lines from the front to the back of the head, were used to obtain the time-series by subtracting the corresponding measurements, as this representation was found to be more robust to volume conduction effects [4].

We analyzed data from three patients with epilepsy and seizures were identified and marked by specialized neurophysiologists (co-authors ESP and SSP). The aforementioned data as well as the functional connectivity graph datasets were created as an intermediate result in previous studies [3,4] and hence a more detailed description can be found

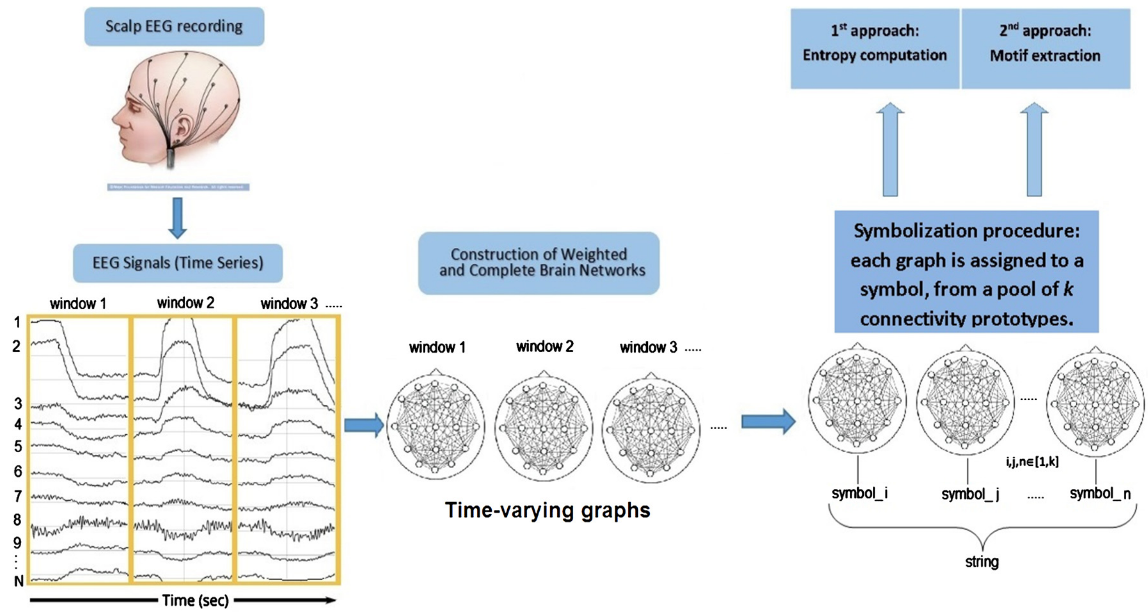

Fig. 1. Outline of the proposed methodological scheme.

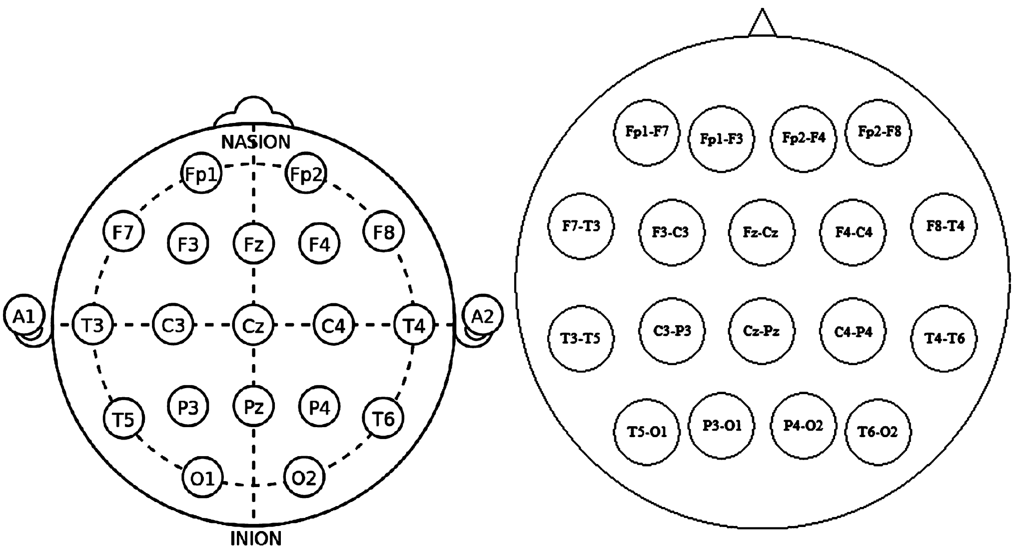

Fig. 2. (a) The 21 electrodes placement according to the 10–20 international system. (b) The spatial layout of the nodes in each slice in the adopted network representation (resulting after the application of bipolar montage).

therein. The data were processed in consecutive non-overlapping windows of 5 seconds length and one functional network for each such window was constructed. All the derived graphs are weighted, undirected and fully connected with 18 nodes. The topological arrangement of the nodes of these graphs is depicted in Fig. 2b. The weight associated with each pair of nodes is the (absolute) strength of the temporal correlation between the corresponding time series.

2.2. Symbolization scheme

This subsection serves as a brief introduction to our symbolization scheme, presented in greater details elsewhere [5,6]. The time series of connectivity patterns, (in the particular case the temporal sequence of (18×18) in size weighted adjacency matrices), is quantized at a finite resolution. Towards this end, a codebook of k prototypical functional connectivity states (i.e. connectivity microstates) is first designed by applying the neural-gas algorithm [16]. This algorithm is an artificial neural network model, which converges efficiently to a small number k of codebook vectors, using a stochastic gradient descent procedure with a soft-max adaptation rule that minimizes the average distortion error [17]. In this way, the bulk of information contained in the time series of connectivity patterns is represented, in a parsimonious way, by a partition matrix U, with elements u_{ij} indicating the assignment of input connectivity patterns to code vectors. Following the inverse procedure, we can rebuild a given time series from the k code vectors, with a small reconstruction error E. The selection of parameter k reflects the trade-off between fidelity and compression level. In this work, it was set as the smaller value to achieve a reconstruction error lower than 35% ($k = 5$). Also, parameter k was chosen in a way that the trade-off between reconstruction error and computational cost could be balanced. Finally, we need to mention that inside the codebook design there is an algorithmic seriation procedure that "ranks" the symbols. As a consequence, the symbolic time series closely follows the underlying functional connectivity dynamics.

2.3. Entropy of Markov trajectories

By adopting the above symbolization, we implicitly consider the observed dynamics (i.e. the time series of connectivity patterns) as observations from a finite-state machine, with the states corresponding to recurrent emerging connectivity patterns or microstates. A Markov chain modeling can be naturally derived from the symbolic time series and appears as a very reasonable, though simplistic, modeling that emphasizes the transition between connectivity microstates. Motivated by the need to identify measurable changes in the connectivity dynamics flow during the course to an epileptic crisis, we resort to a relevant technique that quantifies the entropy of Markov trajectories (i.e. routes from a particular microstate to another). We hypothesized, that the connectivity dynamics may lose "healthy" degrees of freedom and become less variable. This would be reflected as reduction in the entropy of – at least – some Markov trajectories.

Let us consider a finite state irreducible Markov chain with empirical transition matrix P (derived from the symbolic time series). A trajectory $t_{ij} \in T_{ij}$ from state i to state j is a path with initial state i, final state j and no intervening state j. The entropy rate is always well-defined and is given by

$$H(X) = -\sum_{i,j} \mu_i P_{ij} log P_{ij} \tag{1}$$

where μ is the unique solution of the equations below for all j:

$$\mu_j = \sum_i \mu_i P_{ij} \tag{2}$$

For an irreducible Markov chain, the entropy H_{ii} of the random trajectory from state i back to state i is given by

$$H_{ii} = \frac{H(X)}{\mu_i} \tag{3}$$

where μ_i is the stationary probability for state i and $H(X)$ is the entropy rate given in Equation (1).

Finally, if P is the transition matrix of an irreducible finite state Markov chain, then the matrix H of trajectory entropies is given by:

$$H = K - \tilde{K} + H_\Delta \tag{4}$$

where

$$K = (I - P + A)^{(-1)}(H^* - H_\Delta) \tag{5}$$

$$\tilde{K}_{ij} = K_{jj} \tag{6}$$

$$A_{ij} = \mu_i \tag{7}$$

$$H^*_{ij} = H(P_i) \tag{8}$$

for all i, j and

$$(H_\Delta)_{ij} = \begin{cases} H(X)/\mu_i, i = j \\ 0, i \neq j \end{cases} \tag{9}$$

In this paper, we use the finite state irreducible Markov chains modeling scheme and we focus on the observed trajectories T_{ij} (meaning that the dynamical system reached state j from state i).

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2.4. MoTif eXtraction (MoTeX)

Identifying repeated factors that occur in a string of symbols represents an important task in computer science. Such patterns are called motifs and the process of identifying them is called motif extraction. In the context of analyzing epileptic symbolic time series, it was of great interest to study if the frequency of appearance of particular motifs is increased or reduced before the crisis and if such a trend could be exploited for the precise and accurate prediction of epilepsy onset.

Here, we use MoTeX-II [19], which is a publicly available word-based high-performance computing tool that performs structured motif extraction from large-scale datasets. In our case, a motif is a string of letters (word), with predefined length l, on a specific alphabet Σ. The motif extraction problem takes as input a string s on Σ, the maximal allowed distance e (error threshold) and the length l for the motifs. Then it determines all the possible motifs of length l, such that each motif occurs in the input string. Also, MoTeX-II software is guaranteed to find globally optimal motifs [19]. The derived motifs are called valid. When these concepts are transferred to our symbolic time series, a motif is a particular sequence of connectivity patterns (microstates) and, hence, MoTeX results in a repertoire of transitional connectivity dynamics. It was our goal to identify changes in the distribution over this vocabulary that could be considered precursors of epileptic crisis.

Our algorithmic approach starts by placing the valid-motifs in "alphabetical" order. This is achieved by generalizing the seriation step (mentioned in Section 2.2 for the symbols) so as to be applicable to motifs. Then, similarity scores, expressing the matching between each valid motif M_i and every segment $S_t = [s(t), s(t+1), \ldots s(t+l-1)]$ of the symbolic time series are derived and tabulated in matrix SIM with elements: $SIM_{it} = Score(i,t) = e^{-||S_t - M_i||/r_o}$ (where r_o is a scaling parameter that was set equal to the mean distance from motif to segment).

By integrating along discrete time dimension, and within regular time intervals, we estimate profiles that can be considered as soft-computing histograms over the given vocabulary (the set of valid motifs). The consecutively formed histograms are contrasted against the histogram built by integrating over the whole recording time. The discrepancy between the local histogram to the global one (quantified by means of the "cosine distance") is investigated for aberrant trends in the distribution of motif that could point to a forthcoming crisis.

3. Results

3.1. Experiments

Three epileptic datasets that were recorded from three patients with epilepsy were studied in total. We apply the first methodological approach to patients A and B, for which we focus on a fraction of the recorded data two hours before the seizure onset. The reason why we do this and we do not study for example the time period after the seizure onset, is because our main concern is to predict the occurrence of the epileptic episode. Then, we apply a moving window of five minutes, with one minute step, across the whole investigated time period. Consequently it is easily assumed that in our case we studied a total of 115 trajectories. After that, we compute the entropy of these trajectories and form the matrix that corresponds to all pairs among the utilized states-symbols.

Then the second methodological approach is applied to the whole range of the dataset of patient C, which contains two epileptic seizures in total. All the epileptic data were converted to symbolic time series according to the procedure that was described in Section 2.2. After extensive experimentation, the parameter k that defines the number of symbols was set to 5 for all datasets, since at this value the reconstruction error became for the first time lower than 35%. An example of the designed codebook, is provided in Fig. 3 for the case of patient-C's dataset. We need to mention here that a well established clinical fact in epilepsy research is that each person's seizures share a unique idiosyncratic character [1]. For this reason, we do not attempt to describe and represent the connectivity dynamics for all patients collectively.

3.2. Empirical results

We calculated the entropy matrix for all pairs of symbols for patients A and B. Thus, the derived entropy matrix for both cases has a dimension of [5×5] and is expressed as H(i,j), where $(i, j) \in [1, 2, 3, 4, 5]$. Fig. 4 shows the entropy values for two pairs of symbols for patients A and B respectively, that concern a recording period of two hours before the seizure onset. In both cases, a clear decreasing tendency is observed few minutes before the seizure onset.

Fig. 5 depicts the alphabetical sorting of the list of the derived motifs from patient C's dataset. In this paper, as already mentioned, the alphabet consists of five symbols which are the integer numbers from 1 to 5. Next, we use a temporal moving window of 5 minutes to form the quasi-instantaneous distribution over the derived motifs and compare it with a 'baseline' distribution that represents the non-seizure symbolic time series. The profile included in Fig. 6 represents the "difference" between locally and globally formed histogram. It is obvious that before the seizure onset there is a clear deviation, which implies that an epileptic episode is about to take place within the next minutes. The words "S1" and "S2" denote the seizure onset of the first and the second epileptic episode respectively.

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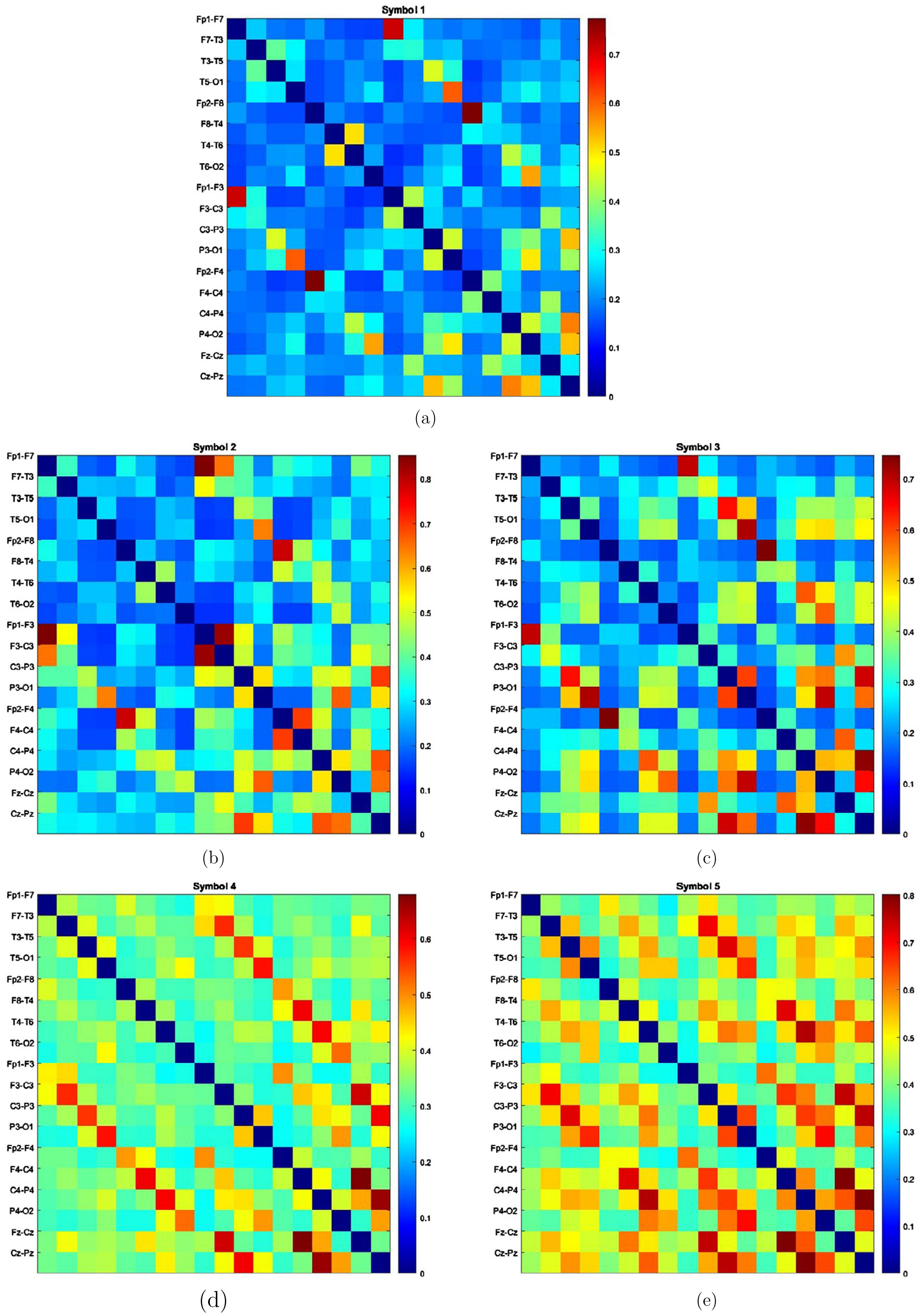
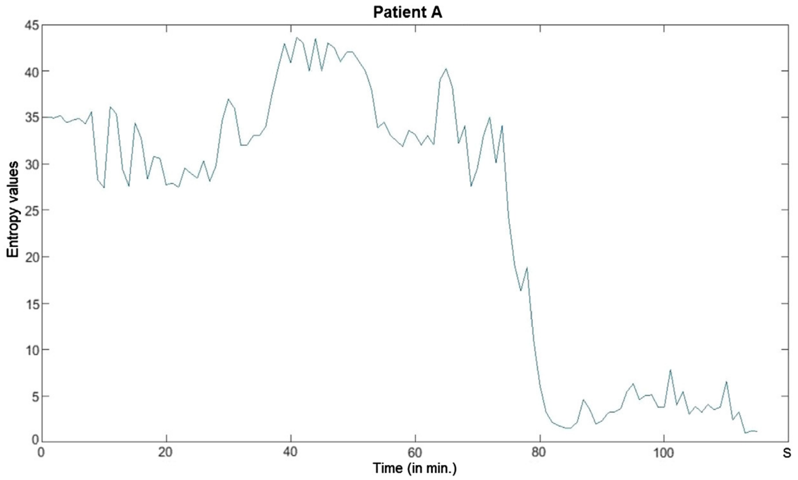
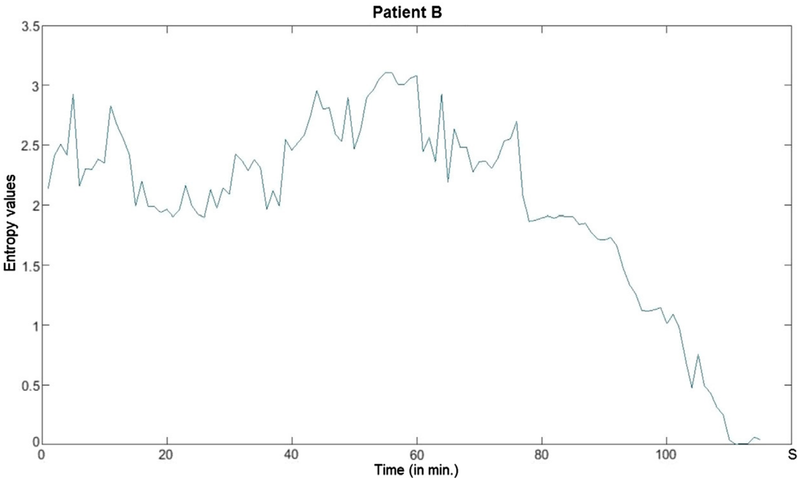


Fig. 3. (a)–(e) The five microstates used for the representation of patient's C dataset. The colorbars on the right indicate the absolute correlation values that correspond to each color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



(a)



(b)

Fig. 4. (a) Entropy values for H(3, 3) of Patient A. (b) Entropy values for H(1, 5) of Patient B.

4. Discussion

This article concerned itself with seizure prediction problem, a task that is widely considered as a very difficult one. Here, we proposed two new techniques that may contribute towards the prediction of an upcoming epileptic seizure. Our main objective was not to provide a definite solution to the problem, but to introduce it to the string algorithms community and provide some evidence that existing string algorithms can find a novel rewarding application area.

We described a methodological framework that efficiently treats the functional EEG data from epileptic recordings and derives symbolic time series that encapsulate the dynamics of network reorganization. Functional connectivity datasets from three patients with epilepsy were employed so as to demonstrate its application to actual data. In all cases, functional connectivity microstates were identified in a data-driven mode, using an existing methodology [5] and symbolic timeseries were constructed that denoted their occurrence along time. In the first of the two introduced techniques, we employed Markov chain modeling to characterize the transitions between connectivity microstates and the entropy of Markov trajectories showed a clear decreasing tendency prior the seizure onset (Fig. 4), an observation that could be exploited in the prediction of upcoming seizures. In the second technique, we applied the well-known MoTeX tool in order to identify motifs from the symbolic time series and compare their frequency of appearance over time. By contrasting the distribution within a small sliding window with the distribution over the whole recording, we observed a clear discrepancy before each seizure onset (Fig. 6), while such a tendency is not apparent in the initial symbolic time series data (Fig. 7).

The presented results constitute a first indication that string algorithms could contribute significantly to the solution of epilepsy prediction problem. Apart from this, the presented techniques are probably the first applications that the emerging

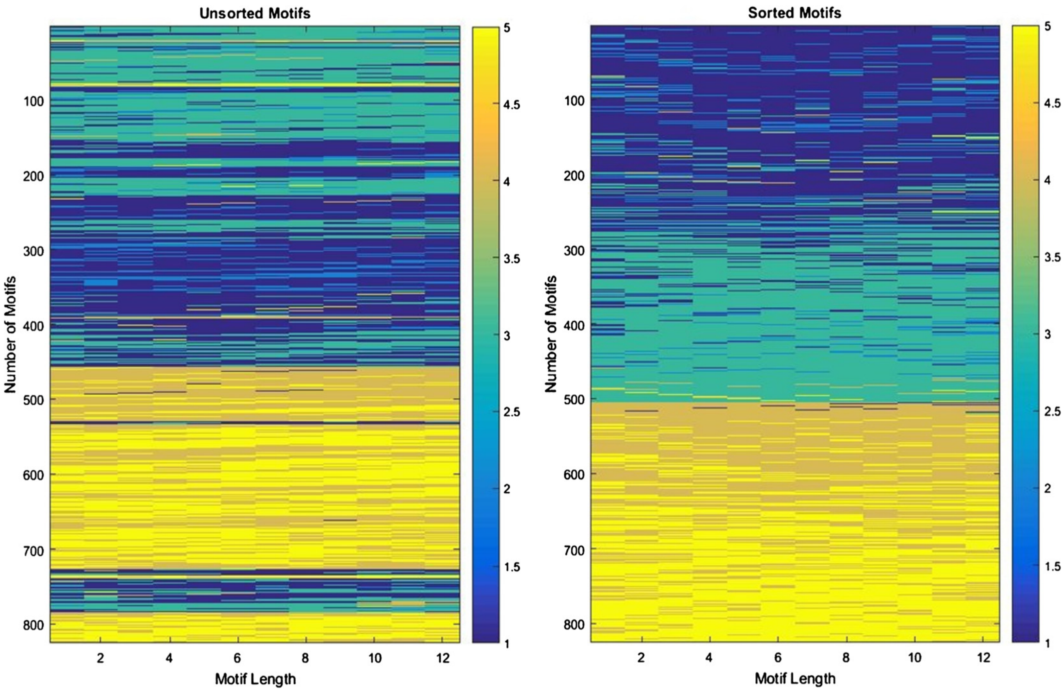


Fig. 5. Sorting the list of derived motifs.

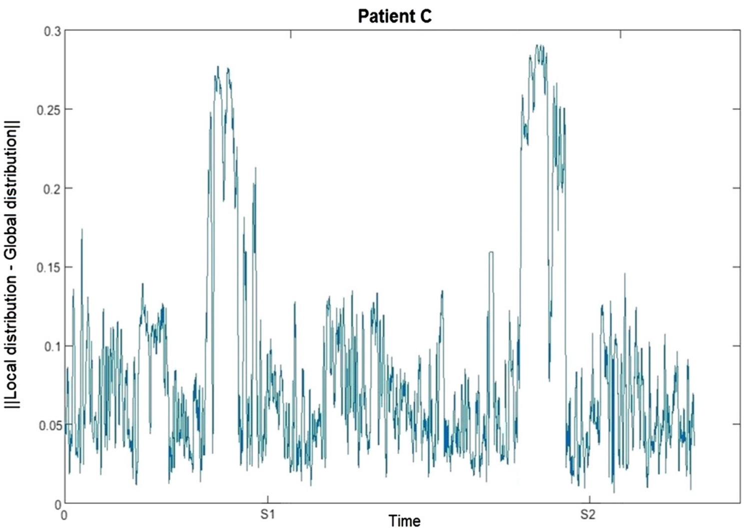


Fig. 6. Discrepancy between local and global distribution in terms of Euclidean distance.

field of "chronnectomics" finds to the analysis of EEG epileptic data. Note that until now the term "chronnectome", which describes metrics that allow a dynamic view of coupling, has only been used in functional magnetic resonance imaging (fMRI) data [2]. Several articles have been published recently regarding EEG epileptic data [12,14], among them an extensive and detailed review regarding current trends in epilepsy [23]. According to them, since now EEG epileptic data have been represented and treated mainly as networks [23], by studying the corresponding networks' organization in patients with epilepsy and sometimes compare it with healthy individuals. Hence, another important innovation and difference of the present article, compared to all the aforementioned ones, is that for the first time EEG epilepsy data are converted to symbolic time series and they are studied as strings, with quite interesting results.

Among the limitations of this study is the lack of extensive experimentation. As already mentioned, our main goal was to introduce the epilepsy prediction problem to the string algorithms community and assert that the proposed techniques can provide promising and interesting results. Another limitation is that our results cannot be directly compared with those of other methods, because neither the representation nor the data are the same with those of other stud-

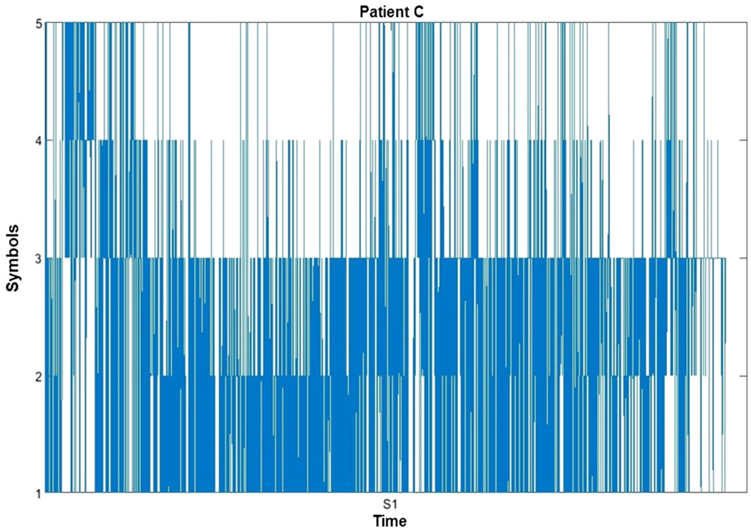


Fig. 7. Representation of the symbolic time series of patient C around Seizure1 (S1).

ies. Note that each person's seizures are unique, with a unique origin and a seizure-related network that the abnormal brain traverse, causing a unique seizure behavior [1]. Thus, we do not attempt to compare different patients with each other.

It is important to mention here, that the proposed methodological scheme can be applied to any other type of (time-indexed) connectivity data. As a future work, we are planning to study extensive time series that include longer recording periods of time and also introduce new techniques that will be able to handle very large strings. However, we have only scratched the surface thus far. A great deal of additional work is still needed to validate the current findings, build improved ones and develop high-level summary statistics.

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