Presentation of two Brainstorm plugins: (1) Brain Entropy in space and time (BEst) for Maximum Entropy on the Mean source imaging (2) NIRSTORM plugin dedicated for fNIRS analysis

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Christophe Grova

Physics Dpt, PERFORM centre, Concordia University Biomedical Engineering Dpt, McGill University Montreal Neurological Institute Centre de Recherches Mathématiques, Montréal Canada

christophe.grova@concordia.ca

Centre PERFORM Centre

Institut-Hônital neurologique de Montréal **Montreal Neurological Institute-Hospital**

Part 1: EEG/MEG source imaging using Maximum Entropy on the Mean (MEM)

http://neuroimage.usc.edu/brainstorm/Tutorials/TutBEst

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EEG recording of epileptic discharges

Intracranial EEG

Tao et al Clin Neurophys 2007

Should we have spatially extended generators to detect epileptic discharges from the scalp. What is the true underlying extent ? *Spike generators of 4 to 8 cm² can generate scalp EEG signals with good SNR A minimum of 3-4 cm²can generate MEG signals with good SNR (Oishi et al Epilepsia 2002)*

An ECoG grid is not covering the whole underlying surface

An ECoG grid is influencing local signal to noise ratio (SNR)

Von Ellenrieder Neuroimage 2014

Courtesy of T. Hedrich

EEG/MEG source imaging and estimation of the underlying spatial extent of the generators

EEG/MEG Source localization using Maximum Entropy on the Mean (MEM)

Recover the spatial extent of the source with good accuracy

MEM plugin available in Brainstorm software

- MEM in the time domain: interesting spatial properties and the ability to recover the spatial extent of the underlying sources
- Wavelet based MEM (wMEM): MEM localization after time-frequency decomposition of the data using discrete wavelets. Ideal to localize oscillations.

 Ridge MEM (rMEM): localization of synchronous sources

Co-Developper / Main Collaborator

Jean-Marc Lina, PhD

Solving the EEG/MEG inverse problem: Maximum Entropy on the Mean (MEM) model

Maximum Entropy on the Mean (MEM)

Prior information on J: Brain activity distributed over K cortical patches

 $d\mu(\mathbf{j}) = \prod_{k=1}^{K} [(1 - \alpha_k)\delta(\mathbf{j}_k) + \alpha_k \mathcal{N}(\mu_k, \Sigma_k)(\mathbf{j}_k)] d\mathbf{j}$

Parcelling of the cortical surface in K parcels:

Grova et al, Neuroimage. 2006;29(3)

Amblard et al, IEEE BME. 2004;51(3)

Chowdhury et al, Neuroimage 2016; 43:175-195

Point Spread Function of an extended source Resolution matrix study

Tanguy Hedrich

Hedrich et al, Neuroimage 2017

Electrical median nerve stimulation in 5 healthy controls in MEG

Clinical yield of MEG source localization using cMEM in epilepsy in 340 studies (49 patients)

Giovanni Pellegrino

Comparison of several distributed sources Localization methods: MEM, MNE, dSPM, sLORETA

Distance to the focus Spatial spread around

the focus

Pellegrino et al, HBM 2018, 2020

Basic principle of source localization and imaging in EEG/MEG

- Validation of EEG/MEG source imaging with intracranial EEG
- EEG/MEG source imaging of oscillatory patterns
- EEG/MEG source imaging of deep activity
- EEG/MEG source imaging of resting state

RESEARCH ARTICLE

Clinical Yield of Electromagnetic Source Imaging and Hemodynamic Responses in Epilepsy

Validation With Intracerebral Data

Chifaou Abdallah, MD, Tanguy Hedrich, PhD, Andreas Koupparis, MD, PhD, Jawata Afnan, MSc, Jeffrey Alan Hall, MD, PhD, Jean Gotman, PhD, Francois Dubeau, MD, Nicolas von Ellenrieder, PhD, Birgit Frauscher, MD, PD, Eliane Kobayashi, MD, PhD, and Christophe Grova, PhD

Neurology® 2022;98:1-13. doi:10.1212/WNL.0000000000200337

Correspondence Dr. Abdallah chifaou.abdallah@mcgill.ca

Quantitative comparison between EEG/MEG fusion using MEM, EEG/fMRI and intracranial EEG

Chifaou Abdallah

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Clinical yield of electromagnetic source imaging and hemodynamic responses in epilepsy: validation with intracerebral data Abdallah et al. Neurology 2022

17 Patients who underwent EEG/MEG, EEG/fMRI and subsequent iEEG were included

EEG/MEG fusion using MEM (Chowdhury et al HBM 2018) and fMRI BOLD response (Khoo et al Neurology 2018) to similar EEG epileptic spikes Identification of the reference SOZ and Primary Irritative Zone (PIZ) from iEEG data Quantitative analysis within the iEEG space: spatial overlap (ROC analysis) and distances

Simultaneous EEG-fMRI: The most significant BOLD response localizing the spike onset

The most significant fMRI BOLD response (pos. or neg.) to interictal discharges delineates a subset of the irritative zone in concordance with the seizure onset zone Spike onset zone

Khoo et al. Epilepsia 2017, Neurology 2018

Quantitative correlation between EEG/MEG sources and iEEG

One can compare **virtual MEG-estimated iEEG potentials** with **real iEEG potentials**

- Same physical entities: electrical potentials in V
- Spatial relationship between the cortical surface and iEEG contact: **iEEG forward model**

Grova et al, Human Brain Mapping 2016

iEEG forward model: infinite volume conductor model

 $(E_j) = \frac{n_i - n_r}{4 \pi \sigma^2}$ $4\pi\sigma$ $\vec{n}_i \cdot \vec{u}$ $V(E_i) = \frac{n_i \cdot n_r}{4}$ j / $=$ 4 π or 2 \rightarrow \bullet =

Electrical potential created by the ith dipolar source of the cortical surface on the jth iEEG electrode contact, located at a distance r from the source

Key parameters Distance and source orientation

Grova et al, Human Brain Mapping 2016

(vi) Recorded iEEG potentials V_{iEEG}

Multimodal comparison involving EEG/MEG fusion, EEG/fMRI and intracranial EEG

A. Spike selection

Spikes with same EEG spatial distribution

EEG/MEG

EEG/fMRI Fp1-F3 underhand how in the wind of the F3-C3 non-monogrammer C3-P3 were more individual P3-01 mondament Fp1-F7 values and property of the F7-T3 monumental monument $T3-T5$ <u>letinin kalendari dala ba</u>ke T5-C1 underversichung Fp2-F4 www.parameterman.com F4C4 which interested in the property C4-P4 winninghousement P4-02 monogroup on monogroup Fp2-F8 windowship month F8-T4 www.myrummun T4-T6 monotungrammondander T6-C2 when we have provided

B. Functional imaging

EEG/MEG source localization

fMRI BOLD analysis

Selection of BOLD cluster with the highest ghsolute t-value

C. Reference selection (SEEG)

D. Projection of functional Imaging results on SEEG channels

 $\bigcap \leftrightarrow \bullet: 0$ mm

 $\bigcap \leftrightarrow \blacksquare$: 0 mm

 $\bigcirc \leftrightarrow \bigcirc$: 3.5 mm

seizure core (maximum of epileptogenicity index)

E. Comparison with SEEG findings

1. Area under the ROC curve (AUC)

 0 .

spike with maximum amplitude \bullet : spike onset Maximum contact $\bigcap \leftrightarrow \bullet: 0$ mm EEG/MEG amplitude $\bigcap \leftrightarrow \bullet$: 10.5 mm $\bigcap \leftrightarrow \blacksquare$: 14mm

Multimodal comparison involving EEG/MEG fusion, EEG/fMRI and intracranial EEG

Multimodal comparison involving EEG/MEG fusion, EEG/fMRI and intracranial EEG

EEG/MEG source imaging vs PIZ EEG/fMRI response vs SOZ

Concordance between EEG/MEG distance and spatial overlap with PIZ

Importance of considering spatial overlap in quantitative evaluation EEG/MEG localized accurately the Primary Irritative Zone (PIZ) whereas fMRI response to similar spikes well localized the Seizure Onset Zone (SOZ)

Abdallah et al. Neurology 2022

EEG/MEG Source localization using Maximum Entropy on the Mean (MEM)

Recover the spatial extent of the source with good accuracy

MEM plugin available in Brainstorm software

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Jean-Marc Lina, PhD

INVERSE PROBLEMS AND SPARSE (WAVELET) REPRESENTATIONS OF SIGNALS

Objective: imaging the local oscillations from MEG/EEGs

Lina et al IEEE TBME 2014

Localization of the Seizure Onset Zone (SOZ) from ictal EEG/MEG data

MEG

EEG

 $BEst$ **Brain Entropy** in space and time

Wavelet-based Maximal Entropy on the Mean (wMEM): distributed inverse solution approach sensitive to the spatial extent of the epileptic generator (Lina et al., IEEE TBME 2014).

 $-200,00uV$
0.3333s

Localization of the Seizure Onset Zone (SOZ) from ictal EEG/MEG data, using MEM

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 $68 - m$

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Pellegrino et al, HBM 2016

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MRP4S-

MRP56

MRPSS

www.company.com/www.com/www.com

MEG/EEG Localization of the SOZ versus Clinical-SOZ

Giovanni Pellegrino

Qualitative analysis

13 Patients

31 seizures:

15 simultaneous EEG/MEG

16 MEG only

Quantitative analysis

8

35

ESI: EEG Source Imaging MSI: MEG Source Imaging

Pellegrino et al, Human Brain Mapping 2016

Localization of Fast Oscillations (FO 40-160 Hz) detected from high-density EEG

Avigdor et al, Clin Neurophys 2021

- Basic principle of source localization and imaging in EEG/MEG
- Validation of EEG/MEG source imaging with intracranial EEG
- EEG/MEG source imaging of oscillatory patterns
- EEG/MEG source imaging of deep activity
- EEG/MEG source imaging of resting state

Jawata Afnan

- 1. MEG source imaging of resting state oscillatory patterns in healthy subjects to be validated at the group level with the iEEG atlas
- 2. Evaluate the ability of wavelet-based MEM, to localize MEG resting state oscillatory sources in different frequency bands in healthy subjects

Ground truth: the iEEG atlas of normal resting state oscillations

- Frauscher et al (2018) proposed the first atlas of normal iEEG data
- Pulling together iEEG data from different patients, from different epilepsy centres, in healthy regions, eyes closed, during wakefulness, dense coverage of most brain regions
- Provides unique opportunity to study the spectral characteristics of normal brain oscillatory patterns at a group level

Atlas of the normal intracranial electroencephalogram: neurophysiological awake activity in different cortical areas

Birgit Frauscher, ^{1,2} Nicolas von Ellenrieder, ¹ Rina Zelmann, ^{1,3} Irena Doležalová, ⁴
Lorella Minotti, ⁵ André Olivier, ¹ Jeffery Hall, ¹ Dominique Hoffmann, ⁵ Dang Khoa Nguyen, ⁶ Philippe Kahane,⁵ François Dubeau¹ and Jean Gotman¹

Birgit Frauscher

MEG localization of resting state oscillations Validation with the iEEG atlas as ground truth

Jawata Afnan

MEG localization of resting state oscillations Validation with the iEEG atlas as ground truth

Comparison of MEG estimated spectra using wMEM with ground truth iEEG: selected ROIs

Afnan et al Neuroimage 2023

MEG localization of resting state oscillations Validation with the iEEG atlas as ground truth

Comparison of oscillatory peaks identified in MEG estimated spectra with MNI

 0.08

 0.05

 0.02

 $_{8}$ 13 Frequency (Hz)

Overall we retrieved accurate MEG resting state oscillations in most cortical regions in different frequency bands

 $_{0.8}$

0.6

 0.5

 10.2

Results were more comparable with the iEEG atlas after removing aperiodic components

Localization in deeper structures was biased by source leakage, cf. widespread large alpha peak

Similar findings when considering wMEM, MNE and Beamformer

Afnan et al Neuroimage 2023

Take home messages

- Several hypotheses associated with each localization method
- From *dipole fitting* (requires excellent knowledge / expertise in electrophysiology) to *source imaging* (less parameters to tune, but be careful when interpretating)
- All methods are useful, some might be wrong, always assess compatibility with scalp topography, be aware of the methods' assumption when interpreting the data
- Comparison between localization methods is always a plus
- Complementarity between MEG and high-density EEG source imaging
- Localizing deep activity remains challenging, even more during resting state
- Estimation of the spatial extent: our plugin using *Maximum Entropy on the Mean* is available in Brainstorm software

MEM is available as a Brainstorm Toolbox

Brainstorm BEst Tutorial http://neuroimage.usc.edu/brainstorm/ Tutorials/TutBEst

Part 2: NIRSTORM analysis of fNIRS data from optimal probe design to 3D reconstruction

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What is functional Near Infra-Red Spectroscopy (fNIRS)?

- **r e** • fNIRS measures non-invasively fluctuations of both oxygenated and deoxygenated hemoglobin (HbO and HbR) in the brain with high temporal resolution
- How does it work?

What is functional Near Infra-Red Spectroscopy (fNIRS)?

- fNIRS measures non-invasively fluctuations of both oxygenated and deoxygenated hemoglobin (HbO and HbR) in the brain with high temporal resolution
- How does it work?

Origins of fNIRS signals

Finger opposition task in fMRI and NIRS

(i) NIRS montage using 8 sources at 690 nm, 8 sources at 830 nm (red squares) an 16 detectors (green circles)

(ii) Installation of Brainsight fibers equipped with low profile prisms on the EEG/NIRS cap

Finger opposition task in fMRI and NIRS

Finger opposition task in fMRI and NIRS

(v) NIRS response on selected contralateral pairs (HbO in red, HbR in blue, HbT in black)

NIRSTORM: a Brainstorm extension dedicated to functional Near Infrared
Spectroscopy (fNIRS) data analysis, advanced 3D reconstructions, and optimal probe design

D Édouard Delaire, Thomas Vincent, **D** Zhengchen Cai, Alexis Machado, Laurent Hugueville, Denis Schwartz, Francois Tadel, Raymundo Cassani, Louis Bherer, Jean-Marc Lina, D Mélanie Pélégrini-Issac, Christophe Grova doi: https://doi.org/10.1101/2024.09.05.611463

A. Sensitivity of a montage to the region of interest (ROI)

B. Optimization of the montage to maximize the sensitivity to the ROI

1. Averaged optical density response at the sensors levels

2. Averaged hemodynamic response on the cortical surface

NIRSTORM

1. fNIRS standard sensor level analysis

Data organization / Data input

Input Data format: .nirs as in Homer .snirf file

…

Standard NIRS data analysis in the sensor space Visualization features

Anatomical Model

subject specific or Template

Overlay on anatomical atlases Optimal fNIRS

montage targeting the right hand knob

Standard fNIRS data analysis in the sensor space Typical preprocessing pipeline

- 1. Importing data and trigger exploration, verification, removal of bad channels
- 2. Motion Detection / Correction
- 3. Conversion in HbO/HbR Modified Beer Lambert Law
- 4. Band Pass Filtering (0.005-0.08Hz), short distance channel regression
- 5. Signal averaging and interaction with the data

Taking benefit from Brainstorm EEG/MEG developments: filtering, PCA, ICA, SSP, Wavelets, connectivity measures …

Personalized fNIRS:

Optimal Montage Design

Optimal Montage Design: motivations

➢ No standard procedures: Many different probe designs proposed

- ➢ Difficulty to assess the cortical area being illuminated
- ➢ Difficult to maintain optode contact for long periods
- ➢ Difficulty to integrate montages with an EEG positioning system

EEG 10-20 international system

Development of personalized "Optimal NIRS montages"

Light sensitivity profile

Δ[HbO] interpolation on the scalp **Machado**

➢ How to ensure that the target area is well illuminated ?

Methodology to find the best optode positions over target brain regions

Machado et al. 2014, Journal of Biomedical Optics Machado et al, 2018, JNS – Methods

Development of personalized "Optimal fNIRS montages"

Anatomical Information Head model for light propagation modeling

Region of Interest

To target

Optodes possible locations on the skin (search space)

Definition of the constraints to search for an Optimal Montage

Machado et al. 2014, Journal of Biomedical Optics Machado et al, 2018, JNS – Methods

Development of personalized "Optimal fNIRS montages"

Targeted right Fronto polar region

fNIRS montage Light sensitivity map Summed Light sensitivity map

Machado et al. 2014, Journal of Biomedical Optics Machado et al, 2018, JNS – Methods

Personalized NIRS using "Optimal NIRS montages"

Definition of a target Volume of Interest to be explored using fNIRS

vertices Maximizing a priori light sensitivity to the target and spatial overlap between channels

B:T1 MRI

A: Possible

optode positions

Mixed integer linear programming problem (CPLEX, IBM)

C: Sensitivity profile

for one couple of

E:Resulting optimal montage

F: Neuronavigation

G: Installation using collodion

D:Target VOI

Personalized NIRS using "Optimal NIRS montages"

Machado et al, J Biomed Optic 2014, JNS – Methods, 2018, Sci. Report 2021

Personalized fNIRS using optimal montage: dataset considered for NIRSTORM webinar

Personalized fNIRS channel layout design using anatomical head MRI

- Optical head model using a Monte Carlo photon simulator (Fang and Boas, 2009)
- Personalized optimal montage targeting the right hand knob (Machado et al., 2018)

What is optimal montage?

- Maximization of spatial sensitivity of fNIRS measurements targeting a specific brain region, and maximizing spatial overlap between sensors
	- Hand knob 16.7 cm² (black profile)
- Pre-set # of sources, detectors and the density of channels

- 3 Sources, 15 Detectors, at least 13 Detectors seeing each source , source-detector separation 1.5~4cm

- Use of collodion to glue optodes on the scalp, ensuring good optical contact for prolonged investigations (Yücel et al., Neuroimage, 2014; Pellegrino et al., Frontiers Neurosc, 2016)
- Finger opposition task at 2Hz, 20 Blocks of 10s with an inter-stimulus period ranging from 30 to 60s, Brainsight fNIRS device (Rogue-Research Inc, Montreal)

Standard NIRS data analysis on data measured using the optimal montage

Optimal Montage targeting the right hand knob region + 1 additional detector between the three sources To obtain three short distance channels

1ax amplitude: 0.039 mmol/l lime window: [-10000, 35000] ms

 $\left| \cdot \right|$

Average response Band pass filter 0.005 – 0.08Hz + Short distance channel regression

Optimal fNIRS montage, taking into account EEG position constraints

Avoiding the positions of an EEG cap

Updating the search space

Optimal fNIRS montage, taking into account EEG position constraints

Targeted right Fronto polar region

fNIRS 3D Reconstructions

Diffuse Optical Tomography (DOT)

fNIRS 3D reconstruction Solving an ill-posed inverse problem

$Y = AX + e \leftarrow$ Noise

Optical Density data at specific wavelengths

fNIRS forward model Light sensitivity maps estimated using Monte Carlo simulations MCXLab (Fang and Boas 2009)

(685, 830 nm) fNIRS 3D reconstruction along the cortical surface

- 1. Minimum Norm Estimate (MNE)
- 2. Maximum Entropy on the Mean (MEM)

fNIRS 3D reconstruction Solving the forward Problem A

fNIRS forward model Light sensitivity maps estimated using Monte Carlo simulations MCXLab (Fang and Boas 2009)

 $Y = AX + e$

Subject Specific (or template base) Head Modeling in 5 tissues (Freesurfer, SPM)

Integration of MCXLab, Monte Carlo Simulation of light transport on GPU (Fang and Boas 2009) http://mcx.space

Monte Carlo eXtreme A GPU-accelerated photon transport simulator

Light sensitivity map on the cortical surface,

fNIRS 3D reconstruction Solving the DOT inverse problem

Zhengchen Cai

 $Y = AX + e$

$$
\hat{X}_{dMNE} = \operatorname{argmin} \left(||(Y - AX)||_{\Sigma_d}^2 + \lambda ||X||_{\Sigma_s}^2 \right)
$$
\n
$$
= (A^T \Sigma_d A + \lambda (\Lambda \Lambda^t)^{-1})^{-1} A^T \Sigma_d Y
$$
\n
$$
\operatorname{diag}(\Lambda) = \frac{1}{\operatorname{diag}((A^T \Sigma_d A))^{\omega}} \longrightarrow
$$
Depth weighting parameter

Maximum Entropy on the Mean (MEM)

Amblard et al 2004, Grova et al 2006, Chowdhury et al 2013, Cai et al Sci Rep 2021

Non linear probabilistic approach Relative entropy with a prior distribution

$$
S_v(dp(x)) = -\int_x \log\left(\frac{dp(x)}{d\nu(x)}\right) dp(x)
$$

Data Fit term

$$
Y - [A|I_q] \begin{bmatrix} E_{dp}[x] \\ e \end{bmatrix} = 0, \qquad dp \in C_m
$$

Regularization using entropy

$$
dp^*(x) = argmax_{dp(x) \in C_m} (S_v(dp(x)))
$$

Flexible framework to define the prior distribution (reference) Recent implementation of depth weighting within MEM

fNIRS 3D reconstruction using the MEM framework originally developed for EEG/MEG source imaging versus MNE 1. Evaluation using realistic simulations (Monte Carlo simulations) fNIRS realistic simulations at different SNR

fNIRS probe and forward model

Cai et al Sci. Report 2022

fNIRS 3D reconstruction using the MEM framework originally developed for EEG/MEG source imaging versus MNE 2. Comparison with finger tapping fMRI in 10 healthy controls

Personalized fNIRS: optimal montage targeting the right hand knob

Cai et al HBM 2021

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Evaluation of a personalized functional near infra-red optical tomography workflow using maximum entropy on the mean

Zhengchen Cai X, Makoto Uji, Ümit Aydin, Giovanni Pellegrino, Amanda Spilkin, Édouard Delaire, Chifaou Abdallah, Jean-Marc Lina, Christophe Grova

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An example of complete multimodal investigation using: fMRI, high density EEG and NIRS

Full multimodal investigation (hdEEG, fMRI, NIRS) during a visual stimulation task

EEG and NIRS 3D Reconstruction using Maximum Entropy on the Mean (MEM) Amblard et al IEEE TBME 2004 Pellegrino et al HBM 2018, 2020 Abdallah et al Neurology 2022 Afnan et al HBM 2024 **NIRSTORM**

MEM in fNIRS: Cai et al, HBM 2021 Cai et al Sci. Report 2021 Cai et al HBM 2023 Delaire et al Bioarxiv 2024

 L Brainstorm BEst Tutorial Tutorials/TutBEst

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Alumni: *Ümit Aydin, Zhengchen Cai, Rasheeda Chowdhury, Tanguy Hedrich, Hassan Khajehpoor, Kangjoo Lee, Giovanni Pellegrino, Amanda Spilkin, Makoto Uji, Yimeng Wang*

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