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The effect of volume conductor modeling on the estimation of cardiac vectors in fetal magnetocardiography

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Abstract

Previous studies based on fetal magnetocardiographic (fMCG) recordings used simplified volume conductor models to estimate the fetal cardiac vector as an unequivocal measure of the cardiac source strength. However, the effect of simplified volume conductor modeling on the accuracy of the fMCG *inverse solution* remains largely unknown. Aiming to determine the sensitivity of the source estimators to the details of the volume conductor model, we performed simulations using fetal-maternal anatomical information from ultrasound images obtained in 20 pregnant women in various stages of pregnancy. The magnetic field produced by a cardiac source model was computed using the boundary element method for a piecewise homogeneous volume conductor with three nested compartments (fetal body, amniotic fluid and maternal abdomen) of different electrical conductivities. For late gestation, we also considered the case of a fourth highly insulating layer of *vernix caseosa* covering the fetus. The errors introduced for simplified volume conductors were assessed by comparing the reconstruction results obtained with realistic versus spherically symmetric models. Our study demonstrates a significant effect of simplified volume conductor modeling, resulting mainly in an underestimation of the cardiac vector magnitude and low goodness-of-fit. These findings are confirmed by the analysis of real fMCG data recorded in mid-gestation.

Keywords

fetal magnetocardiography; cardiac vector; boundary element method; volume conductor

1. INTRODUCTION

Fetal magnetocardiography (fMCG) has emerged as an attractive technique for *in-utero* assessment of cardiac electrophysiology, especially for its significant potential in assessing

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pathophysiological conditions (Leeuwen *et al.* 2000, Wakai *et al.* 1998, Hamada *et al.* 1999, Wakai *et al.* 2003, Cuneo *et al.* 2003, Comani *et al.* 2004). The major advantage of fMCG over fetal electrocardiography (fECG) is given by its notably superior signal quality, as the magnetic field is considerably less affected by tissues with low electrical conductivity (Cuffin 1978), which can drastically diminish the amplitude of the fECG signals. As a result, fECG is rarely recorded successfully in obese individuals, and it is considerably compromised by the formation of the electrically insulating *vernix caseosa* in late pregnancy. In contrast, the magnetic recordings allow high resolution measurements from the second trimester of gestation to birth.

The fECG and fMCG signal morphology is influenced by the fetus position relative to the sensing system, and by the geometry and electrical conductivity of fetal and maternal tissues surrounding the fetal heart. These factors modulate the recorded cardiac cycle waveforms and may prevent a straightforward comparison of the signals amplitude across subjects. One approach to this problem is to examine the fetal cardiac activity in source space rather than sensor space. Early fECG studies investigated the role of volume conductor on the estimation of fetal cardiac vectors and fetal vector loops (FVL) (Oostendorp *et al.* 1989b). Before 28 weeks of gestation, the electric potential distribution at the maternal abdomen was quite well approximated by homogeneous conductors and a dipole model of the fetal heart. FVLs obtained with this approach were similar to those of newborns (Ellison and Restieaux 1972), but the source strength was significantly underestimated when compared to predicted data from animal studies (Nelson *et al.* 1975). The vector magnitude estimates were improved by refining the volume conductors to account for the fetal body and amniotic fluid. After 28 weeks, however, the fECG amplitude drops significantly, and the volume conductor requires additional compartments to model the insulating vernix. Also, the possible presence of non-uniformities or holes in the vernix may play a significant role on the amplitude and distribution of the electric potential measured by fECG.

The volume conductor non-homogeneities affect differently the electric potential (measured by fECG) versus the magnetic field (measured by fMCG). One consequence is that the electric potential on the maternal abdomen vanishes in the presence of insulating layers, while the magnetic field does not. In addition, plane-parallel layered volume conductors, or those with nested compartments approaching spherical symmetry can be approximated by simplified homogeneous models in biomagnetic applications, overcoming the need to know the electrical conductivity or to account for the presence and precise geometry of compartments with different conductivities. Assuming that magnetic fields are less influenced by non-homogeneities in the conductivity of the maternal abdomen and fetal body compartments, more recent fMCG studies (Leeuwen *et al.* 2004, Horigome *et al.* 2001, Popescu *et al.* 2006) used reconstruction techniques to estimate the fetal cardiac vectors by considering either half-space or spherically symmetric volume conductors. These simplified models allow using closed-form analytical solutions of the forward field (Sarvas 1987, Ilmoniemi *et al.* 1985), and do not necessarily require imaging of the fetal-maternal unit, which could represent substantial practical benefits. Although each of these studies acknowledged the potential limitations of the strategy, the results of these efforts showed promise for characterizing the strength of the cardiac vector with fetal growth (Leeuwen *et al.* 2004), or to diagnose prenatal hypertrophy (Horigome *et al.* 2001). On the other hand, data from computational studies indicates that the influence of non-homogeneities in fetal-maternal anatomy on the *forward solution* of the magnetic field can be substantial (Stinstra and Peters 2002). The extent to which these modulations affect the inverse fMCG solution when simplified conductors are employed remains however uncertain.

One way to address this issue is to conduct a systematic investigation looking at how the simplified volume conductor modeling is directly reflected in the accuracy of the fMCG

inverse solution. For this purpose, we used realistic approximations of the volume conductor derived from 3D ultrasound images of the fetal-maternal anatomy. Computer simulations were carried out to characterize middle and late gestation by considering three-compartment (i.e. fetal body, amniotic fluid and maternal abdomen) volume conductors, with a fourth compartment added to account for an *uniform* layer of *vernix caseosa* in late gestation. More complex models, *e.g.* including holes in the vernix have been also considered by studies using forward magnetic field simulations (Stinstra and Peters 2002). For the purpose of our study, however, we focus on only two cases with 3 or 4 nested compartments separated by closed surfaces, which can in principle favor the use of simplified spherical models. The impact of more complex modeling of the vernix layer will be discussed in the last section, in light of the present findings. The geometry of the boundary surfaces for compartments of different conductivity varies significantly between subjects and gestational ages (GA). In addition, the accuracy of the inverse biomagnetic solution may also depend on such factors like the source model, choice of source space and optimization algorithm. Thus, we determined that the use of *e.g.* a single or just a few setups to characterize the effect of volume conductor modeling is insufficient, since the way the findings generalize would remain unknown. To overcome these issues, we use ultrasound data from a relatively large number of subjects, and we evaluate the accuracy of the inverse solution for two optimization schemes, in scenarios that incorporate different volume conductor models, and none or minimal information on the approximate source location. This strategy allows to cross-validate the results and to demonstrate the effect of volume conductor modeling on the accuracy of the inverse fMCG solution. Finally, a comparison of the inverse solutions obtained with realistic approximations of the volume conductor versus spherically symmetric models is conducted using real fMCG data recorded in mid-gestation.

2. METHODS

2.1. Cardiac vector estimation in fMCG

The cardiac muscle depolarization involves spatially propagating waves that can be described by a dense distribution of current sources (Malmivuo and Plonsey 1995). When measurements are performed at relatively large distances from the source distribution, the magnetic field appears to be generated by an equivalent current dipole (ECD), such that the ECD strength and orientation approximate at any time the vector summation of all simultaneously active current sources. This represents the magnetic equivalent of the electric *cardiac vector* concept applied in adult ECG. Under this hypothesis, initial studies have used the ECD model to fit the fMCG data at the peak of the QRS complex (Leeuwen *et al.* 2004, Horigome *et al.* 2001). Since the ventricular depolarization generates fMCG signals that differ substantially across sensors (figure 1), one potential difficulty is to select the QRS time point that corresponds to a unique and well defined phase of ventricular depolarization, *e.g.* the instant of maximum net cardiac current or the maximum cardiac vector magnitude (MCVM). Using a single (*e.g.* most sensitive) channel or the mean global field (MGF) across channels to determine the time point of highest signal amplitude remains vulnerable to uncertainties introduced by the time-varying behavior of the cardiac vector orientation.

In addition, the ECD model is predicated on the assumption of a small size of the fetal heart and a relatively large source-to-sensor distance. The validity of this assumption relates to the spatial resolvability of dipolar sources and depends on factors such as the (unknown) source parameters, or the (known) sensors distribution and configuration. In general, the number of large singular values of the spatio-temporal data matrix indicates that a single fixed dipole may not necessarily explain well the whole QRS data in fMCG recordings. Thus, in our study we evaluate two alternative approaches, which offer more flexible frameworks for fitting the fMCG data on the whole QRS interval: a rotating dipole and a multiple-dipole model. A rotating dipole may be viewed as three collocated fixed dipoles with independent

time series, such that its orientation varies with time. The multi-dipole model does not require individual dipoles to be co-located. In this case, the cardiac vector is obtained from the vector summation of all individual dipoles. Estimating the cardiac vector at any instant in time allows for a direct identification of the MCVM latency on the vector magnitude waveforms. Furthermore, the time-course of the vector magnitude would in principle enable other cardiac measurements of interest such as the waves duration or time-amplitude integrals.

2.2. Ultrasound recordings

Using realistic approximations of the volume conductors in fMCG requires the 3D segmentation of the boundary surfaces of several fetal-maternal anatomical compartments with different electrical conductivities (Stinstra and Peters 2002). The 3D images of the fetus and maternal abdominal tissues must be acquired immediately before or after the fMCG recording (to minimize the risk of fetal repositioning), limiting the use of MRI. For the current study we used the so-called *free-hand* 3D ultrasound, in which a 3D digitizer is attached to an ultrasound probe to record the positions and orientations of the probe simultaneously with the B-scans, for subsequent co-registration and reconstruction of the volumetric data. To achieve this task, we used the Stradwin 3D Ultrasound Acquisition and Visualization software (Cambridge University, UK) with a GE Logiq-P5 ultrasound system and a TrakSTAR positioning digitizer system (Ascension Technology Corp., USA) attached to the ultrasound probe. The calibration of the probe-digitizer system was performed with an ultrasound phantom. For the purpose of our simulation studies, 3D images of the fetus and maternal abdominal tissues were acquired from 20 pregnant women. Informed consent was obtained from each subject before participation in the experiment. The study was approved by the Institutional Review Board of the University of Kansas Medical Center. Data from 10 subjects were recorded between 22 and 28 weeks of gestation, while the remaining 10 subjects were recorded between 32 and 36 weeks. For each case, series of images were acquired by scanning the maternal abdominal surface from side to side and upper to lower abdomen for a total number of ~ 5000–6000 frames.

Co-registration of the ultrasound images with the fMCG sensor array was accomplished using three fiducial markers placed at non-collinear locations on the maternal abdomen (right side, left side, and sternum). Each marker's location was recorded by positioning the center of the ultrasound probe at that location and recording the corresponding frames. These frames were used to identify the markers locations on the volumetric image, but were excluded from subsequent processing. The markers positions relative to the fMCG sensors were determined in the biomagnetometer by localizing three coils placed at those locations.

2.3. Processing of volumetric ultrasound images

We developed a standard approach to model the fetal body compartment of the volume conductor. The fetal head and trunk were approximated for each subject with a sphere and an ellipsoid, respectively. This methodology relied on the manual identification of two fiduciary points, and on performing two standard biometric ultrasound measurements: the abdominal circumference (AC) and the head circumference (HC). Based on these measurements, two parameters used to model the fetal body were derived: (1) the extent of the small axis of the ellipsoid used to model the fetal trunk (using AC), and (2) the radius of a sphere used to model the fetal head (using HC). The fiduciary points used to model the fetal body were the *fetal head center* and the *fetal coccyx*, which were manually identified on the recorded B-scans. The long axis of the ellipsoid (fetal trunk) was defined from the head center to the coccyx, with the ellipsoid center set at the middle of this line. The fetal body was subsequently modeled as the merged volume of the ellipsoid and sphere determined as described above. The amniotic sac (AS) was approximated by an ellipsoid

with size and position determined from manually identified fiduciary points. These points defined the ends of the long axis of the sac ellipsoid in longitudinal cross-sections through the fetal head and spinal cord, and the *amniotic sac center* (middle of the long axis), and were used to estimate the length of the short axis of the ellipsoid (passing through the AS center).

The ultrasound volumes were then resliced using planes oriented in the axial direction relative to the maternal abdomen. Resliced frames along with the coordinates of the fiduciary points were processed in Matlab to set the voxels of the fetal body and AS compartments to predefined intensity levels. An additional dark gray layer has been added to represent the outer maternal abdominal skin. The images were transformed to ANALYZE format for a final processing step involving the segmentation of the different compartments (performed with CURRY 5.0, Compumedics Neuroscan). All compartments were visually inspected, and the AS compartment was locally adjusted using regional 3D dilation and/or setting pass markers to improve its local shape and to ensure that the fetal body and AS compartments did not intersect with each other. The triangularization of the boundary surfaces was done using average triangle sides of 5 mm, 10 mm, and 20 mm for the fetal body, AS and abdominal compartments, respectively. For late gestational data, a 5 mm dilation of the fetus compartment was used to derive a vernix mesh with an average triangle side of 5 mm. Source space points were created inside the middle part of the fetal trunk as a regular grid with 3 mm average spacing and no points at less than 5 mm from the fetal body surface. Surfaces (exemplified in figure 2) and source space points were used for further processing in Matlab. Across subjects and models, the total number of vertices varied between 2598 and 9828.

2.4. BEM feasibility experiments

The BEM algorithms used throughout this study and the specific implementation strategies are described elsewhere (Ferguson *et al.* 1994, Mosher *et al.* 1999, Hämäläinen *et al.* 1993). The numerical algorithms were first tested for accuracy in two feasibility studies. First (feasibility experiment 1) we aimed to characterize the numerical errors bounds of the BEM forward solutions. Since for a radial source in a spherically symmetric conductor the primary and volume currents counterbalance each other's contribution to the magnetic field, geometries approaching a sphere in combination with radial sources can introduce larger numerical errors. We defined a 4-layer spherically symmetric volume conductor, with radii of 6, 6.2, 8 and 15 cm, and conductivities of 0.22, 2×10^{-6} , 1.4, and 0.05 S/m (Oostendorp *et al.* 1989a, Stinstra and Peters 2002) to replicate the approximate size and conductivity of the fetal body, vernix, amniotic fluid and surrounding tissues, respectively. Each of the spherical surfaces was triangulated using 642 triangles per surface. In a second approach, the thin resistive layer was excluded leading to a 3-layer model of the volume conductor. For each case, the analytical solution of the electric potential on the external surface, computed using the Legendre polynomials method (Zhang 1995) with 24 terms in the truncated expansion, and the analytical solution of the magnetic field (Sarvas 1987) for axial gradiometer sensors were compared with the BEM forward solutions for dipoles oriented along the y and z axes, respectively. The dipole position was varied on the x axis. The BEM solutions were computed for both linear-collocation and linear-Galerkin implementations (Mosher *et al.* 1999). For the 4-layer model, the BEM solutions were computed with the Isolated Problem Approach (IPA) (Hämäläinen and Sarvas 1989). Relative Difference Measures (RDM) between the analytical and numerical solutions (figure 3b) indicated adequate accuracy for the BEM linear-collocation approach. The linear-Galerkin approach provided slightly smaller RDMs over a range of source eccentricities, but the computational time was significantly increased. Since the linear-collocation provided accurate solutions and efficient computational times, it was considered optimal for the current studies.

In a second series of simulations (experiment 2) we assessed the errors that can be introduced by variations in the thickness of the vernix. Volume conductors that were not spherically symmetric were obtained by positioning the inner compartments in figure 3a (representing the AS and fetus covered by a thin resistive layer) at different locations inside the outermost spherical compartment. The thickness of the resistive layer was varied at 0.3, 1, 2, 3, 4 and 5 mm. We used the BEM solution (linear-collocation approach with IPA) obtained for 2 mm thickness as a reference, and we computed the RDMs between this reference and the solutions obtained for other thickness values. The results (figure 3c) show that thickness variations of the resistive layer lead to very small differences in the magnetic field, and agree with previous reports (Stinstra and Peters 2002) indicating that volume currents are in this case largely confined to the fetus compartment of the volume conductor. Hence, throughout the simulations in this study, we considered a uniform, 5 mm thick vernix layer. This choice is motivated by the fact that the inner and outer surfaces of the thin layer should in principle be tessellated using triangles of a size comparable to the thickness of the layer, which increases considerably the computational burden for very thin layers.

2.5. Simulation experiments

Simulation experiments were performed for the sensor array of the CTF fetal biomagnetometer with 83 axial gradiometers (with 5 cm distance between the pick-up coils of each sensor). The magnetic field was simulated in two conditions. First, we defined 3-compartment volume conductors for the whole set of 20 subjects (using both middle and late gestation setups). We assigned conductivities of 0.22 S/m to the fetus, 1.4 S/m to the amniotic fluid, and 0.05 S/m to the maternal abdomen (Stinstra and Peters 2002). In a second condition, setups from late gestation (10 subjects) were also used in simulations with 4-compartment volume conductors. In this case, a fourth compartment (5 mm thick, conductivity of 2×10^{-6} S/m) covered the fetus, to test for potential differences introduced by the presence of vernix.

The general principle of our simulation approach is that the cardiac electrical activity can be described as a current distribution of elementary current sources that summate into a few *effective dipoles*, which can be reconstructed from multi-channel fMCG measurements. The number of effective dipoles depends on factors such as the position and orientation of the heart with respect to the sensor array as well as the heart size, and therefore can show significant inter-subject variability. Since the number of effective dipoles is unknown a priori, we modeled the heart using a large number of elementary currents, and we tested the reconstruction algorithms for retrieving the data-driven or subject-dependent (small) number of effective dipoles. Thus, to simulate the forward magnetic field, we used a fetal heart source model that approximates the propagation of the depolarization wave front through the ventricular walls during the QRS interval (Popescu *et al.* 2006). The model uses a modulated profile cylindrical surface to seed elementary current dipoles around the cardiac axis. For middle gestation, the radius of the largest heart circumference was $R=0.75$ cm, and the ventricular dimension along the heart axis was $Z=1.5$ cm. For late gestation, we selected $R=1.5$ cm, and $Z=3.0$ cm. The peak current latencies were parameterized to generate a traveling wave progressing from the apex to the ventricles' upper part. A total of 480 time samples were generated with 1200 Hz sampling rate. The vector magnitude (VM) was derived by vector summation of all currents at each time point, and the currents strengths were scaled such that the peak VM was 853 nAm and 1706 nAm for middle and late gestation, respectively. The heart source model was positioned at the fetal heart location identified on ultrasound images, and the forward magnetic field was computed at the sensor positions using the BEM linear-collocation approach. White Gaussian noise (RMS=3 fT) was added to the data.

2.6. Source reconstruction and evaluation of volume conductor effects

The source reconstruction results were evaluated for two algorithms: (1) multiple dipole search using R-MUSIC (Mosher and Leahy 1999), and (2) fitting of a single rotating-dipole using least-squares source-space scanning (RDSS) to find the location that minimizes the relative residual deviation, ε , between the measured ($\mathbf{B}$) and estimated data ($\mathbf{R}_i$) on the QRS interval:

$$\varepsilon = \frac{\|\mathbf{R}_i - \mathbf{B}\|}{\|\mathbf{B}\|} = \frac{\|\mathbf{L}_i \mathbf{L}_i^+ \mathbf{B} - \mathbf{B}\|}{\|\mathbf{B}\|}, \quad (1)$$

where $\mathbf{L}_i$ is the $m \times 3$ location-wise gain matrix, and (+) denotes the pseudo-inverse of a matrix. Note that in a spherically symmetric volume conductor, radial currents do not produce any magnetic field outside the volume conductor (Sarvas 1987), and in that case $\mathbf{L}_i$ is the $m \times 2$ matrix formed by the gain column vectors along the two local tangential directions.

The source-space scanning approach for fitting a rotating dipole has been preferred to alternative nonlinear minimization algorithms, since the latter can sometimes provide erroneous results due to their vulnerability to getting trapped in local minima (Popescu *et al.* 2006). The R-MUSIC algorithm searches over a 3D grid to find the locations for which a linear combination of columns of the gain matrix $\mathbf{L}_i$ projects entirely onto the *signal subspace* of the spatio-temporal data matrix. This is achieved using *subspace correlation* metrics (Mosher and Leahy 1999). Once a first dipole is identified, the algorithm is repeated to search for other sources which explain the remaining data. The rank of the signal subspace was set to 5 for all our experiments. Also, we used a threshold value of 0.95 for the subspace correlation to represent an adequate correlation of a source. The recursive search stops when the number of found dipoles equals the signal subspace rank, or when no more sources satisfying the threshold subspace correlation are found. When the algorithm stops, the dipoles magnitudes are estimated by multiplying the data matrix by the pseudo-inverse of the dipoles gains matrix.

The MUSIC algorithm appears suited for the problem at hand because it provides a flexible framework to fit multiple dipole sources, and the optimal effective dipoles do not necessarily need to be co-located. Another difference between fitting a rotating dipole (RDSS) versus MUSIC arises from the optimization scheme and the implicit cost function. Minimizing the residual variance in RDSS inherently assigns a greater weight to the channels with maximal amplitude (thus selecting the solution which provides good fitting for those channels) in contrast to MUSIC, which uses subspace correlations.

Each reconstruction scheme was applied within three scenarios characterized by a different choice of the *volume conductor model* and/or *source space* selection. First (*scenario 1*), we evaluated the reconstruction strategies for the case when perfect knowledge of the volume conductor is available and the source space is confined to the middle part of the fetal trunk volume. This evaluation is necessary to characterize the errors introduced by the limited number of sensors, presence of noise in the data, and intrinsic properties of the reconstruction algorithms. Second (*scenario 2*), a sphere fitted to the sensors was used as a simplified volume conductor model. This scenario assumes also that minimal information about the fetal body position is available, such as an approximate fetal heart-to-sensors distance (as proposed for example by Horigome *et al.* 2001). To account for this, the source space was selected to coincide with the grid in scenario 1, *i.e.* confined to the middle part of the fetal trunk. The gains were computed using the Sarvas equations for the forward magnetic field (Sarvas 1987). Finally, *scenario 3* assumed the same spherical volume

conductor model, with a source space that spanned a large (14×25×18 cm) rectangular volume in the upper hemisphere of the volume conductor, to replicate conditions in which anatomical information is unavailable.

The performance of the two reconstruction schemes was evaluated using the estimated cardiac *vector magnitude* ($\tilde{VM}$). For R-MUSIC, $\tilde{VM}$ is the net current strength derived at each time point by vector summation of the reconstructed dipoles. Amplitude errors were assessed by the *relative error* of the peak $\tilde{VM}$ ($re\tilde{VM}$) with respect to the known VM peak amplitude. We use the convention that positive and negative errors indicate VM underestimation and overestimation, respectively. The localization performance was evaluated by the Euclidian distance between the heart's geometrical center and the average location of the retrieved dipoles (R-MUSIC) or the location of the best-fit rotating dipole (RDSS). The relative residual deviation (1) was used to characterize the goodness-of-fit.

3. RESULTS

3.1. Three-Compartment Volume Conductors

Fig. 4 exemplifies the estimated VMs (panels a, b) and summarizes the results for 3-compartment volume conductor models (panels c, d). For perfect knowledge of the volume conductor (scenario 1), the R-MUSIC and RDSS schemes provide good VM estimates (overall mean errors of $3.0\pm9.5\%$ and $1.0\pm11.5\%$, respectively) and small localization errors (overall mean values of 0.9 ± 0.4 cm and 1.0 ± 0.5 cm, respectively), irrespective of the gestational age (early vs. late). $re\tilde{VM}$ for both R-MUSIC and RDSS passed D'Augustino-Pearson omnibus normality tests ($K2s<0.23$, $ps>0.89$), and subsequent two-tailed t -tests indicated that mean $re\tilde{VM}$ values were not significantly different than zero ($ts<1.4$, $ps>0.18$). To test if any reconstruction scheme performs better for this scenario, we conducted a 2×2 ANOVA with $re\tilde{VM}$ as a dependent variable and independent factors *reconstruction algorithm* (with repeated measures R-MUSIC vs. RDSS) and *gestational age* (early vs. late). The test showed no significant main effects or interaction ($Fs<0.32$, $ps>0.58$).

The use of simplified volume conductors led to relatively large $re\tilde{VM}$ s (fig. 4, c) and higher localization errors (fig. 4, d) for each reconstruction scheme and source space selection. $re\tilde{VM}$ s were positive for all subjects and tested scenarios (2 and 3), indicating a clear trend of underestimating the true VM. Similar 2×2 ANOVAs were conducted separately for scenarios 2 and 3, indicating a significant main effect of *reconstruction algorithm* on the $re\tilde{VM}$ in each case (scenario 2: $F=9.6$, $p=0.004$; scenario 3: $F=5.3$, $p=0.03$), but no significant main effect of gestational age or interactions. The optimal reconstruction algorithm for these scenarios (*i.e.* RDSS, which provided lower $re\tilde{VM}$ s, as seen in fig. 4c) has been further tested to see if the selection of the source space affects its performance. This was done using ANOVAs with independent factors *scenario* (with repeated measures scenario 2 vs. scenario 3) and *gestational age* (early vs. late). These tests indicated a significant main effect of *scenario* ($F=11.2$, $p=0.003$) on the localization error, but no significant main effects on $re\tilde{VM}$ ($Fs<1.15$, $ps>0.29$). Thus, high $re\tilde{VM}$ s are largely determined by the mismatch between the gains in realistic and simplified models, and thus, they are not significantly improved by confining of the source space to the fetal trunk.

The *residual deviation* increases when using simplified volume conductors. In *scenario 1*, R-MUSIC and RDSS solutions explained well the signals (mean residual deviation of $7.6\pm6.0\%$ and $5.6\pm3.8\%$, respectively, pooled over gestational ages). For simplified conductors however, a significant part of the signals remains unexplained: the mean residual deviation was $48.4\pm30.6\%$ in scenario 2 and $40.9\pm28.2\%$ in scenario 3 for R-MUSIC, and $31.1\pm13.8\%$ in scenario 2 and $25.8\pm11.3\%$ in scenario 3 for RDSS.

3.2. Impact of vernix caseosa

Figure 4e, f compares the results for 3- vs. 4-compartment volume conductors. Since both models are derived from the same group of subjects in late gestation, the differences reflect the role of the insulating layer of vernix. This layer can change the magnetic field distribution and typically lowers the mean global field across sensors (Fig. 5).

A 2×2 ANOVA was conducted for *scenario 1*, with the dependent variable *reVM* and independent factors *reconstruction algorithm* and *volume conductor model* (with repeated measures for 3- vs. 4-compartment). The test showed a significant main effect of *volume conductor model* ($F=6.4$, $p=0.02$), indicating a trend for both R-MUSIC and RDSS to retrieve less accurate solutions for the 4-compartment data. Additional insights have revealed that the mean accuracy in this case was however affected by the presence of one large misfit in the retrieved solutions for each scheme. In one case, RDSS retrieved a solution farther away from the simulated heart location, associated with a high *reVM* error (−59%). Likewise, R-MUSIC has retrieved a large *reVM* error in one case (−61%). Similar ANOVAs for scenario 2 and 3 showed no significant effects or interactions ($F_s<0.65$, $p_s>0.64$). Thus, the presence of a uniform layer of vernix does not change the effect of imperfect volume conductor modeling. ANOVAs for the *localization error* showed no significant effects in any scenario ($F_s<1.6$, $p_s>0.22$).

3.3. Assessment on real fMCG data

The use of realistic approximations of the volume conductor was tested in a preliminary evaluation with real fMCG measurements collected in mid-gestation, to avoid uncertainties about the presence of vernix. Fifteen pregnant women (gestational age 23 to 25 weeks) undergone a continuous 4 minute fMCG recording (1200 Hz sampling rate, 0.5–200 Hz band-pass). The signals were filtered using ICA (Mantini *et al.* 2006) to segregate the contribution of the fetal cardiac source. Data from 4 subjects were discarded due to gross fetal body movements during the recording, identified as non-stationarities of the QRS amplitude in the sensor signals, associated with shifts of the fetal cardiac source activity from one independent component to another. For the remaining subjects without observable fetal body movement, the QRS peak was detected by an automatic algorithm, and the averaged cardiac beat was estimated and used for source reconstruction. *Free-hand* ultrasound images acquired immediately after the fMCG recordings were processed as explained in Methods to derive 3-layer realistic approximations of the volume conductor.

Figure 6 exemplifies the averaged fMCG data and the reconstructed cardiac vectors using R-MUSIC. Out of the 11 subjects, a good fitting (>90% explained data variance) was obtained in 5 cases, a moderately good fitting (between 75% to 90% explained data variance) was obtained in 4 cases, and a low-quality fit (<75% explained data variance) was obtained in 2 cases. The mean cardiac vector peak-magnitude was 747 ± 259 nAm across the 5 subjects with good fitting, and 872 ± 319 nAm across all 9 subjects with good and moderately good fitting. Simplified spherical models were also used for comparison: with this strategy, the mean peak-magnitude obtained across the same 9 subjects was 227 ± 103 nAm, and the mean explained variance was $52\pm0.25\%$. These results allow making several observations. First, the peak-magnitude estimators obtained with simplified volume conductors generally agree with the ones reported by previous fMCG (Leeuwen *et al.* 2004, Horigome *et al.* 2001) and fECG (Oostendorp *et al.* 1989b) studies using similar reconstruction strategies. Second, the refinement of the volume conductor to include non-homogeneities introduced by the fetal body and amniotic sac *increases* the estimated values of the vector peak-magnitude and improves the goodness-of-fit for most subjects. Lastly, the values of the vector peak-magnitude in these cases are closer to those predicted by studies on vertebrate animals, which indicate an expected mean value of ~750 nAm for this range of gestational ages

(Nelson *et al.* 1975, Alexander *et al.* 1998). Thus, although the magnetic field is apparently less sensitive to the details of the volume conductor than the electric potential, these results indicate that the refinement of the volume conductor model for mid-gestation to account for inhomogeneities introduced by the fetal body and amniotic sac apparently improves the vector magnitude estimation in fMCG in a similar manner as previously reported for fECG (Oostendorp *et al.* 1989b).

4. DISCUSSION

A reliable methodology for the estimation of the cardiac signal strength from fMCG data can extend its clinical usefulness by allowing studies of fetal cardiac electrophysiology in conditions associated with increased risk of cardiac hypertrophy. Our study used realistic approximations of the volume conductor for a relatively large number of subjects and demonstrated the limitations of using simplified models to achieve this objective. These findings are similar to observations made by earlier studies using fECG (Oostendorp *et al.* 1989b), and challenge the view that magnetic recordings would be less sensitive to the details of the volume conductor to such extent that they would allow the use of simplified models in experimental applications.

We showed that the simplified volume conductor models lead to significant and consistent underestimation of the cardiac vector, with a mean retrieved peak amplitude ranging from 20% to 50% across the scenarios tested in our study, irrespective of factors like the selection of the source space or reconstruction scheme. These results, as well as our preliminary findings with real fMCG measurements, can largely explain an apparent discrepancy between the vector peak-magnitude reported previously by fMCG studies using simplified models (Leeuwen *et al.* 2004, Horigome *et al.* 2001) and the values predicted by studies on vertebrate animals (Nelson *et al.* 1975).

For late gestation, the above observations were made using simulations in two limit cases, *i.e.* in the complete absence or presence of a uniform layer of vernix. In real experiments, it is likely that intermediate states (*i.e.* patches of vernix covering partially the fetal body) may be encountered after 28 weeks of gestation. The presence of holes in the vernix has been shown to change the amplitude and distribution of the electric potential on the maternal abdomen, as well as the forward magnetic field (Oostendorp *et al.* 1989b, Stinstra and Peters 2002). The errors in the fMCG inverse solution for simplified models that approximate conductors with nested compartments and uniform layers of vernix indicate that similar or larger inaccuracies would be also obtained for such spherically-symmetric approximations of more complex conductors that include additional inhomogeneities introduced by the presence of holes in the vernix. Since there is no reliable way to gain evidence for the presence of vernix in practical applications, or to determine the existence and size of its holes, efforts to define and use realistic approximations of the volume conductors will most likely find applications in a “window of opportunity” between ~22 weeks of gestation (when reliable fMCG recordings can be obtained) to ~28 weeks (when uncertainties about the presence of vernix would start to impact the modeling and its success rate).

From this perspective, fMCG measurements have several advantages compared to the early fECG studies: (1) the availability of large arrays systems with dense sensor coverage, (2) the availability of new computational methods for eliminating interferences from maternal cardiac and other artifacts (*e.g.* ICA), which allow more accurate estimation of the averaged fetal cardiac signals, and (3) recent advances in *free-hand* ultrasound recording and processing, which can facilitate the definition of realistic approximations of the volume conductor. Whereas the use of simplified volume conductors offers the advantage that inverse calculations do not need to account *explicitly* for the effect of *volume currents*, the

BEM modeling implies (1) the availability of *free-hand* ultrasound systems to collect fetomaternal anatomical information, (2) additional experimental time for ultrasound recordings, and (3) an increased computational burden. Furthermore, BEM modeling requires the 3D segmentation of the compartments with different electrical conductivity from ultrasound images. In this study, we used a standardized approach for modeling the different volume conductor compartments, which is robust to inherent inter-individual variations in ultrasound image quality, but it requires manual definition of several fiducial points, and local manual correction of the amniotic sac boundaries. A fully automatic segmentation of the different compartments of the volume conductor remains contingent to additional development of the image processing techniques. Our preliminary results obtained for real fMCG data in mid-gestation show promise, but additional studies are necessary to address the sensitivity of the source estimators to slight variations in the geometry of the individual volume conductor compartments, within the range of errors that are inherent to the proposed methodology. Definitive answers regarding the sensitivity and specificity of such an approach for the detection of hypertrophy based on the cardiac vector strength await also further studies in fetuses with cardiac hypertrophy confirmed by m-mode cardiac ultrasound examination.

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Figure 1.
fMCG signals exemplifying an averaged QRS complex from a 36 week old fetus.

Figure 2.
 (a) Exemplification of boundary surfaces modeling for a 3-compartment volume conductor.
 (b) Top view of the outer abdominal surface co-registered with the biomagnetic sensor array.

Figure 3.

(a) Setup of the simulations in feasibility experiment 1. (b) RDMs for different orientations of a dipole with strength of 300 nAm, and for the 3- and 4-shells models. Due to spherical symmetry, RDMs for the electric potential are shown only for dipoles orientated along the y-axis. Results are shown for the linear-collocation approach. (c) Results from feasibility experiment 2. RDMs are shown for a four-shells volume conductor, with the center of the third sphere shifted with 3 cm on both y and z axes with respect to the center of the outermost sphere, and the center of the first and second spheres shifted with 1 cm on the x axis relative to the center of the third sphere. RDMs are computed relative to the solution obtained with 2mm thickness.

Figure 4.

(a) Exemplification of cardiac VM estimation for one subject (32 weeks of gestation, 3-layer case, scenario 1). (b) Exemplification of cardiac VM estimation for the same subject in scenario 3. (c) reVM for 3-layer models in different scenarios. (d) Localization errors for 3-layer models in different scenarios. (e) reVMs for 3-layer and 4-layer volume conductors in late gestation. (f) Localization error for 3-layer and 4-layer volume conductors in late gestation.

Figure 5. Exemplification of simulated data with 3-compartment (a) and 4-compartment (b) volume conductors. The dotted lines show the mean global field. The peak-magnetic field distribution is shown on the right.

Figure 6.

Estimates of cardiac vector magnitudes using realistic approximations of the volume conductor are exemplified for three subjects. The left panels show the volume conductor co-registered with the sensor array. One fetus (subject 1, data recorded at 23 weeks, 6 days) was in breech position, while the other two fetuses (subjects 2 and 3, data recorded at 24 weeks, 4 days for each of these two fetuses) were in cephalic positions. The middle panels show the averaged fMCG data, and the right panels show the corresponding VMs. The three cases were selected to exemplify the large variability in amplitude and morphology of the fMCG signals across subjects: the peak-to-peak QRS amplitude varies between ~ 4 pT (subject 1) and ~ 0.7 pT (subject 3).