MEG and fMRI for nonlinear estimation of neural activity

Sergey M. Plis
Computer Science UNM
New Mexico, USA, 87131
Email: pliz@cs.unm.edu

Terran Lane
Computer Science UNM
New Mexico, USA, 87131
Email: terran@cs.unm.edu

Michael P. Weisend
MIND Research Network
New Mexico, USA, 87131
Email: mweisend@mrn.org

Vince D. Calhoun
MIND Research Network
New Mexico, USA, 87131
Email: vdcahoun@mrn.org

Abstract—In this work we demonstrate improvement of the analysis of functional neuroimaging by combining electromagnetic measurements and functional MRI. We show that magnetoencephalography and functional MRI can complement each other improving estimation of neural activity and BOLD response. Tracking hidden neural activity is performed as inference of latent variables in a dynamic Bayesian network with continuous parameters. Inference is performed using a particle filter. We demonstrate that MEG and fMRI fusion improves estimation of the hidden neural activity and smoothes tracking of the BOLD response. We demonstrate that joint analysis stabilizes the differential system and reduces computational requirements.

I. INTRODUCTION

Magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) both provide indirect views of the underlying neural activity. Although the latent neural activity is the same for both modalities, the physical mechanisms of signal generation are quite different and lead to substantial differences in signal properties [1, 2]. Due to a high effective temporal sampling rate, MEG can provide instantaneous measurements of neural activity. On the other hand, the neurovascular transformation of neural activity into the fMRI signal identifies the location of the signal source with millimeter resolution. The two modalities have complementary strengths and weaknesses. Analyzing fMRI and MEG simultaneously allows us to focus on statistical properties of neural activity and overcome limitations accompanying each of these modalities.

We present a Bayesian framework for information fusion of fMRI and MEG data. Our framework ties these two modalities together through a hidden (latent) state variable that represents neural activity. Thus, our model provides a high-resolution statistical estimate of neural activity that takes advantage of the different strengths of fMRI and MEG data. We formulate the problem of information fusion as a general model of latent variable modeling in the context of dynamic Bayesian networks (DBN) [6], and demonstrate integrated analysis of fMRI and MEG using a sequential Monte Carlo method of particle filtering [7]. While the DBN framework is quite general and potentially adaptable to many neuroimaging inference problems, in this paper we focus on a special case. Specifically, we demonstrate the approach on a single activity source.

Information in the data enters the DBN formulation through likelihood functions. In order to construct these for fMRI and MEG we use forward models. Mechanisms of BOLD signal generation as a result of neural activity are currently not fully understood. However, sufficient progress has been made with the Balloon model of [8], where the dynamics of venous volume have been connected to the BOLD response. Changes in cerebral blood flow, venous volume and total deoxyhemoglobin are treated as nonlinear functions of physiological parameters and neuronal activity. The model was updated by [9] with an additional system connecting neuronal activity changes to changes in venous volume. This hemodynamic forward model (HFM) provides a tool for the study of the dynamics of fMRI as an effect of neuronal generation. In contrast to the HFM, the MEG forward model is linear for a source with fixed known locations and has high temporal resolution. If we think of neural activity as the electric activity, then we can compute its instantaneous effect on the measurement. The model is well studied and understood [1].

In this study, we use continuous data for both fMRI and MEG modalities (the observed state) and brain activity (the hidden state). This is in contrast to the methods that quantize the data and treat it as values of discrete random variables [11]. We perform neural activity estimation from fMRI-only, MEG-only and the combined measurements. We compare the results based on the ability to estimate neural activity and track the BOLD response. Comparison with known ground truth of a synthetic dataset allows us to a) reveal exact patterns of the effect of the fusion, b) vary such parameters as signal to noise ratio (SNR) and trace their influence on the analysis. In addition, we perform the analysis on an experimental fMRI and MEG dataset, where both modalities are collected from the same subject in two separate runs using the same visual event related paradigm to align the underlying activity.
Fig. 1. Graphical structure of the DBN that is used in this paper - displayed is a window for a single TR. Observations are denoted by squares (MEG and BOLD); hidden variables are denoted by circles (neural activity in an ROI and unobserved BOLD time points); arrows denote transition and observation models. Due to the sampling frequency difference, many MEG observations are available per single fMRI TR. Time between \( t_i \) and \( t_{i+1} \) corresponds to the MEG sampling time period.

II. DYNAMIC MODEL

If hidden neural activity is represented by a random variable, then several classical approaches can be used to infer the values of this variable through observations. For example, the hidden Markov model (HMM), and Kalman filter and its numerous modifications [6]. All these models are generalized by dynamic Bayesian networks (DBN) [6].

In this study we concentrate on a case with a single hidden variable. Of major importance in this paper is the task of inferring the values of this variable conditioned on the MEG and fMRI observations. The graphical structure of the DBN used in this paper is shown in Fig. 1.

Let us denote the random variable for the ROI with \( R_t \) for BOLD response with \( B \) and for MEG measurements with \( M \). In order to simplify the notation we denote with \( \{B\}, \{M\}, \{B,M\} \). In order to denote a sequence of natural numbers we use the column notation. The probabilistic model associated with the graphical structure of Fig. 1 can be described with the following joint distribution:

\[
P(R_{t_0:t_{TR}}, Z_{t_0:t_{TR}}) = P(R_{t_0})P(B_{t_0}|R_{t_0})P(B_{t_{TR}}|R_{t_{TR}}) \prod_{i=1}^{T_R} P(R_{t_i}|R_{t_{i-1}}) \prod_{i=0}^{T_R} P(M_{t_i}|R_{t_i})
\]

(1)

The graph from Fig. 1 encodes assumptions of the model. The Markov assumption amounts to \( P(R_{t+1} | R_{0:t}) = P(R_{t+1} | R_t) \). We need to define the transition and observation models to complete the description:

- The linear Gaussian transition model from \( R_t \) to \( R_{t+1} \):

\[
R_{t+1} = kR_t + \sigma_R \eta_t,
\]

(2)

where \( \eta_t \) is zero mean, unit variance Gaussian noise, and \( k \) and \( \sigma_R \) are estimated from the data.

- BOLD response observation model:

\[
B_t = \text{HFM}(R_t) + \sigma_B \eta_t,
\]

(3)

where HFM denotes hemodynamic forward model (Section II-A1) and \( \sigma_B \) is the variance parameter for fMRI observations, and \( \eta_t \) is Gaussian as before.

- MEG observation model:

\[
M_t = \text{MFM}(R_t) + \sigma_M \eta_t,
\]

(4)

where MFM denotes MEG forward model, \( \sigma_M \) is the variance parameter for MEG observations, and \( \eta_t \) is Gaussian as before.

The rest of this section describes the forward models used in the observation probability densities and the particle filtering technique, which we use to estimate the posterior distribution of the hidden state of the ROI.

A. Forward models

Neural activity is measured by fMRI and MEG only indirectly. This section describes the observation models used for these modalities.

1) Hemodynamic model: A biomechanical model of dynamic changes in deoxyhemoglobin content during brain activation was derived by [8]. The model connects blood flow to the observed BOLD response using so called Balloon dynamics. It was further developed by [9] to reflect the complete process of BOLD response formation starting from synaptic activity.

Regional cerebral blood flow (rCBF), as introduced by [9], is described by equations (5a) and (5b) driven by synaptic activity \( u(t) \).

\[
\dot{x}_1 = \epsilon u(t) - \frac{x_1}{\tau_s} - \frac{x_2 - 1}{\tau_f}
\]

(5a)

\[
\dot{x}_2 = x_1
\]

(5b)

\[
\dot{x}_3 = \frac{1}{\tau_0} \left( x_2 - f_{\text{out}}(x_3, \alpha) \right)
\]

(5c)

\[
\dot{x}_4 = \frac{1}{\tau_0} \left( E(x_2, E_0) - f_{\text{out}}(x_3, \alpha) x_4 \right),
\]

(5d)

where

\[ f_{\text{out}}(x_3, \alpha) = x_3^{1/\alpha} \]

(6)

\[ E(x_2, E_0) = 1 - (1 - E_0)^{1/x_2} \]

(7)

Relative BOLD response change can be computed from the hemodynamic model using:

\[ \Delta y(t) = V_0(k_1(1-x_4) + k_2(1-x_3^2/x_3) + k_3(1-x_3)) \]

(8)

where \( k_1, k_2, k_3 \) are dimensionless parameters [8].

There is no analytic solution to the nonlinear differential equations system (5) and it needs to be solved numerically. We use the 4th order Runge-Kutta method.

In our model noise enters BOLD measurements on the sensor level. Since the model returns the percentage of BOLD response change the final fitting to the measured signal is done by:

\[ y(t) = k(1 - \Delta y(t)) + \sigma_y \eta_t \]

(9)

where \( y(t) \) is the measurement at time \( t \), \( \eta_t \) is zero mean, unit variance Gaussian noise, and \( \sigma_y \) and \( k \) are estimated parameters.
2) **MEG forward model:** We use the spherical head model of [12] for computing the magnetic field outside the head. The simplicity of its implementation and the speed of execution has made it a commonly used model among researchers in the field. Due to the findings of [13], which states that taking into account only the brain compartment for finding external magnetic field is as good as using a more complex brain-skull-scalp approximation, this model is widely used as sufficiently accurate model for magnetic field measurements.

For a dipole $\mathbf{q}$ at position $\mathbf{r}_0$ inside the head, magnetic field outside the head at $\mathbf{r}$ is expressed as:

$$
\mathbf{b}(\mathbf{r}) = \frac{\mu_0}{4\pi F^2}(F \mathbf{q} \times \mathbf{r}_0 - \mathbf{q} \times \mathbf{r}_0 \cdot \nabla F),
$$

where $F = a(r\mathbf{a} + r^2 - \mathbf{r}_0 \cdot \mathbf{r})$, $\mathbf{a} = \mathbf{r} - \mathbf{r}_0$, $a = |\mathbf{a}|$, $r = |\mathbf{r}|$ and $\nabla F = (r^{-1}a^2 + a^{-1}\mathbf{a} \cdot \mathbf{r} + 2a + 2r)\mathbf{r} - (a + 2r + a^{-1}\mathbf{a} \cdot \mathbf{r})\mathbf{r}_0$.

### B. Particle filtering

A particle filter is a Monte Carlo estimator of the posterior probability of a set of state variables for a system with general probability distributions over hidden variables and potentially nonlinear dynamics [7]. The idea of particle filtering is based on the Monte Carlo histogram estimation. Given a set of samples $\{\mathcal{R}_i^{(t)}\}_{i=1}^N$ from $P(\mathcal{R}_i|\mathbf{Z}_{0:t})$, the distribution can be approximated with:

$$
P(\mathcal{R}_t|\mathbf{Z}_{0:t}) \approx \frac{1}{N} \sum_{i=1}^N \delta(\mathcal{R}_t - \mathcal{R}_t^{(i)}),
$$

where $\delta(\cdot)$ denotes the Dirac delta function. Using this we can approximate expectations of interest with

$$
I(f_t) \approx \frac{1}{N} \sum_{i=1}^N f_t(\mathcal{R}_t^{(i)}).
$$

Drawing samples from $P(\mathcal{R}_t|\mathbf{Z}_{0:t})$ is not easily possible, so samples are generated from $P(\mathcal{R}_t|\mathbf{Z}_{0:t})$. The task is accomplished through importance sampling [7], by sampling from a proposal distribution $Q$ and then weighting the particles with their importance ratio:

$$
w_t = \frac{P(\mathcal{R}_0|\mathbf{Z}_{0:t})}{Q(\mathcal{R}_0|\mathbf{Z}_{0:t})} \times \frac{P(\mathbf{Z}_t|\mathcal{R}_t)P(\mathcal{R}_t|\mathbf{R}_{t-1})}{Q(\mathcal{R}_t|\mathbf{Z}_t, \mathcal{R}_{t-1})} w_{t-1}.
$$

The recursive formulation of the problem leads to sequential algorithm that generates particles at the next time step and then weights them by the likelihood $P(\mathbf{Z}_t|\mathcal{R}_t)$.

fMRI measurements are only available every $\tau$ seconds, where $\tau$ is the length of the TR, which is too long for stability of the ODE system. When only fMRI is used for inference, we integrate the ODE using sampling rate that provides a stable solution. However, resampling and reweighting is performed only at those integration points where the measurements are available.

### III. Results

In this section we first demonstrate our approach on a simulated dataset. Next we demonstrate the approach on a real fMRI/MEG dataset collected in two separate runs with the same visual event related paradigm. Although our model does not limit the exact form of connection between the hidden unit and the observed modalities, in this section we simply treated this activity as an appropriately scaled input to MEG forward model and its absolute value as the input to the HFM.

#### A. Simulation

In order to find out how estimation of neural activity and tracking of the BOLD response depends on the data modality and their combination, we have constructed the following simulation. We use the cortical surface extracted by FreeSurfer software [14] from MRI of a human subject. A single ROI is selected from the FreeSurfer atlas: it is the bank of the superior temporal sulcus of the left hemisphere. Average fMRI activity of this ROI is generated by the hemodynamic forward model from Section II-A from simulated neural activity formed by equally spaced radial basis functions (RBF). In constructing simulation figures, we have expressed the BOLD signal as percentage of change around the baseline. Details of constructing simulated neural activity are described by [5]. Parameters of the HFM were fixed to a value close to the average of what has been estimated by [5]. The values are summarized in Table I. The exact form of the underlying neural activity formed by RBF is shown by the line in the bottom plots of Fig. 2. Using the hemodynamic forward model the activity was transformed into the BOLD response, which is shown in the top plots of Fig. 2 as the thin line.

Simulated neural activity was used to generate the MEG signal for 273 axial gradiometers corresponding to CTF 275 system. In simulations we set MEG sampling rate only 4 times higher than that of fMRI (2Hz). Going to a higher sampling rate (as we do in real data experiments) only improves the situation since more information about temporal dynamics of the system gets represented. To create realistic conditions for MEG, we have added Gaussian noise to this output. Signal to noise ratio (SNR) of simulated MEG signal used in our experiments is set to -40dB.

We have applied and compared three different approaches to estimation of neural activity and tracking BOLD response: using only simulated fMRI measurements (noise not added), using only simulated MEG measurements (-40dB SNR), and using both measurements simultaneously. Fig. 2 highlights the differences in the results with details provided in the caption.

An important improvement provided by the combined analysis is the decreased computational complexity of the filtering.
due to decrease in the number of particles needed. The more particles are used in the filter the better is the estimate of the posterior probability and hence of the quantities of interest. In the limit when number of particles goes to infinity the estimate is exact. For practical reasons, the number of particles should be as small as possible to enable fast computation while providing stable estimates.

For a fixed number of particles we can run the filtering procedure $M$ times, compute an estimate $\theta$ for each of the runs and compute its variance. This variance can be used to control the influence of the number of particles on the estimate. Ideally one would want this variance to be close to zero. However, in practice it suffices to see it stabilize.

For fMRI-only and the combined analysis we compute the estimate of the mean and its variance with $M = 800$ for number of particles $= 100k$ with $k \in \{1..10\}$. Fig. 3 demonstrates that fMRI-only filtering has much higher variance with the number of particles in the selected range and the variance is not stabilized even when 1000 particles are used. On the other hand the combined analysis provides stable results when number of particles is in the range $[400, 1000]$.

B. Real Data Application

Validity of the simulation results is tested on visual stimulation data collected from a healthy adult male subject. Both MEG and fMRI modalities were collected using the same paradigm: 120 trials of an 8 Hz checkerboard reversal; each trial consisted of 1 second of 8 Hz oscillating checkerboard stimulus and 4 sec ISI; with an additional 0-2 seconds of ISI randomly jittered (averaging out to 1 second of jitter).

Functional data were acquired at the remote site with EPI sequences on Siemens Avanto scanners at 1.5 Tesla (T). The imaging sequence parameters for these functional scans are as follow: Pulse sequence = single shot, single echo EPI, scan plane = oblique axial, AC-PC, copy T2 in-plane prescription, FOV = 240 mm, slice thickness = 3 mm, 1 mm skip, TR = 2000 ms, TE = 39 ms, FA = 90 degrees, $64 \times 64$ matrix, 1 shot.

FMRI data were preprocessed using the SPM5 software package. Images were motion-corrected using INRIalign – an algorithm unbiased by local signal changes (Freire and Mangin, 2001; Freire et al., 2002). Data were spatially normalized into the standard Montreal Neurological Institute space (Friston, 1995) and slightly sub-sampled to $3 \times 3 \times 3$ mm, resulting in $53 \times 63 \times 46$ voxels. Next the data were spatially smoothed with a $10 \times 10 \times 10$ mm full width at half-maximum Gaussian kernel. The resulting coordinates were converted to the Talairach and Tournoux standard space for anatomical mapping (Talairach and Tournoux, 1988).

MNE software [15] was used to localize cortical areas in the source space that are active while the task was performed. The areas that exhibited the most stimulus driven activity were manually identified (threshold levels set in MNE were 4.0, 8.5 and 9.5 for ftthresh, fmid and fmax parameters respectively) and corresponding ROIs from FreeSurfer [14] atlas were chosen to represent the forward model (see Fig. 4). All dipoles orthogonal to the cortical surface and belonging to selected ROIs were used to construct the MEG forward model corresponding to the single hidden neural activity node in the DBN structure of Fig. 1. The same ROIs were combined to build the HFM.

The data for both modalities were averaged with reference to the stimulus onset, discarding the first and the last 10 seconds of the run. FMRI data were linearly interpolated to the MEG resolution (1200Hz) before averaging. The averaging of fMRI time courses was performed over all of the voxels belonging to cuneus, precuneus and pericalcarine ROIs of the FreeSurfer atlas.

A substantial difference between our simulations and application of the method to the real dataset is the unknown
parameters of the hemodynamic forward model. In this experiment we have treated them as additional random variables independent of each other and evolving as part of the original DBN model with prior values from Table I. Thus we are able to treat unknown parameters of the HFM together with estimating neural activity and tracking BOLD response under the framework of DBNs. Since the state space increased when parameters were added, we have increased the number of particles to 2000 (an empirical estimate that produced consistent results) to better capture the posterior.

The results of application of our method to the real data are displayed in Fig. 5. They are presented in the same manner as the simulation results of Fig. 2 with detailed explanations given in the caption.

IV. Conclusions

We have presented a way to perform joint analysis of fMRI and MEG data for inferring latent neural activity and tracking the BOLD response in the framework of dynamic Bayesian networks. Nonlinear state estimation and tracking was performed using particle filtering framework. Simulations and real data results demonstrate the advantages of combining fMRI and MEG: improved tracking of the dynamics of neural activity, automatic control for signal delay properties of the BOLD response, improved computational properties of the system due to fewer required particles, and possibility of mitigating the consequences of inverse problem when HFM parameter estimation is required.

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References