Multiple penalized least squares and sign constraints with modified Newton-Raphson algorithms: application to EEG source imaging.

**Short running title:** MNR algorithms for EEG source imaging.

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**Abstract:**

Multiple penalized least squares (MPLS) models are a more flexible approach to find adaptive least squares solutions required to be simultaneously sparse and smooth. This is particularly important when addressing real-life inverse problems where there is no ground truth available, such as electrophysiological source imaging. In this work we formalize a modified Newton-Raphson (MNR) algorithm to estimate general MPLS models, and propose its extension to perform efficient optimization over the active set of selected features (AMNR). This algorithm can be used to minimize continuously differentiable objective functions with multiple restrictions, including sign constraints. We show that these algorithms provide solutions with acceptable reconstruction in simulated scenarios that do not cope with model assumptions, and for low n/p ratios. We then use both algorithms for estimating different electroencephalography (EEG) inverse models with multiple penalties. We also show how the AMNR allows us to estimate new models in the EEG inverse problem context, such as nonnegative versions of Smooth Garrote and Smooth LASSO.
Due to its similarity to the least angle regression (LARS) algorithm, synthetic data were used for a preliminary comparison between solutions obtained using both AMNR and LARS for the same models, according to well-known quality measures. A visual event-related EEG from healthy young subjects and a resting-state EEG study associated to walking speed decline in active elders were used to illustrate its usefulness in the analysis of real experimental data.

**Keywords:** Active set, EEG, inverse problem, nonnegative Garrote, penalized-least-squares.

1. **Introduction**

Linear models are widely used due to their numerous applications. The linear regression model is stated as \( y = X\beta + \epsilon \), where the columns \( (x_1, ..., x_p \in \mathbb{R}^n) \) of the design matrix \( X \) are the predictors, \( y \in \mathbb{R}^n \) is the response vector, \( \beta \in \mathbb{R}^p \) is the vector of coefficients to be estimated and \( \epsilon \in \mathbb{R}^n \) is the error term such that \( \epsilon \sim \mathcal{N}(0, \sigma^2 I_n) \), where \( \sigma^2 \) is the variance of the noise component and \( I_n \) represent the size-\( n \) identity matrix. When \( p \gg n \) this model corresponds to an underdetermined system with no unique solution, which implies the need of introducing constraints to “select” a solution to the problem. This has led to a huge amount of scientific work on how to efficiently and reliably estimate models with different types of additional constraints, with many new extensions of regularization techniques in the last decade (Voronin (2012)). These techniques produce biased but stable linear solutions when using L2 norm penalties, being Ridge regression (Hoerl and Kennard (1970)) the classical example.

The advent of the least absolute shrinkage and selection operator (LASSO) (Tibshirani (1996)) and the emergence of the more general penalized least squares (PLS) formulation (Fan and Li (2001)), allowed the recovery of sparse solutions, where a large number of coefficients are forced to be zero by increased penalization, in contrast to Ridge regression which never produces sparse solutions. Methods producing sparse estimators are considered variable selection techniques in the PLS context. Moreover, the sparsity constraint can be naturally combined with other constraints to obtain estimators with simultaneous sparse, smooth and possibly non-negative characteristics. In this broad sense, the Fused LASSO (Tibshirani et al. (2005)), the Fusion LASSO (FnLASSO) (Land and Friedman (1996)), the Elastic Net (ENET) (Zou and Hastie (2005)) and the
Smooth LASSO (SLASSO) (Hebiri and van de Geer (2011)), can be seen as particular instances. A general model consisting on the combination of any number of penalty terms has been named as Multiple PLS (MPLS) (Vega-Hernández et al. (2008); Sánchez-Bornot et al. (2008)), and stated as follows:

$$\hat{\beta} = \text{argmin}_{\beta} \{(y - X\beta)^T(y - X\beta) + \Psi(\beta)\}, \quad \text{with } \Psi(\beta) = \sum_{r=1}^{R} \lambda_r G_r(\beta)$$

(1.1)

where the penalty term $\Psi(\beta)$ takes the form of a sum of $R$ convex constraints or penalty functions $G_r$, for $r = 1, ..., R$. In turn, these functions can be written, in general, as a sum of functions on each component of a linear combination of the parameters $\beta$, that is: $G_r(\beta) = \sum_{i=1}^{p} g_r\left(|\theta_i^{(r)}|\right)$, where $|\theta_i^{(r)}|$ represents the absolute value of each component of the vector $\theta^{(r)} = L^{(r)} \beta$, with $L^{(r)} \in \mathbb{R}^{N_r \times p}$ being linear operators that impose a structural relationship among coefficients, (e.g. the matrix of first or second differences). In this paper, we assume that $g_r: \mathbb{R} \mapsto \mathbb{R}$, are symmetric, non-negative, non-decreasing and continuous over $(0, +\infty)$, while the regularization parameters $\lambda_r$ establish the relative importance of each constraint. As can be easily shown, LASSO and Ridge regression are instances of equation (1.1) setting $R = 1$, $L^{(r)} = I_p$ (the $p \times p$ identity matrix) and using the L1 and L2 norms as penalty functions, respectively. These and other particular examples are summarized in Table 1 of the supplemental material (online).

To obtain a reliable estimation of solutions in some particular instances of PLS models, many traditional approaches (e.g. conjugate-gradient, coordinate-wise descent and Newton-Raphson) have been used. Specifically, the Local Quadratic Approximation (LQA) (Fan and Li (2001)) and the Majorize-Minimize (MM) (Hunter and Li (2005); Lange (2016)) algorithms have provided a numerical engine to implement PLS methods. These algorithms can be seen as applications of a Newton-Raphson (NR) technique using an approximation of the objective function to produce true sparse solutions, although using a numerical trick to enforce sparsity and to ensure numerical stability (Li et al. (2006)). However, to our knowledge, they haven’t been formulated for a general MPLS model. Another algorithm for solving PLS models is Coordinate Descent (CD), implemented in the popular GLMNET package by Friedman (Friedman, Hastie and Tibshirani (2010)), which has been slightly improved by replacing each CD step with a Coordinate-wise Majorization Descent operation (Yang and Zou (2012)). Alternatively, the least angle
regression (LARS) (Efron (2004)) and the Shooting algorithm (Fu (1998)) also known as coordinate-wise descent (Friedman et al. (2007)), offer efficient implementations for several of these PLS methods with the advantage that they make variable selection and estimation simultaneously. However, despite recent sophisticated algorithms (Rong et al. (2017)), their application scope is not as extensive as that of the LQA and MM approaches.

In addition to using several constraints for handling more complex real-world models, many applications require the use of nonnegative constraints on the solution. This is not an easy task and several attempts have been done since the introduction of the “best subset selection”, which was one of the first variable selection procedures but cannot be represented as a PLS method (Hocking and Leslie (1967)). The instability of this method is well-known and thus, Breiman introduced the Nonnegative Garrote (NNG) as a variable selection technique that shrinks and zeroes the ordinary least squares (OLS) estimator, in order to give intermediate results between OLS and subset selection (Breiman (1995)), (see Table 1 of the supplemental material online). Gijbels and colleagues introduced three robust versions of the nonnegative garrote, namely the M-, LTS, and S-nonnegative garrote (Gijbels and Vrinssen (2015)). They also introduced the MM-nonnegative garrote by combining the S- and M-nonnegative garrote. One of their findings is that the NNG can use other solutions as a reference solution instead of the OLS, leading to a different final estimator. However, one important limitation of NNG is that it is restricted to the \( p < n \) case, which hinders its applications to general inverse problems. Another approach was followed by Mørup (Mørup et al (2008)), who introduced a version of the LARS algorithm to implement the LASSO with nonnegative constraints. However, to our knowledge, algorithms for imposing nonnegativity has not been proposed within the general MPLS approach.

To deal with applications on real-world inverse problems where there is no experimental ground truth available (e.g. the EEG inverse problem), we have focused in the development of efficient algorithms to address flexible MPLS models which may produce smooth/sparse and/or sparse/sign-constrained solutions. In this work, we formalize a modified Newton-Raphson (MNR) algorithm, as a natural extension of the MM approach that allows solving MPLS models with similar convergence properties as those for MM and LQA algorithms. However, it does not offer nonnegative solutions, since the use of sign constraints within the MNR algorithms is not
straightforward. Secondly, we propose an algorithm based on the active set technique for MPLS models, which will be called AMNR and can be seen as an extension of the LARS algorithm for convex and continuously differentiable cost functions in possible nonnegative (nonpositive) scenarios. We introduce the AMNR extension of the NNG to deal with the $p \gg n$ case, and to handle other novel combined methods that we call the Smooth Nonnegative Garrote (SNNG) and the Nonnegative Smooth LASSO (NN-SLASSO).

2. MNR algorithm for MPLS methods

In this section, we formalize a type of MNR algorithm to implement MPLS models. This method follows the philosophy of the MM algorithm introduced by Hunter and Lange (Hunter & Lange (2004)), who showed that the update formula for the MM algorithm is a particular case of the classical Newton-Raphson procedure. The MNR algorithm introduced in this article can be considered as an extension of the MM for dealing with MPLS models. Note that Hunter and Li (Hunter and Li (2005)) proposed a formulation for a penalized least squares (PLS) model that allows the use of different penalty weights for the components of $\beta$. However, under their framework, it is not possible to combine several different penalty functions on the entire vector in the same penalized model.

The model raised by Hunter and Li (Hunter and Li (2005)) can be seen as a particular case of the general MPLS objective function equation (1.1) when rewriting the penalty term as the sum over component-wise functions $G^{(r)}$:

$$
\Psi(\beta) = \sum_{r=1}^{R} \lambda_r \sum_{i=1}^{p} g_r \left( \left| \theta_i^{(r)} \right| \right) = \sum_{i=1}^{p} \sum_{r=1}^{R} \lambda_r g_r \left( \left| \theta_i^{(r)} \right| \right) = \sum_{i=1}^{p} G^{(r)} \left( \left| \theta_i^{(r)} \right| \right).
$$

Recall that we are using a general approach where constraints are applied to any linear combination of the parameters $\beta$. Thus, the scalar magnitude $\theta_i^{(r)}$ is the $i$-th element of $\theta^{(r)} = L^{(r)} \beta$ that models the row-wise correlation structure of $\beta$ and generalizes the use of different weights for each of its components. In this case, the linear operators $L^{(r)} \in \mathbb{R}^{p \times p}$ can be set to $L^{(r)} = I_p$ to imply independence of the components of $\beta$ or to any other matrix structure (e.g. first and second difference operators). We can then follow the same rationale as Hunter and Li on the Majorize–Minimize algorithm to obtain the canonical version of our MNR algorithm, which is shown in the
The basic difference between MM and our MNR algorithm is that in step 5 of Algorithm 1, the sum of the derivatives of all penalty functions are included in the regularization of the inverse of the design matrix. This is precisely what makes this algorithm general for any differentiable penalty \( g_r \) and linear operators \( L(r) \). In section 1 of the supplemental material (online) we present a detailed derivation of the update formula for MPLS and demonstrated the algorithm convergence.

**Algorithm 1. MNR for MPLS** (\( y \in \mathbb{R}^{n \times 1}, X \in \mathbb{R}^{n \times p}, \lambda_1, \ldots, \lambda_R, L^{(1)}, \ldots, L^{(R)} \in \mathbb{R}^{p \times p} \))

1. Start with \( k: k \leftarrow 0 \) and set \( \tau \leftarrow 10^{-8}, \epsilon \leftarrow 10^{-6} \), MaxIter \( \leftarrow 100 \) and \( \Omega \leftarrow I_p \).
2. Set \( k \leftarrow k + 1 \) and compute \( \beta^{(k)} \leftarrow (X^T X + \Omega)^{-1} X^T y \).
3. Set \( \theta^{(r)} \leftarrow L^{(r)} \beta^{(k)} \) for \( r = 1, \ldots, R \) and compute
   \[
   D^{(r)} \leftarrow \text{diag} \left( \frac{g^{(r)'(0_+)}(\theta_1^{(r)})}{\epsilon + |\theta_1^{(r)}|}, \ldots, g^{(r)'(0_+)}(\theta_N^{(r)})/(\epsilon + |\theta_N^{(r)}|) \right).
   \]
4. If \( k = 1 \), then set \( M \leftarrow \max \{ g^{(r)'(0_+)} \} \) and \( \epsilon \leftarrow \frac{\tau}{2RM} \min \{ |\theta_1^{(r)}|: \theta_1^{(r)} \neq 0 \} \).
5. Set \( \Omega \leftarrow \sum \lambda_r L^{(r)T} D^{(r)} L^{(r)} \) and compute \( \delta \leftarrow -X^T y + (X^T X + \Omega) \beta^{(k)} \).
6. If \( |\delta_j| < \tau/2 \) for all \( j \in \{1, \ldots, p\} \) such that \( |\beta_j| \geq \epsilon \), then goto Step 8.
7. If \( k < \text{MaxIter} \), then goto Step 2.
8. Stopping criterion: if convergence is reached then the solution is \( \hat{\beta} \leftarrow \beta^{(k)} \).

This algorithm depends on the regularization parameters \( \lambda_1, \ldots, \lambda_R \), which can be chosen from a given grid of values or from an automatically determined range according to the singular values of \( X \). The selection of the ‘optimal values’ for these parameters is a process that will not be considered here in detail. This is usually done by minimizing information criteria such as Akaike (AIC), Bayesian (BIC) or the generalized cross-validation (GCV) function. For this purpose, it is necessary to compute the degrees of freedom, which can be estimated as proposed in Hunter and Li (Hunter and Li (2005)). In order to avoid the selection of optimal parameters in an \( R \)-dimensional grid, we prefer to set \( \lambda_r = \lambda \mu_r \) and set ad hoc values for the proportions \( \mu_r > 0 \), for \( \forall r = 1, \ldots, R \), (such that \( \sum \mu_r = 1 \)), which represent prior assumptions about relative penalty contributions and allow simplifying the process to estimating only the parameter \( \lambda \).
3. **AMNR technique for MPLS methods**

Although the MNR algorithm allows the implementation of a wide range of MPLS methods, it produces very small coefficients that should be estimated as zero in sparse scenarios, similarly as it happens with classical procedures (Hunter and Lange (2004)). Variable selection and active set algorithms overcome this limitation by doing feature selection and estimation simultaneously, which implicitly guarantees a higher degree of sparsity in the solution. As noticed by Mørup and others, the LARS algorithm can be stated as the iterative application of the Newton-Raphson technique over the space of selected predictors, considering a particular selection of the descent step (Mørup et al. (2008), Hastie el al. (2009)). This strategy has been used to produce the optimal estimators for LASSO and other specific models, avoiding the explicit use (and estimation) of a regularization parameter. In this section, we introduce a technique based on the use of MNR over the active set of salient features (AMNR) which generalizes this type of algorithm to deal with MPLS models including LARS as a particular case.

Let’s consider the MPLS optimization problem defined in the unconstrained variant as in equation (1.1):

\[ \text{minimize}_\beta F(\beta, y, X) \quad \text{with} \quad F(\beta, y, X) = \|y - X\beta\|_2^2 + \Psi(\beta) \]

where \( \Psi(\beta) \) is a sum of convex functions, which guarantees the convexity of the cost function \( F(\beta, y, X) \). Now let’s assume we are at step \( k \) of the minimization of \( F \) with coefficients vector \( \beta_k \) that will be updated as \( \beta_{k+1} = \beta_k + b_k \). If we take into account that the effect of the previous steps can be absorbed by the residuals: \( r_k = y - X\beta_k \), the cost function at step \( k + 1 \) can be expressed as a function of the vector update \( b_k \):

\[ F_{k+1}(b_k) = \|r_k - Xb_k\|_2^2 + \Psi(\beta_k + b_k) \]

The change in the cost function from the previous iteration \( (F_k = F(\beta_k, y, X) = F_{k+1}(b_k)|_{b_k=0}) \) to the next iteration \( (F_{k+1}(b_k) = F(\beta_k + b_k, y, X)) \), can be found using the first-order Taylor approximation around \( b_k = 0 \):

\[ F_{k+1}(b_k) \approx F_k - (2X^Tr_k - \nabla_b\Psi(\beta_k + b_k)|_{b_k=0})^Tb_k \]

Interestingly, the change in the cost function is proportional to the covariance between the residuals and the predictors (columns of \( X \)) minus the gradient of the penalization term (with respect to the
update vector $\mathbf{b}$) evaluated at $\mathbf{b}_k = 0$, and convergence will be achieved when these terms become equals. This equation allows us to follow the same procedure as the LARS algorithm (Efron (2004)), to find the update (size and direction) $\mathbf{b}_k$ that ensures the minimization of the cost function ($F_{k+1} < F_k$) by involving only one nonzero coefficient (and corresponding predictor) in each iteration. The columns of the predictors with nonzero coefficients form the matrix $\mathbf{X}_\mathcal{A}$, with $\mathcal{A}$ representing the so-called active set.

In the more general AMNR formulation, we establish the following LARS-type constraint:

$$
|2\mathbf{X}_\mathcal{A}^T \mathbf{r}_k - \nabla_k \Psi(\mathbf{b}_k)| = C_{\text{max}} \mathbf{1}_\mathcal{A} \text{ with } C_{\text{max}} > 0,
$$

where $\mathbf{1}_\mathcal{A}$ represents a vector of ones with length equal to the cardinality of the active set. The common use of the absolute value in this condition aims at ensuring that the last term in equation (3.1) is positive and leads to the classical practice in LARS to control the sign of the update and avoid flipping the sign of the coefficients included in the active set (Efron (2004)). We will keep this approach for the AMNR implemented here, although future versions of the algorithm might be able to avoid such trick and allow flipping signs in a natural way. Note that equation (3.2) reduces to the equivalent LARS-LASSO constraint for $\Psi$ being the L1 norm of $\beta$ (i.e. the $l_1$ penalty), where the gradient becomes a constant and then predictors are included in the active set in such a way that they have the same correlation with the residuals (equi-angular condition). In the general case of the AMNR, the condition is more complicated and depends on the difference between the correlation with the residuals and the gradient of the penalty function. The update $\mathbf{b}_k$ is taken on the Newton-Raphson direction, which corresponds to the direction of the OLS solution ($\mathbf{b}_k = \alpha (\mathbf{X}_\mathcal{A}^T \mathbf{X}_\mathcal{A})^{-1} \mathbf{X}_\mathcal{A}^T \mathbf{r}_k$) in the case of LARS, but corresponds to the penalized solution, i.e. the MNR solution ($\mathbf{b}_k = \alpha (\mathbf{X}_\mathcal{A}^T \mathbf{X}_\mathcal{A} + \Omega)^{-1} \mathbf{X}_\mathcal{A}^T \mathbf{r}_k$; with $\Omega$ defined as in Step 5 of Algorithm 1) in the case of the AMNR. In both cases, the algorithm is then reduced to find only the step size of the update ($\alpha$) in each iteration, such that the variable selected to be included in the active set, will ensure that equation 3.2 holds for every iteration. Obviously, $C_{\text{max}}$ in equation 3.2 is different for each iteration and will be ideally zero when convergence is reached. For avoiding the flip in signs of the estimated coefficients, a different step size can be easily derived for positive ($\alpha^+$) and negative ($\alpha^-$) coefficients. This allows us to impose nonnegativity (nonpositivity) constraints in a
natural way by just updating positive (negative) coefficients and leaving the rest out of the active set.

Although this formulation leads us to a very flexible algorithm that can deal with general MPLS models, in this paper we implement the simplest versions of the algorithm which correspond to the LASSO and Adaptive LASSO models. Similar to LARS, the AMNR algorithm can also be conveniently established on the constrained equivalent formulation for LASSO:

\[
\min \|y - X\beta\|_2^2 \text{ subject to } \sum_{j=1}^{p} |\beta_j| \leq \tau,
\]

which avoids the explicit use of regularization parameters by replacing them by a thresholding parameter “\(\tau\)”. However, future developments in the algebra of the AMNR approach could potentially lead to finding an explicit relationship between the regularization parameters and the path of solutions of the algorithm, which might provide other conditions for estimating their optimal values. This formulation of the LASSO model is especially relevant as many convex MPLS models are combinations of penalty functions based on L1 and L2 norms. Hence, using the trick of data augmentation (Hebiri and van de Geer (2011)), we can include the L2-based penalty terms into the data fitting term of the cost function, in the case that we do not use an explicit regularization parameter or in that we use it with a value defined ad hoc or computed by minimizing information criteria for the corresponding MNR model before applying the AMNR algorithm. In this sense, many combined models reduce to a LASSO-type model, as is the case of Elastic Net (Zou and Hastie (2005)) and Smooth LASSO (Hebiri and van de Geer (2011)). Additionally, these simple models allow us to use the AMNR for extending models such as the Garrote to the \(p \ll n\) case and introduce novel sign constrained versions of some of the models, as we will show in the next sections (Mørup et al (2008)) . In section 2 of the supplemental material (online), we demonstrate that the AMNR fulfills the optimality conditions and give its derivation for the general Adaptive LASSO model and the pseudo algorithm implemented.

3.1 Addressing new models with AMNR

The capability for establishing nonnegative and non-positive constraints with the AMNR algorithm can be exploited to implement the nonnegative Garrote (NNG) method (Breiman (1995)), which is stated as:
\[ \hat{W} = \arg \min_w \left\{ \frac{1}{2} \| y - \Sigma_{j=1}^p x_j \beta_j^{\text{ols}} w_j \|_2^2 + \lambda \Sigma_{j=1}^p w_j \right\}; \text{with } w_j = (\beta_j / \beta_j^{\text{ols}}) \geq 0 \]

where \( \beta_j^{\text{ols}} \) is the j-th component of the Ordinary Least Squares (OLS) estimator. This is analogous to the following formulation:

\[ \hat{\beta} = \arg \min_\beta \left\{ \frac{1}{2} \| y - X\beta \|_2^2 + \lambda \sum_{j=1}^p (1/|\beta_j^{\text{ols}}|) |\beta_j| \right\} \]

This can be seen as a version of the Adaptive LASSO (ALASSO) model (see Table 1 of the supplemental material (online)) with sign constraints over \( \beta \) and with weights defined as \( y_j = 1/|\beta_j^{\text{ols}}| \). As originally conceived, the NNG is limited to \( p < n \) situations because it depends heavily on the OLS estimator. However, it can be extended to the \( p \gg n \) scenario if we consider making it dependent on other estimators and stating a general approach. In other words, we can use any reference estimator (for example, the LASSO, Fusion LASSO, ENET or SLASSO) and denote it as \( \beta^{\text{ref}} \). The NNG extension to the \( p \gg n \) scenario is then a nonnegative version of an ALASSO model where the weights are defined from other reference solutions previously known (or computed). In this sense, it is clear that an AMNR algorithm can be designed to implement the NNG method for general \( p \gg n \) conditions. It is evident that using a sparse \( \beta^{\text{ref}} \) would be helpful to promote sparsity since those high \( \beta_i^{\text{ref}} \) will imply smaller penalization and those close to zero will push the corresponding variables of the NNG solution to zero. The AMNR algorithms for the ALASSO and the NNG model are respectively shown in sections 4 and 5 of the supplemental material (online).

Another extension that we consider here is the inclusion of other penalty terms in the NNG model (i.e. extend it to MPLS models). The simplest option is just to add a quadratic term for imposing some degree of smoothness:

\[ \hat{\beta} = \arg \min_\beta \left\{ \frac{1}{2} \| y - X\beta \|_2^2 + (\lambda_{sm}/2) \| L\beta \|_2^2 + \lambda_{sp} \sum_{j=1}^p (1/|\beta_j^{\text{ref}}|) |\beta_j| \right\} \]

which is equivalent to

\[ \hat{W} = \arg \min_w \left\{ \frac{1}{2} \| y - \Sigma_{j=1}^p x_j \beta_j^{\text{ref}} w_j \|_2^2 + (\lambda_{sm}/2) \| Lw \|_2^2 + \lambda_{sp} \Sigma_{j=1}^p w_j \right\}; \text{s.t. } w_j \geq 0 \quad (3.4) \]

where \( L = LD, \ D = \text{diag}(\beta_1^{\text{ref}}, \beta_2^{\text{ref}}, ..., \beta_p^{\text{ref}}) \) and \( L \) is a structure matrix that can be set to the identity matrix (i.e. implying independence of \( w_j \)) or to any other matrix (e.g. first or second
difference operators). This extension of the NNG (equation (3.4)) with a smoothness term will be
called the Smooth Nonnegative Garrote (SNNG). In practice, the solution is found by \( \hat{\beta}_j = \hat{w}_j \beta^\text{ref}_j \),

avoiding the division by \( |\beta^\text{ref}_j| \) (in any step of the algorithm) which is very important when \( \beta^\text{ref} \)
is a sparse solution. In that case, the condition \( w_j \geq 0 \) implies that elements that are zero in the
\( \beta^\text{ref} \) will also be zero in \( \beta \), making the problem smaller and the estimation faster as we only need
to re-estimate coefficients that are nonzero in \( \beta^\text{ref} \) and also making the SNNG solution as sparse
as or sparser than the one used as reference.

On the other hand, equation (3.4) can also be seen as a Smooth LASSO model (Hebiri and
van de Geer (2011)) with sign constraints if we set \( \beta^\text{ref}_j = 1, \forall j \), and take \( \mathbf{L} \) as the first difference
matrix. We will call this extension of Smooth LASSO with nonnegative constraints, as NN-
SLASSO. To our knowledge, the SLASSO model has not been treated with nonnegative
restrictions and we will explore its performance to solve ill-posed problems in this paper. Other
extensions that will not be explored here can be easily derived from the more general model, such
as nonnegative versions of ENET and Ridge L (i.e. using \( \lambda_{sp} = 0 \)).

4. Performance of MNR and AMNR: simulation study

The goal of this simulation study is to investigate the performances of MNR and AMNR
algorithms for different penalized models. To this end, we generate 100 independent samples of
the simulation design for three different \( n/p \) relations (\( n/p = \{0.05, 0.25, 0.5\} \)), corresponding to
200 predictors (\( p = 200 \)) and \( n \) observations (\( n = \{10, 50, 100\} \)), respectively. The simulation
design consists in a solution with three active regions (nonzero components) that will be called the
‘bell’, ‘square’ and ‘point’ sources, and the use of the linear model

\[
\mathbf{y} = \mathbf{X} \beta + \epsilon
\]

where \( \beta_j = 0 \) except for:

\[
\beta_j = \begin{cases} 
    e^{-0.015(j-50)^2}, & \text{for } 30 < j < 70 \text{ (bell)} \\
    1, & \text{for } 95 < j < 105 \text{ (square)} \\
    0 & \text{for } j = 150 \text{ (point)}
\end{cases}
\]

The components of \( \mathbf{X}_j \) and \( \epsilon \) are standard normal, which leads to a theoretical SNR of about
13 db. For this data, we estimate \( \beta \) with different penalty methods and algorithms. This simulated
solution is difficult to recover with any of the methods, as it is a piece-wise combination of smooth, constant and isolated coefficients. It is therefore appropriate to evaluate the flexibility of the complex models based on combinations of different penalty functions. To evaluate the performances of the different algorithms, we used three of the quality measures that have been used and described in the literature (Obuchowski et al. (2018)). Area Under the ROC Curve (AUC), Relative Error ($RE = \sum_{i=1}^{n}(\beta_i - \hat{\beta}_i)^2 / \sum_{i=1}^{n} \beta_i^2$), and the computational time (for one solution).

In the analysis of simulated data, we will report boxplots of these measures computed using 100 repetitions corresponding to different noise instances.

Figure 1: Simulated example with $n = 100$ samples and $p = 200$ predictors for testing the LASSO, Fusion LASSO (FnLASSO), Smooth LASSO (SLASSO), and Elastic Net (ENET L) models. Dots represent the true simulated coefficients, the dashed lines correspond to the solutions estimated by LARS algorithm, the solid lines represent those estimated by MNR and the blue dotted lines to those estimated by AMNR.

Figure 1 and Figure 2 illustrate an application of the two proposed algorithms for different models. Both figures show a simulation with $n = 100$ samples and $p = 200$ predictors ($n/p = 0.5$), and the solutions corresponding to those with the median AUC (i.e. the repetition whose AUC is the closest to the median of all AUC). In Figure 1, we compare the LASSO, FnLASSO and SLASSO solutions obtained by using the well-known LARS algorithm as well as with the MNR and AMNR algorithms presented in this paper. Generally, the MNR and the AMNR offered
solutions with similar behavior as those offered by LARS. In the ENET L and FnLASSO, MNR provides the least sparse solutions but reconstructing better all sources (bell, square, point). AMNR seems to estimate over-sparse solutions, missing the point source in the case of SLASSO and ENET L models.

**Figure 2**: Simulated example with \( n = 100 \) samples and \( p = 200 \) predictors for testing the performance of the AMNR algorithm for different models: Ridge, Adaptive LASSO (ALASSO), NonNegative Smooth LASSO (NN-SLASSO), NonNegative Garrote (NNG) and Smooth NonNegative Garrote (SNNG). Dots represent the true simulated coefficients in all panels. For the Ridge model, a dashed line represents the classical solution and the solid line represents the solution using the matrix of second differences (\( L \)). For NNG and SNNG models, we used different reference solutions (\( B_0 \)): dashed, solid and dotted lines correspond to using the ordinary least squares (OLS), Ridge with Laplacian operator (Ridge L) and Fusion LASSO (FnLASSO), respectively.

Figure 2 shows the estimators for Ridge (with and without using the Laplacian operator), ALASSO, NN-SLASSO, NNG and SNNG penalized models, obtained by using the AMNR algorithm. In general, the use of nonnegativity constraints in the NN-SLASSO, or the use of a reference estimator in NNG and SNNG, allows obtaining sparser estimators, more similar to the true simulation. In all cases, the estimator corresponding to the point source suffered from the insufficient data problem and was over shrunk when using smoothness constraint. In particular, the SNNG estimator behaves as a smooth though sparser version of the reference estimator: the most salient features are enhanced while the smaller are discarded. On the contrary, the NNG solution
enhances isolated sources at the cost of degrading the reconstruction of the smooth patches. ALASSO and NN-SLASSO offered good reconstruction of the three regions but with many (small) spurious nonzero coefficients.

Figure 3: Boxplots of Area Under Curve (AUC, in dark gray) and one minus the Relative Error (1-RE, in light grey) for the 100 solutions estimated with each method (combining model and algorithm), from the simulations using 200 predictors ($p = 200$) and 100 observations ($n = 100$). The Ridge solutions were computed with the classical regularized Tikhonov inverse solution (Tikhonov et al. 1995).

For each of the 100 simulations appearing in Figure 1 and Figure 2, for the nine different models and three algorithms, we computed the three measures for a quantitative evaluation of the quality of the reconstruction. Figure 3 presents a boxplot of the AUC and (1-RE) together, for an easier interpretation of results. In both cases we only show the results that are above 0.5. We can see that most of the methods provided medians of AUC and 1-RE above 0.8, but none of them had both measures over 0.9. Only SLASSO (with LARS and AMNR) and ENET L (with AMNR) had median AUC over 0.9 while the lowest RE (<0.1) was given by NN-SLASSO and SNNG (with AMNR) using Ridge L and FnLASSO as reference solutions. Figure 4 presents a boxplot of the computational time (in seconds), showing that besides the non-iterative Ridge solutions- the faster
models are: LASSO using LARS algorithm and NN-SLASSO and NNG using AMNR for whatever reference estimator. As expected, the same models using AMNR were generally faster than when computed with the MNR algorithm.

Figure 4: Boxplots of the time necessary for computing one solution in each combination of model and algorithm, from the simulations using $p = 200$ and $n = 100$. The algorithm for estimating Ridge solutions is not mentioned as it is a simple evaluation of the regularized inverse (Tikhonov) (Tikhonov et al. (1995)).

In Table 1 are summarized the results present in Figure 1 of the supplemental material (online). The Figure show the median of AUC, median Relative Error and median of the computation time across the 100 estimated solutions in the three cases of $n/p$ ratios $\{0.05, 0.25, 0.5\}$ and the mean across these three $n/p$ ratios (black line). The methods with better behavior for any $n/p$ relation were SLASSO (with LARS and AMNR algorithms), ENET L (with LARS and AMNR algorithms), SNNG (with FnLASSO as reference estimator) and the nonnegative version of SLASSO (NN-SLASSO). These results are consistent with the qualitative pictures given in Figure 1 and Figure 2, where SLASSO, ENET L, SNNG and NN-SLASSO are the solutions that better reconstructed the simulated bell and square regions. It is clear that the general difficulties in reconstructing the point source will not be largely reflected in the quantitative measures, as it is
just one out of 200 estimated points. The analysis of the time necessary for computing one solution showed that the fastest methods are Ridge I and Ridge L, NNG (with the three reference solutions) and NN-SLASSO.

| No | Methods (B0) | Algorithm | Mean for three n/p ratios |
|----|--------------|-----------|--------------------------|
|    |              |           | RE   | AUC   | TIME |
| 1  | Ridge I     | Tikhonov  | 0.7547 | 0.6982 | **0.0103** |
| 2  | Ridge L     | LARS      | 0.6341 | 0.7996 | **0.0110** |
| 3  | LASSO       |           | 0.7953 | 0.7984 | 0.4053 |
| 4  | FnLASSO     |           | 0.6892 | 0.7718 | 1.0905 |
| 5  | SLASSO ▲    |           | **0.3416** | **0.8581** | 1.3002 |
| 6  | ENET L ▲    |           | **0.3587** | 0.7861 | 1.2328 |
| 7  | LASSO       | MNR       | 0.7568 | 0.7074 | 5.5728 |
| 8  | FnLASSO     |           | 0.4861 | 0.7760 | 3.4986 |
| 9  | SLASSO      |           | 0.5103 | 0.8104 | 1.4545 |
| 10 | ENET L      |           | 0.4769 | 0.7759 | **0.1001** |
| 11 | LASSO       |           | 0.7706 | 0.8038 | 0.6737 |
| 12 | FnLASSO     |           | 0.7706 | 0.8038 | 0.8614 |
| 13 | SLASSO ▲    |           | **0.3531** | **0.8522** | 1.8470 |
| 14 | ENET L ▲    |           | **0.3295** | **0.8658** | 1.3819 |
| 15 | NNG (OLS)   | AMNR      | 1.4181 | 0.6839 | 0.3558 |
| 16 | NNG (Ridge L) |         | 0.7110 | 0.7895 | 0.3769 |
| 17 | NNG (FnLASSO) |       | 0.7039 | 0.7872 | **0.3226** |
| 18 | SNNG (OLS)  |           | 0.9749 | 0.6521 | 0.9339 |
| 19 | SNNG (Ridge L) |       | 0.5996 | 0.7144 | 2.1342 |
| 20 | FnLASSO ▲   |           | 0.3911 | **0.8366** | 2.1193 |
| 21 | ALASSO      |           | 0.7766 | 0.8003 | 0.5800 |
| 22 | NN-SLASSO ▲ |           | **0.3378** | **0.8179** | **0.2127** |

Table 1: Mean of quantitative quality measures (relative error, area under the curve and computation time) across all n/p ratios for all combinations of models and algorithms. In the case of the NNG and SNNG, B0 represents the reference solution. The best 5 methods in each column were highlighted and the overall best 5 methods were marked with a black triangle.
5. **MNR and AMNR algorithms for solving the EEG inverse problem**

Since the last decade of the past century, much effort has been devoted to the development of methods for EEG/MEG source imaging, i.e. for identifying the generators of the EEG/MEG, which is also known as the EEG/MEG Inverse Problem (EEG IP). Mathematically, this is an ill-posed problem and finding a solution requires the use of additional or prior information about the properties of the sources. Therefore, the EEG IP is usually established as a penalized regression model (Pascual-Marqui et al. (1994); Dale et al. (2000)). However, there is currently no ground truth available about which electrophysiological sources are active in real EEG/MEG experiments. Therefore, the problem of finding the best inverse solution from the many methods proposed (Grech et al. (2008)) is not straightforward. In this context, we have followed the strategy to propose very flexible models that can adjust solutions to the data at hand (Valdés-Sosa et al. (2006)). We have indeed proposed to formalize this problem as a more general MPLS model and have previously studied the performance of inverse solutions obtained from models such as LASSO, FnLASSO and ENET, using LQA and MM in simulated and real EEG data (Vega-Hernández et al. (2008)).

In this section, we explore the use of the AMNR algorithm for solving the EEG inverse problem with multiple penalties. This will allow us to compare the behavior of the recently proposed algorithm with previous MNR techniques in such a difficult problem. In addition, the AMNR will allow us to try models with combination of smoothness/sparsity and sign constraints that have never been applied to the EEG IP before. Simulated and real data were used for a preliminary comparison with the equivalent solutions using the MNR algorithm in terms of quality measures (localization error and blurring) (Vega-Hernández et al. (2008)).

5.1 **Simulated data**

The synthetic data consisted in four different sets of simulated primary current density (PCD) distributions, all of them simulated as a three-dimensional Gaussian source with amplitude of 10 nA/mm$^2$ and width of 10 mm (spherical). Each set contain seven PCDs: a ‘centroid’ PCD with maximum located in a particular anatomical structure of a brain space of 3862 generators, and
6 others derived from this one by locating the maxima in each of the 6 closest neighbor generator. Maximum values of the simulated PCDs were located in 1) the cingulate region left (Cingulate), 2) occipital pole left (Occipital), 3) postcentral gyrus (Postcentral), and temporal gyrus right (Temporal) as shown in the first row of Figure 2 of the supplemental material (online). Talairach Coordinates (Talairach and P. Tournoux, (1988)) of the maximum value of each simulated PCD appear in Table 2 of the supplemental material (online).

The design matrix (known as the Electric Lead Field) for this brain was computed for an array of 19 electrodes from the 10/20 system using a three-spheres piecewise homogenous and isotropic head model (Riera, (1999)). The simulated voltages were obtained through the equation:

$$\mathbf{V}_{(Ne \times 1)} = K_{(Ne \times 3 \times Ng)} \mathbf{j}_{(3 \times Ng \times 1)} + \mathbf{e}_{(Ne \times 1)}$$

where \( \mathbf{j} \) is the simulated PCDs, \( K \) the lead field and \( \mathbf{V} \) is the vector of electric potentials (i.e. simulated EEG as if it was measured on an array of electrodes distributed on the scalp surface). Additive white noise was set up in order to have a signal-to-noise ratio (SNR) of 14.8 db. \( Ne \) represents the number of electrodes (19) and \( Ng \) the number of sources or generators (3862), i.e. the number of grid points obtained from the discretization of the source space inside the brain. Note that as the PCD in each source is a vector magnitude, the solution \( \mathbf{j} \) has \( 3Ng \) elements corresponding to coordinates \( x, y, z \) of the PCD in each source, effectively estimating not only the amplitude but the orientation of the PCD in each voxel.

Using the whole set of simulations, we compared the performance of inverse solutions obtained for all models and algorithms, in terms of the accuracy of the reconstruction (Fawcett (2006)) and of normalized versions of the ‘localization error’ and ‘blurring’, as defined in (Vega-Hernández et al. (2008)). Therefore, all these three quality measures will give values close to 1 for perfect reconstructions and close to 0 for bad reconstructions. Table 2 shows the mean and standard deviation of these normalized quality measures across the 28 estimated inverse solutions.

Results showed that ENET L, SNNG (with Ridge L and FnLASSO as reference solutions) and NN-SLASSO, offered the best overall performance in reconstructing the simulated sources, all of them using the AMNR algorithm (marked with a black triangle in Table 2). In general, models computed with the AMNR offered better accuracy in the reconstruction and better localization of the maximum activation than the same models computed using MNR (LASSO, FnLASSO,
SLASSO, ENET L). The ENET L, SNNG and NN-SLASSO computed by AMNR showed the best localization ability, but among them only the NN-SLASSO presented sources with blurring similar to that of the true simulation. Typically, sparse methods showed better estimation of the blurring, as is the case of NN-SLASSO, NNG, AALASSO and LASSO. Interestingly, both sparse and smooth methods led to solutions with high accuracy when using AMNR and LARS but not with MNR or direct computation (Ridge).

| No | Methods (B0) | Algorithm | Accuracy | Normalized Localization Error | Normalized Blurring |
|----|--------------|-----------|----------|-------------------------------|---------------------|
| 1  | Ridge I      | Tikhonov  | 0.439 ± 0.075 | 0.656 ± 0.215 | 0.022 ± 0.049 |
| 2  | Ridge L      |           | 0.442 ± 0.069 | 0.654 ± 0.164 | 0.009 ± 0.009 |
| 3  | LASSO        | LARS      | 0.951 ± 0.106 | 0.629 ± 0.214 | 0.798 ± 0.198 |
| 4  | FnLASSO      |           | 0.464 ± 0.075 | 0.588 ± 0.242 | 0.802 ± 0.124 |
| 5  | SLASSO       |           | **0.968 ± 0.006** | 0.669 ± 0.167 | 0.486 ± 0.289 |
| 6  | ENET L       |           | **0.968 ± 0.006** | 0.697 ± 0.159 | 0.454 ± 0.290 |
| 7  | LASSO        | MNR       | 0.458 ± 0.100 | 0.635 ± 0.179 | 0.842 ± 0.113 |
| 8  | FnLASSO      |           | 0.444 ± 0.065 | 0.520 ± 0.239 | 0.717 ± 0.134 |
| 9  | SLASSO       |           | 0.828 ± 0.107 | 0.653 ± 0.209 | 0.035 ± 0.164 |
| 10 | ENET L       |           | 0.862 ± 0.116 | 0.522 ± 0.239 | 0.698 ± 0.185 |
| 11 | LASSO        | AMNR      | **0.952 ± 0.101** | 0.652 ± 0.186 | 0.821 ± 0.195 |
| 12 | FnLASSO      |           | **0.952 ± 0.101** | 0.572 ± 0.206 | 0.696 ± 0.378 |
| 13 | SLASSO       |           | 0.949 ± 0.100 | 0.666 ± 0.164 | 0.499 ± 0.290 |
| 14 | ENET L       | AMNR      | **0.952 ± 0.101** | **0.776 ± 0.181** | **0.404 ± 0.349** |
| 15 | NNG (Ridge L)|           | 0.880 ± 0.131 | 0.711 ± 0.190 | **0.869 ± 0.114** |
| 16 | NNG (FnLASSO)|           | 0.893 ± 0.128 | 0.618 ± 0.293 | **0.903 ± 0.087** |
| 17 | SNNG (Ridge L)| AMNR     | **0.952 ± 0.101** | **0.796 ± 0.153** | 0.592 ± 0.437 |
| 18 | SNNG (FnLASSO)| AMNR     | **0.953 ± 0.101** | **0.776 ± 0.180** | 0.628 ± 0.423 |
| 19 | AALASSO      |           | **0.952 ± 0.101** | 0.643 ± 0.208 | 0.856 ± 0.125 |
| 20 | NN-SLASSO    |           | **0.952 ± 0.101** | **0.792 ± 0.193** | **0.914 ± 0.124** |

Table 2: Mean ± standard deviation of the accuracy, normalized Localization Error and normalized Blurring of the 28 inverse solutions for each simulated data. The three best numbers in each column are highlighted.
Maximum intensity projection (glass-brain visualization) of the estimated sources by the best methods according to Table 2 are shown in Figure S3 of the supplemental material (online), corresponding to the simulated ‘centroid’ PCDs in each region. We also added the Ridge L solution, which is mathematically equivalent to a classical solution known as LORETA in the field of EEG source localization (Pascual-Marqui et al (1994)). As expected, the Ridge L solutions are very smooth, while ENET L and SNNG methods (computed with AMNR) offered solutions that fluctuate between different degrees of sparsity/smoothness. Also, the use of sign constraints (allowed by AMNR) in the new inverse solutions SNNG and NN-SLASSO, led to sparser solutions than the unconstrained counterparts. SNNG solutions seem to be sparser versions of the reference solutions but without removing all ghost sources. The NN-SLASSO solutions are over-sparse but showing much less ghost sources as a convenient side effect. This solution also improves the localization of the main source with respect to ENET L, offering a very good localization even for the deepest simulated PCD (Temporal).

5.2 Visual event-related EEG

The real data belongs to a visual event-related experiment, explained in detail in Rodríguez (2012) (Rodríguez et al. (2012)). Briefly, the experiment consisted in presenting to the subject many trials of a sequence of visual stimuli. Each trial started with the presentation of a fixation cross for 200 ms, which was followed by a face or an image (scrambled face) for 83 ms and then immediately masked with a different scrambled image. The total combined duration of the stimulus and mask was fixed at 200 ms. Then a blank screen was presented, and participants had up to 1770 ms to make their response by pressing different keys in the keyboard. Namely, participants were instructed to rate their perception using a 4-point scale: sure (a face was presented), fairly sure (a face was presented), possibly (saw a face), and no impression (of a face). Correct identification of the presentation of a face was assumed in those trials where a face was presented and the response was sure or fairly sure. Incorrect identification of a face was assumed in the same trials when the response was possibly or no impression.
For trials where a face is presented, the brain produces a voltage transient response (known as visual event-related potential, ERP) that can be extracted from noisy EEG recordings by averaging all the stimuli locked data (generally, 1 s-long trials or epochs extracted with respect to the stimuli onset). This ERP typically shows a negative peak around 170 ms (known as N170 component), after presentation of the stimulus. The amplitude of this peak is different for the cases whether the subject correctly recognizes a face or not, where the ERP analysis is conducted by separately averaging only the trials corresponding to each case. For each subject, the N170 amplitudes were measured as the mean voltage within a 30-ms time window centered at the peak of the component, for each condition separately. These amplitudes for all electrodes formed the topographies (maps over the scalp) that were used for source localization (i.e. they were our observed data for solving the EEG inverse problem). The sources of the N170 peak were estimated separately for the topographies corresponding to correct and incorrect responses with the use of Ridge L, the ENET L and NN-SLASSO methods computed by the AMNR algorithm.

Figure 5: Sources of the evoked N170 peak corresponding to topographic maps of correct face detection (upper row) and incorrect detection (bottom row). Maximum intensity projection in the sagittal plane are shown and the amplitudes of the sources are coded in the corresponding color bar to the right of each panel. A and P stand for Anterior and Posterior parts of the brain.

Figure 5 shows the maximum intensity projection in the sagittal plane of the estimated sources of the N170 peak, for each condition: correct responses (top row) and incorrect responses
Sources of the N170 for correct responses were found in the superior temporal gyrus (left and right), in the middle frontal gyrus (left and right) and in the right middle occipital gyrus. Ridge L and ENET L showed less activation on the occipital region for incorrect detection than for the correct detection, while NN-SLASSO offered a sparser solution with no occipital sources in the incorrect condition. On the contrary, the three methods showed stronger activations in the frontal areas in the case of incorrect detection as compared with sources for correct detection. In general, NN-SLASSO showed a cleaner picture than ENET L, while Ridge L gave an over smoothed solution with other confusing activations.

5.3 Resting-state EEG study in active older adults.

Walking speed (or gait speed (GS)) is used in the clinical practice as the main predictor of adverse outcomes and is considered a vital sign of elderly health. It has been linked to disability, hospitalization and death. Walking speed is primarily applied to monitor the functional capacity of older adults and forecast their rate of age-related decline. Recently, there has been an increase in the amount of studies of gait speed as a predictor of a decline in the brain function in older adults. (Rosano et al, (2012); Varma et al, (2016); Pinter et al. (2017)). Main findings suggest that there is an increased brain activation in the prefrontal cortex in response to cognitive tasks during the gait. Because of the complex cognitive processes involved in the speed of the gait, a hypothesis has emerged which states that the slowing down of the motor functions could be an early and sensitive indicator of cognitive sub-clinical deficits in cognitively normal individuals whereas mobility decline and slow gait predict cognitive deterioration and progression to dementia (Mielke y cols., 2012)

In this section we explore the sources of the resting-state EEG measured on a cohort of elders in two different times, to evaluate the correlation with their cognitive decline. This real data is a subset of a prospective study ran in 2010 and 2016, explained in detail in García-Agustein (2020). The original study involved 90 community-dwelling participants over 60 years old that regularly practiced mild-to-moderate exercise in their communities. For this subset, participants were divided into two groups according to their gait speed (GS) as measured in the 2010 and 2016
evaluations. GS was quantified from measuring the time spent to cover 4 meters at a normal pace and was expressed in meters per second (m/s). The main interest was put two groups defines as follows: Group GG, 15 participants with preserved GS (i.e. >0.8 m/s) in both 2010 and 2016 evaluations; Group BB, 15 participants with abnormal GS (<0.8 m/s) in both evaluations.

Figure 6 shown the difference between the estimated sources obtained with the RidgeL and NN-SLASSO solutions from the resting state EEG measurements in 2016 and 2010, represented as cortical generators of the theta band at the 6.25 Hz frequency, for each two groups studied. The maximum activations in each group were found in the frontal inferior, bilateral areas, inferior temporal and occipital regions. Although the two types of solutions have different scales, both show that the energy of these generators in the BB group is greater than in the GG group. In general, NN-SLASSO showed sparser solution than those of Ridge L-, which might help to better interpret all generators, or discard those that are likely to be spurious sources.

These results could indicate that the increase in the magnitude of the generators of theta activity in the supplementary and prefrontal areas in older adults with slower gait speed reflect the brain mechanisms in the alterations in mobility in older adults. These mechanisms have been related both to the cognitive component of gait in older adults (Smith 2017) and to the deficit in multisensory co-activation in these areas, which functions as a compensatory mechanism for peripheral sensory deficit in older adults (Hawkins (2018)).
Figure 6: Surface 3D representation of the difference of cortical generators obtained from 2016 and 2010 resting-state EEG measurements, with the RidgeL and NN-SLASSO inverse solutions in the two groups studied (GG and BB). Sources of Theta band (at 7.03 Hz) in the frontal, left, right and posterior views (from left to right panels) of the brain. The amplitudes of the sources are coded in the corresponding color bar to the left of each panel.

6. Discussion

6.1 New algorithms for multiple penalized least squares models

In this paper we make a formal presentation of the MNR algorithm used in previous studies (Vega-Hernández (2008), Sánchez-Bornot et al (2008)), and showed that the MNR could be applied for estimating general MPLS models. The main advantage is that this open the possibility of recovering sparse and smooth estimators using combinations of L1 and L2 penalty functions. It would also provide an algorithmic framework for exploring others models, such as an extension of SCAD for estimating smooth features, which can be explored in future studies. Known techniques
such as the LQA and MM algorithms can be seen as variants of our MNR technique, since these have been only adapted to implement particular models.

Although the MNR algorithm allows to implement many different penalized models, one disadvantage is that when using sparsity penalties, the estimators still give many small coefficients that should be zero, like in LQA and MM algorithms. This means that a procedure for thresholding the solutions should be included in the algorithm to recover sparse solutions, similar to the approaches implemented in MM and LQA. Another more sophisticated approach is the LQA-Fext (Sánchez-Bornot et al (2008)) which proposes to find a sub-optimal solution, but computationally feasible. To avoid regression with all variables, this procedure makes an iterative statistically selection of variables and, therefore, the final estimate is made using only a set of variables whose coefficients are nonzero. The statistical thresholding is based on the False Discovery Rate (FDR), thus it can be said that the estimated coefficients are significantly different from zero. Unfortunately, the solutions also depend on the arbitrary value of another parameter, in this case the q-value of the FDR.

In this paper we also introduced the AMNR algorithm, which is based on the application of the MNR approach restricted to a space of selected features, i.e. using the “active set” strategy. We showed that this algorithm can be applied to estimate many MPLS models and illustrated its potential application for solving them. The proposed AMNR takes advantage of the fact that the descent direction of the LARS algorithm coincides with the Newton-Rapson (NR) direction in the space of active variables. Moreover, the AMNR allows considering sign constraints in a natural way, in addition to sparsity and/or smoothness.

The proposed AMNR technique can also be regarded as a general template algorithm, where only two main steps need specification: the selection of the next variable to be introduced in the active set and the calculation of the step-length \( \alpha \) in the descent direction. In this general view, the LARS algorithm can be considered as a particular case of AMNR: first, the selection step includes the variable with the highest correlation with the residuals vector (in absolute value) and second, the step \( \alpha \) is taken as the smallest positive value, such that some new variable joins the active set (Efron et al (2004)). Another particular case would be the forward selection method, by selecting
the variable that, together with the variables in the active set, offers the lowest fitting error and then taking $\alpha = 1$ for all iterations.

Using this general framework, we showed that the AMNR can also be applied to other known general nonlinear optimization problems such as Smooth LASSO or Adaptive LASSO. Specifically, the AMNR technique allowed us to propose an extension of the NonNegative Garrote (NNG) method for the $p \gg n$ scenario by using different reference solutions, which conveys the NNG advantages to this challenging scenario. Another family of new methods was also introduced by including an L2 norm penalty to the NNG model to combine sparsity, smoothness and nonnegativity constraints. These were the Smooth NNG (SNNG) and a nonnegative version of the Smooth LASSO (NN-SLASSO). Despite the flexibility of this technique, the application of AMNR to a particular model implies the derivation of a specifically tuned algorithm, which is supported by the algebraic engine that accompanies the procedure.

Similar to any penalized regression approach, another important issue for applying the MNR and AMNR algorithms is the appropriate choices of regularization parameters with respect to variable selection. The accurate estimation of these parameters and the accurate variable selection can be conflicting goals. Indeed, sometimes one gets good performances for the variable selection criteria and not so good performance for the estimation criterion (Gijbels and Vrinssen (2015)). A crucial question is also how to define an appropriate criterion for selecting the regularization parameters when both tasks, estimation and variable selection, are simultaneously addressed. This is a challenging and open research question. In this paper, we evaluated solutions for a grid of different values of the regularization parameters ($\lambda$) and chose the optimal values as those minimizing the generalized cross-validation function (GCV) (Golub, Heath and Wahba, (1979)). Our results suggest that the simultaneous variable selection and estimation performed in the AMNR strategy led to better reconstructions than the use of the MNR algorithm for the same models. This can be explained by an erroneous estimation of optimal regularization parameters by GCV in the MNR.
6.2 Validation of the AMNR algorithm

In a preliminary simulation study, we showed that the AMNR and MNR algorithms provided very similar solutions to those given by the LARS algorithm in the case of known methods like the LASSO family, but the MNR is the slowest of them. Solutions estimated from 100 independent repetitions (changing the additive noise) in three cases of n/p ratio (0.5, 0.25, 0.05), showed that the sparser methods behaved better for smaller n/p ratios. This can be related to the fact that when a smaller amount of data is available, stronger and more precise restrictions are needed. The SLASSO, ENET L, SNNG and NN-SLASSO offered the best reconstructions (median AUC higher than 0.9 and median relative error below 0.1, see Figure 3). The methods NN-SLASSO, ENET L and SLASSO also showed the best overall performance for any n/p relation. This suggested that they are the best methods to study highly underdetermined problems such as the EEG inverse problem.

In the analysis of EEG simulated data the solutions estimated by the AMNR algorithm showed better localization and estimation of the degree of sparsity than the solutions obtained by the MNR algorithm. Also, some of the new methods offered promising solutions to the EEG inverse problem. These models were the Smooth Nonnegative Garrote (SNNG) (using as reference estimators the Ridge L or FnLASSO) and mainly the Nonnegative Smooth LASSO (NN-SLASSO) method. The NN-SLASSO proved to be consistent in finding solutions with low localization error for all different groups of simulations tested, although with a tendency to provide excessively sparse distributions. In general, we found that the NNG and SNNG methods offer solutions which maintain the location of sources shown by the reference solution but with increased sparsity. This result could be exploited in cases where a rough solution with good localization is available, as it is typically the case of Ridge L, which is also fast to compute. The study of the performance of NNG and SNNG when using other more sophisticated solutions as the reference estimator should be carried out in the future.

A major point regarding the evaluation of a good estimation of EEG sources is the capability to correctly locate deep generators (that is, sources that are far from the electrodes). In most of the current methods, specifically those based on penalized regression using L2 norms, solutions are
not capable to correctly locate generators in the temporal lobe or in subcortical regions such as thalamus, brainstem, etc. In our study we observed that sources closer to the electrodes (Postcentral and Cingulate) were better located than those farther from electrodes (Temporal and Occipital) by all methods computed by AMNR (see Figure 2 of the supplemental material online). Although the blurring of the solutions obtained varied in both cases, solutions estimated for deeper regions presented more ghost sources (estimated sources that are not present in the simulation), which usually makes harder the identification of truly activated regions. In our results, it was particularly interesting to find that the NN-SLASSO consistently showed a good location and a low number of ghost sources even for the simulated data from deeper brain regions. This suggests that more exhaustive studies should be made to validate the NN-SLASSO as a promising candidate for stable and sparse EEG source imaging.

Another interesting topic to discuss is the use of nonnegativity constraints in the context of the EEG inverse problem. In our study we found that the use of nonnegativity constraints led to sparser sources without losing real activations. The primary current density (PCD) is a vector field and therefore, an inverse method should be able to provide negative values for a proper estimation of the vector directions. In this sense, the directions obtained by the methods using nonnegativity constraints might be not reliable, and caution must be taken when interpreting results. However, there are other scenarios in which the directions of the vector field might be known or can be constrained by physiological considerations. Alternatively, we could follow a general approach in which signs of nonzero coefficients (after convergence of the sign-constrained solution) can be assigned such that they match the signs of the corresponding coefficients in a -non-sign constrained- reference solution (e.g. OLS, Ridge). Particularly, this can be easily done for the NNG versions proposed here by multiplying the final sign-constrained solution by the sign of the reference solution. Future work should be devoted to a more thorough analysis of the validity and usefulness of this approach for general cases.

Finally, we performed the source localization analysis of two real experimental EEG data with some of the new methodologies in comparison with well-known methods. In a case of a visual event-related EEG from healthy young subjects, the three methods evaluated (Ridge L, ENET L and NN-SLASSO by AMNR) showed PCD distributions with main activations located in brain
areas which were in accordance with previous fMRI studies showing that conscious face detection was linked to activation of fusiform and occipital face areas (see Rodríguez et al (2012) for more details). However, both ENET L and NN-SLASSO presented sparser solutions with an easier interpretation. Although a thorough validation is needed, these results suggest that these new inverse solutions can be used for source localization analysis in other experimental data where ERPs provides relevant information on the physiological brain state. In particular, recent reviews have shown the relevance of using event-related EEG potentials for diagnosis of Alzheimer Disease (AD) (Golub et al. (1979), Cassani et al (2018) and Hedges et al. (2016)). Therefore, it will be very important to perform future studies on the ability of these methods to find differences between healthy people and AD patients in terms of the electrophysiological sources estimated when performing a cognitive task.

Also, in a resting-state EEG study associated to walking speed decline in active elders the two methods evaluated (Ridge L and NN-SLASSO by AMNR) showed that this pattern of abnormalities is characterized by a gradual and focused slowing of brain electrical activity in the supplementary, premotor and prefrontal motor regions. The NN-SLASSO presented sparser solutions with an easier interpretation. Therefore, future studies using these physical performance patterns will be important to determine the probability of having an adverse outcome early.

7. Conclusions

In this work we have introduced a modified Newton-Raphson (MNR) algorithm to estimate multiple penalized least squares (MPLS) models, and its extension to perform efficient optimization over the active set of selected features (AMNR). The proposed MNR technique can be interpreted as a generalization of the Majorize-Minimize (MM) algorithm to include combinations of constraints. The AMNR technique is a general algorithm that allows the implementation of several MPLS models in the same framework. It also allows to naturally include sign constraints in addition to sparsity and/or smoothness, which leads to the introduction of new methods such as the Smooth NonNegative Garrote and NonNegative Smooth LASSO. We showed the usefulness of these new algorithms with simulation studies, specially their advantages to cope
with highly underdetermined problems. Using simulated and real experimental EEG data we showed that solutions obtained with the AMNR algorithm outperformed those with classical MNR techniques such as MM and LQA. Moreover, the new methods based on nonnegativity constraints showed promising results toward the improvement of localization and estimation of more focal sources. However, a full exploration of the validity of these methods to reliably localizing EEG sources in research and clinical applications is still needed. An interesting problem deserving future research is the development of AMNR algorithms to handle nonnegative solutions with methods such as Fusion and Fused LASSO or ENET. We would also like to explore the robustness to noise and doing more general assessments of the methods in the context of EEG/MEG source imaging by using other evaluation measures and by applying them to more complex scenarios.

**Supplementary Material**

The online supplementary material contains the technical proofs, additional simulation and real data results.

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