A multivariate sparse deconvolution algorithm for multi echo fMRI

Master’s thesis

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Abstract

This thesis presents a novel algorithm for the deconvolution of multi echo fMRI data with no prior information on the timings of the neuronal events. Based on previous work on the field, a new signal model is proposed in order to take the processing from a voxelwise analysis to an entire brain one.

Different proximal operators have been studied for solving the optimisation problem present in the deconvolution, since it is an ill-posed inverse problem, and a novel method based on the stability selection procedure has been suggested to answer to the choice of the regularization parameter dilemma. The method takes advantage of the area under the curve (AUC) of the stability paths to avoid the selection of a single regularization parameter. An optimal approach for the thresholding of AUC timeseries is studied and different debiasing methods for removing the sparsity in prolonged events are presented.

The results demonstrate that the MvMESPFM algorithm provides promising results when estimating neuronal-related events even on noisy data. Subject to being thoroughly tested on experimental data, testing conducted on simulated signals suggests that the tool could eventually be introduced to the processing pipelines of different research lines regarding fMRI data analysis.
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Introduction

Functional Magnetic Resonance Imaging (fMRI) is an imaging method that measures regional, time-varying changes in brain metabolism. These metabolic changes can be the result of task-induced cognitive state changes or the result of unregulated processes in the resting brain. Since its origins back in 1990, fMRI has been widely used in an exceptionally large number of studies involving cognitive neurosciences, clinical psychiatry/psychology and presurgical planning. What makes fMRI so popular is, among other aspects, its widespread availability, non-invasive nature and good spatial resolution.

Magnetic Resonance Imaging (MRI) can detect the two primary haemodynamic consequences of increased neural activity, which are increased local cerebral blood flow (CBF) and changes in oxygenation concentration (Blood Oxygen Level Dependent, or BOLD contrast). The change in CBF, which is out of the scope of this work, can be observed using an injected contrast agent and perfusion weighted MRI, first demonstrated by Belliveau, or non-invasively by arterial spin labeling (ASL). BOLD contrast on the other hand, is the contrast that is used in nearly all conventional fMRI experiments. This contrast is a result of the magnetic field surrounding the red blood cells changing based on the oxygen state of the hemoglobin. When fully oxygenated, HbO2 (oxyhemoglobin) is diamagnetic and cannot be magnetically distinguished from the brain tissue. However, fully deoxygenated Hb (deoxyhemoglobin) has 4 unpaired electrons and is highly paramagnetic, which causes loss of signal on MRI and, therefore, generates a natural contrast between highly oxygenated and less oxygenated areas of the brain. During task induced brain activation, there is localized increase in blood flow rich in oxyhemoglobin increasing the MR signal. It is thought that this localized increase in blood flow reflects neuronal activity since both are found to be temporally correlated [1].

The acquisition of fMRI data is commonly performed in the single-echo (SE) manner, where sequences contain one time series in each voxel at a single echo time (TE). The value of TE is usually selected close to the average transverse relaxation time T2 of the gray matter region of interest in order to enhance the sensitivity to the BOLD response. Such a selection of TE maximizes the contrast-to-noise ratio of the signal. Nevertheless, the T2 parameter differs from one brain region to another, and to compensate this variability, a multi-echo (ME) fMRI acquisition can be performed instead, where data is recorded at multiple TEs for each of the time points and can then be optimally combined for improved BOLD sensitivity [2].

The time series of the MR signals that compose the acquired images must be processed in order to obtain maps that represent the activation of the brain. Since the noise can sometimes be larger than the signal of interest, fMRI analysis compare the signal difference between the states using a statistical test. The resulting activation map is a function of the probability of the brain states differing. These statistical tests for activation can be performed using a general linear model (GLM), cross-correlation
with a modeled regressor, or one of several data-driven approaches such as independent components analysis (ICA). These methods model the acquired data against the experimental design of interest as well as “nuisance regressors” of no interest such as signal drift, motion, and noise reflected in global or white-matter signals.

In all cases, the activation testing is preceded by a series of preprocessing steps. These steps can include all or some of the following: 1) time-slice correction, to eliminate differences between the time of acquisition of each slice in the volume; 2) motion coregistration, in which affine head motion is detected and the time series of volumes is resampled to register each time frame to a reference frame, such as the first or middle time series point; 3) correction for physiological noise from breathing and cardiovascular function, low pass and/or high pass temporal filtering to improve the statistics while removing spectral components of no interest; 4) spatial smoothing to improve the signal to noise ratio (SNR) and improve the normality of the noise distribution; 5) normalization to a template based on the stereotaxic atlas.

The analysis of fMRI data has been and continues to be a subject of intense research at this time. As a matter of fact, in the early 2000s, there was a significant shift from the activation clusters to the connectivity analysis in the field of fMRI, motivated by the idea that connectivity is a closer representation of the actual mechanisms of brain function. This was as a result of changes in conceptual focus and methodological procedures with a shift from PET type of analysis to electroencephalography (EEG) and time series type of analysis, which was in part a source of inspiration for this project. While the activation paradigm emphasized the univariate (single-voxel or regional) response in amplitude to an exogenous stimulus, the connectivity paradigm emphasized the bivariate or multivariate covariance.

Nonetheless, not all brain activity can be modeled beforehand using stimulus functions. Unpredictable activity, such as interictal epileptic discharges and resting-state activity to name a few, cannot be inferred from traditional GLM analysis approaches. Therefore, different methodologies that enable the exploration of hemodynamic brain activity without predefined responses have been recently explored. These methods include data-driven methods such as fuzzy clustering [3], temporal clustering analysis (TCA) [4, 5], seed correlation analysis [6], or subspace decomposition methods such as independent component analysis (ICA) [7, 8], canonical correlation analysis (CCA) [9] and agnostic canonical variates analysis (agnostic-CVA) [10]. Among the aforementioned, ICA is probably the most commonly used data-driven method as it provides a bilinear decomposition of the data into components that consist of a spatial map with an associated time course. Its application to fMRI typically relies on spatial statistical independence between the components. However, such criterion is not aimed specifically to identify “activation like” components since no knowledge is taken into account about the hemodynamics or about the type of activity-driven signal.

At the early 2010s a novel model-based method named Paradigm Free Mapping (PFM) was introduced [11]. This method is able to detect and characterize the hemodynamic response to single-trial events without prior information about their timing. Thus, unlike other standard model-based analyses, the method does not require the definition of the onset and duration of the event. This opened up a whole new range of possibilities to study unpredictable events, such as interictal events in epilepsy or signal changes in pharmacological fMRI, as well as providing a new method of studying activity in the resting state with no interaction with the subject.

The PFM method was then refined by applying sparse regression techniques involving the Dantzig selector (DS) in combination with model selection criteria [12]. As a result of this refinement, the fact that individual single-trial events occur sparsely in time was taken into account in the model. This method was named sparse PFM (SPFM) and eluded the definition of a baseline period and the need for amplitude thresholding of the deconvolved signal, which strengthened the detection of notable changes of the underlying signal generating the BOLD response with no prior information on the timings.
However, both PFM and SPFM were only applicable to single echo datasets, thus leaving the necessities in multi echo fMRI signal deconvolution unanswered. For this reason, the researchers behind both these methods proposed yet another refinement to deconvolve multi echo data called Multi Echo Sparse Paradigm Free Mapping (MESPFM) [13]. Unlike previous algorithms that required the combination of the multiple echoes before the deconvolution could be performed, this method directly leveraged the data available in all echoes. In the same fashion as the previous approaches, this algorithm is able to estimate time-varying changes in the transverse relaxation rate ($R_{2}^{*}$) and the net magnetization ($S_{0}$), but in the multi echo scenario.

Another deconvolution method that was also proposed in the early 2010s would feature the so-called Total Activation (TA) method [14]. This method combines both temporal and spatial regularization resulting in structured sparsity with time courses of voxels in the same brain regions being coherent. In addition, the method is able to, through deconvolution, identify the innovation signal as the sparse driver of the BOLD signal. TA also makes use of a fast iterative shrinkage algorithm (FISTA) alternating between the temporal and spatial domain solutions until convergence to obtain the final estimate of the underlying activity-inducing signal.

Unlike in fMRI data analysis, researchers working on M/EEG have been using multivariate models before. Such multivariate methods contemplate the time series of all channels at once when processing the signals. These models could be an analogy to what is found in an fMRI study, where instead of analysing channels, time series of a number of voxels are analysed. For this reason, this work is based on the MESPFM method while adopting the time series type of analysis used in EEG and suggested in [15] precisely. Although MESPFM sought to apply sparsity through temporal regularization, this project also follows the regularization terms proposed in [15], which implements a combination of both temporal and spatial regularization in a similar manner to what TA proposed. Nevertheless, the regularization employed by SPFM has not been discarded since it could serve as a source of comparison between the two methods. Furthermore, a novel procedure based on the stability selection concept in [16] has been applied to this algorithm as a way to improve the estimation of neuronal-related events and net magnetization.

### 1.1 Aim of this thesis

The main objective of this thesis is to develop a novel algorithm for multi echo fMRI data that, unlike previous algorithms that study the data voxelwise, can be applied on the entire brain. The algorithm must be able to detect and characterize the hemodynamic response to single-trial events with no prior information about their timings, as well as estimating the net magnetization term.

On the other hand, some personal objectives have been considered. One of the personal goals would be to outperform previous algorithms, both in precision and speed-wise, so that this new algorithm can replace the existing tools in certain research scenarios regarding multi echo fMRI data analysis. For that same reason, another objective would feature making the algorithm an easy to use tool that can easily be introduced into researcher’s processing pipelines. This would imply that the user should only need to give the tool a short list of parameters in such way that the algorithm takes care of the whole processing with no other user interaction needed. Likewise, the tool should be customizable to a certain extent regarding the selection of the proximal methods, thresholding parameter and masking of the data so that the user can adjust the analysis to better fit each of the studies.
Materials and Methods

As it was previously introduced in chapter 1, this work is based on the signal model proposed in ME-SPFM in [12], deconvolution methods involving the LASSO, the Group-LASSO and the Group and Sparse LASSO proximal operators introduced in [12, 14, 15] and the statistical method called Stability Selection described in [16]. This chapter not only follows the pipeline in the algorithm, but also follows the order on which the different parts that constitute the algorithm were developed.

Regarding the development, the algorithm was entirely developed in MATLAB and makes use of the following MATLAB toolboxes: Parallel Computing Toolbox, Simscape and Statistics, and Machine Learning Toolbox. Likewise, the algorithm uses the SPM software package designed for the analysis of brain imaging data. The main reasons for choosing MATLAB over other programming languages for developing the algorithm were the experience with the language, the active online community when it comes to solving issues our doubts and the fact that there were pieces of code that could be useful for the project already written in MATLAB.

2.1 Multi echo fMRI

So far, algorithms for fMRI data have tackled the deconvolution voxelwise, where the MR signal at time \( t \) for an echo time \( T E_k \) in gradient-echo (GE) echo-planar imaging (EPI) is formulated, as suggested in [13, 17], as:

\[
S(x, t, T E_k) = S_0(x, t)e^{-T E_k R_2^*(x,t)} + n(x, t)
\]  
(2.1)

where \( S_0(x, t) \) and \( R_2^*(x, t) \) are the signal changes in the net magnetization \( S_0 \) and the transverse relaxation rate \( R_2^* \) of the voxel \( x \) at time \( t \), and \( n(x, t) \) is the noise term. The voxel index \( x \) and the noise term will be ignored in order to simplify notation.

If \( S_0(t) \) and \( R_2^*(t) \) are defined as relative changes with respect to their average values in the voxel,

\[
S_0(t) = \bar{S}_0 + \Delta S_0(t), \quad \text{(2.2a)}
\]

\[
R_2^*(t) = \bar{R}_2^* + \Delta R_2^*(t), \quad \text{(2.2b)}
\]

the MR signal can be re-written in the following way:

\[
S(t, T E_k) = (\bar{S}_0 + \Delta S_0(t))e^{-\left(\bar{R}_2^* + \Delta R_2^*(t)\right)T E_k}
\]

\[
= \bar{S}(T E_k) \left(1 + \frac{\Delta S_0(t)}{\bar{S}_0}\right)e^{-\Delta R_2^*(t)T E_k},
\]  
(2.3)

where the mean of the signal is \( \bar{S}(T E_k) = \bar{S}_0e^{-\bar{R}_2^*T E_k} \).
Since $\Delta S_0(t)$ and $\Delta R_2^p(t)$ are significantly smaller than their average values, the last term in equation (2.3) can be approximated with a first-order Taylor expansion as the following one:

$$e^{-\Delta R_2^s(t)TE_k} \approx 1 - \Delta R_2^s(t)TE_k.$$ (2.4)

This approximation can then be replaced in equation (2.3) with $\Delta \rho(t) = \Delta S_0(t)/S_0$, leading to the following expression:

$$S(t,TE_k) = \overline{S}(TE_k) (1 + \Delta \rho(t) - \Delta R_2^s(t)TE_k),$$ (2.5)

where the term resulting from the multiplication of small values of $\Delta R_2^s(t)$ and $\Delta S_0(t)$ can be neglected. Then, expressing fMRI signals in signal percentage changes with respect to the mean of the signal

$$y(t,TE_k) = \left( S(t,TE_k) - \overline{S}(TE_k) \right)/\overline{S}(TE_k),$$ (2.6)

equation (2.5) can be re-written as:

$$y(t,TE_k) \approx \Delta \rho(t) - \Delta R_2^s(t)TE_k.$$ (2.7)

Once the signal model has been approximated and expressed in signal percentage changes, it can be seen as a simple linear regression model with an echo-time-dependent $(TE_k)$ slope that represents the temporal fluctuations related to neuronal events $(\Delta R_2^s(t))$ and the intercept, that is independent from $TE_k$, that expresses the fluctuations related to the net magnetization term $(\Delta S_0(t))$ [13].

2.2 Multi echo SPFM

Furthermore, multi echo SPFM, which is one of the methods this work is based on, suggests that signal changes in $\Delta R_2^s$ can be assumed to produce a hemodynamic response that can be explained by the following expression:

$$\Delta R_2^s(t) = \Delta s(t) * h(t),$$ (2.8)

where $s(t)$ stands for the neuronal activity signal and $h(t)$ is a hemodynamic response function (HRF) that is normalized to have a peak amplitude of 1. Therefore, the signal model in equation (2.7) can be written as

$$y(t,TE_k) = \Delta \rho(t) - TE_k(\Delta s(t) * h(t)).$$ (2.9)

Since the MR signal is sampled every TR seconds $(t = n \cdot TR$ where $n = 1, ..., N$, and $N$ is the number of volumes acquired during the fMRI acquisition), the signal at echo time $TE_k$ and time point $n$ is stated as

$$y_n^k = \Delta \rho_n - TE_k(\Delta s_n * h_n).$$ (2.10)

This model considers all time points as $y_k = [y_1, ..., y_N]^T$, which turns equation (2.10) into

$$y_k = \Delta \rho - TE_kH\Delta s,$$ (2.11)

where $\Delta s \in \mathbb{R}^N$ and $\Delta \rho \in \mathbb{R}^N$ are column vectors of length $N$ that indicate changes in $\Delta R_2^s$ and $\Delta S_0$ respectively, and $H \in \mathbb{R}^{N \times N}$ is a convolution matrix with shifted versions of the HRF $h = [h_0, ..., h_{L-1}]$ that is independent from TE.

Finally, the signal percentage changes of each echo signal can be shaped into vectors in a column vector of length $NK$ leading to the following expression:

$$\begin{bmatrix} y_1 \\ \vdots \\ y_K \end{bmatrix} = \begin{bmatrix} I \\ \vdots \\ I \end{bmatrix} \Delta \rho - \begin{bmatrix} TE_1H \\ \vdots \\ TE_KH \end{bmatrix} \Delta s,$$ (2.12)
where \( I \) is the identity matrix of size \( N \times N \).

Therefore, the deconvolution of the changes in the fMRI signal related to neuronal activity involves the estimation of \( \Delta \rho \) and \( \Delta s \) in equation (2.12). Multi echo SPFM suggests that assuming additive white Gaussian noise, an unbiased estimate of \( \Delta \rho \) and \( \Delta s \) can be obtained with ordinary least squares. Nevertheless, such solution causes estimates with large variability due to the large collinearity between the columns of \( \mathbf{H} \), which is overcome by using Basis pursuit denoising in the following way:

\[
\hat{x} = \text{arg min}_{x} \frac{1}{2} \| \mathbf{y} - \mathbf{T}x \|_2^2 + \lambda \| x \|_1, \tag{2.13}
\]

where \( x^T = [\Delta \rho^T, \Delta a^T] \in \mathbb{R}^{2N} \), \( \mathbf{T} = [\mathbf{I}, \mathbf{H}] \in \mathbb{R}^{KN \times 2N} \) and \( \mathbf{y} = \mathbf{T}x \).

The L1-norm regularization term promotes sparse estimates in a manner that only a few of the coefficients in \( x \) are non-zero, that describe a large variability of the ME-fMRI voxel time series according to the model in equation (2.13). Thus, both variable selection and regularization are performed in such a way that improves prediction accuracy and interpretability of the estimates.

Instead of fixing the regularization parameter \( \lambda \) to a single value, multi echo SPFM suggests computing the entire regularization path and selecting the optimal estimates according to the Bayesian Information Criterion (BIC) as follows:

\[
\hat{x}_{\text{BIC}} = \text{arg min}_{\lambda} NK \log(RSS(\lambda)) + \log(NK)df(\lambda) \tag{2.14}
\]

where \( RSS(\lambda) = \| \mathbf{y} - \mathbf{T}\hat{x}(\lambda) \|_2^2 \) and \( df(\lambda) \) are the residual sum of squares and effective degrees of freedom for each estimate as a function of \( \lambda \), respectively.

Finally, MESPFM proposes performing a debiasing step on the BIC estimates that compensates for the reduction towards zero of the coefficients due to the L1-norm regularization applied in equation (2.13). This step is described in subsection 2.3.5.

### 2.3 Multivariate multi echo sparse paradigm free mapping (MvMESPFM)

#### 2.3.1 Signal model

Transforming the univariate (i.e. voxelwise) signal model shown in (2.12) into a multivariate signal model can be achieved by stacking the voxels columnwise. In other words, \( \Delta s \) and \( \Delta \rho \) shall be defined as follows:

\[
\Delta S = \begin{bmatrix}
  s_1^1 & s_1^2 & \cdots & s_1^n \\
  s_2^1 & s_2^2 & \cdots & s_2^n \\
  \vdots & \vdots & \ddots & \vdots \\
  s_n^1 & s_n^2 & \cdots & s_n^n
\end{bmatrix}, \tag{2.15a}
\]

and

\[
\Delta P = \begin{bmatrix}
  \rho_1^1 & \rho_1^2 & \cdots & \rho_1^n \\
  \rho_2^1 & \rho_2^2 & \cdots & \rho_2^n \\
  \vdots & \vdots & \ddots & \vdots \\
  \rho_n^1 & \rho_n^2 & \cdots & \rho_n^n
\end{bmatrix}, \tag{2.15b}
\]

where \( \Delta S \in \mathbb{R}^{N \times V} \) and \( \Delta P \in \mathbb{R}^{N \times V} \) are matrices of size \( N \times V \).
Finally, the signal percentage changes are represented as a matrix of dimensions $KN \times V$ so that the following model represents the multivariate multi echo signal model:

$$
\begin{bmatrix}
y_{1E_1}^1 & y_{2E_1}^1 & \cdots & y_{VE_1}^1 \\
y_{1E_2}^2 & y_{2E_2}^2 & \cdots & y_{VE_2}^2 \\
\vdots & \vdots & \ddots & \vdots \\
y_{1E_K}^V & y_{2E_K}^V & \cdots & y_{VE_K}^V
\end{bmatrix}
= \hat{Y} \Delta P -
\begin{bmatrix}
TE_1H \\
TE_2H \\
\vdots \\
TE_KH
\end{bmatrix}
\Delta S
$$

(2.16)

where the matrices $\hat{H}$ and $\hat{I}$ are defined as in the univariate model.

### 2.3.2 Optimization problem

Following the ME-SPFM deconvolution method in [13], and as it was introduced in chapter 1, the objective of this algorithm is to map the variations in the BOLD fMRI signal resulting from neuronal activity with no information on the timings. This involves the estimation of $\Delta S$ and $\Delta P$ in equation (2.16). Uncorrelated gaussian noise is assumed so that a least-squares estimation can be used to solve the inverse problem. Furthermore, a regularization term is applied to solve this problem since both the multicollinearity of the matrix $\hat{H}$ and the fact that the number of unknowns is in the order of the number of observations produce estimates with high variability when using least-squares. Based on the univariate inverse problem presented by [13], the following regularized least-squares problem is proposed in this work:

$$
\{\Delta \hat{S}, \Delta \hat{P}\} = \arg \min_{\Delta \hat{S}, \Delta \hat{P}} \frac{1}{2}\|\hat{Y} - \hat{I} \Delta P - \hat{H} \Delta S\|_2^2 + \Omega(\Delta S)
$$

(2.17)

where $\Omega(\Delta S)$ corresponds to the regularization term. Different regularization terms are used in this thesis, as described later. In fact, this optimization problem can be written as

$$
\hat{X} = \arg \min_{\hat{X}} \frac{1}{2}\|\hat{Y} - TX\|_2^2 + \Omega(X)
$$

(2.18)

where $X^T = [\Delta S^T, \Delta P^T] \in \mathbb{R}^{2N \times V}$, $T = [\hat{H}, \hat{I}] \in \mathbb{R}^{KN \times 2N}$ as in [13].

In order to solve this problem, the MvMESPFM algorithm uses a forward-backward splitting approach with the Fast Iterative Shrinkage Thresholding Algorithm (FISTA). Forward-backward splitting allows the optimization of functionals with the sum of two convex functions, $J(X) = f(X) + g(X)$, where $f$ is smooth and $g$ can be non-smooth. In this case, $f(X) = \frac{1}{2}\|Y - TX\|_2^2$ and $g(X) = \Omega(X)$. In the special case of $f$ being the least squares term, the solution can be found with the popular Iterative Shrinkage Thresholding Algorithm (ISTA) with two steps: 1) the forward step: $X_{k+1} = \hat{t}T^T(Y - TX_k)$, where $t$ must be larger than the Lipschitz constant of $f$ (i.e. $L = \rho(T^T T)$, the spectral norm of $H$); 2) the backward step: $X_{k+1} = \text{prox}_t(g)(Z_k)$, where $\text{prox}_t(g)(S)$ denotes the proximal map of $g$.

In this thesis, the FISTA algorithm was used instead of the ISTA algorithm in order to get a faster convergence. Furthermore, to evaluate the performance of the algorithm, three different regularization terms were studied: the LASSO, the Group-LASSO and the $l_1 + l_{2,1}$ norm.

- The $l_1$-norm or LASSO penalty encourages sparse estimates with few non-zero coefficients. Hence, the regularization term $\Omega(X)$ can be rewritten as

$$
\Omega(X) = \lambda |X|_1 = \lambda \sum_{i=1}^{N} |X_i|
$$

(2.19)

In the case of the LASSO, the proximal map is described by the following thresholding operator:

$$
\text{prox}_t(\lambda \cdot |_1)(X) = X_i \max(0, 1 - t\lambda / |X_i|).
$$

(2.20)
The LASSO tends to select only a few variables among a group of highly correlated variables, and neglects any spatial information in the signal model. However, fMRI signals are not completely sparse, but contain some spatial information within.

- The \( l_{2,1} \) norm or Group LASSO should provide the signal model with enough spatial information while maintaining some of the sparsity. The penalty term can be expressed in the following way:

\[
\Omega(X) = \lambda \|X\|_{2,1} = \lambda \sum_{i=1}^{N} \|X_i\|_2
\] (2.21)

The proximity operator for the Group LASSO is described by:

\[
\text{prox}_\lambda (\lambda \| \cdot \|_{2,1} ) (X) = X \max (0, 1 - t\lambda / \|X_i\|_2)
\] (2.22)

where \( \|X_i\|_2 \) stands for the \( l_2 \)-norm of each subvector \( X_i \). This penalty promotes sparsity across groups but retains the \( l_2 \)-norm regularization among group coefficients at the same time.

- The \( l_1 + l_{2,1} \) or the Group and Sparse LASSO promotes sparsity across the time series and have a structuring effect voxelwise. The regularization term in this case is described by the following expression:

\[
\Omega(X) = \lambda (\rho \|X\|_1 + (1 - \rho) \|X\|_{2,1}), \ 0 < \rho < 1
\] (2.23)

where \( \rho \) controls the tradeoff between the \( l_1 \) and \( l_{2,1} \)-norms. When \( \rho = 1 \) the regularization term is the LASSO and when \( \rho = 0 \), the regularization term is the Group LASSO. The proximal method for this composite norm is defined by the following operator:

\[
z_{i,j} = \frac{X_{i,j}}{|X_{i,j}|} \left( |X_{i,j}| - \lambda \rho \right)^+ \left( 1 - \frac{\lambda (1 - \rho)}{\sqrt{\sum_j (|X_{i,j} - \lambda \rho|^2)\!}} \right)^+
\] (2.24)

where \( z = \text{prox}_\lambda (\lambda (\rho \| \cdot \|_1 + (1 - \rho) \| \cdot \|_{2,1})) (X) \) for \( X \in \mathbb{R}, (X)^+ = \max(X, 0) \), and by convention \( \frac{0}{0} = 0 \) \[15\].

Figure 2.1 shows the behaviour of the three regularization terms. First, it shows that the LASSO promotes sparsity in time with no consideration of the spatial information. Furthermore, it shows that the Group LASSO considers the spatial information but does not produce enough sparsity in time. Finally, it shows that the \( l_1 + l_{2,1} \)-norm provides the needed sparsity both voxelwise and timeseries-wise while keeping prolonged events as such with no in-event sparsity. Hence, this final regularization term theoretically provides the optimal behaviour for the MvMESPFM algorithm.

Figure 2.1: Sparsity patterns defined by the different regularization patterns (\( l_1 \)-norm, \( l_{2,1} \)-norm in space and the \( l_1 + l_{2,1} \)-norm). Source: Functional brain imaging with M/EEG using structured sparsity in time-frequency dictionaries by Gramfort et al. (2011) \[15\].
2.3.3 The choice of the regularization parameters

The choice of the regularization parameter $\lambda$ is crucial to obtain appropriate estimates of $\Delta S$ and $\Delta P$ and different approaches have been taken in the literature to evaluate this issue. For instance, multi echo SPFM does not select a fixed value of $\lambda$. Instead, it computes the entire regularization path and selects the optimal estimate according to the Bayesian Information Criterion. Similarly, in this work, the selection of a fixed $\lambda$ is avoided and estimating the entire stability path for all relevant values of $\lambda$ is proposed. The stability paths are the probabilities of each variable being selected when the same optimisation problem is solved in various iterations for random subsamples of the data. This procedure is known as Stability Selection [16]. It is a complement to the usual regularization path plots that show the coefficients of all variables $k = 1, \ldots, p$ as a function of the regularization parameter. It can be seen in figure 2.2 that this simple path plot is potentially very useful for improved variable selection on high dimensional data.

Therefore, for any given regularization parameter $\lambda \in \Lambda$, the selected set $S^\lambda$ is implicitly a function of the samples $I = \{1 \ldots n\}$, where $I$ is originally a random subsample of $\{1 \ldots n\}$ of size $[n/2]$. Thus, for every set $K \subseteq \{1, \ldots, p\}$, the probability of being in the selected set $S^\lambda(I)$ is:

$$\hat{P}_{K} = P^{*}\{K \in S^\lambda(I)\}$$

and for every variable $k = \{1, \ldots, p\}$, the stability path is given by the selection probabilities $\hat{P}_{K}, \lambda \in \Lambda$, where $\Lambda$ is the set of regularization parameters.

In this thesis, a variable is selected when a timepoint in a given voxel has a non-zero value. In contrast to the conventional Stability Selection procedure where variable selection is achieved based on a probability threshold, MvMESPFM proposes a novel method that is described in subsection 2.3.4.

However, another regularization parameter must be selected when using the $l_1 + l_{2.1}$-norm. Since the range of possible values of $\rho$ is very small compared to range of possible values of $\lambda$, $\rho$ is fixed in this work. Furthermore, estimating the stability path with both parameters is computationally very demanding due to the high number of possible combinations. For this reason, different values of $\rho$ have been studied and the one that yields the best results has been selected for further testing and verification of the algorithm.

In this work, two different subsampling methods are proposed. The first one is carried out by randomly selecting 40% of the rows in the HRF matrix in contrast to the $n/2$ subsampling proposed by the original

Figure 2.2: Comparison between the regularization and stability paths.
Stability Selection work in [16]. The rationale for this approach is that in order to have enough points to sample the HRF, two consecutive subsamples could not be used. This first approach required that the same samples were chosen in all echoes, whereas the second technique would avoid such restriction as different timepoints would be selected for different echoes. The probability of each variable being selected is calculated after repeating 100 iterations over each of the regularization parameters. In this thesis, the optimization problem is solved for 50 values of \( \lambda \), the range of which is logarithmically (or linearly) spaced. Values close to the maximum \( \lambda \) would yield very few non-zero coefficients, while lower values of \( \lambda \) will tend to a least squares solution with many non-zero coefficients. This range of \( \lambda \) values is delimited by two percentages of the maximum value possible: 0.05 \( \cdot \lambda_{\text{max}} \) and 0.95 \( \cdot \lambda_{\text{max}} \). The maximum value possible for \( \lambda \) is described by the following expression:

\[
\lambda_{\text{max}} = \max \left| H^T y \right|, \tag{2.26}
\]

### 2.3.4 Novel approach: AUC based on Stability Selection procedure

While the original Stability Selection procedure [16] suggests that stable variables are selected when the probability is higher than a threshold variable (0 < \( \pi_{\text{th}} \) < 1), calculating the area under the curve (AUC) of the stability paths is proposed in this thesis. This calculation yields one AUC value for each of the timepoints of the fMRI signal, hence producing a time series on each voxel. These time series contain higher AUC values on those timepoints with a higher probability of being non-zero, regardless of the regularization parameter. Therefore, instead of working with a set of values of \( \lambda \) to obtain the estimates of \( \Delta R^2_s \) and \( \Delta S_0 \), this approach provides a simpler and more straightforward solution. Indeed, these time series can be directly used to generate the linear model of the active set of coefficients. The AUC value for a given timepoint is expressed as

\[
AUC = \frac{\sum_{l=1}^{L} \Pi^K_l \cdot \lambda_l}{\sum_{l=1}^{L} \lambda_l} \tag{2.27}
\]

for the whole range of values of \( \lambda \) used to draw the stability path, i.e. \( \lambda_l, l = 1, \ldots, L \); where \( \Pi^K_l \) is defined in equation (2.25).

However, AUC values are not completely zero on timepoints where there are no neuronal-related events since low values of \( \lambda \) tend to estimate untrue activations. Therefore, in order to remove false events, AUC time series need to be thresholded. In this thesis, plotting the histogram of AUC values of the region of interest (ROI) against AUC values of regions of non interest is suggested. Voxels in the region of non interest are expected to contain no neuronal-related signals but noise and therefore should have zero (or low) AUC coefficients. Hence, a threshold can be established based on the highest AUC value of the region of non interest. However, this approach is too conservative as some true activation estimates could be ignored. For this reason, using the 99th percentile of the region of non interest is suggested. Even though this approach yields some untrue activations, it ensures that the remaining non-zero AUC coefficients accurately describe true \( \Delta R^2_s \) signal changes.

### 2.3.5 Debiassing

Finally, a debiassing step is applied on the reduced model corresponding to the subset of non-zero coefficients by performing least-squares. The goal of the debiassing step is to overcome the tendency of the proximal methods to shrink estimates towards zero. Let \( A \) denote the support of AUC, i.e. \( A = \text{supp}(AUC) = \{ j | AUC_j \neq 0 \} \), the debiased estimate of \( \hat{X} \) is calculated as

\[
\hat{X}_A = (T_A^T T_A)^{-1} T_A^T Y, \tag{2.28}
\]
where $T_A = [\hat{H}_A, \hat{I}]$, and $\hat{H}_A$ stands for the reduced matrix with the subset of columns of $\hat{H}$ corresponding to the support of $A$. On the other hand, the coefficients of $\Delta S$ that correspond to the AUC values that are not included in $A$ remain as zero.

Furthermore, the debiasing approach implemented in MvMESPFM considers that consecutive non-zero coefficients are grouped and debiased together as the same column in the subset of columns of $\hat{H}$. This is useful in order to estimate prolonged events better. In this thesis, two different options to form such column are proposed: a) calculating the sum of the columns in $\hat{H}$ that correspond to these consecutive coefficients or b) convolving the delta signal these AUC coefficients generate with the main HRF signal. These two approaches reduce the spike-like shape produced by the in-event sparsity of the estimations, favouring block-like or pulse-like shapes, which are closer to what is expected from prolonged neuronal-related events.
The MvMESPFM algorithm was developed and evaluated with simulated signals from the Total Activation Toolbox [14]. The simulated BOLD signals can be seen in figure 3.1. The events producing these signals were convolved with an HRF signal generated with the `spm_hrf` function from the SPM package. Then, white gaussian noise was added to the BOLD signals to make them similar to real fMRI signals. Furthermore, a parcel containing no neuronal events but noise was also simulated. The time echo values were $TE = [15, 35, 50]$ ms and the TR was set to 2 s. Also, variations of the levels of noise and the number of voxels forming each of the parcels were studied so as to evaluate the robustness of the algorithm.

This entire simulated dataset is therefore formed by five different parcels; four of them following the signals in figure 3.1 and another one containing only noise (parcel 5). This dataset provides a wide range of possibilities regarding frequency, length, inter-event intervals and amplitude of neuronal events for testing purposes. In addition, the region with the noisy data serves as a great reference for measuring the specificity of the algorithm.

![Figure 3.1: Simulated neuronal-related events.](image)
Results and Discussion

3.1 Results with the selection of the regularization parameter $\lambda$

This section reports the results of solving the MvMESPFM optimization problem for different regularization terms with fixed values of the regularization parameters $\lambda$ and $\rho$. Figure 3.2 shows the results of the Group-LASSO ($\rho = 0$ and $\lambda = 100$) in all the voxels once the convergence of FISTA is achieved. In order to generate this figure, no debiasing was applied on the data. The bottom figure clearly illustrates that, even though the Group-LASSO estimates the original events, false $\Delta R^*_2$ signal changes are also estimated. The top of the figure demonstrates that the contrast in amplitude between the true and false activations is low specially in parcel 1. This low contrast leads to a more difficult discrimination and interpretability of the events. Besides, the Group-LASSO estimates untrue $\Delta R^*_2$ signal changes in parcel 5, which should contain no estimates.

On the other hand, figure 3.3 shows the results of the LASSO ($\rho = 1$ and $\lambda = 100$) in the same scenario. Unlike the Group-LASSO, the figures illustrate that this regularization does not estimate false $\Delta R^*_2$ signal changes and is considerably more specific in selecting the correct ones. Nevertheless, both in the top and bottom figures, sparsity can be observed in prolonged events, suggesting that this value of $\lambda$ with the LASSO penalizes excessively the estimates towards zero in the search for sparsity. Note that debiasing is not applied here.

Following the previous scenario, figure 3.4 shows the results of the Group and Sparse LASSO ($\rho = 0.5$ and $\lambda = 100$). The bottom figure demonstrates that the specificity of the estimates considerably improves when using the composite norm. In fact, as shown in the top figure, no (or very few) $\Delta R^*_2$ signal changes are detected in voxels with no events, even though these false $\Delta R^*_2$ non-zero coefficients will generate noticeable BOLD signal changes if debiasing was applied. Furthermore, prolonged events do not contain the sparsity that the LASSO promotes, since they are significantly more continuous. These results suggest that the Group and Sparse LASSO yields more accurate estimates, despite the amplitude of prolonged events is not continuous.

The effect of varying the value of $\lambda$ while fixing the value of $\rho$ to 0.75 is shown in figures 3.5, 3.6 and 3.7. The same trend observed with the varying values of $\rho$ can also be seen with the values of $\lambda$: low values of $\lambda$ lead to a greater number of false events and vice versa. This behaviour is clearly shown in figure 3.5 (bottom), where fixing $\lambda$ to 1 yields estimates with more false $\Delta R^*_2$ signal changes. Besides, the top of the figure reassures that false activations can hardly be discriminated from the true ones.

In contrast, $\lambda$ is set to 420 (i.e. high penalization of non-zero $\Delta R^*_2$ signal changes) in figure 3.6. The top figure illustrates that the high penalization yields an optimal solution close to the null one. As shown in the bottom figure, short activations are no longer estimated and only parts of the prolonged events are detected. Therefore, an intermediate value of $\lambda$ is necessary to optimally detect $\Delta R^*_2$ signal changes. Figure 3.7 shows no false activations on either the top or the bottom figures when $\lambda = 100$. However, the bottom figure demonstrates that short events and parts of prolonged activations are not detected.

In summary, these results suggest that most of the $\Delta R^*_2$ signal changes can be correctly estimated with the Group and Sparse LASSO. Nevertheless, this approach implies the search for the optimal values of the two regularization parameters.
Figure 3.2: Results with the Group-LASSO when $\text{std}(n) = 5$ ($\rho = 0$ and $\lambda = 100$; signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
Figure 3.3: Results with the LASSO when std($n$) = 5 ($\rho = 1$ and $\lambda = 100$; signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^*_2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
Figure 3.4: Results with the composite norm with $\rho = 0.5$ and $\lambda = 100$ when std($\alpha$) = 5 (signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
Figure 3.5: Results with the composite norm with $\rho = 0.75$ and $\lambda = 1$ when std($\alpha$) = 5 (signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^*_2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
Figure 3.6: Results with the composite norm with $\rho = 0.75$ and $\lambda = 420$ when $\text{std}(n) = 5$ (signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
Figure 3.7: Results with the composite norm with $\rho = 0.75$ and $\lambda = 100$ when $\text{std}(n) = 5$ (signal intensity is shown in signal percentage change units). Top: timeseries of the simulated, $\Delta R^2$ and BOLD signals in all voxels. Bottom: heatmap of the time series of random voxels.
3.2 Results with the stability selection procedure

Having seen the influence of different values of $\lambda$ on the estimates of the MvMESPFM algorithm, this section reports the results when stability selection is employed. Here, the whole space of $\lambda$ was examined by calculating both the regularization and stability paths. In order to study the robustness of the method, the regularization and stability paths were calculated for different levels of gaussian noise ($\text{std}(n) = 1$, $\text{std}(n) = 3$ and $\text{std}(n) = 5$, which are equivalent to SNR $= 60$, SNR $= 22$ and SNR $= 15$ respectively). The resulting paths can be seen in figures 3.8, 3.9 and 3.10 respectively, where red lines correspond to non-zero $\Delta R^*_2$ coefficients of the simulated data and black lines correspond to timepoints with $\Delta R^*_2$ coefficients equal to zero.

From a certain value of $\lambda$ onwards, many of the non-zero coefficients exhibit a regularization path distinctly separated from zero coefficients. However, the regularization paths also show that increasing the noise leads to a greater number of zero coefficients being incorrectly estimated. This response can clearly be observed in parcel 1, corresponding to the higher frequency signal, and in parcel 5, where no neuronal events were simulated and still lower values of $\lambda$ yield a greater number of non-zero $\Delta R^*_2$ coefficients with increasing noise. Nevertheless, no visually-significant difference is observed in the stability paths among the three levels of noise, which suggests that this method offers certain robustness against different levels of noise, as well as some guidance in identifying non-zero $\Delta R^*_2$ signal changes more accurately. Therefore, the worst case scenario signals ($\text{std}(n) = 5$) were employed to evaluate the stability paths.

The probability of estimating non-zero coefficients with the different values of $\lambda$ was further examined by structuring the stability paths into time series for each $\lambda$ and plot them as heatmaps. These plots can be useful to decide which range of values of $\lambda$ result in adequate selection of nonzero $\Delta R^*_2$ signal changes according to the probability of the corresponding timepoint. Figure 3.11 shows the results in a representative time series in parcel 1. It can be seen that non-negligible probabilities appear with low values of $\lambda$ in timepoints that do not exhibit $\Delta R^*_2$ signal changes, whereas above a certain value of $\lambda$ the non-zero coefficients are correctly estimated and aligned to the original events with more accuracy. Despite the high level of noise, figure 3.12 shows for parcel 2 that the stability selection procedure correctly results in high probabilities in time points with non-zero $\Delta R^*_2$ coefficients. The heatmap illustrates a significant difference between the probabilities of non-zero $\Delta R^*_2$ coefficients and those with no signal change. Such contrast suggests that a reliable probability threshold could be established for a range of regularization parameters $\lambda$ to accurately select non-zero coefficients. Figures 3.13 and 3.14 also corroborate this fact. These figures demonstrate that the coefficients of prolonged events exhibit higher probabilities of being non-zero than brief, more frequent $\Delta R^*_2$ signal changes. Nevertheless, as shown in figure 3.14, even short, weak $\Delta R^*_2$ signal changes can also exhibit high probability values even though additional strong activations occur in the same time series. This result demonstrates the robustness of combining the MvMESPFM algorithm with stability selection for correctly identifying the coefficients of $\Delta R^*_2$ signal changes associated to both brief and isolated activations, as well as strong prolonged activations. On the other hand, Figure 3.15 is a good example of how probabilities tend to zero for a large range of values of $\lambda$, but probabilities start increasing if $\lambda$ approaches zero.

In practice, a probability threshold could be established to select the timepoints with non-zero coefficients based on the probabilities seen in regions where no neuronal activity could take place and thus no neuronal-related $\Delta R^*_2$ signal changes exist. Furthermore, the heatmaps also illustrate that each of the parcels has its own optimal probability threshold and $\lambda$. 

\[ R^2 = \frac{\sum (y - \bar{y})^2}{\sum (y - \bar{y})^2} \]
Results and Discussion

Figure 3.8: Regularization and stability paths when std(\(\sigma\)) = 1 (SNR = 60 and amplitude in signal percentage change units).

Figure 3.9: Regularization and stability paths when std(\(\sigma\)) = 3 (SNR = 22 and amplitude in signal percentage change units).
Results and Discussion

Figure 3.10: Regularization and stability paths when std(n) = 5 (SNR = 15 and amplitude in signal percentage change units).

Figure 3.11: Results of the stability selection in parcel 1 when std(n) = 5 (amplitude in signal percentage change units).
Results and Discussion

Figure 3.12: Results of the stability selection in parcel 2 when std(n) = 5 (amplitude in signal percentage change units).

Figure 3.13: Results of the stability selection in parcel 3 when std(n) = 5 (amplitude in signal percentage change units).
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Figure 3.14: Results of the stability selection in parcel 4 when std(n) = 5 (amplitude in signal percentage change units).

Figure 3.15: Results of the stability selection in parcel 5 when std(n) = 5 (amplitude in signal percentage change units).
3.3 Results with the AUC

Based on the previous observations, one can notice that the AUC of the stability path of coefficients with non-zero $\Delta R_2^*$ signal changes tends to be considerably larger than that of coefficients with null $\Delta R_2^*$ signal changes. Thus, Time series of the AUC of the stability path for each coefficient can be computed to avoid the selection of $\lambda$ and weight the probabilities for a range of $\lambda$. It can be hypothesized that the AUC time series will result in larger contrasts between the non-zero $\Delta R_2^*$ signal changes and the noise. Figure 3.16 shows that nearly all instants where the AUC is non-zero corresponds to timepoints of simulated $\Delta R_2^*$ signal changes. On the other hand, the timepoints with no simulated neuronal events remain zero. In case of parcel 1, the AUC values at the time of the simulated $\Delta R_2^*$ signal changes have ow amplitude since the events are brief and, thus, generate small BOLD signal changes. Instead, the AUC values are considerable higher for parcels 2, 3 and 4 as shown in figures 3.17, 3.18 and 3.19 respectively. The higher AUC values are a result of the longer $\Delta R_2^*$ signal changes. This leads to a higher contrast between time points with non-zero and zero coefficients, thus giving more confidence for setting an optimal threshold based on the AUC time series. As shown in figure 3.20, the values of AUC in parcel 5, which only contains noise, are very low in comparison with the values obtained in the other parcels. This suggests that setting a threshold based on the AUC values of a region with no expected neuronal-related events (e.g. CSF or outside the brain) can be a very reasonable solution to separate the true events from noise.

Importantly, the AUC shows a rippling pattern during long simulated events. In other words, coefficients corresponding to a prolonged event do not contain the same AUC value, some of them are close to zero. This effect is due to the correlation between successive columns of the matrix $\tilde{H}$. If a very strict threshold on AUC were established, these timepoints would not be selected as having non-zero $\Delta R_2^*$ signal changes. This could negatively affect the outcome of the algorithm, as prolonged activations would be split into shorter events. Despite this important consideration, this AUC-based method shows increased specificity and robustness when compared to previous procedures either based on fixed values of $\lambda$ and $\rho$, or based on a fixed probability of the stability selection.

![Image](image_url)
Figure 3.17: Results of the AUC in parcel 2 when \( \text{std}(n) = 5 \) (amplitude in signal percentage change units and \(-R_2^a\) shown in AUC subplot for better readability).

Figure 3.18: Results of the AUC in parcel 3 when \( \text{std}(n) = 5 \) (amplitude in signal percentage change units and \(-R_2^a\) shown in AUC subplot for better readability).
Results and Discussion

Figure 3.19: Results of the AUC in parcel 4 when \( \text{std}(n) = 5 \) (amplitude in signal percentage change units and \( -R_2^* \) shown in AUC subplot for better readability).

Figure 3.20: Results of the AUC in parcel 5 when \( \text{std}(n) = 5 \) (amplitude in signal percentage change units and \( -R_2^* \) shown in AUC subplot for better readability).
The AUC-based method was also evaluated with different levels of noise \( \text{std}(n) = 1, \text{std}(n) = 5 \) and \( \text{std}(n) = 10 \), which are equivalent to SNR = 60, SNR = 15 and SNR = 10 respectively. Figures 3.21, 3.22, 3.23 and 3.24 plot the AUC timecourses for representative voxels of each parcel. In addition, the figures also plot the corresponding timecourse in light blue after thresholding with the 99th percentile of the AUC values in parcel 5 that only contains noise. Figure 3.21 demonstrates that the AUC timecourse accurately follows the timing of the simulated events when \( \text{std}(n) = 1 \), and thresholding has no effect (shown in light blue). With a level of noise of \( \text{std}(n) = 5 \), the AUC time series only captures the simulated \( \Delta R^* \) signal changes, but some of these events are not identified after thresholding. When \( \text{std}(n) = 10 \), noticeable AUC values are also observed at times with no simulated \( \Delta R^* \) signal changes, and more importantly nearly no events are identified after thresholding. Similarly, figures 3.22, 3.23 and 3.24 also indicate that a higher amount of large AUC values are seen at times with no simulated \( \Delta R^* \) signal changes false with increasing levels of noise. However, lowering the SNR is more detrimental for the short \( \Delta R^* \) signal changes than for long \( \Delta R^* \) signal changes which can still be detected in parcels 2, 3 and 4. These observations highlight that setting the threshold based on the AUC values of regions with non-expected \( \Delta R^* \) signal changes becomes critical. False signal changes could be misinterpreted as neuronal-related events with a low threshold, or correctly detected \( \Delta R^* \) signal changes could be neglected if the threshold is too high.

![Figure 3.21: Results of thresholding the AUC with different noise levels in parcel 1 (noise levels of \( \text{std}(n) = 1, \text{std}(n) = 5 \) and \( \text{std}(n) = 10 \), and amplitude of signals in signal percentage change units while amplitude of AUC has no units).](image-url)
Figure 3.22: Results of thresholding the AUC with different noise levels in parcel 2 (noise levels of std(n) = 1, std(n) = 5 and std(n) = 10, amplitude of signals in signal percentage change units while amplitude of AUC has no units).

Figure 3.23: Results of thresholding the AUC with different noise levels in parcel 3 (noise levels of std(n) = 1, std(n) = 5 and std(n) = 10, amplitude of signals in signal percentage change units while amplitude of AUC has no units).
Figure 3.24: Results of thresholding the AUC with different noise levels in parcel 4 (noise levels of \( \text{std}(n) = 1 \), \( \text{std}(n) = 5 \) and \( \text{std}(n) = 10 \), amplitude of signals in signal percentage change units while amplitude of AUC has no units).

Figure 3.25: Results of thresholding the AUC with different noise levels in parcel 5 (noise levels of \( \text{std}(n) = 1 \), \( \text{std}(n) = 5 \) and \( \text{std}(n) = 10 \), amplitude of signals in signal percentage change units while amplitude of AUC has no units).
Figure 3.26: Histogram of AUC values in ROI and region of non interest when std(n) = 1.

To illustrate this fact, figures 3.26, 3.27 and 3.28 show the histogram of AUC values for voxels in parcels 1, 2, 3 and 4 in blue, as well as the corresponding histogram of parcel 5 in orange with lines indicating the maximum AUC and the 95th and 99th percentiles. In the case of std(n) = 1, the stability path of the voxels in parcel 5 is always zero, i.e. no coefficients become non-zero for the selected range of λ. Hence, figure 3.26 only shows the AUC values of parcels 1, 2, 3 and 4. Since the threshold is zero, the AUC timecourses of parcels 1, 2, 3 and 4 remain identical as shown in previous figures. In contrast, figures 3.27 for std(n) = 5 and 3.28 for std(n) = 10 demonstrate that the distribution of AUC values in voxels that only contain noise overlaps the AUC values of voxels in parcels with simulated events, with higher overlap with increasing noise. Based on these figures, establishing the AUC threshold based on the 99th percentile (orange line) might be a good compromise. This threshold is less conservative than the maximum AUC (yellow line), which would make the algorithm be very specific but with reduced sensitivity to detect all true events, and is stricter than the 95th percentile (red line), which would detect all true $\Delta R_2^*$ signal changes but also reveal more false $\Delta R_2^*$ signal changes being detected, i.e. high sensitivity but less specificity.
Figure 3.27: Histogram of AUC values in ROI and region of non interest when \( \text{std}(n) = 5 \).

Figure 3.28: Histogram of AUC values in ROI and region of non interest when \( \text{std}(n) = 10 \).
3.4 Results with debiasing

Figure 3.29 (top) shows the comparison of the debiased estimates against the AUC time series when std(n) = 1, that was thresholded with the 99th percentile. Note that parcel 5 has been excluded since it is a region of non interest and the AUC time series, as well as the $R^2$ events have been scaled to be visible. These results demonstrate that when the noise is minimal, the estimated neuronal-related events and BOLD signals are quasi-perfect (see middle and bottom figures). The only differences with the original signal are a result of AUC values being non-zero in short inter-event intervals. This fact leads to such intervals being considered as part of a prolonged event. Regarding the the difference between debiasing with the sum and the convolution of the HRF signals, the results clearly exhibit that no significant difference exists between the two methods, since differences are minimal and both approaches yield the same BOLD signal estimate.

Figure 3.30 (top) illustrates the results of the debiasing when std(n) = 5. Although a few false events are estimated, the number of correctly estimated events is significantly bigger. This can be clearly observed in the middle figure, where isolated untrue activations are present in the inter-event intervals. In this case, the estimated BOLD signals are slightly different to the original one, unlike when std(n) = 1 where the estimations were quasi-perfect (see bottom figure). Indeed, slight differences in the shape of the BOLD signals can be observed. These results suggest that, even though noise levels increased to a real case scenario, the estimation of $R^2$ and BOLD signals is still accurate.

On the other hand, figure 3.31 (top) demonstrates the robustness of the algorithm, as prolonged events in parcels 2, 3 and 4 are accurately estimated in the worst case scenario, when std(n) = 10. This is clearly exhibited on the heatmaps of both $\Delta R^2$ and BOLD signals (middle and bottom figures). However, the sensitivity for brief activations in parcel 1 significantly reduces as a consequence of the high levels of noise and the brevity the neuronal-related events. It can also be seen that the number of estimated false activations is minimal, regardless of the noise. Regarding the BOLD signals, there is no significant difference between the worst case scenario and when std(n) = 5, which is considered to be the case closest to the real data. These results suggest that the algorithm is able to correctly estimate neuronal-related events in parcels 2, 3 and 4 regardless of the increasing amounts of noise, and is only affected in parcel 1, where activations are brief and have short inter-event intervals.

3.5 Results with different region size ratios

In order to evaluate the robustness of the algorithm against different parcel size ratios, three different scenarios based on the different signal shapes where tested. The first scenario contained 50% of the voxels in parcel 1, 20% of the voxels in parcel 5 and the other three parcels had 10% of the voxels each. The second scenario contained 50% of the voxels on parcel 4, 20% of the voxels in parcel 5 and the other three parcels had 10% of the voxels each. Finally, the last scenario had 60% of the voxels in parcel 5 with the rest of the parcels containing 10% of the voxels each.

Figure 3.32 shows the behaviour of parcel 1 when the ratios are 50% parcel 1, 50% parcel 4 and 60% parcel 5 respectively. No significant differences can be seen among the three plots, which suggests that the high frequency signal in parcel 1 is not influenced by the size of the different regions. As figure 3.33 demonstrates, there are no evidences that suggest estimations are better or worse in parcel 2 in dependance with parcel sizes. Figures 3.34 and 3.35 illustrate that the estimation of prolonged events is not dependent on the size of the regions. In fact, the only differences that can be observed among the plots in each of the figures are a result of the randomized choice of the voxel shown rather than an effect of the varying sizes of the parcels.
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Figure 3.29: Results of the debiasing step (std(n) = 1). Top: time series of the simulated signal, simulated $\Delta R_2^s$ signal, AUC and estimated $\Delta R_2^s$ and BOLD signals after debiasing on random voxels. Middle: heatmap of the simulated vs debiased $\Delta R_2^s$ signals on random voxels. Bottom: heatmap of the simulated vs estimated BOLD signals on random voxels.
Figure 3.30: Results of the debiasing step ($\text{std}(n) = 5$). Top: time series of the simulated signal, simulated $\Delta R_2^*$ signal, AUC and estimated $\Delta R_2^*$ and BOLD signals after debiasing on random voxels. Middle: heatmap of the simulated vs debiased $\Delta R_2^*$ signals on random voxels. Bottom: heatmap of the simulated vs estimated BOLD signals on random voxels.
Figure 3.31: Results of the debiasing step (std(n) = 10). Top: time series of the simulated signal, simulated $\Delta R_2^*_{20}$ signal, AUC and estimated $\Delta R_2^*$ and BOLD signals after debiasing on random voxels. Middle: heatmap of the simulated vs debiased $\Delta R_2^*$ signals on random voxels. Bottom: heatmap of the simulated vs estimated BOLD signals on random voxels.
Figure 3.32: Results of deconvolution in parcel 1 with different parcel size ratios (std($n$) = 5).

Figure 3.33: Results of deconvolution in parcel 2 with different parcel size ratios (std($n$) = 5).
Results and Discussion

Figure 3.34: Results of deconvolution in parcel 3 with different parcel size ratios (std(n) = 5).

Figure 3.35: Results of deconvolution in parcel 4 with different parcel size ratios (std(n) = 5).
Conclusion and future work

A novel algorithm for deconvolution of ME-fMRI data has been developed, named MvMESPFM. This algorithm is able to estimate neuronal events with no prior information about their timings and shifts the voxelwise analysis of fMRI data into an entire brain analysis by solving the optimization problem with a multivariate formulation. This algorithm will be useful for fMRI researchers and will help the ongoing research on scenarios where the timing of neuronal activations cannot be modeled in advance, such as in epilepsy or resting state. A novel procedure for setting the regularization parameter has been developed based on the statistical procedure of stability selection. Different proximal operators and debiasing approaches were studied in order to balance the sparsity in time of the estimates and the spatial structure across voxel time series that make neuronal event estimates more accurate. Each of the steps has been studied and evaluated by testing on simulated multi echo data, and the results demonstrate that the new algorithm accurately estimates $\Delta R^2$ signal changes.

Still, the performance of the algorithm could be further improved by addressing the following points in future work. First, other regularization terms based on the fused LASSO or smooth LASSO [18, 19], which consider the correlation between successive coefficients, could be investigated in combination with the spatial Group LASSO. These operators penalize the difference between successive coefficients and, thus, they will be beneficial in the estimate of prolonged events. Second, a better tuning of the threshold based on AUC could be studied in order to improve the results obtained after debiasing. Third, although the algorithm considers a fixed HRF for modeling the BOLD response associated to $\Delta R^2$ signal changes, it could be modified by defining a model that considers a linear combination of temporal basis functions, for example the canonical HRF, its temporal derivative and its dispersion derivative, in order to account for variability in the shape of the HRF. Fourth, taking into account the dimensionality of the data, future versions of the algorithm could be developed in the CUDA programming language in order to accelerate the processing by running the algorithm in graphical processing units (GPU). Currently, the computational bottleneck of the algorithm is a considerable increase in memory requirements owing to the multivariate model and the multiple repetitions of the stability selection procedure. Finally, the algorithm must be tested on experimental data and compared with other deconvolution approaches, such as its univariate counterpart MESPFM [13].
Conclusion and future work


Declaration on Scientific Integrity

includes Declaration on Plagiarism and Fraud

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Type of work
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Declaration
I hereby declare that this submission is my own work and that I have fully acknowledged the assistance received in completing this work and that it contains no material that has not been formally acknowledged. I have mentioned all source materials used and have cited these in accordance with recognised scientific rules.

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