Single trial characterization of the BOLD response at 3T using structured sparse functionals with paradigm free mapping

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Introduction: Paradigm-free mapping (PFM) enables to map the fMRI BOLD response in space and time without prior knowledge of the timing of the events (i.e., no stimulation paradigm) [1,2]. Assuming a linear hæmodynamic model, PFM is based on the deconvolution of the underlying neuronal related component using regularized estimators (Table 1-Eq.(1)). Such deconvolution approach can take advantage of modern sparsity-promoting estimators, such as the Dantzig Selector or LASSO (Eq.(2)) [3], to improve the accuracy of the recovered signal [2]. Here, we extend PFM by using state-of-the-art hierarchical structured sparsity-promoting estimators to gain robustnesss against variability of the BOLD response with respect to the assumed model. Specifically, we define an extended hæmodynamic dictionary based on the informed basis set (i.e., canonical HRF, and its temporal and dispersion derivatives) [4], and we deploy structured sparsity functionals, such as the LASSO with the extended model (Eq.(3)) [3], Group LASSO (Eq.(4)) [5], Weighted Fusion (Eq.(5)) [6,7], and a new Group Weighted Fusion penalty (Eq.(6)), which are efficiently solved with the monotone fast iterative shrinkage thresholding algorithm (M-FISTA) [8,9]. Our results with simulations and experimental data demonstrate that the use of structured sparse functionals provide superior abilities for a paradigm free characterization of single-trial BOLD responses at 3T.

Eq.(1)	$\mathbf{s}^* = \arg\min_{\mathbf{s}} J(\mathbf{s}) = \frac{1}{2}\|\mathbf{y}-\mathbf{H}\mathbf{s}\|_2^2 + \Omega(\mathbf{s})$	
Eq.(2) LA1	$\Omega(\mathbf{s}) = \lambda_1\|\mathbf{s}\|_1 = \lambda_1\sum_{i=1}^{N}\|s_i\|$	
Eq.(3) LA3	$\Omega(\mathbf{s}) = \lambda_1\|\mathbf{s}\|_1 = \lambda_1\sum_{i=1}^{3N}\|s_i\|$	
Eq.(4) GLA	$\Omega(\mathbf{s}) = \lambda_1\|\mathbf{s}\|_{2,1} = \lambda_1\sum_{i=1}^{N}\|\mathbf{s}_i\|_2$	
Eq.(5) WFU	$\Omega(\mathbf{s}) = \lambda_1\|\mathbf{s}\|_1 + \lambda_2\sum_{i<j}\omega_{ij}\left(s_i - \alpha_{ij}s_j\right)^2$	$\rho_{ij} = \mathbf{h}_i^T\mathbf{h}_j$ $\alpha_{ij} = \mathrm{sgn}(\rho_{ij})$ $\omega_{ij} = \lvert\rho_{ij}\rvert^{0.5}/\left(1-\lvert\rho_{ij}\rvert\right)$
Eq.(6) GWF	$\Omega(\mathbf{s}) = \lambda_1\|\mathbf{s}\|_{2,1} + \lambda_2\sum_{i<j}\omega_{ij}\left(s_i - \alpha_{ij}s_j\right)^2$	

Table 1: Functional Equations

Methods: Synthetic fMRI data: We simulated 100 fMRI voxel time series (duration=256s, TR=1s, i.e. N=256 time points) as $y(t)=s(t)*h(t)+n(t)$, where $x(t)=s(t)*h(t)$ is the neuronal-related hæmodynamic signal, $s(t)$ is the neuronal-related signal (stimulus timecourse with 6 ON periods of duration 0.2s/3s/6s, and random onsets), $h(t)$ is the hæmodynamic response (weighted sum of SPM8 canonical HRF (a_c = 1), its temporal derivative (a_t = 1.5), and its dispersion derivative (a_d = 0.5)), and $n(t)$ is a white Gaussian noise term. The amplitude of $x(t)$ was normalized to 6% signal change, and three different temporal SNR were simulated (tSNR = 30, 55 and 80) which are typically observed in fMRI data at 3T and 7T. In discrete time, this signal model can be rewritten as $\mathbf{y} = \mathbf{H}\mathbf{s} + \mathbf{n}$, where $\mathbf{x} = \mathbf{H}\mathbf{s}$ and $\mathbf{H}$ is the convolution matrix with shifted basis functions of the assumed hæmodynamic model (i.e. $\mathbf{H}$ is a NxN matrix for LA1, and $\mathbf{H}$ is Nx3N otherwise). To assess the accuracy of the deconvolution, we computed the mean square error (MSE) of the estimates of $\mathbf{s}$ (MSEs) and $\mathbf{x}$ (MSEx). For each functional the regularization parameters were set according to an Oracle procedure minimizing MSEs (i.e. $s(t)$ is known) to benchmark all estimators in optimal conditions. **Experimental data:** Three subjects were scanned in a Siemens TIM Trio 3T with 32-ch head coil performing a visual task of 10 events of visual flickering checkerboard with duration 1s and random onsets. Data consisted of 140 T2*-weighted GE-EPI images (TR /TE /FA= 2s/30ms/85°, voxel size = 3.25x3.25x3.5 mm3) that were corrected for head motion, high pass filtered (cutoff period=128s), and smoothed spatially with isotropic Gaussian filter (FWHM=5mm) prior to analysis with the proposed method. The regularization parameters were set to $\lambda_1 = 4\sigma_{MAD}$ to obtain estimates with high specific BOLD responses, $\lambda_2 = 5\sigma_{MAD}$ in the Weighted Fusion penalties to promote the grouping of highly correlated coefficients, and σ_{MAD} is the Median Absolute Deviation (MAD) estimate of the noise standard deviation [10].

		tSNR=30		tSNR=55		tSNR=80	
		MSEs	MSEx	MSEs	MSEx	MSEs	MSEx
0.2 s	LA1	1.003	0.982	1.003	0.981	1.003	0.973
	LA3	1.000	0.980	1.000	0.988	1.252	0.210
	GLA	1.000	0.911	0.853	0.422	0.720	0.199
	WFU	1.000	0.980	1.000	0.986	1.160	0.193
	GWF	**0.977**	**0.803**	**0.827**	**0.361**	**0.706**	**0.192**
3 s	LA1	0.987	0.965	0.958	0.938	0.960	0.844
	LA3	0.981	0.896	0.939	0.701	0.918	0.585
	GLA	0.946	0.781	0.730	0.356	0.598	0.172
	WFU	0.973	0.845	0.927	0.672	0.906	0.549
	GWF	**0.882**	**0.688**	**0.641**	**0.305**	**0.523**	**0.169**
6 s	LA1	0.965	0.938	0.942	0.888	0.943	0.690
	LA3	0.987	0.938	0.960	0.706	0.975	0.343
	GLA	0.975	0.904	0.909	0.581	0.826	0.334
	WFU	0.974	0.793	0.934	0.631	0.944	**0.132**
	GWF	**0.942**	**0.720**	**0.845**	**0.404**	**0.771**	0.291

Table 2: Synthetic data results (MSEs and MSEx)

Results and Discussion: Synthetic data: As shown in Table 2, GWF outperformed the rest of penalty terms in all scenarios, except for the estimation of the hæmodynamic signal at SNR = 80 and event duration of 6 s where WFU resulted in improved operation. In all cases, LA1 using only the canonical HRF yielded unsatisfactory operation proving its lack of sufficient degrees of freedom (provided here by the temporal and dispersion derivatives) to fit a different HRF. As usual, LA1 also tended to yield extremely sparse estimates of $\mathbf{s}$ (i.e. very few coefficients are estimated as non-zero) due to the high pairwise correlation of $\mathbf{H}$. Comparing LA3 with GLA, it can be seen that the extra degrees of freedom must be used in a structured manner as groups of coefficients, and not treated independently as done by LA3. In general, incorporating additional structural information about the model via the weighted fusion penalty further improved the deconvolution. In this case, the Weighted Fusion penalties promote that highly correlated coefficients are to be jointly non-zero when they become significantly relevant to model the voxel timeseries. **Experimental data:** Figure 1 illustrates the results in a voxel located in V1 (see activation map) for a representative subject. As expected, the neuronal related hæmodynamic signal fitted by LA1, GLA and GWF were nearly identical (top). Yet, it can be seen that the GWF estimates of the neuronal-related coefficients (middle) delimit the onset of the hæmodynamic events (or stimuli) better than those obtained by LA1 (bottom). The GLA coefficients were nearly identical to those of GWF due to the high contrast to noise ratio of the BOLD events in this area. However, we observed that the specificity of GLA rapidly deteriorated with lower values of λ_1, in contrast to GWF, a fact that might be relevant to detect BOLD events in cortical areas with lower BOLD sensitivity. Remarkably, the GWF coefficients of the temporal derivative are negative for most of the events, suggesting a slower BOLD response (i.e., longer time-to-peak) than the canonical HRF. This type of characterization is not available if the model only comprises the canonical HRF as in LA1, and LA-1 estimates are slightly delayed with respect to the actual onset of the stimuli to compensate the model mismatch. Access to this kind of information with the new approach enables a more accurate characterization of the single-trial BOLD response, even without information about the timing of the events.

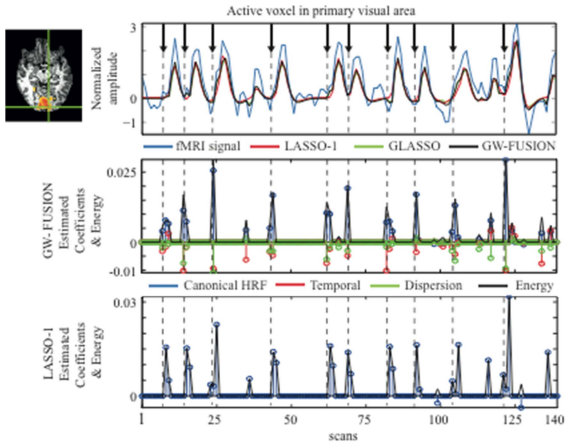

Figure 1: Deconvolution obtained by GW-FUSION, GLASSO and LASSO. Vertical bars indicate onset of visual stimuli. Top: Proprocessed fMRI time series and haemodynamic estimates. Middle and bottom: Coefficient estimates and energy time-series.

Conclusion: Structured sparsity is a promising regularization for PFM deconvolution of the fMRI signal. Structural information was defined in terms of groups of coefficients corresponding to basis functions of the informed basis set describing the BOLD response via the Group LASSO, and their pairwise correlation via a Weighted Fusion. The Group Weighted Fusion functional proposed here gave the best performance among the ones investigated in simulated data. In real fMRI data structured sparsity featured enhanced single-trial fMRI modeling with PFM.

References: **[1]** Caballero-Gaudes, C., et al. (in press) *Hum. Brain Mapp.*; **[2]** Caballero-Gaudes, C., et al. (2011) *Hum. Brain Mapp*. 32:1400-1418; **[3]** Tibshirani, R. (1996) *J.R. Statist. Soc. B*, 58:671-686; **[4]** Friston, K.J., et al. (1998) *Neuroimage* 7:30-40; **[5]** Yuan, M., Lin, Y. (2006) *J. R. Statist. Soc. B*, 68:49-67; **[6]** Daze, Z.J., Jeng, X.J. (2009) *Comput. Stat. Data Anal*. 53:1284-98; **[7]** Slawski, M., et al. (2010) *Annals Applied Statist.* 4:1056-80; **[8]** Beck, A., Teboulle, M. (2009) *IEEE Trans. Imag. Process.* 18:2419-2434; **[9]** Baritaux, J.C., et al. (2011) *IEEE Trans. Med. Imag.* 30:1143-1153; **[10]** Donoho, D., Johnstone I. (1994) Biometrika 81:425-455.