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The Inverse Problem in Electroencephalography and Magnetoencephalography

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The inverse problem in electroencephalography (EEG) and magnetoencephalography is of both theoretical and practical import. Localization based on EEG and MEG depends directly on the ability (at times in disguised form) to make a reasonable guess about current sources and their locations based on measurements from the surface. This is a simple statement of the inverse problem. Unfortunately, theory shows that there is not a unique solution to this problem; noisy data only makes this worse. We will attempt to outline some of the relevant information necessary to gain insight into this problem; we will show why the inverse problem in this case is ill-posed—that is, prone to ambiguities. We will outline some of the approaches being used in practice to handle the inverse problem, as well as approaches with potential for future development. Results will be freely borrowed from the forward problem—in which source geometry as well as the geometry of the conductor are known, and in which the electric potential or magnetic field at selected points is to be derived. We will attempt to maintain a practical motivation, which will at times imply a strong clinical perspective.

WHY THE INVERSE PROBLEM ARISES CLINICALLY

A good way to study the brain, a way used by many, is to look at its functioning. In a recent technical note, Nunez (27) brackets this basic clinical issue neatly between philosophy and physics:

> As implied by Sherrington's enchanted loom allegory, the proper study of the brain would appear to be a study of brain dynamics. The problem of improvement in spatial resolution remains paramount, but the goal is not localization per se because at any fixed instant in time sources can be anywhere and everywhere; it is relative magnitudes and correlations that we hope to connect to sensory and cognitive processes. . . .

A strong hint of the dynamical functioning of the brain is given by the electromagnetic field of the brain.

The electromagnetic field of the human brain varies slowly enough so that the electric and magnetic fields can be considered separately. Yet each of these varies quickly enough so that one speaks of "brain waves." The electric field is measured indirectly through the measurement of the electrical potential by electrodes and highimpedance amplifiers. The magnetic field is measured with induction coils [often coupled to superconducting quantum interference devices (SQUIDS)] and associated circuitry. Both the brain waves obtained with electrodes and those obtained with induction coils vary as their respective sensing devices are moved about the head. That is to say, brain waves measured at different locations are different.

As a result of many experiments, an underlying cause for these waves has been identified and is generally accepted—namely, the electrical activity of the neurons making up the brain tissue [see review by Okada (29)]. However, the causal relationship is somewhat complicated. Wood (46) calls the electric potentials and magnetic fields "aggregate, biased, and incomplete." Nonetheless, the correlation between underlying activity and externally measurable fields is strong.

Since a close correlation can be made between a particular set of electrical or magnetic measurements of the field of the brain and activity of a certain type in a particular place in the brain, one can define a "brain state." The study of the fields of the brain then becomes the study of the states of the brain.

Brain states are already appearing in images produced by positron emission tomography (PET). At present, the temporal resolution of PET is on the order of minutes, so only steady states are revealed. These show, for example, that a focused activity such as reading results in activity localized in a small portion of the brain, whereas an unfocused activity such as meditation results in activity delocalized or distributed about the cortex.

A state space is an abstract space, in much the same way, for example, that a cartesian plot of power versus frequency is a two-dimensional space. One can plot states as points or regions, and the transition between states is represented as trajectories or curves. Some of the groundwork for this has been laid by the somatosensory community, with a spatial topology reaching great levels of abstraction such as Klein bottle mappings from surface receptors to corresponding brain regions (43).

A state space approach to the study of the physical brain is a powerful formalism. What makes this approach valuable now in brain research is that the brain activity can be identified in three space dimensions and in time. The dynamic aspect is due to EEG and MEG. One can speak of a dynamic topology or geography of brain activity.

A state space approach that can deal very well with approximate ambiguous information has not yet been developed. For this reason it is important that the brain states be as well resolved in time and space as possible, at least down to physiologically meaningful levels.

It is easy to provide sufficient resolution in time. Much of the interesting brain activity seems to be in the millisecond range, well within the ability of modern electronics to record. And the electric and magnetic fields of the brain vary in step with the underlying activity.

It is at least straightforward, if not easy, to provide the sufficient resolution in space when electrodes are implanted into the brain. However, since the implantation of electrodes is a highly invasive procedure, another procedure is needed using external measurements from which the position of the underlying activity can be inferred. These inference techniques are part of a general class of problems called "inverse problems."

REVIEWS OF THE INVERSE PROBLEM IN EEG AND MEG

The inverse problem is more general than the biomagnetic inverse problem, and several investigators have reviewed general aspects of inverse theory (31,35). Basic information concerning the inverse problem and the intimately related forward problem in EEG and MEG have appeared in the literature. Plonsey (32), Baule and McFee (2), Rush and Driscoll (34), and Henderson et al. (17) discuss aspects of the forward problem in the framework of "lead field theory." Basic results relevant to the bioelectric forward problem in an inhomogeneous volume conductor are given by Geselowitz (10), and a discussion of the general forward biomagnetic problem and a derivation of basic results for a dipolar source are given by Grynszpan and Geselowitz (12). More recent detailed discussions of the inverse problem in EEG and MEG are given by Sarvas (36), Tripp (42), Hari and Ilmoniemi (15), and Williamson and Kaufman (45). In addition, Sarvas (36) describes some aspects of the least-squares search for both the linear and nonlinear inverse problem. Hari and Ilmoniemi (15) also provide a discussion of the inverse problem from the framework of the current space and lead field perspectives and give some insight into the complementary information provided by EEG and MEG.

WHY THE INVERSE PROBLEM IN EEG AND MEG IS ILL-POSED

The inverse problem as an abstraction has its own literature, which includes at least one dedicated journal (*Inverse Problems*). The inverse problem has been associated with electromagnetism at least as long as the fundamental laws of electromagnetism have been around. The fundamental laws are Maxwell's equations, which describe how the electric and magnetic fields arise and interact.

The idea of a field is built upon the principle of superposition. "Superposition" means that if a source gives rise to a particular field, and another source gives rise to another field, then the field due to both sources is simply the sum of the fields. If two dipoles are close together relative to the distance at which the field is measured, the resulting field can be indistinguishable from the field of a single different dipole.

In part because of superposition, the inverse problem as it arises in bioelectromagnetism is often part of a class of inverse problems called "ill-posed problems."

WHAT IS GENERALLY DONE TO SOLVE ILL-POSED PROBLEMS

In this section we will briefly consider how ill-posed problems are formally defined, and then we will describe what is done (in very broad terms) to find solutions. This will set the stage for the following section on the specific issues that arise in EEG and MEG.

The basic context is that of a mathematical operation which acts on a mathematical object and produces another mathematical object. The operation can represent, for example, the transformation from underlying brain activity to measured magnetic field strength. There are three properties associated with the operation which ensure that the inverse problem is well-posed.

1. *There must exist an inverse*. For example, the inverse of 2 is $\frac{1}{2}$. However, the arithmetical inverse of the number zero is not defined. In EEG and MEG, the inverse is the source.

2. *The inverse must be unique*. Consider the operation of translating coins into monetary value. If I note that I have four quarters in my pocket, one can say that I have $1.00. But if I say that I have $1.00 worth of coins in my pocket, one can only guess whether the coins are four quarters, 10 dimes, etc. For this operation, the inverse is not unique. In EEG and MEG, the inverse is not unique; because of superposition, a variety of sources can result in identical measurements.

3. *The inverse must be stable*. Consider the coins once again. Suppose one had guessed four quarters, and then I said "Well, actually I have only approximately

$1.00; on closer examination, I have $0.99." At that point, a guess of four quarters would require substantial revision. One might make a new guess of three quarters, two dimes, and four pennies. The first guess had four coins, and the second guess had nine—a change of over 100% in coin number. Had one guessed 100 pennies, the revision could be as small as 1%. So the guess of 100 pennies is less elegant and perhaps less likely, but more stable. In EEG and MEG, stability is a consideration in the sensitivity of an inferred source to noise.

Since these three criteria—existence, uniqueness, and stability—are often not met in physical experiments, the interpretation of the cause of the physical observation is often an ill-posed problem. There is a modification of the three criteria, formalized by Tikhonov and Arsenin (40), in which they are required to hold only over a part of the mathematical space. For example, in EEG and MEG the source may be restricted to a volume, often a sphere, which represents the head.

Ultimately, to solve an ill-posed problem, one must appeal to information outside the strict logic of the problem. It is this tack that leads to the realistic modeling of the head as well as to the efforts to use the anatomical information of magnetic resonance imaging (MRI) scans.

In other words, imposing a boundary, whatever it is, is part of the Tikhonov approach. Choosing the particular boundary is part of the auxiliary approach.

HOW THE INVERSE PROBLEM IS SOLVED IN EEG AND MEG

Overview

The basic inverse problem is to make inferences regarding the distribution of sources based on the recording of either surface EEG or MEG. As discussed, in general there is no unique result; nevertheless, there are approaches that are taken to simplify the problem. One may introduce several major constraints that result in more or less tractable problems. One may make assumptions concerning the source such as the single current dipole assumption, and one may similarly make assumptions concerning the geometry and conductivity of the head. The simplest model is a dipole in a homogeneous infinite head, which is not very realistic. In one approach, assumptions are made regarding the source and the head model, and the forward problem may be solved analytically or numerically. In many situations the source depends on a finite parameter set, in which case the inverse problem reduces to estimating the values of the parameters that give a solution that is (in some sense) most like the measured field data. If the constraints are suitably defined, the inverse problem thus reduces to a problem of parameter estimation. Search routines may then be used to make least-square parameter estimates. In practice, validation of models requires comparison of such estimates with actual source parameters from fixed or a priori known sources.

In general, for solution of the biomagnetic forward and inverse problems the starting point is the quasi-static formulation of Maxwell's equations; this approximation is valid as long as the product of the tissue dielectric and field frequency are much less than the tissue conductivity. With frequencies below the kilohertz range, this is valid in most tissues. Further arguments detailing this are given by Tripp (42) and Nunez (26).

Single-Dipole Models

Much of the work that has been done in MEG to date has employed a model of the source as a current dipole. Such a model is certainly reasonable for a small area of cortex which is relatively distant from the measurement point, but this model may be inappropriate when larger areas of cortex are activated. In assuming a dipolar source, there still is much flexibility in that the head model needs to be specified.

1. *Dipolar source, homogeneous head.* This quite simple model allows the estimation of location and depth of the dipole quite readily from measurements made on the field map. In essence, in homogeneous space the forward problem is easily solved; expressions for the potentials and the magnetic field are given below (36):

$$V(\mathbf{r}) = (4\pi\sigma)^{-1} \times \int \mathbf{J}^i(\mathbf{r}')\cdot(\mathbf{r} - \mathbf{r}')/|\mathbf{r} - \mathbf{r}'|^3\, dv'$$

$$\mathbf{B}(\mathbf{r}) = (\mu_0/4\pi) \times \int \mathbf{J}^i(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}')/|\mathbf{r} - \mathbf{r}'|^3\, dv'$$

Here, $\mathbf{J}^i$ is the source current, $\mathbf{r}$ is the measured field point, and the integrals are performed over the same region. For a current dipole of moment $\mathbf{Q}$ at $\mathbf{r}_0$, we have

$$V(\mathbf{r}) = (4\pi\sigma)^{-1}\, \mathbf{Q}\cdot(\mathbf{r} - \mathbf{r}_0)/|\mathbf{r} - \mathbf{r}_0|^3$$

$$\mathbf{B}(\mathbf{r}) = (\mu_0/4\pi)\, \mathbf{Q} \times (\mathbf{r} - \mathbf{r}_0)/|\mathbf{r} - \mathbf{r}_0|^3$$

For the magnetic field the expression reduces to the Biot–Savart law, with only the source current dipole having to be considered. Explicit solution is a simple algebraic problem as given by Williamson and Kaufman (45). The inverse solution amounts to locating the dipole in the designated space and is easily performed inasmuch as the dipole location must be at the midpoint joining the extrema of the field map while the dipole depth is estimated by dividing the inter-extrema distance by the square root of 2.

2. *Dipolar source, spherically symmetric head.* In this case, one is dealing with a homogeneous spherical head and a single current dipole as source. Cuffin and Cohen (7) treated the forward magnetic part of this problem extensively; they also noted that there is no external magnetic field for a radial current dipole. This obviously has important implications for the inverse problem, since it implies that there is no unique inverse in this model. Any derived tangential dipole estimated from magnetic measurements may have an arbitrary radial dipole added without worsening the fit based on purely magnetic measurements. Sarvas (36) and Ilmoniemi et al. (18) have given a relatively simple derivation for the result of the forward problem. An important point also shown by Sarvas (36) is that the radial component of the magnetic field of a tangential dipole depends on the source current and is independent of the volume current. Other components do depend on volume currents, although in principle they are derivable from the radial component. Approaches to this inverse problem have included making the simplistic assumption that only the radial component of the magnetic field is measured, in which case parameters of dipole location can once again be estimated from the dipole map. As demonstrated by Rose et al. (33), in certain brain regions the geometry of the skull and the placement of the magnetometer make it unlikely that only the radial component is measured, in which case one must take into account tangential components of the magnetic field as well. This, in turn, means incorporating volume current effects. The simple derivation given by Ilmoniemi et al. (18) allows easy solution of the forward problem, in which case this inverse problem reduces to a search for the parameters of the dipole that give the best agreement with measured data. The solution of the forward problem highlights the independence of the magnetic field from radial variation in conductivity. Some details of search methods and reliability of estimation are discussed by Sarvas (36).

3. *Dipolar source, nonhomogeneous spherical head.* Acceptance of a spherical head model still requires further treatment when dealing with the forward and inverse problems in EEG. In particular, there are multiple layers of tissue surrounding the brain, and their conductivities vary by as much as a factor of 70 (26). For magnetic measurements, we have noted that as long

as spherical symmetry holds, the magnetic field is independent of radial variation in conductivity; hence, multisphere models are not as important. In contrast, in EEG, solution of the forward and inverse problems depends (to a relatively large extent) on such a treatment and also requires reasonable estimates of the conductivities. Theoretical background for this is given by Sarvas (36), Nunez (26), and Stok (38) and will not be further discussed here except to note that if estimates of conductivity are made, the forward problem may be solved and again a least-squares search for best parameter estimates may be made for the inverse solution.

4. *Dipolar source, realistic head models.* These methods are still being perfected. In general, they rely on the use of imaging studies to define the surfaces of the various interfaces between regions of differing conductivity. In practice, the surfaces are divided into triangles, and the potential on the surfaces may be estimated by a finite element evaluation of the required surface integrals. The surface potentials may then be used to calculate the components of the volume current that contribute to the magnetic field, and finally a term is added for the dipole in an infinite homogeneous conductor. This computer-intensive calculation solves the forward problem for an arbitrary dipole; once again a minimizing search can be performed to attack the inverse problem, although this requires tremendous computing power. Descriptions of this technique are given by Hämäläinen and Sarvas (13), Stok et al. (37), and Meijs et al. (24,25). In the latter paper, some simulations are made and significant differences between the spherical model and the realistic model are shown.

Multiple Dipoles

The principle of superposition allows for the straightforward solution of the forward magnetic or electric problem for multiple dipoles; however, the inverse problem is limited by nonuniqueness. In model studies, several investigators have attempted to gain insight into the circumstances under which the MEG would be able to discriminate multiple dipoles from single dipoles. Thus, in a simulation study, Okada (30) used a statistical technique based on a calculated *F* ratio to establish lack of fit to a single-dipole model. Assuming a single-dipole solution (when in fact two dipoles are simulated), Okada (30) was able to estimate the distance and angular separation of the two simulated dipoles necessary before a single-dipole model would demonstrate lack of fit. With noise levels similar to actual experimental levels, lack of fit was apparent when the dipoles were 1–2 cm apart. As the angular separation of the dipoles increased, lack of fit was more apparent. Importantly, depth estimates based on the single-dipole model worsened as the dipole separation increased, and depth was generally overestimated. A similar simulation has been published by Hari et al. (14), who also considered variables relevant to the measuring apparatus. Nunez (28) has also demonstrated simulations in which the assumption of a single dipole (when, in fact, two are present) may also underestimate dipole depth. Barth et al. (1) have recently demonstrated a method of spatiotemporal analysis using multiple current dipoles which they have applied in several epileptic patients; this method holds promise for further development.

Multipole Treatment

Improvements in the MEG signal-to-noise ratio have opened opportunities to analyze the magnetic field with greater sophistication (8,20). Since the electrocardiogram and magnetocardiogram have much higher signal-to-noise ratios, some of these techniques have already been applied there. In 1958, Yeh et al. (47) described a theory for sources in a homogeneous sphere, with a demonstration that traditional electrocardiographic techniques are approximations of this general approach. This was recently reviewed by Katila and Karp (22) and by Titomir and Kneppo (41). There has also been some work on the multipolar nature of magnetic dust loads in lungs (39).

Generally, a distribution of currents will give rise to a field which can be expressed as a mathematical series. Wikswo and Swinney (44) provide a very general theory deriving and comparing various expansion series for approximately static fields. Among the most useful and elegant is the so-called scalar spherical harmonic series. The first term of the series, the monopole, is a linear term which has not been found to apply to magnetic fields. However, there are practical situations which arise that can approximate a magnetic monopole, and Ferguson and Durand (9) have recently suggested that there are mathematical simplifications inherent in monopoles which make them a good model for certain distributed current sources. The next three terms represent the dipole, which has been described above. The next set of terms represents the quadrupole, which falls off much faster with distance from the source than does the dipole. The series continues ad infinitum, with successive terms typically contributing less to the magnitude of the field. Katila and Karp (22) point out tongue-in-cheek that if too many terms are included, the number of coefficients will exceed the number of measured data and there will be no reduction. Usually the series is cut off after the quadrupole or octapole terms.

A mathematical advantage of including terms higher than the dipole terms is that the second criterion of well-posed inverses is more nearly met—namely, the solution is more nearly unique. However, the third criterion, stability, might become problematic. Small changes in the measured field due to noise have the potential to dramatically change the postulated multipole source.

A potential clinical advantage of the multipole technique is that a distinction can be made between sources that otherwise appear to reside in the same location. However, it is perhaps too soon for clinically relevant encephalographic distinctions to be found in the literature. A clinical disadvantage is the difficulty in thinking of a physiological basis for the multipoles, whereas a dipole arises naturally at the dendritic level and the cortical columnar level.

Distributed Sources

Distributed sources are the most flexible yet computer-intensive of the postulated causes. They are often called model-independent, because no particular geometry is assumed for the source.

Ilmoniemi et al. (18) presented the rationale:

> The inverse problem is easy to state: Calculate the primary current distribution in the brain from the magnetic field outside the head. The solution is not unique: an infinity of different current distributions can explain a given magnetic field. Which of these should we choose? . . . Our goal is to express the neuromagnetic data in the form of estimates of primary currents in the brain. The neuroscientist is not interested in multipole moments, equivalent current loops, not even in the magnetic field or the field gradient. These are mere tools in the determination of the location and other characteristics of brain activity. We present the inverse problem in the framework of estimation theory: from measured magnetic field values and some prior knowledge, we want to construct the best estimate for the primary current distribution.

They then go on to formalize the method. The basic idea is that the source is unknown but can be guessed. In particular, the source is considered to be an array of current elements. Then the measurements that such a guessed source would yield are compared to the actual measurements, and the guessed source is chosen to minimize the difference between the actual measurements and the measurements implied by the guessed source.

This method is very flexible, and various requirements can be imposed along with the minimization just described (21,36). For example, the postulated source should be biologically realistic: 20 ampere sources are unlikely in the human brain. And the sources should be constrained to lie within the volume of interest (6). Such modifications fit naturally into the distributed source methods.

These methods can also be computer-intensive, often requiring many hours of mainframe time, or access to parallel supercomputers (19).

Simulations have shown that the distributed source techniques are capable of revealing complex sources. Kullman et al. (23) and Kado et al. (21) demonstrated the reconstruction of a vortex source. Simulations by Clarke et al. (3) provide empirical evidence that the inferred distributed sources are unique; the inferred sources are resistant to tricks such as moving dipoles close together.

How do the distributed source techniques hold up in experimental conditions? Greenblatt et al. (11) found agreement between the distributed source solution and the dipole solution for the auditory evoked response to 500-Hz tone bursts. Kullmann et al. (23) used a saline phantom to demonstrate that the distributed source technique can distinguish dipoles 3 cm apart, whereas the dipole fit (by design) guesses just one at the midpoint.

An exciting application of the distributed source techniques is dynamic imaging. Ioannides et al. (19) have obtained dynamic images of the sources of the measured magnetic fields. For real data of visual evoked responses to reversing checkerboards, they found a rotating current density pattern.

The dynamic imaging of Ioannides et al. (19) also provides empirical evidence that the inferred distributed sources are stable. A source is inferred from a "snapshot" of a magnetic field configuration. Another source is inferred from a snapshot made a short time later. This process is repeated, with no input to the algorithm of the previous solutions. When the sequence of sources is viewed, the source appears to change smoothly. By definition, a stable solution is one that changes smoothly as the input is varied smoothly.

FUTURE DIRECTIONS

There are several lines of pursuit which appear important to develop further:

1. We have mentioned the attempts by several groups to use increasingly realistic head models based on data from imaging techniques such as MRI. The improvement in localization from such a treatment may justify the increased resources in terms of computer time necessary to utilize such techniques on a broad scale.
2. We have also mentioned ongoing work on more distributed sources. These techniques need to be refined and tested, and they probably are more realistic models of physiologic events than is the single-dipole model.
3. It is also quite important to attempt to utilize the information from both MEG and EEG together. Simplistic approaches such as independent localization utilizing each technique with subsequent averaging of estimated dipole locations are clearly suboptimal (38). A three-step approach has been suggested by Cohen and Cuffin (5) in which the MEG map is used in an inverse way to estimate dipole parameters of the tangential dipole; then a forward solution of surface potential is performed based on this first solution. This forward solution is subtracted from the EEG map to give a residual EEG map (presumably reflecting predominantly components of radial sources). An inverse solution is then performed on this EEG map to localize the radial sources. In principle, measurement of EEG and MEG give independent information about the electrical activity of the brain (4, 15), and techniques

which make optimal use of the differences need to be further developed.

4. Another area in which work needs to be pursued is in making use of the information available in the time dependencies of the signals. The signals from moment to moment have some relatedness, and this information may be useful in visualizing changes in source currents which may, in turn, improve our understanding of cerebral activity. In essence, what can be done is to incorporate some feedback into the inference algorithm. That is, the physiological state is as much a result of the previous state as it is of the input (16). This is called a "Markovian process," and although ignoring it has demonstrated the stability of some inference techniques, it will be important to incorporate this physiologically vital feature into future models.

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