Analysis of Multiple Sclerosis Lesions via Spatially Varying Coefficients

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of the brain and spinal cord that can produce severe disability. Quantitative analyses of MS lesion maps (binary images that mark the exact location of the lesions) are typically "mass univariate" and conducted with standard linear models that are ill suited to the binary nature of the data and ignore the spatial dependence between nearby voxels [1]. Smoothing the lesion maps does not entirely eliminate the non-Gaussian nature of the data and requires an arbitrary choice of the smoothing parameter [2].

Here we present a Bayesian spatial model to accurately model binary lesion maps and the relationship between local lesion incidence and subject specific covariates such as MS subtype, age, gender, disease duration and disease severity measures. We apply our model to T2 lesion maps from 250 MS patients classified into five clinical subtypes, and demonstrate its unique modeling and predictive capabilities over existing methods.

Methods

The Model   We propose a Bayesian spatial model for binary lesion images based on a generalized linear mixed model (GLMM) at each voxel. The covariates can be subject specific (e.g., age) or voxel-wise (e.g., atlas white matter probability). The voxel-wise coefficients [3] are regarded as latent spatial processes and jointly modeled by a multivariate pairwise difference prior model, an instance of the multivariate conditional autoregressive (CAR) model [4], to account for the spatial structure.

Implementation   We introduce continuous latent variables that convert the spatial GLMM into a spatial linear mixed model [5] and sample all full conditional posterior distributions using Gibbs sampler. The computational burden can be reduced by coding the problem to run in parallel on a graphical processing unit (GPU).

Application   We applied our model to T2 lesion maps from 250 MS patients classified into five clinical subtypes of MS. Binary images have voxel size 2x2x2 mm^3 for a total of 274,596 voxels (specifically we used a full brain mask, and did not use a white matter mask). We included patient specific covariates for clinical subtype (coded as five dummy variables), age, gender, disease duration (DD), the Expanded Disability Status Scale (EDSS) score and the Paced Auditory Serial Addition Test (PASAT) score; each of these covariates is associated with spatially varying coefficients. We used one spatially varying covariate shared by all subjects, the white matter probability image (from FSL). All computation can be completed under 8 hours.

Evaluation   We compared our model to a "mass univariate" logistic regression approach, Firth logistic regression [6].

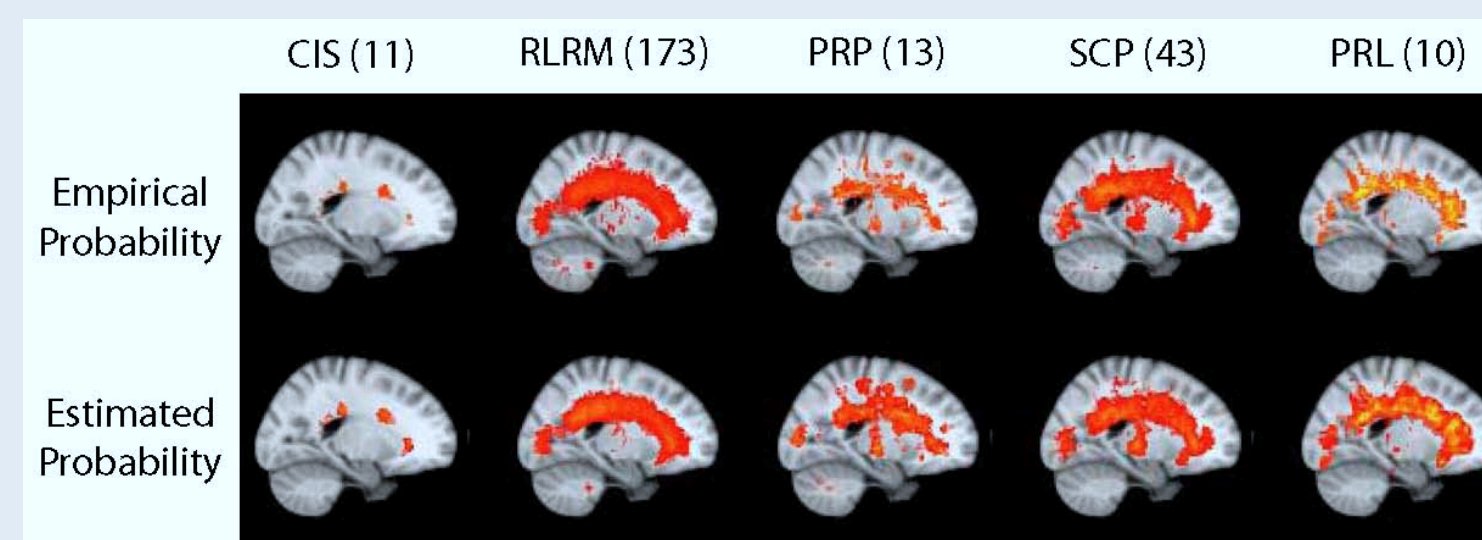## Figure: Comparison of the empirical and model-based lesion probabilities

Figure 1: **Top**: Empirical lesion probabilities for five MS subtypes, clinically isolated syndrome (CIS, 11 subj), relapsed remitting (RLRM, 173 subj), primary progressive (PRP, 13 subj), secondary chronic spatial progressive (SCP, 43 subj) and primary relapsing (PRL, 10 subj). **Bottom**: Model-based (posterior mean) lesion probabilities from our Bayesian model. (Color scale: 1% - 35%)

Figure: Comparison of the statistical significance maps

Figure 2: **Top**: Bayesian standardized spatial maps (posterior mean divided by posterior standard deviation). **Bottom**: Classical statistic spatial maps (mean divided by standard deviation) from the "mass univariate" Firth logistic regression. (Color scale: -5 to -2, 2 to 5)
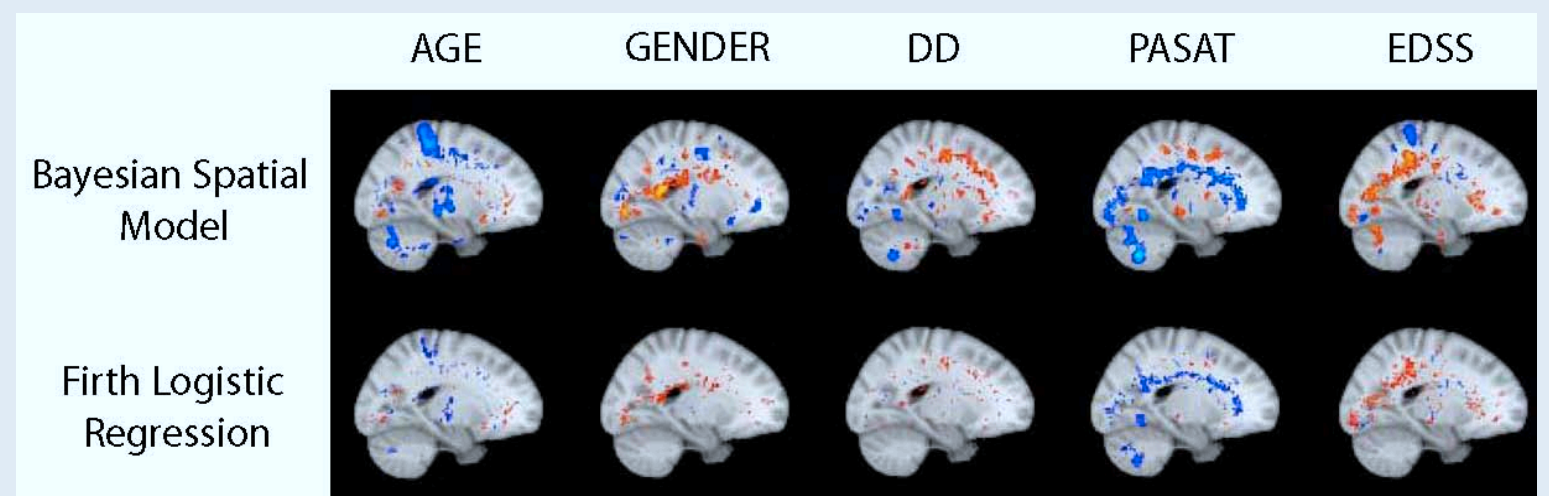

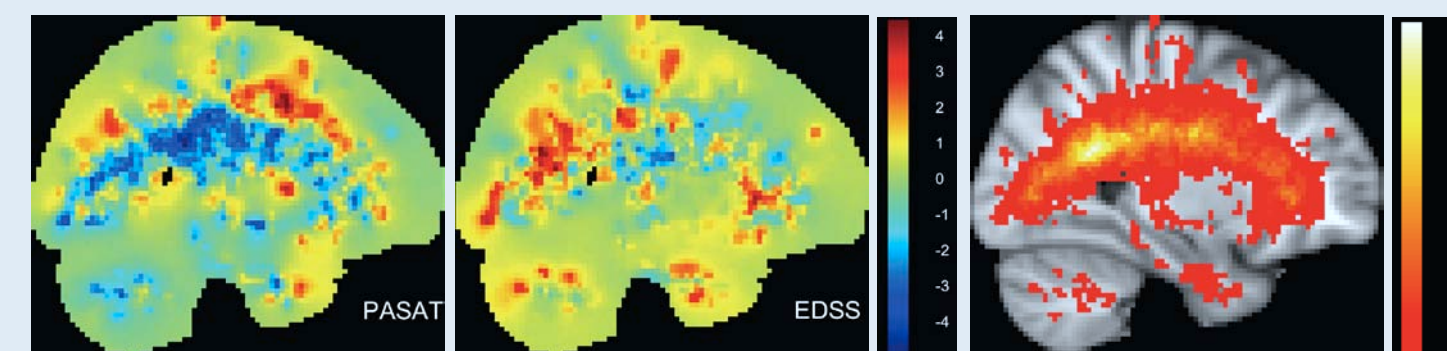## Figure: Statistical significance maps for PASAT and EDSS covariates

Figure 3: **Left**: High PASAT scores correspond to less damage from MS, and hence negative correlation between PASAT score and lesion occurrence along the corpus callosum. **Middle**: Higher EDSS scores correspond to more severe MS, and hence the positive correlation between EDSS score and lesion occurrence in the minor and major forceps. **Right**: T1 MRI template with total empirical lesion counts overlaid for reference.

Tables: Leave-one-out Classification Results

Bayesian Spatial Model (Average classification rate: 82.8%)					
	CIS	RLRM	PRP	SCP	PRL
CIS	**1.000**	0.000	0.000	0.000	0.000
RLRM	0.243	**0.734**	0.000	0.023	0.000
PRP	0.154	0.000	**0.846**	0.000	0.000
SCP	0.140	0.000	0.00	**0.860**	0.000
PRL	0.100	0.000	0.100	0.100	**0.700**

Naïve Bayesian Classifier (Average classification rate: 24.5%)					
	CIS	RLRM	PRP	SCP	PRL
CIS	**0.000**	1.000	0.000	0.000	0.000
RLRM	0.046	**0.757**	0.017	0.093	0.087
PRP	0.077	0.769	**0.000**	0.077	0.077
SCP	0.023	0.744	0.023	**0.070**	0.140
PRL	0.000	0.600	0.000	0.000	**0.400**

Firth Logistic Regression (Average classification rate: 30.0%)					
	CIS	RLRM	PRP	SCP	PRL
CIS	**0.000**	1.000	0.000	0.000	0.000
RLRM	0.052	**0.821**	0.006	0.087	0.034
PRP	0.000	0.538	**0.000**	0.385	0.077
SCP	0.000	0.302	0.023	**0.582**	0.093
PRL	0.000	0.400	0.000	0.500	**0.100**

Tables: The confusion matrices of the leave-one-out cross-validation classification using the Bayesian spatial model (**left**), a Naïve Bayes Classifier (**middle**) and the Firth logistic regression (**right**).

An efficient leave-one-out cross-validation (LOOCV) approach based on importance sampling [7] was also used to predict the clinical subtype of a held-out subject (with knowledge of their covariates). The classification results were compared to a Naïve Bayes Classifier (NBC) and the Firth logistic regression on voxels with at least 2 lesions. Smoothing the data before running the NBC or smoothing the coefficient maps of the Firth regression did not improve predictive performance.

Results

Our model produces regularized (smoothed) estimates of lesion incidence compared to empirical lesion probability maps (Fig. 1). The significance of the spatial parameters is much greater in our model as compared to the "mass univariate" Firth regression (Fig. 2), and spatial profiles of covariate effects are easily obtained (Fig. 3). Moreover, the LOOCV classification results based on our model dramatically outperform the NBC and the Firth logistic regression (Tables).

Conclusions

We have created a Bayesian spatial model that fully respects the binary nature and spatial structure of the lesion maps. It produces regularized estimates of lesion incidence without a fixed smoothing parameter. Our model delivered more sensitive inferences of covariates and group differences, and demonstrated dramatically improved predictive capabilities over existing "mass univariate" methods.

References

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