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Multiscale adaptive generalized estimating equations for longitudinal neuroimaging data ☆

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ABSTRACT

Many large-scale longitudinal imaging studies have been or are being widely conducted to better understand the progress of neuropsychiatric and neurodegenerative disorders and normal brain development. The goal of this article is to develop a multiscale adaptive generalized estimation equation (MAGEE) method for spatial and adaptive analysis of neuroimaging data from longitudinal studies. MAGEE is applicable to making statistical inference on regression coefficients in both balanced and unbalanced longitudinal designs and even in twin and familial studies, whereas standard software platforms have several major limitations in handling these complex studies. Specifically, conventional voxel-based analyses in these software platforms involve Gaussian smoothing imaging data and then independently fitting a statistical model at each voxel. However, the conventional smoothing methods suffer from the lack of spatial adaptivity to the shape and spatial extent of region of interest and the arbitrary choice of smoothing extent, while independently fitting statistical models across voxels does not account for the spatial properties of imaging observations and noise distribution. To address such drawbacks, we adapt a powerful propagation–separation (PS) procedure to sequentially incorporate the neighboring information of each voxel and develop a new novel strategy to solely update a set of parameters of interest, while fixing other nuisance parameters at their initial estimators. Simulation studies and real data analysis show that MAGEE significantly outperforms voxel-based analysis.

Introduction

Many large-scale longitudinal neuroimaging studies including the Alzeimer's disease neuroimaging initiative and the NIH magnetic resonance imaging study of normal brain have been or are being widely conducted to better understand the progress of neuropsychiatric and neurodegenerative diseases or normal brain development (Almli et al., 2007; Evans and Group., B. D. C., 2006; Kim et al., 2010; Meltzer et al., 2009; Petersen et al., 2010; Skup et al., 2011). The primary goal of longitudinal neuroimaging studies is to characterize individual change in neuroimaging measurements (e.g., volumetric and morphometric measurements) over time, and the effect of some covariates (or predictors) of interest, such as diagnostic status and gender, on the individual change (Evans and Group., B. D. C., 2006; Petersen et al., 2010). A distinctive feature of longitudinal neuroimaging data is that neuroimaging data have a temporal order. Imaging measurements of the same individual usually exhibit positive correlation and the strength of the correlation decreases with the time separation. Ignoring temporal correlation structure in imaging measures would likely influence subsequent statistical inference, such as increase in false positive and negative errors, which may lead to misleading scientific inference (Diggle et al., 2002; Fitzmaurice et al., 2004). However, the analysis of longitudinal imaging data has been hindered by the lack of advanced tools, which effectively integrate advanced image processing and statistical tools for analyzing complex and correlated imaging data along with behavioral and clinical data.

Standard software platforms have several major limitations. Standard neuroimaging software platforms including statistical parametric mapping (SPM) (www.fil.ion.ucl.ac.uk/spm/) and FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl/), among many others, cannot accurately model longitudinal data when there are more than two visits (repeated measurements) (Nichols and Waldorp, 2010). Specifically, FSL can only accommodate a univariate measure at the second level (e.g., comparing visit 2–visit 1) and SPM, even though it models the correlation among repeated measures, unrealistically assumes that the correlation is equal

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over the whole brain. In contrast, proper longitudinal modeling is available in standard statistical software platforms including proc MIXED and proc GEE in SAS and *lme4* and *nlme* in R. Recently, analysis of functional neuroImages (AFNI) (afni.nimh.nih.gov/afni/) adopts the linear mixed effects modeling packages *nlme* (Pinheiro et al., 2011) and *lme4* (Bates et al., 2011) in R for longitudinal functional magnetic resonance imaging data. Moreover, the Freesurfer implements the linear mixed effects modeling in the Freesurfer's LME Matlab toolbox (http://surfer.nmr.mgh.harvard.edu/fswiki/LinearMixedEffectsModels) (Bernal-Rusiel et al., 2013). The conventional analyses of longitudinal neuroimaging data, referred to as voxel-based analysis, may be carried out in two major steps: Gaussian smoothing the imaging data and subsequently fitting a statistical model at each voxel by using either SAS or R. As discussed below, the voxel-based analysis is generally not optimal in power and the use of Gaussian smoothing may introduce substantial bias in statistical results.

The voxel-based analysis has several major limitations. First, it is common to apply a single Gaussian kernel with the full width half maximum in the range of 8–16 mm to imaging data in order to account for registration errors, to Gaussianize the data, and to integrate imaging signals from a region, rather than from a single voxel. As pointed out in Ball et al. (2012), Jones et al. (2005), Zhang and Davatzikos (2011), and Zhao et al. (in press), such Gaussian smoothing method can suffer from several major drawbacks including the arbitrary choice of smoothing extent and the lack of spatial adaptivity to the shape and spatial extent of the region of interest. Thus, it is suboptimal in power. In addition, as discussed in Li et al. (2012), directly smoothing imaging data from twin and familial studies can introduce substantial bias in estimating these factors and lead to a dramatic increase of the numbers of false positives and false negatives. Second, as pointed out in Li et al. (2011) and Worsley et al. (2004), the voxel-based analysis essentially treats all voxels as independent units in the estimation stage, and thus it does not explicitly account for the spatial properties (e.g., location and smoothness) of imaging observations.

There are several attempts to address the limitations of voxel-based analysis. In Zhang and Davatzikos (2011), an optimally-discriminative voxel-based analysis was proposed to determine the spatially adaptive smoothing of images, followed by applying voxel-wise group analysis. The key drawback of the optimally-discriminative voxel-based analysis is that it uses the imaging data twice for both optimal weight determination and group analysis, and thus the test statistics calculated for the group analysis do not have a simple asymptotic null distribution, such as the t distribution. Thus, the optimally-discriminative voxel-based analysis has to resort to permutation test to calculate the p-values of test statistics. However, the permutation methods are not only computationally intensive, but also require the so-called complete exchangeability. Such complete exchangeability is in fact a very strong assumption, and thus the optimally-discriminative voxel-based analysis is limited to both univariate imaging measure and two-group comparisons and cannot control for other continuous covariates of interest, such as age. Moreover, the optimally-discriminative voxel-based analysis has not been extended to analyze longitudinal neuroimaging data. In Polzehl et al. (2010) and Tabelow et al. (2006, 2008), the authors generalized a powerful propagation–separation (PS) approach (Polzehl and Spokoiny, 2000, 2006) to develop a multiscale adaptive linear model to adaptively and spatially denoise functional magnetic resonance images and diffusion tensor images from a single subject and analyze neuroimaging data from cross-sectional studies. Recently, in Li et al. (2011), Skup et al. (2012) and Zhu et al. (2009), a multiscale adaptive regression model and a multiscale adaptive generalized method of moments approach were developed to integrate the PS approach (Polzehl and Spokoiny, 2000, 2006) with statistical modeling at each voxel for spatial and adaptive analysis of neuroimaging data from multiple subjects. All these PS related methods, however, only allow simultaneously smoothing all parameters.

This article has two major aims. The first one is to review a class of statistical methods called generalized estimating equation (GEE) for general neuroimaging researchers. We illustrate that GEE is a powerful tool for making statistical inference on regression coefficients in both balanced and unbalanced longitudinal designs and even twin and familial studies. The second aim is to develop a multiscale adaptive generalized estimating equation (MAGEE) for the spatial and adaptive analysis of longitudinal neuroimaging data. Compared with the existing literature including Li et al. (2011), Polzehl et al. (2010), Skup et al. (2012) and Zhu et al. (2009), we make several novel contributions. (i) MAGEE integrates the PS approach with GEE, which is a semiparametric model, into a simultaneous smoothing and estimation framework, allowing adaptively smoothing images while accounting for the spatial pattern of activation regions. (ii) We develop a new novel strategy of estimation and testing hypothesis of interest in MAGEE. Specifically, the new strategy allows solely smoothing the images of a set of parameters of interest, while fixing other parameters at their initial estimates. For instance, the scientific interest of many neuroimaging studies typically focuses on the comparison of imaging measures across diagnostic groups, while controlling for age, gender, and other covariates. MAGEE allows solely smoothing the images for parameter estimates of the diagnostic effect without smoothing the images of other parameter estimates, such as age and gender. (iii) We use simulated data sets to show that the new strategy can dramatically gain statistical power in some scenarios. (iv) Theoretically, in the appendix, the adaptive estimates and test statistics of MAGEE are shown to have appropriate statistical properties. We will validate companion software for MAGEE and release it to the public.

Methods

Balanced versus unbalanced designs

In a typical longitudinal study, one collects a fixed number of repeated measurements on all study participants at a set of common time points. When all individuals have the same number of repeated measurements on a common set of occasions, the study is "balanced" over time. Many of the early statistical methods, such as repeated-measures analysis of variance, have been developed specifically for balanced longitudinal designs. However, in most longitudinal studies over a relatively long duration in the health sciences, some individuals almost always miss their scheduled visit or date of observation. Consequently, the sequence of observation times may vary across individuals. In that case, we call the data "unbalanced" over time.

Missing data

Missing data, a ubiquitous problem in longitudinal studies, can be caused by various reasons, such as skipped assessments, bad MRI scans, or study dropout. Therefore, in practice, the longitudinal data are necessarily unbalanced and they are often called "incomplete" to emphasize the fact that an intended measurement for an individual could not be obtained. Complete case analysis, a common and simple method for handling incomplete data, focuses on all individuals with complete measurements from the analysis. This approach, however, can be highly inefficient when a large proportion of the subjects are excluded. Moreover, when the individuals with complete data are not a random sample from the target population, this approach can also seriously bias estimates of longitudinal change. Fortunately, most statistical methods for longitudinal analysis, such as GEE discussed below, accommodate incomplete data under less stringent assumptions, such as missing at random (Diggle et al., 2002; Fitzmaurice et al., 2004). A good longitudinal analysis should include serious assessment of these assumptions for the data at hand and consideration of the effects of their violation on the results of the