Estimation of the Cortical Connectivity by High-Resolution EEG and Structural Equation Modeling: Simulations and Application to Finger Tapping Data

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Abstract—Today, the concept of brain connectivity plays a central role in the neuroscience. While functional connectivity is defined as the temporal coherence between the activities of different brain areas, the effective connectivity is defined as the simplest brain circuit that would produce the same temporal relationship as observed experimentally between cortical sites. The most used method to estimate effective connectivity in neuroscience is the structural equation modeling (SEM), typically used on data related to the brain hemodynamic behavior. However, the use of hemodynamic measures limits the temporal resolution on which the brain process can be followed. The present research proposes the use of the SEM approach on the cortical waveforms estimated from the high-resolution EEG data, which exhibits a good spatial resolution and a higher temporal resolution than hemodynamic measures. We performed a simulation study, in which different main factors were systematically manipulated in the generation of test signals, and the errors in the estimated connectivity were evaluated by the analysis of variance (ANOVA). Such factors were the signal-to-noise ratio and the duration of the simulated cortical activity. Since SEM technique is based on the use of a model formulated on the basis of anatomical and physiological constraints, different experimental conditions were analyzed, in order to evaluate the effect of errors made in the a priori model formulation on its performances. The feasibility of the proposed approach has been shown in a human study using high-resolution EEG recordings related to finger tapping movements.

Index Terms—Finger tapping movement, high-resolution EEG, structural equation modeling.

I. INTRODUCTION

CHARACTERIZING brain activity in terms of the functional specialization of brain areas can provide only a limited account of the neuronal basis of the underlying processes. Thus, the necessity to describe how different brain areas communicate with each other is gaining more and more importance in neuroscience. The concept of brain connectivity plays a central role, made possible by the increase of noninvasive brain imaging methods [like functional magnetic resonance imaging (fMRI); high-resolution electroencephalography (EEG), or magnetoencephalography (MEG)] that return information about the brain activation during a motor or cognitive task. Two main definitions of brain connectivity have been proposed: the functional and the effective connectivity [1], [2]. While functional connectivity is defined as temporal correlation between spatially remote neurophysiological events [3], the effective connectivity is defined as the simplest brain circuit that would produce the same temporal relationship as observed experimentally between cortical sites [1]. Several computational methods have been proposed to estimate how different brain areas are working together during motor and cognitive tasks by using EEG and fMRI data [4]–[7]. Such methods typically involve the estimation of some covariance properties between the different time series measured from the different spatial sites during the tasks. The estimation returned information about the so-called functional connectivity. On the other hand, structural equation modeling (SEM) is a technique that has been used for a decade to assess effective connectivity between cortical areas in humans by using hemodynamic measurements [8]–[10]. The basic idea of SEM differs from the usual statistical approach of modeling individual observations, since

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SEM considers the covariance structure of the data [8]. So far, this technique has been applied to the estimation of connectivity based on functional imaging data, such as functional Magnetic Resonance Imaging [11], [12] or positron emission tomography [13]. However, the estimation of cortical effective connectivity obtained with the application of the SEM technique on fMRI data has a low temporal resolution (on the order of 10 s) which is far from the time scale at which the brain operates normally. Hence, it is of interest to understand if the SEM technique could be applied to the estimation of cortical activity, as obtained by the application of linear inverse techniques to the high-resolution EEG data [5],[14]–[16]. In this way, it would be possible to study time-varying patterns of brain connectivity, linked to the different parts of the experimental task studied. The importance of SEM technique in the modeling of brain connectivity with respect to the other available techniques of functional connectivity already available for EEG data lies in the possibility to use the a priori information provided by the physical connections furnished by the brain anatomy. The SEM technique merges the anatomical (constrained) model obtained by previous knowledge and the inter-regional covariances of measured brain activity data. The resulting functional model represents the influence of regions on each other through the putative anatomical connections.

Since, to our knowledge, this is the first attempt to apply this technique to the cortical data obtained by high-resolution EEG methods, we first explored the behavior of the SEM technique under different conditions that affects the EEG recordings, mainly the signal-to-noise ratio (factor SNR) and the length of the recordings (factor LENGTH). This was done by designing and implementing a simulation study. In particular, the questions being addressed in the present simulation study are as follows.

1) What is the influence of a variable SNR level imposed on the high-resolution EEG data on the accuracy of the pattern connectivity estimation obtained by SEM?
2) What is the amount of high-resolution EEG data necessary to get a usable accuracy of the estimation of connectivity between cortical areas?
3) How are SEM performances degraded by an imprecise anatomical model formulation? In other words, is this method able to perform a good estimation of connectivity pattern when connections between the cortical areas are not correctly assumed? Which kind of error should be possibly avoided?

In order to answer these questions, we used simulated models with built-in connectivity patterns involving four cortical areas. The estimation process retrieved the cortical connections between the areas under different experimental conditions (variable SNR and signal duration). The connectivity patterns estimated by the SEM technique were compared with those imposed on the simulated signals, and different error measures were then subjected to a statistical multivariate analysis.

Subsequently, we applied the SEM technique to the cortical estimates obtained from high-resolution EEG data related to a simple finger tapping experiment in humans, in order to underline the capability of the proposed methodology to draw patterns of cortical connectivity between brain areas during a simple motor task.

II. METHODS

A. Structural Equation Modeling (SEM)

In SEM, the parameters are estimated by minimizing the difference between the observed covariances and those implied by a structural or path model. In terms of neural systems, a measure of covariance represents the degree to which the activities of two or more regions are related.

The Structural Equation Model consists of a set of linear structural equations containing observed variables and parameters defining causal relationships among the variables. Variables in the equation system can be endogenous (i.e., dependent from the other variables in the model) or exogenous (independent from the model itself). The structural equation model specifies the causal relationship among the variables, describes the causal effects and assigns the explained and the unexplained variance.

Let us consider a set of variables (expressed as deviations from their means) with N observations. In this study, these variables represent the activity estimated in each cortical region, obtained with the procedures described in the following section.

The structural equation model for these variables is the following:

\[ y = Bx + \Gamma x + \zeta \]  

(2.1)

where

- \( y \) is an \((m \times 1)\) vector of dependent (endogenous) variables;
- \( x \) is an \((n \times 1)\) vector of independent (exogenous) variables;
- \( \zeta \) is an \((m \times 1)\) vector of equation errors (random disturbances);
- \( B \) is a \((m \times n)\) matrix of coefficients of the endogenous variables;
- \( \Gamma \) is a \((m \times n)\) matrix of coefficients of the exogenous variables.

\( \zeta \) is assumed to be uncorrelated with the exogenous variables, and \( B \) is supposed to have zeros in its diagonal (i.e., an endogenous variable does not influence itself) and to satisfy the assumption that \((I - B)\) is nonsingular, where \( I \) is the identity matrix.

The covariance matrices of this model are the following:

- \( \Phi = E[xx^T] \) is the \((n \times n)\) covariance matrix of the endogenous variables;
- \( \Psi = E[\zeta \zeta^T] \) is the \((m \times m)\) covariance matrix of the errors.

If \( z \) is a vector containing all the \( p = m + n \) variables, endogenous and exogenous, in the following order:

\[ z^T = [x_1 \ldots x_n y_1 \ldots y_m] \]  

(2.2)

the observed covariances can be expressed as

\[ \Sigma_{obs} = (1/(N - 1)) \cdot Z \cdot Z^T \]  

(2.3)

where \( Z \) is the \( p \times N \) matrix of the \( p \) observed variables for \( N \) observations.

The covariance matrix implied by the model can be obtained as follows:

\[ \Sigma_{mod} \]  

(2.4)

where

\[ E[yy^T] = E[(I - B)^{-1}(x + \zeta)(x + \zeta)^T(I - B)^{-1}] \]  

(2.5)
since the errors $\zeta$ are not correlated with the $x$

$$E[x \zeta^T] = \Phi$$  \hspace{1cm} (2.6)
$$E[x y^T] = ((I - B)^{-1} \Gamma \Phi)^T$$  \hspace{1cm} (2.7)
$$E[y x^T] = (I - B)^{-1} \Gamma \Phi$$  \hspace{1cm} (2.8)

since $\Sigma_{\text{mod}}$ is symmetric.

The resulting covariance matrix, in terms of the model parameters, is the following:

$$\Sigma_{\text{mod}} = \begin{bmatrix}
\Phi & (I - B)^{-1} \Gamma \Phi^T \\
(I - B)^{-1} \Gamma \Phi^T & (I - B)^{-1} (\Gamma \Phi^T + \Psi)(I - B)^{-1} \Gamma \Phi^T
\end{bmatrix}.$$  \hspace{1cm} (2.9)

Without other constraints, the problem of the minimization of the differences between the observed covariances and those implied by the model is underdetermined, because the number of variables (elements of matrices $B$, $\Gamma$, $\Psi$, and $\Phi$) is greater than the number of equations $(m + n)(m + n + 1)/2$. For this reason, the SEM technique is based on the a priori formulation of a model, on the basis of anatomical and physiological constraints. This model implies the existence of just some causal relationships among variables, represented by arcs in a “path” diagram; all the parameters related to arcs not present in the hypothesized model are forced to zero. For this reason, all the parameters to be estimated are called free parameters. If $t$ is the number of free parameters, it must be $t \leq (m + n)(m + n + 1)/2$.

These parameters are estimated by minimizing a function of the observed and implied covariance matrices. The most widely used objective function for SEM is the maximum-likelihood (ML) function

$$F_{\text{ML}} = \log|\Sigma_{\text{mod}}| + \text{tr}(\Sigma_{\text{obs}}^{-1} \Sigma_{\text{mod}}^{-1}) - \log|\Sigma_{\text{obs}}| - p$$  \hspace{1cm} (2.10)

where $\text{tr}(\cdot)$ is the trace of matrix. In the context of multivariate, normally distributed variables the minimum of the ML function, multiplied by $(N - 1)$, follows a $\chi^2$ distribution with $p(p + 1)/2 - t$ degrees of freedom, where $t$ is the number of parameters to be estimated and $p$ is the total number of observed variables (endogenous + exogenous). The $\chi^2$ statistic test can then be used to infer statistical significance of the structural equation model obtained. In the present study, the publicly available software LISREL [17] was used for the implementation of the SEM technique.

**B. Computer Simulation**

We adopted an experimental design that analyzes the recovery of the connectivity of an estimated model with respect to an imposed one. This has been built under different levels of main factors SNR and LENGTH, as they have been imposed during the generation of a set of test signals, simulating cortical average activations and obtained starting from actual cortical data (estimated with the high-resolution EEG procedures already available at the High-Resolution EEG Laboratory at the University of Rome “La Sapienza”).

1) Signal Generation: Different sets of test signals have been generated in order to fit an imposed connectivity pattern [shown in Figs. 1(A), 2(A), 4(A)] and to respect imposed levels of temporal duration (LENGTH) and signal to noise ratio (SNR). In the following, in order to use a more compact notation, signals have been represented with the $z$ vector defined in (2.2), containing both the endogenous and the exogenous variables.

Channel $z_1$ is a reference source waveform, estimated from a high-resolution EEG (128 electrodes) recording in a healthy subject, during the execution of unaimed self-paced movements of the right finger.

Signals $z_2$, $z_3$, and $z_4$ were obtained by contribution of signals from all other channels, with an amplitude variation, plus zero mean uncorrelated white noise processes with appropriate variances, as shown in the following:

$$z = A \ast z + W$$  \hspace{1cm} (2.11)
is the \( n \)-th element of the vector \( \mathbf{a} \).

\( \mathbf{b} \) stands for the generic \( \beta \) parameter of the model.

Let \( B \) be the \( 4 \times 4 \) statistical significance matrix for the \( \beta \) parameters, where \( B_{ij} \) represents the statistical significance of the difference between the \( i \)-th estimated parameter and the \( j \)-th imposed parameter.

The ANOVA performed on the error committed on the arc \( a_{ij} \) (Single Arc Error) is shown in Fig. 2 (C): the means with respect to signal length are 190 or 310 s (25 or 40 trials, 7.5 s per trial). Duncan post-hoc test (Duncan at 5%) shows statistically significant differences between a signal length of 190 or 310 s (25 or 40 trials, 7.5 s per trial). (D) Plot of means with respect to SNR. A statistical influence of factor SNR on the error in the evaluation of the presence of the arc \( a_{ij} \). Duncan post-hoc test (5%) points out that there is no statistically significant difference between levels 3, 5, 10, and 100 of factor SNR.

Fig. 2. (A) Connectivity pattern imposed in the generation of simulated signals. Values on the arcs represent the connections strength (\( a_{21} = 1.4; a_{31} = 1.1; a_{22} = 0.5; a_{43} = 1.2 \)). (B) Connectivity model used for the parameter estimation. Results of ANOVA performed on the error committed on the arc in excess \( a_{ij} \) (Single Arc Error): (C) plot of means with respect to signal length as a function of time (seconds). ANOVA shows a high statistical significance of factor LENGTH (\( F = 9.7, 3.2, p < 0.0001 \)). Post-hoc test (Duncan at 5%) shows statistically significant differences between a signal length of 190 or 310 s (25 or 40 trials, 7.5 s per trial). (D) Plot of means with respect to SNR. A statistical influence of factor SNR on the error in the evaluation of the presence of the arc \( a_{ij} \) is shown (\( F = 7.75, p < 0.0001 \)). Duncan post-hoc test (5%) points out that there is no statistically significant difference between levels 3, 5, 10, and 100 of factor SNR.

where \( \mathbf{z}[n] \) is the \([4 \times 1]\) vector of signals, \( \mathbf{W}[n] \) is the \([4 \times 1]\) noise vector and \( \mathbf{A} \) is the \([4 \times 4]\) parameters matrix obtained from the \( \Gamma \) and \( \mathbf{B} \) matrices in the following way:

\[
\mathbf{A} = \begin{bmatrix}
1 & 0 & 0 & 0 \\
\gamma_1 & \beta_{11} & \beta_{12} & \beta_{13} \\
\gamma_2 & \beta_{21} & \beta_{22} & \beta_{23} \\
\gamma_3 & \beta_{31} & \beta_{32} & \beta_{33} \\
\end{bmatrix} = \begin{bmatrix}
a_{11} & \cdots & a_{14} \\
\vdots & \ddots & \vdots \\
a_{41} & \cdots & a_{44}
\end{bmatrix}
\]

\( \gamma_i \) stands for the generic \((i,j)\) element of the \( \Gamma \) matrix and \( \gamma_i \) is the \( i \)-th element of the vector \( \Gamma \).

All procedures of signal generation were repeated under the following conditions:

- **SNR factors** levels = \([1, 3, 5, 10, 100] \):
- **LENGTH factors** levels = \([60, 190, 310, 610] \) s. This corresponds, for instance, to \([120, 380, 620, 1220] \) EEG epochs, each of which is 500 ms long.

It is worth noticing that the levels chosen for both SNR and LENGTH factors cover the typical range for the cortical activity estimated with high-resolution EEG techniques.

2) Parameter Estimation: The set of simulated signals generated as described above has been given as input to the program LISREL for the estimation of SEM parameters. As mentioned in the methods section, SEM needs a model, based on previous information on the anatomical connections, on which the estimate is successively performed. For this reason, its performance has been observed in different situations, when connections between the four cortical areas are not always correctly assumed. The situations analyzed are as follows:

a) an identical connectivity graph between the generated and the estimated model;

b) a different number of connectivity arcs between the generated and the estimated model; in particular, we analyzed the case of an arc in excess and of an arc missing in the estimated model with respect to the generated one;

c) the same number of connectivity arcs between generated and estimated models, but with an ambiguity on its orientation.

3) Performance Evaluation: In order to evaluate the quality of the performed estimation, the following indexes were computed.

a) The Frobenius norm of the matrix reporting the differences between the values of the estimated (via SEM) and the imposed connections (Relative Error)

\[
E_{\text{relative}} = \frac{\sqrt{\sum_{k=1}^{m} \sum_{j=1}^{n} (a_{ij} - \hat{a}_{ij})^2}}{\sqrt{\sum_{k=1}^{m} \sum_{j=1}^{n} (a_{ij})^2}}.
\]

b) The absolute value of the difference between the estimated parameter and the imposed value on a single particular arc (Single Arc Error)

\[
E_{\text{sing}} = |a_{ij} - \hat{a}_{ij}|.
\]

Simulations were performed by repeating for 50 runs for each connectivity estimation obtained by SEM, in order to increase the robustness of the successive statistical analysis.

4) Statistical Analysis: The results obtained were subjected to separate analysis of variance (ANOVA). The main factors of the ANOVA were the SNR (with five levels: 1, 3, 5, 10, 100) and the LENGTH (with four levels: 60, 190, 310, 610 s). Separate ANOVAs were performed on the error indexes adopted (Relative Error, Single Arc Error). In all the evaluated ANOVAs, the correction of Greenhouse-Geisser for the violation of the spherical hypothesis was used. The post-hoc analysis with the Duncan test at the \( p = 0.05 \) statistical significance level was then performed.

C. High-Resolution EEG Recordings

The estimation of connectivity patterns by using SEM on high-resolution EEG recordings has been applied to the analysis of a simple movement task. In particular, we considered the right
hand finger tapping movement, externally paced by a visual
stimulus. This task was chosen for it has been very well studied
in literature with different brain imaging techniques like EEG or
functional Magnetic Resonance Imaging [4], [7]. The anatom-
ical model employed is based on the principal cortical areas
recognized as active during this simple task in these studies.
Namely, cortical areas used in this human study included the
prefrontal areas (PF), including at large the Brodmann areas 8,
9, and 46; the premotor areas (PM), including the Brodmann
area 6, the sensorimotor areas (SM) including the Brodmann
areas 4, 3, 2, and 1, and the parietal areas (P), generated by the
union of the Brodmann areas 5 and 7. The model employed the
a priori knowledge of the flow of connections between these
macro-areas, as derived from neuroanatomy and fMRI studies.
In particular, information flow were hypothesized to exist from
the parietal (P) areas toward the sensorimotor (SM), the pre-
motor (PM), and the prefrontal (PF) ones [4], [6], [7].

Event related potential (ERP) data were recorded with 96
electrodes on a group of three healthy subjects at the Univer-
sity of Illinois at Chicago. ERP data were recorded with a left
ear reference and submitted to the artifact removal processing.
Six hundred trials of 600 ms of duration were acquired. The
Magnetic Resonance Images of each subject’s head were also
acquired at the University of Illinois at Chicago. Such images
were used for the construction of the realistic head model for
each analyzed subject. Such realistic models are necessary for
the estimation of the cortical activity in the appropriate region
of interest (ROI) by using the linear inverse procedure algorithms
from the scalp recorded ERP data [18]–[20]. The time varying
power spectral values of the estimated cortical activity in the
theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) frequency
bands were also computed in each ROI employed. The cortical
waveforms were then used for the estimation of the connectivity
pattern by using the SEM. We divided the analysis period of
the analyzed ERP recordings into two phases. The first one, la-
beled as “PRE”, considers the 300 ms before the onset of the
electromyographic (EMG) trigger of the finger extension before
the tap, and it is intended as a generic preparation period. The
second phase includes the 300 ms after the EMG trigger up to
the end of ERP recording of a single trial and it is intended to
give results about the arrival of the somatosensory feedback, and
it will labeled “POST” in the following.

D. Estimation of Cortical Source Current Density

The solution of the following linear system:

\[ I_z = d + n \]  

(2.15)

provides an estimate of the dipole source configuration \( z \)
that generates the measured EEG potential distribution \( d \).
The system includes also the measurement noise \( n \), supposed
normally distributed.

In (2.15), \( I \) is the lead field or the forward transmission ma-
trix, in which each \( j \)th column describes the potential distribu-
tion generated on the scalp electrodes by the \( j \)th unitary dipole.
The current density solution vector \( \xi \) was obtained as follows
[21]:

\[ \xi = \arg \min_z \left( ||I_z - d||_M^2 + \lambda ||z||_N^2 \right) \]  

(2.16)

where \( M, N \) are the matrices associated to the metrics of the
data and of the source space, respectively, \( \lambda \) is the regularization
parameter, and \( ||z||_M \) represents the \( M \) norm of the vector \( z \).
The solution of (2.16) is given by the inverse operator \( G \) as follows:

\[ \xi = Ge, \quad G = N^{-1}L'(LN^{-1}L' + \lambda M^{-1}-1) \]  

(2.17)

An optimal regularization of this linear system was obtained
by the L-curve approach [22], [23]. As a metric in the data space
we used the identity matrix, while as a norm in the source space
we use the following metric:

\[ (N^{-1})_{ii} = ||L_{ii}||^{-2} \]  

(2.18)

where \((N^{-1})_{ii}\) is the \( i \)th element of the inverse of the diagonal
matrix \( N \) and all the other matrix elements \( N_{ij} \), for each \( i \neq j \),
are set to 0. The \( L_2 \) norm of the \( i \)th column of the lead field
matrix \( L \) is denoted by \( ||L_{ii}|| \).

By using the relations described above, at each time point of
the gathered ERP data an estimate of the signed magnitude of
the dipolar moment for each of the 5 000 cortical dipoles was
obtained. In fact, since the orientation of the dipole was already
defined to be perpendicular to the local cortical surface of the
model, the estimation process returned a scalar rather than a
vector field. In order to obtain the cortical current waveforms
for all the time points of the recorded EEG time series, we used
a unique “quasioptimal” regularization \( \lambda \) value for all the ana-
alyzed EEG potential distributions. Such quasi-optimal regular-
ization value was computed as an average of the several \( \lambda \) values
obtained by solving the linear inverse problem for a series of
EEG potential distributions. These distributions are character-
ized by an average Global Field Power (GFP) with respect to the
higher and lower GFP values obtained during all the recorded
waveforms. The instantaneous average of the dipole’s signed
magnitude belonging to a particular ROI generates the represen-
tative time value of the cortical activity in that given ROI.
By iterating this procedure on all the time instants of the gath-
ered ERP, the cortical ROI current density waveforms were
obtained and they could be taken as representative of the average
activity of the ROI, during the task performed by the experi-
mental subjects. These waveforms could then be subjected to
the SEM processing in order to estimate the connectivity pattern
between ROIs, by taking into account the time-varying increase
or decrease of the power spectra in the frequency bands of in-
terest. Here, we present the results obtained for the connectivity
pattern in the alpha band (8–12 Hz), since the ERP data related
to the movement preparation and execution are particularly re-
ponsive in such frequency interval (for review, see [24]).

III. RESULTS

A. Computer Simulation Results

1) Correct Formulation of the Connectivity Model: The
first situation analyzed is shown in Fig. 1. A set of signals was
generated as described in the previous section, in order to fit
the connectivity pattern shown in Fig. 1(A). Parameters were
estimated on the model shown in Fig. 1(B), which has exactly the
same structure of Fig. 1(A). We are thus testing the goodness of
the estimation of model parameters via SEM when no errors are
made in the model assumption phase. The appropriate index for
this analysis is the Relative Error, as defined in Section II (2.13). It was computed for each of the 50 runs of the generation-estimation procedure performed for each level of factors SNR and signal LENGTH and then subjected to ANOVA. ANOVA has pointed out a rather strong statistical significance of both factors employed on the performance of SEM. In fact, the factors SNR and LENGTH were both highly significant (p < 0.0001). Fig. 1(C) shows the plot of means of the Relative Error with respect to the signal length levels, which reveals a decrease of the connectivity estimation error with the increase of the length of the available data. Fig. 1(D) shows the plot of means with respect to different SNR levels employed in the simulation. Since the main factors were found highly statistically significant, post-hoc tests (Duncan at 5%) were then applied. Such tests showed statistically significant differences between all levels of the factor LENGTH, while there is no statistically significant difference between levels 3, 5, and 10 of the factor SNR.

2) Hypothesis of a Model With an Arc in Excess or a Missing Arc: Since a perfect formulation of the connectivity model is not always a realistic option, we analyzed several situations in which the connections between the four cortical areas were not correctly assumed in the estimated model.

Arc in Excess: The first one is described in Fig. 2. The SEM parameter estimation was performed on the model shown in Fig. 2(B), containing an arc which is absent in the imposed pattern [Fig. 2(A)]. The aim was to test if the SEM procedure can reject the error made in the model assumption. The appropriate index for this analysis is the Single Arc Error (2.14) on arc α_{2}, i.e., the one which is not present in the correct model. The ANOVA performed on the simulation results showed that both the main factors signal LENGTH and SNR have a statistical influence on the ability of SEM to reveal the modeling error. Fig. 2(C) and (D) shows the plot of means with respect to the different levels of the main factors LENGTH and SNR. As before, they are both significant with p < 0.001 as well as their interaction (SNR × LENGTH) with p < 0.0001. Post-hoc test (performed with the Duncan procedure at 5% level of significance) shows not statistically significant differences between the LENGTH levels of 190 s or 310 s as well as between levels 3, 5, 10, and 100 of the main factor SNR. In order to evaluate the influence of the exceeding arc in the model on the global parameter estimation, the Relative Error (2.6) was also computed. Fig. 3(A) and (B) shows the plot of mean of this index with respect to the two main factors, with a level of statistical significance lower than 0.001.

Missing Arc: In this case the χ^2 statistic test returns no statistical significance of the estimated model. Hence, the corresponding error values were not computed and no statistical analysis was performed.

3) Ambiguosity on an Arc Direction: A situation that can occur is when the existence of a connection between two structures is well known, and there is the need to investigate its direction. Parameters were estimated on a model representing this situation [Fig. 4(B)]. The signals had been generated according to the pattern of Fig. 4(A) and the Single Arc Error made on the arc representing the wrong direction (α_{23}) in this example) was considered. The statistical analysis performed on the simulation results with the ANOVA reported no statistical significance of the main factor SNR, while the factor LENGTH (EEG-TRIAL) is still statistically significant (with p < 0.0001). The plot of means in function of the levels of LENGTH is reported in Fig. 4(C). Fig. 5(A) and (B) shows the plot of means of the Relative Error with respect to the signal LENGTH levels and to different SNR levels employed in the simulation.

B. Human Study

Fig. 6 shows the cortical connectivity patterns obtained for the period preceding the movement onset in the subject #1, in the alpha frequency band. Each pattern is represented with arrows, that connect one cortical area to another one. The colors and sizes of arrows code the level of strength of the functional connectivity observed between ROIs. The labels indicate the names of the ROIs employed. Note that the connectivity pattern during the period preceding the movement in the alpha band involves mainly the parietal left ROI (PL) coincident with the Brodmann areas 5 and 7, functionally connected with the left and right premotor cortical ROIs (PMl and PMr), the left sensorimotor area (SMl), and both the prefrontal ROIs (PFl and PFr). The stronger functional connections are relative to the link between the left parietal and the premotor areas of both cerebral hemispheres. After the preparation and the beginning of the finger movement, in the POST period changes in the connectivity pattern can be noted. In particular, the origin of the functional connectivity links is posi-
Fig. 4. (A) Connectivity pattern imposed in the generation of simulated signals. Values on the arcs represent the connections strength ($a_{21} = 1.4; a_{31} = 1.1; a_{32} = 0.5; a_{42} = 0.7; a_{43} = 1.2$). (B) Connectivity model used for the parameter estimation. No assumption has been made on the direction of arc $a_{42}$ (both directions are present in the model). (C) Results of ANOVA performed on the error committed on the wrong direction arc for the parameter estimation. No assumption has been made on the direction of arc $a_{42}$, not present in the imposed model (Single Arc Error) plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance of factor LENGTH ($F = 8.504, p < 0.0001$). Post-hoc test (Duncan at 5%) shows statistically significant differences between all levels of length.

Fig. 5. Results of ANOVA performed on the Relative Error for the same situation of Fig. 4: (A) plot of means with respect to signal LENGTH as a function of time (seconds). ANOVA shows a high statistical significance for factor LENGTH ($F = 248.00; p < 0.0001$). Post-hoc test (Duncan performed at 5% level of significance) shows statistically significant differences between all levels. (B) Results of ANOVA performed on the Relative Error: plot of means with respect to SNR. Here, too, a high statistical influence of factor SNR on the error in the estimation is shown ($F = 27.00, p < 0.001$). Duncan post-hoc test (performed at 5%) points out that there is no statistically significant difference between levels 3, 5, and 10 of factor SNR.

A. Methodological Considerations

A third question is related to the possible use of different objective function for the minimization process. In fact, it might be argued that with SEM and some searching techniques, it is also possible to generate a complete network reconstruction (including both network structure and connectivity strengths) by the so-called overall model fit (e.g., using Akaike information criterion as the minimized object function). However, in the case a global effect factor (temporal variance), then results are rather stable and reasonable [25]. Connectivity estimates are generally independent of amplitude factors and might produce reasonable results for this particular reason.

IV. DISCUSSION

A. Methodological Considerations

The application of the SEM to the cortical estimated waveforms from high-resolution EEG recordings poses several methodological questions.

The first question is how the SEM estimates of the cortical connectivity could be affected by errors in the amplitude estimates of the cortical waveforms, generated by the application of the linear inverse operator $G$ to the gathered high-resolution EEG data. From the definition of the resolution matrix [21], [25] derives that current density estimates depend upon the linear inverse $G$ (time invariant) but also upon the actual current distribution (time varying). This implies that amplitudes estimated at a given cortical site will depend upon the actual sources activated everywhere else and which change indeed over time. Consequently errors in the amplitude estimation are not necessarily systematic along time. There are however some simulation results and experimental data analysis using linear inverse solutions that suggest that the analysis procedure is independent of
Fig. 6. (A)–(D). Figure shows the cortical connectivity pattern obtained for the period preceding and following the movement onset in the subject, in the alpha (8–12 Hz) frequency band. The realistic head model and cortical envelop of the subject analyzed obtained from sequential MRIs is used to display the connectivity pattern. Such pattern is represented with arrows, that move from one cortical area toward another one. The colors and sizes of arrows code the level of strengths of the functional connectivity observed between ROIs. The labels are relative to the name of the ROIs employed. (A)–(B). Connectivity patterns obtained from ERP data before the onset of the right finger movement (electromyographic onset; EMG), from above (left) and from the left of the head (right). (C)–(D). Connectivity patterns obtained after the EMG onset. Same conventions as above.

of application of that particular overall model fit technique to the EEG or cortical data related to more complex experimental paradigm, like for instance those related to the working memory or attentive process, a larger number of ROIs is required. In this case, the application of such modified procedure could be difficult due to the high number of ROIs, or node, in the model.

A fourth question is related to the possible benefit of the SEM technique to assess cortical connectivity from EEG measurements with respect to the other methodologies often employed to analyzed scalp recorded data. In fact, many approaches to analysis of scalp connectivity have been implemented during the past years, involving the use of different methodologies such as the linear techniques including the cross-correlation or coherence [5], [6], [14] or the non linear ones, like mutual information, mutual dimension, generalized synchronization, and neural complexity [29]–[31]. All these techniques are able to reveal direct flow of information between scalp electrodes in the time domain, although non linear techniques were reported to be more sensitive with respect to the others, and more computationally demanding [32]. However, all these procedures relying on the concept of functional connectivity estimates, that is based on the computation of the correlation structure among the data. In fact, the functional connectivity is defined as the temporal coherence among the activity of different neurons, and measured by cross-correlating the EEG or the recorded spike trains. Functional connectivity is usually inferred by statistical dependencies among signals in coupled neuronal systems. Effective connectivity, a more abstract notion, could be defined as the simplest neuronal-like circuit that would produce the same temporal relationship as observed experimentally between two neurons in a cell assembly. This definition, generated from the spike recordings in primates, can be generalized to the activity of larger patches of the cortical tissue, as obtained from hemodynamic or cortical current density estimates.

SEM is a technique that relying on the concept of effective connectivity with respect to the concept of functional one. In this context, effective connectivity is defined as “the influence that one neural system exerts over another either directly or indirectly” [33]. Functional connectivity reduces to testing the null hypothesis that activity in two regions shares no mutual information. Mutual information is a statistical description of the degree to which two regions demonstrate similar behavior or statistical interdependence [34]. In other words, the characterization of brain activity in terms of functional connectivity is “model free.” In contrast, characterizing brain activity in terms of effective connectivity requires a causal model, in which regions and connections of interest are specified by the researcher, often constrained by a combination of neuroanatomical, neuropsychological, and functional neuroimaging data. This is a crucial point when considering the distinction between functional and effective connectivity because it emphasizes the shift between a description of what the brain does to a theory of how it does it.
B. Experimental Results

The experimental design adopted for the simulation study aimed to analyze the most common situations in which the proposed application of SEM technique to high-resolution EEG data may take place. The levels chosen for main factor levels SNR and LENGTH, as well as the simple errors in the model formulation that have been examined, cover the most typical situations that can occur in such analysis. The results obtained has shown a significant statistical influence of the factors considered on SEM performances.

On the basis of the simulations performed, we are now able to answer the questions raised in Section I.

1) There is statistical influence of a variable SNR level imposed on the high-resolution EEG data on the accuracy of the connectivity pattern estimation. In particular, an SNR = 3 seems to be satisfactory in order to obtain a good accuracy, since there are not significant differences in the performance for higher values.

2) The minimum amount of EEG data necessary to get a usable accuracy of the estimation of connectivity between cortical areas is 190 s of registration (equivalent, for instance, to 380 trials of 500 ms each). However, in this case, an increase of the length of the available EEG data is always related to a decrease of the connectivity estimation error.

3) Different situations, in which the connections between the four cortical areas were not correctly assumed in the estimated model, were evaluated in order to analyze their influence on SEM performances. In the first situation, there was a deliberate error in the hypothesized model, consisting of the presence of an arc not corresponding to an actual influence between areas. The aim was to test if the SEM procedure can reject the error made in the model assumption and to evaluate the influence of the introduction of such modeling error on the goodness of parameter estimation. The analysis of theSingle Arc Error on the arc in excess, revealed that a SNR = 3 and an amount of EEG data of 190 s of registration seems to be satisfactory in order to obtain good accuracy. The effect on the global performance of parameter estimation can be inferred by comparing the Relative Error obtained in this situation to the correct one. From Fig. 1(C) and (D), compared to Fig. 3(A) and (B), it can be seen that the error values remain on the same level in both cases, and the general performance is not decreased by this kind of error. In the second situation analyzed, the voluntary error in the hypothesized model consists in the lack of an arc corresponding to an influence between areas. The performed analysis has not reported statistical significance, as indicated by the $\chi^2$ to degrees of freedom ratio: $\chi^2/df > 1$. This suggests that, in case of results of this kind, an arc can be added to the putative model in order to decrease the $\chi^2$ to degrees of freedom ratio. In the third situation analyzed, the estimated model contained arcs in both directions between two areas, corresponding to a single arc in the model imposed in the signal generation. The Single Arc Error computed on the “wrong direction” arc shows that the error is rather smaller (less than 1.5% for all factors and levels considered) than in the case of an arc in excess in a single direction in the first situation analyzed. On the other hand, it is worth of notice that the general performance, as indicated by the Relative Error [Fig. 5(A) and (B)], is significantly worse in this case than in the case of correct modeling, especially for low values of factor LENGTH [cf. Fig. 1(C) and (D)]. This means that a simple error like the attribution of both directions to a couple of channels causes a significant increase of the error made in the parameter estimation.

In conclusion, the ANOVA results (integrated with the Duncan post-hoc tests performed at $p < 0.05$) indicated a clear influence of different levels of the main factors SNR and LENGTH on the efficacy of the estimation of cortical connectivity via SEM. In particular, it has been noted that at least a SNR equals to 3 and a LENGTH of the measured cortical data of 190 s are necessary to decrease significantly the errors related to the indexes of quality adopted.

It might be argued how these results, obtained by using several levels of cortical SNR, could be directly extended to the SNR related to the scalp recorded EEG data. In general, a difference exists between the imposed SNR at the cortical level and those observed at the scalp level. This difference is due to the errors in the estimation procedure of the cortical activity. Such errors, already described in simulation studies in literature [26]–[28], could be treated as additional source of noise in the propagation from the cortex to the scalp. Such simulations indicated that for high-resolution EEG studies with a realistic head modeling tessellation ranging from 3000 to 5000 dipoles, the Relative Errors in the cortical estimation are less than 10%. Hence, we could insert this 10% error in the cortical estimate due to the inversion process as an additional noise source error. In this hypothesis, the cortical SNR can hardly be higher than 10, even if the scalp SNR is very high, due to the inversion error introduced by the use of the (2.17). On the other hand, when the scalp SNR is much lower than 10, the contribution of the inversion error vanishes. In the intermediate cases, the cortical SNR is only slightly lower than scalp SNR; a scalp SNR equal to 3, for instance, would yield a cortical SNR equal to 2.3. It is worth noticing that these SNR conditions are generally obtained in many standard EEG recordings of event-related activity in humans, usually characterized by values of SNR ranging from 3 (movement related potentials) to 10 (sensory evoked potentials) and a total length of the recordings starting from 50 s [35].

The simulation study has shown that the ability of SEM to perform a good estimate of connectivity pattern, when connections between the four cortical areas are not correctly assumed, depends on the kind of error made in the model formulation. It seems that the error consisting in the lack of a connection arc is the worst, with respect to the parameter estimate, though it can be easily detected by a $\chi^2$ statistical test. Putting in the model an arc not corresponding to an actual influence between areas, on the contrary, does not particularly influence the goodness of general parameter estimate and the exceeding arc is attributed a value near to zero. Putting arcs in both directions between two areas, while the influence is directed only from one to the other, causes larger errors in the parameter estimation, though it allows
to discriminate the right direction with a precision which does not depend on the signal SNR and which is very high for most levels of signal LENGTH.

Although the performance seems to be rather good for a correct assumption of the hypothesized model, it decreases when even a simple error is made, depending on the error type. This degradation of the performance seems to indicate the opportunity to use connectivity models not too detailed, in terms of cortical areas involved, as a first step of the network modeling. By using a coarse model of the cortical network to be fitted on the EEG data, there is an increase of the statistical power and a decrease of the possibility to generate an error in a single arc link [1]. In the present human study, such observation was taken into account by selecting a coarse model for the brain areas subserving the task being analyzed. This simplified model does not take complete account all the possible regions engaged in the task, and all the possible connections between them. Elaborate models, permitting also cyclic connections between regions can become computationally unstable [13].

Our model of interactions between cortical areas is based on previous results on similar tasks obtained with different brain imaging methods. It is sufficient to address some key questions regarding the influence of the premotor and motor areas toward the prefrontal cortical areas during the task analyzed. The finger tapping data analyzed here present a high SNR and a large number of trials, resulting in an extended record of ERP data. Hence, the present simulation results suggest the optimal performance of the SEM method as applied to the human ERP potentials. The connectivity pattern estimated via SEM (Fig. 6) illustrates the potentiality of the methodology employed, that includes the use of high-resolution EEG recordings, the generation of a realistic head model by using sequential MRIs, and the estimation of the cortical activity with the solution of linear inverse problem. With this methodology, it will be possible not only to detect where the cortical areas are activated by a particular task in the brain but also how such areas are effectively connected together subserving the analyzed task. In particular, the role of the parietal area has been observed toward the premotor cortical areas during the task preparation, consistent with the role that the parietal areas have in the engagement of attentional resources as well as temporization, as assigned by several electrophysiological studies on primate or hemodynamical studies on humans [36]. It is of interest noticing the shift of the cortical areas behaving as the most relevant origin of functional links, occurring when the somatosensory reafferences arrive from the periphery to the cortex. In fact, the left sensorimotor area becomes very active with respect to the left parietal one, which, in turn, used to be mainly engaged in the time period preceding the finger movement. Connections between the sensorimotor area and the premotor and left prefrontal areas are appropriate to distribute the information related to the movement of the finger to the higher functional regions (prefrontal and premotor).

Taken together, our results return the information that quite accurate estimation of the cortical connectivity patterns can be achieved by using realistic models for the head and cortical surfaces, high-resolution EEG recordings, and the SEM technique.

REFERENCES


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