EEG source localization

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Background

- **Focal Epilepsy**
- Epilepsy affects 1% of the population
- Seizures prevent healthy development and may cause brain damage
- Focal epilepsy is triggered by pathological electrical activity in a small clump of neurons

- **Current Treatments**
- 35% of focal epilepsy patients do not respond to medication, and must undergo surgical resection of the epileptic focal points
- Surgery requires accurate localization of the foci
- Subdural EEG is currently needed to reconstruct focal sources from voltage measurements, and even with it only about 65% of patients are seizure-free after surgery

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Epilepsy treatment

Background

- Interictal spikes transient events, characteristic of epilepsy, that occur between seizures
- Interictal spikes generated by the brain without any clinical signs, thus allowing multimodal imaging studies
- Scalp EEG recordings have an excellent temporal resolution (~ 1 ms) but its visual interpretation provides only imprecise localization, indicating at best which lobe was involved during the epileptic discharge

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Background

- EEG source localization (ESL) methods may help to determine the regions of the brain where the spikes are generated.
- As opposed to other imaging modalities (such as MRI and PET), EEG or MEG data are the only direct measurements of neuronal activity.
- Performing an accurate localization of EEG sources of interictal spikes is thus of particular interest to better understand their generation and propagation.

Background

- Inferring the source location within brain from a signal acquired on the scalp, i.e., the EEG inverse problem, is an ill posed problem because infinite number of source configurations that can produce exact same potential
- Additional constraints should then be added to obtain a unique solution. Two types of approaches have been proposed
  - (1) "Equivalent current dipole" methods assume potentials are generated by a few dipolar sources.
  - (2) "Distributed source" methods assume that potentials are generated by a large number of dipolar sources distributed within the brain or on the cortical surface.
  - (3) Sparse scanning methods, assessing the presence of an equivalent current dipole on each point of a 3D grid, constitute an intermediate alternative to estimate 3D map of activation indices
**Background**

- **EEG source localization**
  - More accurate source localization to improve post-surgical prognosis
  - Source localization based on non-invasive tests and scans instead of subdural EEG

- **Method**
  - Flexible, modular framework for non-invasive source localization based on scalp EEG
  - Incorporates prior information from MRI and other sources
  - Utilizes state-of-the-art patient-specific head modeling
  - Allows easy switching of prior map, field-solver, or inverse method
  - Tools for processing raw patient data for use with sophisticated field-solving packages

**Fundamentals of ESL**

- Aims to localize the sources of electric currents within the brain that give rise to recordable potential fields at the scalp

**Type of ESL model**

- Two fundamental problems exist in the practice of ESL
  - Forward problem
  - Inverse problem

- Forward problem is solved by specifying a set of conditions (compartments, surfaces, conductivities) for the head model, also referred to as volume conductor or forward model

**Source Localization**

- **The Source Localization Problem**
  - EECL gives us voltage readings at electrodes on the scalp
  - From the quasi-static Maxwell equations we get the state equation relating source currents in the head to voltages on the scalp:
    - \[ \nabla \cdot \left( \sigma \nabla V \right) = \nabla \cdot J \]
    - **Forward problem**: Find voltages at electrodes given source configuration
    - **Inverse problem**: Find source configuration given voltages at electrodes
  - The inverse problem is highly ill-posed and must in practice be solved through iterative solution of the forward problem to search for a current configuration that best explains the voltages measured

**Forward model**

- The forward model is the source, or source network, "performs," its projected (lead) field passing through modeled compartments and tissue interfaces to reach the recording electrodes

- Forward models range from simple (a single spherical shell models the brain surface) to complex (a four-layered realistic model)
  - Its compartments segmented from the patient’s MRI scan, models the brain, cerebrospinal fluid, skull, and scalp surfaces
  - Spherical shell and realistic models are the two versions of forward modeling used in ESL today

**Inverse method**

- The inverse problem, by contrast, has no unique solution.

- Infinite number of source permutations can, in theory, explain a specific potential field recorded at the surface (Helmholtz, 1851)

- Problem attempts to solve in routine clinical practice, traditionally with a mind’s eye rendering of candidate sources drawn from the various EEG montage digital displays

- In practice, "constrains" the infinite possible solutions to the inverse problem by applying their working knowledge of epileptogenesis in the focal epilepsy by information from anatomical or functional imaging studies.

- Similarly in ESL, the inverse problem is made soluble by the incorporation of mathematical constraints into inverse modeling algorithms.
Low-resolution electromagnetic tomography (LORETA)

- One of more familiar distributed modeling algorithms used in ESL.
- LORETA applies a modeling constraint based on the idea that neighboring neuronal populations are more likely (than nonneighboring ones) to undergo synchronous depolarization during spontaneous discharge or an evoked response (Pascual-Marqui et al., 1994).
- LORETA modeling tends to generate broad, smoothed ESL solutions as neighborhood sources are model term conditioned to assume similar strengths.

Forward vs Inverse model

- It is often misunderstood that the inverse and forward problems are interdependent.
- They only interdependent in the sense of mathematical algorithms specified to each problem are independently set (Scherg et al., 1999).
- ESL solution can be reached when any inverse model is coupled with any forward model.
- Two major challenges then, lie in:
  - (a) deciding on which of available forward and inverse models are the most appropriate to apply
  - (b) translating theoretical impact governed by the choice of particular forward–inverse modeling set-up into terms that define the clinical impact of such a choice on the patient’s diagnosis and management.

EEG source localization:
Equivalent Current Dipole (ECD) vs Distributed source

EEG source model is written

\[ M = G J + E \]

Equivalent Current Dipole (ECD):
- non linear problem: \( G, J \)??
- number of sources ?
- what is an ECD ?

Distributed source method:
- Anatomical constraint
- linear problem: \( J \)??
- \( p = 103 \) sources ~ \( n = 102 \) sensors
- ill-conditioned problem
- regularization needed

EEG source localization of interictal spikes

- Depth recordings showed that interictal spike generators are rarely focal (Merlet et al. Clin. Neurophys. 1999).
- ECD are thought to represent the center of mass of such generators.
  - A minimum brain activated area of 6 cm\(^2\) is needed to generate a spike on the scalp (Ebersole J. Clin. Neurophys. 1997)
  - Spike generators may be quite more extended than 6 cm\(^2\) (a whole lobe).

What is the behavioural of distributed source localization methods in the presence of extended sources?

Modeling the Head

- Head Models
  - In order to solve the forward problem we need a model of the head as a volume conductor.
  - Current clinical practice uses simple multishell spherical head models.
  - BEM allows realistic modeling of scalp and skull, but not different brain tissues.
  - FEM allows realistic modeling of scalp, skull, CSF, GM, and WM.

Creating a Head Model

- Use NeuroFEM as the field-solving package to solve the forward problem on a high-resolution FEM head model.
- First segment whole-head MRI using modified watershed segmentation.
- Then we mesh the head volume, assigning a conductivity to each mesh node based on its tissue classification.

Modeling the Electrodes

- Clinical Electrode Placement
  - There are several ways electrodes may be placed in an EEG acquisition.
  - The most common method is the 10-20 system, requiring manual placement of 19–32 electrodes based on anatomical landmarks and relative distances.
  - Better methods include dense electrode nets with standard locations, electrodes with MR-visible markers, and electrode locations recorded with a 3D tracker.
CLINICAL STUDIES IN DIPOLE AND DISTRIBUTED ESL

- Which part of the spike should be modeled?
- How well does ESL corroborate epilepsy surgery findings?
- How well does scalp ESL model interictal and ictal onset as defined by intracranial recordings?

Which part of the spike should be modeled?

- Lantz et al., 2003b observed spike-averaged recordings of 16 patients with symptomatic focal epilepsy. All had an Engel class 1 surgical outcome.
- Using novel spatiotemporal cluster analysis technique, three different voltage field maps during the rising phase of the scalp-recorded spike per patient (range one to five).
- When ESL performed on these different voltage maps, source model location coincided with MRI lesion location for all patients within a fairly narrow time window.

How well does ESL corroborate epilepsy surgery findings?

- Boon et al., 2002 looked at contribution of spatiotemporal dipole modeling to clinical decision making process in 100 presurgical patients with refractory focal epilepsy.
- Most cases (lesional 83%), largest subgroup having unilateral hippocampal sclerosis (53%). Scalp ictal EEG recordings 27-electrode plus three inferior temporal electrode pairs.
- 93 patients who recorded ictal EEG phenomena.
- 62 patients could not undergo ESL analysis due to excessive artifact contamination.
- 31 patients, it was concluded that ESL influenced the clinical interpretation in 14 cases.

Unfortunately, the study contains several methodological deficiencies.
- It was not blinded,
- No information on postsurgical outcome, and it performed zero-phase shift filtering on the EEG raw data.
- The spatiotemporal modeling was actually limited to the use of single (regional) dipole, thus making it difficult to disentangle interlobar or interhemispheric propagation effects from effects potentially attributable to multiple independent sources an ESL outcome.

How well does ESL corroborate epilepsy surgery findings?

- In the largest prospective interictal ESL study to date (Michel et al., 2004b),
  - Heterogeneous group of 44 epilepsy surgery candidates undertook a supplementary 128-channel surface recording for implementation of single-source dipole and temporal modeling (EPIFOCUS).
- 32 patients had identifiable focus, seven underwent invasive recording, all but two patients had concordant ESL findings at a lobar level.
- From subgroup of 24 patients who underwent surgery (17 temporal, seven extratemporal)
  - 18 had an ESL maximum that fell within border of the nearest resection margin
  - Engel class 1 outcome was shared by 16/18 cases.
- Investigators quoted high level of agreement between the intracranially directed interictal and ictal localization and the high-density surface electrode-directed ESL result (five of seven cases).

How well does ESL corroborate epilepsy surgery findings?

- Assaf & Ebersole, 1997 examined EEG recordings of 40 TLE patients who required intracranial electrode implantation.
- All patients had an Engel class 1 outcome one yrs follow up.
- Spatiotemporal dipole modeling was done on scalp data with 25-electrode plus three inferior temporal electrode pairs.
- Dipoles with different orientations were preassigned to model different sublobar divisions of the temporal cortical surface.
- Dipole models were then matched with the ictal localization suggested by intracranial recordings and expressed as positive predictive values.
### ESL Tutorial

- Loading EEG data (functional data) and digitizer EEG files
- Images parameter (MRI brain)
- Co-registering functional and anatomical landmarks
- Data Analysis
  - Volume Conductor Models
  - Dipole analysis

### PCA / ICA Analysis

- Principle Component Analysis (PCA)
- Independent Component Analysis (ICA)
- Statistical techniques akin to factor analysis that are used
  - (1) to reduce the number of variables
  - (2) to detect structure in the relationships among variables.

### Realistic Source Reconstruction

- Volume Conductor Model
  - The electric potentials and magnetic fields generated by a source inside the head distorted by so-called volume currents
  - Size and orientation of these back-flowing currents depend on the electric conductivity values at all points inside the head.
  - In the basic realistic model, the head is divided into three compartments: the skin, the outer skull and the inner skull together with the gray and white matter.
  - Within each compartment, the conductivity is then modeled to be homogeneous, isotropic, so that the Boundary Element Method (BEM) can be used to solve the forward problem

### Conclusion

- Based on the progress made in clinically directed research in the last 5–10 years, ESL will earn a place in the routine work-up of patients with focal epilepsy in the foreseeable future.
  - To get there, the following conditions need to be met:
    - (a) blinded, prospective validation studies conducted on larger clinical groups
    - (b) more routine use of realistic forward models
    - (c) greater awareness of the importance of source orientation in defining inverse modeling solutions, with elimination of the tendency to use source location as cardinal determinant of ESL accuracy
    - (d) Avoidance of restricting source modeling to spike peaks such that earlier spike components are routinely included in the ESL analysis
    - (e) Avoidance of using zero-phase shift filtering on EEG signals
    - (f) the inclusion of error measures, such as confidence ellipsoid volumes, into ESL solutions to improve the statistical robustness of clinically based findings
    - (g) Clarification of the likely clinical impact of choosing single versus averaged spike epochs for ESL

### Conclusion

- ESL has by no means been swept aside by more "advanced" functional imaging modalities of MEG and EEG-fMRI, principally because the three modalities emphasize quite different bio-electromagnetic phenomena
- ESL is better regarded as underutilized three-dimensional extension of traditional two-dimensional EEG analysis
- As this technology is now quite accessible, affordable, noninvasive, and one that is founded on the well-established electrophysiological principles of EEG
- ESL continues to hold promise as a potential clinical tool that offers to teach us much about the recruitment and propagation of interictal and ictal discharges in focal epilepsy