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Cross-bispectrum connectivity of intracranial EEG: A novel approach to seizure onset zone localization

Laura Gagliano, *Student Member, IEEE*, Alex Chang, Leila A. Shokooh, Dènahin H. Toffa, Frédéric Lesage, Mohamad Sawan, *Fellow, IEEE*, Dang K. Nguyen, and Elie Bou Assi, *Member, IEEE*

***Abstract*— Connectivity analyses of intracranial electroencephalography (iEEG) could guide surgical planning for epilepsy surgery by improving the delineation of the seizure onset zone. Traditional approaches fail to quantify important interactions between frequency components. To assess if effective connectivity based on cross-bispectrum –a measure of nonlinear multivariate cross-frequency coupling– can quantitatively identify generators of seizure activity, cross-bispectrum connectivity between channels was computed from iEEG recordings of 5 patients (34 seizures) with good postsurgical outcome. Personalized thresholds of 50% and 80% of the maximum coupling values were used to identify generating electrode channels. In all patients, outflow coupling between α (8-15 Hz) and β (16-31 Hz) frequencies identified at least one electrode inside the resected seizure onset zone. With the 50% and 80% thresholds respectively, an average of 5 (44.7%; specificity = 82.6%) and 2 (22.5%; specificity = 99.0%) resected electrodes were correctly identified. Results show promise for the automatic identification of the seizure onset zone based on cross-bispectrum connectivity analysis.**

I. Introduction

Epilepsy is one of the most prevalent neurological conditions affecting more than 50 million people worldwide [1]. It is a chronic condition characterized by the occurrence of recurrent seizures resulting from abnormal and excessive neuronal discharges in the brain [2]. Despite the availability of several antiseizure medications, there are still 25 to 30% of people with epilepsy (PWE) who live with drug-resistant uncontrolled seizures [3]. Epilepsy surgery can be performed to stop seizures or reduce their frequency in eligible PWE.

Intracranial electroencephalography (iEEG) recordings prior to epilepsy surgery are the gold standard for delineating the seizure onset zone (SOZ), the brain area responsible for seizure generation. Such recordings, often revealing complex seizure generation patterns involving several electrode contacts, are still nowadays analyzed visually (qualitatively) [4], [5]. Quantitative connectivity analyses of iEEG recordings could guide surgical planning by improving delineation of the SOZ to be resected.

Indeed, connectivity analyses can reveal ‘drivers’ of a neural network by exploiting temporal precedence among a set of signals. Our group and others have applied quantitative effective connectivity analyses such as the spectral weighted adaptive directed transfer function and phase locking value on iEEG recordings to better characterize epileptic networks involved in the generation, propagation, and modulation of seizures, with promising results [6] – [10]. While approaches based on the directed transfer function and phase locking value retain the frequency signature of a signal, they fail to quantify important interactions between frequency components of the signal.

In contrast, more informative features measuring cross-frequency coupling (CFC) allow going beyond the linear frequency information of a signal, detecting nonlinearities, deviations from normality, and quadratic phase coupling, as well as estimating time-delay between channels [11], [12]. Recently, iEEG-based investigations found a modulation of fast cortical oscillations in the gamma band (40–120 Hz) by slow cortical potentials [13]. Subsequently, our group investigated univariate bispectrum analysis, a higher-order form of CFC, for seizure prediction and reported promising performances [14] – [16]. These findings suggest that bispectrum analysis can identify epileptic activity in multichannel iEEG. An important bispectrum characteristic is that it can be extrapolated to a bivariate (i.e., cross-bispectrum) form in which coupling is measured between 2 channels. Interestingly, bivariate CFC is asymmetric and thus permits evaluating coupling direction. Connectivity based on directed cross-bispectrum of scalp EEG was recently proposed as a novel biomarker of Alzheimer's disease [17] and showed promise for screening patients with Alzheimer's disease. We hypothesized that connectivity based on cross-bispectrum of iEEG will allow to identify the generators of seizure activity resulting in a better delineation of the SOZ. In this study, we developed an effective connectivity framework based on cross-bispectrum analysis. The proposed method was evaluated on iEEG recordings of PWE previously admitted for surgical evaluation at the University of Montreal Hospital Centre (CHUM). The electrode contacts identified as those

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L.G. is with the Institute of Biomedical Engineering, Polytechnique Montréal, Montreal, QC, Canada (corresponding author phone: +1 514-890-8000; e-mail: laura.gagliano@polymtl.ca).

A.C. is with the Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada (e-mail: alex.chang@umontreal.ca).

L.A.S. was with the Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada, and is now with the Columbia University Irving Medical Center, New York, NY 10032 USA (e-mail: leila.a.shokooh@gmail.com).

D.H.T. is with the Centre de Recherche du Centre Hospitalier de l’Université de Montréal, QC, Canada (e-mail: d.h.toffa@gmail.com).

F.L. is with the Institute of Biomedical Engineering, Polytechnique Montréal, Montreal, QC, Canada (e-mail: frederic.lesage@polymtl.ca).

M.S. is with the CenBRAIN, Westlake University, Hangzhou, China (e-mail: sawan@westlake.edu.cn).

D.K.N. and E.BA. are with the Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada and the Department of Neuroscience, Université de Montréal, Montreal, QC, Canada
(D.K.N. e-mail: d.nguyen@umontreal.ca)
(E.BA. e-mail: elie.bou.assi.chum@ssss.gouv.qc.ca).

generating the seizure activity were compared with electrode contacts located inside the resected SOZ. The various steps of the proposed framework are illustrated in Fig. 1 and described in the methods section.

II. Materials and Methods

A. Database

Retrospective digital iEEG recordings acquired at the CHUM epilepsy monitoring unit (EMU) from 5 patients (2 females; mean age = 35.4 years; age range = 18 – 49 years) who underwent at least one resective surgery with good (Engel class I or II) 1-year postsurgical outcome (complete seizure freedom or significant reduction in seizure frequency) and who had at least 2 seizures during their hospitalization, were used. Recordings of 34 clinical seizures (i.e., seizures > 10 sec in duration with clinical manifestations) were segmented (10 minutes before and 10 minutes after seizure onset) and annotated (seizure onset, seizure offset, channels located within the resected volume) by an expert epileptologist. These consist of iEEG recordings sampled at 2 kHz using up to 128 subdural strip/grid and/or depth electrode contacts implanted underneath the scalp. For all patients, clinical information was retrieved from digital medical charts (e.g., seizure onset zone, 1-year postsurgical outcome). The experimental procedures involving human subjects described in this paper were approved by the CRCHUM Research Ethics Committee.

B. Preprocessing

Annotated recordings were first visually inspected to remove channels with discontinuities or noise (> 10% of recording). The first four seconds of each seizure starting from the annotated electrical seizure onset were then filtered using a 4th order backward-forward Butterworth bandpass (0.5 – 256 Hz) and notch (60 Hz) filter and then down sampled to 512 Hz to reduce the computational complexity of the cross-bispectrum plots.

C. Cross-Bispectrum

A cross-bispectrum (CBS) analysis of two temporal signals yields a 2D mapping of the level of higher-order CFC between every frequency combination present in the signals [11], [17]. For each seizure, directed cross-bispectrum plots between all available iEEG channel pairs were computed using the Higher Order Spectral Analysis Matlab Toolbox from 4-sec segments following electrical seizure onset [18]. Maximum coupling values were then extracted from the non-redundant region of the plots for each combination of the traditional EEG frequency bands of interest for epileptic activity [19]: δ (0.5 − 5Hz), θ (5 –8Hz), α (8 − 16Hz), β (16 − 32Hz) and γ (32 − 100Hz).

D. Connectivity Matrix

For each frequency band combination (25) and each seizure, maximum cross-bispectrum coupling was used to form a directed connectivity matrix where the rows and columns represent the channels. An example of a connectivity matrix is shown in Fig. 2 where each value represents the maximum directed coupling strength between channel i (rows) to channel j (columns). Total outflow of seizure activity for each channel and seizure was computed by integrating across the rows of the cross-bispectrum connectivity matrix.

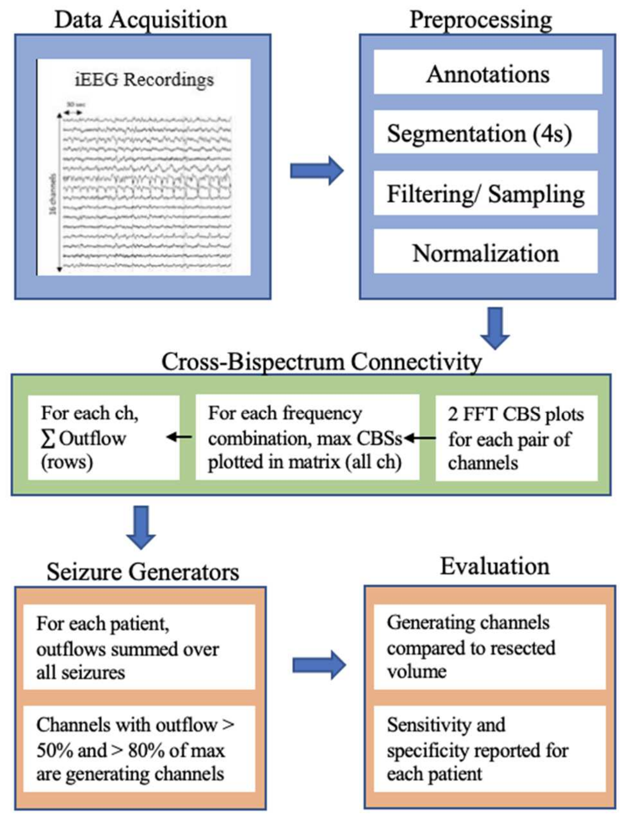

Figure 1. Block diagram of the proposed CFC-based SOZ localization framework.

E. Seizure Onset Zone Localization

In order to identify the seizure onset zone, the generating electrode contacts must be identified for each patient across all of their seizures. Therefore, for each patient, total outflow values of each channel were summed across all seizures. Examples of bar graphs showing the summed outflows for patients 1 and 3 are shown in Fig. 3. Two different patient-specific thresholds were then used to identified seizure-generating electrode contacts. In line with previous investigation, for each patient, generating electrode channels were identified as those with summed (over seizures) outflow values > 50% and > 80% of the maximum summed outflow value for that patient [10]. Selected channels using both thresholds were compared to channels within the resected volume using sensitivity and specificity. This was done for all 25 frequency band combinations.

III. Results

A. Cross-Frequency Coupling Bands

For each patient, the 25 frequency band combinations were used independently with both the 50% and 80% thresholds to identify the electrode contacts which were located within the seizure onset zone. For all patients, the connectivity outflow based on coupling between α (8-16 Hz) and β (16-32 Hz) frequency bands showed the highest performance in identifying the electrode channels inside the resected region. Since the patients all became seizure-free or had a significant reduction in their seizure frequency (good

Figure 2. Cross-bispectrum connectivity matrix for one seizure in the alpha-beta coupling bands.

surgical outcome), the resected volume can be assumed to be the true seizure-generating region (i.e., seizure onset zone).

B. Seizure Onset Zone Localization

In all 5 patients, at least one resected electrode was identified by both thresholds. Overall, the 50% threshold identified an average of 5 (44.7%) resected channels with a specificity of 82.6%. The 80% threshold correctly identified an average of 2 (22.5%) resected channels with a specificity of 99.0%. The results and clinical information per patient are listed in Table 1.

IV. Discussion

This study evaluated the possibility of automatically locating the SOZ in patients with drug-resistant epilepsy who underwent resective epilepsy surgery at the University of Montreal Hospital Centre. A novel connectivity approach was proposed based on cross-bispectrum analysis of iEEG

TABLE I.
Patient Information and Seizure Onset Zone Localization Results

Patient #	Sex, Age in years	# Sz.	# Res. Chan./ Tot. Chan.	SOZ Loc.	50% (Sens, Spec)	80% (Sens, Spec)
1	M, 49	12	5/97	R-P	40%, 100%	20%, 100%
2	F, 29	8	20/61	L-FTI	80%, 20%	20%, 95%
3	F, 18	4	6/105	L-IO	67%, 96%	50%, 100%
4	M, 35	7	7/91	R-F	29%, 98%	14%, 100%
5	M, 46	3	12/88	L-IO	8%, 100%	8%, 100%

Sz: Analyzed clinical seizures, Res. Chan.: Number of resected channels over total analyzed implanted channel. SOZ Loc.: SOZ location are noted as L (left) or R (right) followed by the corresponding lobe. P: Parietal, FTI: Fronto-temporo-insular, IO: Insular-opercular, F: Frontal.

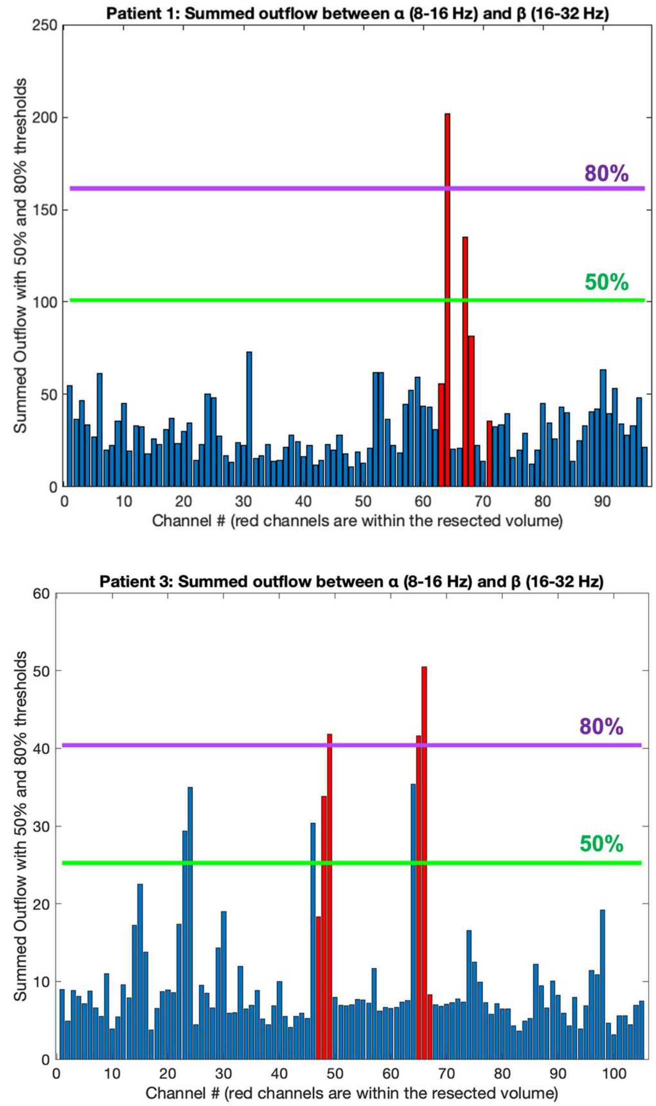

Figure 3. Summed outflow plots for all channels. Channels highlighted in red are within the resected volume.

recordings and tested on a total of 34 seizures from 5 patients who had good postsurgical outcome after 1-year follow-up. Connectivity matrices for each seizure were computed from multivariate CBS analysis which measures higher-order CFC between all electrode channel pairs. For each patient, electrode channels which had the highest generating coupling values towards other channels during the first 4 seconds of seizure generation were identified using personalized thresholds as suspected seizure generating regions. When compared to the resected volume (i.e., the true seizure onset zone which when resected resulted in seizure freedom), both thresholds were successful at identifying electrodes located within the SOZ in all 5 patients with high specificity (82.6% and 99.0%). These results suggest that the proposed technique could guide surgical planning in patients with refractory epilepsy. While the sensitivity of the method remains relatively low (44.7% and 22.5%), combining these results with other evaluation techniques such as visual inspection of noninvasive imaging (e.g., magnetic resonance imaging) to define the extent of the SOZ could result in improved sensitivity. Another, albeit less probable, reason for the low sensitivity would be that the algorithm identifies the true generating region with higher specificity and that perhaps secondary generating tissue surrounding the SOZ was resected. It should also be noted that despite efforts to accurately delineate the SOZ during pre-surgical evaluation [7] – [10], no quantitative method exists which can delineate the extent of the region which is generating seizures [4]. In addition, previous studies have focused primarily on small cohorts of patients with one type of epilepsy (e.g., insular, mesial-temporal, neocortical). In this proof-of-concept study, the proposed cross-bispectrum connectivity technique was successful at identifying the seizure generating region for patients with different epilepsy types which suggests that it could potentially be used as a pre-screening technique for all patients regardless of the location of their epileptogenic brain region.

While these findings are promising, some limitations and avenues of improvement should be considered in prospective studies. First, the study was conducted on a small cohort of patients for whom surgery was successful at stopping or significantly reducing seizures. Evaluating the performance on a larger cohort of patients with both good and bad surgical outcome would be important to better understand and predict surgical outcome based on iEEG evaluation. In addition, patients admitted for invasive pre-surgical evaluation are implanted with different types of electrodes including grid and strip subdural contacts and/or stereotactically inserted depth electrodes which record EEG from deeper brain structures [4]. Comparing the dynamics of seizure and non-seizure connectivity patterns (i.e., outflow and inflow values) between the cortical (strip and grid contacts) and stereotactic (depth electrodes) contacts could provide additional insights into the localization of the SOZ. Furthermore, since seizures are relatively rare and short events, evaluating cross-bispectrum connectivity patterns during non-seizure wake and sleep periods could provide additional information about differences between physiological and epileptic network activity.

V. Conclusion

We propose a novel seizure onset zone localization technique based on cross-bispectrum directed connectivity of human iEEG. Results show promise for automatic identification of the seizure onset zone with high specificity when compared to the resected volume in patients with good postsurgical outcomes. Findings should be confirmed in large patient cohorts. Perspective studies include comparing different electrode types and non-seizure network analysis.

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