Combined EEG/MEG Source Reconstruction of Epileptic Activity using a Two-Phase Spike Clustering Approach.

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***Abstract*—In recent years, several approaches have been introduced for estimating the spike onset zone within the irritative zone in epilepsy diagnosis for presurgical planning. One important direction utilizes source analysis from combined electroencephalography (EEG) and magnetoencephalography (MEG), EMEG, leveraging the benefits from the complementary properties of the two modalities. For EMEG source reconstruction, an average across the marked spikes is often used to improve the signal-to-noise-ratio (SNR). In this contribution, we propose a two-phase clustering of interictal spikes with unsupervised learning methods, namely Self Organizing Maps (SOM) and K-means. In addition, we investigate the accuracy of combined EMEG source analysis on the sorted activity, using an individualized (with regard to both geometry and conductivity) six-compartment finite element head model with calibrated skull conductivity and white matter conductivity anisotropy. The results indicate that SOM eliminates the random variations of K-means and stabilizes the clustering efficiency. In terms of source reconstruction accuracy, this study demonstrates that the combined use of modalities reveals activity around two focal cortical dysplasias (FCDs), one in the right frontal area and one smaller in the left premotor cortex. It is worth mentioning that only EMEG could localize the left premotor FCD, which was then also found in surgery to be the responsible for triggering the epilepsy.**

***Index Terms*—EEG, MEG, Spike Clustering, Epilepsy, Multimodal Imaging, Finite Element Method**

I. Introduction

The advances in presurgical epilepsy diagnosis incorporate non-invasive electrophysiological recordings of the brain activity and analysis of neuronal spiking activity. The source analysis takes often into consideration the average across all the annotated spikes that indicate the epileptic activity from the spike onset zone. However, a smooth peak of the averaged spikes might indicate that the triggers were not set optimally in each single spike and that the underlying activity might thus not only include the spike onset zone, but also already propagated activity [1], [2]. In the context of the present study, we attempt to mitigate this by proposing a two-phase clustering of the EEG and MEG spikes and a source reconstruction of the clustered spikes upon a realistic volume conductor head model. In the following sections, we introduce the concept of clustering in source analysis of an epileptic activity.

Regarding the source analysis accuracy, it often depends on the spike selection and the timepoints relative to the spike maximum [3]. It is impossible to establish beforehand which spikes are the optimal ones for revealing the pathways of the spike onset zones. Therefore an evaluation method is required to select signal patterns and features with an epileptic predisposition. To overcome this limitation, clustering of the spikes is mainly used before source analysis in order to group patterns of similar behavior and enable better source reconstruction, especially in the multifocal epilepsy cases.

Taking into account the limitations existing in this field, our study explores the combined EMEG source reconstruction [2] for characterizing the epileptic activity, paving the way for exploiting the benefits of complementary information and avoiding the implications of invasive diagnostic techniques. Moreover, an attempt to integrate two unsupervised algorithms for spike clustering is proposed with the ultimate goal to alleviate the problem of hidden patterns. Such patterns often have low SNR and thus, they could lead in detection of an epileptic focal area that is correlated with the seizure semiology.

II. Patient and Methods

A. Patient & Ethics Statement

The patient [2] signed all the appropriate consent forms while the data was collected from both electrophysiological measurements and MR acquisitions.

B. Preprocessing of the Data

Initially, two different filters were applied, namely a 4th order Butterworth bandpass filter (passband: 1-100Hz, band of epileptic studies) and a notch filter at 50Hz and its harmonics to discard Power Line Noise. To detect artifactual activity derived by physiological sources (such as cardiac or ocular

activity), the filtered signals were decomposed using Principal and Independent Component Analysis and the components were selected to explain 95% of the variance. The extracted components were then submitted to an artifact detection plan consisting of 3 phases, the metrics calculation (kurtosis, entropy, skewness), the visual inspection and the correlation with the channels recording non brain activity. The suspicious components were rejected if they were associated with cardiac or muscular interference. Alternatively, they were corrected if corresponding to ocular contamination using the Empirical Mode Decomposition [4].

C. Clustering of Epileptic Spikes

The measurements were evaluated by three certified epileptologists who marked 30 MEG and 36 EEG interictal epileptic spikes along the 6 out of the 7 runs. For each spike, we defined 200 ms before and after the spike peak so that we could use them for feature extraction described as follows. We extracted representative features so as to be able to discriminate them or group them together in the clustering procedure. The features selected were Kurtosis, Entropy and Energy. We also performed a 4-level 2-Dimensional Wavelet decomposition with haar wavelets selecting the first 10 wavelet coefficients with the greatest deviation from Gaussian distribution as features [5]. The selection of these coefficients was achieved with Liliefors modification of Kolmogorov Smirnov Test. Turning now to the clustering of the epileptic spikes after having constructed two feature vectors (EEG (36x13) and MEG Spikes Feature Vector (30x13)), we considered a two phase approach for clustering performing first Self Organizing Map (SOM) on a 12x12 grid (chosen by Vesanto rule) and then feeding the output of SOM (assignment to the grid and the color codebook vector) to K-means trying different Ks as input (2-10). The clustering efficiency was evaluated with silhouette score which led to the optimal number of clusters for the 2 Feature vectors.

D. Source Analysis

The source reconstruction of the clustered EEG/MEG and EMEG spikes included a solution of the forward and inverse problem for a given volume conductor model of the head. To construct the head model of the patient, we first produced a segmented head model with six-compartments (scalp, skull compacta and spongiosa, cerebrospinal fluid, grey and white matter) based on the image registration and segmentation of the T1w and T2w MRI [2], [6]. The dMRI was processed for reducing the susceptibility artifacts. A geometry-adapted hexahedral head volume conductor model with white matter anisotropy was constructed, and together with the sensor positions (EEG or MEG) was used for the simulation of the electromagnetic field distribution. We used a surface source space that followed the folding of the gray matter compartment. The Finite Element Method was utilized for calculation of the EEG or MEG leadfield matrix (i.e., the forward simulations) through the SimBio toolbox[1]. We used standard conductivities for scalp, CSF and gray matter while the white matter conductivity was model based on the effective medium approach [2]. Due to the strong effect of skull conductivity on the EEG (and EMEG) source reconstruction, we calibrated the skull conductivity using the SEP/SEF data and a procedure that exploits the complementarity of both EEG and MEG [7]. The combined EMEG reconstruction was performed by solving the inverse problem using the the EEG and MEG leadfields in a concatenated form along with a covariance matrix of the signals in the window between -20 ms and -5 ms for appropriate sensor weighting [8]. We localized at the rising flank of the spike to detect the onset of the epileptic activity and to avoid propagation [1]. For inverse source analysis, we used sLORETA, which has been shown to perform well in situations in which multiple sources need to be accurately localized, which are temporally disentangled or whose leadfields are sufficiently uncorrelated [2], [9]. This approach was applied to every possible combination of the epileptic clusters. The timepoints selected for identifying the epileptic zones were set at: -23 ms, -17 ms, -13 ms, -10 ms, -8 ms, -5 ms, -3.3 ms and 0 ms. These points in time were selected accordingly in order to gain insights into propagation phenomena for epileptic activity and to compare them with the related study of [2].

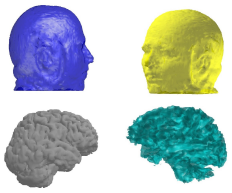


Fig. 1: **The volume conductor model of the head.** Top: scalp, bottom: grey and white matter

III. Results

A. Two-phase Clustering Approach

Having our signals cleaned from contamination, clustering of epileptic activity is performed by applying SOM for the two different feature vectors of the spikes. In Fig. 2 we show how the spikes are asssigned to the SOM grid based on the distance of the nodes' weights from the feature vector of the spikes. Two light-yellow areas could be observed in the top right corner and one in the top middle which indicates that the values of the spike feature vector are grouped into three regions which are clearly separated one to another from the red lines that traverse these groups. On the other hand, the information extracted from SOM is not easily grasped and this is one of the reasons why we decode the output through K-means. In other words we cannot clearly claim which clusters are formed from this figure even though three clusters could be identified in the three yellow areas.

Generally, SOM produces a matrix along with a color codebook vector which stores the information of the assignment . This output is fed to the K-means algorithm which was tested with the silhouette metric for various clusters ranging from 2

[1]Simbio: https://www.mrt.uni-jena.de/simbio/index.php/Main_Page

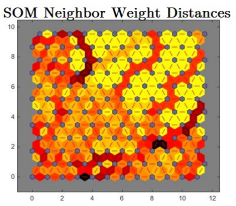


Fig. 2: **Weights Distribution for Feature Vector:** The SOM network has nodes, the SOM neurons, which are compared with the feature vectors of samples in an iterative manner and are weighted reversely proportional to the respective distances. The dark colors represent large distances, while lighter colors represent smaller distances

up to 10 but also for every cluster point for the selected K with the results summarized below.

(a) Mean silhouette value for each K

(b) Silhouette values for K = 3

Fig. 3: Evaluation of K-means clustering

Observing the evaluation of K-means, we could state that the optimal number of epileptic clusters is equal to three since it has mean value close to one but also the majority of the silhouette points of this cluster surpass the mean value. The last step before the source reconstruction is the subaveraging of the spikes which belong to the same cluster. In Figs. 4,5 the signals produced for EEG and MEG clusters are visualized.

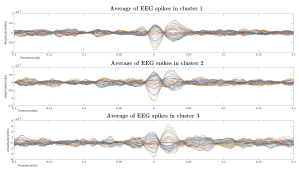


Fig. 4: **Subaverage in EEG clusters**

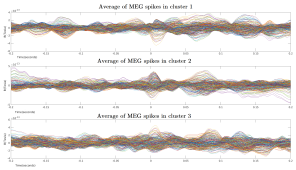


Fig. 5: **Subaverage in MEG clusters**

B. Combined EMEG Source Reconstruction

The inverse problem was solved using sLORETA for the 9 different combinations of the clusters and for each timepoint explained before. The visualization of the detected activity was depicted on the cortical surface selecting a threshold of 85% of the maximum F-value of sLORETA (red areas). Furthermore, the two FCDs were sketched in Figs. 6 and 7 at the locations where MRI Zoom Imaging lesions were marked (black spheres). In the following we outlined the output of the reconstruction for some of the clusters combination. Fig.

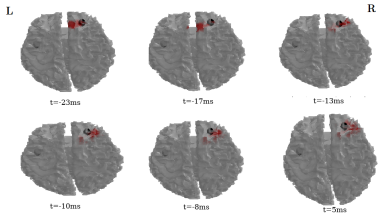
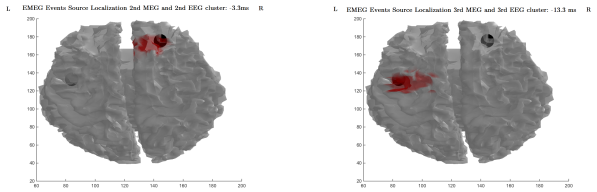


Fig. 6: sLORETA combined EMEG source reconstruction for 2nd EEG & 2nd MEG cluster (t=[-23,-17,-13,-10,-8,-5] ms)

6 shows the reconstruction of the EMEG source in the frontal region near the right FCD, visualized for each time instance prior to the peak. On the contrary, the Fig. 7 represents the results of sLORETA for other cluster combinations which were able to detect activity in the vicinity of the right frontal FCD at time-point -3.3 ms (a) and in the vicinity of the left frontocentral FCD at time-point -13 ms (b).



(a) Underlying activity close to right FCD at -3.3 ms

(b) Underlying activity close to left FCD at -13 ms

Fig. 7: sLORETA EMEG reconstruction leads to FCDs detection

IV. Discussion

The clustering approach proposed in this study demonstrates the ability to discriminate the activity derived from two different areas in separate clusters as observed in the source reconstruction results, see Figs: 6 and 7. In this way, the features extracted are being able to detect patterns that are unique for each activation. This is also shown in Fig. 2 in which the light regions shaped are separated with big distances (red lines, meaning there is variation of the values between the clusters) and thus each region represents a different behaviour-activation. Coupled with this, the single application of K-means would lead to random variations of the spike clusters and alterations in every single run, a fact that substantially affects the localization accuracy and causes misinterpretations. The average of spikes subset within a cluster increased the SNR of the spike signal and improved the localization in the vicinity of the spike onset zone, consisting of two nodes at different time-points. Finally, our method represents a new way of reconstructing epileptic activity in multifocal epilepsy cases by separating the sources from the different foci and aiding in this way to distinguish between onset and propagation nodes in the epileptic network.

Another aspect of our study improving source reconstruction accuracy is the choice to perform sub-cluster averaging at the spike cluster level. Our proposed clustering scheme can enhance the methodological steps of [2] leading to more robust clustering within a subaveraging-based source analysis of the epileptic spikes. While there is also the alternative of localizing each single spike, e.g. with the goal to get more insight on the extent of the spike onset zone, in many cases it is not recommended due to too low SNR [10], so that building clusters like presented here or using subaveraging of visually and topologically hand-chosen spikes like done in [2], [10] might in most cases be superior.

Our case study supports the studies of [1], [2], [10] in also showing that epileptic activity might in some cases be largely propagated when evaluating at the spike peak, even if SNR is optimal there. It also shows that localizations at the spike onset, even if suffering from low SNR, can still be performed successfully with appropriate averaging technologies. Considering this problem, our approach could be compared with the one by [2], [10], where a subaveraging technique enabled the sources with low SNR, underlying the left frontocentral FCD, to be identified as a separate area from the propagated one of higher SNR, underlying the right frontal FCD. Moreover, the detection of activity in the left FCD area suits the patient's seizure semiology (tingling feeling in the right anterior torso region). It also matches the results of [2] where the same patient was investigated and where the propagation of activity from the left to the right FCD from combined EMEG was also already established, with the former being detected at -23ms and the latter close to the spike peak. Specifically, our results in Fig. 7 support very well the EMEG source analysis results of [2] that guided ZOOMit MRI (0.5 mm voxel edge length) in the detection of the left frontocentral FCD. In contrast, the activity visualized in Fig. 6 in the right frontal FCD is not in accordance with the seizure semiology and presents already clearly propagated activity with a localization far from the spike onset origin. This explains our argument for choosing earlier points in time to detect the activity prior to the propagation phenomena.

We should also mention that our non-invasive EMEG approach and the localization of the spike onset zone close to the subtle left frontocentral FCD was supported by stereoEEG and the outcome of radiofrequency-thermocoagulation (RFTC) as presented in [12]. On the other side, we would also like to mention that the SOM clustering for very large input datasets could be unstable specifically in the initial stages of training and might not always be able to disentangle the inputs correctly. Last but not least, our study enables new directions to be explored in future work, such as the effective connectivity between the underlying sources to even shed more light into the propagation phenomenon.

V. Conclusions

In this study the combination of Self Organizing Maps with K-means helped us disentangling the sources associated with two FCDs from which the subtle earlier one with low SNR could be reconstructed from combined EMEG data in the left frontocentral area, fitting well with the patients semiology. The combined use of EEG and MEG in both data acquisition and source reconstruction paved the way for accurate reconstructions of the epileptogenic zone, as proved by later sEEG and the surgical procedure using radiofrequency-thermocoagulation. Our results show that combined EMEG source analysis using a calibrated realistic head model and a sophisticated spike clustering approach can be an important additional tool in presurgical epilepsy diagnosis. Hence, the main outcome of this study is a process pipeline that can be used to guide epilepsy diagnosis and treatment.

Acknowledgments

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