A semi-parametric model of the hemodynamic response for multi-subject fMRI data

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ABSTRACT

A semi-parametric model for estimating hemodynamic response function (HRF) from multi-subject fMRI data is introduced within the context of the General Linear Model. The new model assumes that the HRFs for a fixed brain voxel under a given stimulus share the same unknown functional form across subjects, but differ in height, time to peak, and width. A nonparametric spline-smoothing method is developed to evaluate this common functional form, based on which subject-specific characteristics of the HRFs can be estimated. This semi-parametric model explicitly characterizes the common properties shared across subjects and is flexible in describing various brain hemodynamic activities across different regions and stimuli. In addition, the temporal differentiability of the employed spline basis enables an easy-to-compute way of evaluating latency and width differences in hemodynamic activity. The proposed method is applied to data collected as part of an ongoing study of socially mediated emotion regulation. Comparison with several existing methods is conducted through simulations and real data analysis.

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Introduction

Functional magnetic resonance imaging (fMRI) measures brain activity through monitoring blood oxygen level dependent (BOLD) contrasts between two or more experimental conditions — an approach that requires the ability to track changes in blood flow with high spatial resolution (Ogawa et al., 1992). BOLD imaging has played a major role in neuropsychological experiments designed to associate various psychological phenomena with specific regions or circuits of the brain. Complex, multi-subject fMRI designs involving multisensory stimuli are growing more common. Such designs are very informative for investigating brain activity across different regions, stimuli, and subjects. But complex experimental designs also introduce nontrivial challenges for joint modeling, analysis, and computation of BOLD imaging data.

A widely-used framework for analyzing fMRI data is the General Linear Model (GLM) (Friston et al., 1995a; Friston et al., 1995b; Worsley and Friston, 1995), where the observed BOLD time series are modeled as a convolution of the experimentally-designed stimulus paradigm and the hemodynamic response function (HRF). The key to analysis lies in estimating the HRF. Within the framework of the GLM, estimation methods differ in their assumptions about the shape of the HRF. Parametric approaches, which assume the HRF follows a known functional form with a number of free parameters, include the canonical form of mixtures of gamma functions (Friston et al., 1998; Glover, 1999; Worsley et al., 2002), poisson function (Friston et al., 1994), inverse logit function (Lindquist and Wager, 2007) and radial basis functions (Riera et al., 2004). When the underlying HRF deviates from the assumed functional form, however, parametric methods may be inadequate. By contrast, nonparametric approaches make no explicit assumptions about the functional form of the HRF. These include methods that represent the HRF with a linear combination of functional bases (Aguirre et al., 1998; Vakorin et al., 2007; Woolrich et al., 2004; Zarahn, 2002), and methods that treat the HRF at every time point as a free parameter (Dale, 1999; Lange et al., 1999). Ultimately, nonparametric methods allow for more flexibility in accommodating the variability in brain activity across stimuli, brain regions and individuals.

Since nonparametric methods usually involve a large number of free parameters and the HRFs are generally believed to be smooth (Buxton et al., 2004), smoothing techniques such as kernel smoothing and regularization are commonly employed. For example, the smooth finite impulse response (SFIR) method (Glover, 1999; Goutte et al., 2000; Ollinger et al., 2001) exploits a regularization term to obtain smooth HRF estimates that satisfy a boundary condition. Vakorin et al. (2007) and Zhang et al. (2007) fitted the HRF by spline bases, and used Tikhonov regularization to achieve smoothness. More recently, Casanova et al. (2008, 2009) combined Tikhonov regularization and generalized cross validation (Tik-GCV) to improve the computation. Strategies that combine kernel smoothing and Tikhonov regularization (BTik-Kern) have also been developed (Zhang et al., 2012).

In analyzing multi-subject fMRI data, standard approaches apply a selected method – one of the above, for example – to each subject's data independently to account for the variability across subjects

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(e.g., Aguirre et al., 1998; Handwerker et al., 2004). Intuitively, exploiting population-wide common characteristics may improve the HRF estimation, especially when the data from each individual have a low signal-to-noise ratio (SNR). One way to achieve this is to develop mixed-effect and random-effect models (Friston et al., 1999; Mumford and Nichols, 2006). Another way is to explicitly assume that the HRFs of different subjects in a population have a similar shape. For example, Friston et al. (1998), Liao et al. (2002) and Henson et al. (2002) used Taylor expansion to evaluate subject-specific magnitudes and latencies with a fixed canonical HRF shape. Zhang et al. (2012) used the sample-averaged HRF to conduct bias correction for the Tikhonov-regularized nonparametric estimator. However, the former approach does not readily accommodate the variability in the HRF shapes across different brain areas and stimuli, while the latter produces well-performing estimates mainly when the difference in the magnitude accounts for most variation in the HRFs across subjects.

The GLM can be viewed as a special case of the generalized functional linear model (GFLM, Ramsay and Silverman, 2005), where the functional parameters of interest are the HRFs. Despite the vast statistical literature on GFLM (Müller and Stadtmüller, 2005; Yao et al., 2005; Crainiceanu et al., 2009; Di et al., 2009; Li et al. (2010); to name a few), few of these methods can readily accommodate the unique features of fMRI. In this article, within the framework of the GLM, we propose a novel semi-parametric model for multi-subject fMRI data, assuming that the HRFs for a fixed brain voxel associated with a given stimulus share a common but unknown functional form across subjects, but differ in height, time to peak, and width. We use nonparametric spline expansions (De Boor, 2001; Eubank, 1988; Ruppert et al., 2003; Wahba, 1990) to estimate this functional form. This semi-parametric model explicitly characterizes the common properties shared across subjects and is highly flexible in describing various brain hemodynamic activities across different regions and stimuli. In addition, we develop a new fast-to-compute algorithm for model estimation that is scalable to large-scale multi-subject fMRI data.

The rest of the article is organized as follows. In the Materials and methods section , we first propose the semi-parametric model for the HRFs from multi-subject data, then introduce the estimation method based on spline-basis expansion. A fast algorithm to choose the key tuning parameters is also developed. In the Results section, we compare the proposed method with several existing methods via simulated data and apply it to the fMRI data collected during a social emotion regulation experiment involving threat and safety stimuli while alone or during hand holding by friends and strangers (cf., Coan et al., 2012). The Conclusion section concludes with a brief discussion.

Materials and methods

A general semi-parametric model for HRF

Let $y_i(t)$ for $t = \delta, \cdots, T \cdot \delta$ and $i = 1, \cdots, n$ be the observed fMRI time series of a given brain voxel of subject i, where δ is the experiment time unit when each 3D scan is captured. In most experiments, δ ranges from 0.5 to 2 s. The GLM is

$$y_i(t) = X_i(t) \cdot d_i + \sum_{k=1}^{K} \int_0^m h_{i,k}(u) \cdot v_{i,k}(t-u) du + \varepsilon_i(t), \tag{1}$$

where $X_i(t) \in \Re^p$ is a vector of time-varying covariates, $v_{i,k}(t - u)$ are known functions, m is a fixed constant, and $\varepsilon_i(t)$ is an error term. The HRF $h_{i,k}(u)$ describes the brain response of subject i to the kth stimulus in a given region, and the research interest lies in estimating $h_{i,k}(u)$ for all i, k. In fMRI studies, the $v_{i,k}(t)$ is called stimulus function, which characterizes the experiment for subject i under the kth stimulus: $v_{i,k}(t) = 1$ if the kth stimulus is evoked at time t; otherwise, it equals 0. The covariates $X_i(t)$ characterize the BOLD signal from other known sources, such

as respiration and heartbeat. Usually, the $X_i(t) \cdot d_i$ is a low-order polynomial of t modeling the low-frequency drift due to physiological noise or subject motion. Following the common practice in the literature (Brosch et al., 2002; Luo and Puthusserypady, 2008; Smith et al., 1999), we assume $X_i(t) = (1, t, t^2)$ with the drifting parameters $d_i = (d_{0,i}, d_{1,i}, d_{2,i})'$.

Here we propose a flexible semi-parametric model for the HRF that efficiently utilizes the multi-subject information. We assume the HRFs for a fixed voxel under stimulus k, the $h_{i,k}$'s, share a common functional form but differ in magnitude and latency across subjects, as follows,

$$h_{i,k}(t) = A_{i,k} \cdot f_k\left(t + D_{i,k}\right), \tag{2}$$

where $A_{i,k}$ and $D_{i,k}$ represent magnitude and latency of the chosen voxel's reaction to the kth stimulus of subject i, respectively. The function $f_k(t)$ can be viewed as the population-average HRF. No parametric assumption of $f_k(t)$ except differentiability is imposed, distinct from the proposal by Friston et al. (1998) and Henson et al. (2002) where $f_k(t)$ is fixed as the canonical HRF. Model (2) has two major advantages: first, by assuming all the subjects have a common functional form of the HRF it enables "borrowing" information across subjects while allowing for subject-specific characteristics; second, the nonparametric nature of $f_k(t)$ provides maximum flexibility in modeling heterogeneous brain activities across regions and stimuli.

We note that a shape-invariant model similar to Eq. (2) has been proposed before for longitudinal data analysis (Ladd and Lindstrom, 2000; Lindstrom, 1995). However, the different contexts lead to fundamental distinctions in inference and computation between these works and ours. First, in the GLM for fMRI data, the mean outcome is a sum of convolutions of HRFs with associated stimuli, and there are no direct observations from the target functions (the HRFs). The models used for standard longitudinal data analysis, on the other hand, do not involve convolutions and deal with only observed data, making the estimation more straightforward. Second, our model allows multiple HRFs in possibly distinct shapes to account for different stimulus effects, while models in standard functional data analysis, including the aforementioned ones typically only allow one shape-invariant function. Third, as fMRI data usually contain thousands to hundreds of thousands time series for each subject as opposed to tens to hundreds in standard longitudinal data, computation is much more challenging in the former and new computational algorithms need to be developed.

Model (2) only considers differences in magnitude and latency across subjects. To accommodate the variation of the functional width $W_{i,k}$, which measures the duration of brain activity, we will also investigate the following extension:

$$h_{i,k}(t) = A_{i,k} \cdot f_k\left(\frac{t + D_{i,k}}{W_{i,k}}\right). \tag{3}$$

Parameter estimation via spline

We propose an estimation strategy for model (2) using spline-basis expansions. Spline-based methods have been widely used in functional representation and estimation, where a model with parameter functions becomes a generalized linear model with scalar parameters (basis coefficients). Overfitting can be overcome through basis selection or penalization (for details see Eubank, 1988; Parker and Rice, 1985; Wahba, 1990; Green and Silverman, 1994; and Ramsay and Silverman, 2005). However, these methods are only applicable for estimating each subject's HRFs independently without accounting for the population-wide common structure. The proposed strategy here aims at incorporating both population-wide and subject-specific characteristics into the