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Comparison of spherical and realistically shaped boundary element head models for transcranial magnetic stimulation navigation

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Abstract

Objective—MRI-guided real-time transcranial magnetic stimulation (TMS) navigators that apply electromagnetic modeling have improved the utility of TMS. However, their accuracy and speed depends on the assumed volume conductor geometry. Spherical models found in present navigators are computationally fast but may be inaccurate in some areas. Realistically-shaped boundary-element models (BEMs) could increase accuracy at a moderate computational cost, but it is unknown which model features have the largest influence on accuracy. Thus, we compared different types of spherical models and BEMs.

Methods—Globally and locally fitted spherical models and different BEMs with either one or three compartments and with different skull-to-brain conductivity ratios (1/1 – 1/80) were compared against a reference BEM.

Results—The one-compartment BEM at inner skull surface was almost as accurate as the reference BEM. Skull/brain conductivity ratio in the range 1/10 – 1/80 had only a minor influence. BEMs were superior to spherical models especially in frontal and temporal areas (up to 20 mm localization and 40% intensity improvement); in motor cortex all models provided similar results.

Conclusions—One-compartment BEMs offer a good balance between accuracy and computational cost.

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Disclosure

Dr. Risto Ilmoniemi is inventor in several patents and patent applications in TMS and is a founder, former Chairman and CEO, minority stock-owner, and consultant of Nexstim Ltd. Dr. Yoshio Okada is the founder and owner of Moment Technologies, LLC, Boston, MA. No financial gain is expected for Dr. Ilmoniemi or Dr. Okada as a result of this work.

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Significance—Realistically-shaped BEMs may increase TMS navigation accuracy in several brain areas, such as in prefrontal regions often targeted in clinical applications.

Keywords

Transcranial magnetic stimulation; image guided navigation; electromagnetic modeling; boundary element method

1 Introduction

The motivation to improve electromagnetic modeling of transcranial magnetic stimulation (TMS) stems from the need for accurate yet practical methods for quantifying and navigating TMS. In TMS (Barker et al., 1985) a current pulse is applied to a coil located on the subject's scalp, which generates a magnetic field (B field). The time-varying B field induces an electric field (E field) that alters the transmembrane voltage of neurons to the extent of triggering action potentials (see, e.g., Ilmoniemi et al., 1999). The intensity, spatial distribution, and maxima of the E-field depend on (i) the TMS coil geometry (for example, a small figure-of-eight TMS coil produces a reasonably focal E field) and (ii) the head shape and conductivity properties. Without sufficiently accurate physical models of the head ("volume conductor models"), navigated TMS systems may falsely guide the stimulation to a sub-optimal location and/or intensity. The accuracy that is needed or that could be achieved with navigated TMS is presently not well characterized. However, even a subtle difference in coil location, orientation, or stimulus amplitude may determine, for instance, which finger is stimulated, or whether a given experimental effect is present or absent (see, e.g., Lisanby et al., 2000; Pascual-Leone et al., 2000; Sack et al., 2009). Therapeutic effects of TMS might also depend on navigation accuracy, as suggested by TMS and epidural cortical stimulation studies in depression (Herbsman et al., 2009; Kopell et al., 2011).

The TMS-induced E field is determined by the Maxwell–Faraday law of induction $\nabla \times \vec{E} = -\partial \vec{B} / \partial t$, from which it follows that the *total E field* has the general form $\vec{E} = -\nabla A - \frac{1}{c} \frac{\partial \vec{A}}{\partial t}$. The first term involving the vector potential A corresponds to the *primary field* induced by the current in the coil, whereas the second term involving the scalar potential is determined by the boundary conditions of the volume conduction problem and is called the *secondary field*. The total E field drives passive ohmic currents in the volume conductor $\vec{J} = \sigma \vec{E}$, and if it is tentatively assumed that the head is a homogeneous passive volume conductor with conductivity σ immersed in a non-conducting medium (air), then it follows by charge conservation that charge must accumulate on the conductivity boundary to render the current into the non-conducting medium equal to zero. This surface charge is responsible for generating the secondary E field $\vec{E}_s$.

The charge accumulation has been computationally determined for a semi-infinite space in (Tofts, 1990), and an appropriate measurement using a dipole probe was described in (Tofts and Branston, 1991). Other groups have presented techniques for calculating and measuring the E field for specific geometries, such as a sphere, further demonstrating that the conductivity boundaries substantially influence the total E field induced by TMS (Cohen and Cuffin, 1991, Durand et al., 1992, Roth et al., 1990, Yunokuchi and Cohen, 1991). An important theoretical connection, based on the principle of reciprocity (Plonsey, 1972), between magnetoencephalography (MEG) and TMS was utilized by (Heller and van Hulteyn, 1992): the TMS E field can be obtained directly by applying computational methods employed in MEG forward modeling. Perhaps the most drastic effect of the secondary E field for a spherically symmetric volume conductor was immediately re-derived: independent of the TMS coil position, orientation, and shape, the radial component of the total E field is zero inside the volume conductor. This reflects the well-known fact

that radial primary currents in a spherically symmetric volume conductor do not produce external magnetic fields (Baule and McFee, 1965, Grynszpan and Geselowitz, 1973). This theoretical prediction has also been experimentally confirmed (Cohen and Cuffin, 1991, Yunokuchi and Cohen, 1991).

The charge accumulation, giving rise to the secondary fields, potentially occurs on all locations of the volume conductor where the conductivity changes. Thus, both inhomogeneity and anisotropy of tissue conductivity may have an effect on the E field (Miranda et al., 2003) except in special cases (Ilmoniemi, 1995). With increasing computational power, development of numerical methods, imaging technologies, and image processing algorithms, several groups have tackled the problem of calculating the effects of tissue conductivity on the TMS E field in an anatomically realistic head model, typically obtained from magnetic resonance imaging (MRI) data. The tissue types that have different conductivities include (but are not limited to), skin, skull, cerebro-spinal fluid (CSF), gray matter, and white matter. The effects of tissue heterogeneity on TMS-induced E fields have been studied using the Boundary Element Method (BEM) (Salinas et al., 2009), the Finite Element Method (FEM) (Chen and Mogul, 2009, Thielscher et al., 2011, Wagner et al., 2004), and the Finite Difference Method (FDM) (Toschi et al., 2008). The effects of the conductivity anisotropy in white matter have been studied with FEM (De Lucia et al., 2007, Opitz et al., 2011) utilizing diffusion tensor imaging (DTI) to estimate the conductivity tensor (Tuch et al., 2001). The effects of tissue heterogeneity and anisotropy have varied across studies, partially due to the assumed conductivity values and methods used (Gabriel et al., 2009). However, it is clear that anatomically realistic modeling of the TMS-induced E fields is useful.

All currently existing on-line TMS navigation devices estimate the induced E fields using spherical conductor models, and may display the results overlaid with the individual anatomical MRI to assist in positioning the coil (Hannula et al., 2005, Ruohonen and Karhu, 2010). Increasing the realism and detail of the conductor model has the potential to increase targeting and dosing accuracy, but it comes at a significant computational cost: the most complex models are presently incompatible with real-time TMS navigation. The ideal level of conductor model complexity depends also on whether on-line instantaneous results are required for navigation during the experiment, or if more accurate but slower off-line computations are desired (e.g., for planning of post-stroke therapy sessions in the presence of tissue pathology). Moreover, highly refined conductor models employing FEM with anisotropic tissue conductivities typically require significant imaging resources in the form of several types of MRI scans and/or high-resolution computer tomography (CT), and even then building the model may take a significant amount of manual work and expertise for each subject/patient (Windhoff et al., 2013) which may partially explain why such models have not been used in large-scale studies.

It is therefore useful to examine where the computational and imaging resources should be placed to provide the largest gains in targeting and dosing accuracy. In this article, we present a computationally efficient and robust BEM approach for anatomically realistic modeling of the E fields, based on a three-compartment model of the head. BEM models are presently routinely used in MEG studies, and thus can be adapted to TMS as well. In the present study, we systematically quantified the effect of volume conductor shape (realistic vs. spherical) and the choice of skull conductivity value on TMS-induced E fields at different locations on the surface of the brain; we are not aware of prior studies with this focus. We varied the realism of the conductor model shape (globally or locally fitted spherical, or realistically shaped), number of BEM layers (one or three), and the skull-to-brain conductivity ratio. The presented methods and results are practical in the sense that they can be readily applied to off-line computations to improve their precision but could also

be developed to accommodate on-line navigation. The most complex volume conductor models, which incorporate tissue anisotropies using FEMs, are currently clearly incompatible with (near) real-time applications. Moreover, the work required to construct FEMs (see, e.g., Windhoff et al., 2013) hamper their applicability to large-scale empirical studies even for off-line applications. Consequently, FEMs are not included in the present comparisons (see also Discussion).

Methods

Computational methods

According to the electromagnetic reciprocity principle (Heller and van Hulsteyn, 1992, Plonsey, 1972), the quasi-static E field induced by current $I(t)$ in a coil satisfies the following relationship:

$$\vec{Q}(\mathbf{r}_q) \cdot \vec{E}(\mathbf{r}_q, t) = -\frac{dI(t)}{dt} \sum_i \int_{C_i} \vec{B}(\mathbf{r}) \cdot d\vec{S}_i(\mathbf{r}), \quad (1)$$

where $\vec{B}(\mathbf{r})$ is the magnetic field at location $\mathbf{r}$ due to a current dipole $\vec{Q}(\mathbf{r}_q)$ located at $\mathbf{r}_q$ inside the volume conductor, and $d\vec{S}_i(\mathbf{r})$ is the differential area element of the surface which is bound by the coil winding C_i . Using equation (1), the E field can be calculated at an arbitrary location and orientation by varying the location and orientation of the (unit) current dipole. Equation (1) can be compactly expressed as $\vec{E}(\mathbf{r}, t) = -(\frac{dI(t)}{dt})\vec{L}(\mathbf{r})$, where $\vec{L}(\mathbf{r})$ depends solely on the coil and volume conductor geometry and is the so-called lead field in MEG parlance (see, e.g., Ilmoniemi et al., 1999). In the present study, two different numerical BEM schemes for computation of $\vec{B}(\mathbf{r})$ were used for the realistically-shaped head model: (i) The computationally efficient Linear Collocation Isolated Source Approach (LC-ISA) as described in (Hämäläinen and Sarvas, 1989, Stenroos et al., 2007, Stenroos and Sarvas, 2012), and (ii) numerically more accurate but computationally more intensive Galerkin ISA (G-ISA) as described in (Stenroos and Sarvas, 2012). For the spherical model, we used an analytical solution (Sarvas, 1987). All computational methods and analyses were implemented in MATLAB (R2012a, The Mathworks, Inc., Natick, MA, USA). A brief summary of the field computation strategies is presented in Appendix A.

Head models

The anatomical MRI data were acquired from a healthy male subject using a 3T scanner (Tim Trio, Siemens Medical Solutions, Erlangen, Germany) after obtaining an informed consent from the subject and approval by the local Institutional Review Board. The realistically-shaped head model consists of three homogeneous compartments: the scalp, the skull, and the intracranial space. Figure 1(A–B) shows the different tissue compartments that were automatically segmented from two 3D multi-echo FLASH sequences (5/30 degree flip angles) (Fischl et al., 2004a). Each of the BEM surfaces consisted of 2562 vertices and 5120 triangular elements. The cortical surface was extracted from a T1-weighted MPAGE volume using the FreeSurfer software (Dale et al., 1999, Fischl, 2012, Fischl et al., 1999). Since the goal of our study was to compare different volume conductor properties, we present the results on a smooth surface approximately at the depth of the gray-white matter junction at gyral crowns. The results could also have been computed at the cortical surface, but then the highly convoluted gyral landscape would have confounded the figures of merit quantifying the conductor model differences. The surface was obtained by shrinking the inner skull surface by 7.5 mm and increasing the vertex density by upsampling the mesh (Figure 1(C)). The resulting surface had an average vertex-to-vertex distance of 2.3 mm. Further, as shown in Figure 1(D), the scalp and skull thicknesses vary locally, meaning that the distance from the scalp to the field computation surface also varies. This causes a

corresponding systematic variability of E-field amplitude across brain regions, which was taken into account in the analysis (see section *Figures of merit*). Finally, to study differences between brain areas quantitatively, we used the anatomically defined FreeSurfer cortical surface parcellation (Desikan et al., 2006, Fischl et al., 2004b) shown in Figure 1(E), picked four regions of interest (ROIs) (ROI 1 = precentral, ROI 2 = superior temporal, ROI 3 = rostral middle frontal, ROI 4 = inferior parietal), and projected them to the E-field computation surface (Figure 1(F)).

In addition to the realistically shaped BEMs, two spherical models were considered. In the first model, a globally best-fitting sphere in the least-squares sense was determined based on the inner skull surface points leading to a sphere covering almost all of the brain, including the frontal areas. The fitting procedure is described in the Appendix A. In the second model, the sphere was selected according to the local curvature of the inner skull surface close to a given location of the TMS coil. This was achieved by selecting inner-skull-surface points within a five-centimeter radius from the projected coil location, and performing a similar least-squares fit as for the global sphere. For the locally fitted sphere, the E field was set to zero for those locations of the field computation surface of Figure 1(C) that were outside the fitted sphere (for details, see (Sarvas, 1987) and Appendix A), since the E field at distant locations was observed to be distorted in some cases, and because the locally fitted sphere is assumed to give accurate results only locally.

Simulations

Figure 1(A) shows the coil locations covering the right hemisphere (magenta dots) and the arrangement of the two oppositely wound TMS coils. In each of the 893 locations, the coil normal (green arrow) was aligned along the normal of the scalp BEM surface. Four coil directions with 0-, 45-, 90-, and 135-degree rotations around the coil normal were assumed, with 0-degree direction aligned with the anterior–posterior direction (black arrow). Both wings of the figure-of-eight coil in our model had an inner diameter of 22 mm and outer diameter of 75 mm and consisted of 10 co-centric and co-planar equally spaced filamentary windings. For calculation of the integral in equation (1), the area under the coil was divided into 622 triangular elements. The triangle areas, their normal vectors, and their midpoints were then used to approximate the differential area elements $dS_i(\mathbf{r})$. An insulating coil housing of 2 mm was assumed between the wire and scalp, and since each filament was assumed to represent the average current distribution of a copper wire with height 11 mm, the plane of the filaments was positioned a total of 7.5 mm above the tangential plane of the scalp at each location (see Figure 1(A)). A nominal value for peak current rate-of-change of 50 A/ μ s was assumed in the E-field calculation. As the field computation problem is linear with respect to the magnitude of the current rate-of-change (see Equation 1) and we used relative metrics, the actual value is irrelevant, but for sake of concreteness our selection was based on what is typically empirically observed at motor threshold for similar coil geometry as what was used in the simulation. This was used to verify that the E-field amplitude values agree with what is typically observed using navigated TMS.

Based on resistivity data from the literature, we assumed fixed conductivity values of $(brain) = (scalp) = 0.33$ S/m (Haueisen et al., 1997, Wolters et al., 2002). The parameter of our three-compartment model that is subject to most uncertainty is the conductivity of the skull. Reported estimates for skull-to-brain conductivity ratio $(skull) / (brain)$ have varied from 1/80 (Cohen and Cuffin, 1983, Rush and Driscoll, 1968) to as high as 1/15 (Oostendorp et al., 2000). To investigate the effects of this uncertainty, we varied the skull-to-brain conductivity ratio parametrically, including the limiting cases of a three-compartment model in which all compartments had identical conductivity (uniform conductivity head), and a case in which the conductivity outside the inner skull surface was

set to zero with formal skull-to-brain conductivity ratio zero, resulting in a single-layer BEM. Since recently published empirically derived *in vivo* values of the skull-to-brain conductivity ratios are about 1/20 (Zhang et al., 2006), we selected this value for the reference model with the numerically more accurate G-ISA. The models are listed in Table 1.

Figures of merit

To quantitatively compare the different models, we defined figures of merit to describe the differences in the spatial distributions of the E fields. These were calculated for each coil location and orientation using Model 1 as the reference ground truth.

For ROI analysis, the localization error (LOC) was defined as $LOC(i) = |\mathbf{r}(1)_{E_{\max}} - \mathbf{r}(i)_{E_{\max}}|$, with i referring to the model number and $\mathbf{r}(i)_{E_{\max}}$ referring to the locus of the E-field maximum. Similarly, orientation error (ORI) was defined as the angle between the E-field vectors at the locations of the E-field maxima. Since the absolute value of the E-field maximum depends on the distance from the coil to the surface, which varies across the scalp locations (Figure 1(D)), we defined E-field magnitude error (EAB) as the relative difference (in per cent) of the E-field maxima with respect to the reference model $EAB(i) = 100\% \cdot [E_{\max}(i) - E_{\max}(1)] / E_{\max}(1)$. Note that this convention preserves the sign: when the E-field maximum amplitude is smaller than that of the reference model, this figure of merit will be negative. We also defined two figures of merit to account for the focality (shape and extent) of the E-field distribution around its maximum. These correspond roughly to the two “main axes” of the oval area that can be seen in Figure 1(C). Specifically, we identified the three orthogonal dimensions of maximal variance for the 3D set of points for which the E field exceeded 75% of the maximum. This was accomplished using singular-value decomposition similarly to principal component analysis. The longitudinal focality (FOC_L) was associated with the direction of largest variance, and transverse focality (FOC_T) with the second largest. Similar to EAB, the figures of merit FOC_L and FOC_T were defined as relative differences (percent) with respect to the reference model. For calculation of the ROI averages, a scalp coil location/orientation was associated with a given ROI, if the E-field maximum of the reference model (#1) was found inside that ROI.

Assuming symmetry of the head with respect to midline, the analyses were limited to the right hemisphere. In some regions, the E-field values within >90% threshold were spread out over a more extended area, and the single E-field maximum location point could jump from vertex to vertex in a somewhat random fashion across neighboring TMS coil locations. Therefore, to investigate the differences in the induced E-field amplitude and maximum location at each individual coil location and orientation, we defined robust estimates of the peak E-field amplitude and location. The robust E-field amplitude R-EAB was defined as the average E field of those locations where the E field exceeded 90% of the maximum. This was defined analogously to EAB as a relative difference percent with respect to the reference model. A robust measure of the peak E-field localization error R-LOC for each model was defined using the E-field “center-of-mass” of locations exceeding 90% of the maximum.

Results

Qualitative model comparison

To obtain insight into the properties of different models, we first manually selected representative scalp locations over the center of each ROI. For the BEM models #3 – 6, the spatial distributions of the E fields were highly similar to the reference model. Figure 2 shows the results for the remaining models. The uniform-conductivity head model #2 clearly

overestimated the amplitude of the E field and the spatial spread around the maximum over the frontal ROI [3] and temporal ROI [2]. The single-compartment model, on the contrary, provided underestimates. This was expected, since the uniform-conductivity head model neglects the charge accumulation at the inner skull surface, and the single-layer model boosts this effect, as everything outside the inner skull is assumed electrically isolating. The locally-fitted sphere model #8 systematically underestimated the E-field amplitude, apparently because of “too small” radii of curvature obtained with the present choice of fitting algorithm and the rather large area of skull surface in the fitting (see also Supplementary Figure S2). However, in the parietal ROI [4], the locally fitted sphere yielded similar values as the reference model. At the superior temporal ROI [2] and frontal ROI [3], the locations of E-field maxima also appeared displaced and the shapes of the distributions distorted. The globally-fitted sphere model #9 appeared otherwise similar to the locally fitted sphere except that for the frontal ROI [3] the E-field amplitude was overestimated, locus of the E-field maximum was displaced, and the shape of the distribution distorted. While one might think that this distortion could be caused by the fact that the frontal region only partially fits inside the globally fitted sphere, this is not the sole explanation, since for the spherical model the induced E field does not explicitly depend on the sphere radius, but only on the location of the center of symmetry (for details, see Appendix A and Supplementary Figure S2).

Quantitative model comparison

First, we studied the dependence of E-field localization and amplitude error on the location and orientation of the TMS coil for selected conductor models. Figure 3 shows the localization error and Figure 4 the amplitude error as function of coil location over the entire right hemisphere. The three-compartment BEM with 1/1 skull–brain conductivity ratio (model #2) produced small localization errors, but the amplitudes are overestimated by up to 40% over the prefrontal lateral cortex (visualization threshold maximum is 20%). The three-compartment BEM with 1/20 skull/brain conductivity ratio (model #4) showed negligible errors, suggesting that the improved numerical accuracy offered by the Galerkin method (model #1) did not influence the results; consequently, the observed errors are due to differences between conductor models rather than numerical inaccuracies. The one-compartment BEM (model #7), despite its simplicity, produced quite robust results, with only one problem area close to the eye at one of the coil orientations (90°). The locally-fitted sphere (model #8) showed good localization accuracy except in inferior lateral areas where the local skull profile is not very spherical; the corresponding amplitude estimates, however, strongly underestimated the values by up to 20% over most brain areas (see Supplementary Figure S2). The globally-fitted sphere (model #9) produced localization errors of up to 20 mm in frontal areas but these depended strongly on the coil orientation; the corresponding amplitude values under- or overestimated the intensities by up to 20% depending on the brain area. A coil location that yielded an unusually large localization error for one-compartment BEM is shown in Supplementary Figure S1.

Next, we quantified these trends in the 4 ROIs. Figure 5 shows the within-ROI averages for all figures of merit. Overall, the trends were in agreement with the qualitative analysis. For EAB, the uniform-conductivity head model systematically over-estimated the E-field maximum amplitude, up to 10% average at the frontal ROI [3]. EAB monotonically decreased as a function of conductivity ratio for all of the BEM models, crossing zero at conductivity ratio 1/20, as expected. Spherical models underestimated the E-field amplitude, except for the globally fitted sphere at the frontal ROI [3], where it yielded an average overestimate of 15%. The focality measures FOC_L and FOC_T were also quite small for all of the BEM models except for the uniform head model, which showed average changes within a range of 10%. Both spherical models (#8 and #9) showed more scattered values apart from

ROI [4]. The effects were most pronounced at the temporal ROI [2] and larger for the longitudinal focality. LOC and ORI showed a similar pattern, exhibiting small differences for all BEM models except model #2 and model #7. The LOC and ORI were smaller for locally-fitted spheres, except at temporal ROI [2] in the anterior temporal area where it is difficult to capture the complex shape of the inner skull surface with a sphere. The ORI differences for the sphere model were in fact quite large, most likely because of the fact that there were no radial E-field components due to the spherical symmetry. Finally, for the BEM model #4, which had the same skull–brain conductivity ratio as the reference model #1, all figures of merit were close to zero, and thus numerical accuracy of the LC-BEM was adequate for this case.

The ROI averages are useful for quantifying the trends in the accuracies of different models, but it is also important to study the distributions of the figures of merit within each ROI to gain insight into details beyond averages. To this end, Figure 6 shows histograms of the key quantities EAB and LOC, separately for ROIs [1] and [3] and for the worse-performing models #2, #7, #8, and #9. For ROI [1], the distributions of EAU were quite well characterized by their mean. For the BEM models #2 and #7, the distributions of LOC revealed that in 30% and 60% of the cases, respectively, the maximum of the E field was found at the same point of the surface as for the reference model (frequency of LOC = 0 mm cases in the histogram). For most of the coil locations over ROI [1], the LOC was < 5 mm for these BEM models. For the spherical models (#8 and #9), the percentage of correctly determined points was 40% and 45%, respectively, and most of the differences were < 10 mm, but some outliers with large localization difference were observed due to those locations closer to temporal lobe (see Figure 1(F)), where the shape of the skull is rather non-spherical, therefore hampering the fitting procedure and undermining the assumption of spherical symmetry. For ROI [3], the EAU distribution of model #2 had a heavy tail, extending up to 30% difference in the E-field maximum. For the global-sphere model (#9), EAU distribution extended on both sides of the origin, indicating that for some coil locations/orientations the E-field maximum was underestimated by up to 10%. From the distribution of LOC at ROI [3], we observed that the percentage of correctly determined E-field maxima dropped to 23% and 14% for the globally and locally-fitted sphere models, respectively, and that the distributions extended to localization errors of 12 mm. The BEM model #7 again showed an outlier where the LOC was as large as 25 mm (Figure 3 and Supplementary Figure S1).

Evaluation of computational performance

Since the focus here was to compare different volume conductor models, the computational pipeline was not optimized for speed. The optimization would require further analysis on how dense BEM meshes, coil models, and E-field computation surfaces are needed. However, to provide some insight into the relative speeds, we compared the CPU usage of different models using one processor of a standard Linux analysis workstation (Intel Xeon X5650 at 2.67 GHz, 6 cores). The results are shown in Table 2. In Step 1, the BEM volume conductor model is built. This needs to be done only once for each subject, and thus it does not influence speed during navigation. For each coil position, Steps 2 and 3 need to be carried out. We see that, for each coil position, the time for computing the fields with the 1-layer BEM (8.4 seconds) is comparable with the locally-fitted spherical model (6.8 seconds); further enhancements could be achieved by optimizing the codes for speed. All other computations were done in single core except the matrix inversions in Step 1 that used all six cores of the CPU.

Discussion

Here, for the first time, we present a computationally efficient and robust approach for anatomically realistic modeling of the TMS-induced E fields using single- and three-compartment BEM models. We compared the results with those obtained from two types of spherical models. We also investigated the effect of the skull-to-brain conductivity ratio on the E field, and found the results to be very similar in the range $1/10 - 1/80$. However, when the whole head was assumed to be of uniform conductivity ($1/1$ skull-to-brain conductivity ratio), the E fields were substantially over-estimated at frontal regions. On the other hand, when conductivity was set equal to zero outside the inner skull surface (single-compartment BEM), the E-field amplitudes were under-estimated by up to 10–15% at some prefrontal regions. With the globally-fitted sphere model, localization errors up to 10–20 mm were observed in addition to the amplitude errors. The locally-fitted sphere model decreased the frontal localization errors, but led to deteriorated performance at temporal lobe and a tendency to underestimate the E-field amplitude compared with the reference model.

Our results are qualitatively in line with related MEG source localization work (Tarkiainen et al., 2003), as expected by the TMS-MEG reciprocity. However, in MEG the magnetic fields are globally measured in a helmet-shaped array 2 – 3 cm above the skin and the quality of the forward calculation is typically assessed either by comparing the patterns measured by the array or by quantifying the error in single current dipole fitting due to a simplification of the forward model. Therefore, the MEG results cannot be directly quantitatively translated into TMS, where the relevant figures of merit are different.

As with any simulation study, it is important to consider the inherent numerical accuracy of the method itself. Here, we used a more accurate but computationally intensive Galerkin ISA BEM as a reference. The differences to the Linear Collocation ISA were extremely small (Figures 3–4, Model #1 vs. Model #4), and consequently the differences observed were due to different volume-conductor models. However, to facilitate comparisons especially with the spherical models, the E field was calculated on a surface at about 7.5 mm from the inner skull surface. As reported in (Stenroos and Nenonen, 2012, Stenroos and Sarvas, 2012), the accuracy of the Linear Collocation BEM deteriorates rapidly when the E field is calculated closer to the inner surface of the skull than what is appropriate for a given level of discretization of the surface. Therefore, if extending the present work by computing E fields on a realistically-shaped cortical surface, where the gyral crowns are often very close to the inner skull surface, it might be useful to either increase the density of points used to represent the inner skull surface when using Linear Collocation, or to adhere to the Quick Galerkin (Stenroos and Nenonen, 2012) or Galerkin method. On the other hand, TMS is thought to be most effective when the induced electric field is perpendicular to the local cortical surface (Fox et al., 2004). Since the E field is essentially tangential to scalp, the main activation by TMS may instead occur in sulci, which are situated deeper than gyri. Thus, the comparison of anatomically realistic and spherical models using cortical surface-based geometries would be an important topic for further work.

The presented modeling approach could benefit practical TMS research in several ways. It may be used to improve the individual targeting and dosing of TMS. Using the computational methods presented here, one could evaluate the E field over a target cortical region with coil position and orientation varied in steps of, say, 5 millimeters and 5 degrees, and then select the optimal coil position and orientation to result in maximal stimulation of the desired cortical structure. In the frontal regions, using a spherical model may result in targeting errors of about 1 cm and stimulation intensity offsets of about 20%. Targeting and dosing differences of this magnitude may have a substantial influence on the effects of stimulation (Herbsman et al., 2009, Sack et al., 2009). This, however, does not mean that the

locally-fitted spherical models are useless. They certainly can work very accurately, for instance, at the occipital and parietal areas, where the inner skull surface is more spherical. The localization accuracy is also very good in the posterior part of the frontal lobe over the precentral gyrus ROI [1] including the primary motor cortex. The spherical models might be also be further improved by refining the local sphere-fitting procedure (see also Supplementary Figure S2).

As all models, our realistically shaped three-compartment head model is an approximation. The one- and three layer BEMs omit CSF, the segregation of cerebral tissue into gray and white matter, and the anisotropy of white matter conductivity. However, making the model more realistic by inclusion of these aspects also increases the number of unknown parameters, numerical errors, modeling assumptions based on uncertain knowledge, and tissue compartment segmentation errors that may go unnoticed. In that sense, the one- and three-compartment BEMs are very simple to construct, are sufficiently accurate in most circumstances, and are therefore currently the preferred choice over more complex models (such as FEMs) in clinical and scientific MEG/EEG source modeling, see, e.g., (Fuchs et al., 2007). On the other hand, oversimplification of the model is also expected to decrease the accuracy. At this time there is insufficient data to tell which error is larger.

To estimate the effect of CSF, we conducted an additional simulation using a four-layer BEM approach in one coil location where the differences between the three-shell and spherical models were particularly pronounced (see Appendix B for details on implementation). Figure 7 shows the corresponding realistical cortical surfaces. Figure 8 shows that the results between the four-layer and three-layer BEMs are quite similar, whereas using a locally-fitted sphere changed the distribution and amplitudes clearly. In addition, the 4-layer BEM seemed to slightly increase the E field amplitude estimates at gyral crowns compared with the 3-layer BEM. Recent FEM simulation studies have reported similar CSF effects at gyral crowns, but the magnitude has varied across reports (Bijsterbosch et al., 2012, Thielscher et al., 2011). Reliably estimating the size of this effect across brain regions would benefit from further validation studies of the numerical implementation of different E-field solvers, since the CSF layer can be extremely thin at certain locations. In conclusion, the largest changes were observed between the spherical model and the 3-layer BEM, and adding a CSF layer in the BEM had a limited effect. It therefore seems that omitting the CSF is a reasonable approach to reduce the computational load while maintaining most benefits of an anatomically realistic head model. In the nomenclature of Table 2, the bulk of the computational load increase in the 4-layer case comes from Step 1 that ran overnight. Step 2 is about an order of magnitude slower for the 4-layer than for the 1-layer BEM, while Step 3 is the same across all BEM approaches. Step 1 does not need to be repeated for each coil location, but is carried out only once, so assuming that enough memory is available the on-line computational aspects of the 4-layer BEM are about an order of magnitude slower than for 1-layer BEM.

The present work showed that the accuracy is largely insensitive to skull conductivity, the exact value of which is not well known, assuming that the BEM surfaces have been correctly constructed. One computational bottleneck of BEM approaches is that they become memory-intensive and slow when the number of discretization elements representing the conductivity boundary surfaces becomes large. As discussed above and in Appendix B, it is possible to incorporate the CSF layer into the BEM model, but adding a fifth surface at the cortical gray - white matter boundary would result in that the memory requirements become prohibitively large. If modeling of white-gray matter conductivity boundary is desired, this bottleneck might be mitigated by utilizing fast multipole methods to accelerate BEM computations (Kybic et al., 2005, Rokhlin, 1983), suggesting another direction for future research. As another possible application of the presented modeling

approach, the E fields computed with any conductor model (spherical, BEM, FEM) can be presented on the individual cortical surfaces. However, showing the present results on a gyral landscape would complicate the quantification of the conductor model effects that are the focus of the present study.

It should also be noted that computing the present results with a highly detailed FEM would have been quite challenging. The actual computation time depends on the implementation of the FEM solver, but according to recent literature, solving a single TMS coil location/orientation using an anisotropic FEM takes 1 – 2.5 hours on a standard PC workstation (Opitz et al., 2011, Windhoff et al., 2013). Hence, computing the present results with a FEM could have taken 2.4 years per hemisphere (1 hour x 893 coil locations x 4 different orientations x 6 brain-to-skull conductivity values = 21,432 hours). Consequently, while FEMs are theoretically interesting, might offer some benefits, and continue to be an area of active investigation in several laboratories (including ours), they are not necessarily the tool of choice for every study and application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A

The principles of calculating MEG lead fields (the same principles apply for TMS) are documented in detail elsewhere (Hämäläinen et al., 1993); here we will only give a brief outline of the procedure. To calculate the E field using (1), one must be able to compute the B field $\vec{B}(\mathbf{r})$ due to a current dipole in the volume conductor. When a quasi-static dipolar primary current element with current density $\vec{J}_p(\mathbf{r}) = Q(\mathbf{r}_q) (\mathbf{r} - \mathbf{r}_q)$ is immersed in a volume conductor, it gives rise to a conservative electric field $\vec{E}_v(\mathbf{r}) = -\nabla V(\mathbf{r})$ and corresponding ohmic volume currents $\vec{J}_v(\mathbf{r}) = \sigma(\mathbf{r}) \vec{E}_v(\mathbf{r}) = -\sigma(\mathbf{r}) \nabla V(\mathbf{r})$, where $\sigma(\mathbf{r})$ is the conductivity of the medium. The magnetic field $\vec{B}(\mathbf{r})$ can be calculated by using the Biot–Savart law for the total current $\vec{J}(\mathbf{r}) = \vec{J}_p(\mathbf{r}) + \vec{J}_v(\mathbf{r})$:

$$\vec{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \frac{(\vec{J}_p(\mathbf{r}') - \sigma(\mathbf{r}') \nabla' V(\mathbf{r}')) \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} d^3\mathbf{r}'. \quad (\text{A1})$$

The potential is determined by the quasi-static condition for the total current $\nabla \cdot \vec{J}(\mathbf{r}) = 0$, which yields:

$$\nabla \cdot (\sigma(\mathbf{r}) \nabla V(\mathbf{r})) = \nabla \cdot \vec{J}_p(\mathbf{r}). \quad (\text{A2})$$

In principle, one solves the potential $V(\mathbf{r})$ from (A2) and then obtains the magnetic field from (A1). If we assume that the volume conductor consists of homogeneous conductivity compartments, the solution of (A1) and (A2) can be formulated as integral equations on the boundary surfaces (Ferguson and Stroink, 1997, Geselowitz, 1967, 1970). This is the rationale behind the BEM approach, where each of the conductivity boundary surfaces is discretized into triangular elements, and the surface integrals can be evaluated by suitable numerical approximation schemes (for detailed accounts, see, e.g., Mosher et al., 1999; Stenroos et al., 2007). The poor conductivity of the skull may cause numerical problems in the procedure, which can be tamed by the isolated source approach (ISA) for the BEM solution (Hämäläinen and Sarvas, 1989).

For the special case of a spherically symmetric volume conductor with conductivity $\sigma(\mathbf{r}) = \sigma(|\mathbf{r}|)$, an analytical solution for (A1) exists (Sarvas, 1987):

$$\vec{B}(\mathbf{r}) = (\mu_0/4\pi F(\mathbf{r}_q, \mathbf{r})^2) [F(\mathbf{r}_q, \mathbf{r}) \vec{Q}(\mathbf{r}_q) \times \mathbf{r}_q - \vec{Q}(\mathbf{r}_q) \times \mathbf{r}_q \cdot \mathbf{r} \nabla F(\mathbf{r}_q, \mathbf{r})], \quad (\text{A3})$$

where $F(\mathbf{r}_q, \mathbf{r}) = a(ra + r^2 - \mathbf{r}_q \cdot \mathbf{r})$, $\mathbf{a} = \mathbf{r} - \mathbf{r}_q$, $a = |\mathbf{a}|$, and $r = |\mathbf{r}|$. We note that the magnetic field and consequently the induced E field do not explicitly depend on the radial conductivity profile $(|\mathbf{r}|)$. Therefore, the exact radius of the spherical volume is irrelevant within the assumptions of the derivation (Sarvas, 1987). Equation (A3) assumes that the dipole location $\mathbf{r}_q$ is inside the spherical volume, the field point $\mathbf{r}$ outside of it, and the coordinate system origin coinciding with the center of spherical symmetry.

A sphere that approximates a given discretized surface can be obtained as follows. Denoting by x_c, y_c and z_c the unknown center coordinates and by R the unknown radius of the approximating sphere, we can write the general equation:

$$(x - x_c)^2 + (y - y_c)^2 + (z - z_c)^2 = R^2.$$

Assuming that we have a set of points $x = x_i, y = y_i, z = z_i, i = 1, \dots, N$ belonging to the discretized surface, we can write a similar equation for each point. Defining $R_c^2 = x_c^2 + y_c^2 + z_c^2$ and $R_i^2 = x_i^2 + y_i^2 + z_i^2$, and expanding the powers, we get for one point:

$$R_i^2 + R_c^2 + [-2x_i - 2y_i - 2z_i][x_c \ y_c \ z_c]^T = R^2.$$

Re-arranging further gives:

$$[2x_i \ 2y_i \ 2z_i \ 1][x_c \ y_c \ z_c \ (R^2 - R_i^2)]^T = R_i^2.$$

Concatenation of such equation for each of the data points results in an over-determined system of linear equations in the form of $\mathbf{Ax} = \mathbf{y}$, where $\mathbf{x} = [x_c \ y_c \ z_c \ (R^2 - R_c^2)]^T$ and so on. Applying the standard least-squares estimate, $\mathbf{x} = (\mathbf{AA}^T)^{-1} \mathbf{A}^T \mathbf{y}$, from which the unknown center and radius can be obtained. Other methods for fitting a sphere to a set of points could also be developed. It remains the subject of future studies to investigate the optimal choice of such a method and also the optimal area under the coil to which the sphere should be fitted.

Appendix B

Here we provide an estimate of the effects of CSF on induced electric fields. We constructed a four-layer model assuming that the space between inner skull and pial surfaces consisted of CSF. The pial surfaces of both cortical hemispheres from standard FreeSurfer reconstruction were first merged, then converted into a volume, smoothed, and ultimately decimated to a coarser surface consisting of 14882 vertices and 30072 triangular elements. Similarly, the FreeSurfer white-gray matter boundary surface was decimated to approximately 9890 vertices and was used as the surface on which the E fields were calculated. The surface manipulations were performed utilizing the iso2mesh toolbox (Fang and Boas, 2009). Figure 7 shows the resulting surfaces. The inner skull, outer skull, and outer skin surfaces were essentially identical to those shown in Figure 1(A) – (B) with the exception that the inner skull surface was slightly expanded such that the thickness of the CSF layer was at least 2 mm in order to avoid numerical errors possibly associated with very thin conductivity layers. The minimum thickness of 2 mm was estimated sufficient for

numerical accuracy using the validation of the four-layer BEM approach against a spherical model as a guideline (Stenroos and Sarvas, 2012).

Due to the increase in computational load caused by adding the CSF layer, the analysis was limited to a prefrontal coil position where the differences between the three-shell and spherical model were largest (Figure 2). The four-layer model was implemented using the Galerkin method with isolated source approach applied at the inner skull surface (Stenroos and Sarvas, 2012). The conductivity of CSF was assumed 1.79 S/m and the skull-to-brain conductivity ratio was assumed 1/20. Thus, the skull-to-CSF conductivity ratio was approximately 1/108. Figure 8 shows the resulting E-fields on an inflated cortical surface (created using SPM 8) for the four coil orientations. The results from the 4- and 3-layer BEMs were highly similar. In addition, in agreement with results from some FEM simulation studies (Bijsterbosch et al., 2012; Thielscher et al., 2011) adding a CSF layer seemed to result in slightly larger E field amplitudes at the gyral crowns. Our analysis, however, clearly suggests that the difference between the four- and three-layer models is smaller than the difference between three-layer and spherical models. Further work is needed to quantify the magnitude of the CSF effect across different brain regions.

Highlights

Volume conductor models influence TMS electric field estimates.

Present TMS navigation systems use computationally simple spherical conductor models.

Anatomically realistic boundary-element models can improve TMS targeting especially at prefrontal and temporal regions.

Figure 1.

(A) An example figure-of-eight TMS coil model on top of the outer skin BEM surface. At each of the locations marked with the magenta dots, a TMS coil model was assumed with four different directions (example direction shown with black arrow). (B) The outer (transparent green) and inner (blue) BEM surface of the skull along with the mid-sagittal slice from the anatomical MRI. (C) The TMS-induced E field was computed on a surface obtained by shrinking the inner surface of the skull by ~ 7.5 mm. An example of the magnitude of the E field, assuming coil current rate of change $50 \text{ A}/\mu\text{s}$, is shown on the color scale. (D) The distance from each simulated coil location to the E-field computation surface. (E) Anatomical parcellation of FreeSurfer was utilized in creating ROIs for quantitative model comparison. (F) Four representative anatomical ROIs were selected from different lobes of the brain, and the corresponding ROIs were projected on the E-field computation surface for averaging.

Figure 2.

E fields resulting from placing the coil with prescribed orientation and current over different ROIs (Row 1). The coil locations (Rows 2–5). The E-field distributions for different conductivity models.

Figure 3. Robust localization error (R-LOC) maps as function of coil location over the right hemisphere. Four leftmost columns show the errors separately for the different coil orientations. The rightmost column shows the average error across the four coil orientations.

Figure 4. Robust E-field amplitude error (R-EAB) maps as function of coil location over the right hemisphere. Four leftmost columns show the errors separately for the different coil orientations. The rightmost column shows the average error across the four coil orientations.

Figure 5.
Within-ROI averages for the figures of merit for the each of the models.

Figure 6. Histograms for figures of merit EAU and LOC within ROI [1] and ROI [3] for models #2, #7, #8, and #9.

Figure 7. The surfaces used in a 4-layer BEM control analysis. (A) The pial surface used as the inner boundary of the CSF compartment. (B) The right hemisphere gray-white matter boundary surface on which the E fields were computed.

Figure 8.

The effect of adding a CSF layer (4-layer BEM control analysis). The estimated E fields in a prefrontal coil location are shown on an inflated cortical surface for different coil orientations and conductivity models. The color scale for each coil orientation is the same across all head models.

Table 1

Description of the different conductivity models.

Model # / (description)	(skull) / (brain)	Method
1 (reference model)	1/20	three-compartment G-ISA BEM
2 (uniform head model)	1/1	three-compartment LC-ISA BEM
3	1/10	three-compartment LC-ISA BEM
4	1/20	three-compartment LC-ISA BEM
5	1/40	three-compartment LC-ISA BEM
6	1/80	three-compartment LC-ISA BEM
7 (inner skull model)	0	one-compartment LC-ISA BEM
8 Locally-fitted sphere	N/A	Sphere
9 Globally-fitted sphere	N/A	Sphere

Table 2

Computation times (in seconds) for a TMS coil model with 1224 integration points solved with 3- and 1-layer LC BEM models comprising 2562 vertices per layer and with a locally-fitted spherical model.

	3-layer BEM	1-layer BEM	Sphere
Step 1: Volume conductor model	105.7	13.4	N/A
Step 2: Coil preparation	15.4	5.2	0.2
Step 3: Forward computation	3.2	3.2	6.6