An Integrative Strategy for Solving the EEG Inverse Problem and the Estimation of Brain Effective Connectivity in Epilepsy. A Proof-of-Concept Study.

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***Abstract*—This study presents an integrative strategy for simultaneously localizing brain sources and inferring effective connectivity. The proposed approach leverages the model underlying the events of interest as a regularizer in the electroencephalographic inverse problem. The effectiveness of this strategy is confirmed using realistic simulated high resolution electroencephalographic signals in the context of epilepsy, and compared to the conventional sequential strategy, where connectivity estimation is performed after solving the electroencephalographic inverse problem.**

Keywords- Effective connectivity; inverse problem; optimization; EEG; epilepsy.

I. INTRODUCTION

Inferring effective connectivity among brain regions from surface High Resolution (HR)-ElectroEncephaloGraphic (EEG) recordings is typically performed through a sequential process involving: (i) preprocessing EEG data to remove artifacts and detect Events of Interest (EIs); (ii) solving the EEG inverse problem to pinpoint the spatial location of brain regions responsible for the observed EIs and reconstruct their neural activities; and (iii) inferring effective connectivity among these identified regions based on their reconstructed neural activities. However, this sequential approach faces two major limitations: (i) the error propagation phenomenon across the successive steps, and (ii) the absence of the optimal pairing of source localization methods and effective connectivity measures. Furthermore, even if such an optimal pairing exists, it is highly dependent on the specific application. To address these limitations, a Proof-of-Concept (PoC) study of an integrative strategy that combines both source localization and brain effective connectivity inference steps into a single one is presented here. Note that a similar strategy was recently proposed in [1] but within the context of functional connectivity. The proposed integrative strategy is evaluated here in the context of drug-resistant epilepsy [2], where identifying brain connectivity is essential for localizing regions responsible for seizure initiation and propagation. This information is valuable for surgical treatments aimed at reducing or eliminating seizures. The performance of the proposed integrative strategy is tested using realistic simulated HR-EEG signals and compared to the conventional sequential strategy, where brain connectivity is determined after solving the EEG inverse problem. The remainder of this paper is organized as follows: Section II details the proposed integrative strategy, including the EEG observation model and optimization framework. Section III presents simulation results, comparing its performance to the conventional sequential method. Finally, Section IV summarizes the findings, discusses implications for epilepsy research, and suggests future directions.

II. TOWARDS AN INTEGRATIVE STRATEGY

This section presents the concept of the proposed integrative strategy, emphasizing the key idea of combining the brain source localization problem with brain effective connectivity inference.

A. EEG observation model

From now on, HR-EEG recordings are assumed to be preprocessed, with artifacts removed and EOIs (pre-ictal epileptic spikes) detected. Assume that the brain is divided into P regions, each consisting of synchronized dipoles in the source space. Then, the brain electrical activity over T time points, observed by N scalp EEG sensors, follows the linear model:

$$\boldsymbol{X} = \boldsymbol{G}\boldsymbol{Y} + \boldsymbol{X}_b$$

where $\boldsymbol{X} \in \mathbb{R}^{N \times T}$ is the spatio-temporal observation matrix, $\boldsymbol{G} \in \mathbb{R}^{N \times P}$ is the lead field matrix, which is a known matrix encoding the transfer medium between the cortical surface (source space) and the scalp (observation space), $\boldsymbol{Y} \in \mathbb{R}^{P \times T}$ collects the neural activities of epileptic regions, and $\boldsymbol{X}_b \in \mathbb{R}^{N \times T}$ corresponds to background brain activity.

B. EEG inverse problem

The EEG inverse problem involves estimating the positions of brain sources underlying the EIs ($e.g.$, pre-ictal epileptic spikes) and reconstructing their corresponding electrical activities. To this end, the following optimization problem is to be solved:

$$\underset{\boldsymbol{Y}}{\text{Minimize}}\ ||\boldsymbol{X} - \boldsymbol{G}\boldsymbol{Y}||_{\mathrm{F}}^2 + \sum_{c=1}^{C} \lambda_c f_c(\boldsymbol{Y}) \tag{1}$$

Here, f_c represents the c-th regularization term, encoding prior information about the latent source matrix $\boldsymbol{Y}$, $\lambda_c \in \mathbb{R}_+^*$ is the associated penalty parameter, and $\|.\|_{\mathrm{F}}$ is the Frobenius norm. For example, in the Weighted Minimum Norm Estimate (wMNE) approach [3][4], widely used to solve the EEG inverse problem for its simplicity and efficiency, the regularization term is $f_1(\boldsymbol{Y}) = \|\boldsymbol{B}\boldsymbol{Y}\|_{\mathrm{F}}^2$, where $\boldsymbol{B}$ is a weighting matrix with diagonal entries $B_{p,p} = \|\boldsymbol{g}_p\|_2^{-1}$. Here, $\boldsymbol{g}_p$ denotes the p-th column of $\boldsymbol{G} \in \mathbb{R}^{N \times P}$. The role of $\boldsymbol{B}$ is to compensate for the bias in the estimation of deep brain sources.

C. The proposed integrative strategy

As previously mentioned, the proposed integrative strategy unifies source localization and brain effective connectivity inference into a single step. In the context of epilepsy, pre-ictal epileptic spikes, events occurring just before seizure onset, offer valuable insights into the brain regions initiating seizures. The key idea of the integrative strategy is to incorporate the mathematical model underlying the EOIs as an additional regularization term in the EEG inverse problem. In this PoC study, a MultiVariate AutoRegressive (MVAR) model is employed to describe the pre-ictal epileptic spikes. Albeit suboptimal as neural activities exhibit rather nonlinear interactions, the MVAR model is widely adopted in effective connectivity measures ($e.g.$, Granger index [5][6]). An MVAR modeling of $\boldsymbol{Y}$ is given by:

$$\boldsymbol{Y} = \sum_{l=1}^{L} \boldsymbol{\Theta}^l \boldsymbol{Y}^l + \boldsymbol{W} \tag{2}$$

where $\boldsymbol{\Theta}^l \in \mathbb{R}^{P \times P}$ denotes the matrix of model coefficients, $\boldsymbol{Y}^l \in \mathbb{R}^{P \times T}$ is a delayed version of $\boldsymbol{Y} \in \mathbb{R}^{P \times T}$ associated with the l-th time lag, and $\boldsymbol{W}$ accounts for the model residual, where the (i, j)-th entry of $\boldsymbol{W}$ verifies $W_{i,j} \sim \mathcal{N}(0, \sigma)$. The elements of the L matrices $\boldsymbol{\Theta}^l$ reflect, to a large extent, causal effects that those delayed signals have on the signal they are constituting. Thus, estimating these coefficients will lead to infer the causal relationships among different epileptic sources. Now, by considering the well-known wMNE algorithm for source localization and the MVAR model as a model underlying the observed pre-ictal epileptic spikes, the proposed integrative strategy consists in solving the following optimization problem:

$$\underset{\boldsymbol{Y}, \{\boldsymbol{Y}^l\}_{1 \le l \le L}, \{\boldsymbol{\Theta}^l\}_{1 \le l \le L}}{\text{Minimize}} \; ||\boldsymbol{X} - \boldsymbol{G}\boldsymbol{Y}||_F^2 + \gamma ||\boldsymbol{Y} - \sum_{l=1}^{L} \boldsymbol{\Theta}^l \boldsymbol{Y}^l||_F^2$$
$$+ \lambda ||\boldsymbol{B}\boldsymbol{Y}||_F^2 + \xi \sum_{l=1}^{L} ||\boldsymbol{B}\boldsymbol{Y}^l||_F^2 + \beta \sum_{l=1}^{L} ||\boldsymbol{\Theta}^l||_1 \tag{3}$$

where γ, λ, ξ, and β are hyperparameters optimized using a grid search strategy to achieve the best results. The inclusion of the L_1-norm term emphasizes the selection of only the most significant connections among brain regions. Solving the above optimization problem is performed by minimizing instead its associated augmented Lagrangian function, where the Proximal Alternating Linearized Minimization (PALM) algorithm [7] is used as a solver.

III. Numerical Results

To assess the feasibility and performance of the proposed integrative strategy, a realistic simulated 257-channel HR-EEG dataset of 60 seconds with a sampling frequency of 1024 Hz was generated to model a focal epileptic seizure. In this simulation, the right frontal pole (r-FP) region was defined as the seizure onset zone, while the right middle temporal gyrus (r-MT) region represented the propagation zone, establishing a causal effect from r-FP to r-MT. The dataset was created using the "Coalia" software [8], which incorporates realistic head models. The brain was parcellated into 66 regions based on the Desikan-Killiany atlas [9]. As far as the regularization parameters γ, λ, ξ and β, were concerned, they were set to $0.5, 23, 1$ and 1, respectively. The proposed strategy was compared to the traditional sequential approach, where the wMNE algorithm was employed to solve the EEG inverse problem, followed by Granger causality [5] to estimate effective connectivity among the localized neural sources based on their reconstructed activities. For both strategies, the study was conducted over a time period of 6 seconds right before the onset of the epileptic seizure. In terms of source localization, the proposed integrative strategy demonstrated clear superiority over the sequential strategy based on the wMNE algorithm [3], [4], as illustrated in Figure 1.

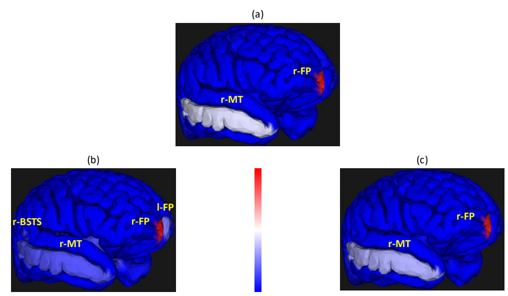

Figure 1. Epileptic source localization. (a) ground truth, (b) sequential strategy with wMNE, (c) proposed integrative strategy.

Specifically, in addition to correctly localizing the brain regions associated with the seizure (r-FP for the onset region and r-MT for the propagation region), the sequential strategy where the wMNE algorithm is used to solve the EEG inverse problem, followed by the Granger causality measure for inferring effective connectivity, also identified other spurious brain regions, such as the left frontal pole (l-FP) region as an onset region and the right banks of the superior temporal sulcus (r-BSTS) as a propagation region. In contrast, the proposed integrative strategy did not identify any spurious regions, providing a more accurate and reliable result. Both strategies successfully identified the correct causal effect between the two brain regions, r-FP and r-MT. This effect is highlighted in bold, as shown in Table I for the conventional sequential strategy and Table II for the proposed integrative strategy, where the interactions are ranked from highest (leftmost) to lowest (rightmost).

TABLE I
Estimated effective connectivity using the sequential strategy.

Interaction 1	Interaction 2	Interaction 3	Interaction 4
l-FP $\to$ r-MT	**r-FP $\to$ r-MT**	r-FP $\to$ r-BSTS	l-FP $\to$ r-BSTS

TABLE II
ESTIMATED EFFECTIVE CONNECTIVITY USING THE INTEGRATIVE STRATEGY.

Lag	Interaction 1	Interaction 2
3	**r-FP → r-MT**	×
5	**r-FP → r-MT**	×
6	×	**r-FP → r-MT**
Average	**r-FP → r-MT**	

It is noteworthy that the connectivity matrices obtained for each strategy were thresholded such that all values in the matrices that were less than 90% of the largest value were set to zero. This thresholding step ensured that only the most significant connectivity relationships were retained for further analysis. However, compared to the sequential strategy, the proposed integrative strategy offers the possibility for a dynamic analysis of the effective connectivity over the different time lags. For some time lags ($i.e.$, $l \in \{3, 5\}$), the highest estimated causal interaction ($i.e.$, Interaction 1), corresponds to the true effective connectivity while for other time lags ($i.e.$, $l = 6$), it stands for the second most important connectivity value ($i.e.$, Interaction 2). Thus, contrary to the sequential strategy, where the true causal effect is ranked as the second most important connectivity pattern (see Table I), the integrative strategy offers an average effective connectivity over the considered time lags, where the true effective connectivity accounts for the most significant connectivity pattern (see Table II). It is noteworthy that Table II highlights only the interactions among the regions of interest (i.e., r-FP and r-MT).

IV. CONCLUSION AND FUTURE WORK

In this communication a PoC study of an integrative strategy for simultaneous brain source localization and effective connectivity estimation was proposed. The strategy relied mainly on the model underlying the EIs as an additional regularization term in the source localization problem. This strategy was evaluated in the context of focal epilepsy with pre-ictal epileptic spikes as EIs that were assumed to follow an MVAR model. The effectiveness of this integrative solution was confirmed using realistic surface HR-EEG recordings compared with the conventional sequential strategy, where wMNE was considered for source localization and Granger causality for effective connectivity estimation. Future work will focus on evaluating the proposed strategy in more complex scenarios, such as incorporating multiple epileptic sources and evaluating its performance on real HR-EEG data from multiple epileptic patients.

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