

# Hemodynamic Deconvolution Demystified: Sparsity-Driven Regularization at Work

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## Abstract

Deconvolution of the hemodynamic response is an important step to access short timescales of brain activity recorded by functional magnetic resonance imaging (fMRI). Albeit conventional deconvolution algorithms have been around for a long time (e.g., Wiener deconvolution), recent state-of-the-art methods based on sparsity-pursuing regularization are attracting increasing interest to investigate brain dynamics and connectivity. This technical note revisits the main concepts underlying two main methods, Paradigm Free Mapping and Total Activation, in the most accessible way. Despite their apparent differences, these methods are theoretically equivalent as they represent the synthesis and analysis sides of the same problem. We demonstrate this equivalence in practice with their best-available implementations using both simulations, with different signal-to-noise ratios, and experimental data of motor task and resting-state fMRI. We evaluate the parameter settings that lead to equivalent results, and showcase the potential of these algorithms compared to other widely-used approaches. This note is useful for practitioners interested in having a better understanding of state-of-the-art hemodynamic deconvolution, and who want to make use of them in the most efficient implementation.

*Keywords:* fMRI deconvolution, paradigm free mapping, total activation, temporal regularization

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## 1. Introduction

Functional magnetic resonance imaging (fMRI) data analysis is often directed to identify and disentangle the neural processes that occur in different brain regions during task or at rest. As the blood oxygenation level-dependent (BOLD) signal of fMRI is only a proxy for neuronal activity mediated through neurovascular coupling, an intermediate step that estimates the activity-inducing signal, at the timescale of fMRI, from the BOLD timeseries can be useful. Conventional analysis of task fMRI data relies on the general linear models (GLM) to establish statistical parametric maps

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of brain activity by regression of the empirical timecourses against hypothetical ones built from the knowledge of the experimental paradigm. However, timing information of the paradigm can be unknown, inaccurate, or insufficient in some scenarios such as naturalistic stimuli, resting-state, or clinically-relevant assessments.

Deconvolution and methods alike are aiming to estimate neuronal activity by undoing the blurring effect of the hemodynamic response, characterized as a hemodynamic response function (HRF). Given the inherently ill-posed nature of hemodynamic deconvolution, due to the strong temporal low-pass characteristics of the HRF, the key is to introduce additional constraints in the estimation problem that are typically expressed as regularizers. For instance, the so-called Wiener deconvolution is expressing a “minimal energy” constraint on the deconvolved signal, and has been used in the framework of psychophysiological interactions analysis to compute the interaction between a seed’s activity timecourse and an experimental modulation (Glover 1999; Gitelman et al. 2003; Gerchen et al. 2014; Di and Biswal 2018; Freitas et al. 2020). Complementarily, the interest in deconvolution has increased to explore time-varying activity in resting-state fMRI data (Prete et al. 2017; Keilholz et al. 2017; Lurie et al. 2020; Bolton et al. 2020). In that case, the aim is to gain better insights into the neural signals that drive functional connectivity at short time scales, as well as how the spatio-temporal structure of functional components that dynamically construct resting-state networks and their interactions (Karahanoğlu and Ville 2017).

Deconvolution of the resting-state fMRI signal has illustrated the significance of transient, sparse spontaneous events (Petridou et al. 2012; Allan et al. 2015) that refine the hierarchical clusterization of functional networks (Karahanoğlu et al. 2013) and reveal their temporal overlap based on their signal innovations not only in the human brain (Karahanoğlu and Ville 2015), but also in the spinal cord (Kinany et al. 2020). Similar to task-related studies, deconvolution allows to investigate modulatory interactions within and between resting-state functional networks (Di and Biswal 2013, 2015). In addition, decoding of the deconvolved spontaneous events allows to decipher the flow of spontaneous thoughts across cognitive domains while at rest (Karahanoğlu and Ville 2015; Gonzalez-Castillo et al. 2019). Beyond findings on healthy subjects, deconvolution techniques has also proven its utility in clinical conditions to characterize functional alterations of patients with a progressive stage of multiple sclerosis at rest (Bommarito et al. 2020), to find functional signatures of prodromal psychotic symptoms and anxiety at rest on patients suffering from schizophrenia (Zöller et al. 2019), to detect the foci of interictal events in epilepsy patients without an EEG recording (Lopes et al. 2012; Karahanoglu et al. 2013), or to study functional dissociations observed during non-rapid eye movement sleep that are associated with reduced consolidation of information and impaired consciousness (Tarun et al. 2020).

The algorithms for hemodynamic deconvolution can be classified based on the assumed hemodynamic model and the optimization problem used to estimate the neuronal-related signal. Most approaches assume a linear time-invariant model for the hemodynamic response that is inverted by means of variational (regularized) least squares estimators (Glover 1999; Gitelman et al. 2003; Gaudes et al. 2010, 2012, 2013; Caballero-Gaudes et al. 2019; Hernandez-Garcia and Ulfarsson 2011; Karahanoğlu et al. 2013; Cherkaoui et al. 2019; Costantini et al. 2021; Hütel et al. 2021), logistic functions (Bush and Cisler 2013; Bush et al. 2015; Loula et al. 2018), probabilistic mixture models (Pidnebesna et al. (2019)), convolutional autoencoders (Hütel et al. 2018) or nonparametric homomorphic filtering (Sreenivasan et al. 2015). Alternatively, several methods have also been proposed to invert non-linear models of the neuronal and hemodynamic coupling (Riera et al. 2004; Friston et al. 2008; Havlicek et al. 2011; Aslan et al. 2016; Madi and Karameh 2017; Ruiz-Euler et al. 2018).

Among the variety of approaches, those based on regularized least squares estimators have been

more employed due to their appropriate performance at small spatial scales (e.g. voxelwise). Relevant for this work, two different formulations can be established for the regularized least squares problem, either based on a synthesis-based or analysis-based model (Elad et al. 2007; Ortelli and van de Geer 2019). The rationale of the synthesis-based model is that we know or suspect that the true signal (here, the neuronally-driven BOLD component of the fMRI signal) can be represented as a linear combination of predefined patterns or dictionary atoms (for instance, the hemodynamic response function). In contrast, the analysis-based approach considers that the true signal is analyzed by some relevant operator and the resulting signal is small (i.e. sparse).

This note revisits synthesis- and analysis-based deconvolution methods for fMRI data and comprises four sections. In the first, we present the theory behind two state-of-the-art deconvolution approaches based on regularized least squares estimators that promote sparsity: Paradigm Free Mapping (PFM) (Gaudes et al. 2013) — available in AFNI as *3dPFM* and *3dMEPFM* for single-echo and multi-echo data, respectively — and Total Activation (TA) (Karahanoglu et al. 2013) — available as part of the *iCAPs toolbox*. We then assess their performance controlling for a fair comparison on simulated and experimental data. Finally, we discuss the benefits and shortcomings of each technique and conclude with our vision on potential extensions and developments.

## 2. Theory

### 2.1. Notations and definitions

Matrices of size  $N$  rows and  $M$  columns are denoted by boldface capital letters, e.g.,  $\mathbf{X} \in \mathcal{R}^{N \times M}$ , whereas column vectors of length  $N$  are denoted as boldface lowercase letters, e.g.  $\mathbf{x} \in \mathcal{R}^N$ . Scalars are denoted by lowercase letters, e.g.,  $k$ . Continuous functions are denoted by brackets, e.g.,  $h(t)$ , while discrete functions are denoted by square brackets, e.g.,  $x[k]$ . The euclidean norm of a matrix  $\mathbf{X}$  is denoted as  $\|\mathbf{X}\|_2$ , the  $\ell_1$ -norm is denoted by  $\|\mathbf{X}\|_1$  and the Frobenius norm is denoted by  $\|\mathbf{X}\|_F$ .

### 2.2. Conventional general linear model analysis

Conventional general linear model (GLM) analysis puts forward a number of regressors incorporating hypothetical knowledge about the paradigm or behavior. For instance, the timing of epochs for a certain condition can be modeled as an indicator function  $p(t)$  (e.g. Dirac functions for event-related designs or box-car functions for block-designs) convolved with the hemodynamic response function (HRF)  $h(t)$ , and sampled at TR resolution (Friston et al. 1994, 1998; Boynton et al. 1996; Cohen 1997):

$$p(t) \rightarrow p * h(t) \rightarrow x[k] = p * h(k \cdot \text{TR}).$$

The vector  $\mathbf{x} = [x[k]]_{k=1,\dots,N} \in \mathcal{R}^N$  then constitutes the regressor modelling the hypothetical response, and several of them can be stacked as columns of the design matrix  $\mathbf{X} = [\mathbf{x}_1 \dots \mathbf{x}_L] \in \mathcal{R}^{N \times L}$ , leading to the well-known GLM formulation:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}, \quad (1)$$

where the empirical timecourse  $\mathbf{y} \in \mathcal{R}^N$  is explained by a linear combination of the regressors in  $\mathbf{X}$  weighted by the parameters in  $\boldsymbol{\beta} \in \mathcal{R}^L$  and corrupted by additive noise  $\mathbf{e} \in \mathcal{R}^N$ . Under independent and identically distributed Gaussian assumptions of the latter, the maximum likelihood estimate of the parameter weights reverts to the ordinary least-squares estimator; i.e., minimizing the residual sum of squares between the fitted model and measurements. The number of regressors  $L$  is typically

much less than the number of measurements  $N$ , and thus the regression problem is over-determined  
<sup>85</sup> and does no require additional constraints or assumptions.

In the deconvolution approach, no prior knowledge of the hypothetical response is taken into account, and the purpose is to estimate the deconvolved activity-inducing signal  $\mathbf{s}$  from the measurements  $\mathbf{y}$ , which can be formulated as the signal model

$$\mathbf{y} = \mathbf{H}\mathbf{s} + \mathbf{e}, \quad (2)$$

where  $\mathbf{H} \in \mathcal{N} \times \mathcal{N}$  is a Toeplitz matrix that represents the discrete convolution with the HRF, and  $\mathbf{s} \in \mathcal{R}^N$  is a length- $N$  vector with the unknown activity-inducing signal. Note that the temporal resolution of the activiy-inducing signal and the corresponding Toeplitz matrix is generally assumed to be equal to TR of the acquisition, but it could also be higher if an upsampled estimate is desired. Despite the apparent similarity with the GLM equation, there are two important differences. First, the multiplication with the design matrix of the GLM is an expansion as a weighted linear combination of its columns, while the multiplication with the HRF matrix represents a convolution operator. Second, determining  $\mathbf{s}$  is an ill-posed problem given the nature of the HRF. As it can be seen intuitively, the rows of the convolution matrix  $\mathbf{H}$  are highly correlated due to large overlap between shifted HRFs (see Figure 2C), thus introducing large variability in the estimates of  $\mathbf{s}$ . Consequently, additional assumptions under the form of regularization terms (or priors) in the estimate are needed to reduce their variance. In the least squares sense, the optimization problem to solve is given as

$$\hat{\mathbf{s}} = \arg \min_{\mathbf{s}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{s}\|_2^2 + \Omega(\mathbf{s}), \quad (3)$$

The first term quantifies data fitness, which can be justified as the log-likelihood term derived from Gaussian noise assumptions, while the second term  $\Omega(\mathbf{s})$  brings in regularization and be interpreted as a prior on the activity-inducing signal. For example, the  $\ell_2$ -norm of  $\mathbf{s}$  is imposed (i.e.,  $\Omega(\mathbf{s}) = \lambda \|\mathbf{s}\|_2^2$ ) for ridge regression or Wiener deconvolution, which introduces a trade-off between the data fit term and “energy” of the estimates that is controlled by the regularization parameter  $\lambda$ .  
<sup>90</sup>

### 2.3. Paradigm free mapping

In paradigm free mapping (PFM), the formulation of Eq. (3) was considered equivalently as fitting the measurements using the atoms of the HRF dictionary (i.e. columns of  $\mathbf{H}$ ) with corresponding weights (entries of  $\mathbf{s}$ ). This model corresponds to a synthesis formulation. In Gaudes et al. 2013 a sparsity-pursuing regularization was introduced on  $\mathbf{s}$ , which in a strict way reverts to choosing  $\Omega(\mathbf{s}) = \lambda \|\mathbf{s}\|_0$  as the regularization term and solving the optimization problem (Bruckstein et al. 2009). However, finding the optimal solution to the problem demands an exhaustive search across all possible combinations of the columns of  $\mathbf{H}$ . Hence, a pragmatic solution is to solve the convex-relaxed optimization problem for the  $\ell_1$ -norm, commonly known as Basis Pursuit Denoising (Chen et al. 2001) or equivalently as the least absolute shrinkage and selection operator (LASSO) (Tibshirani 1996):

$$\hat{\mathbf{s}} = \arg \min_{\mathbf{s}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{s}\|_2^2 + \lambda \|\mathbf{s}\|_1, \quad (4)$$

which provides fast convergence to a global solution. Imposing sparsity on the activity-inducing signal implies that it is assumed to be well represented by a reduced subset of very few non-zero coefficients at the fMRI timescale of seconds that trigger brief event-related BOLD responses.  
<sup>95</sup> Hereinafter, we refer to this assumption as the spike model.

## 2.4. Total activation

Alternatively, deconvolution can be formulated as if the signal to be recovered directly fits the measurements and at the same time satisfies some suitable regularization, which leads to

$$\hat{\mathbf{x}} = \arg \min_{\mathbf{x}} \frac{1}{2} \|\mathbf{y} - \mathbf{x}\|_2^2 + \Omega(\mathbf{x}). \quad (5)$$

Under this analysis formulation, total variation (TV), i.e. the  $\ell_1$ -norm of the derivative  $\Omega(\mathbf{x}) = \lambda \|\mathbf{Dx}\|_1$ , is a powerful regularizer since it favors recovery of piecewise-constant signals (Chambolle 2004). Going beyond, the approach of generalized TV introduces an additional differential operator  $\mathbf{D}_H$  in the regularizer that can be tailored as the inverse operator of a linear system (Karananoglu et al. 2011), that is,  $\Omega(\mathbf{x}) = \lambda \|\mathbf{DD}_H\mathbf{x}\|_1$ . In the context of hemodynamic deconvolution, total activation is proposed for which the discrete operator  $\mathbf{D}_H$  is derived from the inverse of the continuous-domain linearized Balloon-Windkessel model (Buxton et al. 1998; Friston et al. 2000). Exchanging the poles and zeros of the latter's linear-system characterization leads to a differential operator of the form

$$D_H = \prod_{i=1}^{M_1} (D - \alpha_i I) \left( \prod_{j=1}^{M_2} (D - \gamma_j I) \right)^{-1}, \quad (6)$$

where  $D$  is the derivative operator,  $\alpha_i$  the zeros, and  $\gamma_j$  the poles. The interested reader is referred to (Khalidov et al. 2011; Karahanoglu et al. 2013) for a detailed description.

Therefore, the solution of the total-activation problem

$$\hat{\mathbf{x}} = \arg \min_{\mathbf{x}} \frac{1}{2} \|\mathbf{y} - \mathbf{x}\|_2^2 + \lambda \|\mathbf{DD}_H\mathbf{x}\|_1 \quad (7)$$

will render the activity-related signal  $\mathbf{x}$  for which the activity-inducing signal  $\mathbf{s} = \mathbf{D}_H\mathbf{x}$  and the so-called innovation signal  $\mathbf{u} = \mathbf{Ds}$  will also be available, as they are required for the regularization. We refer to modelling the activity-inducing signal based on the innovation signal as the block model.

## 2.5. Unifying both perspectives

PFM and TA are based on the synthesis- and analysis-based formulation of the deconvolution problem, respectively. In the first case, the recovered deconvolved signal is synthesized to be matched to the measurements, while in the second case, the recovered signal is directly matched to the measurements but needs to satisfy its analysis in terms of deconvolution. This also corresponds to using the forward or backward model of the hemodynamic system, respectively. Hence, it should be possible to make both approaches equivalent (Elad et al. 2007)<sup>1</sup>.

First, TA can be made equivalent to PFM by removing the derivative operator  $\mathbf{D}$  of the regularizer in Eq. (7). It can then be readily verified that replacing in that case  $\mathbf{x} = \mathbf{Hs}$  leads to identical equations and thus both assume a spike model.

Second, the PFM optimization problem in Eq. (4) can also be made equivalent to the TA block model in Eq. (7) by considering the modified forward model  $\mathbf{y} = \mathbf{HLu} + \mathbf{e}$ . Here, the activity-inducing signal  $\mathbf{s}$  is rewritten in terms of the innovation signal  $\mathbf{u}$  as  $\mathbf{s} = \mathbf{Lu}$  where the matrix  $\mathbf{L}$  is

I would exclude this part of Equation 6, and refer to the paper of activelets and TA for more information

It might be adequate to indicate the relationship between the matrices  $\mathbf{H}$  and  $\mathbf{D}_H$ , and also write down  $\mathbf{D}$  and  $\mathbf{L}$  analytically

<sup>1</sup>Without dwelling into technicalities, this equivalence is correct up to the constant, which is in the null space of the derivative operator.

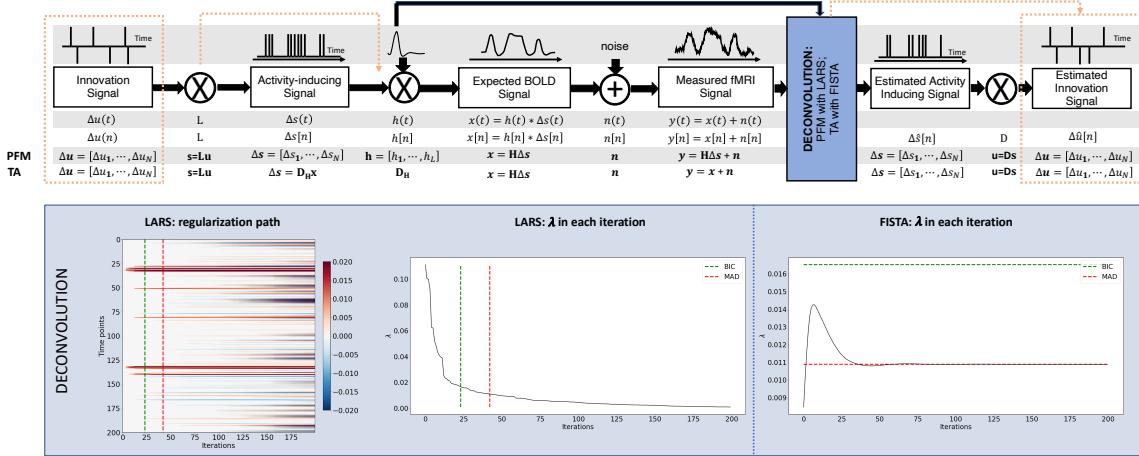


Figure 1: Flowchart detailing the different steps of the fMRI signal and the deconvolution methods described. The orange arrows indicate the flow to estimate the innovation signals. The blue box depicts the two algorithms used in this paper to solve the PFM and TA deconvolution problems. The regularization path obtained with LARS is shown on the left, where the x-axis illustrates the different iterations of the algorithm, the y-axis represents points in time, and the color describes the amplitude of the estimated signal. The green and red dashed lines illustrate the BIC and MAD solutions, respectively. The  $\lambda$  values in the regularization path are shown in the center, with the  $\lambda$  corresponding to the BIC and MAD solutions indicated with dashed lines. Comparatively, the changes in  $\lambda$  when the FISTA method is made to converge to the MAD estimate of the noise are shown on the right. Likewise, the  $\lambda$  corresponding to the BIC and MAD solutions are shown with dashed lines.

the first-order integration operator (Cherkaoui et al. 2019; Uruñuela et al. 2020). This way, PFM can also estimate the innovation signal  $\mathbf{u}$  as follows:

$$\hat{\mathbf{u}} = \arg \min_{\mathbf{u}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{L}\mathbf{u}\|_2^2 + \lambda \|\mathbf{u}\|_1, \quad (8)$$

and becomes equivalent to TA by replacing  $\mathbf{u} = \mathbf{D}\mathbf{D}_{\mathbf{H}}\mathbf{x}$ , and thus adopting the block model.

This work evaluates the core of the two techniques, i.e., the regularized least-squares problem with temporal regularization. Therefore, we do not study the impact of spatial constraints, as we assume that spatial regularization terms should perform identically on both methods.

## 2.6. Algorithms and parameter selection

Despite their analytical equivalence, the PFM and TA methods proposed different different strategies to solve the corresponding optimization problem and select an adequate regularization parameter  $\lambda$ . The PFM implementation available in AFNI employs the least angle regression (LARS) (Efron et al. 2004), whereas the TA implementation uses the fast iterative shrinkage-thresholding algorithm (FISTA) (Beck and Teboulle 2009).

On the one hand, LARS is a homotopy approach that computes all the possible solutions to the optimization problem and their corresponding value of  $\lambda$ , i.e., the regularization path, and the solution according to the Bayesian Information Criterion (BIC) (Schwarz 1978) is considered appropriate in the case of PFM approaches (Gaudes et al. 2013; Caballero-Gaudes et al. 2019).

Alternatively, the regularization parameter  $\lambda$  can also be updated in every iteration of the FISTA so that the residuals of the data fit converge to a previously estimated noise level of the data  $\tilde{\sigma}$ .

This pre-estimated noise level is calculated from the median absolute deviation (MAD) of fine-scale wavelet coefficients (Daubechies, order 3):

$$\lambda^{n+1} = \frac{N\tilde{\sigma}}{\frac{1}{2}\|\mathbf{y} - \mathbf{x}^n\|_F^2} \lambda^n, \quad (9)$$

where  $x^n$  is the  $n^{th}$  iteration estimate,  $\lambda^n$  and  $\lambda^{n+1}$  are the  $n^{th}$  and  $n+1^{th}$  iteration values for the regularization parameter  $\lambda$ , and  $N$  is the number of points in the time-course. The MAD criterion has been adopted in TA (Karahanoglu et al. 2013). Of note, similar formulations based on the MAD estimate have also been applied in PFM formulations (Gaudes et al. 2012, 2011).

### 3. Methods

#### 3.1. Simulated data

In order to compare the two methods while controlling for their correct performance, we created a simulation scenario that can be found in the GitHub repository shared in section 6. For the sake of illustration, we describe here the simulations corresponding to a timecourse with a duration of 400 seconds (TR = 2 s) where the activity-inducing signal includes 5 events, which are convolved it with the canonical HRF. Different noise sources (physiological, thermal, and motion-related) were also added and we simulated three different scenarios with varying signal-to-noise ratios (SNR = [20 dB, 10 dB, 3 dB]) that represent low, medium and high contrast-to-noise ratios as shown in Figure 2A. Noise was created following the procedure in (Gaudes et al. 2013) as the sum of uncorrelated Gaussian noise and sinusoidal signals to simulate a realistic noise model with thermal noise, cardiac and respiratory physiological fluctuations, respectivity. The physiological signals were generated as

$$\sum_{i=1}^2 \frac{1}{2^{i-1}} (\sin(2\pi f_{r,i}t + \phi_{r,i}) + \sin(2\pi f_{c,i}t + \phi_{c,i})), \quad (10)$$

with up to second-order harmonics per cardiac ( $f_{c,i}$ ) and respiratory ( $f_{r,i}$ ) component that were randomly generated following normal distributions with variance 0.04 and mean  $if_r$  and  $if_c$ , for  $i = [1, 2]$ . We set the fundamental frequencies to  $f_r = 0.3$  Hz for the respiratory component (Birn et al. 2006) and  $f_c = 1.1$  Hz for the cardiac component (Shmueli et al. 2007). The phases of each harmonic  $\phi$  were randomly selected from a uniform distribution between 0 and  $2\pi$  radians. To simulate physiological noise that is proportional to the change in BOLD signal, a variable ratio between the physiological ( $\sigma_P$ ) and the thermal ( $\sigma_0$ ) noise was modeled as  $\sigma_P/\sigma_0 = a(tSNR)^b + c$ , where  $a = 5.01 \times 10^{-6}$ ,  $b = 2.81$ , and  $c = 0.397$ , following the experimental measures available in Table 3 in (Triantafyllou et al. 2005).

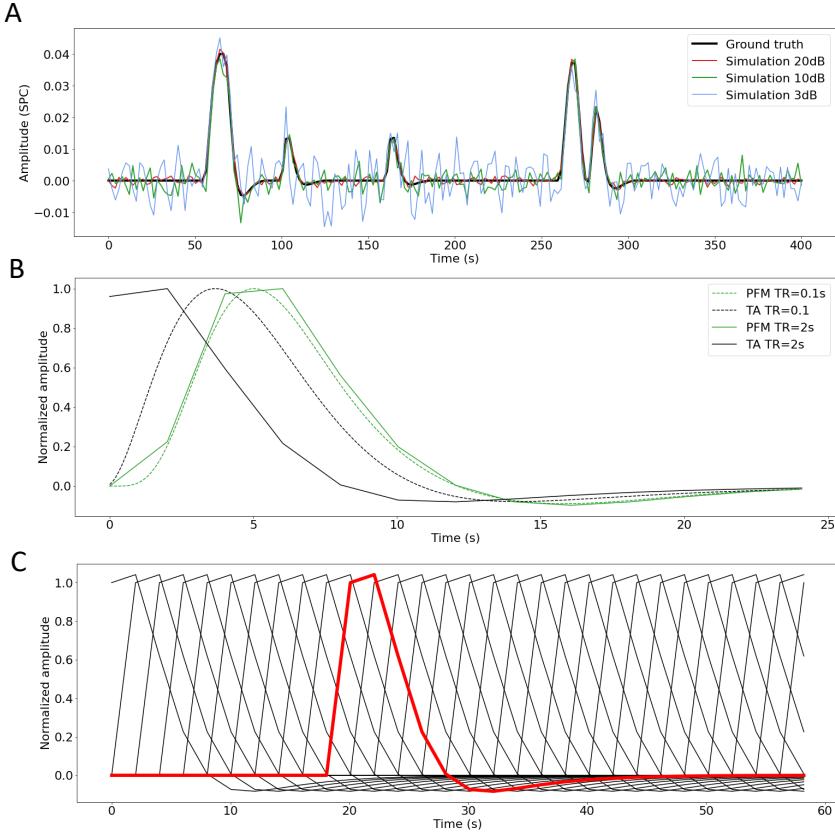


Figure 2: A) Simulated signal with different SNRs (20 dB, 10 dB and 3 dB) and ground truth. B) Canonical HRF models typically used by PFM (green) and TA (black) at TR = 0.1 s (dashed lines) and TR = 2 s (solid lines). Without loss of generality, the waveforms are scaled to unit amplitude for visualization. C) Representation of shifted HRFs at TR = 2 s that build the design matrix for PFM when the HRF model has been matched to that in TA. The red line corresponds to one of the columns of the HRF matrix.

### 3.2. Experimental data

To compare the performance of the two approaches as well as illustrate their operation, we employ two representative experimental datasets.

**145 Motor task dataset:** One healthy subject was scanned in a 3T MR scanner (Siemens) under a Basque Center on Cognition, Brain and Language Review Board-approved protocol. T2\*-weighted multi-echo fMRI data was acquired with a simultaneous-multislice multi-echo gradient echo-planar imaging sequence, kindly provided by the Center of Magnetic Resonance Research (University of Minnesota, USA) (Feinberg et al. 2010; Moeller et al. 2010; Setsompop et al. 2011), with the following parameters: 340 scans, 52 slices, Partial-Fourier = 6/8, voxel size =  $2.4 \times 2.4 \times 3$  mm<sup>3</sup>, TR = 1.5 s, TEs = 10.6/28.69/46.78/64.87/82.96 ms, flip angle = 70°, multiband factor = 4, GRAPPA = 2. During the fMRI acquisition, subjects performed a motor task consisting of five different movements (left-hand finger tapping, right-hand finger tapping, moving the left toes, moving the right toes and moving the tongue) that were visually cued through a mirror located on the head coil.

155 These conditions were randomly intermixed every 16 seconds, and were only repeated once the entire  
set of stimuli were presented. Data preprocessing in AFNI and TEDANA (Community et al. 2021)  
consisted of optimally combining the echo time datasets, detrending of up to 5<sup>th</sup>-order Legendre  
polynomials, within-brain spatial smoothing (3 mm FWHM) and voxelwise signal normalization  
to percentage change. The onset and duration of the different conditions can be seen in Figure 5,  
160 along with the time-series of representative voxels located in the motor areas corresponding to each  
of the conditions.

165 **Resting-state datasets:** One healthy subject was scanned in a 3T MR scanner (Siemens)  
under a Basque Center on Cognition, Brain and Language Review Board-approved protocol. Two  
runs of T2\*-weighted fMRI data were acquired during resting-state, each with 10 min duration,  
170 with 1) a standard gradient-echo echo-planar imaging sequence (monoband) (TR = 2000 ms, TE  
= 29 ms, flip-angle = 78°, matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm<sup>3</sup>, 33 axial slices  
with interleaved acquisition, slice gap = 0.6 mm) and 2) a simultaneous-multislice gradient-echo  
echo-planar imaging sequence (multiband factor = 3, TR = 800 ms, TE = 29 ms, flip-angle = 60°,  
matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm<sup>3</sup>, 42 axial slices with interleaved acquisition, no  
slice gap). Single-band reference images were also collected in both resting-state acquisitions for  
head motion realignment. Field maps were also obtained to correct for field distortions.

175 During both acquisitions, participants were instructed to keep their eyes open, fixating a white  
cross that they saw through a mirror located on the head coil, and not think about anything specific.  
The data was pre-processed using AFNI (Cox 1996). First, volumes corresponding to the initial 10  
seconds were removed to allow for a steady-state magnetization. Then, the voxel time-series were  
180 despiked to reduce large-amplitude deviations and slice-time corrected. Inhomogeneities caused by  
magnetic susceptibility were corrected with FUGUE (FSL) using the field map images (Jenkinson  
et al. 2012). Next, functional images were realigned to a base volume (monoband: volume with  
the lowest head motion; multiband: single-band reference image). Finally, a simultaneous nuisance  
185 regression step was performed comprising up to 6th-order Legendre polynomials, low-pass filtering  
with a cutoff frequency of 0.25 Hz (only on multiband data to match the frequency content of  
the monoband), 6 realignment parameters plus temporal derivatives, 5 principal components of  
white matter (WM), 5 principal components of lateral ventricle voxels (anatomical CompCor) and  
5 principal components of the brain's edge voxels. WM, CSF and brain's edge-voxel masks were  
190 obtained from Freesurfer tissue and brain segmentations. In addition, scans with potential artifacts  
were identified and censored when the euclidean norm of the temporal derivative of the realignment  
parameters (ENORM) was larger than 0.4, and the proportion of voxels adjusted in the despiking  
step exceeded 10%.

### 3.3. Selection of the hemodynamic response function

190 By default, PFM and TA employ different shapes of the discrete-time hemodynamic response  
functions to estimate neuronal-related signals: the canonical HRF in the case of PFM, and an  
HRF resulting from the linear differential operator  $\mathbf{D}_H$  in the case of TA. Their temporal patterns  
are shown in Figure 2B). Consequently, to ensure a fair comparison between the two methods, we  
build the synthesis operator  $\mathbf{H}$  with shifted versions of the HRF given by the analysis operator (see  
195 Figure 2C) taking advantage of its versatile structure.

### 3.4. Selection of the regularization parameter

We use the simulated data to compare the performance of the two deconvolution algorithms  
with both criteria to choose the regularization parameter  $\lambda$ : a selection based on the BIC solution,

check pre-  
processing:  
geometric  
distortions,  
steady-state  
magnetiza-  
tion, realign-  
ment, elastic

and a selection based on the MAD estimate of the noise (see section 2.6). We also evaluate if the  
200 algorithms behave differently in terms of the estimation of the activity-inducing signal  $\hat{s}$  using the spike model described in in (4) and the block model based on the innovation signal  $\hat{u}$  in (8).

For selection based on the BIC, LARS was initially performed with the PFM deconvolution model to obtain the solution for every possible  $\lambda$  in the regularization path. Then, the values of  $\lambda$  corresponding to the BIC solution was adopted to solve the TA deconvolution model by means of  
205 FISTA.

For a selection based on the MAD estimate of the noise, we apply the temporal regularization in its original form for TA, whereas for PFM the selected  $\lambda$  corresponds to the solution whose residuals have the closest standard deviation to the estimated noise level of the data  $\tilde{\sigma}$ .

### 3.5. Analyses in experimental fMRI data

**Difference between approaches:** To assess the extent of the discrepancies between both approaches when applied on experimental fMRI data, we calculate the sum of squares of the differences (SSD) between the activity-inducing signals estimated with PFM and TA on the three experimental datasets as

$$SSD = \frac{\sum_k (\hat{s}_{\text{PFM}}[k] - \hat{s}_{\text{TA}}[k])^2}{N}, \quad (11)$$

210 where  $N$  is the number of timepoints of the acquisition. The SSD of the innovation signals  $\hat{u}$  was computed equally.

**Task fMRI data:** In the analysis of the motor task data, we evaluate the performance of PFM and TA in comparison with a conventional General Linear Model analysis that takes advantage of the information about the duration and onsets of the motor trials. Given the block design of the  
215 motor task, we only make this comparison with the block model.

**Resting-state fMRI data:** We also illustrate the usefulness of deconvolution approaches in the analysis of resting state data where information about the timings of neuronal-related BOLD activity cannot be predicted. Apart from being able to explore individual the maps of deconvolved activity (i.e. innovation signals, activity-inducing signal or hemodynamic signals) at the temporal  
220 resolution of the acquisition (or deconvolution), here we calculate the co-activation patterns (CAPs) and innovation-driven co-activation patterns (iCAPs) from the obtained activity-inducing and innovation signals. To achieve this, we calculate the average time-series in a seed of 9 voxels located in the precuneus, supramarginal gyrus and occipital gyri independently, and solve the deconvolution problem to find the activity-inducing and innovation signals in the seeds. We then apply a 95th  
225 percentile threshold and average the maps of the time-frames that survive the threshold. Finally, we apply the same procedure to the original— i.e., non-deconvolved— signal in the seed and compare the results with the widely-used seed correlation approach.

## 4. Results

### 4.1. Performance based on the regularization parameter

230 Figure 3A shows the regularization paths of PFM and TA side by side obtained for the spike model in (4) for SNR=3 dB. The solutions for all thre SNR conditions are showin in Figure S1 and S2. Starting from the maximum  $\lambda$  corresponding to a null estimate and for decreasing values of  $\lambda$ , LARS computes a new estimate at the value of  $\lambda$  that reduces the sparsity promoted by the  $l_1$ -norm and causes a change in the active set of non-zero coefficients of the estimate (i.e. a zero coefficient

235 of becomes non-zero, or viceversa) as shown in the x-axis of the heatmaps. Vertical black lines  
 236 depict the selection of the regularization parameter based on BIC, and thus, the colored coefficients  
 237 indicated by the vertical lines depict the estimated activity-inducing signal  $\hat{s}$ . Figure 3B illustrates  
 238 the resulting estimates of the activity-inducing and neuronal-related hemodynamic signals when  
 239 basing the selection of  $\lambda$  on BIC for SNR=3 dB. Given that the regularization paths of both  
 240 techniques are identical, it can be clearly observed that the BIC-based estimates are identical too  
 241 for the corresponding  $\lambda$ . Thus, Figure 3A and B demonstrate that, regardless of the simulated SNR  
 242 condition, the spike model of both deconvolution algorithms produce identical regularization paths  
 243 when the same HRF and regularization parameters are applied, and hence, identical estimates of  
 244 the activity-inducing signal  $\hat{s}$  and neuronal-related hemodynamic signal  $\hat{x}$ . Likewise, Figure 3C  
 245 demonstrates that the regularization paths for the block model in (8) also yield virtually identical  
 246 estimates of the innovation signals for both PFM and TA methods. Again, the BIC-based selection  
 247 of  $\lambda$  is identical for both PFM and TA. As illustrated in Figure 3D, the estimates of the innovation  
 248 signal  $u$  also show no distinguishable differences between the algorithms. Hence, Figures 3 A-D  
 249 demonstrate that both PFM and TA yield equivalent regularization paths and estimates of the  
 250 innovation signal and activity-inducing signal regardless of the simulated SNR condition when  
 251 applying the same HRF and regularization parameters with the block and spike models.

252 As for selecting  $\lambda$  according to the MAD criterion in (9), Figure 3E depicts the estimated activity-  
 253 inducing, innovation, and activity-related signals for the three simulated SNR settings using the  
 254 spike model, while Figure 3F shows the estimated signals corresponding to the block model. Both  
 255 plots in Figure 3E and F depict nearly identical results between PFM and TA with both models.  
 256 Given that the regularization paths of both techniques are identical, minor differences are owing to  
 257 the slight dissimilarities in the convergence of the residuals to the estimated noise level of the data.

Last sentence could be skipped and moved to a general conclusion paper in the discussion

#### 4.2. Performance on experimental data

258 Figure 4 depicts the sum of squares difference (SSD) between PFM and TA estimates of the spike  
 259 (Figure 4A and C) and block (Figure 4B and D) models for the three experimental fMRI datasets:  
 260 motor, monoband and multiband. It can be seen that the SSD values are virtually negligible (i.e.  
 261 depicted in yellow) in most of the within-brain voxels and clearly lower than the amplitude of the  
 262 estimates of the activity-inducing and innovation signals. Based on the maximum value of the range  
 263 shown in each image, we observe that the similarity between both approaches is more evident for the  
 264 spike model (with both selection criteria) and the block model with the BIC selection. However, a  
 265 selection of the regularization parameter  $\lambda$  based on the MAD estimate of the noise using the block  
 266 model produces SSD values that are comparable to those of the innovation signal, and the largest  
 267 differences occur in regions with high vasculature, likely resulting from differences in amplitude of  
 268 activity-inducing and innovation signals derived from the noisy nature of the fMRI signal in those  
 269 areas of the brain. These areas also correspond to the highest values of  $\lambda$  (Figure S3) and the  
 270 highest MAD estimates of the noise (Figure S4).

[Expand more on interpretation of this Figure](#)

271 Figure 5 depicts the results of the analysis of the Motor dataset with the PFM and TA algorithms  
 272 using the BIC selection of  $\lambda$  (see Figure S5 for results with MAD selection), as well as a conventional  
 273 GLM approach. The Activation Time Series (top left), calculated as the sum of squares of all voxel  
 274 amplitudes (positive vs. negative) for a given moment in time, obtained with PFM and TA show  
 275 nearly identical patterns. These ATS help to summarize the four dimensional information available  
 276 in the results across the spatial domain and identify instances of significant BOLD activity. The

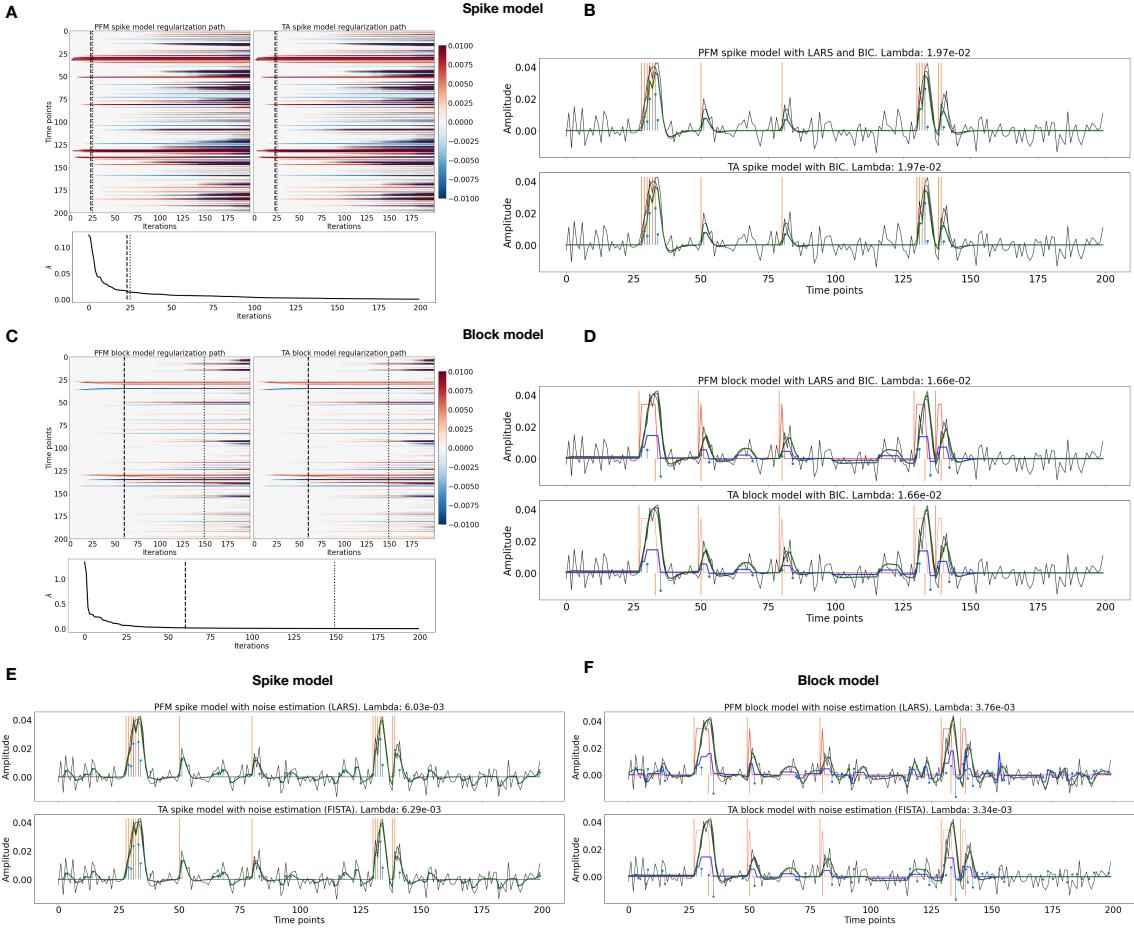


Figure 3: (A) Heatmap of the regularization paths of the activity-inducing signals (spike model) estimated with PFM and TA as a function of  $\lambda$  for the simulated data with SNR = 3 dB (x-axis: increasing number of iterations or  $\lambda$  as given by LARS; y-axis: time; color: amplitude). Vertical lines denote iterations corresponding to the BIC (dashed line) and MAD (dotted line) selection of  $\lambda$ . (B) Estimated activity-inducing (blue) and activity-related (green) signals with a selection of  $\lambda$  based on BIC. (C) Heatmap of the regularization paths of the innovation signals (block model) estimated with PFM and TA as a function of  $\lambda$  for the simulated data with SNR = 3 dB. (D) Estimated innovation (blue), activity-inducing (darker blue), and activity-related (green) signals with a selection of  $\lambda$  based on BIC. (E) Estimated activity-inducing, innovation and activity-related (fit,  $\times$ ) signals estimated with PFM (top) and TA (bottom) when  $\lambda$  is selected based on the MAD method with the spike model, and (F) with the block model for the simulated data with SNR = 3 dB.

differences observed with the block model and a selection of  $\lambda$  based on the MAD estimate shown in Figure 4 are reflected on the ATS shown in Figure S5. The rows below show the voxel timeseries and the corresponding activity-related, activity-inducing and innovation signals obtained with PFM using the BIC criterion of representative voxels in the regions activated in each of the motor tasks. The TA-estimated time-series are not shown because they were equivalent. The maps shown on the right correspond to statistical parametric map obtained with the GLM for each motor condition

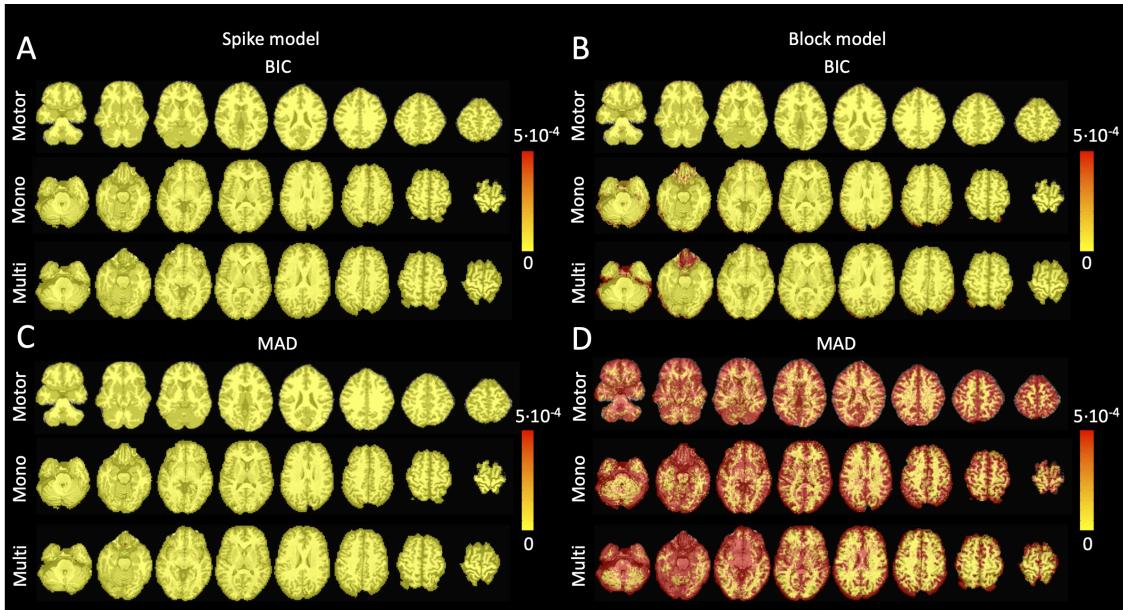


Figure 4: Sum of squares of the differences (SSD) between the estimates obtained with PFM and TA for (A) spike model (activity-inducing signal) and BIC selection of  $\lambda$ , (B) block model (innovation signal) and BIC, (C) spike model (activity-inducing signal) and MAD, (D) block model (innovation signal) and MAD. SSD maps are shown for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets. Note the differences in the maximum value of each figure.

( $p < 0.001$ ) as well as the maps of the PFM and TA estimates at the onsets of individual motor events (indicated with arrows in the timecourse). The estimated activity-related, activity-inducing and innovation signals clearly reveal the activity patterns of each condition in the task, as they exhibit a BOLD response locked to the onset and duration of the conditions. Overall, activity maps of the innovation signal obtained with PFM and TA highly resemble those obtained with a GLM for individual events.

As an illustration of the insights that deconvolution methods can provide in the analysis of resting-state data, Figure 6 depicts the CAPs and iCAPs obtained from thresholding and averaging the activity-inducing and innovation signals, respectively, estimated from the resting-state multiband data using PFM with the BIC to select  $\lambda$ . The activity-inducing CAPs obtained via deconvolution show spatial patterns of the default mode network (DMN), dorsal attention network (DAN) and visual network (VIS) that highly resemble the maps obtained with conventional seed correlation analysis using Pearson correlation, and the CAPs based on the amplitude of the signal (i.e. with no deconvolution). With deconvolution, the CAPs seem to depict less spurious voxels (mainly negative) and more accurate spatial delineation (i.e. less smoothness) than those obtained from the original data, while maintaining the structure of the networks. The BIC-informed selection of  $\lambda$  yields spatial patterns of CAPs and iCAPs that are more sparse than those obtained with a selection of  $\lambda$  based on the MAD estimate (see Figure S6). On the other hand, the spatial patterns of the iCAPs based on the innovation signals using the block model yield complementary information to that obtained with activity-inducing signal since iCAPs allows to reveal regions with

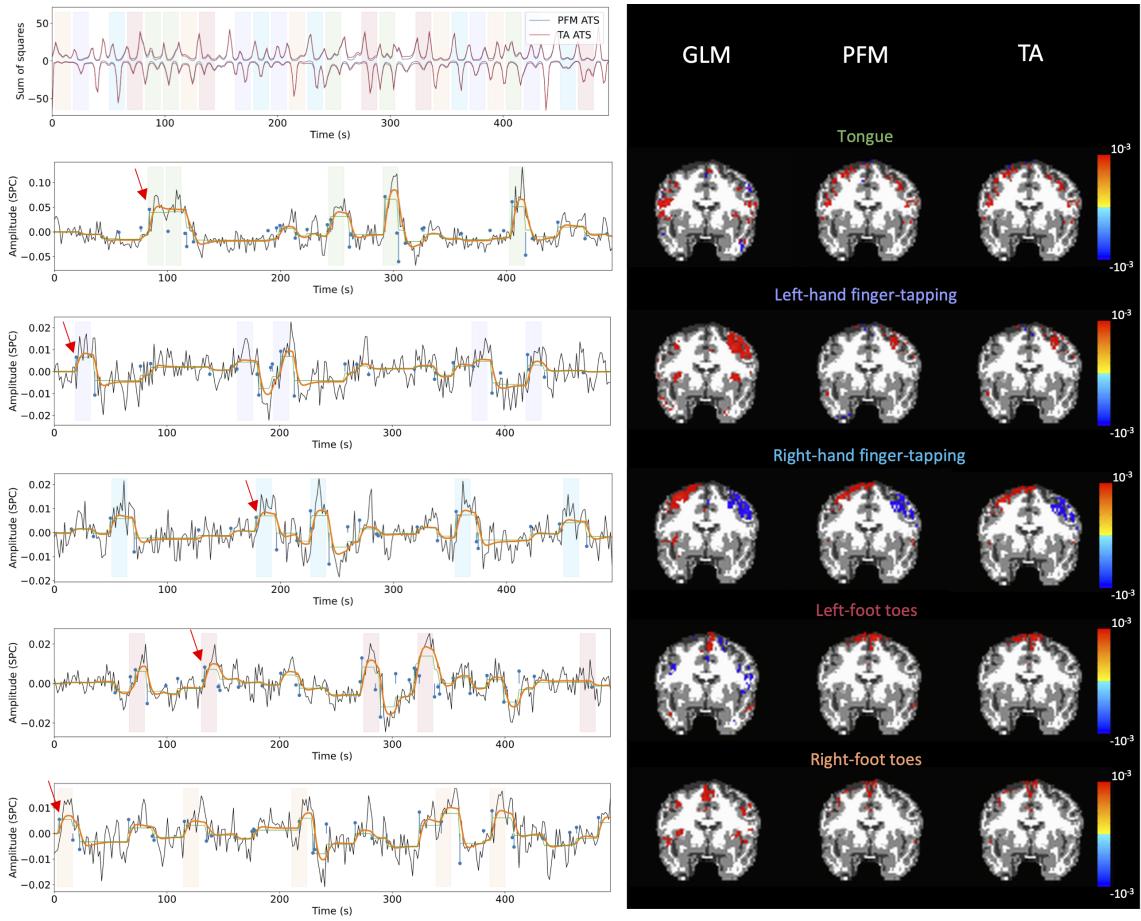


Figure 5: Activity maps of the motor task using a selection of  $\lambda$  based on the MAD estimate. Row 1: Activation time-series of the innovation signals estimated by PFM (in blue) or TA (in red) calculated as the sum of squares of all voxels at every timepoint. Positive-valued and negative-valued contributions were separated into two distinct timecourses. Color-bands indicate the onset and duration of each condition in the task (green: tongue, purple: left-hand finger-tapping, blue: right-hand finger-tapping, red: left-foot toes, orange: right-foot toes). Rows 2-6: time-series of a representative voxel for each task with the PFM-estimated innovation (blue), PFM-estimated activity-inducing (green), and activity-related (i.e., fitted, orange) signals, with their corresponding GLM, PFM, and TA maps on the right. The maps shown on the right are sampled at the time-point labeled with the red arrows and display the innovation signals at that moment across the whole brain.

305 synchronous innovations, i.e. with the same upregulating and downregulating events. For instance, it is interesting to observe that the structure of the visual network nearly disappears in its corresponding iCAPs, suggesting the existence of different temporal neuronal patterns across voxels in the primary and secondary visual cortices.

What about computation time? Do something similar as Hamza in his PhD?

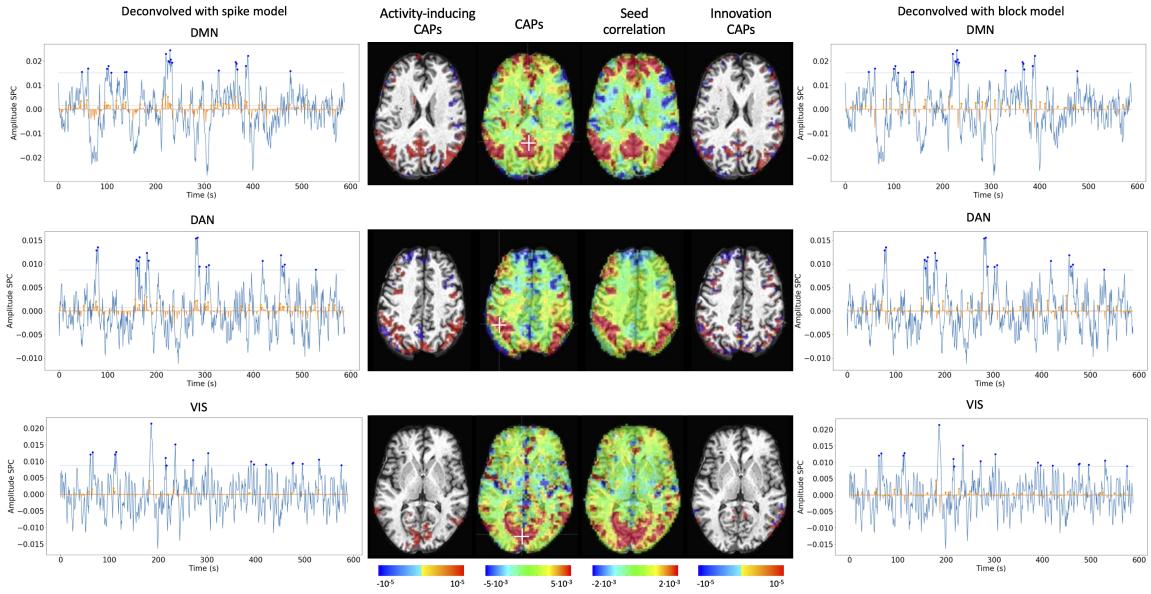


Figure 6: Activity-inducing CAPs (left) and innovation CAPs (right) obtained with the PFM-estimated activity-inducing and innovation signals respectively, using a MAD-based selection of  $\lambda$ . Time-points selected with a 95th percentile threshold are shown over the average time-series (blue) in the seed region (white-cross) and the deconvolved signal (orange). CAPs and seed correlation maps are illustrated in the center.

## 310 5. Discussion

Folks, I think we need to polish the message for the reader further. If the methods are equivalent, either the reader has learned something about different types of optimization (but this is not yet well described in the paper), or there is a clear practical take-home message.

This work demonstrates that PFM and TA algorithms yield practically identical results when the same HRF model and equivalent regularization parameters are employed, demonstrating that synthesis and analysis-based formulations are comparable for temporal hemodynamic deconvolution of fMRI data under a linear-time invariant model of the neurovascular coupling. Hence, we argue that previously observed differences in performance can be explained in terms of differences in usage options, such as the specific HRF model and selection of the regularization parameter, convergence thresholds, as well as the addition of a spatial regularization term by TA as described in Karahanoglu et al. 2013. With the equivalence in the temporal deconvolution demonstrated, incorporating extra spatial or temporal regularization terms in the optimization problem would not modify this equivalence providing convex operators are employed. In terms of convergence, this equivalence is particularly relevant when the convex optimization problem (i.e. with a unique global solution) is solved by means of iterative shrinkage thresholding procedures that alternate between the different regularization terms of the functional, such as the Generalized Forward-Backward Splitting (Raguet et al. 2013) technique originally proposed for TA. Our findings are in line with the equivalence of analysis and synthesis methods in under-determined cases ( $N \leq V$ ) demonstrated in (Elad et al. 315 2007) and (Ortelli and van de Geer 2019).

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Nevertheless, the differences between analysis and synthesis deconvolution methods must be considered to achieve optimal performance with any research question in hand. For instance, while TA uses the same HRF to solve both the spike and block models using the Generalized Total Variation formulation Karahanoglu et al. 2011), PFM incorporates the discrete differentiator operator into forward model along with the HRF to estimate innovation signals. The more flexible approach adopted by PFM offers the advantage that the synthesis operator allows for any HRF shape (Elad et al. 2007), only requiring that the coefficients are given at the desired temporal resolution of the deconvolved estimates, which is typically equal to TR of the acquisition. Given its more intuitive and versatile structure, the synthesis formulation proposed by PFM can easily be extended for deconvolution of multiple fMRI inputs with a common neuronal-related signal, for example for the estimation of neuronal-related events on multi-echo data (Caballero-Gaudes et al. 2019).

At the same time, deconvolution techniques can be used prior to the analysis of functional networks as they estimate interactions between brain regions that occur at the neuronal level, which are significantly less affected the sluggishness of the hemodynamic response and confounding effects than directly analyzing hemodynamic interactions (Gitelman et al. 2003). In addition, deconvolution approaches have a close parallelism to recent methodologies aiming to understand the dynamics of neuronal activations and interactions at short temporal resolution and that focus on extreme events in the fMRI signal. For example, Figure 6 illustrates that the innovation- or activity-inducing CAPs computed from deconvolved events in a single resting-state fMRI dataset closely resemble the conventional CAPs computed directly from extreme events of the fMRI signal (Liu and Duyn 2013; Liu et al. 2013, 2018; Cifre et al. 2020a,b; Zhang et al. 2020; Tagliazucchi et al. 2011, 2012, 2016; Rolls et al. 2021). Similarly, we hypothesize that these extreme events will also show a close resemblance to intrinsic ignition events (Deco and Kringelbach 2017; Deco et al. 2017). As shown in the maps, deconvolution approaches can offer a more straightforward interpretability of the activation events and resulting functional connectivity patterns. For the sake of illustration, CAPs were computed here as the average of spatial maps corresponding to the events of a single dataset. Beyond simple averaging, other clustering algorithms (e.g. K-means, consensus clustering) can be employed to discern multiple CAPs at the whole-brain level when a larger number of subjects or datasets is available (e.g. see Karahanoglu and Ville 2015). Likewise, the dynamics of functional connectivity have recently been investigated with the use of co-fluctuations and edge-centric techniques (Faskowitz et al. 2020; Esfahlani et al. 2020; Jo et al. 2021; Sporns et al. 2021). The Activation Time Series shown in Figure 5 aim to offer equivalent information of instances of significant brain activity to the root of sum of squares timecourses used in edge-centric approaches. Future work could address which type of information is redundant or distinct across frameworks. In summary, these examples illustrate that deconvolution techniques can be employed prior to other computational approaches and could serve as an effective way of denoising the fMRI data. We foresee an increase in the number of studies that take advantage of the potential benefits of using deconvolution methods prior to functional connectivity analyses.

Finally, taking into account the equivalent performance of analysis and synthesis deconvolution approaches, and the advantages and disadvantages discussed here, it is clear that fMRI deconvolution methods still have room for improvement and their capabilities can be extended to reach a wider community of researchers. Of particular relevance are deconvolution formulations aiming to account for HRF variability, for example using structured regularization terms along with multiple basis functions (Gaudes et al. 2012) or iterative procedures that estimate the HRF shape in an iterative fashion Farouj et al. 2019; Cherkaoui et al. 2020. Another venue of research are

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multivariate deconvolution approaches that operate at the whole-brain level, instead of voxelwise, for instance using low rank decompositions (Cherkaoui et al. 2020) or group (a.k.a. mixed norm) regularization terms (Uruñuela-Tremiño et al. 2019). Methods for a more robust selection of the regularization parameter could also be explored, for instance based on stability selection (Meinshausen and Bühlmann 2010; Uruñuela et al. 2020). Furthermore, the use of non-convex  $\ell_{p,q}$ -norm regularization terms (e.g.,  $p < 1$ ) could avoid the extra debiasing step that is necessary to overcome the shrinkage towards zero of the estimates Gaudes et al. 2013; Caballero-Gaudes et al. 2019. Alternatively, recent developments on physics-informed deep learning for inverse problems (Akçakaya et al. 2021; Monga et al. 2021; Ongie et al. 2020) could become an interesting venue of research to reduce the computational time and gain flexibility.

## 6. Code and data availability

The code and materials used in this work can be found in the following GitHub repository: [https://github.com/eurunuela/pfm\\_vs\\_ta](https://github.com/eurunuela/pfm_vs_ta). We encourage the reader to explore the parameters (e.g. SNR, varying HRF options and mismatch between algorithms, TR, number of events, onsets, and durations) in the provided Jupyter notebooks. Likewise, the data used to produce the figures can be found in <https://osf.io/f3ryg/>.

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## Supplementary Material for Hemodynamic Deconvolution Demystified: Sparsity-Driven Regularization at Work

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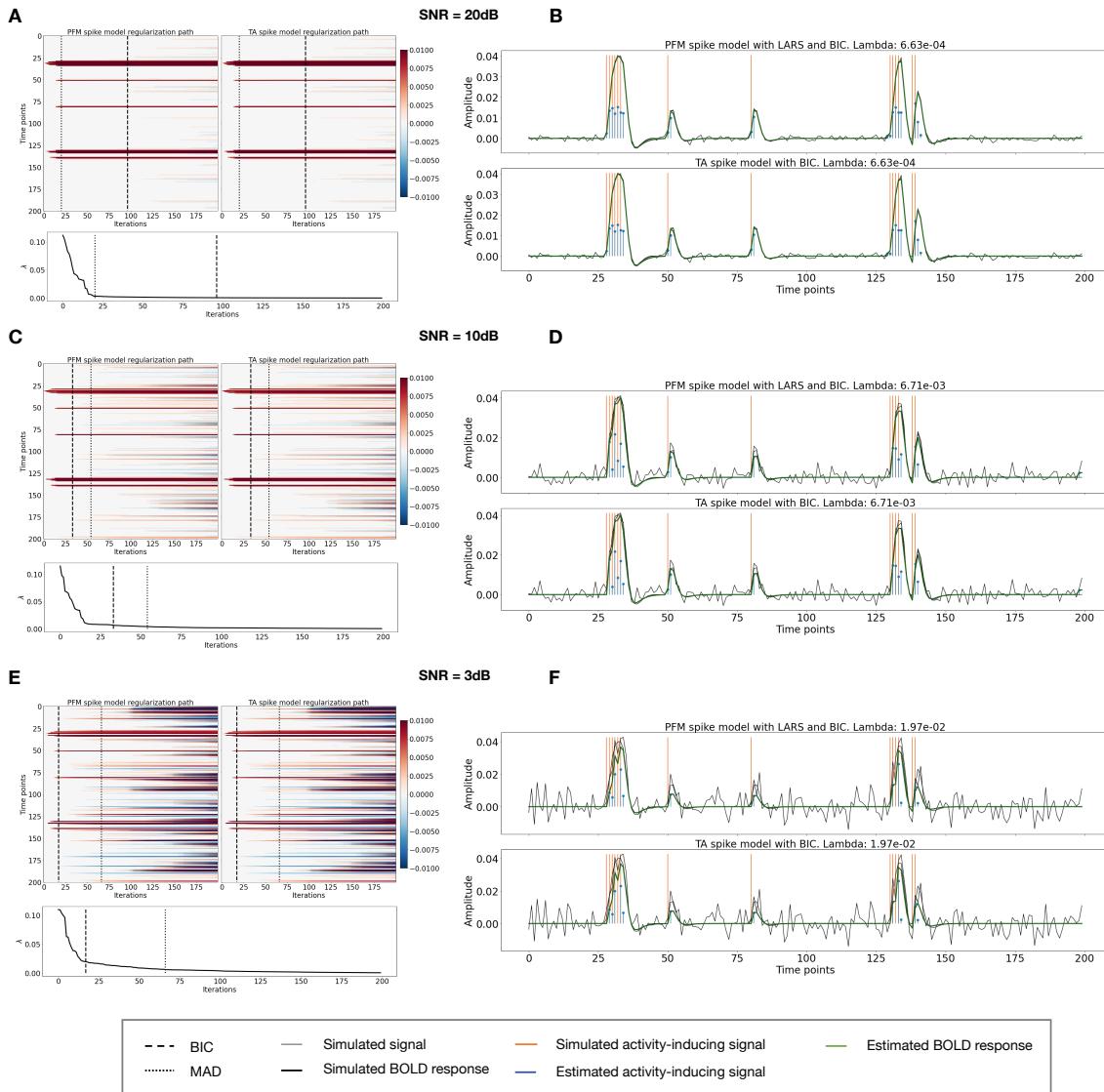


Figure S1: Spike model simulations. (Left) Heatmap of the regularization paths of the activity-inducing signal estimated with PFM and TA as a function of  $\lambda$  (increasing number of iterations in x-axis), whereas each row in the y-axis shows one time-point. Vertical lines denote iterations corresponding to the Akaike and Bayesian Information Criteria (AIC and BIC) optima. (Right) Estimated activity-inducing (blue) and activity-related (green) signals when set based on BIC. All estimates of are identical, regardless of SNR.

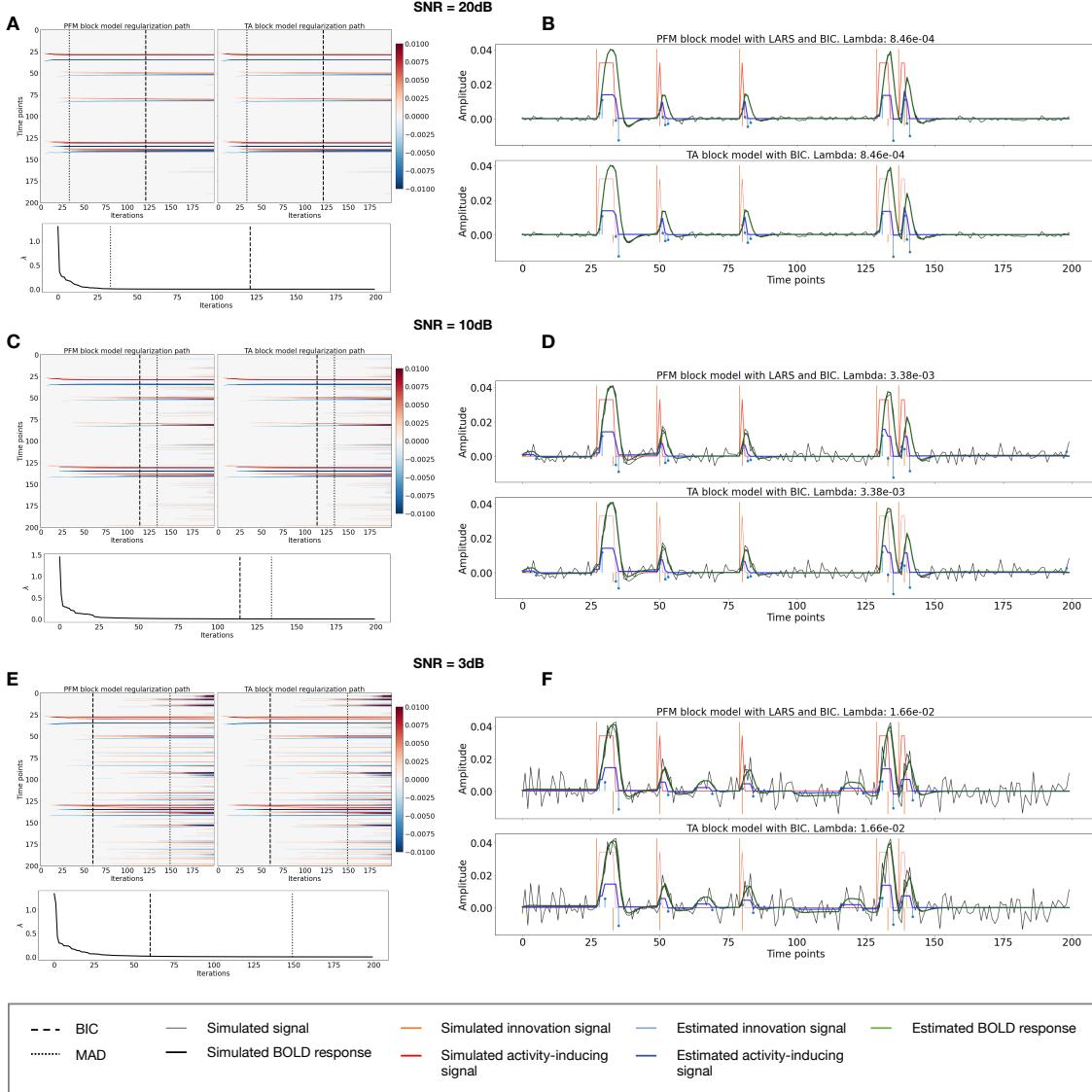


Figure S2: Block model simulations. (Left) Heatmap of the regularization paths of the innovation signal estimated with PFM and TA as a function of  $\lambda$  (increasing number of iterations in x-axis), whereas each row in the y-axis illustrates one time-point. Vertical lines denote iterations corresponding to the Akaike and Bayesian Information Criteria (AIC and BIC) optima. (Right) Estimated innovation (blue) and activity-related (green) signals when  $\lambda$  is set based on BIC. All the estimates are identical when compared between the PFM and TA cases, regardless of SNR.

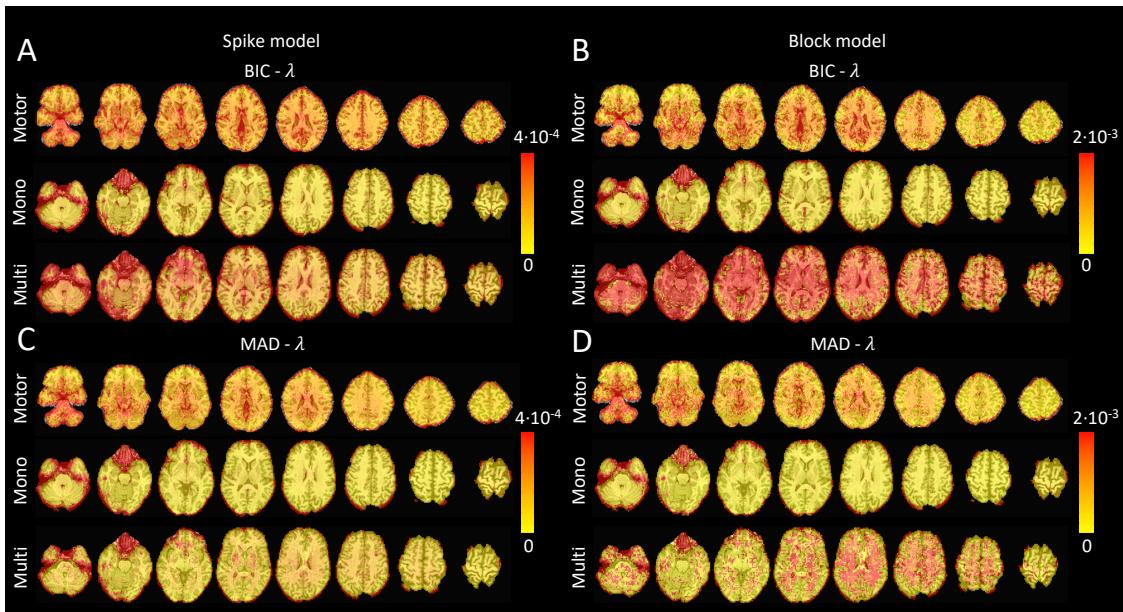


Figure S3: Values of  $\lambda$  across the different voxels in the brain used to estimate (A) the activity-inducing signal (spike model) and (B) the innovation signal (block model) with the BIC selection, as well as (C) the activity-inducing signal (block model) and (D) the innovation signal (block model) with a MAD-based selection. The  $\lambda$  maps are shown for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets.

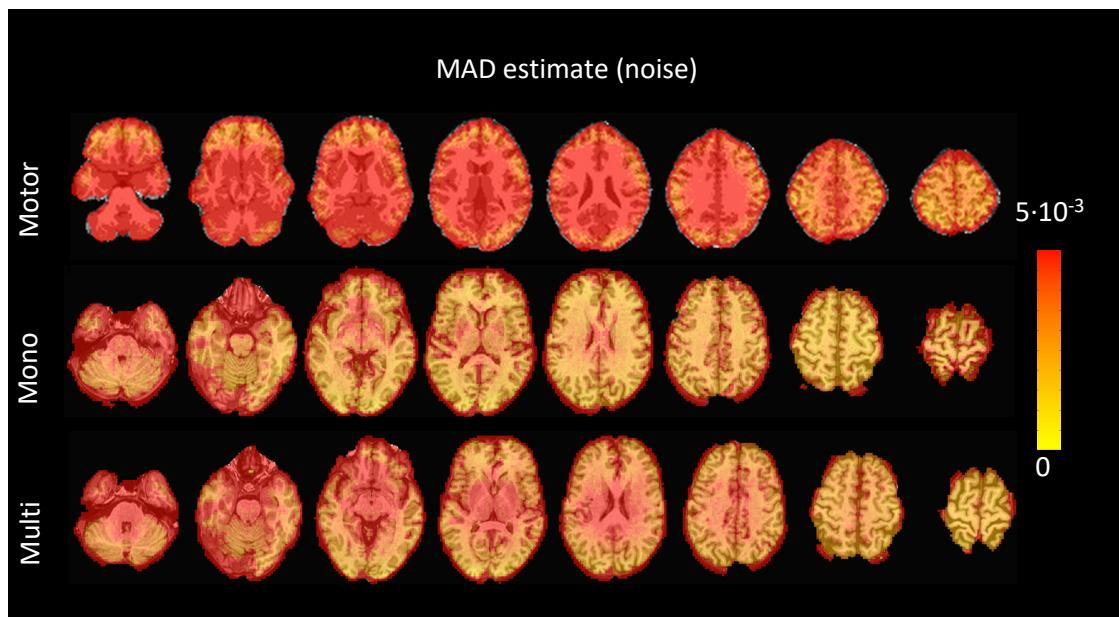


Figure S4: Values of the MAD estimate of the noise across the different voxels in the brain for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets.

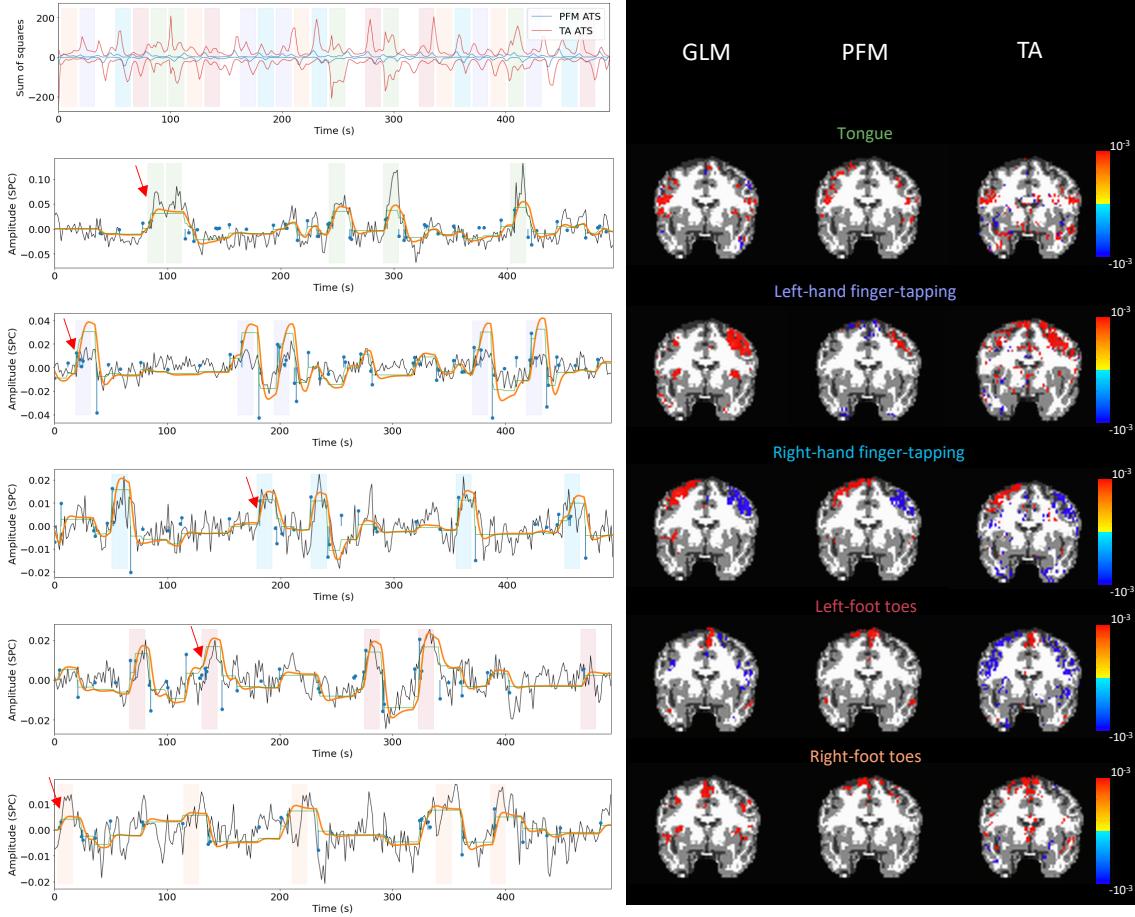


Figure S5: Activity maps of the motor task using a selection of  $\lambda$  based on the MAD estimate. Row 1: Activation time-series of the innovation signals estimated by PFM (in blue) or TA (in red) calculated as the sum of squares of all voxels at every timepoint. Positive-valued and negative-valued contributions were separated into two distinct time-courses. Color-bands indicate the onset and duration of each condition in the task (green: tongue, purple: left-hand finger-tapping, blue: right-hand finger-tapping, red: left-foot toes, orange: right-foot toes). Rows 2-6: time-series of a representative voxel for each task with the PFM-estimated innovation (blue), PFM-estimated activity-inducing (green), and activity-related (i.e., fitted, orange) signals, with their corresponding GLM, PFM, and TA maps on the right. The maps shown on the right are sampled at the time-point labeled with the red arrows and display the innovation signals at that moment across the whole brain.

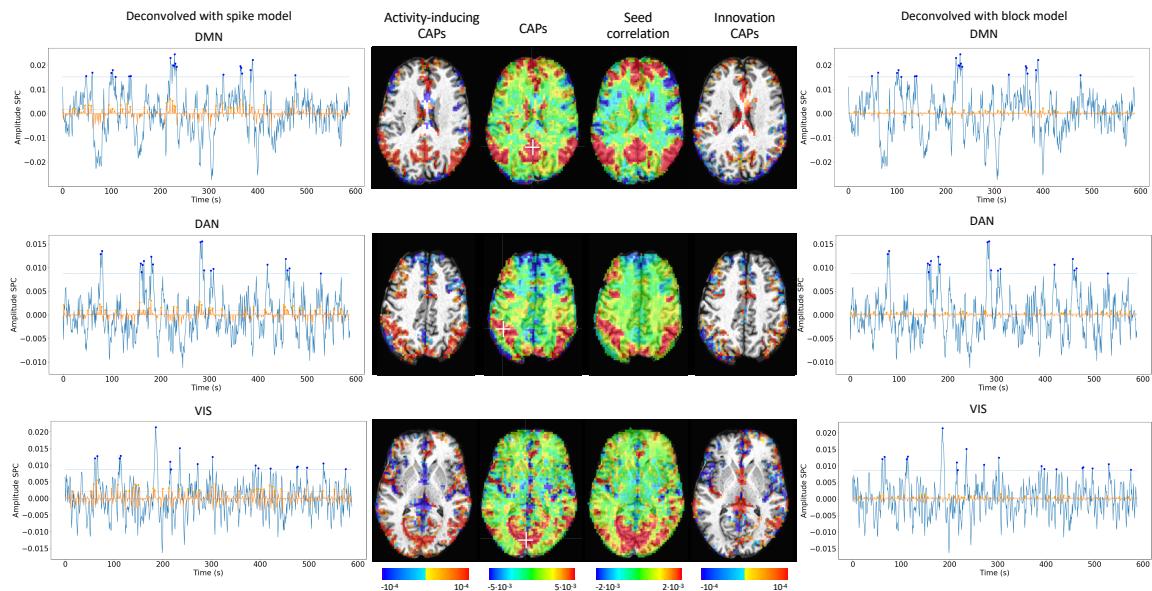


Figure S6: Activity-inducing CAPs (left) and innovation CAPs (right) obtained with the PFM-estimated activity-inducing and innovation signals respectively, using a MAD-based selection of  $\lambda$ . Time-points selected with a 95th percentile threshold are shown over the average time-series (blue) in the seed region (white-cross) and the deconvolved signal (orange). CAPs and seed correlation maps are illustrated in the center.