Discussing the Capabilities of Laplacian Minimization

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Abstract: This paper discusses the properties and capabilities of linear inverse solutions to the neuroelectromagnetic inverse problem obtained under the assumption of smoothness (Laplacian Minimization). Simple simulated counterexamples using smooth current distributions as well as single or multiple active dipoles are presented to refute some properties attributed to a particular implementation of the Laplacian Minimization coined LORETA. The problem of the selection of the test sources to be used in the evaluation is addressed and it is demonstrated that single dipoles are far from being the worst test case for a smooth solution as generally believed. The simulations confirm that the dipole localization error cannot constitute the tool to evaluate distributed inverse solutions designed to deal with multiple sources and that the necessary condition for the correct performance of an inverse is the adequate characterization of the source space, i.e., the characterization of the properties of the actual generators.

Key words: Linear inverse solutions; Laplacian minimization.

Introduction

The localization of the generators of the electromagnetic activity of the brain, i.e., the solution of the neuroelectromagnetic inverse problem, is an alternative to imaging brain functioning. The efforts devoted to the solution of this mathematical problem have recently grown as witnessed by the increasing number of publications and presentations on this topic. In brief, this problem has infinite solutions and for that, it is called an ill-posed problem. To gain in uniqueness some supplementary a priori information has to be added. There are multiple examples of linear and non linear constraints which have been already used in this inverse problem ranging from the single dipole fitting to a global framework encompassing spatial and temporal restrictions. A question remains open: Is there any solution that can be considered as superior to the others for the analysis of arbitrary data sets? Although the answer to this question seems to be clear for mathematically oriented authors, (see Fuchs et al. 1994; Greenblatt 1994; Mosher and George 1994; Valdes et al. 1994; Hamalainen 1995; Nunez 1995; Ilmoniemi 1995), other authors attribute special properties to a solution that relies in smoothness as a constraint (LORETA). Even though these properties were the subject of an extensive discussion in the special issues of ISBET Newsletter: ISBET Newsletter No. 5, 1994 (IN94) and ISBET Newsletter No. 6, 1995 (IN95), the debate mainly concentrated on theoretical arguments which are non necessarily well understood by non mathematical readers. Thus, the main goal of this work is to discuss the main properties of LORETA by means of simple simulations intended to reach potential users of inverse solutions who lack a formal background in mathematics.

Smoothness is a natural and elegant mathematical way to solve ill-posed problems extensively used during this century (see Wahba 1990 and references therein). Many textbooks refer to this technique in the particular context of inverse problems (Tihonov and Arsenin 1977; Golberg 1978; Groetch 1984). Smoothness have been also considered for the solution of bioelectromagnetic inverse problems, e.g., Huiskamp and van Osterom (1988), Messinger-Rapport and Rudy (1988), van Osterom (1992), Pascual-Marqui et al. (1995), Wagner et al. (1996), Grave and Gonzalez (1998), Fuchs et al. (1999) among others. The rationale behind this regularization technique is that the uncertainty in the unknown function can be replaced by some a priori information (smoothness) that imposes a structure on the solution.

A common way to measure the smoothness (or roughness) of a function is through the evaluation of derivatives of different order, e.g., first order (gradient), second order (laplacian and mixed partial derivatives), etc. A formal framework using arbitrary differential operators

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and their associated weighting functions as well as other approaches to smoothness based on general interpolation rules can be found in Grave and Gonzalez (1999). Under the smoothness constraint, the values of the unknown function are related and thus the problem can have a unique solution. Even if the solution is unique, this constraint does not necessarily reflects actual features of the sources but constitutes a mathematical palliative to the lack of information about their properties.

In LORETA, smoothness is implemented via a minimization of a non-singular Laplacian of the weighted unknown. Up today there are no neurophysiological evidences to justify this weight selection or the use of the smoothness constraint for characterizing neural currents. In spite of that, LORETA is claimed to be the only tomographic linear inverse solution capable of localizing in 3D the generators of the brain electromagnetic activity. This is concluded after analyzing the properties of LORETA for the retrieval of isolated dipolar sources and applying the apparently sound reasoning that a solution unable to localize isolated dipoles at any depth have to fail for the localization of the neurophysiological generators. The last two simulations of this paper shed light on the inexactness of this point which is a crucial aspect in the design of strategies for solving this inverse problem. It is shown that the simple minimum norm perfectly retrieves a generator configuration for which LORETA fails. This example is used to support the conclusion that the only reasonable manner of designing inverse solutions is the mathematical characterization of the physical/neurophysiological properties of the source space. For instance, a reliable solution does not need to localize isolated generators at any depth if the purpose is to describe simultaneous neurophysiological sources confined to the cortical mantle.

This paper starts describing the simulation conditions considered, namely, the sensor configuration, solution space and source and head model. The selected conditions are propitious for the adequate performance of any inverse solution. The second section enumerates the presumed features of LORETA and illustrates by simple counterexamples that these conjectures do not hold. Some simulations are intended to illustrate limitations to consider when interpreting inverse maps associated to real data while others are selected to bring the discussion upon specific aspects such as inverse solutions evaluation and design.

Materials and Methods

The following simulations and examples consider data identical to those described in IN94 and IN95. The whole configuration is briefly described below.

Head model

Three-shell spherical model representing the scalp, the skull and the brain. The origin of coordinates is placed at the center of the spheres. A right hand oriented system is used with X-axis increasing from innion to nasion and Y-axis increasing from left to right ear. The external (scalp) radius is one.

Sensor configuration

148 electrodes located on the scalp surface, extending lower than the upper half of the sphere.

Solution Points (source space)

The solution space is formed by 817 solution points homogeneously distributed in 10 axial (orthogonal to Z-axis) slices within the innermost head model compartment (radius=0.8).

Data

All the data used in the simulations were kindly provided by Pascual-Marqui. The data include the 817 solution points, the Lead field matrix and the Inverse matrices for the Mimimun Laplacian (LORETA) and Minimum Norm (MN). All the modeling aspects that can influence the simulations, namely, volume conductor model, sensor positioning, conductivity profile and measurements are assumed perfectly known and accurate (up to the floating-point arithmetic used). None of the examples takes into account noise or imperfect knowledge of the parameters. Sources at intermediate positions, i.e., at sites not coincident with one solution point are dismissed since this is equivalent to include noise in the measurements. Trivially, all the simulation conditions selected are unrealistically propitious for the adequate performance of an inverse solutions and thus any limitation detected can only worsen in a more realistic situation, e.g., less sensors, noisy data, etc. Also, note that the sensor distribution covers a scalp area that extends below the brain (source space) which is rarely the case in many clinical or experimental setups. While the simulations are restricted to the case of electric measurements, there is no theoretical reason to expect different results for the magnetic case.

In what follows the term test source is used to denote an isolated dipole at a given solution point with its dipolar moment parallel to one of the Cartesian axis. At each solution point, there are three test sources of unitary dipolar moments (1,0,0), (0,1,0) and (0,0,1) respectively. Each column of the lead field matrix coincides with the potential produced on the whole electrode array by one of the test sources. Consequently, the scalp potential produced by the three test sources associated to the p-th solution point is given by the lead field columns (p-1)*3+k with k=1,2,3. In all the simulations described in next section this notation is adopted to indicate the exact test sources used to generate the measurements. For instances, a reference to the test source 1152 indicates a dipole placed at solution point 384, oriented parallel to the z-axis (k=3).

Results and discussion

The presumed properties of LORETA are:

C1) "LORETA's main property": "if the actual source is exactly a single dipole, then LORETA produces a 3D blurred image of the point conserving the original location" (IN94, page 6)

C2) "With LORETA… maxima indicate real sources, but possibly blurred" (IN94, page 22).

C3) "General form of LORETA's main property": "due to the principle of superposition, LORETA produces a blurred image of any arbitrary 3D source distribution" (IN94, page 6).

C4) "If the actual 3D source distribution is neurophysiologically smooth, then LORETA can recover it exactly" (IN94, page 7).

C5) "If the actual 3D source distribution is not neurophysiologically smooth then LORETA produces a blurred version" (IN94, page 7).

In what follows simple counterexamples refuting conjectures C1-C5 are presented. Other source configurations for which the same difficulties hold are indicated also in the text. All the figures depict the modulus of the current density vector over the set of solution points forming each slice. The slices are plotted as seen from a top view (axial slices, viewed from Cz=[0,0,1]) and ordered from bottom to up. The uppermost slice is constituted by a single point. No interpolation is used in the plots.

Properties C1 and C2

For the discussion of C1 and C2, it is enough to consider single sources. A solution, for which these two properties hold, will reconstruct an arbitrary test source as a spot (due to the blurring) around the correct location. Such solution cannot produce ghost sources since this would correspond to a maximum not associated to a real source (C2). Figure 1 shows that this is not the case for test source 133 (figure 1a), where the reconstruction (figure 1b) clearly show two maxima and none of them is located at the correct place. Note that some graphical interpolation might mask the presence of these ghost sources. Additional examples of ghostly reconstruction can be mentioned, namely, test sources 101, 103, 104, 106, 109, 124, 127, 130, 133, 134, 136, 139, 2410, etc. Still these examples do not exhaust the list.

Property C3

Since statement C3 refers to arbitrary source distributions, we can consider an example with two single test sources. Figures 1c and 1d show the real distribution and the reconstruction provided by LORETA for test source 1960, while figure 1e and 1f depicts the same for test source 2310. Figure 1h shows the reconstruction when both (1900 and 2300) test sources are simultaneously active. The real distribution is depicted in figure 1g. It is clear that even when the positions (but not the amplitude) of both test sources are approximately retrieved when acting alone, the simultaneous reconstruction (figure 1h) suggests the existence of only one source, i.e., there is a lost source. This happens because the strengths were incorrectly estimated by the inverse. In addition the reconstruction of 1900 and 2300 together (figure 1h) is not equal to the sum of the maps reconstructed in figures 1d and 1f, since the principle of superposition does not apply for the maps of the modulus, as presumed in C3. There exist a huge amount of examples composed by two or more test sources that are poorly retrieved by LORETA. As a rule of thumb, test sources of similar intensity but different eccentricities suffer from this limitation as shown in Grave and Gonzalez (1998). As it is the case for other linear inverse solutions, there are pairs of sources that can be fairly well reconstructed.

These two unavoidable drawbacks, i.e., the existence of ghost and lost sources, impede LORETA to fulfill C1, C2 and C3, and thus not even a "blurred image" can be guaranteed for all single test sources and obviously neither for an "arbitrary 3D source distribution".

A point to discuss here is if whether these limitations arise because isolated dipolar sources are "the worst test case" for a distributed solution based on smoothness. To answer this question, consider the intuitive (non-mathematical) idea of smoothness. Roughly speaking smoothness expresses that the solution should have very similar values everywhere except for sites where the measured data (EEG/EMG) force a difference. The test sources used here and in IN94 and IN95 consider a distribution composed by zeros everywhere except for one point where the value is one, that is, (0,…,1,...,0). Thus, there is only one point where the hypothesis of smoothness is not fulfilled. It is not difficult to see that a distribution composed by two, three or more simultaneously active test sources is less smooth. Consequently, a difficult test case should contain a distribution of sources alternatively distributed over the whole solution space since generally the performance of linear inverse solutions deteriorates with the increase in complexity of the source distribution.

Properties C4 and C5

Consider a source distribution d1 which is zero everywhere except at the component 456 where the value is

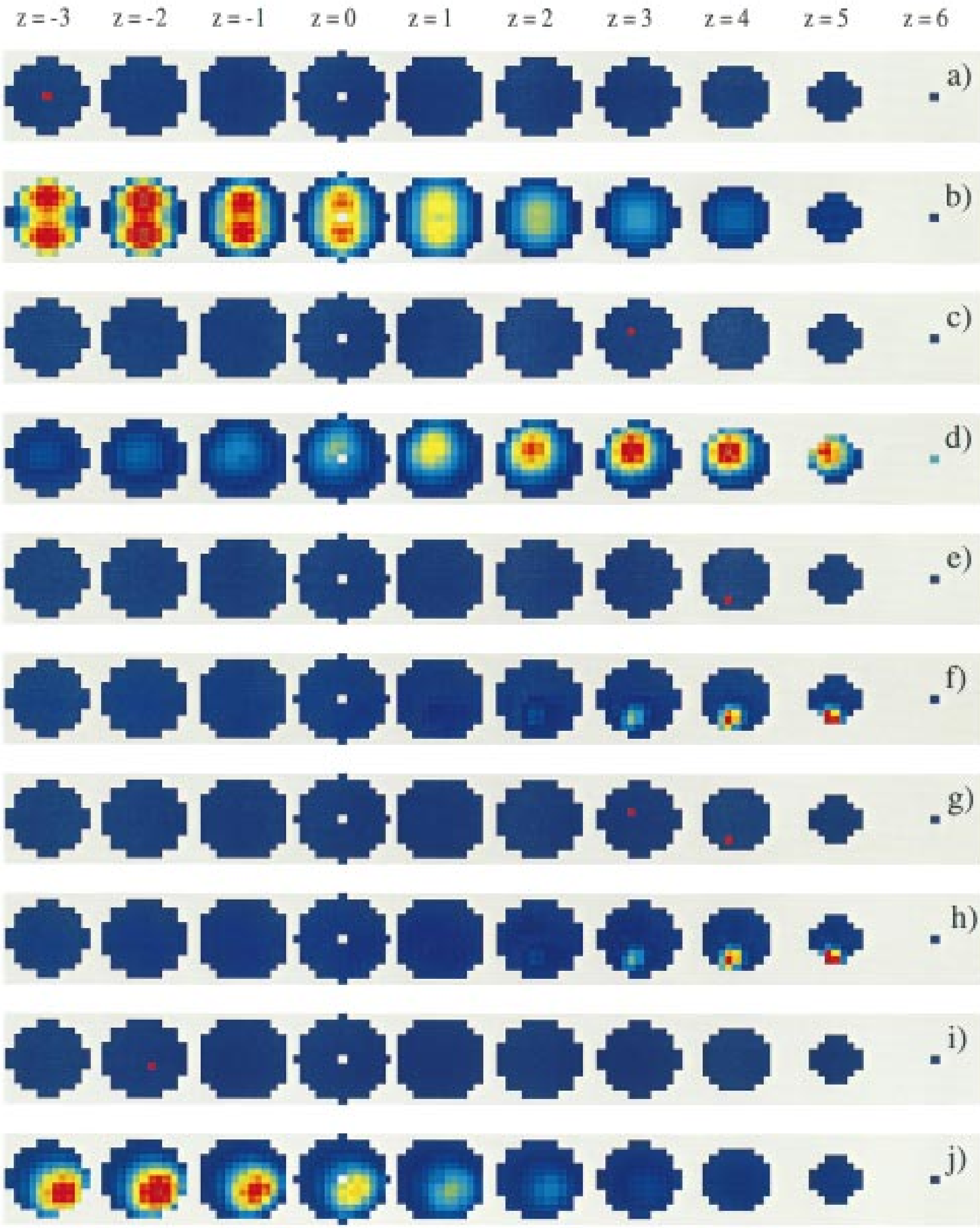

Figure 1. a) Original source distribution for test source 133. b) Reconstruction obtained with LORETA for (a). c) Original source distribution for test source 1960. d) Reconstruction obtained with LORETA for (c). e) Original source distribution for test source 2310. f) Reconstruction obtained with LORETA for (e). g) Original source distribution for test sources 1960 and 2310. h) Reconstruction obtained with LORETA for the two sources showed in (g). i) Original source distribution d1 corresponding to test source 456. j) Reconstruction obtained with LORETA for (i). The color scale goes from blue to red with blue representing the minimum of the modulus and red the maximum.

one, i.e., d1=(0,0,0…,1,…0,0,0). Adding one to all elements in d1 produces a distribution d2=(1,1,1…,2,…1,1,1), with ones everywhere except at component 456 where the value is two. Both distributions have the same profile (landscape) and exactly the same degree of smoothness for a measure that does not depend on a DC level. There is a constant background value, and one source (456) that exceed this background in one. Figure 1i depicts distribution d1 (test source 456) and figure 1j its reconstruction by LORETA. Figures 2a and 2b show distribution d2 and LORETA's reconstruction respectively. While d1 and its reconstruction seems adequate, the pattern retrieved by LORETA for d2, is quite different an inaccurate. This leads to the question: If smoothness is the property that allows retrieving correctly d1 why does it fail for d2?

The answer to this question resides on the fact that in d1 there is only one active source while in d2 multiple sites light up together. This is why, when analyzing a distributed solution, it is necessary to measure the influence in the reconstruction of one source of all possible active sources elsewhere. This influence can be measured by means of the concept of resolution kernels derived by Backus and Gilbert (1968) for the geophysical inverse problem. Definition, applications and intuitive description of resolution kernels to the bioelectromagnetic inverse problem can be found in Grave et al. 1996, 1997; Lütkenhöner and Grave 1997. While in d1 (isolated source) all other test sources are silent and thus we can neglect the resolution kernels, when considering d2 (multiple active sources), the amplitudes of the resolution kernels dramatically influence the reconstruction.

Another example of multiple test sources that cannot be properly retrieved by LORETA is the (smooth) constant distribution, that is, d=(1,1,1…,1,…,1,1,1). Figures 2c and 2d show the original distribution d and the reconstruction provided by LORETA. Note the similarity with the reconstruction of previously described d2 shown in figure 2b. In fact, we have found that when the number of test sources are near/over the number of sensors and the sources are uniformly distributed, LORETA produce the same fixed pattern. This pattern coincides with that of figures 2b and 2d. Note that this example also disproves conjectures C4 and C5, since d is a smooth distribution (perhaps one of the smoothest that exist) that cannot be reconstructed by LORETA.

Conjectures C4 and C5 can be refuted on a more rigorously way. In Grave and Gonzalez (1998), a general result is proved, that for the particular case of smoothness reads: Even when a solution aims to retrieve smooth sources, there are non-silent smooth sources that cannot be retrieved. Without coming into the mathematical details, the proof is based on the fact that for any inverse different to the Minimum Norm, e.g. LORETA, there is an orthogonal space that contains non-silent sources, i.e., the projection of these source distributions over the columns of the inverse is zero! In other words, the reconstruction provided by LORETA is orthogonal to the original distribution and thus, LORETA cannot retrieve these smooth source distributions.

Figures 2e, 2f and 2g, 2h, present respectively the real distribution and the reconstruction for two smooth source distributions, namely J(x,y,z)=(z,x,y), and J(x,y,z)=(x^2,y^2,z^2). Note that both source distributions have minima within the brain and tend to grow when approaching the cortex (see figures 2e and 2g) which is far from being a non-plausible neurophysiological distribution. Still in the reconstruction (figures 2f and 2h) the position of the maxima and minima are exchanged. This effect is due to the Laplacian (singular or not) that penalize the activity at the borders of the grid (cortex) while favoring maxima at interior points. This confirms again that C4 does not hold, i.e., it is not true that "LORETA can recover exactly" all the smooth source distributions. If this happens for some smooth distributions, which are favored by the solution, it is obvious that the quality of the reconstruction cannot be granted for arbitrary non-smooth distributions, and thus, C5 cannot hold.

To summarize we can say that the Minimum Laplacian solution, as any linear inverse solution, suffers from some limitations, namely:

a) It is not possible to estimate correctly the position and the strength of all single test sources.

b) Ghost and lost sources can affect the reconstruction even for the case of very simple configurations, e.g., isolated dipoles (test sources).

c) Because of (a) and (b), neither maxima indicate all the time real sources, nor minima stand always for silent regions.

d) The reconstruction of arbitrary source distributions will be perfect if and only if the original source distribution belong to the space generated by the columns of the inverse. The farther are the sources from this space the poorest is the reconstruction.

These results reflect the difficulties inherent to the solution of the bioelectromagnetic inverse problem, i.e., determination of a three components vector at a large number of solution points with a very small set of measurements. With this scarce information, it is possible to essay to optimize the estimation of single test sources in terms of position and strength. This alternative looks appealing because this is a sufficient condition for the good performance of an inverse. Still the measurements are not informative enough to reach this goal as illustrated by these simulations and a large collection of theoretical results (Backus and Gilbert 1968; Menke 1989; Grave de Peralta and Gonzalez 1998.),

To see that a low dipole localization error alone is not a necessary condition for a good performance, con-

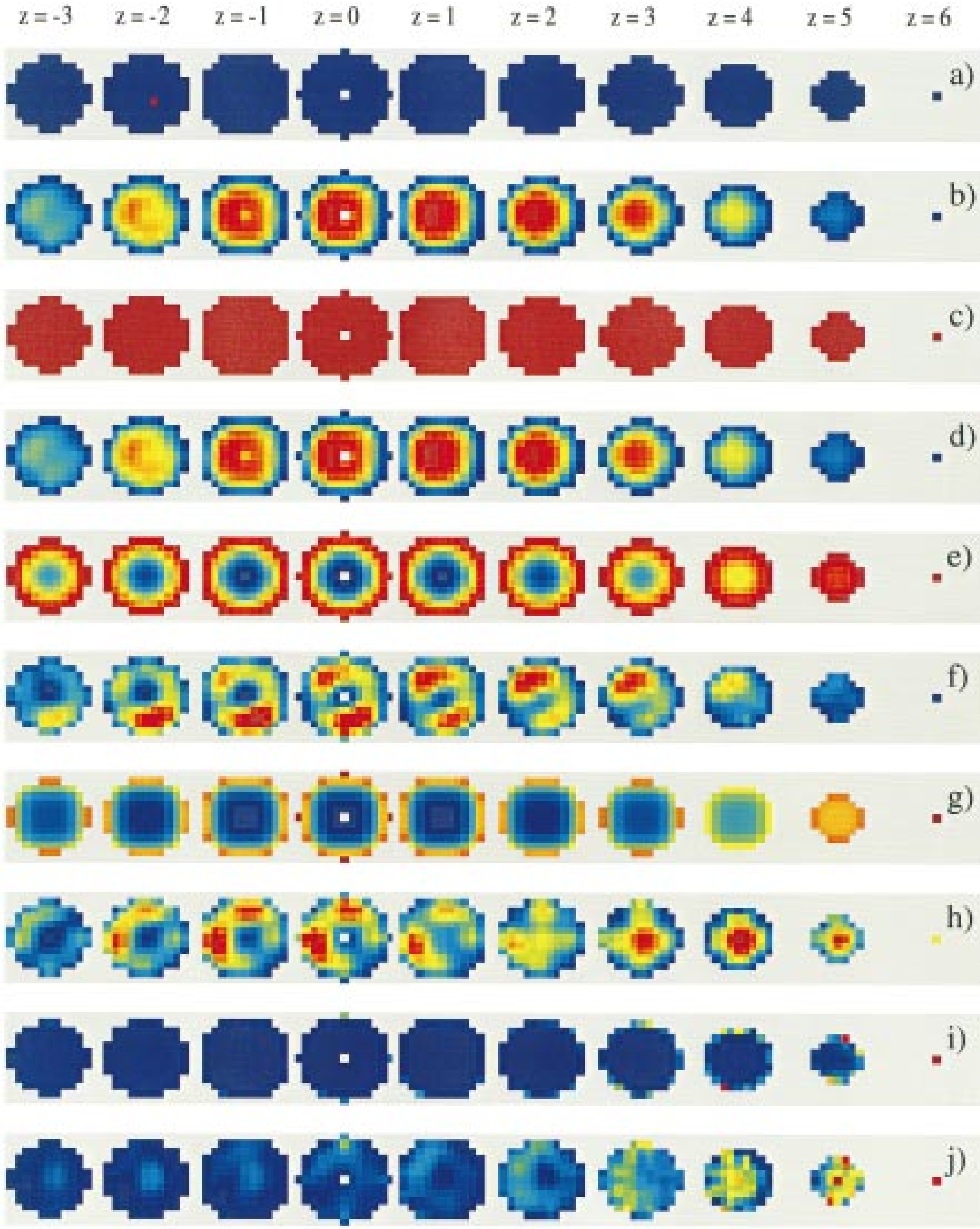

Figure 2. a) Original source distribution d2 obtained by adding one to all components of d1. Distributions d1 and d2 have similar plots and the same degree of smoothness. b) Reconstruction obtained with LORETA for distribution d2. c) Original source distribution d corresponding to a constant source distribution. d) Reconstruction obtained with LORETA for the constant distribution depicted in (c). Note the similarity between the reconstructions (b) and (d) associated to two different original distributions (a) and (c). e) Original smooth source distribution J(x,y,z)=(z,x,y). f) Reconstruction obtained with LORETA for the smooth distribution in (e). g) Original smooth source distribution $J(x,y,z)=(x^2,y^2,z^2)$. h) Reconstruction obtained with LORETA for the smooth distribution in (g). i) Original source distribution obtained adding the columns 20 to 30 of the MN inverse matrix. Coincides with the reconstruction obtained with the MN solution. j) Reconstruction obtained with LORETA for the source belonging to the column space of the MN inverse matrix depicted in (i).

sider the following example. Let be G (for good) and B (for bad), two inverse solutions such that G retrieve approximately all single source location while B yields to poor dipole localization errors (e.g., Minimum Norm). If the actual generators are arbitrary combinations of the columns of B, the performance of B will be perfect while the performance of G cannot be predicted. It will depend on the projection of the real distribution on the subspace determined by the columns of G. Obviously, the perfect performance of B refute the hypothesis that low dipole localization error is "a necessary condition for correct localization in general", and thus disqualify the dipole localization error as a basic tool to predict the performance of a distributed inverse solution. Figures 2i and 2j illustrate this situation for LORETA and the Minimum Norm solution (MN). Figure 2i corresponds to the original source distribution, created as a sum of 10 columns of the MN inverse matrix (columns 20 to 30) and obviously coincides with the reconstruction provided by MN. Figure 2j presents the reconstruction provided by LORETA. The images clearly show that LORETA fails estimating this source distribution independently of its behavior for single sources. This example allows concluding that it is better to characterize the subspace that better explains the sources than to concentrate the efforts in reducing the dipole localization error for single sources alone. Note that we are not telling that Laplacian minimization (or LORETA) is optimal for dipole localization. For latter purpose methods better suited than distributed inverse solutions exist already.

Let us remark that the expression "characterize the subspace that better explains the sources" is not a general philosophical truth but a goal of many research groups. There are an increasing number of papers that combine different neuroimaging techniques, e.g., fMRI and inverse solutions, or impose restrictions on the temporal behavior of the generators. In Grave et al. 2000, the generators are restricted to be irrotational which are the sole currents responsible for the generation of electric scalp maps. This solution called ELECTRA might fail if tested for single test sources. Still the underlying physical model of the generators (intracranial potentials) is of undeniable validity when dealing with electric measurements (EEG, ERP). Such solution has therefore bigger chances to succeed with electrophysiological data. In summary, the strategy to design and evaluate inverse solutions has to be consequent in the sense that a solution designed to optimally retrieve a certain neurophysiological feature of the sources should not be evaluated in terms of its localization properties for isolated dipoles. The contrary also hold, a solution "optimal" for isolated single dipoles could be far from optimality when dealing with neurophysiological generators. The current dipole is an approximated description of the electrical process occurring at a microscopic level which has proven to be helpful in many data analysis but which can neither constitute the golden rule to evaluate inverse solutions nor necessarily the best model to describe neurophysiological generators at the level of intracranial recordings (Alarcon et al. 1994). In summary, even if distributed inverse solutions are doomed to failure for arbitrary, mathematically constructed source distributions this is not necessarily the case for the actual brain generators.

Conclusion

This paper discussed the capabilities of a linear inverse solutions obtained under the assumption of smoothness (Laplacian Minimization). Clear counterexamples are shown to illustrate that the presumed features of one implementation (LORETA) of this general principle do not hold. The selection of test cases is also discussed and it is shown that single dipoles are far from being the "worst case test" for a smooth solution. It is finally shown that while smoothness can be an effective constraint for retrieving isolated sources, it can fail for patterns with the same degree of smoothness but composed by multiple active sources. The use of the dipole localization error as the golden rule to evaluate and design distributed inverses is criticized. The conclusion derived from this paper is the necessity of a mathematical characterization of the subspace that contains the neurophysiological generators as the most reasonable alternative to design solutions to the bioelectromagnetic inverse problem.

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