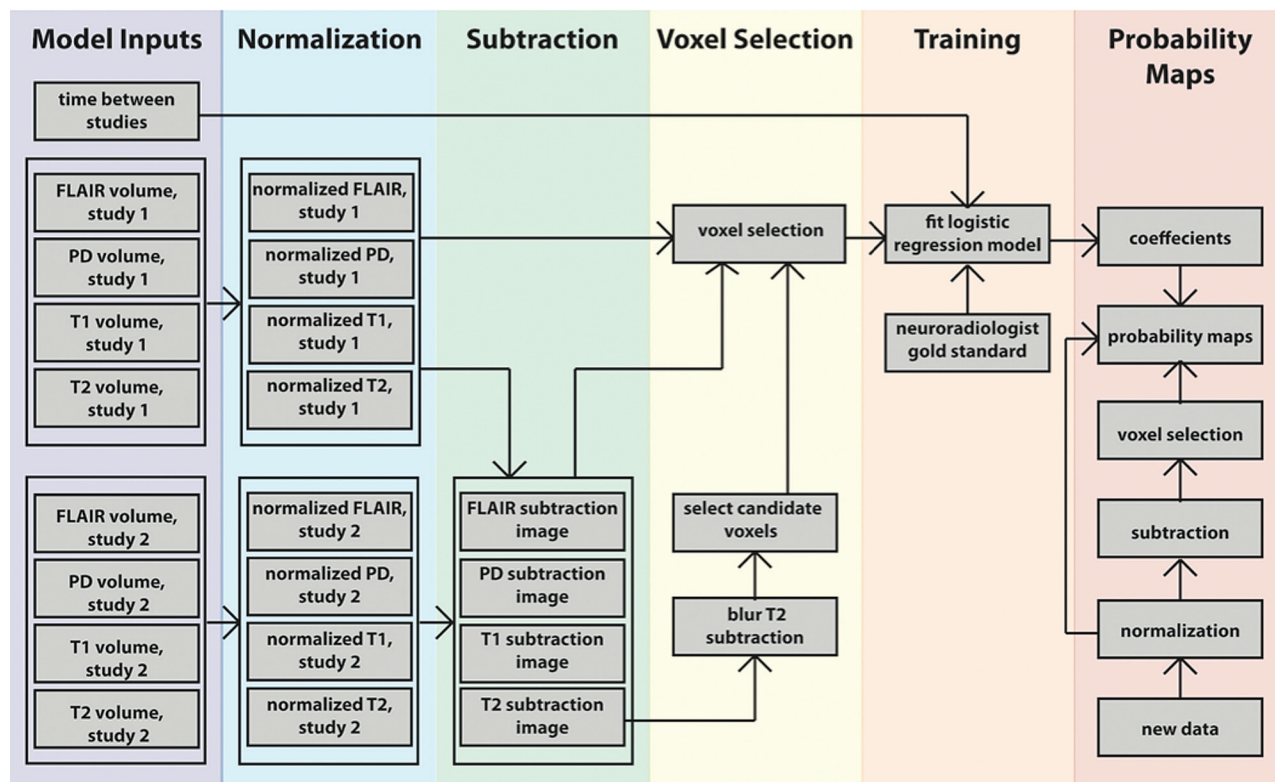


## On-line Appendix

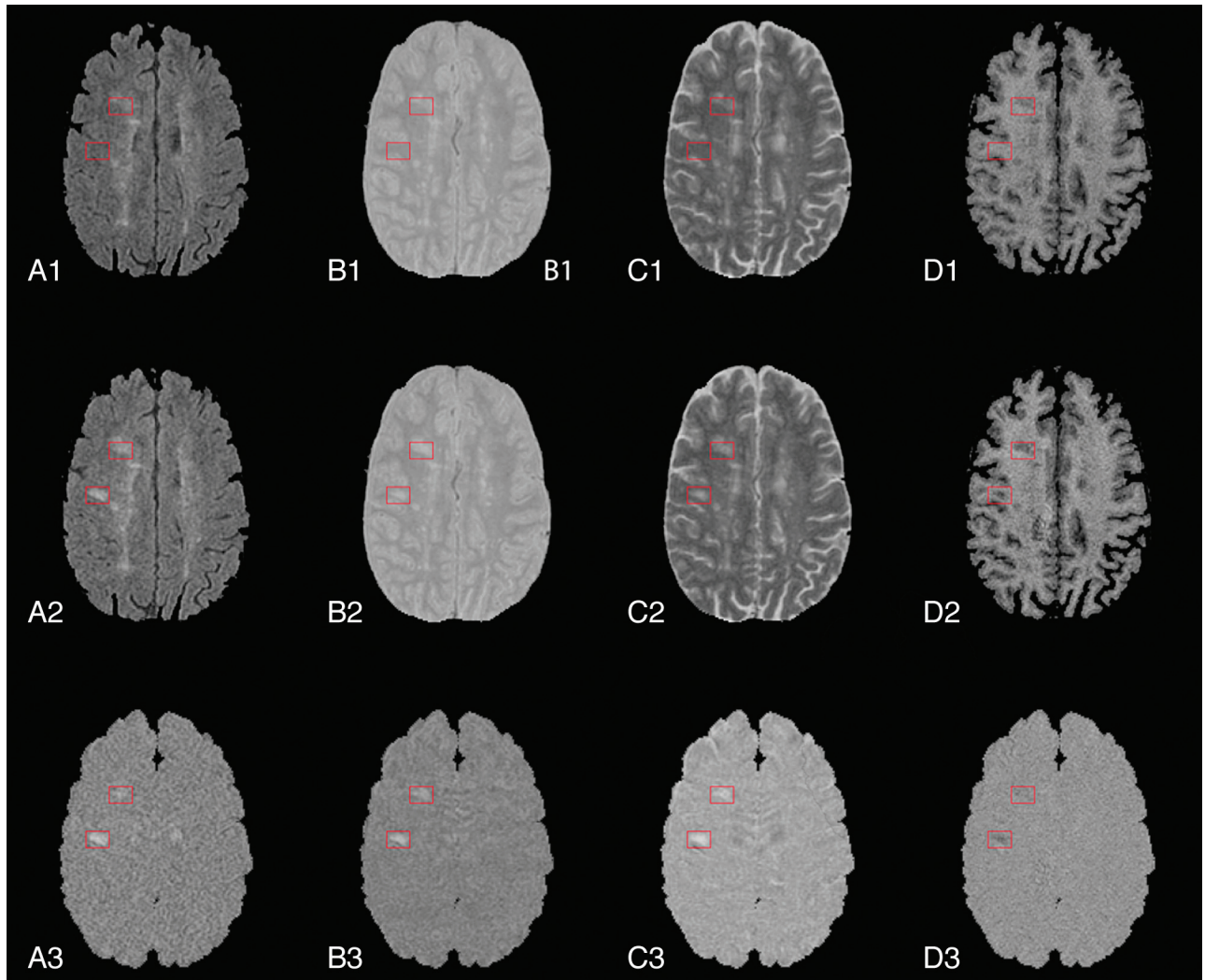
The following is a flow chart describing SuBLIME. The chart is divided into 6 color-coded sections: model inputs, normaliza-

tion, subtraction, voxel selection, training, and probability maps. The products of SuBLIME are probability maps of voxel level lesion incidence.



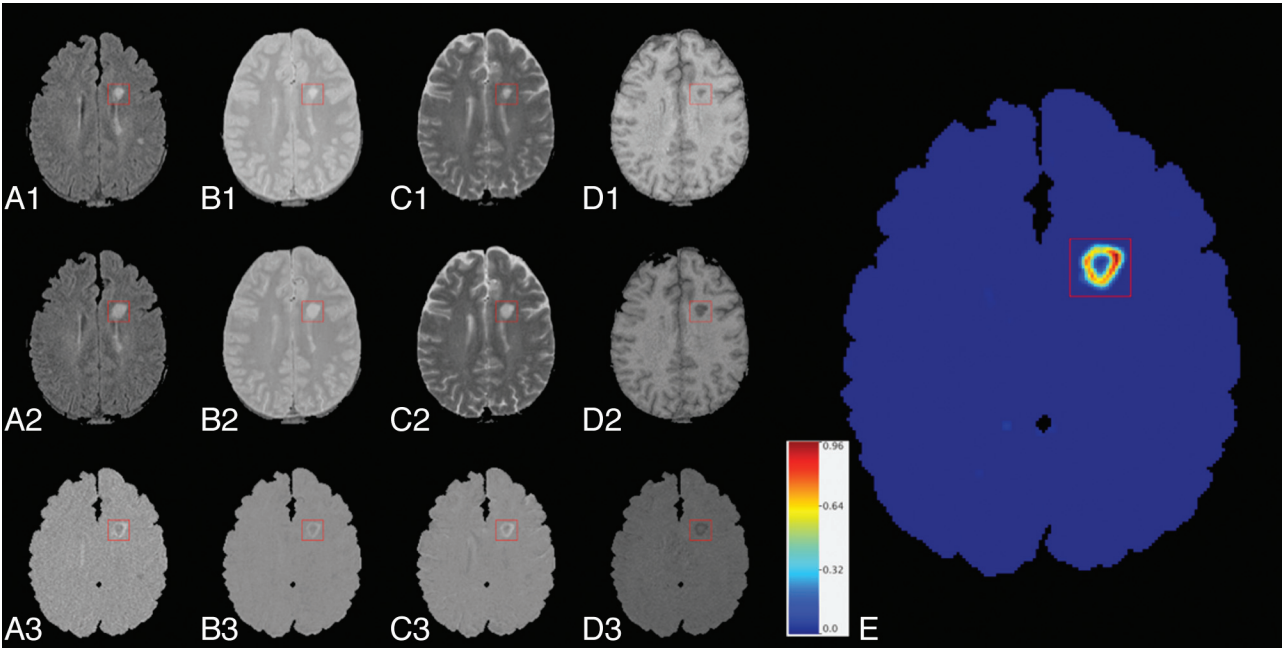
The following are axial sections from brain MR imaging of a single subject from 2 consecutive time points and the subtraction images created from these time points. Areas with lesion incidence between the 2 time points are indicated with red boxes. In the serial MR imaging, lesions are characterized by hyperintensities in the FLAIR, PD, and T2-weighted images and hypointensities in the T1-weighted image. In the subtraction images, lesion incidence and enlargement is characterized

by hyperintensities in the FLAIR, PD, and T2-weighted subtraction images and hypointensities in the T1-weighted image. A1, FLAIR at time 1; A2, FLAIR at time 2; A3, FLAIR subtraction image; B1, PD at time 1; B2, PD at time 2; B3, PD subtraction image; C1, T2-weighted at time 1; C2, T2-weighted at time 2; C3, T2-weighted subtraction image; D1, T1-weighted at time 1; D2, T1-weighted at time 2; D3, T1-weighted subtraction image.



The following are axial sections from brain MR imaging of a single subject from 2 consecutive time points, the subtraction images created from these time points, and the probability map produced with the full model. An enlarging lesion is indicated in all images with a red box. A1, FLAIR at time 1; A2,

FLAIR at time 2; A3, FLAIR subtraction image; B1, PD at time 1; B2, PD at time 2; B3, PD subtraction image; C1, T2-weighted at time 1; C2, T2-weighted at time 2; C3, T2-weighted subtraction image; D1, T1-weighted at time 1; D2, T1-weighted at time 2; D3, T1-weighted subtraction image; E, probability map.



The following is a summary of the full fitted model on a total of 1.3 million candidate voxels from 110 MRI studies of 10 subjects.

	Coefficient	Standard Error
Intercept	−9.1008	0.6628
$\Delta t$	0.0021	0.0018
FLAIR	0.7388	0.1751
$\Delta \text{FLAIR}$	−0.0540	0.2315
$\Delta \text{FLAIR} \times \Delta t$	0.0001	0.0004
PD	0.5606	0.1739
$\Delta \text{PD}$	0.3959	0.1265
$\Delta \text{PD} \times \Delta t$	−0.001	0.0004
T2	−0.2531	0.2342
$\Delta \text{T2}$	0.6503	0.3138
$\Delta \text{T2} \times \Delta t$	−0.0003	0.0007
T1	0.5098	0.1836
$\Delta \text{T1}$	−0.8282	0.1830
$\Delta \text{T1} \times \Delta t$	0.0020	0.0004

The coefficients for each technique are the log odds ratios of lesion incidence for voxels corresponding to an increased intensity of 1 normalized unit, fixing all other predictors. Lesions are characterized by hyperintensities in the FLAIR, PD, and T2-weighted images and hypointensities in the T1-weighted image, though not all lesions will appear on the T1-weighted image. As expected, the signs of coefficients for the FLAIR and PD intensities are positive. The coefficient of negative sign for the T2-weighted and positive sign for the T1-weighted images are interpreted in the context where all other predictors are fixed. Due to the strong correlation among the imaging modalities, it is difficult to visualize the impact that a 1-SD increase in the NAWM intensity in T2-weighted or T1-weighted images has on the log odds ratio when all other modalities are kept constant. The coefficients for the subtraction are more difficult to interpret. These must be interpreted when the change in time is equal to zero, which never happens in our dataset. Lesion incidence is characterized by hyperintensities in FLAIR, PD, and T2-weighted subtraction images and by hypointensities in the T1-weighted subtraction image. The signs of the coefficients for PD subtraction and T2-weighted subtraction are positive, and T1-weighted subtraction is negative. The sign for FLAIR subtraction is negative; this is again due to the correlation and must be interpreted while fixing all other predictors and the fact that this is interpreted when the change in time is equal to zero. The coefficients for the change in time and the interaction between the subtraction images and change in time were, in some cases, not statistically significant.

The following is a summary of the SuBLIME model with only the T2-weighted image on a total of 1.3 million candidate voxels from 110 MRI studies of 10 subjects.

	Coefficient	Standard Error
Intercept	−8.3640	0.7484
$\Delta t$	0.0018	0.0020
T2	−0.0298	0.0764
$\Delta T2$	1.0163	0.2616
$\Delta T2 \times \Delta t$	−0.0004	0.0008

The following plot shows the partial ROC curves for the nested SuBLIME models with only 3 sequences; a model fit using only the FLAIR, T2-weighted, and T1-weighted; a model fit with the PD, T2-weighted, and T1-weighted; and a model with the FLAIR, PD, and T2-weighted. Due to the small number of subjects available for this analysis, there was not a statistically significant difference between the nested models and the full model.

