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Non-Invasive Estimation of Local Field Potentials for Neuroprosthesis Control

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Abstract: Recent experiments have shown the possibility to use the brain electrical activity to directly control the movement of robots or prosthetic devices in real time. Such neuroprostheses can be invasive or non-invasive, depending on how the brain signals are recorded. In principle, invasive approaches will provide a more natural and flexible control of neuroprostheses, but their use in humans is debatable given the inherent medical risks. Non-invasive approaches mainly use scalp electroencephalogram (EEG) signals and their main disadvantage is that these signals represent the noisy spatiotemporal overlapping of activity arising from very diverse brain regions; i.e., a single scalp electrode picks up and mixes the temporal activity of myriads of neurons at very different brain areas. In order to combine the benefits of both approaches, we propose to rely on the non-invasive estimation of local field potentials (LFP) in the whole human brain from the scalp measured EEG data using a recently developed inverse solution (ELECTRA) to the EEG inverse problem. The goal of a linear inverse procedure is to de-convolve or un-mix the scalp signals attributing to each brain area its own temporal activity. To illustrate the advantage of this approach we compare, using identical set of spectral features, classification of rapid voluntary finger self-tapping with left and right hands based on scalp EEG and non-invasively estimated LFP on two subjects using different number of electrodes.

Keywords: Non-invasive neuroprosthesis, electroencephalogram, local field potentials, inverse solutions.

1. Introduction

Recent experiments have shown the possibility to use the brain electrical activity to directly control the movement of robots or prosthetic devices in real time (Wessberg *et al.*, 2000; Pfurtscheller and Neuper, 2001; Meeker *et al.*, 2002; Serruya *et al.*, 2002; Taylor *et al.*, 2002; Carmena *et al.*, 2003; Mehring *et al.*, 2003; Millán *et al.*, 2004). Such a kind of brain-controlled assistive system is a natural way to augment human capabilities by providing a new interaction link with the outside world. As such, it is particularly relevant as an aid for paralyzed humans, although it also opens up new possibilities in human-robot interaction for able-bodied people.

Initial demonstrations of the feasibility of controlling complex neuroprostheses have relied on intracranial electrodes implanted in the brain of monkeys (Wessberg *et al.*, 2000; Meeker *et al.*, 2002; Serruya *et al.*, 2002; Taylor *et al.*, 2002; Carmena *et al.*, 2003; Mehring *et al.*, 2003). In these experiments, one or more array of microelectrodes records the extracellular activity of single neurons (their spiking rate) in different areas of the cortex related to planning and execution of movements—motor, premotor and posterior parietal cortex. Then, from the real-time analysis of the activity of the neuronal population, it has been possible to predict either the animal's movement intention (Meeker *et al.*, 2002; Mehring *et al.*, 2003) or the monkey's hand trajectory (Wessberg *et al.*, 2000; Taylor *et al.*, 2002; Carmena *et al.*, 2003), and to drive a computer cursor to desired targets (Serruya *et al.*, 2002; Taylor *et al.*, 2002). The motivation for these invasive approaches is that it has been widely shown that motor parameters related to hand and arm movements are encoded in a distributed and redundant way by ensembles of neurons in the motor system of the brain (for a review see Schwartz *et al.*, 2001).

For humans, however, non-invasive methods based on electroencephalogram (EEG) signals are preferable because of ethical concerns and medical risks. The main source of the EEG—the brain electrical activity recorded from electrodes placed over the scalp—is the synchronous activity of thousands of cortical neurons. Thus, EEG signals suffer from a reduced spatial resolution and increased noise due to measurements on the scalp. As a consequence, current EEG-based brain-actuated devices are limited by a low channel capacity and are considered too slow for controlling rapid and complex sequences of movements. So far control tasks based on human EEG have been limited to simple exercises such as moving a computer cursor to the corners of the screen (Wolpaw and McFarland, 1994) or opening a hand orthosis (Pfurtscheller and Neuper, 2001). But recently Millán and coworkers (2004) have shown for the first time that asynchronous analysis of EEG signals is sufficient for humans to continuously control a mobile robot. Two human subjects learned to mentally drive the robot between rooms in a house-like environment using an EEG-based brain interface that recognized three mental states. Furthermore, mental control was only marginally worse than manual control on the same task. A key element of this brain-actuated robot is a suitable combination of intelligent robotics, asynchronous EEG analysis and machine learning that only requires the user to deliver high-level commands, which the robot performs autonomously, at any time[1].

Despite this latter demonstration of the feasibility of EEG-based neuroprostheses, it is still believed that only invasive approaches will provide natural and flexible control of robots (Nicolelis, 2001; Donoghue, 2002). The rationale is that surgically implanted arrays of electrodes will be required to properly record the brain signals because the non-invasive scalp-recordings with the EEG lack spatial resolution. However, recent advances in EEG analysis techniques have shown that the sources of the electric activity in the brain can be estimated from the surface signals with high spatial accuracy. We believe that such EEG source analysis techniques overcome the lack of spatial resolution and may lead to surface EEG-based neuroprostheses that parallel invasive ones.

The basic question addressed in this paper is the feasibility of non-invasive brain interfaces to reproduce the prediction properties of the invasive systems evaluated in animals while suppressing their risks. For doing that we propose the non-invasive estimation of local field potentials (LFP) in the whole human brain from the scalp measured EEG data using recently developed distributed linear inverse

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[1] This is possible because the operation of the brain interface is asynchronous and, unlike synchronous approaches (Wolpaw and McFarland, 1994; Birbaumer *et al.,* 1999; Donchin, *et al.,* 2000; Roberts and Penny, 2000; Pfurtscheller and Neuper, 2001), does not require waiting for external cues that arrive at a fixed pace of 4-10 s.

solution termed ELECTRA (Grave de Peralta Menendez *et al.*, 2000). The use of linear inversion procedures yields an on-line implementation of the method, a key aspect for real-time applications.

The development of a brain interface based on ELECTRA—i.e., non-invasive estimates of LFP—allows to apply methods identical to those used for EEG-based brain interfaces but with the advantage of targeting the activity at specific brain areas. In this respect our approach aims to parallel the invasive approaches described before that directly feeds intracranial signals into the classification stage of the brain interface, except that we calculate these intracranial signals from the surface EEG data. An additional advantage of our approach over scalp EEG is that the latter represents the noisy spatio-temporal overlapping of activity arising from very diverse brain regions; i.e., a single scalp electrode picks up and mixes the temporal activity of myriads of neurons at very different brain areas. Consequently, temporal and spectral features, which are probably specific to different parallel processes arising at different brain areas, are intermixed on the same recording. This certainly complicates the classification task by misleading even the most sophisticated analysis methods. For example, an electrode placed on the frontal midline picks up and mix activity related to different motor areas known to have different functional roles such as the primary motor cortex, supplementary motor areas, anterior cingulate cortex, and motor cingulate areas.

On the other hand, the proposed approach bears two main advantages over invasive approaches. Firstly, it avoids any ethical concern and the medical risks associated to intracranial electrocorticographic recordings in humans. Secondly, the quality of the signals directly recorded on the brain deteriorates over time requiring new surgical interventions and implants in order to keep the functionality of the device.

The feasibility of this non-invasive LFP approach is shown here in the analysis of single trials recorded during self-paced finger tapping with right and left hands. To illustrate the generalization of our approach and the influence of the number of electrodes, we report results obtained with two normal volunteers using 111 and 32 electrodes, respectively. The capability to predict and differentiate the laterality of the movement using scalp EEG is compared with that of LFP estimated using ELECTRA inverse solution.

2. METHODS

A. Data Recording

Two healthy right-handed young subjects (males, 30 and 32 years) completed a self-paced finger-tapping task. Subject were instructed to press at their own pace the left mouse button with the index finger of a given hand while fixating a white cross at the middle of the computer screen. The intervals between successive movements were rather stable for the two subjects, namely around 500 ms and 2000 ms for subjects 'A' and 'B', respectively. Subjects performed several sessions of the task with breaks of around 5-10 minutes in between.

The EEG was recorded at 1000 Hz from 111 scalp-electrodes (Electric Geodesic Inc. system, subject 'A') and at 512 Hz from 32 scalp-electrodes (Biosemi ActiveTwo system, subject 'B'). Head position was stabilized with a head and chin rest. In the first case (i.e., 111 electrodes) off-line processing of the scalp data consisted uniquely in the rejection of bad channels and their interpolation using a simple nearest neighbor's algorithm. This procedure was not necessary with the 32-electrode system. Since digitized electrode positions were not available, we used standard spherical positions and the 10-10 system. These positions were projected onto the scalp of the segmented average MNI brain[2].

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[2] This projection is based on the best fitting sphere with center and radius selected to fit the scalp region used by the electrodes. This method requires a careful positioning of the electrodes based on anatomical landmarks—i.e., vertex electrode (Cz), middle line, frontal electrodes (Fp) etc. Note that, due to the inaccuracies of boundary detection algorithms, there is no rigid transformation able to "land" a set of electrodes on the scalp detected from the MRI. For this reason, most landing procedures need, at some stage, to project electrode positions on the detected scalp. This procedure has been widely used and tested in clinical studies using standard EEG configurations (e.g., 10-20 and 10-10 systems) where subject's MRI is not available as well as in the construction of realistic head models for presurgical evaluation of epileptic patients. Still, minor differences between electrodes location might be expected from one session to another. These variations can be considered as noise in the data and its influence can be alleviated with regularization strategies.

The pace selected by the subjects allowed for the construction of trials aligned by the response consisting of 400 ms before key press. We recorded 680 trials of the left index tapping and 634 trials of the right index tapping for subject 'A', while for subject 'B' we recorded 140 left trials and 145 right trials. We did not apply any visual or automatic artifact rejection and so kept all trials for analysis[3].

B. Local Field Potentials Estimates from Scalp EEG Recordings

The electroencephalogram (EEG) measures the extracranial electric fields produced by neuronal activity within a living brain. When the positions and orientations of the active neurons in the brain are known, it is possible to calculate the patterns of electric potentials on the surface of the head produced by these sources. This process is called the forward problem. If instead the only available information is the measured pattern of electric potential on the scalp surface, then one is interested in determining the intracranial distribution of neural activity. This is called the inverse problem or the source localization problem, for which there is no unique solution. The only hope is that additional information can be used to constrain the infinite set of possible solutions to a single one. Depending on the additional information added, different inverse solutions—i.e., different reconstructions of neural activities with different properties—can be obtained (van Oosterom, 1991; Scherg, 1994).

Classical constraints used to solve the EEG inverse problem rely on considering the neural generators as current dipoles (Ilmoniemi, 1993). In this case the magnitude to estimate is the dipole model supposed to represent a current density vector that can be distributed over the whole gray matter mantle or confined to a single point. When the dipole is assumed to be confined to a single or few brain sites, the task is to solve a nonlinear optimization problem aimed to find simultaneously the position and dipolar model of the dipoles (Scherg, 1992; Mosher *et al.*, 1999). When the dipoles are distributed over a discrete set of solution points within the brain, the task is to find the magnitude of the dipolar model for each dipole

[3] After a visual a posteriori artifact check of the trials we found no evidence of muscular artifacts that could have contaminated one condition differently from the other.

leading to an underdetermined inverse problem which is usually solved by adding linear constraints such as minimum norm, etc. (Hamalainen and Ilmoniemi, 1994; Grave de Peralta-Menendez and Gonzalez Andino, 1998). In both approaches, single dipoles or distributed dipoles, the magnitude to be estimated is a vector field commonly termed the current density vector. However, in the second approach that considers distributed models, the values of the current density vector are obtained for the whole gray matter akin to the tomographic images produced by other modalities of functional neuroimaging (fMRI, PET or SPECT) but with temporal resolution in the order of milliseconds.

A change in the formulation of the EEG inverse problem takes place when the fact that neurophysiological currents are ohmic and can therefore be expressed as gradients of potential fields is included as constraint in the formalism of the problem (Grave de Peralta Menendez *et al.*, 2000). With this neurophysiological constraint we can reformulate the EEG inverse problem in more restrictive terms, providing the basis for the non-invasive estimation of intracranial local field potentials (a scalar field) instead of the current density vector (a 3D vector field) (Grave de Peralta Menendez *et al.*, 2004). This solution is termed ELECTRA.

ELECTRA can be intuitively described as the non-invasive estimation of local field potentials by means of virtual intracranial electrodes. The advantages of this method are:

1. mathematical simplicity and computational efficiency compared to models based on current density estimation, since the number of unknowns estimated by the inverse model is three-fold fewer—i.e., the unknowns decrease from a vector field to a scalar field;
2. contrary to dipolar models, distributed linear solutions provide simultaneous temporal estimates for all brain areas not being confined to a few sites;
3. the temporal reconstructions provided by linear distributed inverse solutions are better than those of discrete spatiotemporal models or L1 based reconstructions (Liu *et al.,* 1998). A few comparisons with intracranial data are also extremely appealing, suggesting systematically that temporal reconstructions of the generators are more reliable than their spatial counterparts;
4. since these are linear methods, computation of the intracranial estimates reduces to a simple

inverse matrix by vector product, which warrants efficient on-line implementation.

The analysis that follows relies on the estimation for each single trial of the 3D distribution of the Local Field Potentials using ELECTRA source model. The head model, relating intracranial sources to scalp measurements, was derived from the Montreal Neurological Institute average brain. The LFP were then estimated at 4024 pixels distributed on a six millimeters regular grid restricted to the gray matter of the brain model.

C. Statistical Classifier

The different mental tasks are recognized by a Gaussian classifier trained to classify samples (single trials) as class "left" or "right" (Millán *et al.*, 2002b, 2004). The output of this statistical classifier is an estimation of the posterior class probability distribution for a sample; i.e., the probability that a given single trial belongs either to class "left" or class "right".

In this statistical classifier, every Gaussian unit represents a prototype of one of the mental tasks (or classes) to be recognized. We use several prototypes per mental task. We assume that the class-conditional probability density function of class C_k is a superposition of N_k Gaussians (or prototypes) and that classes have equal prior probabilities. In our case, all the classes have the same number of prototypes. In addition, we assume that all prototypes have an equal weight of $1/N_k$. The challenge is to find the appropriate position of the Gaussian prototype as well as an appropriate variance.

Usually, each prototype of a given class C_k has its own covariance matrix Σ_k^i. In our case, in order to reduce the number of parameters, we restrict our model to a diagonal covariance matrix Σ_k that is common to all the prototypes of the class C_k.

To initialize the center of the prototypes, μ_k^i, of the class C_k we run a clustering algorithm—typically, self-organizing maps (Kohonen, 1997). We then initialize the diagonal covariance matrix by setting

$$(\Sigma_k)_{mm} = \frac{1}{|S_k|} \sum_{n \in S_k} \left(x^n - \mu_k^{i^*(n)} \right)_m^2 \tag{1}$$

where S_k denotes the set of indexes of samples belonging to the class C_k, $|S_k|$ is the cardinality of this set, $i^*(n)$ is the nearest prototype of this class to the sample x^n, and $\mu_k^{i^*(n)}$ is its center. The index *m* denotes the element of a vector, and *mm* the diagonal element of a matrix.

During learning we improve these initial estimations iteratively by stochastic gradient descent so as to minimize the mean square error $E = \frac{1}{2}\sum_j (y_j - t_j)^2$, where t_j is the jth component of the target vector in the form *1-of-c*; e.g., the target vector for class "left" is coded as (0,1).

After updating μ_k^i and Σ_k^i for a given training sample, the covariance matrices of all the prototypes of the same class are averaged to obtain the common class covariance matrix Σ_k. This simple operation leads to better performance than if separate covariance matrices are kept for each individual prototype. It is also worth noting that given the relatively low number of parameters of the covariance matrices to be estimated, as compared to when we use the full matrices, usual regularization techniques (e.g., Hastie *et al.*, 2001) do not improve performance. The interpretation of this rule is that, during training, the centers of the Gaussians are pulled towards the samples of the mental task they represent and are pushed away from samples of other task.

D. Feature Extraction

To test the capability of our LFP approach to discriminate between left and right finger movements, we have done a 10-fold cross-validation study and also have compared the performance of the LFP-based classifier to an EEG-based classifier.

In the case of using scalp EEG signals, each single trial of 400 ms of raw EEG potentials is first spatially filtered by means of a common average reference method (removal of the average activity over all the electrodes). Spatial filtering yields new potentials that represent better the cortical activity due only to local sources below the electrodes. The superiority of this kind of transformed potentials over raw potentials for the operation of a brain interface has been demonstrated in different studies (e.g., Babiloni *et al.*, 2000). Then the power spectral density (PSD) in the band 8-30 Hz was estimated for the 10 channels CPz, Pz, FC3, FC4, C3, C4, CP3, CP4, P3, P4, which cover the motor cortex bilaterally. We have successfully used these PSD features in previous experiments (Millán *et al.*,2002b, 2004). In particular, we have computed the PSD using modern multitaper methods (Thomson, 1982). These methods have shown to be particularly well suited for spectral analysis of short segments of noisy data, and have been successfully applied to the analysis of neuronal recordings in behaving animals (e.g., Pesaran *et al.*,2002). Specifically, the PSD was estimated using 7 Slepian data tapers.

In the case of the classifier based on the estimated LFP, we have also computed the PSD in the band 8-30 Hz using multitaper methods with 7 Slepian data tapers. The PSD was estimated for each single trial of 400 ms on the 50 most relevant pixels (out of 4024) as selected by a feature selection algorithm that is a variant of the so-called Relief method (Kira and Rendell, 1992). Relief has been successfully applied to the selection of relevant spectral features for the classification of EEG signals (Millán *et al.*,2002a). Feature selection was only applied to the estimated LFP because of the large number of potential pixels that can be fed to the classifier. In the case of scalp EEG, it has been widely shown that only channels over the motor cortex suffice for good recognition of bimanual movements. Also, feature selection was done on the training set of each cross-validation step.

3. RESULTS

Table 1 shows the results of this comparative study based, as explained before, in a 10-fold cross-validation using the Gaussian classifier. This means that all the available single trials of each class are split in 10 different subsets, and then we take 9 of them to train the classifier and the remaining for testing the generalization capabilities. This process is repeated 10 times to get an average of the performance of the classifier based on PSD features computed either on surface EEG or non-invasive estimates of LFP.

Classification based on surface EEG achieves error rates similar to previous studies (11% on average for the two subjects), and that despite the short time windows used to estimate the PSD, namely 400 ms. In particular, performance is worse for subject ‘A’ than for subject ‘B’ (11.6% vs. 10.5%), what illustrates the difficulty of recognizing rapid motor decisions (500 ms tapping pace vs. 2000 ms) based on short segments of brain electrical activity.

On the contrary, the performance of the Gaussian classifier based on non-invasive LFP is extremely good as it only makes 3.7% and 4.9% errors for subjects 'A' and 'B', respectively. These performances are 3 times and twice better than when using surface EEG features, respectively. This clearly shows the advantage of using non-invasive estimations of LFP over surface EEG. This is particularly the case for subject 'A' for whom we recorded from 111 electrodes. In addition, it is also worth noting that performance is still very good for subject 'B' even if the LFP were estimated from only 32 scalp electrodes.

Table 1. Error rates in the recognition of "left" versus "right" finger movements made by a Gaussian classifier based on PSD features computed either on surface EEG or non-invasive LFP using the multitaper method for subjects 'A' and 'B'. Results are the average of a 10-fold cross-validation study.

	Subject	
Method	*'A'*	*'B'*
EEG - Multitaper	11.6%	10.5%
LFP - Multitaper	3.7%	4.9%

Regarding the spatial distribution of the pixels selected by the feature selection algorithm, they form clusters located on the frontal cortex with tendency to have the most relevant ones at the dorso-lateral premotor cortex and including different frequency values. Altogether, these results suggest that the prediction capabilities of brain interfaces based on non-invasive estimations of LFP might parallel those of invasive approaches.

4. DISCUSSION

The goal of a linear inverse procedure is to de-convolve or un-mix the scalp signals attributing to each brain area its own temporal activity. By targeting on the particular temporal/spectral features at specific brain areas we can select a low number of features that capture information related to the state of the individual in a way that is relatively invariant to time. Eventually, this may avoid long training periods and increase the reliability and efficiency of the classifiers. For the case of paralyzed patients the classification stage can be improved by focusing on the specific brain areas known to participate and code the different steps of voluntary or imagined motor action trough temporal and spectral features.

Distributed inverse solutions, as any other inverse method, suffer from limitations inherent to the ill-posed nature of the problem. The limitations of these methods have been already described (Grave de Peralta-Menendez and Gonzalez Andino, 1998) and concern basically: 1) errors on the estimation of the sources amplitudes for the instantaneous maps and 2) inherent blurring, i.e., the spatial extent of the actual source is usually overestimated. However, several theoretical and experimental studies showed that spectral and temporal features are quite well preserved by these methods (Grave de Peralta Menendez *et al.*, 2000) that surpass non linear and dipolar methods (Liu *et al.*, 1998). The analysis strategy selected in our research plan relies on temporal and spectral features disregarding estimated amplitudes so as to alleviate these limitations.

Finally, since the head model is stable for the same subject over time, the inverse matrix requires to be computed only once for each subject and is invariant over recording sessions. On-line estimation of intracranial field potentials is reduced to a simple inverse-matrix-by-data-product, which yields an on-line implementation, a key aspect for real-time applications. However, despite a careful positioning of the electrodes and the regularization used to deal with the noise associated to electrode misplacement, the estimated activity might still result displaced to a neighbor location out of the strict boundaries defined in anatomical atlas. This could happen because of the differences between the subject head and the average MNI head model or due to the differences in electrode locations from one session to another. Based on the results of the extensive studies of pre-surgical evaluation of epileptic patients, we should expect low errors using realistic head models based on subject's MRI. However, since pre-surgical studies barely use more than one EEG recording session, the second source of error requires further study.

Regarding the possibility of using biophysically-constrained inverse solutions for the control of neuroprostheses, the results reported in this paper are highly encouraging. They suggest that recognition of motor intents is possible from non-averaged inverse solutions and are even superior to systems based on scalp EEG. This could be the basis of the non-invasive brain-computer interface put forward by Grave de Peralta Menendez and coworkers (2003) allowing for a real-time anticipation of the direction of the upcoming movements. While such anticipation is possible from invasive recordings from neuronal populations in the motor cortex of monkeys (Carmena *et al.*, 2003) as well as from local field potentials recorded from the motor cortex of monkeys (Mehring *et al.*, 2003), the possibility of doing the same non-invasively is appealing for its much higher potential with humans. Finally, the use of non-invasive estimations of local field potentials at specific brain areas allows for the replacement of most of the empirical features used in classical EEG-based brain interfaces by features with a priori established neurophysiological information.

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