Web Based Supplementary Material: Scan Stratified Case-Control Sampling for Modeling Blood-Brain Barrier Integrity in Multiple Sclerosis

GM. Pomann,∗E.M. Sweeney, D.S. Reich, AM. Staicu a** and R.T. Shinohara d**

1. Data Pre-Processing

The data are processed using the methods of [1]. The following is the description of pre-processing steps presented therein:

Images were acquired on either a 1.5T or a 3T MR imaging scanner (Signa Excite HDxt; GE Healthcare, Milwaukee, Wisconsin) by using the body coil for transmission and an 8-channel receive coil array (Invivo, Gainesville, Florida) for signal-intensity detection. Depending on the platform, the sequence parameters differed. T1-weighted scans were obtained before contrast administration by using a 3D FSPGR sequence, with TR=9, TE=3.5ms, T1=450ms, FA=13°, and nominal VV=1-1.2 mm³. T2-weighted scans were acquired before contrast administration by using a 2D fast spin-echo sequence (TR = 5-6 seconds, TE ~ 120 ms, FA= 90°, VV= 1-2 mm³).

An intravenous infusion of 0.1 mmol/kg of gadopentate dimeglumine (Magnevist; Bayer HealthCare, Leverkusen, Germany) via a power injector (Solaris; Medrad, Indianola, Pennsylvania) was administered to the subjects. T1-weighted scans were also obtained a median of 8 minutes (IQR, 6-15 minutes) after contrast injection by using either a 2D spin-echo sequence (TR=600 ms, TE= 16ms, FA=90°, VV=2 mm³) or the same 3D FSPGR sequence used for pre-contrast T1-weighted scans. T2-weighted FLAIR scans were obtained at a median of 15 minutes (IQR, 14-45 minutes) after contrast injection. The T2-weighted FLAIR acquisition was conducted using either a 2D fast spin-echo sequence on the 1.5T scanner (TR=10 seconds, TE ~ 123 ms, TI=2250 ms, FA=90°, VV=3.5 mm³) or a 3D variable FA sequence on the 3T scanner (TR=6 seconds, TE ~ 126 ms, TI ~ 1860 ms, VV=1 mm³). Post-contrast T2-weighted FLAIR scans facilitate

†** These authors contributed equally.

∗ Correspondence to: Department of Statistics, North Carolina State University, Raleigh, NC. E-mail: gpomann@gmail.com

Copyright © 2014 John Wiley & Sons, Ltd.

Prepared using simauth.cls [Version: 2010/03/10 v3.00]
detection of contrast-enhancing lesions without changing the signal intensity of non-enhancing lesions so that the signal intensity within lesions on post-contrast scans is at least as great as that on precontrast scans [2] [3].

Medical Image Processing Analysis and Visualization (http://mipav.cit.nih.gov) and Java Image Science Toolkit (http://nitrc.org/projects/jist) were used for processing the images. All statistical calculations and modeling were conducted by using the software environment R (version 3.1.0; R Foundation for Statistical Computing, Vienna, Austria).

All acquired volumes were rigidly registered to the pregadolinium T1-weighted volume and then rigidly aligned to the Montreal Neurologic Institute standard template. Nonparametric intensity-nonuniformity normalization was used to address scanner-related inhomogeneity [4]. All scans were interpolated to a voxel size of 1mm$^3$. Skull and extracranial voxels were masked out by using a skull-stripping procedure [5]. The volume was eroded by 2mm in each direction to remove much of the residual extracerebral tissue. This should not remove voxels consisting white matter where lesions may occur. To more completely remove the normally enhancing meninges and to focus our attention on the white matter where most enhancing voxels are located, we removed all voxels below axial section 52 (the inferior temporal lobes) and above the axial section 156 (the top of the brain).

2. SuBLIME Map Estimation

Researchers have asserted that new or enlarging MS lesions are more likely to enhance [6]. To account for this, we include a covariate that is an indicator of new or enlarging lesion voxels to improve predictive ability in the proposed predictive model. Classification of voxels as belonging to new or enlarging MS lesions can be obtained manually by a radiologist. However, manual identification is extremely time consuming and prone to errors even for the most expert neuroradiologists in this field. Additionally, the process is subject to both intra-observer and inter-observer variability [7]. Therefore, we propose the use of the SuBLIME method to estimate the probability that a voxel belongs to a new or enlarging lesion [8].

The proposed modeling procedure is a two-step process. First, for each voxel used for fitting the model, we acquire a historical covariate that denotes whether the voxel belongs to a new or enlarging lesion. The second step is to use this covariate in the proposed logistic model. The indicator of incidence as a binary variable is defined as, $W_{ij}(v,t_{ij})$, which is equal to one if subject $i$ has new lesion incidence in voxel $v$ at time $t_{ij}$ and zero otherwise. The SuBLIME probability maps, $SP_{ij}(v,t_{ij}) := Pr[W_{ij}(v,t_{ij}) = 1]$, are the probabilities that voxel $v$ is with a new or enlarging lesion at time $t_{ij}$.

As described in the previous section, these maps are obtained using longitudinal study information. The following is the model proposed by [8] to estimate the probability maps of interest.

\[
\text{logit}[Pr(W_{ij}(v,t_{ij}))] = \beta_0 + \beta_1 \Delta t_i + \beta_2 M_{i,1}(v,t_{ij}) + \beta_3 \Delta M_{i,1}(v,t_{ij}) + \beta_4 M_{i,1}(v,t_{ij}) \times \Delta t_i + \beta_5 M_{i,2}(v,t_{ij}) + \beta_6 \Delta M_{i,2}(v,t_{ij}) + \beta_7 M_{i,2}(v,t_{ij}) \times \Delta t_i + \beta_8 M_{i,3}(v,t_{ij}) + \beta_9 \Delta M_{i,3}(v,t_{ij}) + \beta_{10} M_{i,3}(v,t_{ij}) \times \Delta t_i + \beta_{11} M_{i,4}(v,t_{ij}) + \beta_{12} \Delta M_{i,4}(v,t_{ij}) + \beta_{13} M_{i,4}(v,t_{ij}) \times \Delta t_i
\]

The covariates in this model are defined as follows: $M_{i,1} :=$ T1w image for patient $i$, $M_{i,2} :=$ T2w image for patient $i$, $M_{i,3} :=$ FLAIR image for patient $i$, $M_{i,4} :=$ PD image for patient $i$, $\Delta t_i :=$ time in days between consecutive studies for patient $i$, $\Delta M_{i,k}(v,t_{ij}) = M_{i,k}(v,t_{ij}) - M_{i,k}(v,t_{ij-1})$ : subtraction image for patient $i$ and imaging modality $k$. By using subtraction images and the interaction with the time differences between scans, this model incorporates the longitudinal information.
3. Full AUC Results

The table below provides the full AUC estimates corresponding to the partial AUC (pAUC) results presented in Table 1 in the paper.

**Table 1.** Full AUC estimates and corresponding 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>95% CI</td>
</tr>
<tr>
<td>All Voxels</td>
<td>0.87</td>
<td>(0.86,0.89)</td>
</tr>
<tr>
<td>1% FLAIR</td>
<td>0.79</td>
<td>(0.77,0.81)</td>
</tr>
<tr>
<td>SSCC</td>
<td>0.88</td>
<td>(0.87,0.89)</td>
</tr>
</tbody>
</table>

4. Modeling Dependence

To explore a model that accounts for correlation across voxels within scan, we use generalized estimating equations (GEE) with a compound symmetric correlations structure across voxels. We use the `geeglm` function in the `geepack` package in R to obtain these results for the SSCC sample and were unable to obtain results when using the full data set (All Voxels) due to computational limitations on a 128-core high-performance computing node with 512 GB of memory. The results are displayed in Table 1 for the SSCC sampling scheme. The GEE procedure performs comparably to the GLM estimation with a working independence assumption for Model 1, but has inferior predictive performance for Model 2.

**Table 2.** AUC estimates and corresponding 95% confidence intervals (CI) using the GEE with compound symmetric correlation structure over voxels within each scan.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pAUC</td>
<td>95% CI</td>
</tr>
<tr>
<td>SSCC</td>
<td>0.52</td>
<td>(0.49,0.55)</td>
</tr>
<tr>
<td>full AUC</td>
<td>0.88</td>
<td>(0.87,0.89)</td>
</tr>
</tbody>
</table>

References

