Inverse localization of electric dipole current sources in finite element models of the human head

Helmut Buchner a,b,*, Gunter Knoll b, Manfred Fuchs c, Adrian Rienäcker b, Rainer Beckmann a, Michael Wagner c, Jiri Silny d, Jörg Pesch d

a Department of Neurology, RWTH, Pauwelsstrasse 30, 52074 Aachen, Germany
b Institute for Machine Elements and Tribology, University of Kassel, Kassel, Germany
c Philips Research, Hamburg, Germany
d Helmholtz Institute of Biomedical Engineering, RWTH Aachen, Germany

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Abstract

The paper describes finite element related procedures for inverse localization of multiple sources in realistically shaped head models. Dipole sources are modeled by placing proper monopole sources on neighboring nodes. Lead field operators are established for dipole sources. Two different strategies for the solution of inverse problems, namely combinatorial optimization techniques and regularization methods are discussed and applied to visually evoked potentials, for which exemplary results are shown. Most of the procedures described are fully automatic and require only proper input preparation. The overall work for the example presented (from EEG recording to visual inspection of the results) can be performed in roughly a week, most of which is waiting time for the computation of the lead field matrix or inverse calculations on a standard and affordable engineering workstation. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Source localization of cerebral activity with respect to individual anatomy is a prominent goal of electroencephalography. A mathematical treatment of this problem on the basis of physical principles and computer techniques was first proposed by Brazier (1949) and implemented by Henderson et al. (1975). Their approach based on representing the head by a spherical volume conductor model and the locus and orientation of the source by an 'equivalent dipole'. The dipole approximation is a convenient representation of the source in the case of synchronous polarization of a few square centimetres or less of cortical surface (for review see Fender (1987) and Nunez (1990)). However, a sphere or multiple layer spheres are an oversimplified model because: the geometry of the head is not properly represented by a sphere (Law and Nunez, 1991; Myslobodsky et al., 1991), the thickness of skin and skull are not uniform (Law, 1993), electric conductivity varies in different parts of the head (Law, 1993), and the conduction properties of the compartments of the head depend on the direction of current flow (for review see Fender, 1991). Recent studies demonstrated, that head modeling with respect to individual head anatomy is required for exact localization (Roth et al., 1993; Buchner et al., 1996b).

While the finite element method (FEM) is known to be able to treat geometries of arbitrary complexity and is able to model variable material properties and anisotropy in computer simulations (Zienkiewicz, 1984), it is rarely applied to the problem discussed here (Srebro, 1990; Yan et al., 1991; Bertrand et al., 1991).

In this paper, we present recently developed methods for the automatic construction of finite element meshes from MR data and finite element related techniques for forward and inverse solutions (source localization).
While the main part of this paper is devoted to the methods developed and implemented, we also present an example of inverse analysis on the basis of visually evoked potentials. It is shown, that the analysis can be performed on affordable hardware platforms and therefore is suited to assisting clinical and experimental research.

2. Methods

2.1. Forward solution techniques

In the quasistatic approximation of Maxwell’s system of coupled partial differential equations for electric and magnetic fields, the distribution of electric potentials \( V(x_k) \) in domains \( \Omega(x_k) \) of conductivity \( \sigma(x_k) \), resulting from current source density distributions \( j(x_k) \) is governed by the second order elliptic partial differential equation (Eq. (1)) in which the index \( k \) ranges over all spatial dimensions \( (x_k=x, y, z) \) and summation over repeated (dummy) indices is implied 2.

\[
\frac{\partial}{\partial x_k} \left( \sigma \frac{\partial V}{\partial x_k} \right) - j^{(0)} = 0
\]  

(1)

The boundary conditions under consideration are of Dirichlet type (specified potentials, Eq. (2)) on a non-vanishing segment \( \Gamma_D \) of the boundary \( \Gamma(x_k) \) and of Neumann type (specified current outflow from the system, Eq. (3)) on the rest \( \Gamma_C = \Gamma - \Gamma_D \) of the boundary.

\[
V|_{\Gamma_D} = \alpha(x_k)
\]

(2)

\[
V|_{\Gamma_C} = \alpha(x_k)
\]

(3)

\[
\sigma \frac{\partial V}{\partial n} \bigg|_{\Gamma_C} = j^{(\Gamma_C)}
\]

In a forward solution the potential is determined for a given current source configuration and known boundary conditions. The forward problem is well posed, the solution unique and one can choose from a broad variety of analytical techniques, such as the Greens function method and the related method of images or numerical methods, such as finite differences (FD), finite volumes (FV), boundary elements (BEM) or finite elements (FEM) for finding a solution (Smythe, 1989; Lapidus and Pinder, 1982).

In the present approach the finite element method is used for the calculation of forward solutions because of its ability to treat geometries of arbitrary complexity, the possibility to consider material properties on a node to node or element basis and because of its high accuracy, especially in the treatment of Neumann boundary conditions which are important in the application considered.

2.2. Finite element dipole approximation

While the vectors \( b_i \) and \( c_i \) from Eq. (4) contain volume and surface current sources, so called monopoles, it is desirable to utilize the concept of a dipole in the analysis (Nunez, 1990). Physiological observations indicate that mainly the effects of dipole current sources can be observed on the head’s surface, while from a more practical point of view we find that dipole vectors contain more information (strength and direction) and ease the interpretation of inversely calculated source configurations.

In addition many sources that are sought in inverse analyses originate from the cortical surface and are oriented normal to it (Lorente de No, 1938; Mitzdorf, 1985; Nunez, 1990). Such a configuration can conveniently be modeled with dipoles.

The principal problem related to dipole modeling in finite element meshes is that mesh geometries are irregular in general. Such a situation is depicted in Fig. 1 in which part of a complex mesh is shown (two-dimensionally for illustration).

The dipole vector for node \( i \) with components \( M_i \) pointing in arbitrary direction is modeled by placing current sources \( j^{(D)} \) on only the neighboring nodes \( k \) such that the resultant dipole moment matches that of a theoretical dipole and a number of additional conditions are met (for mathematical details see Section 5).

Application of variational and finite element techniques (see the appendix for details) yields an algebraic system of equations to be solved for the unknown nodal potentials.

\[
\int_{(\Omega)} \left( \frac{\partial \psi_i}{\partial x_k} \frac{\partial \psi_j}{\partial x_k} \right) d\Omega V_j + \int_{(\Omega)} \psi_i j^{(D)} d\Omega - \int_{(\Gamma)} \psi_i j^{(\Gamma_C)} d\Gamma = 0,
\]

(4)

One of the appealing features of the finite element method is that homogeneous Neumann boundary conditions \( j^{(\Gamma_C)} = 0 \), physically representing insulated boundaries, are considered by practically doing nothing, i.e. leaving the particular nodal entry in the vector \( c_i \) at zero value.

Another advantage of the method is its integral formulation which permits to choose global interpolation functions of very simple nature, for which differentiability is required only where differentials are evaluated and only integrability is required over all of the domain.

The system of Eq. (4) is solved iteratively with a conjugate gradient (CG) algorithm with scaling and an incomplete cholesky factorization method for preconditioning, taking full advantage of the sparsity of the matrix. A single solution for the finite element model used in this paper takes less than 25 CPU seconds on a typical engineering workstation (IBM RS/6000, model 375) and the nonzero elements of the matrix together with the preconditioning matrix and the necessary indexing information need less than 3 Megabytes of memory.

2 The chosen notation directly relates to the programmed code.
This is justified on the theoretical foundation of Saint Venant’s principle which states that the specific (fine) details of load application do not influence the results (i.e. potentials) observed some distance away from the locus of load application.

To illustrate the validity of the chosen model, Fig. 2 shows the correlation

\[ C = \frac{\int_{-1}^{1} V_{\text{FEM}} \cdot V_{\text{SMYTHE}} \, dt}{\int_{-1}^{1} V_{\text{SMYTHE}} \cdot V_{\text{SMYTHE}} \, dt} \]  

of the surface potential distribution with an analytical expression given by Smythe (1989) for a radially oriented dipole in an homogeneous, insulated sphere as a function of dipole eccentricity \( e = r/R \) for two typical combinations of model parameters as outlined in Section 5.

For low to middle eccentricities no difference between the two FEM dipole solutions can be observed, and the correlation close to unity \( C = 1 \) indicates that both of the numerical solutions yield the same surface potentials as Smythe’s analytical solution. Differences can be observed for large eccentricities \( e > 0.8 \), where the surface of the sphere and the dipole node are separated by very few elements and thus the discrete model inevitably differs from an analytical solution where source and sink are separated by only a small distance. In the application considered this difference is not critical since possible source and sensor locations are separated by multiple layers of elements.

The finite element dipole model presented is independent of the assumption that nodes of the cortical surface coincide with nodes of the finite element volume structure. If, with respect to limitations of computer resources, one is willing to sacrifice an exact representation of the volume conductor model, which requires a very fine meshing, it is still possible to retain the information from a detailed representation of the cortical surface for dipole source analysis. It is thus possible to assign conductivities to elements of a relatively coarse mesh, while dipole sources may originate from a very fine, independent, representation of the true cortical surface, in which the constraint is justified that dipole directions must coincide with local surface normal directions.

2.2.1. Lead field operator

For the lead field operator potentials are recorded with a limited number of electrodes (say \( n_m = 64 \) or \( n_m = 128 \) with modern equipment) while dipole sources with \( n_s \), directional components can originate from only a discrete number of influence nodes \( n_d \). For inverse solutions we are mainly interested in the potentials at the evaluation (measurement) nodes \( i \) due to a dipole source distribution spread over all influence nodes \( j \). Since the differential equation is linear, it is possible to set up a so called lead field operator \( L_{ij} \) (sometimes denoted influence matrix) of order \( n_m \cdot n_d \cdot n_s \), prior to inverse calculations. A row of the lead field operator is established by placing a unit dipole source with direction \( r \) on node \( j \) and recording potentials on all evaluation nodes \( i \). For an arbitrary dipole source distribution \( M_f \) the potentials at the measurement nodes are evaluated inexpensively by the matrix-vector operation

\[ V_i = L_{ij} \cdot M_f. \]  

While setting up the lead field operator involves \( n_d \cdot n_s \) individual forward solutions and thus takes on the order of a day (for the mesh used in this paper), it is possible to use the same operator for many inverse calculations since it is independent of time, measured potentials or specific source configurations. In addition, simple physiological arguments regarding the possible locations of sources may lead to a substantial reduction of \( n_d \cdot n_s \) in inverse analyses.

2.3. Inverse solution strategies

A straightforward approach to the solution of the inverse problem would select the unknown dipole moment load such that measured potentials \( V_i \) match closely with calculated potentials \( (L_{ij}M_f) \). In the mathematical form of a least
squares expression we seek a dipole moment configuration $M'_t$ that minimizes the quadratic functional $J \geq 0$

$$J = \frac{1}{2} \left( \sum_v V_i - L^0_t M'_t \right) \left( \sum_v V_i - L^0_k M'_k \right) \stackrel{!}{=} \min.$$  

Exploiting the necessary condition for the minimum, the system of equations

$$\left[ L^0_{iu} L^0_{i\ell} \right] M'_t - L^0_{iu} \sum_v V_i = 0'_u$$

is derived.

In this system of equations we try to determine a large number of unknowns $M'_t$ from a small number of measured potentials, of course an impossible task as discussed for instance by Snyder (1991). Mathematically the system matrix is singular when unknowns outnumber independent equations and only two strategies will alleviate the problem: first the number of unknowns must be reduced or second the number of independent equations must be increased.

Interpretation of Eq. (8) also indicates that once a realistic volume conductor model is established, the use of higher order interpolation functions ($p$-concept of finite element methods) will only slightly improve the quality of inversely calculated results since the principal restriction in inverse analyses lies in the limited amount of measured information. With respect to the geometric complexities of head anatomy it seems to be more desirable to employ local mesh refinement in conjunction with simple linear interpolation functions instead ($h$-concept of finite element methods).

2.3.1. Combinatorial optimization: simulated annealing

The first class of solutions utilizes concepts of combinatorial optimization, namely the simulated annealing algorithm (for details see Press et al. (1992), Gerson et al. (1994), Haneishi et al. (1994), for finding the subset $n_{subset}$ of all conceivable dipole locations (typically one chooses $n_{subset} = 2 \ldots 5$ nodes) which assigns the lowest value to the functional $J$. Since potentials depend linearly on dipole moment strengths (for a fixed dipole location and component (direction) of the dipole vector) and nonlinearly on dipole location, the procedure of finding the best configuration is split in two stages:

- Sets of dipole nodes $n_{subset}$ are selected according to the random procedures discussed for instance by Press et al. (1992), while
- Linear least squares methods yield the dipole vector components that ensure best fit between measured and calculated potentials for the given set of dipole nodes.

For each configuration (combination of $n_{subset}$ dipole

4 Nevertheless the computer code developed permits one to choose isoparametric interpolation functions up to cubic order.

nodes) the measure for goodness of fit $J$ can be evaluated and, via the simulated annealing procedure, a good approximation of the global minimum be found.

Computationally this procedure typically involves a couple of million solutions (singular value decompositions) of small systems of equations (6 ... 15 unknown components of dipole moment vectors) and takes on the order of a few hours of computing time.

2.3.2. Regularization

The second class of solutions is based on the concept of spatial regularization (as explained by Press et al. (1992) for finite difference applications) and is closely linked to the availability of a geometric description of the part of the domain over which spatial regularization shall be formulated.

Spatial regularization adds information to the above system of Eq. (8) via the method of Lagrange multipliers. The functional $J$ above becomes part of a more general functional $I$ in which the constraints $S$ are added:

$$I = J + \lambda S.$$  

The constraints $S$ are formulated such that the solution for the unknown dipole moment shall vary smoothly in space, while the Lagrange multiplier is assigned a small value such that a unique solution is selected from all conceivable solutions which brings measured and calculated potentials to a very close match and is smooth, where measured potentials fail to give the information required to make the system matrix regular. The functional $S > 0$ can be written in the general form

$$S = M'_t \, s'^{r}_t \, M'_t,$$  

where $s'^{r}_t$ is a smoothing operator, which in this particular case is chosen in the form

$$s'^{r}_t = G_{ij} \delta^{rs},$$

where $G_{ij}$ is a typical finite element matrix and $\delta^{rs}$ is the Kronecker delta (unit matrix) applied to the spatial directions. This formulation implies that each directional component $r$ of the dipole moment distribution $M'_t$ is regularized separately.

The system of equations arising from the minimization of the functional $I$ is:

$$\left[ L^0_{iu} L^0_{i\ell} + \lambda G_{iu} \delta^{rs} \right] M'_t - L^0_{iu} \sum_v V_i = 0'_u.$$  

Further details depend on the special form of the finite element regularizer $G_{ij}$. In this context we can first assume that a solution must be sought for all nodes within the cortical volume (obviously sources cannot originate from scalp, skull or liquor). Second we can assume that dipole

5 A good choice reflects orders of magnitude in $J$, $S$ and signal to noise ratio.
sources must be located on the cortical surface only. In the second case it is possible to add the further restriction that dipoles must point in the direction of the local normal vector of the surface, a restriction which reduces computational efforts by a factor of three and is especially appealing if discretization is fine enough to capture geometric details of the cortical surface.

2.3.2.1. Volume regularization. The special concept of smoothness implies minimizing curvature of the solution. Since curvature is closely related to second order derivatives, which cannot be modeled with linear interpolation functions, we utilize a more general approach to smoothness by choosing zeroth and first order spatial FEM regularizers of the form

\[ C_{ij}^{(0)} = \int_{\Omega} \nabla \psi_1 \cdot \nabla \psi_2 \, d\Omega \]

\[ C_{ij}^{(1)} = \int_{\Omega} \frac{\partial \psi_1}{\partial x} \frac{\partial \psi_2}{\partial x} \, d\Omega \]

which seek to minimize values or gradients of the source distribution.

We would like to emphasize that the integral formulation by itself ensures smooth source distributions (in contrast to the most primitive operator \( G_{ij} = \delta_{ij} \) conceivable in this context), while the special form of the integrand effects only minor changes in the inverse solution.

The similarity between the weak form of the Laplacian\(^a\) operator in the forward problem (matrix \( A_{ij} \) in Eq. (4)) and operator \( G_{ij}^{(1)} \) (Eq. (13)) shows that regularization with respect to the governing differential equation is invoked, as used in LORETA by Pascual-Marqui and Michel (1994). In contrast to LORETA, our proposed finite element regularization operator does not require evaluation of second derivatives. Depth weighting of the sources, is employed in a straightforward fashion, either by column scaling of the lead field operator in Eq. (8), or by omitting scaling of the smoothing operator in Eq. (28).

2.3.2.2. Surface regularization. Surface regularizers can be defined in formal analogy to volume regularizers.

\[ C_{ij}^{(0)} = \int_{\partial \Omega} \psi_1 \psi_2 \, d\Gamma \]

\[ C_{ij}^{(1)} = \int_{\partial \Omega} \frac{\partial \psi_1}{\partial x} \frac{\partial \psi_2}{\partial x} \, d\Gamma \]

Implementation of \( G_{ij}^{(1)} \) however involves evaluation of shape function derivatives along natural (tangential plane) directions \( u_k \) of surfaces in three-dimensional space and projection of these derivatives onto cartesian axes \( x_k \). Inte-

\(^a\)The more appropriate denotation quasiharmonic appears to be unpopular.

Regularized inverse solutions represent measured potentials almost exactly, which is not only advantageous since noise and the signal itself are optimized with equal weight. Direct solutions of Eq. (12) are possible only for small meshes with few nodes, since the matrix is fully populated. For the treatment of larger problems a tailored conjugate gradient solution, in which explicit formulation (and storage) of the matrix is completely avoided (see Section 5 for details) is applied.

With the tailored solution scheme regularized inverse solutions become computationally very attractive because the arising system of equations is linear and iteration is avoided completely. For large problems, where simulated annealing procedures take hours of CPU time, regularized solutions can be calculated in minutes despite the large order of the system of equations. Transient inverse solutions, involving on the order of 200 time steps can be calculated overnight.

2.3.3. Relation between regularization and spatial deblurring

The concept of spatial deblurring for the estimation of potential distributions on some inner surface (the inner surface of the skull or the cortical surface may be of major interest) was introduced by Gevins et al. (1994). In this method the volume enclosed by the surface is removed from the finite element model of the head, so that the surface becomes a boundary of the remaining domain which is free of sources \((J^{(1)} = 0)\) if the chosen surface lies between cortex and outer skin. In the course of the process potential (Dirichlet) boundary conditions on this bounding surface are optimized such that the measured EEG potentials are met and the differential equation (Eq. (1)), \( J^{(1)} = 0 \) is satisfied.

Instead of optimizing Dirichlet boundary conditions on this surface, one could choose to optimize current flow boundary conditions \( J^{(1)} \) (Eq. (3)) with equal justification and very similar results. Since unknown boundary conditions will outnumber measured potentials in normal applications, an inverse problem is defined for which spatial regularization techniques yield smooth solutions in a single solution of a linear system of equations and nonlinear optimization is avoided.

If the eliminated part of the volume conductor is inserted again, surface sources \( J^{(1)} \) will become volume sources
which by Eq. (4) are treated in a very similar fashion in the forward solution and consequently in the inverse solution also.

If possible source locations are restricted on the basis of physiological arguments, the regularization techniques proposed in this paper are established, and the relation between spatial deblurring and inverse regularization becomes apparent.

2.4. Validation

To validate the program developed we perform a number of checks on a regular basis. Forward solutions for arbitrary distributions of dipoles in homogeneous and insulated spheres are checked against the analytical solution given by Smythe (1989) and lead field operators are checked against forward solutions for random loads. For small systems we apply direct and iterative solutions to the inverse system of equations and compare the results. Finally, each inverse dipole source distribution must yield potentials in close agreement to the measured potentials in a forward solution.

An overall strategy for checking inverse solutions in principal is to select an arbitrary source configuration, determine noise-free 'measurements' in a forward solution (a reference solution), perform an inverse analysis and compare reference and inverse source configurations directly (visually and/or by error norms or correlation coefficients). This procedure was applied to a number of interesting 'unsolvable' test cases where the reference source configurations were in obvious contrast to the basic assumptions of either annealing or regularization procedures. For simulated annealing procedures, distributed source configurations were chosen, such that the number of reference dipoles was much larger than the number of permitted dipoles in the inverse search, while reference source configurations for the regularization method were chosen to be extremely nonsmooth. An interesting result from these test cases is that despite the impossibility of finding the exact solution, both solution strategies are still able to capture the essential features of the reference source configuration in the inverse calculation.

In addition test calculations indicate that the two proposed strategies bracket the 'true' solution with respect to assumed sharpness (simulated annealing approach) and smoothness (regularization approach) of the dipole distribution.

With respect to the question of accuracy in the discrete finite element model, forward solutions were carried out for single, eccentric radial and tangential dipoles in a finite element sphere with four shells (conductivities 0.336(1/Ωm) for the brain and scalp, 1.0(1/Ωm) for the liquor and 0.0042(1/Ωm) for the skull, thickness of scalp 7 mm, skull 8 mm, liquor 7 mm radius 85 mm). Potentials in the discrete model (average edge distance 4.4 mm) were recorded at 64 locations evenly spaced on the upper part of the sphere. Electrode positions and potentials were read into the CURRY (Philips, Hamburg) software. In a sphere (radius 85 mm, same conductivities and thicknesses of scalp, skull and liquor) inverse (single moving dipole) solutions were carried out on the basis of analytical expressions for the potential distribution.

A comparison between source locations (forward-discrete vs. inverse analytical) is shown in Fig. 3 for radially and tangentially oriented dipoles as a function of dipole eccentricity for a single moving dipole. One remarkable result from this investigation is that mislocation falls below 2 mm in most cases and never exceeds 3 mm.

In a further investigation (Pesch, 1995) measurements were taken on a phantom head, especially constructed for this purpose. A 3D-MR was recorded from the saline water filled realistically shaped plastic model of a human skull and the inner volume subsequently discretized with a mesh of 17196 nodes and an average edge length of 4 mm.

One to three simultaneously active radial and tangential dipole sources were modeled by monopoles, separated by small distances and placed to five positions within the phantom (Fig. 4). Potentials were measured from 65 Electrodes (10/10 system), located at the inner surface of the skull. Due to the resolution of the MR image and the limited precision in coordinate measurements dipole positions were experimentally determined with an accuracy of about 3.5 mm. An
additional error of about half of the average finite element edge length must be assumed and tolerated for an inverse analysis. Inverse analyses (simulated annealing) showed mislocations in the range from 2 to 7 mm with an average mislocation of 3.8 mm. It was found that localization error mainly depends on mesh fineness around the dipole source. Local mesh refinement to 2 mm edge distance around sources improved localization accuracy to less than 3.5 mm with a mean of 2.3 mm even for multiple dipole sources.

Despite the increased number of possible sources of error (coordinate determination, MR resolution, segmentation) the results obtained from the phantom agree well with the former comparison (Fig. 3).

3. Analysis of visually evoked potentials

3.1. Subject

VEPs and 3D-MR-tomography were obtained from a normal right handed male subject who gave his informed consent.

3.2. VEP recording

VEPs were stimulated by a visual full field checkerboard screen and recorded from 64 scalp electrodes against a reference at Cz. Signals were sampled with 300 points over a 200 ms pre- and 400 ms poststimulus period. Recording bandpass was set to 1–250 Hz on the two 32-channel Nicolet SM 2000 amplifiers. Four replications of 500 sweeps were averaged for each stimulation using the Scan system (NeuroScan, Herndon, VA). After VEP measurements, the position of each electrode was marked by replacing it with a small wooden disk. Disks had a 3-mm hole filled with fat to visualize the position on the 3D-MR.

3.3. MR acquisition

MR was performed after the VEP recording on the same day using a 1.5-T superconducting magnet and a circular polarized head coil. After parallel alignment of the interhemispheric plane of the brain with the sagittal imaging plane, a strongly T1-weighted gradient echo pulse sequence (fast-low-angle-shoot) was applied. For all MRs the technical factors were: 50 ms repetition time, 5 ms echo time, 40° flip angle, one excitation, 30-cm field of view, 256 x 256 image matrix (12-bit resolution). This resulted in 128 contiguous slices with a thickness of 1.56 mm and a pixel size of 1.17 mm.

3.4. MR preprocessing

MRs were read into the CURRY-software package (Philips, Hamburg). The original slices were reduced to 8-bit resolution and Gaussian interpolated to get an isotropic three dimensional data set. A surface reconstruction of the head was done by radial search thresholding from outside for optimal visualization of the positions of the electrode markers.

3.5. Surface segmentation and finite element model

The surface of the brain, the inner and outer skull and the skin were segmented out of the isotropic 3D-MR as follows: The cortical surface was found by application of a three-dimensional region growing algorithm (Wagner et al., 1995), starting within the brain and stopping at a gray value representing the border between white and gray matter. In critical regions, such as the temporal pole and the orbita, where the automatic process was not able to find the surface, 'boundary markers', guiding the algorithm, were inserted by hand. The surface of the inner skull was approximated by smoothing and dilating the brain's surface. After setting all gray values inside the inner skull’s surface to black, the surface of the outer skull was found by three dimensional region growing starting from the center, stopping at a gray value representing the border between the skull and the skin. After setting all gray values inside the outer skull to white, the skin’s surface was also found by region growing from the center, stopping at a gray value representing the skin’s surface.

The number of surface points was decreased to a grid with 2 mm average spacing for visualization of the surface and 4–6 mm for the FE mesh. Surface elements (triangles) were generated from this mesh (Wagner et al., 1995) and stored together with the corresponding surface normals. Normals were approximated from the local geometry of the surface.

The tetrahedral finite element mesh (Fig. 5) for the volume conductor was created according to the procedure described in the appendix. Finally the conductivities of skin

Fig. 5. Sagittal cut through the finite element mesh (18322 nodes, 105327 elements, 2914 nodes on the cortex)
and brain were set to 0.336(1/Ωm), liquor conductivity was set to 1.0(1/Ωm), and skull conductivity was set to 0.0042(1/Ωm).

3.6. Results

Both, combinatorial optimization and regularization procedures were applied for inverse analyses at the maximum of the P100 peak. In all solutions the search was restricted to the cortical surface, a triangulated structure (2914 nodes) with edges of 4–6 mm length. This discretization follows most ondulations of the outer hull of the true cortex but does not reach into deep and narrow sulci. Consequently the direction of dipoles on the cortex was not restricted to coincide with local normal directions of the surface mesh, leaving an overall of 8742 unknown dipole components and a lead field matrix of about 4.5 MB.

Figs. 6 and 7 show the solution for annealing with three dipoles and the regularized solution. Solutions with two and three dipoles obtained from the simulated annealing algorithm are almost identical. The strength of the third dipole, located in the right front part of the brain, is negligible compared to the strength of the other two dipoles, indicating that only two centers of activity exist.

The residual variance between calculated and measured signals for three dipoles is 1.58%, which yields a standard deviation of 12.57% compared to an assumed noise of 10% in the signal. Both of the strong dipoles are located in the visual cortex region, with a clear orientation to the right for the dipole located on the left hemisphere and a substantial component to the left for the dipole located on the right hemisphere. The latter also exhibits strong components oriented from top to bottom and from back to front.

In the graphical representation of the regularized solution all dipoles below a threshold of 25% of the maximum recorded dipole strength are not shown. Dipoles above that threshold reveal two activated areas, one on each hemisphere of the visual cortex and also with strong components from left to right on the left hemisphere and from right to left on the right hemisphere. Compared to the annealing solution the center of activity on the right hemisphere is located in a lower region, while the center of activity on the left hemisphere is almost identical for both solutions.

4. Discussion

With the methods applied, inverse localization of multiple dipole current sources in realistically shaped finite element models of the individual anatomy is feasible in clinical research.

Most of the procedures described are fully automatic and require only proper input preparation and a careful look at the results. The overall work for the example presented (from EEG recording to visual inspection of the results) can be performed in roughly a week, most of which is waiting time for the computation of the lead field matrix or inverse calculations on a standard and affordable engineering workstation.

Improved accuracy in inverse calculations may be expected from the use of a finer mesh for volume conductor. Few studies with limited data (Roth et al., 1993; Buchner et al., 1996b) support this point.

A second advantage of realistic head modelling is the availability of a realistic approximation of the cortical surface. This provides: (1) the possibility to use anatomical constraints in the inverse solution, enhancing the accuracy of source localization (Akhtari et al., 1994; Fuchs et al., 1994; Wang, 1994; Buchner et al., 1996a), (2) an overlay of functional and morphological images for advanced and improved functional diagnosis showing the correlation between structure and functional areas.

Additional insights can be expected from the comparison of the two inverse strategies described in this paper, one of them searching a singular (center of activity) solution, the other looking for a distributed, smooth dipole source configuration.

Single or multiple dipoles at discrete locations provide a convenient approximation of single or multiple sources arising from a few square centimeters of activated cortex (Fender, 1987; Nunez, 1990; Lopes da Silva et al., 1991). The
implemented simulated annealing algorithm was shown to be robust in finding global optima (Gerson et al., 1994; Haneishi et al., 1994). While a single or multiple dipole solution pinpoints the center of activity, this model gives only indirect information about the spatial extent of the activated cortex (Lopes da Silva et al., 1991; Fuchs et al., 1994). In contrast a different class of inverse solutions, using additional physiological constraints does in principle provide information about the spatial extent of the activated cortical area.

In this context, most often the minimal norm criterion, basing on the assumption that the measured field should be explained by a source configuration with minimum activity (Wischmann et al., 1992; Wang et al., 1993), is used.

The proposed alternative here is the smooth-in-space criterion (regularization), in which the assumption that source activity at the cortex shall have a smooth spatial distribution is expressed. The solution obtained however overestimates the spatial extent of the sources. Recent work (Wagner et al., 1997a; Wagner et al., 1997b) shows, that regularization using nonlinear operators may alleviate this problem.

The presented exemplary application to visual evoked potentials shows: (1) reasonable locations of the two centers of activity at the visual cortex with more activity at the left side for the right handed subject (Abe and Kuroiwa, 1990). (2) A reasonable (though too widespread) distribution of sources over activated areas, reflecting the spatial extent of the visual cortex (Lopes da Silva et al., 1991).

Despite mathematical soundness, the suspected power of the presented methods must be further evaluated in experimental and clinical applications. One way to do this is to compare the results with other functional imaging techniques as PET and functional MR.

5. Appendix: finite element and computational details

5.1. Finite element mesh creation

An essential prerequisite for using the finite element method is the generation of a finite element mesh representing the geometric and electric properties of the volume conductor under concern and representing details of the parts of the brain where sources can originate from. In the scope of this work tetrahedral tessellations of the relevant compartments of the individual human head are used. The compartments, characterized by their borders and conductivities, are: skin and fat, skull, liquor, brain, ventricular system. A conductivity tensor may be assigned to each tetrahedron. The tetrahedra should be regularly shaped and evenly sized with respect to the local geometry and the spatial resolution of the finite element dipole approximation (see Section 5.3). This results in an optimal tetrahedral side length of only a few millimeters, where somewhat larger tetrahedra are allowed further below the brain surface.

Image processing, segmentation, mesh generation and display of results is performed using the PHILIPS software CURRY (CURREnt Reconstruction and Imaging). We assume that an MR image of the subject's head has been taken and that the borders of the conducting compartments have been segmented. This results in a segmentation of the head, whose outer surface is the skin surface and interior surfaces represent borders between compartments.

In a first step of automatic mesh creation, additional auxiliary surfaces with a given distance $d_a$ from the existing ones are generated within the segmented object. This step is repeated recursively until a set of layered surfaces, some of which are compartment borders and some are auxiliary surfaces, is obtained.

In a second step, the vertices of the tetrahedral mesh are generated. This is done by subsampling or "thinning" the surfaces, using a thinning distance $d_t$ for compartment borders and $d_a$ for auxiliary surfaces. Subsampling means in this context, that vertices are distributed densely on a surface in such a way, that no two of them are nearer to each other than $d_a$ or $d_t$, respectively. The distances $d_t$ and $d_a$ are measured along the surfaces.

Now the three-dimensional Delaunay triangulation of all generated vertices is computed. The Delaunay criterion demands that no vertex resides inside the circumsphere of any generated tetrahedron. It guarantees the generation of tetrahedra that are as regular as possible. To speed up tetrahedrization, the fact that an upper limit for the circumsphere radius of any tetrahedron in the tesselation is known in advance is exploited. This limit is a function of the thinning distances $d_a$, $d_t$ and $d_a$. It is a measure for the volume that has to be regarded in an iterative 3D triangulation algorithm.

If the surface of the head has concavities, spurious tetrahedra spanning vertices around such concavities are generated. These tetrahedra are iteratively deleted until the hull of the mesh is the triangulated surface of the skin.

In a last step, each generated tetrahedron must be labeled as to which compartment it belongs to. If the MR image segmentation is still available, this task may be performed by computing the centers of the inscribed spheres of each tetrahedron and determining the compartments in which they reside.

As a result, a tetrahedral finite element mesh encoding the geometric and electric properties of the volume conductor is generated. The parameters $d_a$, $d_t$ and $d_a$ control the size of the elements.

5.2. Finite element details

Finite element systems of equations can be derived from functionals operating on distributed field variables of continuum mechanics.

In the present formulation the unique distribution of electric potentials $V(x_k)$ is selected from all admissible potential distributions $V'(x_k)$ (satisfying the so called essential Dirichlet boundary conditions of the problem) which minimizes the quadratic functional $F(V')$. 
In the calculus of variations all admissible potential distributions are composed of the true solution \( V(x) \) and the variation \( \delta V(x_k) \), which without loss of generality can be expressed by the product of a real number \( \epsilon \) and a coordinate function \( \phi(x_k) \) describing the spatial variation of \( \delta V(x_k) \).

\[
V^*(x_k) = V(x_k) + \delta V(x_k) = V(x_k) + \epsilon \phi(x_k)
\]  

Differentiation shows that the solution \( V \) not only minimizes the given functional but also solves the differential Eq. (1) in conjunction with so called natural (Neumann) boundary conditions (Eq. (2)).

\[
\frac{\partial F}{\partial \varepsilon} \bigg|_{\varepsilon=0} = -\int_{\Omega} \left( \frac{\partial \psi_k}{\partial x_k} \frac{\partial \psi_k}{\partial x_k} - J^{(\Omega)} \right) \phi d\Omega + \int_{\Gamma} \left( \frac{\partial \psi_k}{\partial n} - J^{(\Gamma)} \right) \phi d\Gamma = 0
\]  

natural boundary conditions

In the finite element method field variables (potentials, conductivities and coordinates) are expressed by sums over nodal values and global interpolation functions \( \psi_k \) which are nonzero only over a small subregion of the domain (the local support).

\[
V = \psi_k(x_k) V_k
\]  

In a nutshell: the global interpolation function of node \( k \) takes unit value at \( k \) itself, zero value at all other nodes of the mesh and nonzero values only in those elements adjacent to \( k \). In addition the sum of all global interpolation functions in any point of the domain takes unit value.

With respect to Eq. (17) and Eq. (19) admissible potential distributions are restricted to those which follow the general shape of the interpolation functions within elements.

The now discrete functional from Eq. (17) takes the form

\[
F(V_k^*) = \frac{1}{2} \int_{\Omega} \sigma \left( \frac{\partial \psi_i}{\partial x_k} \frac{\partial \psi_i}{\partial x_k} \right) d\Omega V_k^* V_k^* + \int_{\Omega} \psi_i^{(\partial)} d\Omega V_k^* - \int_{\Gamma} \psi_i^* J^{(\Gamma)} V_k^* = \min
\]  

and by differentiation with respect to the nodal unknowns \( V_k^* \) a system of algebraic equations arises from which the set of nodal potentials \( V_k \) minimizing \( F \), is determined (Eq. (4)).

5.3. Finite element current dipole approximation

The theoretical model of a dipole consists of only two monopoles, a source and a sink of equal strength, separated by a small distance \( d \) (up to \( d = 3 \text{ mm} \) may be realistic). Such a configuration can be expressed in terms of an infinite series of moments

\[
\text{Order 0 : } 0_T = J(d/2)^0 - J(-d/2)^0 = 0
\]

\[
\text{Order 1 : } 1_T = J(d/2)^1 - J(-d/2)^1 = Jd
\]

\[
\text{Order 2 : } 2_T = J(d/2)^2 - J(-d/2)^2 = 0
\]

\[
\text{Order } n_0 : \ n_0 T = J(d/2)^{n_0} - J(-d/2)^{n_0},
\]

of which the zeroth order is simply the sum of the two sources, the first order is the dipole moment and so forth.

If a target dipole moment load \( T_j = T \) with (first order) components \( \{T_i, T_j, T_k\} \) shall be generated at node \( i \), we propose to do this by placing proper monopole sources \( J_k \) on only the neighboring nodes \( k \), ensuring \( a \) priori that the dipole source configuration is of very local extent.

For a given current source distribution \( J_k \) we determine resultant moments \( n_0 M_j \) of order \( n_0 \) in direction \( r \), normalized so that the physical dimension is that of a current source \( (n_0 M_j) = 0 \), by evaluating Eq. (23)

\[
n_0 M_j = \left( \frac{\Delta x_k^r}{a_{ref}} \right)^{n_0} J_k = (\Delta x_k^r)^{n_0} J_k,
\]

in which \( \Delta x_k^r \) denotes the \( r \)-component of the vector from node \( i \) to node \( k \) and \( a_{ref} \) denotes a proper reference distance ensuring the decay of the series

\[
\left( \frac{\Delta x_k^r}{a_{ref}} \right)^{n_0}
\]

to zero with growing order \( n_0 \). This notation implies that \( (\Delta x_k^r)^{n_0} \) is a matrix, even in the one-dimensional case so that the system of Eq. (23) can be listed as follows:

\[
\begin{pmatrix}
0 M_i^x & \cdots & 0 M_i^z \\
\vdots & \ddots & \vdots \\
n_0 M_i^x & \cdots & n_0 M_i^z
\end{pmatrix}
\begin{pmatrix}
(\Delta x_k^r)^0 & \cdots & (\Delta x_k^r)^0 \\
\vdots & \ddots & \vdots \\
(\Delta x_k^r)^{n_0} & \cdots & (\Delta x_k^r)^{n_0}
\end{pmatrix}
\begin{pmatrix}
J_1 \\
\vdots \\
J_k
\end{pmatrix}
\]

This example also clarifies that the exponent \( n_0 \) can be treated like an ordinary index in the following matrix and vector calculations.

In the spirit of a least squares expression and inverse regularization techniques discussed more extensively in the main body of this paper, we formulate a quadratic and positive functional \( D \geq 0 \)

Note that all even orders will yield zero.
\[ D = \text{accurate} + \lambda_D \text{smooth} \]
\[ = \frac{1}{2} \left( (\Delta \mathbf{F}_i^a) - (\Delta \mathbf{F}_i^b) \right) \left( (\Delta \mathbf{F}_i^a) - (\Delta \mathbf{F}_i^b) \right) \]
\[ + \lambda_D \frac{1}{2} \mathbf{g}_{ki} \mathbf{j}_k \]
\[ g_{ki} = \begin{cases} 
(\Delta \mathbf{F}_i^a) \Delta \mathbf{F}_i^b)^{1/2} & \text{if } k = s \\
0 & \text{if } k \neq s 
\end{cases} \]
(25)

in which the first part ensures that the difference between the moments \( \mathbf{F}_i^a \), arising from source distribution \( \mathbf{J}_i \) and the target moments \( \mathbf{F}_i^b \) is minimized, while the second part minimizes the sources \( \mathbf{J}_k \) in a weighted sense (note that if \( n_\alpha = 0 \), \( \mathbf{g}_{ki} \) reduces to the Kronecker symbol \( \delta_{ki} \) (unity matrix) and \( \text{smooth} = 1/2 \Delta \mathbf{F}_i^a \).

By differentiating \( D \) with respect to the yet unknown sources \( \mathbf{J}_i \), the condition for the minimum is expressed and a linear system of equations is established.

\[ \left( (\Delta \mathbf{F}_i^a) \Delta \mathbf{F}_i^b \right)^{1/2} \mathbf{n}_\alpha \mathbf{T}_i = 0. \]
(26)

It is to be noted that this symmetric and positive definite system of equations is of an order defined by the number of nodes adjacent to node \( i \) (typically about 30), and thus solved fast.

In the proposed finite element dipole model several parameters must be chosen appropriately. The Lagrange multiplier \( \lambda_D \) will normally be chosen as small as possible, ensuring that the desired dipole moments are modeled accurately, but large enough to avoid singularity of the system of equations (which by definition arises when the number of neighbors \( k \) is larger than the number of conditions built into the system of equations). A sensible choice of the order \( n_\alpha \) to which moments shall be modeled will be \( n_\alpha = 1, 2 \), where \( n_\alpha = 2 \) effects a spatial concentration of loads \( \mathbf{J}_k \) in the dipole axis and a sensible choice for the exponent \( n_\alpha \) of the spatial regularizer \( \mathbf{g}_{ki} \), will be in the range \( n_\alpha \in [0, 4] \), where again a higher exponent stresses the spatial concentration of loads around the dipole node.

### 5.4. Iterative solution of the regularized inverse system of equations

The system matrix of the symmetric and positive definite system of equations

\[ [L_{mn}]^\tau L_{mm} + \lambda G_{mn} \delta_{m} = L_{mn}^\tau \mathbf{B} \]

is fully populated with nonzero elements, thus restricting direct solutions to a very limited number of unknowns. Since problems encountered with realistic finite element head models are usually quite large, an iterative conjugate gradient solution with scaling to improve the generally ill condition was developed.

\[ d_{\alpha i}^m \mathbf{L}_{mn}^\tau \mathbf{J}_i + \lambda G_{mn} \delta_{m} = L_{mn}^\tau \mathbf{B} \]

The scaling operator \( d_{\alpha i}^m \) is of diagonal form and thus trivial to invert.

\[ d_{\alpha i}^m = \begin{cases} 
1/\sqrt{\alpha_{mn}} & \text{if } u = s, v = r \\
0 & \text{else} 
\end{cases} \]
(29)

Kernel of the conjugate gradient method is the evaluation of the product of the system matrix and a direction vector \( \mathbf{p} \).

This product is determined in five steps as indicated in Table 1 in the tailored stepwise calculation of the matrix-vector product for the iterative (CG) solution of regularized inverse problems, thus eliminating the need to compile and store the matrix \( d_{\alpha i}^m \).

<table>
<thead>
<tr>
<th>Operation</th>
<th>Multiplications</th>
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<tbody>
<tr>
<td>( \mathbf{u}_s^m )</td>
<td>( d_{\alpha i}^m \mathbf{u}_s^m )</td>
</tr>
<tr>
<td>( \mathbf{g}_{ri} )</td>
<td>( L_{ri} \mathbf{V}_r^m )</td>
</tr>
<tr>
<td>( \mathbf{C} )</td>
<td>( \beta_{ri} \mathbf{C} )</td>
</tr>
<tr>
<td>( \mathbf{d}_{\alpha i}^m )</td>
<td>( \mathbf{d}<em>{\alpha i}^m + \lambda \mathbf{d}</em>{\alpha i}^m )</td>
</tr>
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</table>

Table 1
Tailored stepwise calculation of the matrix vector product for the iterative (CG) solution of regularized inverse problems

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### References


