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Source Localization: Continuing Discussion of the Inverse Problem

by Wolfgang Skrandies. Institute of Physiology, Justus Liebig University, Aulweg 129, 35392 Giessen, Germany. e-mail: Wolfgang.Skrandies@physiologie.med.uni-giessen.de

In the last issue of the Newsletter the central point was a discussion of "low resolution tomography". This was well received by the readership, and it was also referred to in other publications. This time there is a new round with three new commentaries on source localization methods.

In the next section you find the papers raising questions about "LORETA" by Matti Hämäläinen, Risto Ilmoniemi, and Paul Nunez. These will be followed by a response of Robert Pascual-Marqui, and we have decided that all authors should have the opportunity for a "last word" which you will find at the end of this section.

In addition to these papers, those who are interested in more detail, the reconstruction matrices discussed in the text are available at ftp://neuro.hut.fi/pub/ LORETA_discussion/

I wish to thank all authors for their contributions, and their cooperation that made this most interesting discussion possible.

Discrete and Distributed Source Estimates

Matti Hämäläinen. Low Temperature Laboratory Helsinki University of Technology, FIN-02150 Espoo, Finland. e-mail: msh@neuro.hut.fi

General

The introduction of the LORETA source estimation approach (Pascual-Marqui et al. 1994) prompted the interesting discussion in the November 1994 ISBET newsletter (Skrandies 1994) . The present article is a follow-up to this discussion.

It is well known that electromagnetic measurements outside the source region do not convey enough information to reconstruct the primary current distribution uniquely. However, there is an infinite number of ways to constrain the problem to yield a unique solution. For example, in the class of generalized minimum-norm solutions one can get a continuum of current estimates on the basis of given data by changing the weighting matrix, one particular choice being that taken in the LORETA algorithm.

Time-varying dipole models

The first source estimation approach taken in MEG and EEG was the use of a single moving current dipole. Subsequently, this model was extended (Scherg 1990) to include multiple, fixed-location sources whose amplitudes are allowed to vary with time. This model is based on a few physiologically and physically sound ideas. On the cortex, the current dipole is considered to represent the sum of the postsynaptic currents of the synchronously activated cortical pyramidal cells within an area of a few cm^2. Adjacent cytoarchitectonic areas on the cortex are likely to have different orientations. One can, therefore, often assign closeby dipoles with nonparallel current flow to different areas, thereby enabling further physiological interpretation of the time course of the dipole amplitudes.

The time-varying dipole model has a few problems which could be, eventually, addressed with more sophisticated models:

1. The locations of the sources have to be determined with a nonlinear least- squares search. Apart from simple situations with sources separated by several centimeters or forming a large angle with respect to each other, the conventional search methods are not guaranteed to reach the global minimum of the least- squares criterion function without sufficiently good initial estimates for the dipole positions. Furthermore, the number of sources has to be determined before starting the minimization. Therefore, an approach which is capable of estimating the number of active areas and their locations reliably is highly desirable.

2. The concept of a discrete dipole is a mathematical simplification of the actual distributed current source. It would be very informative if one could estimate the actual extent of the source on the cortex, possibly with help of supporting information available.

Minimum-norm approaches

One way to meet the above challenges it to release the constraints imposed by the dipole model by resorting to a distributed source solution making minimal assumptions about the source. The first distributed source model was the simple minimum-norm solution introduced by Risto Ilmoniemi and myself more than a decade ago (Hämäläinen and Ilmoniemi 1984) . We required that the current estimate would reproduce the measured data. The solution was made unique by selecting the current distribution with minimum overall amplitude, i.e., by minimizing the ordinary quadratic L2 norm of the current distribution.

During the last few years, more sophisticated approaches based on the L2 norm have been developed, including LORETA (for references, see, (Skrandies 1994)). The purpose of the diagonal or more general weighting matrices employed is essentially to remove the intrinsic bias of the original minimum-norm solutions towards superficial currents. All these approaches share the property of producing a blurred image of a point source, commonly used to test these algorithms. It is interesting to note that many of the authors of these approaches at least implicitly accept the idea of compact actual sources of limited spatial extent. Still, they explicitly choose an approach in favor of widespread solutions. In my opinion, the quest for compact solutions should be made explicit in the model. This kind of approaches include, for example, the FOCUSS algorithm (Gorodnitsky et al. 1995) and L1-norm based solutions (Matsuura and Okabe 1995).

LORETA

LORETA is a generalized minimum-norm estimate for the current distribution. The weighting matrix is chosen minimize the Laplacian of the current distribution with a depth weighting by the dipole signal strength. I will consider a few open questions associated with LORETA below.

Smoothness

LORETA is claimed to be 'neurophysiologically smooth'. However, as pointed out by Fuchs et al. (Skrandies 1994) , the scale of smoothness is quite different from the neural scale. The authors of LORETA respond to this by claiming that the reconstruction grid can, in fact, be made dense enough to match the neural length scale. I am afraid, however, that it is very difficult, if not impossible, to reconstruct in practice the actual detailed shape of the current distribution from noisy measurements made far away from the sources. Therefore, 'neurophysiological smoothness' is rather irrelevant from the practical point of view.

Ghost sources

Our initial experience of LORETA reconstructions from MEG data shows that the introduction of the 'Laplacian smoothness' makes the LORETA images even more blurred that the weighted minimum-norm solutions. Therefore, LORETA, indeed, produces a blurred image of a point source, which, according to the data presented in (Pascual-Marqui et al. 1994) , always peaks at the actual location of the test source. The authors of LORETA further claim that the images of point sources never interfere constructively to produce false 'ghost' sources often seen in other reconstructions.

It is very easy to construct examples with ghost sources in conventional minimum- norm based solutions. For example, consider two parallel dipoles. Depending on their distance, the return current paths in the images of the two dipoles may sum up to produce an apparent additional source between the two actual dipoles. In a linear current estimate the image of the linear combination of two or more current sources is an necessarily a similar linear combination of the images of the composite current sources. However, as shown by the above example, this superposition principle does not guarantee that the human interpreting the data would be able to discern the locations of the original sources from the composite image.

It is difficult to believe that LORETA would be totally free of ghost sources, often prominent in other approaches. It may be that the shape of the point source image allows one to readily show that ghost sources can be excluded. If this is not possible, special cases, like the one described above, should be analyzed to provide more confidence.

Source extent

It would be interesting to obtain an estimate of the size of neural tissue activated. Since the distance of between the sensors and the detectors is relatively large and the measured data are disturbed by noise, it is likely that the spread seen in the current estimates is caused by these technical limitations rather than the actual extent of the current we are looking at. It would be interesting, though, to see an analysis of the possibilities of discerning a point source from a distributed one on the basis of the calculated distributed current estimates.

Realistic examples

The published experience of LORETA with measured data is limited to a few examples provided by its authors. From these data it not easy to evaluate the actual benefits of LORETA in the analysis of real data.

One way to study the merits and problems of the LORETA approach would be to analyze 'realistic' simulated data. In this approach, the starting point would be a viable solution found from measured data with, for example, time-varying dipole modeling. One would then calculate the time varying fields and potentials produced by these 'real' sources, add noise with known characteristics, and produce a time-varying current estimate with LORETA. Good candidates for such comparative analysis would be, for example, the somatosensory evoked fields with four sources (Forss et al. 1994) and auditory fields with sources on the auditory cortices of the two hemispheres. With such relevant examples successfully worked it would be easier to trust a LORETA solution predicting some new features of brain activity estimated from the electromagnetic signals.

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Estimating Brain Source Distributions: Comments on LORETA

Risto J. Ilmoniemi. BioMag Laboratory, Medical Engineering Center, Helsinki University Central Hospital, F-00290 Helsinki, Finland. email: rji@biomag.helsinki.fi

In ISBET Newsletter No. 5 [1], Pascual-Marqui and Michel (PM) presented their "LORETA" procedure to estimate the 3D source distribution in the brain on the basis of EEG or MEG data. The paper was followed by comments and critique by Fuchs, Wischmann, and Wagner (FWW) [2], Greenblatt [3], Mosher and George (MG) [4], Ueno [5], and by Valdes, Grave de Peralta, and Gonzalez [6] and by a reply by PM [7]. LORETA has been published also in [8]. PM should be commended for entering the difficult but important arena of source estimation with an interesting and thought-provoking approach.

LORETA selects from the infinite set of solutions (that explain the data) to the EEG/MEG inverse problem the one that is maximally "smooth" in the sense that the norm of the 3D discrete Laplacian of the (suitably depth-weighted) current distribution is minimized. Thus, clearly, as pointed out by MG [4], this is a weighted minimum-norm solution, although the weighting matrix is not diagonal, as PM [7] emphasize. The several technical difficulties in the implementation of LORETA by PM were already discussed by FWW [2] and MG [3]; here we should concentrate on the method itself and on the justification for its use.

There is nothing intrinsically wrong in LORETA or any other mapping from data space to source distribution space, one just needs to understand when or whether to use each method. To illustrate this point, it may be in order to restate some of the properties of the (unweighted) minimum-norm solution [9,10,11], since its characteristics and proper usage are well understood.

The minimum-norm estimate (MNE) is the current distribution (in a given volume, surface, line, or set of points or any combination of these, with or without direction constraints) with the smallest (L2) norm among those current distributions that would explain the MEG/EEG data. The reason for using MNE should not, however, be the desire for minimizing the norm, because that is not our objective in studying the brain. Our goal is to reconstruct the source distribution with as small an error as possible. The MNE provides an optimal solution in a specific case: it is the solution minimizing the expected squared error given the data and the source region but minimal a priori information about source currents [12]. If no additional information is available or assumed, there is no way to improve the solution from MNE. One must remember that MNE is not a general-purpose tool; it is the best estimate only in its narrow scope of applicability. Similar statements can e made about weighted MNE and other methods. The weighted MNE and other proposed methods should be used equally cautiously, i.e., when appropriate supplementary information is available but not otherwise. Weighted solutions are optimal only when a priori knowledge implies that certain (e.g., deep or localized) source distributions are more probable than others.

Since LORETA (at least in its regularized form) is a well-defined and robust procedure, we should, instead of criticizing the method itself, ask the following question: When should one favor the solution with minimized norm of the Laplacian of the weighted current distribution (i.e., when should LORETA be used?)

PM justify the applicability of LORETA by saying that cortical activity tends to be "smooth", i.e., activity between closely-lying patches of cortex is correlated. This is so, but as pointed out by FWW [2], the length scale imposed by LORETA is in the order of centimeters and this can not be helped much by a denser grid because of the limited spatial resolution of EEG/MEG. Thus, cortico-cortical local correlations (millimeter scale) do not seem to provide validation for LORETA. Should one want to utilize the existence of spatial correlations, the actual length scale as well as numerical estimates for the correlation should be taken into account explicitly and distance should be measured along the cortex as done by Dale and Sereno [13].

Unfortunately, no satisfactory answer has been presented to the question presented above (When should LORETA be used?). PM [1] say that "if the actual 3D source distribution is 'neurophysiologically smooth', then LORETA can recover it exactly." As MG point out, an analogous statement can be made about an arbitrary inversion method. Suppose we have a source-estimation procedure X that selects a solution with maximal y-ness (some property). Then we could say: "if the actual 3D source distribution is `neurophysiologically y´ then X can recover it exactly".

PM claim that "there is sufficient information in extracranial measurements for the approximate determination of the 3D generator distribution". This is of course true if sufficient supplementary information is available but, interestingly enough, since any extracranial EEG/MEG field distribution can be produced by currents confined to a 2D shell at an arbitrary depth within the head, one can fairly say that extracranial fields provide no depth information whatsoever.

To summarize:

1. LORETA provides a specific mapping from data space to source-distribution space.

2. LORETA minimizes the norm of the Laplacian of the (weighted) current distribution.

3. Cortico-cortical correlations do not seem to provide sufficient justification to LORETA, but these correlations may be worth taking into account in other ways [13].

4. LORETA would give authentic 3D inverse solutions only provided that the underlying current distribution would have minimal norm of the Laplacian (PM [1] use the term "neurophysiologically smooth"). Unfortunately, smoothness in 3D of this kind can not be found in the brain, because source currents tend to be concentrated in the 2D cortical mantle. See, however, my last comment.

5. While LORETA produces images that have a maximum at depth, it remains to be demonstrated whether the reliability of depth estimation is better than in other methods (for example, diagonal-matrix-weighted MNE).

6. I do not understand the benefit of requiring the solution to tend to zero at the

surface of the reconstruction volume. About 50% of the cortex is at the surface of the brain. To allow superficial sources, one should relax this constraint or extend the grid outside the brain.

7. When it is not practical to take into account the detailed form of the cortex, LORETA may be useful in providing a rough idea of where the sources may be. A nice example is provided in Greenblatt´s software [14].

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Comments on LORETA

Paul L. Nunez. Department of Biomedical Engineering, Tulane University New Orleans, LA 70118, USA. e-mail: pnunez@mailhost.tcs.tulane.edu

I am impressed by competent mathematical and physical level of the discussion of LORETA and other approaches to 3D functional imaging in the November ISBET newsletter. In the early 1970's, suggestions for obtaining inverse solutions to Poisson's equation often elicited nonsensical comments like "a Gaussian approach seems more appropriate" or "have Maxwell's equations been verified ?". The field has certainly advanced over the past 25 years. Some elecroencephalographers have said (perhaps half jokingly) that the main contribution of MEG has been to bring physicists to brain research.

It is important to distinguish two approaches to the inverse problem:

1. Cortical imaging (including surface Laplacian estimates) is based on the unique relation between outer and inner surface potentials when no sources occur between the two surfaces. Thus predictions of cortical surface potential using scalp data are "only" limited by imperfect head models, spatial sampling, and noise. Unfortunately, there is widespread confusion (even among some physicists) about the Laplacian, which provides a biased estimate of cortical surface potential. However, the Laplacian bias is much smaller than the raw potential

bias. Furthermore, the spline surface Laplacian provides a robust estimate of cortical potential with respect to head model errors and uncorrelated noise, independent of assumptions about sources (Nunez et.al., 1994; Nunez, 1995; Srinivasan et. al., 1995). Cortical imaging and spline Laplacian estimates are, however, not true inverse solutions. They provide inverse solutions only when combined with source constraints such as limiting sources to cortex. In most applications, however, more accurate estimates of cortical potential distribution provides significant improvement in our understanding of brain dynamics, even though we may not have actually located the sources.

2. Three dimensional functional imaging is based on the non-unique relation between current sources and surface potential. Thus physiological constraints must be imposed, e.g., by limiting sources to a small number of discrete sources smooth in the time domain (BESA), by excluding sources from certain regions (perhaps using MRI to eliminate CSF sources), or by applying smoothness criteria to the spatial domain (LORETTA). If inverse solutions are limited to cortical sources, the 3D methods become physiologically (but not necessarily mathematically) equivalent to cortical imaging or spline Laplacian estimates.

These differing approaches suggest the following question concerning the accuracy of 3D localization. Suppose we have perfect potential information on the upper surface of a head of known outer geometry, but the conductivity tensor used in the inverse solution has errors. (Please do not confuse such errors with uncorrelated noise; errors in the conductivity tensor can generate unknown virtual sources that are correlated to physiologic sources.) Let X refer to the inverse solution constrained exclusively to cortical sources. Let Y be a solution constrained only by some smoothness criteria. My basic question is "How small must be the conductivity errors such that we can find a solution Y which is a significantly better fit to surface potential than provided by solution X." If the required conductivity accuracy is not realistic, 3D imaging problems appear to fall into one of three categories:

1. Cases in which we cannot exclude cortical sources on physiologic grounds and have no independent knowledge of such sources (most EEG experiments). In these cases, I see no practical purpose for 3D localization. We must be satisfied with cortical imaging or spline Laplacians which may, nevertheless, provide us with a far better picture of spatial-temporal dynamic properties than we can obtain from unprocessed potentials.

2. Cases in which we can exclude cortical sources on physiologic grounds (early components of evoked potentials, for example). Three-D imaging may then provide us with important information, albeit limited by uncertainty in the conductivity tensor.

3. Cases in which we have independent information on cortical sources (primary sensory sources, local cortical electrodes, or independent estimates with Laplacian or MEG methods which are less sensitive to deep sources than potential, for example). In these cases, known cortical sources provide additional constraints on 3D imaging methods.

Ideally, 3D imaging methods should be tested first with concentric spheres models, second with finite element or boundary element models, and third in phantom and human heads. It is also recommended that some of these be blind tests, with forward and inverse solutions obtained at different laboratories. The idea that we can settle accuracy issues only experimentally (which has gained some credence in the collective clinical consciousness) is wrong. Realistic experiments are practically limited to a much smaller number than can actually be carried out. For example, showing that one can locate a few isolated sources in one subject is a necessary, but not nearly sufficient, condition to allow reasonable inference that the method will work in subjects with unknown sources. Tests of our spline-Laplacian involved more than 1000 simulations to study the effects of noise, spatial sampling, source distributions (using up to 4200 cortical sources combined with a few deep sources), and skull resistivity variations to access the accuracy of estimated cortical potential. Certainly, 3D imaging requires an event more comprehensive effort to evaluate accuracy.

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Reply to Comments by Hämäläinen, Ilmoniemi, and Nunez

R.D. Pascual-Marqui. The Key Institute for Brain-Mind Research, University Hospital of Psychiatry, Lenggstr. 31, CH-8029 Zürich, Switzerland. e-mail: pascualm@key.unizh.ch. http://www.unizh.ch/keyinst/

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I greatly appreciate the invitation made by Prof. W. Skrandies to a second round of discussions on the issue of inverse solutions in the ISBET Newsletter. I also thank the invited reviewers for their very profound and critical comments, which have motivated my lengthy and tardy reply, for which I must apologize. This paper includes a Results Section and an extensive mathematical Appendix which will hopefully satisfy most of their questions.

Reply to comments by M. Hämäläinen.

1. Hämäläinen states that diagonal or more general weighting matrices essentially remove the intrinsic bias of the pure minimum norm solution towards superficial currents. In the Results Subsection, Figure 1 (see also Tables I and II) demosntrates that this is not so for the diagonal weight case, i.e. the weighted minimum norm solution does not localize depth, while LORETA does. The technical details can be found in the Appendix, mainly Subsection A.6. I am not aware of any published literature on <u>linear</u> inverse solutions in full <u>3D</u> space that localize depth correctly. I would appreciate to be provided with some reference, pre-dating the LORETA publication.

2. The use of "point sources" as "test sources" for distributed solutions is criticized. I have two arguments to justify why point sources <u>must</u> be used for distributed <u>linear</u> inverse solutions. On the one hand, due to linearity, any distributed source is a linear combination of point sources (this statement is valid for the true source and for the estimated source.) Therefore, the localization capability of the inverse can be completely characterized by studying its response to point sources. The full theoretical basis and justification for this methodology, which is valid despite the curse of non-uniqueness, can be found in [11] (see also Subsection A.6 and references quoted therein). On the other hand, the point source is simply the "worst case test" for a distributed solution.

3. The "neurophysiological smoothness" basis of LORETA is criticized. In my reply to Ilmoniemi I discuss this point.

4. Hämäläinen states that in his experience, MEG LORETA produces even more blurring than minimum norm. I ask: was a 3D or a 2D solution space used? In any case, the results presented in Table II show

that this is not so: LORETA and minimum norm produce essentially the same blurring. But there is a much more important problem. The original LORETA equations introduced in [13] and published in [2] and [4] are correct for EEG, but regrettably incorrect for MEG! The correct equations for MEG can be found in Subsections A.3, A.4.1, A.4.2, and A.4.3. I ask: was the MEG LORETA implementation made by Hämäläinen incorrect? In the published literature on weighted minimum norm solutions for MEG, correct equations can be found in [16], and invalid equations can be found in the FOCUSS algorithm [17] (see equations (2) with (3), (4), or (5) therein; see my equation (20) here in Subsection A.3).

5. It is stated that it is difficult to believe that LORETA does not produce "ghost sources". I honestly cannot reply to this point since I have made no tests to this effect. However, all the inverse matrices and the lead field matrices used in the Results section are available upon request, and may be used freely. I would appreciate that Hämäläinen tests the correct LORETA matrices for blurring and for ghost sources. I would just have one request: that a fair comparison be made to minimum norm and weighted minimum norm solutions.

6. With respect to the comment on source extent. I believe that LORETA cannot solve this problem. Actually, once LORETA produces a blurred image, the uncertainty rules: was it truly blurred, or was it localized but blurred by LORETA? The same problem holds for minimum norm and weighted minimum norm.

7. With respect to the comment on realistic examples. I am completely for it, but with really realistic data! Why should time-varying multiple dipoles be the basis for validating LORETA or any other inverse solution? I would prefer the situation in which we would all have access to a free-for-all and open data bank with human EEG/MEG measurements obtained under well controlled physiological conditions. Then we should compare different inverse solution results. However, do we know how the brain actually works? This is the problem of validation, more thoroughly discussed by Nunez.

Reply to comments by R. Ilmoniemi.

1. The "neurophysiological smoothness" basis of LORETA is criticized (also by Hämäläinen.). However, the statement that "neighboring cortical patches are likely to be positively correlated" seems to be a valid neurophysiological fact accepted by Ilmoniemi, with respect to which he quotes the Dale-Sereno [6] inverse solution as a valid formulation embodying this fact. I ask: is this not the same thing as "neurophysiological smoothness"? The proof for the equivalence of both formulations (LORETA and the Dale-Sereno inverse) with respect to "neurophysiological smoothness" can be found in the Appendix, Subsection A.5. Therefore, if "neurophysiological smoothness" is accepted as valid for one formulation, it must be accepted for the other one as well.

It is true that 3D smoothness does not have any neurophysiological justification if it is known for certain that the sole generators exist on the cortex. In this case, the cortical-LORETA described in the Appendix, Subsection A.2 must be used. A close examination of my definition for cortical-LORETA should make clear that there will be no smoothing of sources opposed across a sulcus, i.e. distances are measured along the cortex.

With respect to Ilmoniemi's statement: "..the length scale imposed by LORETA is in the order of centimeters and this can not be helped much by a denser grid because of the limited spatial resolution of EEG/MEG." I find this difficult to accept. In the first place, resolution of the measurement space is definitely not equivalent to resolution of the solution space. An inter-electrode distance of 1 cm for scalp EEG electrodes does not imply a 1 cm resolution for an inverse solution. In the second place, even if our resolution is experimentally limited, this does not mean that we are not allowed to model and express mathematically with exact resolution the fact that "neighboring neurons are tightly connected."

2. Ilmoniemi criticizes the claim that "if the actual 3D source distribution is neurophysiologically smooth, then LORETA can recover it exactly," since the same can be stated for any other solution with any neurophysiologically X-ness property. I completely agree. However, except for the Dale-Sereno [6] inverse solution, which also takes into account neurophysiological smoothness, I would appreciate to be provided with some reference to any other linear inverse solution based on other neurophysiological properties. The word property here does not include statements of the kind: "the generators are restricted to the cortex."

3. Ilmoniemi's argument that EEG/MEG provides no depth information is true. But again, if the human brain operates under neurophysiological smoothness, then EEG/MEG measurements do contain depth information.

4. Proof is required whether LORETA provides better depth localization than weighted minimum norm. The results in Figure 1 demonstrate that weighted minimum norm does not localize depth correctly; but also see my reply to Hämäläinen (the first point) for more details.

5. The original Laplacian definition (introduced in [13] and published in [2] and [4]) is criticized because it unnecessarily forces the estimated current density to zero at the boundary of the reconstruction volume. This is absolutely correct, and I modified the original definition to solve this problem (see Appendix, Subsection A.1). The new Laplacian produces better results (i.e. smaller localization errors) than the old one.

Reply to comments by P. Nunez.

1. Unfortunately, I can not reply to the questions: What effect does incorrect knowledge of the conductivity tensor have on LORETA? Which would be better in this case, a cortical solution, or 3D LORETA? These questions would require an extensive study, and lately I've concentrated most of my efforts along other aspects of the inverse problem. Needless to emphasize that these questions are essential.

2. The use of 3D LORETA in the case where it is know *a priori* that all generators are cortical is criticized. I completely agree. In this case the cortical-LORETA should be used (see Appendix, Subsection A.2.)

3. I completely agree with the discussion by Nunez on the validation issue. However, I would like to emphasize one point. Cortical inverse solutions in the form of cortical imaging techniques or spline Laplacian estimates are essentially linear inverse solutions. Therefore, their localization properties can be completely characterized from the mathematical and physical points of view by the resolution operator of Backus and Gilbert [11], as discussed in the Appendix, Subsection A.6. This approach would perhaps alleviate the computational burden of performing many simulations.

A concluding remark.

A very fundamental question was posed by Ilmoniemi: when should one favor the use of a particular inverse solution over another? I would safely, but conditionally, reply: for the *no-a-priori* knowledge case, where the solution space is full 3D, LORETA performs better than minimum norm and weighted minimum norm, as demonstrated here. If it is known *a priori* that the solution space is the cortex, then I will conjecture that LORETA would still perform better, since a real human cortex is almost as "bad" as the 3D solution space case, due to the many convoluted twists and turns of sulci. However, this conjecture remains to be demonstrated.

Results: The comparison of linear inverse solutions.

The detailed methodology for comparing different linear inverse solutions is presented in the Appendix, Subsection A.6. The theoretical framework for the comparison was developed by Backus and Gilbert [11], and is based on the fact that a complete characterization of the localization power of a linear inverse solution (corresponding to a singular operator) is given by the resolution operator.

The main requirements for making a valid and fair comparison are to use the same measurement space, the same solution space, and the same head model. The unit radius 3-shell spherical head model was used here [14]. The solution space consisted of 817 grid points, corresponding to a 3D regular cubic grid with minimum inter-point distance d=0.133, confined to a maximum radius of 0.8, with vertical coordinate values $Z \geq -0.4$, and excluding the point at the sphere center (see Appendix, Subsection A.7, for exact coordinates). The measurement space consisted of 148 points. In the MEG case the magnetometer measurements corresponded to the radial magnetic field component, with all sensors at a radius of 1.2. In the EEG case, average reference measurements were used, with electrodes having the same coordinates as the magnetic sensors, but scaled to a radius of 1. The sensor coordinates used here were proposed by Lütkenhoner and Mosher [15], and can be found in Table III.

The 3D EEG LORETA formulation corresponds to equations (4), and (6)-(8) (note that the lead field normalization and the Laplacian operator have been redefined), as described in the Appendix, Subsection A.1. The 3D EEG minimum norm formulation corresponds to the same set of equations, but with (**BW**) set to be the identity matrix. The 3D EEG weighted minimum norm formulation corresponds to the same set of equations, but with (**B**) set to be the identity matrix.

The 3D MEG LORETA formulation corresponds to equation (1) with the additional constraint (18), and to equation (20), as described in the Appendix, Subsection A.3. The 3D MEG minimum norm formulation corresponds to the same set of equations, but with (**BW**) set to be the identity matrix. The 3D MEG weighted minimum norm formulation corresponds to the same set of equations, but with (**B**) set to be the identity matrix.

Localization errors obtained from the resolution operators of the different inverse solutions, corresponding to more than 2400 test sources (Appendix, Subsection A.6), are summarized in Table I in terms of their frequency distributions. The results clearly demonstrate the superiority of LORETA over minmum norm and over weighted minimum norm. However, these results are not detailed enough to distinguish between an inverse solution that simply produces some localization error, or one that is utterly incapable of localizing. Figure 1 shows in detail the localization errors as a function of source eccentricity, and demostrates that minimum norm and weighted minimum norm solutions are incapable of depth localization, while LORETA has a constant mean localization error of one single grid point, independent of depth.

Table II summarizes the blurring (spatial dispersion) produced by the different inverse solutions, based on the corresponding resolution operators (see Appendix, Subsection A.6). As can be seen, LORETA does not produce more blurring than minimum norm. And apparently, in the magnetic case, weighted minimum norm produces less blurring than LORETA. However, a small blurring is meaningless if the inverse solution is incapable of 3D localization, as is the case for the weighted minimum norm (see Figure 1).

The inverse matrices and the lead field matrices for all three methods (and for

EEG and MEG) used in this work are available upon request to the author ***[available from FTP site (anonymous login): neuro.hut.fi/pub/LORETA_discussion/]***. This will allow the interested reader to verify all the results presented here, and also it may serve as a basis for an objective comparison of other linear inverse solutions, using the same yard-stick, i.e. the resolution matrix of Backus and Gilbert [11].

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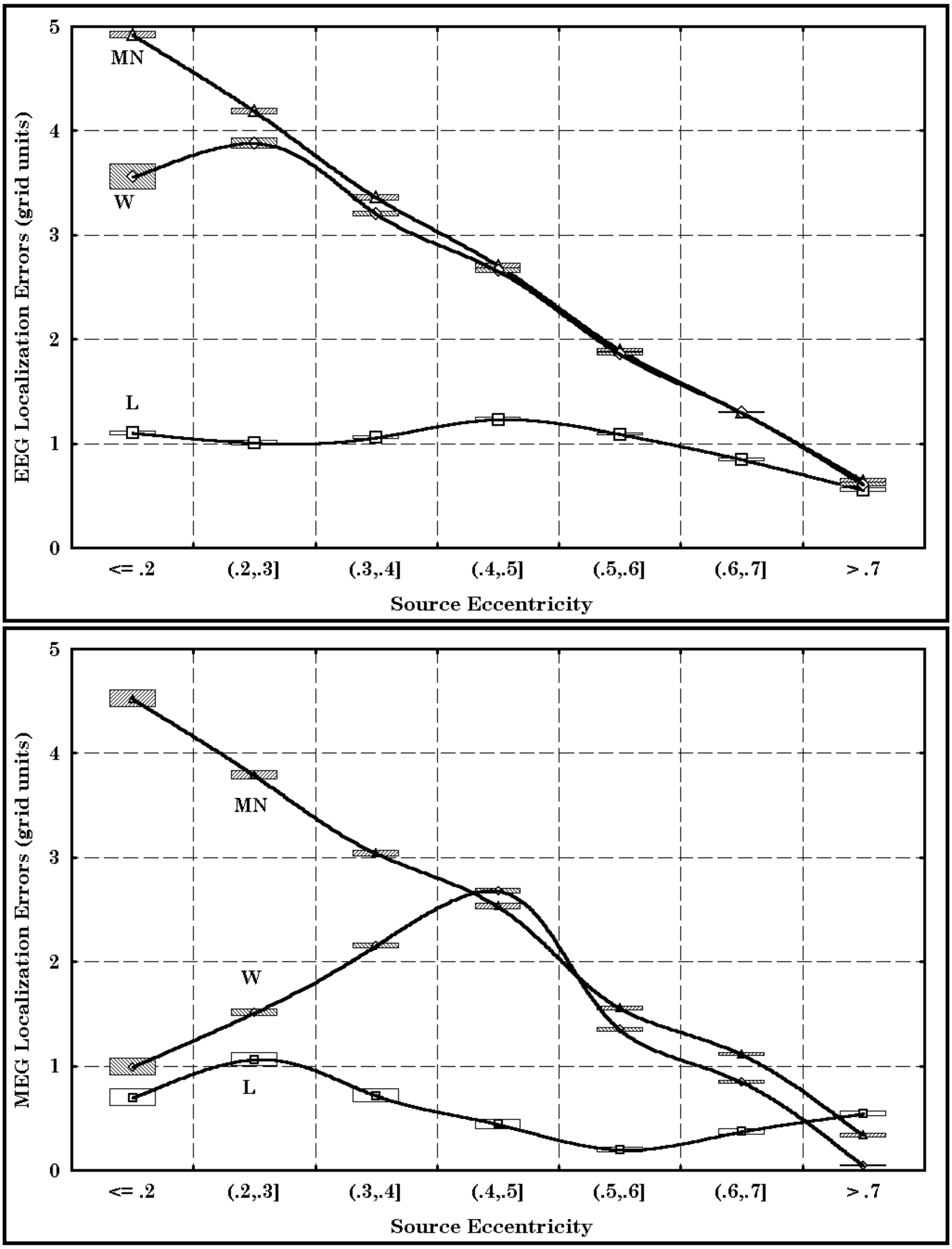

Figure 1: Localization errors (1 unit=minimum grid inter-point distance) as a function of the eccentricity of the test source. L: LORETA; MN: Minimum norm; W: Weighted minimum norm (with weights defined as in equation (1)). Number of non-silent test sources used in MEG was 2418; and in EEG was 2451. For each eccentricity range, the boxes correspond to ±1 Std.Dev. Note that neither weighted minimum norm (W) nor minimum norm (MN) can localize source depth correctly, i.e. they do not localize in 3D.

Table I
LOCALIZATION ERRORS

Loc.Err.	L(EEG)	L(EEG)	MN(EEG)	MN(EEG)	W(EEG)	W(EEG)	L(MEG)	L(MEG)	MN(MEG)	MN(MEG)	W(MEG)	W(MEG)
	%	Cum.%	%	Cum.%	%	Cum.%	%	Cum.%	%	Cum.%	%	Cum.%
[0.0,0.5)	20.52	20.52	13.42	13.42	14.24	14.24	69.60	69.60	23.66	23.66	34.53	34.53
[0.5,1.0)	0.00	20.52	0.00	13.42	0.00	14.24	0.00	69.60	0.00	23.66	0.00	34.53
[1.0,1.5)	75.32	95.84	39.78	53.20	39.90	54.14	19.35	88.96	37.59	61.25	38.09	72.62
[1.5,2.0)	0.65	96.49	7.71	60.91	7.43	61.57	1.41	90.36	4.30	65.55	5.29	77.92
[2.0,2.5)	3.47	99.96	17.79	78.70	18.65	80.21	8.27	98.64	18.16	83.71	12.49	90.41
[2.5,3.0)	0.00	99.96	1.06	79.76	1.06	81.27	0.00	98.64	1.57	85.28	1.82	92.23
[3.0,3.5)	0.04	100.00	10.32	90.09	11.87	93.15	1.36	100.00	7.82	93.09	6.70	98.92
[3.5,4.0)	0.00	100.00	1.80	91.88	2.12	95.27	0.00	100.00	2.23	95.33	1.07	100.00
[4.0,4.5)	0.00	100.00	5.34	97.23	3.92	99.18	0.00	100.00	3.18	98.51	0.00	100.00
[4.5,5.0)	0.00	100.00	0.90	98.12	0.29	99.47	0.00	100.00	0.62	99.13	0.00	100.00
[5.0,5.5)	0.00	100.00	1.88	100.00	0.53	100.00	0.00	100.00	0.86	100.00	0.00	100.00

Localization errors are summarized as the % of test sources (dipoles) that were localized with errors in the ranges indicated in the first column (1 unit=minimum grid inter-point distance). L: LORETA; MN: Minimum norm; W: Weighted minimum norm (with weights defined as in equation (1)). Number of non-silent test sources used in MEG was 2418; and in EEG was 2451. LORETA localization errors are smaller than for the other inverse solutions.

Table II
SPATIAL DISPERSION (BLURRING)

	L(EEG)	MN(EEG)	W(EEG)	L(MEG)	MN(MEG)	W(MEG)
Mean	3.24	3.28	3.24	3.39	3.40	2.99
Std.Dev.	0.55	1.27	1.13	0.72	1.36	0.57

Spatial dispersion (blurring) for all test sources (as described in Table I) are approximately Gaussian distributed, and are summarized in terms of the mean and standard deviation. L: LORETA; MN: Minimum norm; W: Weighted minimum norm (with weights defined as in equation (1)). Note that a small mean spatial dispersion value is meaningless if the inverse solution does not localize in 3D, which is the case for minimum norm and weighted minimum norm (see Figure 1).

Appendix

A.1. LORETA in 3D solution space; scalp electric potential measurements: modifications to the lead field normalization and to the 3D Laplacian.

For noise-free-instantaneous measurements, the discrete solution is obtained by solving the problem:

$$\min_{\mathbf{J}} \left\| \mathbf{B}\,\mathbf{W}\,\mathbf{J} \right\|^2 \text{, under constraint: } \Phi = \mathbf{K}\,\mathbf{J} \qquad (1)$$

where Φ is an N-vector comprised of scalp electric potential measurements; $\mathbf{J} = \left(\mathbf{j}_1^T, \mathbf{j}_2^T, \ldots, \mathbf{j}_M^T\right)^T$ is a $3M$-vector comprised of the current densities $\mathbf{j}$ (3-vector) at M points with known locations within the brain volume; $\mathbf{K}$ is a transfer $N \bullet 3M$-matrix with α-th row $\left(\mathbf{k}_{\alpha 1}^T, \mathbf{k}_{\alpha 2}^T, \ldots, \mathbf{k}_{\alpha M}^T\right)$, where $\mathbf{k}$ is the electric lead field (3-vector); $\mathbf{W}$ is a diagonal $3M \bullet 3M$-matrix now defined as $\mathbf{W}=\Omega\otimes\mathbf{I}$, where $\otimes$

denotes the Kronecker product (see e.g. [1], p.459), $\mathbf{I}$ is the identity 3•3-matrix, and Ω is a diagonal $M \bullet M$-matrix with $\Omega_{ii} = \sqrt{\sum_{\alpha=1}^{N} \mathbf{k}_{\alpha i}^T \mathbf{k}_{\alpha i}}$ (the original definition introduced in [13], published in [2] and [4], consisted of a column by column normalization of the lead field; now I use a single normalization factor for all three components of the dipole moment at each grid point); and $\mathbf{B}$ is the discrete 3D Laplacian operator $3M \bullet 3M$-matrix. Specifically, let $\mathbf{Z} = \mathbf{W}\mathbf{J} = \left(\mathbf{z}_1^T, \mathbf{z}_2^T, \ldots, \mathbf{z}_M^T\right)^T$, where $\mathbf{z}$ (3-vector) is the weighted current density, and let $\mathbf{B}\,\mathbf{Z} = \left(\mathbf{l}_1^T, \mathbf{l}_2^T, \ldots, \mathbf{l}_M^T\right)^T$ be the corresponding discrete Laplacian. In the original definition introduced in [13], published in [2] and [4], for a regular cubic grid of points with minimum inter-point distance d confined to the brain volume, the matrix $\mathbf{B}$ satisfied:

$$\mathbf{l}_i = \frac{6}{d^2}\left(\frac{\sum_p \mathbf{z}_p}{6} - \mathbf{z}_i\right), \ \forall p, \text{ under constraint } \left\|\mathbf{r}_i - \mathbf{r}_p\right\| = d \qquad (2)$$

where $\mathbf{r}_i$ and $\mathbf{r}_p$ are grid point position vectors. The Laplacian as defined by (2) corresponds to the boundary condition where the current density $\mathbf{J}$ is extended outside the solution space and is known to be explicitly zero, thus forcing the computed current density at the borders to be smaller than it might actually be. An alternative boundary condition may be considered, where the Laplacian is defined to satisfy:

$$\mathbf{l}_i = \frac{6}{d^2}\left(\frac{\sum_p \mathbf{z}_p}{\sum_p 1} - \mathbf{z}_i\right), \ \forall p, \text{ under constraint } \left\|\mathbf{r}_i - \mathbf{r}_p\right\| = d \qquad (2')$$

Both Laplacian operators (2) and (2') are identical for non-boundary grid points. However, Laplacian operator (2') is singular. In the results reported here I used the "mixed" boundary condition consisting of the average of (2) and (2'), which gives a non-singular Laplacian that does not force $\mathbf{J}$ to zero at the borders:

$$\mathbf{l}_i = \frac{6}{d^2}\left(\frac{\left(6 + \sum_p 1\right)}{12 \sum_p 1} \sum_p \mathbf{z}_p - \mathbf{z}_i\right), \ \forall p, \text{ under constraint } \left\|\mathbf{r}_i - \mathbf{r}_p\right\| = d \qquad (2'')$$

For a dense grid ($3M>>N$), if $\mathbf{W}$ and $\mathbf{B}$ are non-singular, the unique solution to (1) corresponds to a minimum seminorm restricted solution of a consistent linear system of equations [3], and is:

$$\hat{\mathbf{J}} = \mathbf{T}\Phi \text{, with: } \mathbf{T} = \left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathbf{K}^T\left\{\mathbf{K}\left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathbf{K}^T\right\}^{-1} \qquad (3)$$

The estimated 3D distribution of the electrically active neural tissue is given by $\hat{\mathbf{J}}$ (LORETA).

Equation (3) is valid only if the matrix $\mathbf{K}$ is of full rank, which is the case when all potential differences are measured between cephalic electrodes. For monopolar measurements made with respect to a non-cephalic reference electrode, the coordinates of the reference are not explicitly known. Then problem (1) must be rewritten as:

$$\min_{\mathbf{J}} \left\|\mathbf{B}\,\mathbf{W}\,\mathbf{J}\right\|^2 \text{, under constraint: } \Phi = \mathbf{K}\,\mathbf{J} + c\mathbf{1} \qquad (4)$$

where $\mathbf{1}$ is an N-vector comprised of one's, c is an arbitrary unknown constant, and $\mathbf{K}$ corresponds to any fixed reference. The solution to this problem is obtained in two steps. First consider that c is given, and solve (4) for $\mathbf{J}$, which is a function of c. In the second step substitute the result into (4) and minimize with respect to c, without the constraint (it is already satisfied). It can be shown (proof omitted) that (4) is equivalent to:

$$\min_{\mathbf{J}} \left\|\mathbf{B}\,\mathbf{W}\,\mathbf{J}\right\|^2 \text{, under constraint: } \mathbf{H}\Phi = \mathbf{H}\mathbf{K}\,\mathbf{J} \qquad (5)$$

where:

$$\mathbf{H} = \mathbf{I} - \mathbf{1}\mathbf{1}^T / \mathbf{1}^T\mathbf{1} \tag{6}$$

is the "average reference operator". The unique general solution to (4) or (5), independent of any monopolar reference electrode (cephalic or not), is:

$$\hat{\mathbf{J}} = \mathcal{T}\Phi \text{, with: } \mathcal{T} = \left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathcal{K}^T\left\{\mathcal{K}\left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathcal{K}^T\right\}^+ \tag{7}$$

with:

$$\mathcal{K}=\mathbf{H}\mathbf{K} \tag{8}$$

and where $\mathbf{A}^+$ denotes the Moore-Penrose pseudoinverse of matrix **A**. In equation (7), which is more general than (3), the Moore-Penrose pseudoinverse is absolutely necessary.

Finally, the regularized problems, for any given $\alpha>0$:

$$\min_{\mathbf{J}}\left\{\left\|\Phi - \mathbf{K}\,\mathbf{J}\right\|^2 + \alpha\left\|\mathbf{B}\,\mathbf{W}\,\mathbf{J}\right\|^2\right\} \tag{9}$$

$$\min_{\mathbf{J},c}\left\{\left\|\Phi - \mathbf{K}\,\mathbf{J} - c\mathbf{1}\right\|^2 + \alpha\left\|\mathbf{B}\,\mathbf{W}\,\mathbf{J}\right\|^2\right\} \tag{9'}$$

have solutions (proof omitted):

$$\hat{\mathbf{J}} = \mathbf{T}_\alpha\Phi \text{, with: } \mathbf{T}_\alpha = \left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathbf{K}^T\left\{\mathbf{K}\left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathbf{K}^T + \alpha\mathbf{I}\right\}^{-1} \tag{10}$$

$$\hat{\mathbf{J}} = \mathcal{T}_\alpha\Phi \text{, with: } \mathcal{T}_\alpha = \left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathcal{K}^T\left\{\mathcal{K}\left(\mathbf{W}\mathbf{B}^T\mathbf{B}\mathbf{W}\right)^{-1}\mathcal{K}^T + \alpha\mathbf{H}\right\}^+ \tag{10'}$$

respectively.

A.2. Cortical LORETA; scalp electric potential measurements.

For noise-free-instantaneous measurements, the discrete cortical solution is now obtained by solving the problem:

$$\min_{\mathbf{J}_0}\left\|\mathbf{C}\,\mathbf{W}\,\mathbf{J}_0\right\|^2 \text{, under constraint: } \Phi = \left(\mathbf{K}\,\mathbf{N}\right)\mathbf{J}_0 \tag{11}$$

where $\mathbf{J}_0$ is an M-vector comprised of the current density amplitudes at M points with known locations on the cortex;

$$\mathbf{J}=\mathbf{N}\mathbf{J}_0 \tag{12}$$

$$\left.\begin{aligned}
\mathbf{N}_1 &= \left(\vartheta_1^T, \mathbf{0}^T, \mathbf{0}^T, \ldots, \mathbf{0}^T, \mathbf{0}^T\right)^T \\
\mathbf{N}_2 &= \left(\mathbf{0}^T, \vartheta_2^T, \mathbf{0}^T, \ldots, \mathbf{0}^T, \mathbf{0}^T\right)^T \\
&. \\
&. \\
&. \\
\mathbf{N}_M &= \left(\mathbf{0}^T, \mathbf{0}^T, \ldots, \mathbf{0}^T, \mathbf{0}^T, \vartheta_M^T\right)^T
\end{aligned}\right\} \tag{13}$$

N is a $3M \bullet M$-matrix, $\mathbf{N}_i$ is the i-th column of matrix **N**, **0** is a 3-vector of zeros, and ϑ_i is the outward normal vector to the cortical surface at the i-th grid point on the cortex; **(KN)** is now a transfer $N \bullet M$-matrix with α-th row $\left(\mathbf{k}_{\alpha 1}^T\vartheta_1, \mathbf{k}_{\alpha 2}^T\vartheta_2, \ldots, \mathbf{k}_{\alpha M}^T\vartheta_M\right)$; **W** is now a diagonal $M \bullet M$-matrix with $w_{ii} = \left\|(\mathbf{KN})_i\right\|$, where $(\mathbf{KN})_i$ is the i-th column of **(KN)**; and **C** is the discrete cortical Laplacian operator $M \bullet M$-matrix. This Laplacian operator does not smooth in 3D, i.e. it would not smooth two different sources opposed across a sulcus. This Laplacian operator smoothes exclusively along the cortex. To make this point clear, let $\mathbf{Z} = \mathbf{W}\mathbf{J}_0 = \left(z_1, z_2, \ldots, z_M\right)^T$, where z (scalar) is the weighted current density amplitude, and let $\mathbf{C}\,\mathbf{Z} = \left(l_1, l_2, \ldots, l_M\right)^T$ be the corresponding discrete cortical Laplacian. Then for an ideal-unrealistic cortex consisting of a simple plane inside the brain volume, and for a regular square grid of points with minimum inter-point distance d confined to this cortical surface, the matrix **C** is defined to satisfy:

$$l_i = \frac{4}{d^2}\left(\frac{\left(4+\sum_p 1\right)}{8\sum_p 1}\sum_p z_p - z_i\right), \; \forall p, \text{ under constraint } \left\|\mathbf{r}_i - \mathbf{r}_p\right\| = d \qquad (14)$$

where $\mathbf{r}_i$ and $\mathbf{r}_p$ are cortical grid point position vectors. Note that the cortical Laplacian defined by equation (14) is the 2D version of the 3D Laplacian in (2") above. For a real cortical surface both the grid and the Laplacian operator **C** have to be appropriately defined.

For a dense cortical grid (M>>N), the unique solution to (11) corresponds to a minimum seminorm restricted solution of a consistent linear system of equations [3], and is:

$$\left.\begin{aligned}&\hat{\mathbf{J}}_0 = \mathbf{T}_0\Phi \text{ with:}\\ &\mathbf{T}_0 = \left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathbf{K}^T\left\{\mathbf{K}\mathbf{N}\left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathbf{K}^T\right\}^{-1}\end{aligned}\right\} \qquad (15)$$

The estimated neuronal generator distribution on the cortex is given by $\hat{\mathbf{J}}_0$ (cortical-LORETA).

In analogy with equations (9)-(9') and (10)-(10') above, the regularized problems for any given α>0 are now:

$$\min_{\mathbf{J}_0}\left\{\left\|\Phi - \mathbf{K}\mathbf{N}\mathbf{J}_0\right\|^2 + \alpha\left\|\mathbf{C}\mathbf{W}\mathbf{J}_0\right\|^2\right\} \qquad (16)$$

$$\min_{\mathbf{J}_0, c}\left\{\left\|\Phi - \mathbf{K}\mathbf{N}\mathbf{J}_0 - c\mathbf{1}\right\|^2 + \alpha\left\|\mathbf{C}\mathbf{W}\mathbf{J}_0\right\|^2\right\} \qquad (16')$$

and have solutions (proof omitted):

$$\left.\begin{aligned}&\hat{\mathbf{J}}_0 = \mathbf{T}_{0\alpha}\Phi \text{ with:}\\ &\mathbf{T}_{0\alpha} = \left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathbf{K}^T\left\{\mathbf{K}\mathbf{N}\left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathbf{K}^T + \alpha\mathbf{I}\right\}^{-1}\end{aligned}\right\} \qquad (17)$$

$$\left.\begin{aligned}&\hat{\mathbf{J}}_0 = \mathcal{T}_{0\alpha}\Phi \text{ with:}\\ &\mathcal{T}_{0\alpha} = \left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathcal{K}^T\left\{\mathcal{K}\mathbf{N}\left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}\mathbf{N}^T\mathcal{K}^T + \alpha\mathbf{H}\right\}^{+}\end{aligned}\right\} \qquad (17')$$

respectively.

A.3. LORETA for magnetic field measurements; spherical head model; 3D solution space.

The formulation for magnetic field measurements corresponding to the spherical head model is similar to **Subsection-A.1** above. However, solution (3) is ***incorrect***. I regret having erroneously stated in previous publications ([2] and [4]) that equation (1) was also valid for MEG measurements.

Specifically, let Φ correspond to magnetic field measurements, **K** to the magnetic lead field, and let the sphere center be at the coordinate origin. Then a further explicit constraint must be added to equation (1) for this magnetic case:

$$\mathbf{RJ}=\mathbf{0} \qquad (18)$$

where **R** is a block diagonal $3M$•$3M$-matrix, where each sub-block is a 3•3-matrix, with the i-th diagonal sub-block given by:

$$\mathbf{R}_{ii} = \frac{\mathbf{r}_i\mathbf{r}_i^T}{\left\|\mathbf{r}_i\right\|^2} \qquad (19)$$

where $\mathbf{r}_i$ is the position vector of the i-the grid point in the brain. The grid point at the sphere center with **r**=**0** should not be included in the solution space.

Constraint (18) indicates that the radial component of the current density field is silent. In terms of the Rao-Mitra general theorem (see Lemma 6.2 in [3]), this means that the solution to (1) belongs to the linear manifold $\mathcal{M}$(**I-R**), the space spanned by the columns of (**I-R**). The correct solution is:

$$\left.\begin{aligned}&\hat{\mathbf{J}} = \mathbf{T}\Phi\text{, with:}\\&\quad\mathbf{T} = \mathbf{D}\left(\mathbf{DWB}^T\mathbf{BWD}\right)^+\mathbf{DK}^T\left\{\mathbf{KD}\left(\mathbf{DWB}^T\mathbf{BWD}\right)^+\mathbf{DK}^T\right\}^{-1}\end{aligned}\right\}\qquad(20)$$

where **D**=**I**-**R**. Equation (20) can be considerably simplified by noting that **KD**=**K**, and **DW**=**WD** (with the new definition for **W** given in (1)). If **W** corresponds to a column by column normalization of the lead field, then **DW**≠**WD**. This is the reason why the weighted minimum norm solution in [16] is correct, while the one used in FOCUSS [17] is invalid (although it is a solution, it is not of minimum norm in the metric of **W**.)

The regularized problem, for any given $\alpha>0$:

$$\left.\begin{aligned}&\min_{\mathbf{J}}\left\{\left\|\Phi - \mathbf{K}\mathbf{J}\right\|^2 + \alpha\left\|\mathbf{B}\,\mathbf{W}\,\mathbf{J}\right\|^2\right\},\\&\quad\text{under constraint: } \mathbf{J}\text{ belongs to }\mathcal{M}(\mathbf{I}-\mathbf{R})\end{aligned}\right\}\qquad(21)$$

has solution (proof omitted):

$$\left.\begin{aligned}&\hat{\mathbf{J}} = \mathbf{T}_\alpha\Phi\text{, with:}\\&\quad\mathbf{T}_\alpha = \mathbf{D}\left(\mathbf{DWB}^T\mathbf{BWD}\right)^+\mathbf{DK}^T\left\{\mathbf{KD}\left(\mathbf{DWB}^T\mathbf{BWD}\right)^+\mathbf{DK}^T + \alpha\mathbf{I}\right\}^{-1}\end{aligned}\right\}\qquad(22)$$

A.4. Other cases.

A.4.1 LORETA for magnetic field measurements; realistic head shape; 3D solution space.

Theoretically, equations (1), (2''), and (3) would be valid in this case. However, formidable numerical problems may arise since the magnetic lead field for a typically shaped human head is approximately the same as the spherical lead field, at least for sources in brain regions other than frontal and fronto-temporal [5]. I suggest the following practical solution to this problem. Consider the 3•3-matrix $\sum_{\alpha=1}^{N}\mathbf{k}_{\alpha i}\mathbf{k}_{\alpha i}^T$, and its singular value decomposition $\sum_{j=1}^{3}\lambda_j\Gamma_j\Gamma_j^T$, where the eigenvalues are ordered as $\lambda_1\geq\lambda_2\geq\lambda_3$. It can be shown that in the spherical head model $\lambda_3=0$ and $\mathbf{R}_{ii}\equiv\mathbf{I}-\sum_{j=1}^{2}\Gamma_j\Gamma_j^T\equiv\Gamma_3\Gamma_3^T$ (see equation (19)). Therefore, for the realistically shaped head model, equations (20) or (22) can be used with:

$$\mathbf{R}_{ii} = \mathbf{I} - \sum_j\Gamma_j\Gamma_j^T,\ \forall j,\ \text{under constraint: } \lambda_j/\lambda_1 > \varepsilon\qquad(23)$$

where ε can be taken as, e.g. 10^{-6}. This procedure would eliminate the "almost" silent part (if any) of the moment of the current density field.

A.4.2. Cortical LORETA; magnetic field measurements.

The equations of **Subsection-A.2**, excluding (16') and (17'), hold for this case, as long as silent cortical sources are excluded. Also note that equation (14) is only an example, and not the general cortical Laplacian.

A.4.3. LORETA on an arbitrary 2D solution space.

If the solution space is an arbitrary 2D manifold, and the current density moment is not restricted to be orthogonal to the 2D surface, then the equations of **Subsection-A.1** and **Subsection-A.3** hold for EEG and MEG, respectively, ***except*** for the Laplacian **B**, which must be in this case a surface Laplacian operator, i.e. it must consider derivatives only along the surface. This type of solution space been systematically treated by Hämäläinen and Ilmoniemi ([9] and [10]).

A.5. The Dale-Sereno inverse solution [6] and LORETA: similarities and differences.

Their inverse solution is:

$$\hat{\mathbf{J}} = \mathbf{T}_{DS}\Phi \text{, with: } \mathbf{T}_{DS} = \mathbf{R}_{DS}\mathbf{K}^T\left\{\mathbf{K}\mathbf{R}_{DS}\mathbf{K}^T + \mathbf{C}_{DS}\right\}^{-1} \quad (24)$$

where $\mathbf{R}_{DS}$ and $\mathbf{C}_{DS}$ are the variance-covariance matrices for the sources and for the measurement noise, respectively. This solution corresponds to a Bayesian formulation of the inverse problem, which can be found exactly, for example, in [7] (see p.189, eq. 4.5c, therein). For a cortical solution space, a formal "forced" comparison of (24) and (17) produces the relations $\mathbf{R}_{DS} \sim \left(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W}\right)^{-1}$ and $\mathbf{C}_{DS} \sim \alpha\mathbf{I}$. This formal similarity is to be expected if LORETA is viewed as a spline-like solution (which it is), since spline estimates are also Bayes estimates (see e.g. [8], p.14).

In the Dale-Sereno formulation, $\mathbf{R}_{DS}$ must be known *a priori*. Dale and Sereno suggested [6] that the correlation as a function of distance can be experimentally estimated. However, their paper does not give any quantitative information on which correlation structure was actually used there, simulated, assumed, measured, or otherwise. In the LORETA formulation there is a correlation structure implicit in $(\mathbf{W}\mathbf{C}^T\mathbf{C}\mathbf{W})^{-1}$ which is forced onto the solution: neighboring cortical patches (grid points) are positively correlated (which is in complete qualitative agreement with Dale and Sereno [6]). The amount and the spatial extent of this type of correlation can be regulated by using the more general *p*-iterated Laplacian, as in splines (see e.g. [8]), i.e. minimize in (11) the functional $\left\|\mathbf{C}^p\mathbf{W}\mathbf{J}_0\right\|^2$, with $p \geq 1$.

In the Dale-Sereno formulation, the variance of the sources (contained in $\mathbf{R}_{DS}$) must be known *a priori*, also. Dale and Sereno suggested [6] an algorithm for estimating such variances based on time varying data, where it is assumed that the source distribution consists of a finite number of distinct point sources with time varying amplitudes. Without time varying data, and without these assumptions, solution (24) cannot be used, i.e. solution (24) cannot be used if the available data consists of instantaneous measurements of scalp electric potentials and/or magnetic fields. In contrast, LORETA does not need neither the time varying data nor the source assumptions of Dale and Sereno to produce an inverse solution.

A.6. The comparison of linear inverse solutions based on the resolution matrix: the unique methodology for testing which inverse solution is better.

Given a linear inverse problem in the form $\Phi=\mathbf{K}\mathbf{J}_{true}$ (where Φ and $\mathbf{K}$ are known, $\mathbf{J}_{true}$ is unknown), and given a linear inverse solution in the form $\mathbf{J}_{estimated}=\mathbf{T}\Phi$, we obtain the following relation between the true and estimated primary current densities:

$$\mathbf{J}_{estimated}=\mathbf{T}\mathbf{K}\mathbf{J}_{true}, \quad (25)$$

where the matrix **TK** is the resolution matrix of Backus and Gilbert [11] (see also [12] pp.64-78, and [7] pp.199-201, p.494). If **TK**=**I**, then the inverse problem has a unique solution, and $\mathbf{J}_{estimated}\equiv\mathbf{J}_{true}$, which is not our case. Therefore, a detailed analysis of how the matrix **TK** deviates from the identity matrix will show how good or bad a particular inverse solution is, and will allow a rigorous quantitative comparison of different inverse solutions. Due to linearity and to the discrete nature of the solution space, it will suffice to study how the "filter" **TK** "distorts" all possible point sources. This is the reason why point sources are used as test sources, since any distributed primary current density can be expressed as a weighted sum of point sources. Furthermore, the “worst case test” for a distributed inverse solution is the point source.

Consider the 3D solution space case. Suppose that in (25) we set $\mathbf{J}_{true}=\delta_i=(0,0,....,0,0,1,0,0,....,0)^T$, where all entries are zero except the *i*-th which is unity. Physically, this is a unit strength point source (a dipole). Let $\mathbf{r}_i$ denote the corresponding position vector of this point source. The estimated primary current density is simply the *i*-th column of **TK**, which will be denoted as the vector $\mathbf{J}^i_{estimated}$, with entries $\mathbf{j}^{ik}_{estimated}$ (3-vector, k=1..M), which is the estimated primary current density at the *k*-th grid point. In this paper I define the localization error as the distance between the actual point source at $\mathbf{r}_i$ and the location of the maximum of the estimated inverse solution, i.e.:

$$E_i = \left\| \mathbf{r}_i - \mathbf{r}_{\hat{i}} \right\|$$

where:

$$\hat{i} = \arg\max_k \left\{ \left\| \mathbf{j}^{ik}_{estimated} \right\|^2 \right\}$$

I define the spatial dispersion (blurring) of the estimated solution as:

$$D_i = \sqrt{\sum_{k=1}^{M} \left\| \mathbf{r}_k - \mathbf{r}_{\hat{i}} \right\|^2 \left\| \mathbf{j}^{ik}_{estimated} \right\|^2 \Big/ \sum_{k=1}^{M} \left\| \mathbf{j}^{ik}_{estimated} \right\|^2}$$

The sets of localization errors $\{E_i\}$ and spatial dispersions $\{D_i\}$ will serve as a basis to compare different linear inverse solutions.

Reply to Comments by R.D. Pascual-Marqui
by Matti Hämäläinen

After receiving the comments of R.D. Pascual-Marqui I have carried out a few simulations using the LORETA reconstruction matrices provided by him.

Localization and blurring

The localization and blurring data provided by Pascual-Marqui for the noiseless case show that the three methods discussed have approximately equal average spatial dispersion. As far as localization error is concerned LORETA is shown to be superior to the weighted minimum-norm solution. As pointed out by Ilmoniemi in his reply, the discussion of unweighted minimum-norm solutions is rather irrelevant, because they have not been claimed to provide localization in a full 3D source space.

In the future, the analysis of localization and blurring should be extended to noisy data and to source locations between the reconstruction grid points. I fully agree with Pascual-Marqui that these basic capabilities of reconstruction methods can be adequately addressed by analyzing the images of single point sources.

Combinations of multiple sources

My simulations using the data provided by Pascual-Marqui indicated that additional 'ghost' sources may well appear in LORETA reconstructions. In particular, I considered two symmetrically located sources on the two hemispheres, simulating the activity of the two auditory cortices. LORETA was able to reconstruct the two source locations correctly. However, depending on the exact location of the sources, LORETA reconstructions showed an additional maximum in the frontal or posterior areas, or both.

Another test employed a four-source configuration simulating somatosensory activity. In this case the reconstruction from noiseless data was essentially free of significant ghost images. I haven't yet systematically considered the effects of noise and regularization in these cases.

Simulations and realistic examples

Pascual-Marqui argues for using experimental data to analyze the performance of inverse problem algorithms. However, the step from artificial simulations to real data is possibly too large. Therefore, in parallel with analyzing experimental data, we should carefully consider simulated signals based on simple, well controlled, experiments. With such examples, we have complete control of both our target sources and noise. We can, for example, calculate a noise correlation matrix from the measured background activity and thereby study the effects of correlated noise on our reconstructions. A set of physiologically sound time-varying dipole sources provide at least a reasonable estimate for the activity that might occur in the brain. In the analysis results similarities between dipolar and distributed source solutions indicate that we can recover the locations of several source areas reliably. On the other hand, discrepancies between the two types of solutions may indicate possibilities to recover more information about the actual current distributions in the brain.

Reply to Comments by R.D. Pascual-Marqui
by Risto J. Ilmoniemi

It is a pleasure to see that the present discussion is gradually converging towards common understanding. The results of simulations provided by Pascual-Marqui

(P-M) and those performed by Matti Hämäläinen (see his reply) appear to show that LORETA is indeed capable of locating simple sources at least in the limit of no noise, i.e., when no regularization is needed.

Many of my comments on LORETA were answered by P-M in a satisfactory way, but a quick further reply is still in place.

* I still believe that neurophysiological smoothness is present on such a short length scale in the cortex that it can not be used to justify the use of LORETA. The situation is not helped much by a denser EEG or MEG grid, because the information in the extracranial electromagnetic field is limited to fairly small spatial frequencies.

* The 2D formulation of LORETA now introduced by P-M appears to be a step forward in cases when the geometry of the cortex is available, although even this procedure has to be evaluated in practice.

* It indeed appears that simple sources are better located in depth with LORETA than with weighted minimum-norm estimate. Because P-M evaluated the depth localization of with the minimum-norm estimate (MNE) with uniform weighting, it should be emphasized that this algorithm was never meant for depth estimation. Thus, to evaluate MNE with this measure does not give proper characterization of the method.

We agree on the need to clarify when LORETA and other methods should be favored. While the minimum-norm estimate is optimal in the (perhaps hypothetical) minimal-a-priori knowledge case as explained in my Comments, LORETA appears to be suitable for locating patches of activity in 3D when one can assume a priori that the activity is clustered. Evidence supporting brain activation in patches is accumulating from PET and fMRI studies. Keeping in mind the comments above and the need for further clarifications, I welcome LORETA as a useful practical tool for MEG and EEG.

Reply to Comments by R.D. Pascual-Marqui
by Paul L. Nunez

The main difference between my concern about inverse solutions and those expressed by Dr.'s Pascual-Marqui, Hämäläinen, and IImoniemi appears to one of emphasis. They have focused mostly on several important mathematical issues. My concern is that applications to genuine EEG/MEG data require that we fully appreciate both the "forest" (the overall neurophysiological problem) and the "trees" (the mathematical issues). Any scalp potential distribution (at fixed time) can be fitted to a distribution of exclusively cortical sources. Furthermore, since these sources are closest to the surface and can be strongly correlated, they are often the most likely sources based only on physiological grounds. We can reject the hypothesis of exclusively cortical sources only by combining strong physiological arguments with our mathematical methods. Inverse solutions involving deep sources are not credible in cases where the physiological bases for rejecting cortical sources are not reliable.