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Removal of interference from fetal MEG by frequency dependent subtraction

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Abstract

Fetal magnetoencephalography (fMEG) recordings are contaminated by maternal and fetal magnetocardiography (MCG) signals and by other biological and environmental interference. Currently, all methods for the attenuation of these signals are based on a time-domain approach. We have developed and tested a frequency dependent procedure for removal of MCG and other interference from the fMEG recordings. The method uses a set of reference channels and performs subtraction of interference in the frequency domain (SUBTR). The interference-free frequency domain signals are converted back to the time domain. We compare the performance of the frequency dependent approach with our present approach for MCG attenuation based on orthogonal projection (OP). SUBTR has an advantage over OP and similar template approaches because it removes not only the MCG but also other small amplitude biological interference, avoids the difficulties with inaccurate determination of the OP operator, provides more consistent and stable fMEG results, does not cause signal redistribution, and if references are selected judiciously, it does not reduce fMEG signal amplitude. SUBTR was found to perform well in simulations and on real fMEG recordings, and has a potential to improve the detection of fetal brain signals. The SUBTR removes interference without the need for a model of the individual interference sources. The method may be of interest for any sensor array noise reduction application where signal-free reference channels are available.

Keywords

Magnetoencephalography; interference cancellation; frequency dependent subtraction; orthogonal projection; spontaneous fetal brain signals

1. INTRODUCTION

Fetal magnetoencephalography (fMEG) has a potential to provide neurological assessment of a developing fetus. Unfortunately, the fMEG signals are small and are easily

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overshadowed by interference from maternal and fetal magnetocardiogram (mMCG and fMCG), and various fetal, maternal, and environmental interference (Lengle et al., 2001; Eswaran et al., 2002a). The environmental interference can be successfully suppressed by shielding and noise cancellation within the MEG sensors (Vrba 2000; Taulu et al., 2005; Huotilainen et al 2005). We have used environmental noise cancellation by 3rd-order synthetic gradiometer (Vrba 2000). The method is similar to Signal Space Separation (SSS) (Taulu et al., 2005), as it can be shown that SSS expansion truncated to external order $L_{out} = 3$ is equivalent to the 3rd-order synthetic gradiometer. Also, we have not considered SSS because it requires better knowledge of fetal head position than was available during the work described in the paper. A variety of methods exist for separation of fMEG from noise and interference and each has advantages and disadvantages: principal component (PCA) based methods (Maier et al., 1987; Achim et al., 1988) were shown to attenuate the MEG signal (Kawakatsu et al., 2000); independent component-based methods (Cardoso 1998; Hyvarinen 1999; Makeig et al., 1997; Ziehe et al., 2000) are well suited to detect MCG signals, however exhibit permutation uncertainty and separation of noise and brain signals is difficult. Note that the clustering approach to ICA (Himberg et al., 2004) addresses this permutation uncertainty impediment. The methods based on nonlinear dynamics (Cawley and Hsu 1992) contain large numbers of adjustable parameters; and spatial filtering methods, such as beamformers (Van Veen et al., 1992; Spencer et al., 1992; Sekihara and Scholz 1996; Van Veen et al., 1997; Robinson and Vrba 1999), require knowledge of the fetal brain conductive model, which presently is imperfect because the fetal head position is known only approximately. To avoid the modeling errors, beamformers are used in a search mode where different fetal head models are placed on a grid within the maternal abdomen and beamformer outputs are computed for every model (Robinson and Vrba 2004; McCubbin et al., 2007; McCubbin et al., 2010; Vrba et al., 2007). The model which produces largest beamformer response is then considered to be the most accurate one. Unfortunately, such strategy is subject to ambiguity (Vrba et al., 2007) and models in a certain abdominal region will all produce comparable signals. Beamformer source localization is sensitive to non-stationarity and therefore is not well suited for longer records required for spontaneous signal analysis. Alternately, nearby mMCG and fMCG can be attenuated by spatiotemporal SSS (tSSS) (Taulu and Simola 2006). However this MCG suppression approach is not applicable in the current application, because the position of the fetal head in our work was not known well enough to accurately partition the abdominal space into internal and external volumes.

The mMCG and fMCG signals can be 100 or more times stronger than fMEG. Because the MCG signals are reasonably repeatable at every heart beat, a procedure was devised which averages the heart beats and constructs an orthogonal projection (OP) operator to project the MCG out of the fMEG recording (Teschke et al., 1995; Uusitalo and Ilmoniemi 1997; Huotilainen et al., 1995; Robinson et al., 2002; Eswaran et al., 2002b). The noise, interference other than MCG, and the MCG non-stationarity cause the OP operator to be constructed imperfectly. Because of these OP imperfections, small fMEG signals are difficult to separate from the large MCG interference. In spite of these potential difficulties, the fMEG was successfully detected by OP in the previous work (Robinson et al., 2002; Eswaran et al., 2002b).

Because the OP method was specifically designed to remove the MCG signals, it will not remove any other interference. Addition of PCA vectors corresponding to large eigenvalues would cause the OP to remove large, typically external, interference. However the PCA components of smaller amplitude interference of biological origin cannot be reliably distinguished from fMEG components, so OP cannot be used to suppress small amplitude interference. The OP method also causes signal redistribution (Vrba et al., 2004a; Vrba et al., 2004b). Such redistribution makes the signal maps difficult to interpret visually and the

OP operator must also be included in any analytic method. In addition, if the OP subspace happens to overlap the fMEG subspace, the fMEG signal magnitude will be reduced by OP.

To avoid the above problems we have adapted an input-output modeling (Bendat and Piersol 1986) to subtract interference from fMEG recording. The method uses a set of reference channels selected from sensors which are not near the fetal head, and it determines frequency dependent gains between the references and the measurement channels, using cross-spectral density matrix. The gains describe the coherent part between the reference and measurement channels. The interference is subtracted in frequency domain and the interference-free frequency domain signals are converted back into the time domain. The method will be referred to as SUBTR. The SUBTR method is similar to multiple-regression in frequency domain (e.g., Gasser et al 1985). SUBTR utilizes recorded data as references and does not use parametric modeling (e.g., Lange and Zeger 1997), and it utilizes Fourier transform processing rather than filtering data into multiple frequency bands and applying variable time shifts to it (e.g., Bayraktaroglu et al 2011). A method similar to SUBTR was proposed and used in the past (Preissl et al., 2001a; Preissl et al., 2001b) where the results depended on reference selection and it typically required use of maternal electrocardiogram in addition to MEG sensors. We have improved the method of reference selection and the internal algorithm and obtained a robust SUBTR method.

The reference channels for SUBTR must be selected from a sensor region which is sufficiently distant from the fetal head; otherwise the detected fMEG signals would be reduced by SUBTR. Therefore, for correct use of SUBTR, it is necessary to have an approximate knowledge of the fetal head position.

We demonstrate the superior performance of SUBTR over OP in the present work. The paper is organized as follows: In Section 2 the OP and SUBTR methods are reviewed and simulation and fMEG data are described. Results of OP and SUBTR application to simulation are shown in Section 3.1 and to spontaneous fMEG recordings in Section 3.2. Discussion and conclusions are presented in Section 4.

2. MATERIALS AND METHODS

2.1. OP

Fetal MEG recording is contaminated by maternal and fetal MCG (mMCG and fMCG). The MCG interference can be removed by OP (Tesche et al., 1995; Uusitalo et al., 1997; Huotilainen et al., 1995; Robinson et al., 2002; Eswaran et al., 2002b). It is assumed that the heart beats of the same type (i.e., maternal or fetal) are similar and can be averaged. First, the mMCG QRS complexes are marked and the fMEG recording is averaged to them. The time sample with the largest magnitude is selected to represent the most significant mMCG vector. This vector is projected from the data, data is re-averaged, and the next largest vector is selected and added to the list of mMCG vectors. The procedure is repeated until the residual averaged mMCG signal is less than a specified rms level, n_{rms0} . Then the procedure is repeated for fMCG. The mMCG and fMCG column vectors, $\mathbf{v}_k$, $k = 1, \dots, K$ are collected into an $M \times K$ matrix $\mathbf{V} = (\mathbf{v}_1, \dots, \mathbf{v}_K)$, where M is the number of channels. The orthogonal projection operator is constructed as (Sorenson 1980)

$$\mathbf{P}_{ortho} = \mathbf{I} - \mathbf{V}(\mathbf{V}^T \mathbf{V})^{-1} \mathbf{V}^T \quad (1)$$

where $\mathbf{I}$ is the identity matrix. The MCG vectors $\mathbf{v}_k$ are not known accurately, because they are measured from noisy data and in the presence of interference and non-stationarity. Assuming that noise and interference are normally distributed and isotropic in the sensor

space, a simple model can be derived which determines detectable fMEG amplitude as

$A_{fMEG_o} \approx \beta^{-1} \kappa^{-1/2} n_{rms0} N_{ave}^{-1/2}$, where N_{ave} is the number of averages used for fMEG processing ($N_{ave} = 1$ for spontaneous data, and $N_{ave} \approx 100$ for evoked data), n_{rms0} is the rms threshold for determination of the orthogonal projection vectors, κ is a fraction of raw fMEG channels in which the MCG interference is large, and β is a fraction by which the residual MCG interference is required to be smaller than the fMEG signal amplitude. The fMEG signal with amplitude A_{fMEG} will be detectable by the OP method if $A_{fMEG} > A_{fMEG_o}$.

Assume the following model parameters: $\beta = 1$, $\kappa = 0.3 - 0.5$ (about $\frac{1}{3}$ to $\frac{1}{2}$ of MEG channels contain large MCG interference), and $n_{rms0} = 100$ to 300 fT rms (the usual threshold for MCG vector determination). Then the model predicts that for evoked fMEG with $N_{ave} \approx 100$, the detectable amplitudes would be in the range of 15 to 50 fT, and for spontaneous fMEG with $N_{ave} = 1$ they would be in the range of 150 to 500 fT. These detectable fMEG amplitudes are just barely equal to the nominal fMEG amplitudes, indicating that the successful fMEG detection by OP cannot be guaranteed. This result may explain partially why fMEG signals were detected successfully by OP from some measurements and were not detected from others.

2.2. SUBTR

The SUBTR method is based on a general input-output model (Bendat and Piersol 1986). Denote outputs of MEG channels by $x_m(t)$, $m = 1, \dots, M$, where M is the number of channels. It is assumed that non-zero means are removed from the measurements. The fMEG signals are weak, and their amplitude will exceed the sensor and other noise only in channels which are close to the fetal head. In contrast the mMCG and fMCG sources are strong and the MCG signals will contaminate outputs of a majority of raw fMEG channels.

The interference will be removed from the raw fMEG one channel at a time. To simplify notation, denote the channel k from which the interference is being removed by $y(t) = x_k(t)$. To remove interference from channel k , we can assume that recording $y(t) = x_k(t)$ is likely to be contaminated by MCG and other interference and it may or may not contain fMEG. Thus $y(t)$ can be written as a superposition of fMEG (if present) and interference, $y(t) = b(t) + c(t)$, where $b(t)$ represents the fetal brain signal and $c(t)$ the MCG and other interference in channel k .

Select $n = 1, \dots, N_{ref}$ reference channels which are sufficiently distant from the fetal head such that they do not contain fMEG signal amplitudes above the noise threshold. In typical measurements, magnitude of the interference $c(t)$ is large, about 1 to 10 pT or more, while the magnitude of the fetal brain signal $b(t)$ is only about 10 to several hundred fT. Assume that the interference part of the $y(t)$ can be described as a linear combination of the reference channels (this is confirmed by observations), as

$$\hat{y}(t) \approx \hat{c}(t) = \sum_{n=1}^{N_{ref}} \int_0^{\infty} h_n(\tau) x_n(t - \tau) d\tau \quad (2)$$

where $h_n(\tau)$ are time dependent coefficients of the linear combination, $h_n(\tau) = 0$ for $\tau < 0$ for physically realizable systems, and the 'hat' signifies that the parameter has been estimated. It is assumed in Eq.2 that the reference channels were selected from the sensor array region where the fMEG signal is negligible and the right-hand side of Eq.2 describes mostly the interference. Interdependencies of all outputs are assumed to be frequency dependent and all equations will be expressed in frequency domain. The lower case letters denote time domain parameters and the capital letters their Fourier transforms. Then $Y(f) = B(f) + C(f)$, and

$$\widehat{y}(f) \approx \widehat{C}(f) = \sum_{n=1}^{N_{ref}} H_n(f) X_n(f) \quad (3.a)$$

where $H_n(f)$ are frequency dependent transfer functions between the references $n = 1, \dots, N_{ref}$ and the channel k . Eq.3.a may be rewritten in a matrix form as

$$\widehat{Y}(f) = \mathbf{H}^T(f) \mathbf{X}(f) \quad (3.b)$$

where $\mathbf{X}(f)$ is a column vector of reference signals at frequency f , $\mathbf{H}(f)$ is a column vector of the transfer functions between the references and the channel k , both with dimensions $N_{ref} \times 1$.

The fMEG signal in channel k can then be estimated as

$$\widehat{B}(f) = Y(f) - \widehat{Y}(f) \approx Y(f) - \widehat{C}_k(f) = B_k(f) + R_k(f) \approx B_k(f), \quad (4)$$

because the subtraction residual is small, $R_k(f) = C_k(f) - \widehat{C}_k(f) \approx 0$. The $\widehat{B}_k(f)$ is converted from frequency to time domain to obtain the estimated time course of fMEG signal from channel k .

The subtraction is done independently for each channel. The same references may be used for all channels, but the transfer functions $H_n(f)$ are determined separately for each channel k .

Not all references are equally important to the subtraction. In the absence of any knowledge about the reference precedence, the references should be ordered by ordinary coherence function between each input reference and the channel k (Bendat and Piersol 1986). The coherence should be computed at frequencies with dominant signal (frequency peaks), or, the ordering can be different at different frequencies.

The reference channels may be correlated among themselves. To further simplify the model, the inputs are also conditioned to make them uncorrelated since solution of the input-output model with uncorrelated inputs is simpler than that with correlated inputs (Bendat and Piersol 1986). The conditioning removes correlations among references. It proceeds iteratively on the ordered references by first removing the correlated part of the first reference from the second reference, then removing the correlated parts of the first and second references from the third reference, and so on. Transfer functions of the ordered and conditioned system are denoted by $L_{kn}(f)$.

The computation proceeds by converting all data records into frequency domain via Fourier transforms, ordering and conditioning the references, computing cross-spectral density matrix, $\mathbf{G}(f)$ between the ordered and conditioned channels, computing transfer functions $L_{kn}(f)$, computing transfer functions $H_{kn}(f)$ from $L_{kn}(f)$, computing estimated interference contributions, and removing them from the target channel (Bendat and Piersol 1986). Finally, the estimated fMEG signal is converted from frequency domain into time domain.

We have adopted the computational approach of ordering and conditioning the references because it allows arbitrary number of references with arbitrary correlations and does not have a problem with ill conditioned matrix inversion. Determination of the transfer functions

H_n in Eq.3.a can be better illustrated using the matrix notation in Eq.3.b. Transposing Eq. 3.b, multiplying it from the left by complex conjugated $\mathbf{X}(f)$, normalizing and taking expected value of both sides will yield

$$\mathbf{G}_{xy}(f) = \mathbf{G}_{xx}(f) \mathbf{H}(f) \quad (5)$$

where $\mathbf{G}_{xx}(f)$ is the cross-spectral density matrix of references and $\mathbf{G}_{xy}(f)$ is the cross-spectral density vector between the references and the measured channel k . If the inverse of $\mathbf{G}_{xx}$ exists, the transfer functions can be determined as $\mathbf{H}(f) = \mathbf{G}_{xx}^{-1}(f) \mathbf{G}_{xy}(f)$. In the presence of noise, this form of $\mathbf{H}(f)$ is optimal and minimizes the effect of noise in least square sense.

To estimate the cross-spectral density functions accurately, the data must be divided into trials and the cross-spectral density estimated by averaging over the trials. The trials are usually overlapping.

To avoid spectral leakage, the trials are shaped by a cosine window before computing Fourier transforms. The number of points within a trial, L , is computed from the desirable frequency resolution, f_{res} , and sample rate, f_s , as $L = f_s / f_{res}$. Fourier transforms for each channel and each trial are computed and arranged into a matrix $\mathbf{F}(f)$ of Fourier transforms with elements $F_{ij}(f)$ corresponding to channel i and trial j . The cross-spectral density matrix is computed as

$$\mathbf{G}(f) = N_{tr}^{-1} \mathbf{F}^*(f) \mathbf{F}^T(f) \quad (6)$$

where N_{tr} is the number of trials, '*' denotes complex conjugation, and 'T' denotes transpose (not conjugated transpose). The data is usually high-pass filtered with corner frequency f_o to remove slow variations at frequencies $< f_o$. The trial length must be matched to f_o , otherwise the fMEG signal will be distorted and its amplitude diminished. The correct matching condition is $L \geq f_s / f_o$ or $f_{res} \leq f_o$.

In present experiments, the fetal head position relative to the sensor array is known only approximately. The fetal head position can be determined from ultrasound (Micheli et al., 2010), placement of a marker coil on the maternal abdomen (Micheli et al., 2010), or from phase slip analysis (Govindan et al., 2009). Then sensors in the vicinity of the fetal head (a reference exclusion zone) are removed from the potential reference channel list.

The exclusion zone was defined as a region of the sensor surface where the signal is larger than noise. This is an irregular area, but we can approximate it by a conservative circle centered on a nearest point of the fetal head to the sensor array, and encompassing all sensor surface area where the signal is larger than noise. This exclusion zone radius depends on the source magnitude, position, and orientation within the fetal head. For evoked signals, source magnitudes of about 10 nA.m were estimated (Huotilainen et al, 2003), and source magnitudes of 4 to 40 nA.m were also reported (McCubbin et al, 2007).

The exclusion zone radius was determined by simulations over the range of fetal head depths below the maternal surface of 2 to 5 cm and over all possible source positions and orientations for sources at distance of 4 cm from the center of the fetal head. The threshold sensor noise level was 16 fT rms, corresponding to 5 fT/ $\sqrt{\text{Hz}}$ white noise density and 10 Hz bandwidth (larger bandwidths will result in larger noise thresholds and smaller exclusion zone radii). For the source magnitudes in the range from 4 to 40 nA.m, the maximum exclusion zone radius ranged from about 2.5 to 5 or 6 sensor spacing (the SARA sensor

spacing is about 3.1 cm). For typical source magnitude of about 10 nA.m, the exclusion zone radius would be 3 to 4 sensor spacing.

If the reference channels also detect the fMEG signal, then the change of the fMEG signal by the SUBTR was estimated to be αa fraction of the maximum detectable fMEG signal (the fMEG signal can be increased or decreased by the fraction αa). The parameter $a \approx 1$ describes ratio of interference (MCG) magnitude in the measurement and reference channels, and the parameter α is a fraction of the maximum detected fMEG signal seen by the references. Generally, change of the detected fMEG signal of about $\alpha = 0.1$ up to 0.2 can be tolerated. In addition, the interference (MCG) detected by the measurement channel is often less than that detected by the references and $a < 1$. In these situations the influence of SUBTR on the detected fMEG signal is further reduced.

Therefore, if a modest 10% to 20% change (either reduction or increase) of the signal amplitude by SUBTR was tolerated, the references would be allowed to detect about 10 to 20% of the peak fMEG signal. If the conditions for these signal amplitude changes were considered together with the above discussed noise conditions, the exclusion zone radius would be reduced by about 0.5 to 1 sensor spacing for the large sources (about 40 nA.m) and the exclusion zone radius would be practically unchanged for small source magnitudes.

The channels outside the exclusion zone may be spatially re-sampled with sampling distance of 6 to 9 cm (2 to 3 inter-channel spacing) to obtain the reference channels. The re-sampling is not strictly necessary but it reduces the computational load. However, in some cases the fMCG interference is localized to only a few channels outside the exclusion zone and therefore could be inadequately represented in the re-sampled reference list. We have used a hybrid approach in test analysis of an evoked data series; we selected all channels outside the exclusion zone and within 10 cm of the channel with maximum fMCG amplitude (obtained by averaging to fMCG markers) and then we added additional references by resampling the remainder of the channels outside the exclusion zone.

2.3. Methods for comparison of SUBTR and OP

The fMEG signal space vector orientation should be temporally stable for a reasonably stationary fetus. The degree of stability of the SUBTR and OP signal space vectors can be used to quantitatively compare the SUBTR and OP outcomes. To determine the fMEG signal space vector stability, first a reference signal space vector is determined from a time sample at which the fMEG data exhibits large deflection. Then normalized dot-products (correlation coefficients) between the reference vector and signal space vectors at the time samples at which the fMEG signal is larger than a certain threshold are computed, and their histogram is examined. If the fMEG vector is stable, the histogram will exhibit a single, relatively sharp peak. If the vector is not stationary and/or is contaminated by interference, the histogram will show multiple peaks or be excessively broad. Thus the histogram shapes provide quantitative comparisons of the SUBTR and OP vector stabilities.

Simulations and analytic computation for a perfectly stable vector in the presence of normally distributed and isotropic noise indicate that such measure of the vector stability should produce reasonably narrow histogram peaks even if the data SNR is low. But in the presence of noise the histogram peak will be shifted to correlation coefficients < 1 (or the vector angles > 0).

In addition, the SUBTR and OP results were also compared qualitatively by overlaying their time traces and matching their spatial distributions.

2.4. fMEG recordings

The fMEG data was collected using a 151 channel MEG system (SARA) (Robinson et al., 2000; Lowery et al., 2006). Subjects with normal pregnancies were recruited with informed consent and measurement protocols were approved by the institutional review board. An ultrasound exam was conducted immediately prior to the MEG session according to standard procedures and the following measures were estimated from the images: fetal head-center to heart-center distance, fetal orientation relative to maternal abdomen, fetal head major and minor diameters and circumference, and fetal head surface to maternal abdominal surface distance.

Localization coils were placed on the subject's left and right hips and spine. A fourth coil was positioned roughly over the fetal head location determined from the ultrasound exam (Micheli et al., 2010). Coil locations were measured at the beginning of each MEG session and were used as a rough registration of the subject to the MEG array.

Spontaneous fMEG data were recorded with sample rate $f_s = 312.5$ Hz and data was high-pass filtered with 0.5 Hz 6th order Butterworth filter. During the processing, frequency resolution for the SUBTR method was 0.4 Hz, window overlap was 50%, and 35 samples long median filter (0.112 sec) was applied in some cases. Data was smoothed by 0.05 sec window prior to rms calculations, and if used, Hilbert data envelopes were smoothed by 0.15 sec window.

Analysis discussed in this paper used data from a single non-moving fetus in quiet sleep state with gestational age (GA) of 32 weeks. Duration of the fMEG spontaneous activity recording was 30 min. The mother was still during the study and slept most of the time. The fetal head was in vertex position with head in the lower left maternal abdominal quadrant. Distance from maternal skin to fetal head presenting surface was 53.0 mm before and 53.4 mm after the study.

2.5. Simulations

Simulation geometry is shown in Fig.1. The sensor array was the actual SARA array. The data was simulated with sample rate $f_s = 312.5$ Hz and record duration $T = 100$ sec.

All sources used in simulation were current dipoles positioned in their respective conductive models. The following simulation sources were used: Maternal body: two mMCG sources, source of breathing artifact, and an interference source (e.g., maternal motion); fetal torso: two fMCG sources, one stationary and the other intermittent; fetal head: source of spontaneous fMEG. The interference waveforms were designed to be easily distinguishable from the fMEG waveform. Details of the source position and electrical characteristics are shown in Appendix A.

3. RESULTS

3.1. Simulations

To illustrate the analytic approach and various comparison methods, the simulation results are discussed in greater detail. The maternal and fetal MCG interference was cancelled by OP with the projection operator constructed in the usual manner from the exactly known MCG vectors, and by SUBTR employing 8 reference channels from the upper part of the sensor array. Spatial distributions of rms magnitude computed over all time samples, during various phases of processing, are shown in Fig.2.

Fig.2.a shows the noiseless fMEG signal. The signal is largest in two localized regions positioned roughly in the center of the sensor array and the peak rms magnitude is about 263

fT. The raw data which contains superposition of fMEG signal and all other maternal and fetal interference is shown in Fig.2.b. The signal is dominated by the interference and its peak rms amplitude is about 35 pT (more than 130× larger than that of the pure fMEG signal in Fig.2.a).

Signal distribution after MCG interference removal by OP is shown in Fig.2.c. The distribution does not resemble that of the pure signal in Fig.2.a, mostly because the non-MCG interference has not been cancelled by OP. Magnitude of the peak residual OP rms is about 493 fT. Finally, the signal distribution after SUBTR is shown in Fig.2.d. In this case the interference has been cancelled and the distribution closely resembles that of pure fMEG in Fig.2.a and rms amplitude is 196 fT.

A more detailed view of signal time traces is shown in Fig.3. Fig.3.a shows that OP removes the MCG interference, but leaves behind non-MCG interference (gray, bursts of about 1.5 Hz oscillations). When fMEG and interference do not overlap, as in the 19 to 22 sec time interval, the fMEG is retrieved by the OP; when they overlap, as in the 33 to 36 sec interval in Fig.3.a, the fMEG is not retrieved by the OP. In contrast, the SUBTR trace in Fig.3.b removes both the MCG and other interference so that the pure fMEG signal (black trace) and the SUBTR signal (gray trace) are in rough agreement. Note that the fMEG magnitude is slightly reduced by both SUBTR and OP (gray). The SUBTR reduction is caused by the references selected too close to the fetal head (see Section 2.2 for more quantitative discussion), and the OP reduction (19 to 22 sec interval in Fig.3.a) is caused by an overlap of the fMEG and MCG subspaces (normalized dot products between the fMEG and mMCG vectors were about 0.15 and between fMEG and the two fMCG vectors were 0.12 and 0.44, respectively).

Stability analysis of OP and SUBTR vectors is illustrated in Fig.4. Figs.4.a and 4.c show rms over all channels computed at each time sample in the range of 15 to 40 sec. For SUBTR in Fig.4.a the dominant feature is signal visible in time intervals of 19 to 22 sec and 33 to 36 sec (same time intervals as in Fig.3.b). For OP in Fig.4.c the dominant feature is the residual interference in the intervals of 23 to 28 sec and 33 to 38 sec. Signal is visible only in the interval 19 to 22 sec, and the signal in the interval of 33 to 36 sec is masked by the interference.

To evaluate the stability of spatial vectors, the reference vector was determined from a sample at which the fMEG attains a large value. The fMEG magnitude was judged from the channel LF1.

The SUBTR signal, similar to that in Fig.3, was displayed and the peak signal was manually selected at time sample of 9.03 sec. The reference vector was then constructed from output of all channels at this time sample. Angles between the reference vector and all SUBTR and all OP samples for which the signal exceeded the threshold (dashed horizontal lines at about 66 fT in Figs.4.a and 4.c) were computed as $\cos^{-1}$ of normalized dot product. Histograms of the angles are shown in Figs.4.b and 4.d.

The histogram in Fig.4.b (SUBTR) exhibits a single sharp peak, indicating that a single signal vector is present. In contrast, the histogram in Fig.4.d (OP) exhibits two peaks, indicating presence of two vectors. The first peak at 21 deg corresponds to the signal vector and the second, larger peak at about 82 deg corresponds to the interference vector. The interference peak has a larger number of counts because the interference magnitude is large and a larger number of samples exceed the threshold.

The vector stability measure in Fig.4 confirms that the SUBTR output corresponds to one stable vector, while the spatial pattern of OP alternates between the signal and the

interference vectors. With no temporal overlap between the fMEG and MCG signals, both SUBTR and OP perform equally well in simulations.

3.2. Spontaneous fMEG recordings

The performance of the SUBTR method was evaluated on a single fMEG data set, selected because the fetus was in quiet sleep state during the study. In quiet sleep state the fetus is not moving and the heart rate is stable. The absence of motion was indicated by actocardiogram (Govindan et al., 2010).

The mMCG can be completely cancelled by using 6 references in the upper part of the sensor array: RQ3, CQ0, LQ3, RP1, RP2, LP3 (Appendix B). Our previous experience indicates that as few as 2 or 3 references in the upper part of the sensor array are typically sufficient to remove the mMCG. After subtracting the mMCG, fMCG dominates the signal and the peak-to-peak amplitude over the sensor array is reduced from $(-20.7, 9.8)$ pT to $(-1.3, 3.2)$ pT. This improvement is sufficient to reveal spontaneous activity in the sensor rows A and B, even though the spontaneous activity is still contaminated by fMCG, which peaks in the middle of the sensor array in rows F, G, and H (see Appendix B for channel row naming).

In most cases, the fMCG is cancelled by a small number of additional references (one or two), but other sources of noise (environmental residual or noise from within the maternal body) require more references to be successfully cancelled. The SUBTR procedure was run with different sets of references comprising 11, 13, 16, 18, and 33 channels (all reference sets included the above mentioned 6 references for the mMCG cancellation). Geometrical positions of the 33 references are shown in Fig.5.a by black blocks.

To better characterize the reference performance, rms value of each channel and correlation coefficients between all pairs of channels were computed and plotted.

The correlation coefficient between the channel LA1 (close to the fetal head) and all other channels is shown in Fig.5.c for SUBTR and 33 references. The correlation coefficient is large for channels located in the vicinity of the fetal head (rows A, B, C, D) and is nearly zero between LA1 and channels in rows F to Q. Topography of the correlation coefficients relative to the channel LA1 is practically independent of the choice of the reference set and it always looks like Fig.5.c. This indicates that after SUBTR, the residual signal in the channels distant from the fetal head is uncorrelated to the spontaneous fMEG.

For SUBTR with 33 references shown in Fig.5.a, the correlation coefficient between a channel distant from the fetal head and all other channels is large only in the immediate vicinity of the 'distant' channel. An example is shown in Fig.5.d for channel RM1. This correlation between a 'distant' channel and all other channels depends on the reference set and for fewer references there may be extended islands of larger correlation throughout the sensor array, indicating presence of correlated interference. However, this interference signal remains uncorrelated with the fMEG signal in rows A, B, C, D for all reference sets tested.

The situation is different for OP. Correlation coefficient between LA1 and all other channels for OP is shown in Fig.5.f. Again, the channels in the rows A, B, C are strongly correlated to LA1 (which is similar to the SUBTR correlation in Fig.5.c). But, for OP the correlation between LA1 and distant channels is also large, exhibiting alternating spatial regions of positive and negative correlations. These correlated regions are due to either imperfect interference cancellation by OP or to signal redistribution by OP (Vrba et al., 2004a; Vrba et al., 2004b).

Correlation between a channel distant from the fetal head and all other channels for OP also shows areas of alternating spatial regions with large positive and negative correlations. This is illustrated in Fig.5.g for correlation between RM1 and all other channels. Explanation is similar to that presented for Fig.5.f.

Finally, rms computed over all channels is shown for SUBTR in Fig.5.b and for OP in Fig. 5.e. SUBTR shows large rms value only in the lower channels, rows A to D (or E), while OP shows large rms values for a majority of channels. There appears to be slight OP maxima in the lower channels A to C and in the center of the array, rows G to J (see Appendix B for the channel labeling).

Low frequency signal variations (spontaneous fMEG activity) as seen in the channel rows A to C is illustrated on an expanded scale in time domain for channel CB0 for time intervals 0 to 30 sec and 240 to 270 sec in Fig.6. The traces contain several large low frequency deflections at times 10–12, 26–28, and 251–253 sec.

The channel trace after high-pass filtering and subtraction of mMCG and fMCG in Fig.6 contains noise (but no residual MCG). To reduce this noise, a median filter with 35 sample length (0.112 sec) was applied to the data in Fig.6. Resulting channel CB0 time traces after median filtering for SUBTR and OP are compared in Fig.7.

Fig.7 indicates that in the channels where the fMEG signal is large, the OP and SUBTR traces show roughly similar behavior. Large signal amplitudes are observed in roughly the same time intervals, but their morphology does not always match accurately. For example, both SUBTR and OP exhibit large waveforms at the intervals 10 – 12 sec, 26 – 30 sec, and 250 – 255 sec. But accurate match of the SUBTR and OP waveforms exists only at time 27 sec. Note also that the magnitude of the OP signal in Fig.7 is about a factor of 2 smaller than that of the SUBTR signal (to facilitate the comparison, the OP in Fig.7 was multiplied by a factor of 2).

It was also shown that the morphology of the SUBTR traces is practically independent of the reference selection, and is nearly the same for channels where the fMEG spontaneous signal is large (channels rows A to D, see Appendix B).

While the SUBTR signal is large only in the channel rows A to D, the OP signal is also large in different parts of the sensor array and it is difficult to decide which part of the OP signal corresponds to the actual fMEG. This is illustrated in Fig.8, where three maps for OP and SUBTR are shown at different time instances. To create these maps, the Hilbert envelope of the data was computed, the envelope was resampled to 10 Hz sample rate, and a map was drawn for every sample for which the envelope magnitude exceeded 0.7 of the maximum envelope magnitude observed in the whole time interval. Three maps were selected for each OP and SUBTR. For SUBTR, all maps were similar and it did not matter which maps were selected. For OP, however, there was a large variation among the maps and the three OP maps in Fig.8 were selected to illustrate these diverse patterns. Because of the waveform variability shown in Fig.7, the OP and SUBTR maps in Fig.8 were selected at different times.

The maps in Figs.8.a to 8.c show that the vector obtained by OP has complex spatial time dependence and is switching among different orientation, while the spatial fMEG vector retrieved by SUBTR is reasonably stable over time. This is further emphasized in Fig.9 where the vector stability histograms are shown.

The histograms were drawn using only those time samples for which the rms computed over all channels exceeded the threshold of ≈ 25 fT rms. The threshold selection assures that only

the peaks of the rms over all channels are used for the construction of stability histograms. This avoids broadening of the histograms by noise. Because of large differences between the OP and SUBTR maps, the reference vectors for computation of angle distribution histograms in Fig.9 were selected separately for OP and SUBTR data.

The histograms in Fig.9 show that the fMEG vector obtained from SUBTR is more stable in time than the vector obtained from OP. The SUBTR histogram exhibits one relatively sharp peak at an angle of about 25 deg, while the OP histogram shows a broad range of values for angles between 40 and 90 deg. The peak shift to 25 deg is explainable by the noise in the system. The number of counts for SUBTR is about 2.6 times larger than that for OP and therefore broadening of the OP histogram is not due to introduction of noise by low threshold level.

The SARA system is equipped with reference magnetometers and gradiometer used for noise cancellation. The noise cancellation system contains four subunits, each consisting of full tensor gradiometer and vector magnetometer (Robinson et al., 2000; Lowery et al., 2006). It was thought that SUBTR could use these noise cancellation channels as references instead of (or in combination with) the sensing channels. This approach was tested for the fMEG data but it did not work well. Use of the noise cancellation channels as SUBTR references accurately reproduced the low frequency traces in the channel rows A to D (they were identical to that shown in Fig.7 for SUBTR). However, the MCG was not cancelled completely in differing regions of the sensor array.

4. DISCUSSION AND CONCLUSIONS

A frequency dependent procedure for removal of MCG and other interference from fMEG recordings was outlined. The method uses a set of reference channels and performs subtraction of interference in frequency domain. The interference-free frequency domain signals are converted back into the time domain. The method was called SUBTR.

Spontaneous fMEG was simulated together with mMCG, fMCG, maternal breathing or other biological interference originating from within the maternal body. The simulated data was processed by OP with a perfect projection operator (using the exact simulation vectors), and was also analyzed by SUBTR with 7 references. As expected, the OP was unable to cancel the biological interference, because the orthogonal projection operator was derived only from the MCG vectors. In contrast, the SUBTR cancelled both the MCG and biological interference and recovered the target fMEG signal well. The SUBTR method has an advantage over the OP method because it can also suppress all other interference in addition to MCG. The OP method could be extended to suppress other interference with dominant PCA components as well as MCG, but it cannot suppress interference with smaller PCA components which cannot be reliably distinguished from the fMEG components.

In situations where there is very little interference and maternal MCG is not present (e.g., in neonate subjects), both SUBTR and OP provide nearly identical results.

Because of the noise and other interference, the OP operator is not constructed accurately. The magnitude of this inaccuracy is high such that adequate suppression of MCG by OP and the subsequent successful detection of fMEG signals cannot be guaranteed. This is illustrated by variable spatial maps of fMEG signal after OP processing (Fig.8), which indicate that the recovered fMEG vector is not stable. The instability is caused by OP residuals. In contrast, SUBTR provides more consistent and stable fMEG vectors in situations where OP results are uncertain.

The OP method causes signal redistribution while the SUBTR method does not. Also, if the MCG and fMEG subspaces overlap, OP will reduce the fMEG magnitude. This magnitude reduction by OP as large as a factor of 4 relative to SUBTR was observed (factor of 2 reduction is demonstrated in Fig.7). SUBTR preserves the fMEG amplitude provided that the reference channels are selected from regions which are sufficiently distant from the fetal head, i.e., if the references are selected from channels in which there is no fMEG signal present above the noise level.

SUBTR was also applied to evoked data. Direct application of SUBTR to the data resulted in a rate of successful fMEG detections comparable to (or even slightly better than) that obtained by beamformer. An advantage of SUBTR over beamformer analysis is that SUBTR does not require accurate knowledge of the conducting model, but only an approximate knowledge of the sensor region above the fetal head. Furthermore, SUBTR is less sensitive to non-stationarity than the beamformer analysis. Reliable results were obtained with SUBTR processing over the entire 10 minute stimulated data segment while beamformer processing required the subdivision of the data segment into 2 minute analysis windows for reliable performance (McCubbin et al., 2010). The successful application of SUBTR to a large series of data (90 datasets) including a standardized and automated reference selection criteria has demonstrated the potential utility of the method.

It can be speculated that SUBTR could be applied as a pre-processing for beamformer analysis and could, in principle, improve the beamformer performance (because it would reduce the number of interference vectors which the beamformer must suppress). However, this hypothesis must be tested experimentally. It is known that application of OP prior to the beamformer computation does not change the beamformer outcome provided that the OP operators are included in the beamformer equations. Since SUBTR does not cause signal redistribution among the channels, it does not need to be included in the beamformer forward solution.

Interestingly channels of the SARA noise cancellation system were not suitable for the SUBTR method. It can be speculated that the cancellation failure for these channels was caused by larger separation between them and the maternal abdomen (which resulted in different spatial content).

In conclusion, the SUBTR method for removal of interference from fMEG data was outlined. The method was tested by simulation and on several real data sets, both for spontaneous and evoked fMEG data. SUBTR was found to perform well, and has potential to provide results which are as good as or better than the previously used OP and beamformer methods. The SUBTR method is particularly well suited for spontaneous data analysis where longer records are required and which may include non-stationarity. Also, the SUBTR can suppress other interference in addition to MCG with no need for individual source modeling (as e.g., in beamforming methods). However, the application of the method must still be investigated for a more extensive range of data. Finally, the method outlined here may be applied to sensor array data from other applications provided that reference channels can be selected which do not contain signal of interest.

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APPENDIX A: Simulation parameters

Maternal body model:

Radius = 40 cm, position relative to sensor center = (0, 0, -20) cm. Positions of the maternal sources are given relative to the center of the maternal conductive model.

mMCG source 1: position = (5, 6, 7) cm, orientation = 0.2 rad, magnitude = 400 $\mu\text{A.m}$, number of triggers = 87, at each trigger there was a spike with 0.1 sec width and 0.1 sec latency.

mMCG source 2: position = (1, 7, 6) cm, orientation = 1.2 rad, magnitude = 400 $\mu\text{A.m}$, same triggers as source 1, at each trigger there was a spike with 0.2 sec width and 0.6 sec latency.

Maternal breathing source: position = (-5, -2, 5) cm, orientation = 0.2 rad, magnitude = 25 $\mu\text{A.m}$, source was driven by a sinusoidal waveform with frequency = 0.25 Hz and random amplitude variation of 30%.

Maternal interference source: position = (0, 1, 0) cm, orientation = 0.01 rad, magnitude = 150 $\mu\text{A.m}$, number of triggers = 8, source waveform was burst of 1.5 Hz frequency with duration of 5 sec.

Fetal brain model:

Fetal head position relative to the maternal model center: (1, -12, -1) cm, fetal head radius: 4 cm, fetal source position is measured relative to the fetal head center.

Fetal brain source: position = (-2.5, 0, 2.5) cm, orientation = 0, magnitude = 2 nA.m, number of triggers = 6, signal waveform: a randomized burst of 0.7 Hz frequency with duration of 3 sec.

Note: Waveforms of the maternal interference source and the fetal brain source were specifically designed to be easily distinguishable. In reality, low frequency interference and fMEG source waveforms could have similar appearance.

Fetal torso model:

Fetal torso position relative to the maternal model center: (-3, -1, -5) cm, and the fetal torso model radius: 8 cm. Fetal torso source position is measured relative to the fetal torso center.

fMCG source 1: position = (-2, -5, 2) cm, orientation = 1.6 rad, magnitude = 7 $\mu\text{A.m}$, number of triggers = 197. There was a spike with 10 msec width and 0 sec latency at each trigger. The source was on at all times.

fMCG source 2: position = (-2, -5, 2) cm, orientation = 0, magnitude = 8 $\mu\text{A.m}$, number of triggers = 70. Trigger separation was as for fMCG source 1, but the triggers were placed in several intermittent groups. At each trigger there was a spike with 10 msec width and 0 sec latency. Note that the fMCG source 2 has different orientation than the fMCG source 1.

APPENDIX B: Organization and labeling of SARA 151 channels

Channels are organized in nearly straight rows (in x-y projection) and the labels roughly correspond to the geometrical channel positions (Robinson et al., 2000; Lowery et al., 2006). Row A is in the perineal area, and the row Q is at the top of the maternal abdomen. Prefixes L and R indicate channels on the left and right side of the mother, respectively, and prefix C indicate channels on the maternal body axis. Channels LC1, LN4, LP2, shown in *italics*, were disabled.

LQ3, LQ2, LQ1, CQ0, RQ1, RQ2, RQ3
 LP3, LP2, LP1, RP1, RP2, RP3
 LO4, LO3, LO2, LO1, CO0, RO1, RO2, RO3, RO4
 LN5, LN4, LN3, LN2, LN1, RN1, RN2, RN3, RN4, RN5
 LM5, LM4, LM3, LM2, LM1, CM0, RM1, RM2, RM3, RM4, RM5
 LL6, LL5, LL4, LL3, LL2, LL1, RL1, RL2, RL3, RL4, RL5, RL6
 LK6, LK5, LK4, LK3, LK2, LK1, CK0, RK1, RK2, RK3, RK4, RK5, RK6
 LJ6, LJ5, LJ4, LJ3, LJ2, LJ1, RJ1, RJ2, RJ3, RJ4, RJ5, RJ6
 LI6, LI5, LI4, LI3, LI2, LI1, CI0, RI1, RI2, RI3, RI4, RI5, RI6
 LH6, LH5, LH4, LH3, LH2, LH1, RH1, RH2, RH3, RH4, RH5, RH6
 LG5, LG4, LG3, LG2, LG1, CG0, RG1, RG2, RG3, RG4, RG5
 LF4, LF3, LF2, LF1, RF1, RF2, RF3, RF4
 LE3, LE2, LE1, CE0, RE1, RE2, RE3
 LD3, LD2, LD1, RD1, RD2, RD3
 LC2, LC1, CC0, RC1, RC2
 LB2, LB1, CB0, RB1, RB2
 LA2, LA1, RA1, RA2

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Fig.1. Simulation geometry and source locations, projected onto y - z plane. Thick curved line – symbolic representation of sensor array (real SARA sensor array was used). Small circle – fetal head, dashed circle – fetal torso, gray – maternal body. Dots – positions of sources (see Appendix A for details).

Fig.2.

Rms computed over all channels. Height of the blocks indicate rms magnitude. (a) Pure fMEG data, peak rms = 263 fT, (b) Raw data consisting of fMEG and all interference (mMCG, maternal breathing, interference source, and fMCG), peak rms = 37 pT; (c) After application of interference removal by OP, peak rms = 493 fT; (d) After application of interference removal by SUBTR: high-pass filtering (0.5 Hz, 6th order Butterworth filter), mMCG subtraction using references RQ3, RQ2, LQ3, LQ2, RP1 (see Appendix B), fMCG subtraction using references RJ2, RJ4, and LJ5, and median filtering with 35 samples window. Peak rms = 196 fT.

Fig.3.

Simulation, comparison of noiseless signal with OP and SUBTR results, channel LF1 (see Appendix B). Black – noiseless fMEG signal, gray – after OP or SUBTR. Interference: bursts of about 7 to 8 periods of 1.5 Hz oscillations. fMEG signal: burst of about 2 periods of 0.7 Hz oscillations. Perfect OP vectors for mMCG and fMCG were used. Vertical axis is in fT. (a) OP and noiseless signal; (b) SUBTR and noiseless signal.

Fig.4. Stability of spatial distribution at threshold level ≈ 66 fT. Upper plots – rms computed over all channels in fT as a function of time. Data smoothed by 0.05 sec window before computation of rms. Dashed horizontal lines: threshold rms. Lower plots – Distribution of angle λ with bin size 2 deg. Reference vector derived from SUBTR channel LF1 at time 9.03 sec. (a, c) Rms over all channels; (b, d) Angle distribution histograms; (a, b) SUBTR; (c, d) OP.

Fig.5.

Spontaneous fMEG data, comparison of SUBTR and OP for 5 min of data. The data was median filtered with 35 sample window after application of SUBTR or OP. For correlation coefficients the black blocks indicate positive, and the gray blocks negative, and the block height indicates the correlation coefficient magnitude. (a) Black blocks indicate 33 reference positions for SUBTR obtained by nearly uniform spatial resampling, three empty blocks at the bottom are markers for the largest spontaneous fMEG signal; (b) Rms for all channels after SUBTR, rms is in the range (0, 50.5) fT; (c) Correlation coefficient between channel LA1 and all other channels for SUBTR; (d) Correlation coefficient between channel RM1 and all other channels for SUBTR; (e) Rms over all channels after OP, rms is in the range (8.84, 31.0) fT; (f) Correlation coefficient between channel LA1 and all other channels for OP; (g) Correlation coefficient between channel RM1 and all other channels for OP.

Fig.6. Spontaneous fMEG time traces in the intervals 0 – 30 sec and 240 – 270 sec after high pass filtering with filter frequency of 0.5 Hz and subsequent removal of mMCG and fMCG by SUBTR using reference set shown in Fig.5.a. Channel CB0.

Fig.7. Spontaneous fMEG, comparison of SUBTR and OP traces for channel CB0, both median filtered with 35 samples window. OP was multiplied by a factor of 2 and inverted to better match the amplitude and phase of the SUBTR trace. Black – SUBTR, gray – OP.

Fig.8.

Spontaneous fMEG data, maps of source activity at times when the envelope amplitude exceeded 0.7 of the maximum envelope amplitude in the whole plot. Data was examined in 0.1 sec increments. Length of the vertical bars indicates signal magnitude at each channel.

Black – positive, gray – negative. (a, b, c) OP; (d, e, f) SUBTR; (a) Amplitude (–63.7, 104) fT; (b) (–46.6, 124) fT; (c) (–84.4, 123) fT; (d) (–29.8, 193) fT; (e) (–203, 29.9) fT; (f) (–25.3, 178) fT.

Fig.9.

Spontaneous fMEG data, stability of spatial distribution at threshold level ≈ 25 fT. (a, c) Rms computed over all channels (in fT) as a function of time. Data was smoothed by 0.05 sec window before computation of rms. Dashed horizontal line: threshold level; (b, d) Distribution of angle λ with bin size 2 deg. Number of counts is about 2,800 for SUBTR, and 1,090 for OP; (a, b) SUBTR, reference vector derived from SUBTR channel CB0 at time 13.4 s; (c, d) OP, reference vector derived from OP channel CB0 at time 17.2 s.