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Nonparametric inference of the hemodynamic response using multi-subject fMRI data

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ABSTRACT

Estimation and inferences for the hemodynamic response functions (HRF) using multi-subject fMRI data are considered. Within the context of the General Linear Model, two new nonparametric estimators for the HRF are proposed. The first is a kernel-smoothed estimator, which is used to construct hypothesis tests on the entire HRF curve, in contrast to only summaries of the curve as in most existing tests. To cope with the inherent large data variance, we introduce a second approach which imposes Tikhonov regularization on the kernel-smoothed estimator. An additional bias-correction step, which uses multi-subject averaged information, is introduced to further improve efficiency and reduce the bias in estimation for individual HRFs. By utilizing the common properties of brain activity shared across subjects, this is the main improvement over the standard methods where each subject's data is usually analyzed independently. A fast algorithm is also developed to select the optimal regularization and smoothing parameters. The proposed methods are compared with several existing regularization methods through simulations. The methods are illustrated by an application to the fMRI data collected under a psychology design employing the Monetary Incentive Delay (MID) task.

Introduction

There is a vast literature in functional magnetic resonance imaging (fMRI) data analysis on estimating the hemodynamic response function (HRF) within the framework of the General Linear Model (GLM) (Friston et al., 1995a, 1995b; Worsley and Friston, 1995). These methods differ in their assumptions about the shape of the HRFs. Standard parametric approaches assume a functional form for the HRF with a number of free parameters, such as 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). Except for the model using the canonical form and its derivatives, estimation for parametric models with even a moderate number of parameters often relies on computationally-intensive iterative methods (such as the Gauss–Newton method), which can lead to unstable estimates when the algorithms do not converge (Liao, et al., 2002). This paper alternatively focuses on nonparametric approaches, which are flexible and usually fast to compute. Bai et al. (2009) and Wang et al. (2011) constructed nonparametric estimates of the HRF in the frequency domain. Nonparametric methods in the time domain mainly fall into two types: representing the HRF with a linear combination of functional bases (Aguirre et al., 1998; Vakorin et al., 2007; Woolrich et al., 2004; Zarahn, 2002), or treating the HRF at every unit time point as a free parameter (Dale, 1999; Lange et al., 1999). In this paper we adopt the latter approach in the time domain to develop nonparametric estimation and inferences for HRFs.

Since nonparametric methods for HRF estimation involve many free parameters and the HRF is generally believed to be smooth (Buxton et al., 2004), smoothing techniques are often employed. Kernel smoothing is a popular nonparametric statistical method for increasing temporal continuity of functional estimates (Eubank, 1988; Härdle, 1990). It has been used for temporal smoothing of fMRI time series (e.g., Friston et al., 1994; Worsley and Friston, 1995), but has rarely been used for HRF estimation. In this paper, we first introduce a kernel-smoothed HRF estimator, based on which we construct hypothesis tests on the entire HRF curve, in contrast to the common practice of testing only some characteristics of the HRF.

Regularization is another increasingly popular technique used in nonparametric estimation that allows smoothness constraints to be imposed on the HRF estimates. One example is the smooth finite impulse response method (SFIR, Glover, 1999; Goutte et al., 2000; Ollinger et al., 2001), which exploits a regularization term to obtain smooth estimates that satisfy a boundary condition. Another example is given in Marrelec et al. (2001, 2003), where the HRF is represented by orthogonal functional bases and a smoothness constraint is imposed through regularizing the norm of its second order derivative. Similarly, representing the HRF by spline bases, Vakorin et al. (2007) and Zhang

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et al. (2007) used Tikhonov regularization (Tikhonov and Arsenin, 1977). The estimator proposed by Casanova et al. (2008, 2009) combines Tikhonov regularization and generalized cross validation (Wahba, 1990) (referred to Tik-GCV hereafter), greatly reducing the computational burden involved in parameter selection. Motivated by these developments, a second goal of this paper is to propose a new nonparametric estimator that combines kernel smoothing with Tikhonov regularization. Distinct from previous methods, this approach controls the degree of temporal smoothness and the norm of the estimates by two separate parameters. This separation makes the estimator more adaptive to different combinations of HRF temporal resolution and signal-to-noise ratio (SNR).

In analyzing multi-subject fMRI data, many existing methods, both parametric and nonparametric, estimate each subject's HRF independently to account for its variability across subjects (Aguirre et al., 1998; Handwerker et al., 2004). When data from each individual has a low SNR, utilizing the common characteristics of the HRFs shared across the population may improve the estimation efficiency. Moreover, for such data, though a strong scale of regularization is effective in stabilizing estimates, it also introduces additional biases. Thus, bias correction can be considered to improve over the regularized estimates (e.g., Zhang et al., 2007). Assuming that, under the same stimulus and in the same brain regions, the HRFs have similar functional shapes across subjects (Friston et al., 1998; Handwerker et al., 2004), we propose to use sample-averaged HRF estimates to conduct bias correction for the regularization-based estimates. A fast algorithm is developed to select regularization and smoothing parameters and to evaluate the new estimators. Through simulations, the proposed bias-corrected estimator demonstrates significant improvement over the estimators without the bias-correction step.

The article is organized as follows. In the Materials and methods section, we briefly review the GLM framework and propose the nonparametric kernel-smoothed estimator for hypothesis testing on the whole curve of the HRF. We then refine the estimator by adding Tikhonov regularization and applying bias correction. Two fast algorithms for parameter selection are also developed. The Results section presents results from applying the proposed methods to both simulated data and real fMRI data, and comparisons are drawn to several existing methods. The Conclusions section concludes with a discussion.

Materials and methods

The GLM

We conduct massive univariate analysis of fMRI data in the context of the GLM. Since the same approach applies to each voxel, the subscript for voxel is omitted here. Let $y_i(t)$ for $t=1,\cdots,T$ and $i=1,\cdots,N$ be the fMRI time series for a pre-specified voxel of subject i, where T is the total observation time and N is the number of subjects. Suppose the design has K stimuli. Let $v_{i,k}(t)$ be the kth $(k=1,\cdots,K)$ stimulus function for subject i with $v_{i,k}(t)=1$ if the stimulus is evoked at time t and 0 otherwise. The GLM represents the observed fMRI time series as a convolution of the HRF and the stimuli: $y_i(t)=\sum_{k=1}^{K}\int_0^m h_{i,k}(u)v_{i,k}(t-u)du+\varepsilon_i(t)$, where $h_{i,k}$ is the HRF of the pre-specified voxel in subject i under stimulus k, m is a known positive constant beyond which the HRF equals zero, and $\varepsilon_i(t)$ is an identically-distributed error term. The blood oxygen level dependent (BOLD) fMRI signal often contains a low-frequency drift due to physiological noise or subject motion (Brosch et al., 2002; Luo and Puthusserypady, 2008; Smith et al., 1999); this can be modeled by adding a polynomial term of time t (Lindquist, 2008; Mattay et al., 1996; Worsley et al., 2002) to the above GLM as

$$y_i(t)=d_{0,i}+d_{1,i}\cdot t+d_{2,i}\cdot t^2+\sum_{k=1}^{K}\int_0^m h_{i,k}(u)v_{i,k}(t-u)du+\varepsilon_i(t), \tag{1}$$

where the drift parameters $d_{0,i}, d_{1,i}$, and $d_{2,i}$ are allowed to vary across subjects.

Kernel-smoothed nonparametric estimator

We treat each HRF at every unit time as a free parameter. Let Δ be the time unit representing the discretization of the HRF temporal resolution. Since it is possible to have the temporal resolution of the HRF shorter than that of the fMRI data (Casanova et al., 2008; Ciuciu et al., 2003), Δ can be smaller than the repetition time unit (TR) of the experimental design. For each subject i, let $\mathbf{Y}_i=(y_i(1),\ldots,y_i(T))'$ be the observed fMRI time series. Denote the discretized values of the HRF under stimulus k by $\beta_{i,k}=(\beta_{i,k}(1),\cdots,\beta_{i,k}(m))'$, where $\beta_{i,k}(t)=\int_{(t-1)\cdot\Delta}^{t\cdot\Delta}h_{i,k}(u)du$ in a block design or $\beta_{i,k}(t)=h_{i,k}(t\cdot\Delta)$ in an event-related design (Josephs et al., 1997). Let $\beta_i=(\beta_{i,1}',\cdots,\beta_{i,K}')'$. Denoting all the coefficients $(d_{0,i},d_{1,i},d_{2,i},\beta_i')'$ by $\boldsymbol{\eta}_i$, the GLM Eq. (1) can be written in a matrix form as

$$\boldsymbol{Y}_i=\mathbf{X}_i\boldsymbol{\eta}_i+\varepsilon_i, \tag{2}$$

where $\mathbf{X}_i$ is the design matrix corresponding to the time covariates and the stimulus functions for subject i, and $\varepsilon_i=(\varepsilon_i(1),\cdots,\varepsilon_i(T))'\sim N(0,\sigma_i^2\Sigma_i)$ with unknown variance σ_i^2 and correlation matrix Σ_i. Since $h_{i,k}(t)$ is random across subjects, the coefficients β_i are also random. As a result, model (2) is a linear random-effect model. For each subject, we can remove the drift term through ordinary least square (OLS) regression and obtain an unbiased OLS estimate of β_i, denoted by $\hat{\beta}_i=\left(\hat{\beta}_{i,1}(1),\cdots,\hat{\beta}_{i,1}(m),\hat{\beta}_{i,2}(1),\cdots,\hat{\beta}_{i,K}(m)\right)'$. As noted in Goutte et al. (2000), $\hat{\beta}_i$ usually has an artificial high-frequency noise due to the large number of parameters under estimation and experimental designs with interleaved stimuli and inter-stimulus intervals. This can be clearly seen from the simulation example in Fig. 2(a). Therefore, smoothing techniques are often employed to reduce the unnatural ruggedness of the estimates.

Previous approaches have typically applied temporal smoothing directly to $y_i(t)$ to increase the statistical power for detecting responsive regions (e.g., Friston et al., 1994, 1995b; Worsley and Friston, 1995). The HRFs are generally believed to be smooth (e.g., Buxton et al., 2004); while smoothing the HRF estimated from the fMRI time series guarantees the smoothness of the resulting curve, directly smoothing the original fMRI times series does not, especially in complex designs with multiple stimuli. Since our interest lies in estimating the HRF and the degree of smoothness may vary across HRFs under different stimuli, we choose to conduct kernel smoothing on the OLS estimates $\hat{\beta}_i$. Specifically, we propose to use the Nadaraya–Watson kernel estimator:

$$\tilde{\beta}_{i,k}(t)=\sum_{u=t-l}^{t+l}W_{t,u}\cdot\hat{\beta}_{i,k}(u),\ \text{ with }W_{t,u}=\frac{f\left(\frac{t-u}{h}\right)/h}{\sum_{u=t-l}^{t+l}f\left(\frac{t-u}{h}\right)/h}. \tag{3}$$

Here h is a pre-specified bandwidth controlling the degree of smoothing, $f(t)$ is a given symmetric density function (kernel), and l is a pre-specified constant giving an upper bound on the number of data points used for the estimation. In this article, we let $f(t)$ be a standard Gaussian density and $l=m$. Existing results suggest that the choice of these two values has only a small effect on the estimation (Eubank, 1988; Härdle, 1990). The choice of the key bandwidth parameter h is elaborated in Algorithms for parameter selection section. The underlying idea of kernel smoothing is to borrow information from the neighboring data: the estimate $\tilde{\beta}_{i,k}(t)$ is a weighted average of the neighboring OLS estimates and the weight $W_{t,u}$ is negatively correlated with the distance $|u-t|$. The boundary condition of $\beta_{i,k}(t)=0$ for $t<0$ and $t>m$ is imposed by setting $\hat{\beta}_{i,k}(u)=0$ for $u<1$ and $u>m$ in the estimator (3). Letting $\hat{\beta}_{i,k}=\left(\hat{\beta}_{i,k}(1),\cdots,\hat{\beta}_{i,k}(m)\right)'$ and $\tilde{\beta}_{i,k}=\left(\tilde{\beta}_{i,k}(1),\cdots,\tilde{\beta}_{i,k}(m)\right)'$,