Identifying Complex Brain Networks Using Penalized Regression Methods

Eduardo Martínez-Montes · Mayrim Vega-Hernández ·
José M. Sánchez-Bornot · Pedro A. Valdés-Sosa

Received: 14 January 2008 / Accepted: 11 April 2008 /
Published online: 5 July 2008
© Springer Science + Business Media B.V. 2008

Abstract The recorded electrical activity of complex brain networks through the EEG reflects their intrinsic spatial, temporal and spectral properties. In this work we study the application of new penalized regression methods to i) the spatial characterization of the brain networks associated with the identification of faces and ii) the PARAFAC analysis of resting-state EEG. The use of appropriate constraints through non-convex penalties allowed three types of inverse solutions (Loreta, Lasso Fusion and ENet L) to spatially localize networks in agreement with previous studies with fMRI. Furthermore, we propose a new penalty based in the Information Entropy for the constrained PARAFAC analysis of resting EEG that allowed the identification in time, frequency and space of those brain networks with minimum spectral entropy. This study is an initial attempt to explicitly include complexity descriptors as a constraint in multilinear EEG analysis.

Keywords Information Entropy · PARAFAC · EEG inverse problem ·
Multiple penalized least squares model · Complex brain networks

1 Introduction

The complexity of neuronal networks is clearly apparent in their dynamics, which is driven by the activity and interaction of a large number of neurons in each network. This has created the need for developing advanced statistical tools that deal with a huge amount of data, especially where the main challenge is the analysis of neuroimaging data in which the number of hidden parameters to estimate is much greater than the number of observations. Major examples are the cases of the well-known inverse problem of Electroencephalography (EEG) [1], the dimensionality reduction (time–frequency, principal and independent components, parallel factor) analysis of EEG [2–4], and the estimation of connectivity

E. Martínez-Montes (✉) · M. Vega-Hernández · J. M. Sánchez-Bornot · P. A. Valdés-Sosa
Neurostatistics Department, Cuban Neuroscience Center, Ave. 25, esq 158, #15202, Cubanacán,
Havana, Cuba PO Box: 6414
e-mail: eduardo@cneuro.edu.cu

patterns from functional Magnetic Resonance Imaging (fMRI) time series [5]. Despite some attempts to model nonlinear aspects of these complex scenarios [6], the use of linear models is the most popular approach and still demonstrates its capacity of dealing with new facets of neuroscience problems [7, 8]. In this context, very often one has to use different sources of knowledge (anatomical, physiological) about the parameters of interest to achieve interpretable results, which has made the use of the Bayesian framework and penalized least squares (PLS) regression, two of the most appealing approaches.

PLS models have been addressed as multivariate linear regressions with regularization with efficient and flexible techniques to solve variable selection problems. Interestingly, the use of non-convex penalty functions (non-quadratic, continuous and with a singularity at the origin) has been proposed to obtain sparse and stable solutions [9], such as the Least Absolute Shrinkage Selection Operator (Lasso) [10] and the Smoothed Clipped Absolute Deviation [9], which also produces unbiased estimators. Moreover, this approach can be extended to use any combination of penalties, leading to solutions sharing properties such as smoothness and sparseness, e.g. Elastic Net (ENet) [11] combines a Lasso-type penalty term and a quadratic penalty term. These nonlinear models are estimated by modified Newton–Raphson algorithms such as the Local Quadratic Approximation [9] and the Minorization–Maximization [12], which are based on an iterative estimation of (Ridge) quadratic regression and have recently been generalized to deal with multiple penalty terms simultaneously, i.e. to tackle the Multiple Penalized Least Squares (MPLS) model [13].

In this work we present the application of this methodology to the spatial characterization of the brain networks associated with the identification of faces and to the Parallel Factor Analysis (PARAFAC) of resting-state EEG. The PARAFAC analysis of the time-varying spectra of the multichannel EEG allows for an identification of brain networks responsible for spontaneous rhythms, characterizing them simultaneously in time, frequency and space. In both cases we explore the usefulness of different non-convex penalties already described in the literature. Further, we propose a new penalty based on the Information Entropy to be applied in the identification of neuronal networks with minimum spectral entropy in the spontaneous EEG.

2 Materials and Methods

2.1 MPLS Model and Entropy–Ridge Penalty

Consider the multivariate linear regression model: $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}$, where $\boldsymbol{\beta}$ is the vector of parameters to estimate; $\mathbf{y}$ the data vector; $\mathbf{X}$ the given design matrix and $\mathbf{e}$ the vector of independent and identically distributed random errors. Then, the MPLS model for $\boldsymbol{\beta}$ is stated as:

$$\hat{\boldsymbol{\beta}} = \arg \min \left\{ (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^T (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}) + \sum \lambda_m p_m(\boldsymbol{\beta}) \right\} \quad (1)$$

where the sum is over $m=1, \dots, N$ penalties, which impose different kinds of constraints through $p_m(\boldsymbol{\beta})$, with corresponding weighting parameters λ_m . In this work we will use the following penalty functions: (1) Ridge, which is the usual l_2 -norm of the vector of coefficients and produces stable and non-sparse solutions; (2) Lasso, which is the l_1 -norm of the vector of coefficients and produces very sparse solutions; (3) Lasso Fusion [14], which is the l_1 -norm of the application of the first differences operator on the coefficients and produces sparse solutions with piece-wise flat behavior; (4) ENet, which is a sum of an l_1 -norm term and an

l_2 -norm term, producing sparse solutions with piece-wise smooth behavior. These penalty functions are defined in the second column of Table 1, and their plots are depicted in Fig. 1.

When β can be considered as a probability density function (pdf), i.e. when it is normalized to unity, the Information Entropy is defined as $H(\beta) = -k \sum \beta_j \ln \beta_j$, with $j=1, \dots, n$ and k is a positive constant [15]. This measure will be maximum for $\beta_j = 1/n; \forall j$ and minimum ($H(\beta)=0$) when $\beta_l = 1$ and $\beta_j = 0; \forall j \neq l$. Therefore it is a measure of the “peakness” of the pdf. If we use this measure as a penalty in MPLS, we are constraining the solution to have minimum Entropy, i.e. to be the sharpest one. Note that this penalty differs from the so called entropy-penalty or l_0 penalty, defined as the l_0 -norm of the parameters to estimate [9].

According to the conditions given by [9], modified to cope with our model in equation 1, a penalty function of the form $p(\beta) = \sum \bar{p}(\beta_j)$ with $\beta_j > 0$, produces (1) sparse solutions iff $\min\{\bar{p}'(\beta_j)/2 + \beta_j\} > 0$ and (2) unbiased solutions iff $\bar{p}'(\beta_j) = 0$ for $\beta_j = 1$. It is easy to find that the penalty function $H(\beta)$ produces sparse solutions if $k < 2$ but does not satisfy the unbiasedness condition. However, it is easy to derive a sparse and unbiased estimator with the use of a penalty which combines the Entropy with a Ridge penalizer, of the form:

$$p(\beta) = -\sum \left(\beta_j \ln \beta_j - \beta_j^2 / 2 \right).$$

In effect, for each element β_j , $\arg \min \{\bar{p}'(\beta_j)/2 + \beta_j\} = 1/3$, which leads to fulfill condition 1 since $\bar{p}'(1/3)/2 + 1/3 = (\ln 3)/2 > 0$. On the other hand, $\bar{p}'(\beta_j = 1) = -\ln(1) - 1 + 1 = 0$, thus fulfilling condition 2. We will call this function the Entropy–Ridge penalty and its shape is shown in Fig. 1.

2.2 Spatial Localization of Neural Sources

The inverse problem (IP) of the EEG consists in the identification of the neural current sources inside the brain generating the voltage field measured over an array of sensors distributed on the scalp surface. The mathematical relation between these voltages ($\mathbf{y}$) and the Primary Current Density (PCD, β) can be written as a system of linear equations:

$$\mathbf{y} = \mathbf{K}\beta + \epsilon \quad (2)$$

where ϵ represents the experimental noise and $\mathbf{K}$ is known as the electric lead field: a matrix that comprise the geometrical and electrical properties of the model assumed for the head. This system is highly underdetermined since the number of unknown generators inside the brain is much higher than the number of sensors. Therefore, there is no unique solution and the IP is ill-posed.

The additional (prior) information or constraints used for obtaining a unique solution characterizes each of the known inverse solutions [1]. Also, different approaches have

Table 1 Some inverse solutions derived from MPLS model

Name	$\sum \lambda_m p_m(\beta)$	Inverse solution
Ridge	$\lambda \beta^T \mathbf{Q}^T \mathbf{Q} \beta$	If $\mathbf{Q} = \mathbf{I} \rightarrow$ Minimum Norm; if $\mathbf{Q} = \mathbf{L} \rightarrow$ Loreta
Lasso	$\lambda \sum \mathbf{q}_j \beta $	If $\mathbf{Q} = \mathbf{I} \rightarrow$ Lasso; if $\mathbf{Q} = \mathbf{L} \rightarrow$ Lasso Fusion
ENet	$\lambda_1 \beta^T \mathbf{R}^T \mathbf{R} \beta + \lambda_2 \sum \mathbf{q}_j \beta $	If $\mathbf{Q} = \mathbf{R} = \mathbf{I} \rightarrow$ ENet; if $\mathbf{Q} = \mathbf{R} = \mathbf{L} \rightarrow$ ENet L

$\mathbf{Q}$ ($\mathbf{q}_j$ as j -th row) and $\mathbf{R}$ are linear operators. $\mathbf{I}$ is the identity matrix, and $\mathbf{L}$ a discrete version of Laplacian operator. ENet stands for Elastic Net.

Fig. 1 Penalty functions: Ridge (solid), Lasso (dash), ENet (dot), Entropy-Ridge (dot-dash)

been used (Bayesian, Dipole fitting) but the most popular is the regularization, which is equivalent to a PLS regression. Therefore, the IP can be formulated as a general MPLS model in the form of equation 1, where the lead field is the design matrix. This formulation encompasses several known inverse solutions as particular cases, e.g. Minimum Norm and Low Resolution Electromagnetic Tomography (Loreta, see Table 1 and [1]). On the other hand, the use of non-convex penalty functions allows to obtain new types of inverse solutions [16], whose performance is explored here in the source analysis of face recognition. As a first approximation, optimal values for λ_m will be found by generalized cross-validation [17].

2.3 Penalized PARAFAC

The multidimensional nature of neuroscience data has made the use of multiway statistical analysis suitable in this field. Many bidimensional approaches such as Independent and Principal Components Analysis (PCA) are very popular but offer non-interpretable results when higher dimensional structure is hidden in the data. PARAFAC analysis is a generalization of PCA to deal with multidimensional data. For example, the EEG time-varying spectra is a three dimensional array ($\mathbf{Y}_{(I \times J \times K)}$), indexed by channels, time points and frequencies [4]. The PARAFAC model is then stated as:

$$y_{ijk} = \sum a_{if} b_{jf} c_{kf} + \varepsilon_{ijk}$$

where a_{if} , b_{jf} and c_{kf} are the elements of loading matrices $\mathbf{A}_{(I \times F)}$, $\mathbf{B}_{(J \times F)}$ and $\mathbf{C}_{(K \times F)}$, respectively, and ε_{ijk} represents the noise. The sum is over $f=1, \dots, F$, which represents components or atoms. For each component the corresponding columns of $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$ define the spatial (topographic), temporal and spectral signatures respectively. The spectral signatures show the frequency content of the present activities and allow the identification of brain rhythms. The corresponding spatial and temporal signatures give the topographic map and dynamics of the neuronal networks producing those rhythms.

The main advantage of PARAFAC is that the decomposition is unique (up to a scale factor or permutation of components) under very mild conditions without requiring orthogonality or independence among components [18]. However, physiologically acceptable constraints are of help in the interpretation of results. The matrix formulation of PARAFAC allows the estimation of the loading matrices via the Alternating Least Squares (ALS) algorithm [18], in which, iteratively, each loading is (least squares-) estimated conditionally on the others. Substituting each least squares step in ALS by an MPLS regression allows us to introduce different types of constraints in the PARAFAC decomposition.

In the case of the time-varying spectra of the EEG, we have explored the use of smoothness constraints for the spectral loading, with the Ridge penalty, using a Laplacian operator [19]. Here we further use the ENet L (ENet using a Laplacian operator, see Table 1) and the Entropy–Ridge penalties in the estimation of spectral signatures. The former is aimed to find sparse spectra with smooth patches in the relevant frequencies, while the latter would imply to constraining the loadings to have minimum spectral Entropy, which can be interpreted as finding those functional brain networks with a well-defined frequency of oscillation. This is possible since the spectral signatures obtained from PARAFAC are normalized to unity as a scaling convention to deal with the scale indeterminacy.

3 Results

3.1 Source Localization of Face Recognition

The analyzed data set corresponds to an experiment in which subjects are presented with images of faces or non-faces followed by a mask image after 30 ms. They are required to respond if a face was presented or not. This kind of experiment evokes a voltage transient that appears in the EEG as a negative peak around 170 ms after presentation of the stimulus and is known as N170 peak. The amplitudes of this peak for each electrode form a topography, corresponding to vector $\mathbf{y}$ in equation 2. Sources of the evoked N170 peak were sought separately for the topographies corresponding to correct and incorrect responses (averaged across 80 trials), as well as for the differential topography (correct minus incorrect) with the use of Loretta, Lasso Fusion and ENet L (Table 1) methods. Note that the map found in the case of differential topography with these nonlinear inverse methods is not necessarily the difference between the maps found from correct and incorrect topographies. Since the PCD is a vector field, the Hotelling's T^2 statistic [20] was computed across 10 subjects for each condition and for the difference between them.

Figure 2 shows the maximum intensity projection in the coronal view of the estimated Hotelling's T^2 images by the three methods for each condition: correct response (top row), incorrect response (middle row) and differential topography (bottom row). Significant activations for the correct and incorrect detection of faces were found in the right inferior and superior temporal gyrus, in the middle frontal gyrus (right and left) and in the right middle occipital gyrus, although with different degree of activation. These areas are in agreement with previous fMRI studies on the conscious perception of faces [21]. Significant differential sources were located mainly in the right inferior temporal and middle occipital gyri.

Fig. 2 Hotelling's T^2 images of sources of evoked N170 peak corresponding to topographic maps of correct face detection (*upper panel*), incorrect face detection (*middle panel*), and the difference between correct and incorrect detection (*bottom panel*)

On the other hand, it can be seen that the use of l_1 -norm (Lasso Fusion) allows for much more concentrated (sparser) solutions, dividing the usual low resolution image given by Loreta in several sources. ENet L, in turn, offers solutions with intermediate degree of sparseness and smoothness (that can be tuned through the regularization parameters) and which are more physiologically plausible.

3.2 Penalized PARAFAC Analysis of Resting EEG

The time-varying spectral density of a resting-state EEG was obtained with Thomson's multitaper method, organized as a three-dimensional array (indexed by channels, time points and frequencies) and decomposed by unconstrained and constrained PARAFAC into three components with corresponding topographic, temporal and spectral signatures [22]. The latter allowed the identification of spontaneous brain rhythms. Figure 3a shows unconstrained spectral loadings which, although presenting clear main peaks, have negative values and some oscillating behavior that might be due to fitting residual noise. Figure 3b presents the smoother loadings given by constrained PARAFAC using a Ridge penalty with a Laplacian operator.

Figure 4a shows the piece-wise smooth spectral loading as estimated by using an ENet penalty, and Fig. 4b the sparser loadings obtained with the Entropy-Ridge penalty. The three constrained versions are more reasonable and physiologically sound options for the

Fig. 3 Spectral signatures found by: **a)** unconstrained PARAFAC, **b)** PARAFAC with MPLS using a Ridge penalty. Components are identified as alpha (*solid*), theta (*dash*) and gamma (*dot-dash*)

interpretability of the results than the unconstrained signatures. However, Ridge and ENet solutions do not avoid the negative values and the oscillating behavior for frequencies far from the main peak.

4 Conclusions

In this work we have applied a general statistical tool, MPLS, to the identification of neuronal networks. This approach allows the use of known as well as yet unexplored types of constraints in neuroscience (even in a combined way), that can represent better the physiological or physical knowledge of complex brain activity.

As a first example of the usefulness of the methodology, three inverse solutions (Loreta, Lasso Fusion and ENet L) found sources in agreement with previous studies with fMRI. In addition, it was shown that by combining l_1 - and l_2 -norm terms, ENet L offers solutions with intermediate levels of blurring between Loreta (too smooth) and Lasso Fusion (too sparse). However, this method strongly depends on the selection of optimal regularization parameters. Therefore, further research on the use of appropriate (nonlinear) methods is

Fig. 4 Spectral signatures found by: **a)** PARAFAC with MPLS using ENet penalty, **b)** PARAFAC with MPLS using Entropy-Ridge penalty. Components are identified as alpha (*solid*), theta (*dash*) and gamma (*dot-dash*)

needed. In general, the formulation of the EEG inverse problem in terms of an MPLS model, offers the possibility of exploring a wide range of new kind of inverse solutions.

On the other hand, application of MPLS to PARAFAC analysis can also lead to more interpretable results. In this work, we proposed a new penalty based in the Information Entropy of the EEG spectral density that allowed the estimation of non-negative and piecewise smooth spectral loadings with PARAFAC. This is interpreted as the identification in time, frequency and space of those brain networks with minimum spectral Entropy, i.e. whose dynamics shows oscillations in a very well-defined frequency band. Since the PARAFAC decomposition is unique, weighting parameters can be tuned to obtain different degrees of constraint. However, future work is needed on the selection of their optimal values using cross-validation or other information criteria.

In general, this study can be considered as an initial attempt to include the complexity of the brain activities of interest as a constraint in the analysis of the neuroimaging data reflecting them. The use of other measures of complexity as constraints (with penalized regression methods) in the search of complex brain networks should also be carried out. This approach can be of importance in the study of other types of cognitive and pathological activity, such as epilepsy and Alzheimer's disease, where changes in complexity might reflect the functional or health state of the brain.

Acknowledgments The authors thank Mark Cohen and Jhoanna Pérez-Hidalgo-Gato for kindly providing the data of the resting EEG and face identification experiment used in this study.

References

1. Pascual-Marqui, R.D.: Review of methods for solving the EEG inverse problem. *Int. J. Bioelectromagn.* **1**, (1), 75–86 (1999)
2. Durka, P.J., Blinowska, K.J.: A unified time–frequency parametrization of EEG. *IEEE Eng. Med. Biol.* **20**, (5), 47–53 (2001)
3. Makeig, S., Westerfield, M., Jung, T.P., Enghoff, S., Townsend, J., Courchesne, E., Sejnowski, T.J.: Dynamic brain sources of visual evoked responses. *Science* **295**, 690–694 (2002)
4. Miwakeichi, F., Martínez-Montes, E., Valdés-Sosa, P.A., Nishiyama, N., Mizuhara, H., Yamaguchi, Y.: Decomposing EEG data into space–time–frequency components using Parallel Factor Analysis. *Neuroimage* **22**, (3), 1035–1045 (2004)
5. Harrison, L., Penny, W.D., Friston, K.: Multivariate autoregressive modeling of fMRI time series. *Neuroimage* **19**, 1477–1491 (2003)
6. Freiwald, W.A., Valdés, P.A., Bosch, J., Biscay, R., Jiménez, J.C., Rodríguez, L.M., Kreiter, A.K., Singer, W.: Testing non-linearity and directness of interactions between neural groups in the macaque inferotemporal cortex. *J. Neurosci. Methods* **94**, 105–119 (1999)
7. Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., Frackowiak, R.S.J.: Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.* **2**, (4), 189–210 (1994)
8. Kiebel, S.J., Tallon-Baudry, C., Friston, K.J.: Parametric analysis of oscillatory activity as measured with EEG/MEG. *Hum. Brain Mapp.* **26**, 170–177 (2005)
9. Fan, J.Q., Li, R.Z.: Variable selection via nonconcave penalized likelihood and its oracle properties. *J. Am. Stat. Assoc.* **96**, 1348–1360 (2001)
10. Tibshirani, R.: Regression shrinkage and variable selection via the lasso. *J. R. Stat. Soc. Ser. B* **58**, 267–288 (1996)
11. Zou, H., Hastie, T.: Regularization and variable selection via the elastic net. *J. R. Stat. Soc. Ser. B* **67**, 301–320 (2005)
12. Hunter, D.R., Li, R.: Variable selection using MM algorithms. *Ann. Stat.* **33**, 1617–1642 (2005)
13. Valdés-Sosa, P.A., Sánchez-Bornot, J.M., Vega-Hernández, M., Melie-García, L., Lage-Castellanos, A., Canales-Rodríguez, E.: Granger causality on spatial manifolds: applications to neuroimaging. In: Schelter, B., Winterhalter, M., Timmer, J. (eds.) *Handbook of Time Series Analysis: Recent Theoretical Developments and Applications*, pp. 461–492. Wiley-VCH, Weinheim (2006)

14. Land, S., Friedman, J.: Variable fusion: a new method of adaptive signal regression. Technical Report. Department of Statistics, Stanford University, Stanford (1996)
15. Shannon, C.E.: A mathematical theory of communication. *Bell Syst. Tech. J.* **27**, 379–423, 623–656 (1948)
16. Vega-Hernández, M., Sánchez-Bornot, J.M., Lage-Castellanos, A., Martínez-Montes, E., Valdés-Sosa, P.A.: Penalized regression methods for solving the EEG inverse problem. *NeuroImage* **27**(1) (2006) (CD-ROM)
17. Golub, G.H., Heat, M., Wahba, G.: Generalized cross-validation as a method for choosing a good ridge parameter. *Technometrics* **21**, 215–223 (1979)
18. Bro, R.: Multi-way analysis in the food industry: Models, algorithms and applications. PhD thesis, University of Amsterdam and Royal Veterinary and Agricultural University, Denmark, (1998)
19. Martínez-Montes, E., Sánchez-Bornot, J.M., Valdés-Sosa, P.A.: Generalized penalized PARAFAC analysis of EEG time series. *NeuroImage*, **36**(S1), (2007) (CD-ROM)
20. Mardia, K., Kent, J., Bibby, J.: Multivariate analysis. Academic Press, San Diego, CA (1979)
21. Kanwisher, N., McDermott, J., Chon, M.M.: The fusiform area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* **17**, 4302–4311 (1997)
22. Martínez-Montes, E., Valdés-Sosa, P.A., Miwakeichi, F., Goldman, R.I., Cohen, M.S.: Concurrent EEG/fMRI analysis by multi-way partial least squares. *NeuroImage* **22**, (3), 1023–1034 (2004)