Electromagnetic Imaging of Brain Function

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Magnetoencephalography

- MEG signals ~ 50-500fT (cf. Earth’s magnetic field ~50mT)
- Detected using SQUID magnetometers
- Gradiometers and magnetic screening reduce interference
- Alternative to scalp potential recordings (EEG)
Neuromagnetic Fields

- Magnetic fields are produced by current flow in apical dendrites in cortical pyramidal neurons

- Interested in spontaneous and event related fields

- Event-locked averaging typically required for adequate SNR in ERPs/ERFs

from Ritta Salmelin, low temperature lab, Helsinki university of Technology
Basic Source Model

- Columnar organization of cortex and spatial functional specialization on cortical surface lead to *current dipole model* to represent focal regions of activation.

- **Source Estimation Problem:** find one or more current dipoles representing current sources in cortex (with orientation normal to the surface)
Forward Problem

Forward problem

Current source distribution in the brain

Biot-Savart law

Magnetic field measurement outside the head
Forward Models

- Use quasistatic EM model to map from current source to measured fields
- Interested in “primary” rather than “volume” currents
- Spherical head: closed form
- Real head shape & conductivity from MR: use BEM or FEM
Forward Model: BEM

\[ b(r) = b_\infty(r) - \frac{\mu_0}{4\pi} \sum_{i=1}^{m} (\sigma_i^- - \sigma_i^+) \left( \int_{S_i} v(r') n_i(r') \times d / d^3 \right) da' \]

where: \[ b_\infty(r) = \frac{\mu_0}{4\pi} \int_G j^p(r') \times d / d^3 dr' \]

\[ v_\infty(r) = \frac{\sigma_j^- + \sigma_j^+}{2} v(r) + \sum_{i=1}^{M} \frac{(\sigma_i^- - \sigma_i^+)}{4\pi} \int_{S_i} v(r') n_i(r') \frac{d}{d^3} da' \]

where

\[ v_\infty(r) = \frac{1}{4\pi} \int_G j^p(r') \cdot d / d^3 dr' \]
Tesselated Surfaces

- Smoothed skull, scalp and brain surfaces for use in BEM forward computation
- High resolution cortical surface for use in cortically constrained imaging
Forward Model: Generic Head

- In absence of MRI, use a standard brain/head atlas – warped to subject landmarks – for head modeling (rather than sphere).
- Use inverse warp to map sources back to stereotactic atlas space for inter-subject studies.
- Warp based on thin-plate spline match of 25 cranial/scalp landmarks:
Mean dipole localization error (n=10 subjects) vs. true dipole location on cortex.

Localization using generic head model and TPS warp

Localization using spherical head model and TPS warp
Forward and Inverse Problems

**Forward problem**
- Current source distribution in the brain
- Biot-Savart law

**Inverse problem**
- Magnetic field measurement outside the head
- Source localization
\[
\begin{bmatrix}
  b_1(n) \\
  \vdots \\
  b_M(n)
\end{bmatrix}
= 
\begin{bmatrix}
  A_{11} & A_{21} \\
  \vdots & \vdots \\
  A_{1M} & A_{2M}
\end{bmatrix}
\begin{bmatrix}
  y_1(n) \\
  y_2(n)
\end{bmatrix}
\]

\[n = 1, \ldots, N\]
General Form of Forward Problem

- Magnetic fields are \textit{linear function} of the dipole amplitudes or moments
- Magnetic fields are \textit{nonlinear function} of the dipole locations and head model
- All inverse methods reduce to (approximately) solving

\[ b = Ay + n \]
Inverse Methods

- Competing requirements
  - Representation of complex spatio-temporal sources
  - Deal with relatively small number of spatial measurements

- Approaches
  - Cortically constrained imaging
  - Parametric source estimation
  - Scanning beamformers ("virtual depth electrode")
Imaging

- Place current dipole at each element in cortical surface tesselation
- Constrain dipole orientation using cortical surface normals
- Solve resulting set of linear equations for dipole amplitudes
- Equations highly underdetermined (~300 measurements, 100,000 unknowns?)
- Use regularization or Bayesian approach
Minimum Norm Imaging

Solve:

$$\min \left\| b - Ay \right\|_2^2 + \lambda \left\| Wy \right\|_2^2$$

Choice of weight function:

» \( W = I \) : minimum energy solution

» \( W = W_{\text{norm}} = \text{diag}\left[1/\|a_1\|, \ldots, 1/\|a_N\|\right] \) : column-weighted min-norm

» \( W = W_{\text{norm}} B \) where \( B \) is the Laplacian operator: LORETA (Pascual-Marquï et al 94)
Simulation Study

- 122 planar gradiometers (Neuromag-122)
- 100k cortical triangles
- 3 distributed sources
Minimum-Norm Solutions

Simulated

Estimated
Improving Image Resolution

- Introduce prior information (fMRI) in weighting function [Dale & Sereno 93, Liu, Belliveau, Dale 98]
- Non-quadratic penalty function, e.g.

\[
\min \left\| y \right\|_p = \left\| \sum_i y_i^p \right\|_{1/p} \quad \text{subject to} \quad \left\| b - Ay \right\| \leq \varepsilon
\]

[Jeffs & Leahy 87 (p <1), Matsuura & Okabe 95 (p=1)]

- Nonlinear Bayesian imaging methods [Baillet et al ‘98, Phillips et al ‘98, Shmidt et al ‘01…]
Sparse Focal Source Prior

Triangular Tessellation

Pixel of interest
Nine nearest pixels
Complete neighborhood

$Q = 1, \alpha = 0.2, \beta = 0.20$
$Q = 2, \alpha = 0.2, \beta = 0.06$
$Q = 3, \alpha = 0.2, \beta = 0.017$
Parametric Methods

- Current dipole fitting
  - Assume few current dipoles, unknown locations and moments (Brenner, Williamson, Kaufman 78)
  - Nonlinear least squares estimation problem with five parameters per dipole (Wood 82)

\[
\min_{y, \theta} \left\| b - A(\theta)y \right\|_2^2
\]

- For dynamic data (Scherg Von Cramon 85):

\[
\min_{Y, \theta} \left\| B - A(\theta)Y \right\|_2^2
\]
Limitations of Dipole Modeling

- Current dipoles may not adequately represent more distributed activation
- Non-convex numerical problem
- Can be difficult to interpret if sources not in cortex

- Use multipolar models
- Use subspace scanning methods
- Use cortical remapping
Multiple Sources

$$\begin{bmatrix} f_1(n) \\ \vdots \\ f_M(n) \end{bmatrix} = \begin{bmatrix} a_{11} & a_{21} \\ \vdots & \vdots \\ a_{1M} & a_{2M} \end{bmatrix} \begin{bmatrix} s_1(n) \\ s_2(n) \end{bmatrix}$$

$$n = 1, \ldots, N$$

$$F = AS^T$$
MUSIC Source Localization

- Column space of $F$ contains linear combinations of “gain vectors” for each source
- Span of column space can be found from SVD of data:
  \[
  \Sigma = F U V^T
  \]
- **MUSIC:**
  » compute gain vectors for each potential source location and project onto signal subspace:
  \[
  \frac{\| U^T a \|}{\| a \|} \leq 1
  \]
Cortically Remapped Sources

- Use patch-growing for cortical remapping
Multipolar Models

- ECD
- 1st Order Multipole

Increasing Source Size/Complexity
Use of multipolar models in cortical source localization
Virtual Depth Electrodes

- Adaptive beamforming or spatial filtering
  \[ y = W(x_0)^T \]
  \[ F = W(x_0)^T AS^T \]

  » Design weights with constraint:
  \[ W(x_0)^T G(x) = I \]

  » Control degrees of freedom by minimizing output power:
  \[ \min \ E[y^T y] = tr[W^T C_F W] \]
Solution

\[ W^T = \left[ G^T R_F^{-1} G \right]^{-1} G^T R_F^{-1} \]

- Scan over cortical surface
- weight by noise-only response: “Neural Activity Index”

“The cerebral oscillatory network of parkinsonian resting tremor”

Timmermann et al., Brain, 2002
Performance Analysis
And
Validation
Sources of Variability and Error

- Background environmental and physiological noise
- Intrinsic trial-to-trial variability in brain response
- Registration: MEG vs. anatomy
- Head models
- Data acquisition system model
Quantifying Performance

- Simulation/theory:
  - Theoretical: e.g. CR bounds
  - Monte Carlo simulations
  - Simulation-based ROC analysis

- Phantom studies
  - Localization accuracy

- Real data
  - bootstrap analysis
  - Permutation and RF based activation detection
  - Cross-modality (MEG vs. fMRI, depth electrodes....)
MEG vs. Depth electrode data

Dale et al., 2000

Dale et al., Neuron, 2000
Phantom Study

- 32 current dipoles in human skull phantom
- Ground truth from CT scan
- MEG data from Neuromag-22
- Sources fit using R-MUSIC, spherical and realistic BEM forward models
Phantom Localization Errors

- Average error for 32 dipoles using spherical head model: 4.1mm
- Average error for 32 dipoles using BEM head model: 3.4mm
Objective Task-Based Evaluation: ROC analysis

- **Sensitivity**: Probability of calling an actually-positive case “Positive”
  
  \[\text{TPF} = \frac{TP}{TP + FN}\]

- **Specificity**: Probability of calling an actually-negative case “Negative”
  
  \[\text{TNF} = \frac{TN}{TN + FP}\]
Objective Task-Based Evaluation: ROC analysis

- **Standard ROC analysis**
  - Binary decision for the presence of a target; location known

- **Location-Response ROC (LROC)**
  - Specify the location of a target
  - Only one target allowed

- **Free-Response ROC (FROC)**
  - Presentation and detection of multiple targets per image
  - Suitable for neuroimaging studies; we expect many simultaneously activated brain areas
Timeseries of two uncorrelated patches randomly positioned on the cortical surface

FROC curves for different regularization parameters (Tiknonov-Regularized Min-Norm reconstruction)

FROC curves for MUSIC, LCMV Beamformer, and Min-Norm reconstruction
Experimental data: Bootstrap of Dipole Localization

- **Approach:**
  - Epochs can be viewed as a set of independent realizations of the brain’s response
  - Sample with replacement from epochs and average to produce “new” data sets
  - Apply inverse procedure to each bootstrap data set
  - Cluster resulting dipoles (GMM)
  - Estimate statistics (mean and standard deviation) from the bootstrap resamples

- **Applied to** somatosensory stimulation data sets for 4 left and right hand digits, 30-60ms post stimulus; 500 trials per digit, 5000 bootstrap resamples
Somatosensory data
Electric stimulation of 4 digits of left and right hand

Locations

Time series
Activation Detection: Control of FWER in Cortical Imaging

- Imaging methods result in low resolution reconstruction maps
- Noise exhibits highly nonuniform spatial correlation
- We need a principled way of identifying true activation versus noise artifacts
- How: threshold voxel-wise statistic on the image to control FWER.
Permutation Test

Illustration of the summarizing procedure used to construct empirical distributions from the permuted data:

- **M** permutation samples are produced from the original data.
- The data are summarized successively in epochs, time, and space.
- The empirical distribution of $S_j$ can be used to draw statistical inferences for the original data.

$t$: Time index

$i$: Spatial index

$j$: Permutation index

$k$: Epoch index

### Table: Summarizing Statistics

<table>
<thead>
<tr>
<th>Method</th>
<th>Epoch-Summarizing</th>
<th>Time-Summarizing</th>
<th>Space-Summarizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$E_{ij}(t)$</td>
<td>$T_{ij}$</td>
<td>$S_j$</td>
</tr>
<tr>
<td>2</td>
<td>$E_{ij}(t)$</td>
<td>$T_{ij}$</td>
<td>$S_j$</td>
</tr>
</tbody>
</table>

- **Epoch-Summarizing**
  - Method 1: $\text{mean}_k \{ Y_{ijk}(t) \}$
  - Method 2: $\text{mean}_k \{ Y_{ijk}(t) \}$

- **Time-Summarizing**
  - $T_{ij}$

- **Space-Summarizing**
  - $S_j$

- $E_{ij}(t)$: Original current densities

- $E_{ij}(t)$: Normalized epoch summaries

- $T_{ij}$: Normalized time summaries

- $S_j$: Normalized space summaries
Simulation study

- Two sources where simulated. Source 1 (left) and source 2 (right) are shown on the original and smoothed version of a cortical surface.

- Timecourse of simulated sources and points of source identification at $\alpha=0.123$. Triangles for both methods, circles for only method 1.
Examples of significant activation maps for method 1 and 2 for two time instances. Reconstruction appears spread on the smooth cortical surface, but active sources are in neighboring sulci in the original cortical surface. The lowest achieved FWER for method 2 is $\alpha=0.123$. 
The data acquisition was done using a CTF Systems Inc. Omega 151 system. The somatosensory stimulation was an electrical square-wave pulse delivered to the right thumb of a healthy right-handed subject.

Method 2 appear to be more sensitive. At t = 22 ms it appears to correct the current density map, which shows the main activity in the ipsilateral hemisphere.
The BrainStorm ToolBox

Software:
http://neuroimage.usc.edu

BrainStorm

BrainSuite