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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Epilepsy

Epilepsy: A brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures.

Epileptic seizure: induced by abnormal excessive or synchronous neural activity in the brain

□ Around 50 million people worldwide have epilepsy



globometer.com/maladies-epilepsie.php who.int/news-room/fact-sheets/detail/epilepsy









Epilepsy









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Epilepsy









Epilepsy



Vagus Nerve Stimulation (VNS)



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N. Child, M. Stead, E. C. Wirrell et al., Chronic subthreshold subdural cortical stimulation for the treatment of focal epilepsy originating from eloquent cortex, Epilepsia, vol. 55, no. 3, pp. 18-21, 2014.







Ultimate goal

□ Inferring brain epileptic network underlying the initiation and/or the propagation of epileptic seizure using surface Electroencephalographic (EEG) signals.



A graph $\mathcal{G}(\mathbb{V}, \mathbb{E}, A)$ is a set \mathbb{V} of vertices linked using a set \mathbb{E} of edges with weights defined in the adjacency matrix A









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Brain connectivity



Structural

- Structural connectivity also called
 "anatomical connectivity"
- A network of physical or structural links (synaptic connections) between pairs of brain regions







Brain connectivity



- Statistical dependencies among remote neurophysiological events
- Temporal correlation among the activities of neural assemblies
- Undirected graph
- Connectivity matrix (symmetric)







Brain connectivity



- Completes the structural and functional connectivities
- Causal influences between different neurons or neuronal populations
- Directed graph
- Connectivity matrix (asymmetric)







Conventional strategy







Brain source localization

- Observations model: $X = GY + X_{art} + X_{inst}$
 - $X \in \mathbb{R}^{N \times T}$: observations
 - $\boldsymbol{G} \in \mathbb{R}^{N \times D}$: Leadfield matrix
 - $Y \in \mathbb{R}^{D \times T}$: source matrix
 - $X_{art} \in \mathbb{R}^{N \times T}$: contributions of physiological artefacts
 - $X_{inst} \in \mathbb{R}^{N \times T}$: instrumental noise



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EEG





N: Number of sensors

D : Number de dipoles

T: Number of temporal samples





Brain source localization

- Observations model: $X = GY + X_{art} + X_{inst}$
 - $X \in \mathbb{R}^{N \times T}$: observations
 - $\boldsymbol{G} \in \mathbb{R}^{N \times D}$: Leadfield matrix
 - $Y \in \mathbb{R}^{D \times T}$: source matrix
 - $X_{art} \in \mathbb{R}^{N \times T}$: contributions of physiological artefacts
 - $X_{inst} \in \mathbb{R}^{N \times T}$: instrumental noise
- Denoised model:

 $X_d = GY = GY^{(e)} + GY^{(b)}$ $= GY^{(e)} + X^{(b)}$

- $X_d \in \mathbb{R}^{N \times T}$: denoised EEG signals
- $Y^{(e)} \in \mathbb{R}^{D \times T}$: epileptic activities
- $Y^{(b)} \in \mathbb{R}^{D \times T}$: background activity
- $X^{(b)} \in \mathbb{R}^{N \times T}$: noise related to the denoised observations

N: Number of sensors

- D: Number de dipoles
- T: Number of temporal samples



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EEG









□ Brain source localization

- Locating epileptic sources on the cortical surface
- Reconstruction of neural activity of each localized sources

$$\mathbf{Y}^{(e)^*} = \underset{\mathbf{Y}^{(e)}}{\operatorname{argmin}} \left\| \mathbf{X}_d - \mathbf{G} \mathbf{Y}^{(e)} \right\|_{\mathrm{F}}^2$$



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EEG











Brain source localization

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EEG



Inverse problem









Brain source localization

- Locating epileptic sources on the cortical surface
- Reconstruction of neural activity of each localized sources



 $\lambda_c : c^{\text{ème}}$ regularization parameter $f_c(\mathbf{Y}^{(e)}) : c^{\text{th}}$ regularization term $\|.\|_{\text{F}}$: Frobenius norm



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EEG



Inverse problem







Brain source localization

- Locating epileptic sources on the cortical surface
- Reconstruction of neural activity of each localized sources



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EEG





 $\lambda_c : c^{\text{ème}}$ regularization parameter $f_c(\mathbf{Y}^{(e)}) : c^{\text{th}}$ regularization term $\|.\|_{\mathbf{F}}$: Frobenius norm







Gamma Effective connectivity inference

- Data-driven techniques
 - Directed coherence
 - Mutual information
 - Transfer entropy
 - Granger measure
 - Directed transfer function (DTF)
 - Partial directed coherence (PDC)

- Model-based techniques
 - Structural equation modeling (SEM)
 - Dynamic causal modeling (DCM)









Conventional strategy

□ Limitations



Network inference quality is subject to the source localization's one



Lack of the best combination brain source localization method - brain connectivity measure









Motivation









Motivation









□ Physiological assumptions:

- Epileptic sources of minimal spatial energy (ex. MNE, wMNE algorithms)
- Synchronized neural activities:
 - ✓ among current dipoles inside each extended epileptic sources

M. S. Hämäläinen, R. J. Ilmoneimi, Interpreting measured magnetic fields of the brain : minimum norm estimates of current distributions, Technical Report TKK-F-A559, Helsinki University of Technology, 1984. R. D. Pascual-Marqui, C. M. Michel, D. Lehmann, Low resolution electromagnetic tomography: A new method for localizing electrical activity in the brain, International Journal of Psychophysiology, vol. 18, no. 1, pp. 49-65, 1994.



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MVAR modelling of the pre-ictal epileptic spikes

$$\boldsymbol{Y}^{(\boldsymbol{e})} = \sum_{l=1}^{L} \boldsymbol{\Theta}^{l} \boldsymbol{Y}_{l}^{(\boldsymbol{e})} + \boldsymbol{W}$$

 $\lambda_c, \beta > 0$: Régularisation parameters ($1 \le c \le C$)

- $\Theta \in \mathbb{R}^{D \times D}$: Matrix of model parameters
- $Y^{(e)} \in \mathbb{R}^{D \times T}$: Spatio-temporal depth source matrix
- $Y_{l}^{(e)} \in \mathbb{R}^{D \times T}$: Delayed spatio-temporal depth source matrix
- $\Theta^{l} \in \mathbb{R}^{D \times D}$: Matrix of model parameters associated with l^{th} time lag

 $\boldsymbol{W} \in \mathbb{R}^{D \times T}$: Model error









MVAR model for each current electrical dipole Computational burden









MVAR model for each current electrical dipole Computational burden

Solution: Region-wise MVAR modelling









□ Dipole-wise → Region-wise manner

- ✓ Reformulating the problem at the level of brain regions
- ✓ Dipoles belonging to the same region \rightarrow Region's steering vector as a

linear combination of dipoles' steering vectors

 $\begin{aligned} \boldsymbol{X}_{d} &= \overline{\boldsymbol{G}} \overline{\boldsymbol{Y}}^{(e)} + \overline{\boldsymbol{G}} \overline{\boldsymbol{Y}}^{(b)} \\ &= \overline{\boldsymbol{G}} \overline{\boldsymbol{Y}}^{(e)} + \overline{\boldsymbol{X}}^{(b)} \end{aligned}$

$$\begin{split} N &: \text{Number of sensors} \\ H &: \text{Number of regions} \\ T &: \text{Number of time samples} \\ \overline{\pmb{G}} &= [\overline{\pmb{g}}_1, \cdots, \overline{\pmb{g}}_H] \in \mathbb{R}^{N \times H} : \text{Region-wise Leadfield matrix} \\ \overline{\pmb{Y}}^{(e)} \in \mathbb{R}^{H \times T} : \text{Region-wise sources matrix} \end{split}$$









□ Dipole-wise → Region-wise manner

- \checkmark Reformulating the problem at the level of brain regions.
- ✓ Dipoles belonging to the same region \rightarrow Region's steering vector as a

linear combination of dipoles' steering vectors

 $X_{d} = \overline{G}\overline{Y}^{(e)} + \overline{G}\overline{Y}^{(b)}$ $= \overline{G}\overline{Y}^{(e)} + \overline{X}^{(b)}$

N : Number of sensorsH : Number of regionsT : Number of time samples

 $\overline{\mathbf{G}} = [\overline{\mathbf{g}}_1, \cdots, \overline{\mathbf{g}}_H] \in \mathbb{R}^{N \times H}$: Region-wise Leadfield matrix

 $\overline{\mathbf{Y}}^{(e)} \in \mathbb{R}^{H \times T}$: Region-wise sources matrix









Problem formulation

$$\begin{split} \overline{Y}^{(e)*}, \left\{\overline{Y}_{l}^{(e)}\right\}_{1 \leq l \leq L}, \left\{\overline{\Theta}^{l*}\right\}_{1 \leq l \leq L}, \\ &= \operatorname{argmin}_{\overline{Y}^{(e)}, \left\{\overline{Y}_{l}^{(e)}\right\}_{1 \leq l \leq L}, \left\{\overline{\Theta}^{l}\right\}_{1 \leq l \leq L}} \left\|X_{d} - \overline{G}\overline{Y}_{l}^{(e)}\right\|_{F}^{2} + \lambda \left\|\overline{B}\overline{Y}^{(e)}\right\|_{F}^{2} + \xi \sum_{l=1}^{L} \left\|\overline{B}\overline{Y}_{l}^{(e)}\right\|_{F}^{2} + \gamma \left\|\overline{Y}^{(e)} - \sum_{l=1}^{L} \overline{\Theta}^{l}\overline{Y}_{l}^{(e)}\right\|_{F}^{2} + \beta \sum_{l=1}^{L} \left\|\overline{\Theta}^{l}\right\|_{1} \\ &\quad \forall l \in \{1, \dots, L\} \end{split}$$

Weighting matrix:
$$\overline{B} = \begin{pmatrix} \frac{1}{\|\overline{g}_1\|_2} & 0 \\ & \ddots & \\ 0 & & \frac{1}{\|\overline{g}_p\|_2} \end{pmatrix}$$







Problem formulation

$$\overline{Y}^{(e)*}, \left\{\overline{Y}_{l}^{(e)}\right\}_{1 \leq l \leq L}, \left\{\overline{\Theta}^{l*}\right\}_{1 \leq l \leq L}, \left\{\overline{\Theta}^{l*}\right\}_{1 \leq l \leq L}, \left\|X_{d} - \overline{G}\overline{Y}_{l}^{(e)}\right\|_{F}^{2} + \lambda \|\overline{B}\overline{Y}^{(e)}\|_{F}^{2} + \xi \sum_{l=1}^{L} \|\overline{B}\overline{Y}_{l}^{(e)}\|_{F}^{2} + \gamma \left\|\overline{Y}^{(e)} - \sum_{l=1}^{L} \overline{\Theta}^{l}\overline{Y}_{l}^{(e)}\right\|_{F}^{2} + \beta \sum_{l=1}^{L} \|\overline{\Theta}^{l}\|_{1} +$$

- Solution within the framework of proximal optimisation
 - > Iterative approach
 - > The PALM method as a solver

 $\lambda, \gamma, \beta > 0$: Regularization parameters $\overline{\mathbf{G}} = [\overline{\mathbf{g}}_1, \cdots, \overline{\mathbf{g}}_H] \in \mathbb{R}^{N \times H}$: Region-wise Leadfield matrix $\overline{\mathbf{Y}}^l \in \mathbb{R}^{D \times T}$: Delayed version of $\overline{\mathbf{Y}}$ $\overline{\mathbf{\Theta}}^l \in \mathbb{R}^{D \times D}$: region-wise connectivity matrix related to the l^{th} time lag MVAR : MultiVariate AutoregRessive L: MVAR model order









- Desikan-Killiany atlas (66 regions)
- Two connected epileptic regions with information flow ''r-FP'' → ''r-MT''
- 257 High-Resolution electroencephalography recordings, 60 sec length
- Samplng frequency 1024 Hz
- Comparison with the conventional strategy :
 - wMNE method for source localization
 - Granger causality for effective connectivity inference







Ground truth: Pre-ictal phase









Brain source localization



r-: right hemisphere l-: left hemisphere r-FP : right Frontal Pole I-FP: left Frontal Pole

r-MT : right Middle Temporal







□ Brain source localization – reconstructed neural activities



r-BSTS : right Banks of the Superior Temporal Sulcus

l-BSTS : left Banks of the Superior Temporal Sulcus

wMNE: weighted Minimum Norm Estimate







Effective connectivity inference: Conventional strategy



Conventional strategy (90% thresholding)





Ground truth

Interaction 1	Interaction 2	Interaction 3	Interaction 4
l-FP → r-MT	r-FP → r-MT	r-FP → r-BSTS	l-FP → r-BSTS

Information flow (90% thresholding)

- r- : right hemisphere l- : left hemisphere
- r-FP : right Frontal Pole
- l-FP : left Frontal Pole
- r-MT : right Middle Temporal
- r-BSTS : right Banks of the Superior Temporal Sulcus l-BSTS : left Banks of the Superior Temporal Sulcus wMNE : weighted Minimum Norm Estimate







 Θ^l

 $r-LOF \rightarrow I-FP$

 $I-SP \rightarrow r-CMF$

 1^{st} time lag





Integrative strategy (90% thresholding)



Ground truth

r- : right hemisphere I- : left hemisphere

LOF : Lateral OrbitoFrontal gyrus FP : Frontal Pole SP : Superior Parietal gyrus CMF : Caudal Middle Frontal gyrus MT : Middle Temporal gyrus SF : Superior Frontal gyrus CUN : CUNeus PREC : PRECentral gyrus PSTC : PoSTCentral gyrus ST : Superior Temporal gyrus PCAL : Pericalcarine Cortex 21







st

 Θ^l

 $r-LOF \rightarrow I-FP$

2nd time lag





Integrative strategy (90% thresholding)



Ground truth

r- : right hemisphere I- : left hemisphere

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LOF : Lateral OrbitoFrontal gyrus
FP : Frontal Pole
SP : Superior Parietal gyrus
CMF : Caudal Middle Frontal gyrus
MT : Middle Temporal gyrus
SF : Superior Frontal gyrus
CUN : CUNeus
PREC : PRECentral gyrus
PSTC : PoSTCentral gyrus
ST : Superior Temporal gyrus
PCAL : Pericalcarine Cortex
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FP : Frontal Pole SP : Superior Parietal gyrus CMF : Caudal Middle Frontal gyrus MT : Middle Temporal gyrus SF : Superior Frontal gyrus CUN : CUNeus PREC : PRECentral gyrus PSTC : PoSTCentral gyrus ST : Superior Temporal gyrus PCAL : Pericalcarine Cortex



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Take-home points

- A feasibility of an integrative strategy for brain source localization & effective connectivity inference
- Physiological assumptions
- MVAR modelling of pre-ictal epileptic spikes as a regularizer
- More focal brain source localization
- Inference and dynamic analysis of brain effective connectivity

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