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3D spatially-adaptive canonical correlation analysis: Local and global methods

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ABSTRACT

Local spatially-adaptive canonical correlation analysis (local CCA) with spatial constraints has been introduced to fMRI multivariate analysis for improved modeling of activation patterns. However, current algorithms require complicated spatial constraints that have only been applied to 2D local neighborhoods because the computational time would be exponentially increased if the same method is applied to 3D spatial neighborhoods.

In this study, an efficient and accurate line search *sequential quadratic programming* (SQP) algorithm has been developed to efficiently solve the 3D local CCA problem with spatial constraints. In addition, a spatially-adaptive kernel CCA (KCCA) method is proposed to increase accuracy of fMRI activation maps. With oriented 3D spatial filters anisotropic shapes can be estimated during the KCCA analysis of fMRI time courses. These filters are orientation-adaptive leading to rotational invariance to better match arbitrary oriented fMRI activation patterns, resulting in improved sensitivity of activation detection while significantly reducing spatial blurring artifacts. The kernel method in its basic form does not require any spatial constraints and analyzes the whole-brain fMRI time series to construct an activation map. Finally, we have developed a penalized kernel CCA model that involves spatial low-pass filter constraints to increase the specificity of the method.

The kernel CCA methods are compared with the standard univariate method and with two different local CCA methods that were solved by the SQP algorithm. Results show that SQP is the most efficient algorithm to solve the local constrained CCA problem, and the proposed kernel CCA methods outperformed univariate and local CCA methods in detecting activations for both simulated and real fMRI episodic memory data.

Introduction

Spatially-adaptive multivariate methods have been used for fMRI data analysis as an alternative to the most commonly used *single voxel analysis* with isotropic Gaussian smoothing (SV) (Almodóvar-Rivera and Maitra, 2017; Borga and Rydell, 2007; Cordes et al., 2012; Friman et al., 2001; Harrison et al., 2008; Luessi et al., 2011; Tabelow et al., 2006; Weeda et al., 2009; Yue et al., 2010; Zhuang et al., 2017). While Gaussian smoothing can improve the signal-to-noise ratio (SNR) of fMRI data (Kriegeskorte and Bandettini, 2007), it also introduces spatial blurring of activation patterns leading to poor specificity.

One such spatially adaptive method is local canonical correlation analysis (local CCA), where fMRI time series are convolved with spatially anisotropic basis functions with unknown weight coefficients (Cordes et al., 2012; Friman et al., 2001, 2003). These basis functions act as low-pass spatial filters to better match arbitrary activation patterns. CCA (Hotelling, 1936) is then applied to determine the optimal weight coefficients of the spatial basis functions contingent on the design matrix that specifies the temporal regressors. Because CCA has more degrees of freedom than a univariate analysis that contains only one filter function (i.e. a spatial Gaussian function), spatial constraints on the weight coefficients are required to improve specificity of activation detection.

Friman et al. (2003) used 2D spatially oriented steerable filters (Kass and Witkin, 1988; Knutsson et al., 1983) as spatial basis functions for local CCA and restricted the weights of the basis functions to be nonnegative, so that the spatial filter acts as an adaptive spatial low-pass

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filter on the data. Cordes et al. (2012) showed how different spatial constraints impact the sensitivity and specificity of local CCA using time series convolved with 9 spatial 2D Dirac delta functions (2D-δ functions) on 3×3 in-plane neighboring voxels. Three different spatial constraints were investigated, namely a *nonnegative* constraint (the weights of all spatial basis functions are nonnegative), a so-called *dominant* constraint (the weight of the spatial basis functions acting on the center voxel is greater than the weights of all other spatial basis functions acting on neighboring voxels) and a so-called *sum* constraint (the weight of the spatial basis functions acting on the center voxel is greater *than the sum of weights* of all other spatial basis functions acting on neighboring voxels). The technique used to solve the constrained CCA problem is called *restricted CCA* (Das and Sen, 1994) and works by repeatedly excluding one or more unknown coefficients from the CCA equation until a solution satisfying all spatial constraints is found. Consequently, the computational time exponentially increases with the number of unknown variables. Recently, Zhuang et al. (2017) generalized these three spatial constrained models and implemented a *family of constraints model* controlled by two parameters, which includes previous constrained models as specific cases. Local CCA with the *family of constraints* was solved by nonlinear optimization algorithms such as the *Broyden--Fletcher-Goldfarb-Shanno* (BFGS) algorithm, the *Generalized Reduced Gradient* method (GRG) and the *Augmented Lagrangian* (AL) method. It was shown that GRG is the most time-efficient method and BFGS is the most accurate method among these three algorithms.

The first unsolved problem in local CCA of fMRI data is how to analyze data when 3D spatial filter functions (such as 3D-δ functions) are specified for local neighborhoods in 3D (such as cubic neighborhoods containing $3 \times 3 \times 3$ voxels). Current local CCA methods are exclusively focused on analyzing 2D in-plane (same slice) neighborhoods which create activation maps that may depend on the direction of the slice acquisition. A justification for only analyzing 2D neighborhoods is that the in-plane (within a slice) resolution of fMRI data is usually higher than the out-of-plane (between slices) resolution to limit the number of slices required for full brain coverage at an acceptable scanning time. For data with isotropic voxel sizes, 3D local CCA methods are more appropriate because neighbors from all directions of a given center voxel are equally relevant to the center voxel and accurate brain maps can be produced independently of the direction of slice acquisition. However, existing algorithms, e.g. BFGS, for local constrained CCA with 2D spatial constraints cannot be extended to the 3D case because the number of *variable partitionings* is exponentially increased going from 2D to 3D and the 3D CCA problems become intractable. To solve local CCA with 3D spatial constraints, a fundamentally-different optimization algorithm is required.

The second unsolved problem in local CCA (whether with 2D or 3D spatial constraints) is how to correctly specify the functional form of the spatial constraints. A spatial constraint that is too strict will lower sensitivity of activation detection and leads to less correctly identified active voxels whereas a constraint that is too loose (as in conventional unconstrained CCA) will lower the specificity of detection and give a smaller proportion of correctly identified inactive voxels. In principle, the spatial constraint together with the spatial filter functions should better fit fMRI activation patterns.

The kernel variant of the CCA method is an attractive method in terms of computational efficiency, since this method analyzes whole-brain fMRI data simultaneously. This global method has been introduced in fMRI data analysis (Blaschko et al., 2011; Hardoon et al., 2007; Murayama et al., 2010; Bießmann et al., 2009). Hardoon et al. (2007) applied KCCA as an unsupervised machine learning algorithm on task fMRI data with pleasant and unpleasant visual stimuli. Blaschko et al. (2011) implemented supervised and semi-supervised KCCA on video-task fMRI data and obtained brain spatial weight maps corresponding to different types of visual processing. Murayama et al. (2010) and Bießmann et al. (2009) associated neural signals with time-delayed fMRI signals.

However, current methods involving KCCA are limited in their application to fMRI data. The first deficiency is that KCCA is restricted to a simple contrast design and can obtain only activation maps equivalent to a one-sample *t*-test. KCCA has not been formulated for a more general contrast design specified by a contrast matrix. Unlike KCCA, any local CCA and standard general linear model analysis of fMRI data can be carried out for any arbitrary contrast matrix of interest to determine contrast-specific statistical activation maps. A second deficiency is that the data in current KCCA methods are spatially smoothed by an isotropic Gaussian filter with a *fixed* full-width at-half-maximum (FWHM) in a preprocessing step. Thus KCCA, in its current form, does not adaptively fit activation patterns.

In this study, our main goal is twofold: First, we developed a 3D local constrained CCA method and solved it with a sequential quadratic programming method (SQP) (Nocedal and Wright, 2006). Second, we proposed a global spatially-adaptive KCCA method, called *steerable filter* KCCA (sf-KCCA), and developed a penalized sf-KCCA model (sf-pKCCA). These two KCCA methods can handle any general linear contrast of interests defined by an arbitrary contrast matrix to compute t- and F-statistical maps of the task design.

To test the time efficiency and accuracy of the SQP algorithm, we compared SQP with BFGS and the GRG algorithms for local CCA with 2D and 3D constraints. To evaluate the performance of the sf-KCCA method, we used nonnegative constrained CCA with the same steerable filters (sf-nonnegCCA). Along with the standard SV method, the best constrained CCA model in Cordes et al. (2012), namely the *sum constraint* CCA (sumCCA) with spatial δ functions as filters was used in addition. As sf-KCCA uses 3D neighboring information for analysis, the sf-nonnegCCA and sumCCA methods were also applied with 3D local neighboring information and solved using the SQP algorithm. We evaluated the performance of these methods with simulated data using receiver operating characteristic (ROC) curves. The same analysis methods were applied on real fMRI episodic memory data where *single-domain* amnestic mild cognitive impairment (aMCI) subjects and normal controls (NCs) performed a visual memory task. We also estimated ROC curves for real fMRI data (Nandy and Cordes, 2003a,b; Nandy and Cordes, 2004) to evaluate the performance of the different methods. We computed activation maps and applied a radial basis function network (RBFN) technique and support vector machine (SVM) method to classify the population of subjects. The computed prediction accuracies provide a realistic assessment of the performance for the different analysis methods in classification and prediction of a neurodegenerative disorder.

Method

Spatial modeling and CCA

Classical univariate methods for analyzing fMRI data rely on isotropic data smoothing using a fixed Gaussian spatial low-pass filter. This type of smoothing is optimal for detecting activation patterns only if the spatial filter function matches the size and shape of the activated voxels. This is, however, not the case for fMRI data because shapes of active brain regions vary considerably depending on the task performed (Friman et al., 2003). Furthermore, a fixed spatial filter will lead to blurring of gray matter activation patterns into white matter regions.

For episodic memory tasks, it is known that important activation patterns of the medial temporal lobes covering the hippocampus and adjacent regions have a small contrast-to-noise ratio. If the spatial filter is non-adaptive it is less likely to obtain optimal activation detection using classical univariate methods (Nandy and Cordes, 2003a,b). It was shown that the use of adaptive spatial basis functions in the framework of multivariate CCA can lead to an increased sensitivity for a given specificity to detect episodic memory activations (Cordes et al., 2012). In general, using adaptive spatial basis functions in a multivariate analysis may improve activation detection not only for episodic task data but also may improve activation detection for arbitrary fMRI data as well.

The conventional general linear model (GLM) uses a single spatial