Space and Temporal Distribution Analysis of Interictal Spike in Epilepsy

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Abstract: Stereo-electroencephalography (SEEG) is the main investigation method for pre-surgical evaluation of patients suffering from drug-resistant partial epilepsy. SEEG signals reflect two types of paroxysmal activity: ictal activity and interictal activity or interictal spikes (IS). The relationship between IS and ictal activity is an essential and recurrent question in epileptology. In this paper, we present a distributed and parallel architecture for space and temporal distribution analysis of IS, based on a distributed and collaborative methodology. The proposed approach exploits the SEEG data using vector analysis of the corresponding signals among multi-agents system. The objective is to present a new method to analyze and classify IS during wakefulness (W), light sleep (LS) and deep sleep (DS) stages. Temporal and spatial relationships between IS and seizure onset zone are compared during wakefulness, light sleep and deep sleep. Results show that space and temporal distribution for real data are not random but correlated.

Key words: Epilepsy, sleep stage, stereo-electroencephalography (SEEG), interictal spike, signal processing, multi-agent system.

1. Introduction

Epilepsy is a chronic disease, a consequence of many and various causes. It is a complex pathology that the symptoms exteriorized by the patient depend directly on the cerebral structures involved in the propagation of the seizure. Around 60% epilepsy are partial and 20-25% of partial epilepsy are drug-resistant, and a surgical treatment can be necessary [1]. Therefore the spikes space and temporal distribution can help in pre-chirurgical evaluation.

Among the investigation methods allowing determining the origin of the paroxysmal discharges, stereo-electroencephalography (SEEG) is essential. This standard method (SEEG) makes it possible to directly collect intracerebral signals of an excellent temporal resolution, which inform about the electrical activity of the concerned structures as shown in Fig. 1. SEEG signals reflect two types of paroxysmal activities: ictal activity and interictal activity (interictal spikes). The interictal spikes (IS) are observed at 1 percent of the non-epileptic subjects and around 60-90% of the epileptic subjects (Bourien, Schaul and Binnie) [2-4]. They are a complementary source of information in the diagnosis and localization of epilepsy. They are characterized by a brief initial phase, sharp and strong amplitude and occur as transitional events (< 1 second). The interictal spikes occurrence is higher than the seizures frequency. They appear in wave but sometimes they appear isolated. The IS are classified in spikes or waves according to their duration, between 20 and 70 ms, 70 and 200 ms respectively. Their amplitude, significantly higher than those background activity’s, features them. The clinical characterizations of the IS are based on their density, morphology, and topography. The study of relationship between interictal and ictal activity brings a significant complement in the pre-surgical...
evaluation of patients suffering from drug-resistant partial epilepsy. The relationship between the IS and the seizures are badly known, in spite of the fact that these two types of paroxysmal activity are qualitatively taken into account in the visual analysis of SEEG signals [5].

In this paper, the authors analyzed the dynamics of interactions between different explored cerebral areas during pre-surgical evaluation. The authors present a distributed and parallel architecture for spatio-temporal distribution analysis of IS through a distributed and collaborative approach.

One major step is to design a distributed platform able to follow the dynamics of cerebral structures networks, which are co-activated in order to show the various reorganizations of cerebral structures interactions following various states of patients. We can answer some of following questions: how is it possible to model and simulate situated interactions between cerebral structures? How to simultaneously provide views of locally and globally situated phenomenon? Is it possible to define a detailed spatiotemporal representation in a vector environment?

These issues will be addressed in the next section.

2. Materials and Methods

In this section the authors explain the method to design platform for the analyze space and temporal distribution of IS. This method consists of transposing the vector EEG signals processing in a distributed and collaborative vector platform. Each channel (SEEG signal) is associated with an autonomous process and all entities system cooperate to analyze the whole system. Our approach is based on cooperative and auto-organized mechanisms at the local level (mono-IS) and global phenomenon analysis (multi-IS) as explained in section 2.3.

2.1 SEEG Signal Recording

Stereo-electroencephalography (SEEG) method is shown in Fig. 1. This method of investigation used in epilepsy, make it possible to better understand the mechanisms involved of the initiation of the paroxystic discharges in a given subset of cerebral structures and their propagation to other structures. SEEG signals recorded show sharp variations of ictal activity and of interictal activity, illustrating the various cerebral activities. The method uses a high temporal resolution to provide the accurate localization of distinct interictal activities in each explored structure. SEEG signals inform various peculiarities of a structural entity, an organ or a system. Their interpretation is multi-factor and therefore, it isn’t easy; the normality for a given modality varies from subject to subject according the age, the history and protocols of examinations (rest, physical stress, stimulations, etc.).

2.2 Related Works

Many methods have been developed to establish functional connections between brain areas in the frequency domain by using EEG or MEG recordings [6]. Additionally numerous methods have been made to detect a reliable spike, some approaches measure the “sharpness” of the EEG signal [7, 8], while other use nonlinear modelling method [9] or wavelets and

Fig. 1 Intracerebral EEG and interictal spikes distribution. a) MRI showing the implementation of electrodes. b) Plan of an electrode with staged contacts. c) Example of recording SEEG.
time-frequency approaches [10] to characterize the occurrence of IS.

Valenti and Cazamajou [11] propose a data mining classification technique to build an automatic detection of IS. Their method didn’t however take into account the precise signal form (morphology). In spatiotemporal analysis field, Badier and Chauvel [12] proposed a spatiotemporal mapping technique to study the IS during the pre-surgical evaluation of their epileptogenic zone prior to surgery. Asano’s work [13] shows that overall spike frequency may be increased during the sleep, but the spatial distribution of spike frequency appears similar during wakefulness and sleep in children with focal seizures. In conclusion, the authors have variability of results, heterogeneity of signals and methods (scalp/intracerebral EEG, automatic/manual detection …) for interictal spikes analysis.

2.3 Method Description

2.3.1 Global Description

The method of distributed signal processing is not a well-explored area, however numerous solutions allowing to better analyze problem of space and temporal distribution have been proposed. We characterize the topological properties of the cerebral networks by using a theoretical graph approach following Watts and Strogatz [14]. We consider each depth-EEG channel as an object (process) with a dynamical state, which depends on its cerebral structure activities. The cerebral structures network is considered as a system that can generate, on a temporal sliding window, interictal spikes (IS) in the form of various combinations. Let N be the number of selected SEEG channels. We consider SEEG signals recording at a vector signal \( S(t) = [S_1(t) \ldots S_N(t)] \) observed on an interval \([0, T]\).

The method consists of: (i) characterizing IS on each SEEG channel \( S_i(t) \); (ii) determining the temporal relations between the various channels; (iii) studying the organization of subsets of co-activated structures (SCAS); (iv) finally analyzing spatiotemporal distribution of IS. We further analyze statistically the SCAS and we perform a global representation of SCAS dynamics as described below.

We note \( i = 1, \ldots, N \) the channel index, \( T \) is the observation duration, \( n_i \) is the number of spike detected on channel \( i \), \( j = 1, \ldots, n_i \) is the index of detected event and \( t_{i,j} \) is detection time of spike \( j \) on channel \( i \). Our approach associates to each signal \( S_i(t) \) (Fig. 2), an agent (noted \( C_i \)) where is implemented the local treatment for channel \( i \).

The implemented approach is situated, reactive, cooperative and decentralized. Calculations, control mechanisms and signal processing algorithms are spatially distributed in the various system entities (agents). Each process (channel) has a local memory, and is able to communicate with each other by sending and receiving messages. Messages can be ordering in multicast or point-to-point communication according to the sender choice. All process runs in parallel and in a concerted way. Process Manager is used to coordinate processing. The method proceeds in four steps: (i) automatic detection of monochannel interictal spikes (mono-IS); (ii) collaborative formation of subsets of co-activated structures (multichannel interictal spikes multi-IS); (iii) automatic extraction of statistical co-activated structures; (iv) global representation of spatiotemporal distribution of IS.

Fig. 2  Multichannel event formation, distributive collaborative approach.
2.3.2 Detection of Monochannel Interictal Spikes (mono-IS)

The automatic detection of mono-IS is made as follows. At each sample time in each channel, the mean value of squared modulus of a wavelet filter bank outputs is calculated. The amplitude of this quantity $q(t)$ is random with high mean value during spike and low mean value during background SEEG. In the second stage, a Page-Hinkley algorithm [2, 16] was used to automatically estimate time instants corresponding to abrupt changes of $q(t)$. Fig. 3 shows the interictal spike detection for each channel.

2.3.3 Formation of Subsets of Co-Actived Structures (SCAS or multi-IS)

The authors consider that two processes (channels) are in interaction if they detect IS at the same time. The collaborative approach is proposed to extract SCAS. The analysis is made by cycle that is explored in parallel and synchronous way on a sliding window $w$, which has a size of $\Delta t$. A cycle comprises three successive steps: (i) identification of the reference time of cycle $t_R$, which corresponds to the estimate time to first spike detected after the previous cycle; (ii) sliding the window at this time ($t_R$); (iii) extraction SCAS by grouping all the channels, which detected a spike in this window ($w$). SCAS can be constituted by one or several structures (Fig. 4).

To group together cerebral structures, which detect a spike at the same time, each channel informs the other channels of its detection on the current sliding window ($w$). The size of the window determines the time delay below which we consider two detections of two different channels as co-activated.

![Fig. 3 Monochannel detection of interictal spikes (mono-IS).](image)

2.3.4 Simulation and Statistical Analysis

The density distribution of spikes is one of the most important aspect considered in IS analysis. To show that this distribution obeys on specific rules depending on the patient, the authors tried to simulate a random distribution following an exponential law, called Poisson distribution. The simulation consists of regenerating the same number of spikes on each channel (each agent signal) randomly. The times ($t_{i,j}^s$) where the simulated spikes occur, are determined by equation (1):

$$t_{i,j}^{s+1} = t_{i,j}^{s} + \frac{1}{\lambda_i} \log(R\text{andom})$$

where $0 < \text{Random} < 1$ and $\lambda_i$ is the average of interval between spikes. For each channel $C_i$ we generate a simulate channel $C_{i,s}$.

The statistical analysis enumerates number of detections, detection times and probability of apparition for each SCAS. The results of statistical analysis and simulation are presented in section 5.

2.3.5 Graph Properties of Subset of Co-Actived Structures (SCAS)

Milgram who studied the structure of social networks [14], has first identified the concept of “Small World Phenomenon” in 1967. The study of these networks was revived and extended in many other areas by Watts and Strogatz [15]. Our work tries to explain whether multichannel interictal spikes
distribution can be considered as a “Small World Phenomenon” or not. The structural properties of small world network are quantified by two parameters: the characteristic path length \( L \) and the clustering coefficient \( C \). Characteristic path length \( L \) is the number of vertex in the shortest path between two vertices, the value of \( L \) is averaged over all pairs of vertices. Clustering coefficient \( C \) takes values in the range \([0, 1]\) and it measures the tendency of the network to form highly interconnected regions.

Watts and Strogatz mathematically formulated “Small World Phenomenon” graphs [14].

The clustering index \( C \) for vertices introduced by Watts is defined as follows [15]. Given a vertex \( v \), which has \( K_v \) neighbours in the network, its vertex clustering coefficient \( C_v \) is defined by equation (2):

\[
C_v = \frac{2 \times r_v}{k_v(k_v - 1)}
\]  

(2)

with \( r_v \) is the amount of the vertices link connected to \( v \) (neighbours of \( v \)).

\( r_v = \sum e_{ij}, i \neq v; j \neq v \); \( i \) and \( j \) are directly connected to \( v \) and \( e_{ij} \) define the link of \( i \) to \( j \).

\( C_v \) measures the “probability” that two co-activated structures with another structure can be co-activated between them. The clustering index \( C \) of a graph is given by the following equation (3):

\[
C = \frac{1}{N} \sum_{i=1}^{N} C_v
\]  

(3)

The authors use Floyd’s algorithm to evaluate the shortest path between all pairs of vertices.

5. Results

In order to analyze and simulate the IS distribution, the system is implemented in “Madkit” (Multi-agent development kit), a distributed and generic platform, developed by Gutknecht and Ferber [17]. To present preliminary results, the data used in this study were recorded from 4 patients (BRE, MAL, PAS, LAU) suffering from a temporal lobe epilepsy (TLE). Temporal and spatial relationships between IS and seizure onset zone are compared during wakefulness, light sleep and deep sleep.

The Fig. 5 represents the percentage of seizure occurring for the four patients during wakefulness and sleep stages.

The Table 1 presents the mean spike rate per hour during the different stages. As depicted in this table, the spike rate increase with sleep depth. The global spike rate increases from wakefulness towards sleep \((W \rightarrow LS \rightarrow DS)\) for all patients.

Fig. 6 shows the maximum number of cerebral structures involved during the three stages \((W, LS \text{ and DS})\). Fig. 6 presents also the results on simulated data for the first patient (BRE). Simulation consists of generating the same number of spikes in each channel by random distribution model. These results show that space and temporal distribution for real data are not random but correlated; the distribution follows a well-determined law.

Fig. 7 represents graphs that model the cerebral structures interactions networks at any time and figure 8 is a global representation of analysis.

**Table 1** Mean spike rate (/h) during wakefulness (W), light sleep (LS) and deep sleep stages (DS).

<table>
<thead>
<tr>
<th>Stage type</th>
<th>Patient 1 (BRE)</th>
<th>Patient 2 (MAL)</th>
<th>Patient 3 (PAS)</th>
<th>Patient 4 (LAU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>2,542</td>
<td>2,368</td>
<td>2,062</td>
<td>678</td>
</tr>
<tr>
<td>LS</td>
<td>5,052</td>
<td>5,062</td>
<td>6,027</td>
<td>1,291</td>
</tr>
<tr>
<td>DS</td>
<td>11,490</td>
<td>14,565</td>
<td>9,133</td>
<td>4,582</td>
</tr>
</tbody>
</table>
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Fig. 6 Maximum number of cerebral structures involved during wakefulness (W), light sleep (LS) and deep sleep (DS) stages.

Fig. 7 Representation of one multichannel IS (SCAS) detected at $t = 8.649609$ s included left structures: internal temporal pole (TP'), internal and external entorhinal cortex (TB') and amygdale (A').

Fig. 8 Global graph shows frequency of intracerebral structures generate EPICs at same time.
Table 2  Comparison between real and simulated data for first patient 2 (MAL).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Data type</th>
<th>IS number</th>
<th>SCAS number</th>
<th>N₁</th>
<th>N₂</th>
<th>N₃</th>
<th>N₄</th>
<th>N₅</th>
<th>N₆</th>
<th>N₇</th>
<th>N₈</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wakefulness (W)</td>
<td>Real</td>
<td>2368</td>
<td>107</td>
<td>10</td>
<td>30</td>
<td>30</td>
<td>21</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Simulation</td>
<td>2368</td>
<td>39</td>
<td>11</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Light sleep (LS)</td>
<td>Real</td>
<td>5062</td>
<td>90</td>
<td>10</td>
<td>29</td>
<td>25</td>
<td>15</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Simulation</td>
<td>5062</td>
<td>58</td>
<td>9</td>
<td>30</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deep sleep (DS)</td>
<td>Real</td>
<td>14565</td>
<td>119</td>
<td>10</td>
<td>32</td>
<td>38</td>
<td>24</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Simulation</td>
<td>14565</td>
<td>81</td>
<td>10</td>
<td>37</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Nₙ is the number of different SCAS included n structures.

The multi-IS (SCAS) event in Fig. 7 appears only 39 times and it is included in another graph 79 times. The platform offers access to every mono-IS event and/or multi-IS event identified during analysis. This representation also offers access to statistical information of each event: the number of times where it appears alone, the number of times where it appears included in another graph (other event). Statistical information concerns the probability of occurrence of each event, the number of events and the number of different events.

The platform can also automatically generate simulated data according to the model presented in section 2.3.4. We applied the detection, formation and counting SCAS events on simulated data and the results show that the probability of having two brain structures (simulation) that discharge at the same time is almost zero (Table 2). This proves that the organization of multi-IS event is not random.

A “Small World Phenomenon” has two properties:
(1) its L is much smaller than a given value noted L_random which is the characteristic path length of a random graph with the same number of vertices; and
(2) its C is much larger than a given value noted C_random, the clustering coefficient of a random graph (L << L_random and C >> C_random).

The authors’ results show that cerebral interictal spikes networks present small word characteristics. The probability of observing several cerebral structures generating EPICs in same time is almost zero for the simulated data. This means that L_random→∞ and C_random→0 (rV = 0).

Table 2 also shows that the probability of observing several cerebral structures (SCAS) generating EPICs in the same time is smaller for the simulated data and important for the real data. The random law for simulated data shows that the underlying phenomenon is not random.

6. Conclusions

In this paper we have presented a new method to analyze and classify interictal spikes during wakefulness, light sleep and deep sleep. The results show that IS distribution is not random and sleep may alter the overall frequency of interictal spike. The authors’ approach makes the following contributions. Firstly, it allows the designer for a distributed and parallel application to specify the desired temporal behaviour of system. Secondly, it shows local and global representation of IS distribution for various states of patients. Thirdly it measures the relationship between IS and ictal discharges in human drug-resistant partial epilepsy. These results indicate that an analysis of sleep causes changes in depth spike activity. This can be helpful in improving predictions concerning epileptogenicity.

The perspectives of this work concern a more significant exploitation of the potentialities of the cooperative agents approach by integrating larger cohort of patients (lateral temporal epilepsy, extra-temporal epilepsy and so on). It would be also interesting to analyze the morphological spike.
Acknowledgments

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References