MARM: Multiscale Adaptive Regression Models for Neuroimaging Data

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Introduction Anatomical and functional magnetic resonance imaging (MRI) are important tools for understanding the neural substrates of neuropsychiatric disorders, substance abuse, and normal brains. Much effort has been devoted to developing voxel-wise methods for analyzing various imaging measures including cortical thickness using numerical simulations and theoretical reasoning. Most of these methods have been implemented in the existing neuroimaging software platforms, such as SPM (http://www.fil.ion.ucl.ac.uk), among many others. However, the voxel-wise approach based on the linear model and methods for correcting multiple comparisons has several obvious limitations for the analyses of imaging data, underscoring the great need for methodological development. First, the voxel-wise approach essentially treats all voxels as independent units [1], whereas neuroimaging data are spatially correlated in nature and spatially contiguous regions of activation with rather sharp edges are usually expected. Second, the initial smoothing step before the voxel-wise approach often blurs the image data near the edges of activated regions and thus it can dramatically increase the numbers of false positives and false negatives [1-4]. Finally, the voxel-wise approach is also based on a strong assumption that after an image warping procedure, the location of a voxel in the image of one person is assumed to be in precisely the same location as the voxel identified in another person–an assumption that is demonstrably false.

Methods This abstract aimed to develop and apply a multiscale adaptive regression model (MARM) for the joint analysis of neuroimaging data with behavioral and clinical variables, and then to demonstrate its superiority over the voxel-wise approach using both simulated and real imaging data. The MARM is a spatial, hierarchical and adaptive procedure. (i) The MARM builds a small sphere around each voxel and use these consecutively connected spheres across all voxels to capture local and global spatial dependence among imaging observations. Thus, the MARM explicitly utilizes the spatial information to carry out statistical inference. (ii) The MARM also builds hierarchically nested spheres by increasing the radius of a spherical neighborhood around each voxel and combine all the data in a given radius of each voxel with appropriate weights to adaptively calculate parameter estimates and test statistics. The hierarchical nature of the MARM can dramatically reduce the computational complexity in computing parameter estimates. (iii) The adaptive feature of the MARM can efficiently utilize all available information in the neighboring voxels to estimate parameters and calculate test statistics, which substantially increase the precision of parameter estimates and the power of test statistics. The MARM represents a novel generalization of the propagation-separation (PS) approach, which was originally developed for nonparametric estimation of regression curves or surfaces [1-4], in several aspects. The MARM provides a general framework for carrying out statistical inference on imaging data, whereas the PS is applied to smooth the images of parameter estimates obtained from the voxel-wise approach based on classical linear models (LMs)[1]. Our results show that it is inadequate to directly use the PS approach to smooth the images of parameter estimates, which are obtained from the voxel-wise method for most regression models, such as nonlinear regression. Compared to the parametric assumptions in the PS method for the LM, the MARM avoids specifying any parametric distribution for imaging data. This feature is desirable for the analysis of real neuroimaging data, including brain morphological measures, because the distribution of the univariate (or multivariate) neuroimaging measurements often deviates from the Gaussian distribution. We also use stochastic approximation algorithm to adaptively carry out statistical inference such as test statistics and show the theoretical properties of the MARM, which differs substantially from those of the original PS approach developed for nonparametric estimation of regression curves or surfaces based on observations from the exponential family model [4,5].

Results Both simulated data and real MRI data are used to evaluate the performance of the proposed method. We applied a simulation model to automatically simulate realistic intra-individual deformations associated with tissue atrophy or structural growth in the two groups of brains [6]. We chose a specified location and a fixed radius in the white matter and then simulated spherical atrophy for all 20 subjects in each group (Fig. 1). The growth rates for each subject in the first and second groups were generated from $N(0.95, 0.01)$ and $N(1, 0.01)$, respectively. The true deformation area was highlighted in red in Fig. 1a. We calculated the ratio of detected voxels within the true deformation area, whose p-values are smaller than 0.0001 as 49% for the voxel-wise method and 68% for MARM, respectively. Our results (49% v.s. 68%) show a clear advantage of the MARM in detecting an accurate group difference as we increase the bandwidth of the spherical neighborhood (Fig 1). Alzheimer's disease (AD) is the most common form of dementia in people over 65 years of age. MRI has been used to develop imaging-based biomarkers for AD, measuring spatial patterns of atrophy, and their evolution with disease progressions. We used a subset of a large MRI dataset obtained from the Alzheimer's Disease Neuroimaging Initiative database (www.loni.ucla.edu/ADNI). Our dataset included 90 subjects, comprising of 45 cognitively normal individuals (CN) (mean age ± S.D., 77.07 ± 3.89), and 45 AD patients (77.32 ± 6.01). The two groups were relatively well-balanced in terms of gender (23 and 25 women in each of the 2 groups, respectively). We identify the spatial patterns of brain atrophy in AD via the analysis of the tissue density maps of GM and WM [7]. To control for the effects of covariates (diagnosis, age, weight, and gender), we considered a linear model for respective tissue density maps at each voxel. We applied the MARM procedure to carry out the statistical analysis. Figure 2 shows a clear advantage of the MARM in detecting more significant and smoothly area for the group differences between CN and AD. We observed the significant difference between CN and AD in the hippocampus and the entorhinal cortex.

Fig.1. Results from simulated MRI data: (a) True deformation area in red; (b) -log10(p) map based on the voxel-wise method; (c) -log10(p) map based on the MARM method.

Conclusion We have developed the MARM for spatial and adaptive analysis of imaging data. We have used both simulated and real imaging data to demonstrate that the MARM significantly outperforms classical voxel-wise approach. We are currently applying our method to a large dataset.

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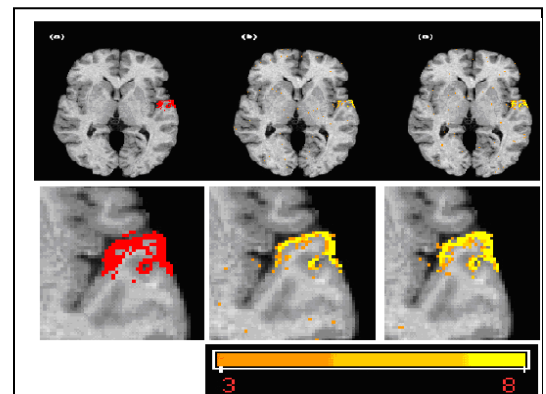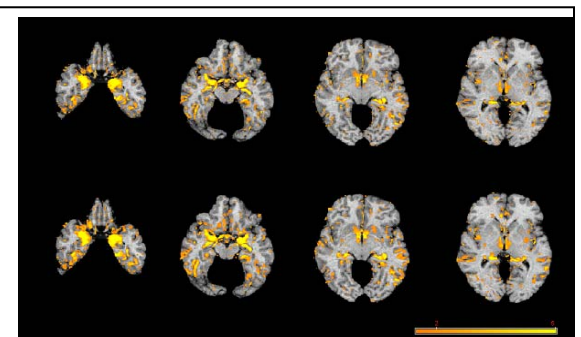[7] Shen, D., et al. (2003), *NeuroImage*, 18(1), 28-41.

Fig 2. Voxel-based analysis of group difference between CN and AD based on the raw -log10 (p) values of the Wald test statistics. Four selected slices are presented. The upper and lower rows represent the results from the voxel-wise method and the MARM, respectively.