CHARACTERIZING ABSENCE EPILEPTIC SEIZURES FROM DEPTH CORTICAL MEASUREMENTS

S. Akhavan[1,2] *R. Phlypo*[1] *H. Soltanian-Zadeh*[2,3] *F. Studer*[4] *A. Depaulis*[4] *C. Jutten*[1,5]

[1]GIPSA-LAB, University Grenoble-Alpes, Grenoble, France. [2]University of Tehran, Tehran, Iran.
[3]Medical Image Analysis Lab., Henry Ford Health System, Detroit, MI, USA.
[4]INSERM U1216, Grenoble Institut des Neurosciences, Grenoble, France.
[5]Institut Universitaire de France, Paris, France.

ABSTRACT

In this paper, we are going to localize the onset regions and investigate the dynamics of absence epileptic seizures using local field potential recording by depth electrode. We assume that there are some hidden states (under Markovian model) during the seizure and each spike of the seizure is generated when one of the states is activated. Each state is considered as the linear superposition of a few epileptic activities (substates) and each epileptic activity is described by two characteristics: 1) the spatial topography and 2) the temporal representation. Experimental results demonstrate the generality of the proposed model in characterizing absence epileptic seizures.

Index Terms— Absence seizure, state, substate, spike

1. INTRODUCTION

Absence epilepsy is one of the several kinds of epilepsy. Sudden emergence of seizures associated with spike discharges on electroencephalogram (EEG) signals of the patients, is indication of this syndrome. Some of the people suffering from absence epilepsy have drug resistance epilepsy. For this reason, researchers try to better understand the generation process of absence epileptic seizures using animal models.

Localizing the origin of absence epileptic seizures (spatial analysis) and investigating the dynamics of them (temporal analysis) have been challenging problems over the past decades [1–5].

As one of the major works in spatial analysis, [1] studies the non-linear associations between signals recorded from multiple zones of the cortex and thalamus in the WAG/Rij rat model of absence epilepsy. They reported that during the first cycles of the seizure one region of the cortex (somatosensory cortex) drives the thalamus, while thereafter cortex and thalamus mutually drive each other. Existence of a cortical starter has also been recognized in Genetic Absence Epilepsy Rat from Strasbourg (GAERS), another well-validated animal model for absence epilepsy [4]. Many researchers wonder if absence epilepsy is truly sudden generalized synchronous activity with immediate global cortical involvement [1–3].

In [5], the challenge is about the temporal dynamics of brain activities during a seizure. At first, source separation methods were applied on temporal sliding windows of data and the relevant temporal sources were estimated for each window. Then, the temporal sources were compared quantitatively, giving a map of dynamic behavior. By analyzing this map, it has been shown that the temporal relevant sources become more stable after a latency from onset of seizures. The dynamic analysis of absence seizures also has been done in humans. In [3], it has been reported that the cortical activations and deactivations tend to occur earlier than thalamic responses during absence epileptic seizures.

In order to attain better spatio-temporal analysis of absence epileptic seizures, a new data set was acquired at the Grenoble Institute of Neurosciences (GIN) from different layers of somatosensory cortex (the onset region of absence epilepsy) in GAERS. Our goals are to 1) model the dynamics of seizures (temporal analysis) and 2) estimate onset layers during seizures (spatial analysis).

To achieve our goals, we assume that there are some hidden states (under Markovian model) during the seizures and each spike is generated condition on that the state is activated. Each state consists of a few typical epileptic activities. We call each of these activities as one substate. Each substate is described with two important characteristics: the first one is spatial topography which shows the interaction of the sources and sinks in the different layers of cortex for that substate and the second one is temporal representation which shows the shape of the spike for that substate. Extraction of the explained states and their substates and validation of the proposed model is the main target of this paper.

2. MATERIALS

2.1. Data

Extracellular field potential was recorded from different layers of somatosensory cortex of 4 adult GAERS rats by means

ISBN 978-0-9928626-7-1 © EURASIP 2017

of one electrode with E =16 sensors. The sampling rate was $f_s = 20\,\text{KHz}$ and the distance between each pair of adjacent sensors was $150\,\mu\text{m}$ (Fig. 1).

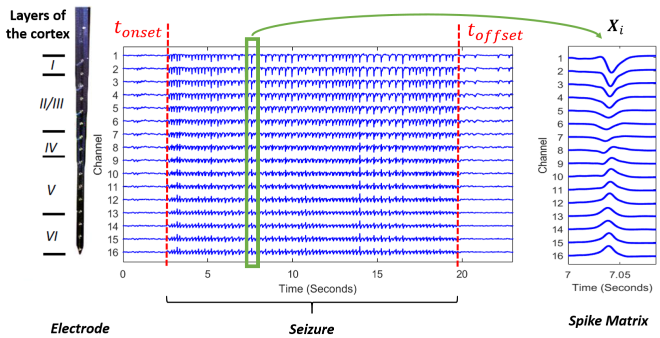

Fig. 1. Recording electrode (left), one seizure (center) and one spike matrix (right).

2.2. Model For Absence Seizures

Since spikes are the most important epileptic events during seizures, we are going to analyze the seizures based on spikes. As shown in Fig. 1, approximate simultaneous appearance of spikes in different channels during the seizure is the most typical characteristic of this data due to volume conduction theory. In other words, when one spike appears in one channel, we have one matrix of spikes (spike matrix). Therefore, we can consider each seizure as a train of spikes (spike matrices).

Model for Generation of Train of Spikes: We assume, there are a few hidden states (R) during seizure and each spike is generated when the corresponding state is activated. This assumption is based on pseudo periodic behavior of spikes and similarity of them during seizures. To model the dynamic of the activation of these states, we also assume there is a Markovian model with fixed transition probability matrix $\mathbf{P}$ ($\in \mathbb{R}^{R\times R}$) in activation of the states.

Model for Generation of One Spike: We assume that each spike is generated by a linear combination of a few epileptic activities. Linearity is a logical assumption since we are going to process local field potentials which are low frequencies part of the data and there is not any effect of capacity or induction. So there is no building up of charges and we can directly measure the fields. Mathematically, if we consider rank one decomposition of one spike matrix ($\mathbf{X}_i$) as follows (e.g. singular value decomposition):

$$\mathbf{X}_i = \sum_{j=1}^{N} c_{ij}\ \mathbf{a}_j \mathbf{b}_j^T \tag{1}$$

We can assume that $\mathbf{X}_i$ has been generated by linear superposition of N different substates and we can consider each substate as one epileptic activity. c_{ij}, $\mathbf{a}_j$ and $\mathbf{b}_j$ respectively show the contribution of j^{th} substate in generation of $\mathbf{X}_i$, the spatial topography and temporal representation of j^{th} substate. The main advantage of this decomposition is that $\mathbf{a}_j$ can be interpreted using current source density (CSD) concept [6] and clarifies the interaction between different layers in each substate. Also, $\mathbf{b}_j$ informs us about the shape of the spike in each substate. In fact, we assume that each explained state in previous part, consists of a few substates (N) and when one state is activated, the linear combination of its substates will generate the corresponding spike matrix.

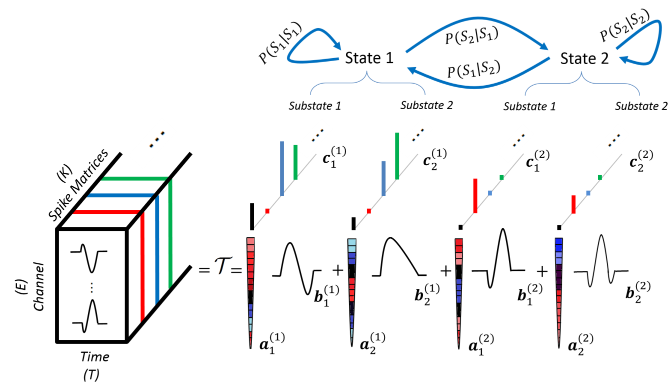

Fig. 2. Considered model for generation of spike matrices.

2.3. Problem Formulation

If we stack all of the spike matrices of one seizure in one three dimensional tensor $\mathcal{T}$ ($\in \mathbb{R}^{E\times T\times K}$), the desired decomposition for $\mathcal{T}$ is as follows:

$$\mathcal{T} \simeq \sum_{s=1}^{R}\sum_{j=1}^{N} \mathbf{a}_j^{(s)} \otimes \mathbf{b}_j^{(s)} \otimes \mathbf{c}_j^{(s)} \tag{2}$$

where E, T, K are respectively number of channels, samples of each spike and spike matrices. $\otimes$ denotes the tensor product. $\mathbf{a}_j^{(s)}$ ($\in \mathbb{R}^{E\times 1}$) and $\mathbf{b}_j^{(s)}$ ($\in \mathbb{R}^{T\times 1}$) respectively show the spatial topography and temporal representation of j^{th} substate from s^{th} state. $\mathbf{c}_j^{(s)}$ ($\in \mathbb{R}^{K\times 1}$) shows the contribution of different substates in generation of spike matrices. Fig. 2 shows the desired decomposition by considering $R = N = 2$. For having fair comparison between different substates, we assume that $\mathbf{a}_j^{(s)}$ and $\mathbf{b}_j^{(s)}$ are unit norm vectors and entries of $\mathbf{c}_j^{(s)}$ are considered positive because we want to have the same polarization for $\mathbf{a_j^{(s)}}$ and $\mathbf{b_j^{(s)}}$ in all of the spike matrices. The set of unknown parameters is as follow:

$$\Theta = \{\mathbf{A}^{(1)}, \mathbf{B}^{(1)}, \mathbf{C}^{(1)}, \ldots, \mathbf{A}^{(R)}, \mathbf{B}^{(R)}, \mathbf{C}^{(R)}, \mathbf{P}\} \tag{3}$$

where $\mathbf{A}^{(s)} = [\mathbf{a}_1^{(s)}\ \ \mathbf{a}_2^{(s)}\ \ \ldots\ \ \mathbf{a}_N^{(s)}]$, $\mathbf{B}^{(s)} = [\mathbf{b}_1^{(s)}\ \ \mathbf{b}_2^{(s)}\ \ \ldots\ \ \mathbf{b}_N^{(s)}]$, $\mathbf{C}^{(s)} = [\mathbf{c}_1^{(s)}\ \ \mathbf{c}_2^{(s)}\ \ \ldots\ \ \mathbf{c}_N^{(s)}]$ and $[\mathbf{C}^{(s)}]_{ij} = c_{ij}^{(s)}$. The set of unknown parameters also can be shown shortly by,

$$\Theta = \{\mathbf{A}, \mathbf{B}, \mathbf{C}, \mathbf{P}, \sigma_0^2\} \tag{4}$$

ISBN 978-0-9928626-7-1

where $\mathbf{A} = [\mathbf{A}^{(1)} ... \mathbf{A}^{(R)}]$, $\mathbf{B} = [\mathbf{B}^{(1)} ... \mathbf{B}^{(R)}]$ and $\mathbf{C} = [\mathbf{C}^{(1)} ... \mathbf{C}^{(R)}]$. Now, the model definition and problem statement is complete and the target is finding the hidden states, their substates and the transition probability matrix which will be explained in one framework.

3. PROPOSED FRAMEWORK

The whole procedure of the proposed framework for extracting the unknown parameters of the considered model is shown in Fig. 3. As shown there are three main stages in this framework, pre-processing, proposed method and cross validation which are explained in the following.

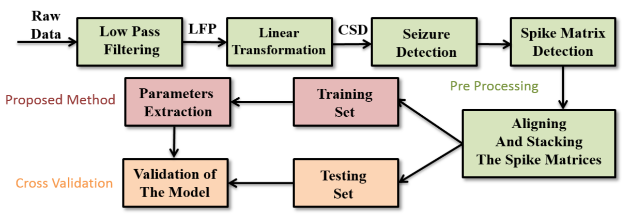

Fig. 3. Block diagram of the proposed framework. LFP and CSD respectively stand for local field potential and current source density.

3.1. Pre-Processing

The signal of each channel is filtered by a fifth-order low pass Butterworth filter with cutoff frequency equal to 100 Hz to extract the Local Field Potential (LFP) [6]. Then, the obtained signals are converted to current source density (CSD) using one linear transformation proposed in [7]. We are going to investigate seizures, so we must separate the seizures from the data. Since the amplitude of the signal changes significantly at the beginning and end of the seizures, we separate the seizures from the data by simple thresholding. Once the seizures were separated from the data, we detect the spikes using thresholding, following the proposed method in [8] and construct the spike matrices ($T = 1750$ samples).

Finally, we align the spike matrices using improved version of Woody's method proposed in [9] and stack them in 3-way data tensor $\mathcal{T}$ with dimensions $E \times T \times K$ (Fig. 2). Now, the data is prepared for extracting the states, substates and the transition probability matrix.

3.2. Proposed Method

Since we do not have any prior information about the number of states (R) and substates (N), at first we should fix them and extract the unknown parameters. we should consider that we are looking for logical results which have the best bio-physiological interpretation. So, we first extract the unknown parameters for different R and N, then we select that representation which has the best bio-physiological interpretation. We consider three assumptions in activation of states and generation of spike matrices:

1- The $(i+1)^{th}$ state is only depending on the i^{th} state (first-order Markovian model).

2- Each spike matrix ($\mathbf{X_i}$) is generated through additive white Gaussian noise channel, i.e,

$$\mathcal{H}^s_{(i)} : \quad \mathbf{X_i} = \sum_{j=1}^{N} c^{(s)}_{ij} \mathbf{a}^{(s)}_j \mathbf{b}^{(s)^T}_j + \mathbf{N_i} \tag{5}$$

where $\mathcal{H}^s_{(i)}$ ($s = 1, 2, ..., R$) means if state s were active for generating i^{th} spike matrix. $\mathbf{N_i}$ is additive white Gaussian noise with independent entries and each entry of this matrix has normal distribution with zero mean and unknown variance σ_0^2 (in fact $\Theta = \{\mathbf{A}, \mathbf{B}, \mathbf{C}, \mathbf{P}, \sigma_0^2\}$). So, we have:

$$f(\mathbf{X_i}|\mathcal{H}^s_{(i)}, \Theta) =$$

$$\left(\frac{1}{\sqrt{2\pi\sigma_0^2}}\right)^{E\times T} exp\left(-\frac{\|\mathbf{X_i} - \sum_{j=1}^{N} c^{(s)}_{ij} \mathbf{a}^{(s)}_j \mathbf{b}^{(s)^T}_j\|_F^2}{2\sigma_0^2}\right) \tag{6}$$

Considering these assumptions, we use maximum likelihood estimator (MLE) to find the set of unknown parameters, i.e.,

$$\Theta^* = \underset{\Theta}{argmax} \quad f(\mathcal{T}|\Theta) \tag{7}$$

and we have:

$$f(\mathcal{T}|\Theta) = \prod_{i=1}^{K} f(\mathbf{X_i}|\Theta) = \prod_{i=1}^{K} \sum_{s=1}^{R} p(\mathcal{H}^s_{(i)}) f(\mathbf{X_i}|\mathcal{H}^s_{(i)}, \Theta) \tag{8}$$

where $p(\mathcal{H}^s_{(i)})$ is the probability of activation of s^{th} state in generation of i^{th} spike matrix. Since $p(\mathcal{H}^s_{(i)})$ is unknown, and it operates like a mathematical expectation, we solve this optimization problem using Expectation Maximization (EM) method. The procedure of solving this optimization problem is very similar to hidden Markov models introduced in [10]. The final set of unknown parameters are extracted by performing a few iterations between E-step and M-step. The transition probability matrix ($\mathbf{P}$) is also determined in this procedure using $p(\mathcal{H}^s_{(i)})$.

Although we found the parameters, we still must determine the sequence of states and assign each spike matrix to one state. For this purpose, since we have found all characteristics of the states, the sequence of states can be easily determined using Viterbi algorithm [10]. After determination of the sequence of states, we must apply one minor modification on matrix $\mathbf{C}$. In each row of $\mathbf{C}$, we should have just non zero entries for one single state. So, regarding the obtained sequence of states by Viterbi algorithm, we keep the entries of corresponding activated state (substates) and make other entries equal to zero. Now the set of unknown parameters Θ is determined.

ISBN 978-0-9928626-7-1 © EURASIP 2017

3.3. Cross Validation

To generalize the considered model, we should check the compatibility of the proposed model and its parameters for different seizures. For this purpose, as shown in block diagram of the proposed framework (Fig. 3), we split the data into two groups of training set and testing set in order to validate the extracted results. So, following leave-one-out cross validation approach, we split $\mathcal{T}$ into $\mathcal{T}_{train}$ and $\mathcal{T}_{test}$. $\mathcal{T}_{train}$ consists of spike matrices of only one seizure and $\mathcal{T}_{test} = \{\mathcal{T}_{test}^{(1)}, \mathcal{T}_{test}^{(2)}, ..., \mathcal{T}_{test}^{(M)}\}$ consists of spike matrices of M seizures.

Training Phase: We apply the proposed method on $\mathcal{T}_{train}$ and extract the set of parameters (Θ^*). In order to show that the considered model is adapted to the training data, we should have good reconstruction using extracted parameters. It means the following normalized reconstruction error must be small:

$$\text{Error}_{train} = \frac{\|\mathcal{T}_{train} - \sum_{s=1}^{R}\sum_{j=1}^{N} \mathbf{a}_j^{(s)^*} \otimes \mathbf{b}_j^{(s)^*} \otimes \mathbf{c}_j^{(s)^*}\|_F^2}{\|\mathcal{T}_{train}\|_F^2} \tag{9}$$

In fact, we should check this error to see whether the considered model is basically correct model or not.

Testing Phase: Now, the set of model parameters $\{\mathbf{A}^*_{\mathbf{train}}, \mathbf{B}^*_{\mathbf{train}}, \mathbf{P}^*_{\mathbf{train}}, \sigma^{2*}_{0\mathbf{train}}\}$ is determined and we want to check if these parameters are adapted to unseen testing data or not. For this purpose, we perform the following steps for each $\mathcal{T}_{test}^{(m)}$ $(m = 1, 2, ..., M)$ in the testing set:

1- Since all of the parameters of model except $\mathbf{C}$ are known, we extract the sequence of states using Viterbi algorithm.

2- Once the sequence of states is determined, we project each spike matrix on the corresponding state (substates) and find $\widehat{\mathbf{C}}_{\mathbf{test}}$. Positivity of the coefficients must also be considered in this decomposition.

3- Finally, to show that the considered model is also adapted to the testing data, we must have good reconstruction using known parameters $(\mathbf{A}^*_{\mathbf{train}}, \mathbf{B}^*_{\mathbf{train}})$ and extracted parameter $(\widehat{\mathbf{C}}_{\mathbf{test}})$, i.e, the following normalized reconstruction error must be small:

$$\text{Error}_{test}^{(m)} = \frac{\|\mathcal{T}_{test}^{(m)} - \sum_{s=1}^{R}\sum_{j=1}^{N} \mathbf{a}_j^{(s)^*} \otimes \mathbf{b}_j^{(s)^*} \otimes \widehat{\mathbf{c}}_j^{(s)}\|_F^2}{\|\mathcal{T}_{test}^{(m)}\|_F^2} \tag{10}$$

In fact we should check this error to see whether the considered model is adapted to unseen data or not.

4. EXPERIMENTAL RESULTS

As discussed before, since we did not have any information about the number of states (R) and substates (N), we applied the proposed method on the data with different R and N, then we selected the best model order by considering these two points:

1- According to (9) and (10), we should have small normalized recontruction error. This condition is not enough because if we increase R and N, naturally the reconstruction error will be decreased.

2- The chosen substates must have a bio-physiological interpretation (e.g. shape of the spike must be smooth).

Considering these two points, the best results were obtained using two states ($R = 2$) and two substates ($N = 2$). The spatial topography and temporal representation of the extracted substates are shown in Fig. 4. The extracted parameters were approximately the same for all of the seizures. The obtained noise variance is $\sigma_0^{2*} \simeq 1$ and the extracted transition probability matrix is as follows:

$$\mathbf{P} = \begin{bmatrix} P(S_1|S_1) & P(S_2|S_1) \\ P(S_1|S_2) & P(S_2|S_2) \end{bmatrix} = \begin{bmatrix} 0.01 & 0.99 \\ 0.26 & 0.74 \end{bmatrix} \tag{11}$$

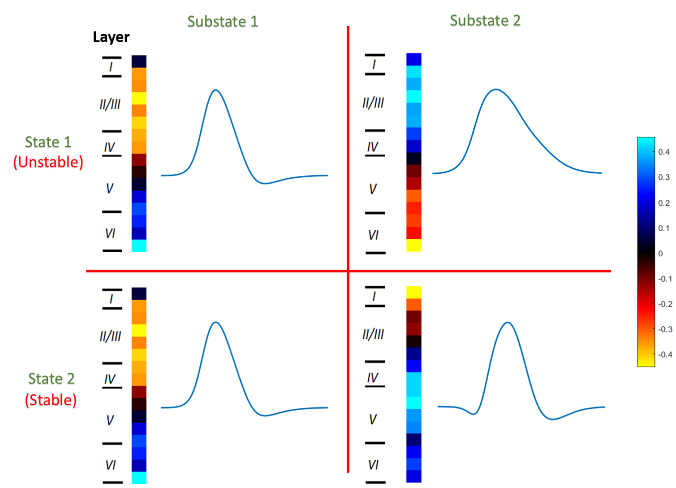

Fig. 4. Final spatial topography and temporal representation of the states and substates.

For 5 seizures from the same rat, the reconstruction errors are reported in Table 1.

Table 1. Reconstruction error for 5 different seizures from the same rat for $N = R = 2$. The seizures respectively consist of $K_1 = 87$, $K_2 = 390$, $K_3 = 94$, $K_4 = 95$ and $K_5 = 88$ spikes. The diagonal and non-diagonal entries of the table respectively show Error_{train} and Error_{test}.

Training on \Testing on	$\mathcal{T}_1$	$\mathcal{T}_2$	$\mathcal{T}_3$	$\mathcal{T}_4$	$\mathcal{T}_5$
$\mathcal{T}_1$	**0.06**	0.09	0.14	0.13	0.13
$\mathcal{T}_2$	0.08	**0.05**	0.11	0.10	0.11
$\mathcal{T}_3$	0.10	0.10	**0.07**	0.11	0.12
$\mathcal{T}_4$	0.12	0.11	0.12	**0.09**	0.10
$\mathcal{T}_5$	0.11	0.10	0.12	0.13	**0.07**

ISBN 978-0-9928626-7-1 © EURASIP 2017

These results show the accuracy and generality of the proposed model in generation of spike matrices during absence epileptic seizures. After determination of the model parameters, the sequence of states for different seizures was extracted using Viterbi algorithm. The obtained sequence for the second seizure is shown in Fig. 5.

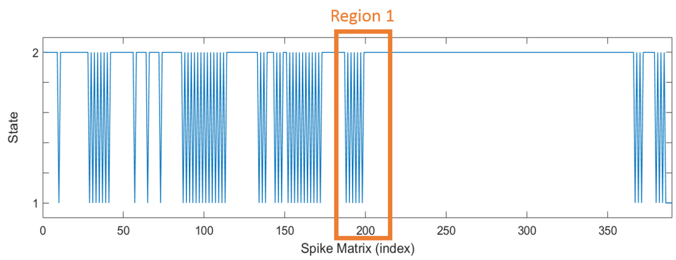

Fig. 5. Sequence of states for the second seizure.

To see behavior of the spike matrices and their corresponding states during this seizure, the spike matrices and their states during the marked region (on Fig. 5) are shown in Fig. 6.

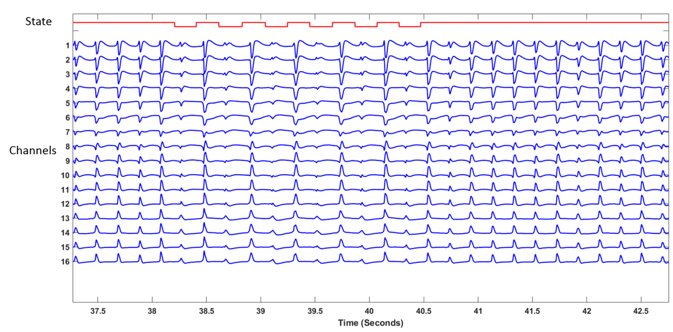

Fig. 6. Spike matrices and their states during the second seizure in region 1 (see Fig. 5).

5. CONCLUSION

Based on the obtained results, we can conclude that the first state is not at all stable because $P(S_1|S_1)$ is very small (temporal analysis). According to Fig. 4, the most interesting point is that the first substate of the both of states are the same. So we can upgrade our model. We can say there is one background activity during the seizure and there are two states (with one substate in each one) which are activated during seizures under Markovian model (temporal analysis).

In the new model, for background activity (or the first substate of previous model), there is an interaction circuit between layer 2/3 and layer 6 (based on extracted CSD in Fig. 4). In the first state, there is an interaction circuit between layer 6 and layer 2/3 while in the second state, there is an interaction circuit between layer 1 and layer 5 (spatial analysis).

6. ACKNOWLEDGMENT

This work has been partly supported by the European project 2012-ERC-AdG-320684 CHESS.

REFERENCES

[1] H. K. M. Meeren, J. P. M. Pijn, A. M. L. Coenen, and O. H. Lopes Da Silva, “Cortical Focus Drives Widespread Corticothalamic Networks During Spontaneous Absence Seizures in Rats.” *J. Neurosci*, vol. 22, pp. 1480–1495, 2002.

[2] F. Amor, S. Baillet, V. Navarro, C. Adam, J. Martinerie, and M. Le Van Quyen, “Cortical Local and Long-range Synchronization Interplay in Human Absence Seizure Initiation.” *Neuroimage*, vol. 45, no. 3, pp. 950–962, Apr 2009.

[3] F. Moeller, P. LeVan, H. Muhle, U. Stephani, F. Dubeau, M. Siniatchkin, and J. Gotman, “Dynamic analysis of absence seizures in humans: all the same but all different,” *Neuropediatrics*, vol. 41, no. 02, p. V1287, 2010.

[4] P.-O. Polack, I. Guillemain, E. Hu, C. Deransart, A. Depaulis, and S. Charpier, “Deep Layer Somatosensory Cortical Neurons Initiate Spike-and-Wave Discharges in a Genetic Model of Absence Seizures,” *J. Neurosci*, vol. 27, no. 24, pp. 6590–6599, 2007.

[5] L. Amini, C. Jutten, B. Pouyatos, A. Depaulis, and C. Roucard, “Dynamical Analysis Of Brain Seizure Activity From EEG Signals,” in *EUSIPCO 2014 Conference Proceedings*, 2014, pp. 1–5.

[6] G. T. Einevoll, C. Kayser, N. K. Logothetis, and S. Panzeri, “Modelling and analysis of local field potentials for studying the function of cortical circuits,” *Nature Reviews Neuroscience*, vol. 14, pp. 770–785, 2013.

[7] K. H. Pettersen, A. Devor, I. Ulbert, A. M. Dale, and G. T. Einevoll, “Current-source density estimation based on inversion of electrostatic forward solution: Effects of finite extent of neuronal activity and conductivity discontinuities,” *J. Neurosci.*, vol. 154, no. 12, pp. 116 – 133, 2006.

[8] R. Q. Quiroga, Z. Nadasdy, and Y. Ben-Shaul, “Unsupervised Spike Detection And Sorting With Wavelets And Superparamagnetic Clustering,” *Neural Comput*, vol. 16, no. 8, pp. 1661–1687, Aug 2004.

[9] A. Cabasson and O. Meste, “Time delay estimation: A new insight into the woody’s method,” *IEEE Signal Processing Letters*, vol. 15, pp. 573–576, 2008.

[10] L. R. Rabiner, “A tutorial on hidden markov models and selected applications in speech recognition,” *Proceedings of the IEEE*, vol. 77, no. 2, pp. 257–286, Feb 1989.