Boosted Spatial and Temporal Precision in Functional Brain Imaging via Multimodal Analysis

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Ph.D. Thesis Proposal
### The Goal

**General**

Develop methods to achieve superior spatio-temporal resolution by combining signals from different brain imaging modalities that possess complementary temporal and spatial advantages.

**Specific**

Show that it is possible to obtain trustworthy estimate of neuronal activity at superior spatio-temporal resolution by combining EEG/MEG with fMRI data whenever forward models of the signals are appropriate to describe the data in terms of underlying neuronal processes.
## Motivating Questions for Brain Scientists

<table>
<thead>
<tr>
<th>Fundamental</th>
<th>How can we understand brain function?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization</td>
<td>Which areas of the brain are involved in the processing during a specific task?</td>
</tr>
<tr>
<td>Brain dynamics</td>
<td>What are the interactions among the areas during a specific task?</td>
</tr>
<tr>
<td>Motivating Questions for Engineers</td>
<td></td>
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<tr>
<td>-----------------------------------</td>
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<tr>
<td><strong>Forward problem</strong></td>
<td></td>
</tr>
<tr>
<td>How brain signals and stored information can be modeled to produce registered measurements?</td>
<td></td>
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<tr>
<td><strong>Inverse problem</strong></td>
<td></td>
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<tr>
<td>How viable estimates of the neuronal processes inside the brain can be obtained from a limited set of observations outside the brain?</td>
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<tr>
<td><strong>Signal processing</strong></td>
<td></td>
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<tr>
<td>What characteristics (e.g. non-stationarity, statistical or frequency features, <em>etc.</em>) of the brain imaging data should be explored under heavy noise conditions?</td>
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</tbody>
</table>
Outline

1. The “State of Art”
2. Research Issues
3. Problem Area
4. Simulations
5. Research Plan and Timeline
Brain Imaging

- Anatomical
  - CT
  - MRI
- Functional
  - Non-Invasive
  - Indirect Imaging
    - EEG
    - NIRS
    - fMRI (BOLD)
    - fMRI (Perfusion)
  - Invasive
  - Intracranial Recordings
    - PET
    - SPECT
  - Agents Driven

- Simulations

- Plan
Non-Invasive Unimodal Brain Imaging

EEG

MEG

MRI
# Introduction

Non-Invasive Unimodal Brain Imaging

# Electro- and Magnito- EncephaloGraphy

## Common features
- Passive technique
- Post-synaptic ionic currents of synchronized pyramidal neurons generate the electro-magnetic field registered by E/MEG

## Differences

<table>
<thead>
<tr>
<th>EEG</th>
<th>MEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>On the head surface</td>
<td>Outside of the head</td>
</tr>
<tr>
<td>Electric potential</td>
<td>Magnetic field</td>
</tr>
<tr>
<td>Reference electrode</td>
<td>Reference-free</td>
</tr>
<tr>
<td>Silent to solenoidal</td>
<td>Silent to radially oriented currents</td>
</tr>
<tr>
<td>currents</td>
<td></td>
</tr>
</tbody>
</table>
Non-Invasive Unimodal Brain Imaging

E/MEG Brain Imaging

Linear formulation: DECD

Both magnetic and electric fields linearly depend on the current strength at densely sampled fixed spatial locations

\[ \mathbf{X} = \mathbf{GQ} \]

\( \mathbf{X} (M \times T) \) – E/MEG data;
\( \mathbf{G} (M \times N) \) – spatial filter (lead-field/gain matrix);
\( \mathbf{Q} (N \times T) \) – current strengths at each location

Easy!

For the linear case the solution is \( \hat{\mathbf{Q}} = \mathbf{G}^+ \mathbf{X} \)
Non-Invasive Unimodal Brain Imaging

Not That Easy: Inverse Problem
Inverse Problem

Why it is problematic

**Ill-posed:** the number of possible signal source locations \((N)\) greatly exceeds the number of sensors \((M)\) – infinite number of solutions

**Ill-conditioned:** instrumental and brain noise prevents from achieving stable solution by simply increasing number of sensors
Non-Invasive Unimodal Brain Imaging

\( \varepsilon/\mu\text{MEG} \) Inverse Regularization

**Minimal 2-nd norm solution: pseudo-inverse**

\[ G^\dagger = G^\top (GG^\top)^{-1} \]

**Regularization: general formulation**

\[ G^+ = W_Q G^\top (GW_Q G^\top + \lambda W_X)^{-1}, \]

where \( W_X^{-1} \) and \( W_Q^{-1} \) are weighting matrices in sensor and source spaces correspondingly.
**Non-Invasive Unimodal Brain Imaging**

\(\text{E/MEG Pro et Contra}\)

**Pros: great temporal resolution**
- Great for any event related design
- Epileptic spikes detection
- Coherence analysis
- Human brain interface

**Cons: poor localization in space**
- Non-linear optimization in the case of dipole modeling
- Inverse problem in the case of distributed dipole modeling
Non-Invasive Unimodal Brain Imaging

**fMRI: Blood Oxygenation Level Dependent**

**Pros**

- **Great spatial resolution:** 1 mm and higher
- **Safe:** does not require injections of radioactive isotopes

**Cons**

- **Indirect measurement:** BOLD response reflects oxygenation
- **Low temporal resolution:**
  - Full volume can be acquired just every 2-4 seconds
  - BOLD signal itself is of convolved nature
- **Noise:**
  - Inhomogeneities
  - Blood vessels influence
Motivation for Multimodal Imaging

- Superior spatial resolution of fMRI
- Fine temporal resolution of EEG/MEG
- Reported agreement between EEG/MEG and BOLD signals
Existing Multimodal Techniques

- Correlative analysis
- Decomposition analysis
- Constrained equivalent current dipole (ECD) modeling
- FMRI-conditioned distributed ECD modeling
- Beamforming with fMRI-conditioned covariance
- Bayesian inference
Absent generative model of BOLD signal
Variability of BOLD across subjects and within the brain
True neural signal is not known
Methods do not make use of temporal fMRI information
Major Obstacle: Absent Generative BOLD Model

**Linear Time Invariant System**

\[ f(t) = (h \ast q)(t) \]

**Hemodynamic Response Function**

[Graph showing canonical and subject-specific HRF for motor and visual cortex]

[Kalina Christoff, 2001]
Observation
Convolutional model is valid in many cases

Convolutional model
- provides good agreement between LFP and BOLD response
- permits the estimation of convolution kernel using simple stimulus
- has been used in most of the fMRI studies
- can be augmented with non-linearity to accommodate divergence from LTIS model
Forward Models

Temporally and spatially superior modality $\mathbf{Q}$ ($N \times T$) is used to reconstruct both $\mathbf{F}$ and $\mathbf{X}$ observed signals.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Data Matrix</th>
<th>Size</th>
<th>Model</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/MEG</td>
<td>$\mathbf{X}$</td>
<td>$M \times T$</td>
<td>$\hat{\mathbf{X}} = \mathbf{GQ}$</td>
<td>Spatial Filter</td>
</tr>
<tr>
<td>fMRI</td>
<td>$\mathbf{F}$</td>
<td>$N \times U$</td>
<td>$\hat{\mathbf{F}} = \tilde{\mathbf{QB}}$</td>
<td>Temporal Filter</td>
</tr>
</tbody>
</table>

Advantages

- Modeling both E/MEG and fMRI makes use of temporal and spatial information from both modalities.
- Reconstruction of fMRI along with E/MEG provides regularization to the inverse E/MEG problem.
The Unknown: Dipole Strength ↔ BOLD

Scaling between dipole strength and BOLD signal is not known and can vary from location to location.

Solutions

- Restrict range of applications to activations in small (thus approximately homogeneous) regions
- For the area of interest estimate scaling along with convolution kernel using simple experimental design
- Augment the model to include scaling parameter per each local region
Reconstruction Error

Residuals

\[ \Delta_x(Q) = \frac{\hat{X}(Q) - X}{\sqrt{\nu_X MT}} \quad \text{and} \quad \Delta_F(Q) = \frac{\hat{F}(Q) - F}{\sqrt{\nu_F NU}} \]

Quality of the reconstruction criterion:

\[ \mathcal{E}_r(Q) = \| \Delta_x(Q) \|_l + \alpha \| \Delta_F(Q) \|_l + \lambda \mathcal{C}(Q) \]

where

\[ l \in \{1, 2\} : \text{the norm of error cost function} \]

\[ \mathcal{C}(Q) : \text{additional regularization term} \]
Integration

$l = 2$: Gradient Descent Optimization

\[
\frac{\partial \mathcal{E}_r(Q)}{\partial Q} = \frac{\partial \Delta_X(Q)}{\partial Q} + \alpha \frac{\partial \Delta_F(Q)}{\partial Q} + \lambda \frac{\partial C(Q)}{\partial Q}
\]

\[
\frac{\partial \Delta_X(Q)}{\partial Q} = 2G^T(X - GQ), \quad \frac{\partial \Delta_F(Q)}{\partial Q} = 2\Theta \star \left( (F - \tilde{Q}B)B^T \right)
\]

Problems

- Optimization can fall into local minima
Linear Programming Formulation

Minimization task can be formulated as an LP problem

\[
\hat{X} + \Delta X = X \quad \text{Constraints}
\]
\[
\hat{F} + \Delta F = F
\]
\[
\tilde{q}_{ij} \geq 0 \quad \text{Region}
\]
\[
\mathcal{E} = \|\Delta X\|_1 + \alpha\|\Delta F\|_1 \quad \text{Objective}
\]

Problems

- Efficient LP solvers are necessary due to the large size of LP problem (MOSEK)
- Possibly poor performance if noise is indeed Gaussian
Localization Workflow

- Neuronal Activations
- Statistical Map
- Thresholding
  - Simple
  - Cluster
Localization Workflow

- Neuronal Activations
- Statistical Map
- Classifier Sensitivity Map

Thresholding
- Simple
- Cluster
Classifier as a Localizer

Localization using classifiers

**Temporal:** trained classifier

**Spatial:** sensitivity map of the classifier

Advantages

- Notion of **generalization**
- **Fast classification** after the classifier has been trained

Disadvantages

- Training can be lengthy
- Might not generalize
- Sensitivity map might reflect just a **subset** of activations
Localization Using SVM

- Great ability to generalize
- Fast to train (constrained quadratic problem)
- Can easily work with data of huge dimensionality
- Sensitivity map of linear SVM is given by the decision hyper-plane normal
- Results are consistent with conventional analysis
Somatotopy: Mapping of the Primary Motor (M1)

- Simple motor response
- Experiment is easily reproducible
- Coarse information about spatial organization is available
- Temporal separation between events is easily controllable
**Possible problems**

- Convolutional model might not be valid
- Activations in other areas (PMA, SMA and PI) can interfere with registration of the signal of interest
- Suggested multimodal analysis methods may not produce good estimates of neuronal activity

**Solutions**

- Carry out a pilot experiment to verify applicability of the convolutional model
- Augment the model with non-linearity if necessary
- Preprocess the data to extract signal components of interest (ICA?, SOBI?)
Region of Interest: M1 “hand area”

(a) Cortical Mesh

(b) 895 Surrounding 2 mm Voxels
### Datasets

**\(\text{E/MEG sensors:}\)** 30 sensors (895 voxels)

**Sampling rate:** Sources (and \(\text{E/MEG}\)): 16 [Hz], fMRI: 1 [Hz]

**Duration:** Sources (and \(\text{E/MEG}\)): 1 [sec], fMRI: 10 [sec]

**Noise:** (1) Gaussian white and (2) empirical

**Noise levels:** \(\varepsilon = \sigma_{\varepsilon} / \max(s) \in [0, 0.1, 0.2, 0.4, 0.6]\)

**An activation:** Modeled as a Gaussian (\(\sigma=50\) [ms])

**Trials:** 30 trials

**Arrangement:** 5 datasets

- Spatially non-overlapping: [1, 10, 100, 895] active
- Spatially overlapping: 10 randomly activated locations followed by 2nd activation within next 100–300 [ms]
FMRI Conditioned $\mathcal{E}/\mathcal{M}$EG Inverse (FMRI-DECD)

\[ \hat{Q} = G^+ X, \text{ where } G^+ = W_Q G^T (G W_Q G^T)^{-1} \]

**Conditioning of the inverse:**
- Truncated SVD of $(G W_Q G^T)$

**Gain matrix normalization:**
- $W_Q = W_n = (\text{diag} (G^T G))^{-1}$

**Relative fMRI weighting:**
- $(W_{f\text{MRI}})_{ii} = \nu_0 + (1 - \nu_0) \Delta_i / \Delta_{\text{max}}$. \\
  $\nu_0 \in [1.0, 0.5, 0.1]$ which corresponds to 0, 50, and 90% of relative fMRI weighting

**Dipole orientations:**
- Variable and Fixed
\[ \hat{Q} = \arg \min_Q \| \Delta X(Q) \|_2 + \alpha \| \Delta F(Q) \|_2 \]

**Trade-off Parameter** :
\[ \alpha = [0.5, 1, 10] \] for a tradeoff between E/MEG and FMRI fit was used.
Reconstruction Quality Criterion

Relative noise energy brought into the source signal estimation

\[ E = \left( \frac{\|\hat{Q} - Q\|_2}{\|Q\|_2} \right)^2 \]

Minimal value \( E = 0 \) corresponds to the perfect restoration of the sources time course.

The best result obtained with fMRI conditioned E/MEG inverse was chosen to be compared against \( L_2 \) -Fusion results.
Source Reconstruction Results

A Single Active Source

Empirical

Gaussian

Noise level $\varepsilon$

Reconstruction Error $C$

EEG

MEG
Source Reconstruction Results

10 Active Sources

Empirical

Gaussian

EEG

MEG
100 Active Sources

Empirical

Gaussian

Source Reconstruction Results

**EMG**

**MEG**

Noise level $\varepsilon$

Reconstruction Error $C$

Noise level $\varepsilon$

Reconstruction Error $C$

Noise level $\varepsilon$

Reconstruction Error $C$

Noise level $\varepsilon$

Reconstruction Error $C$
Source Reconstruction Results

**895 Active Sources**

**Empirical**

- EEG
  - Noise level $\varepsilon$
  - Reconstruction Error $C$

- MEG
  - Noise level $\varepsilon$
  - Reconstruction Error $C$

**Gaussian**

- EEG
  - Noise level $\varepsilon$
  - Reconstruction Error $C$

- MEG
  - Noise level $\varepsilon$
  - Reconstruction Error $C$
Source Reconstruction Results

10 Spatially Overlapping Active Sources

**Empirical**

**Gaussian**

**EEG**

**MEG**
**Summary**

$L_2$-Fusion Outperforms FMRI-DECD

- $L_2$-Fusion is **more noise-robust** than FMRI-DECD
- $L_2$-Fusion constantly outperforms FMRI-DECD on the large number of non-overlapping sources
- $L_2$-Fusion performs as well as FMRI-DECD on overlapping sources in case of MEG and **outperforms** it with EEG
- FMRI-DECD on MEG data **fails** with increased number of sources
- Gaussian noise model is well suited for modeling of E/MEG instrumental noise
Summary: Completed Work

- An overview of the existing multimodal imaging approaches revealed advantages, drawbacks and difficulties associated with any particular method.

- Two novel methods ($L_1$ - and $L_2$ -Fusion) of multimodal analysis were suggested.

- Neuroimaging problem to be tackled with multimodal methods was chosen.

- The simulation environment for a somatotopic experiment was created to facilitate comparative performance analysis of different methods.

- Simulated data was used to compare $L_2$ -Fusion with the conventional methods under different noise conditions and source arrangements.
Proposed Work Timeline

Sep – Oct 2005

- Evaluate the quality of reconstruction achieved using $L_1$-Fusion on the simulated dataset
- Apply proposed localization method to the simulated data to assess its performance
- Carry out a pilot fMRI/EEG experiment to verify applicability of the convolutional model for fMRI
Nov – Dec 2005

- Analyze the trade-off between spatial and temporal resolution achieved by the proposed methods on simulated data
- Setup fMRI acquisition protocol to achieve reliable sub-mm spatial resolution over the region of interest
- Design somatotopic experiment based on resolution limits of the methods revealed by simulation studies
Proposed Work Timeline: Continued

31 Dec 2005 – 02 Jan 2006
- Celebrate New Year

Jan – Mar 2006
- Collect fMRI and EEG data
- Perform the described analysis and draw conclusions
- Complete the dissertation
Do Not Forget to Shut Down the Lights

Thank you