Single Module Disease Marker

1 Motivation

It is believed that the development of Alzgeimers disease takes place over an 20 year prodromal period. Pathological manifestations of Alzheimer's disease begin many years before the patient can be diagnosed by cognitive tests We need to develop some biomarkers that reliably signal the onset of nasscent disease before the emergence of cognitive impairment. Even though CSF measures and PET scan have shown encouraging results. They have their own drawbacks. CSF is highly invasive and PET is very costly. MRI is non-invasive and largely available in clinical environment. Thus, develop MRI image-based marker to characterize prominent neurodegnerative patterns during prodromal stage is promising.

More specifically, we are studying people who are cognitively normal, middle-aged but at increase risk of Alzhimier's disease. We refer them as asymptomatic group. We are only using T1-weighted MRI scan as our primary source of information to develop our image marker

2 Experiment Setup

2.1 Data

Data used in the evaluation of our algorithm were taken from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www. loni.ucla.edu/ADNI), ADRC and WRAP. In WRAP, three group of subjects are used, including MRT, PDT, PIPR. In ADRC, IMPACT subjects are used. Only MRI-T1 images are used in generating SMDM scores. FDG-PET and PIB images are used in analysising results.

Group	Number of Subjects	Age (mean ± std)	Gender (M/F)	Education (mean ± std)	APOE Carrier (Non/Any)	Family History (Pos/Neg)
AD	182	75.38 ± 7.54	94/88	14.81 ± 3.10	62/120	74/106
MCI	385	74.44 ± 7.42	248/137	15.71 ± 2.98	178/207	161/222
CN	225	75.94 ± 5.00	116/109	16.02 ± 2.86	165/60	96/126
Asymptomatic	534	59.24 ± 6.45	169/375	16.10 ± 2.38	320/224	412/132

2.2 Pipeline

First we do a tissue segmentation and a warping to MNI space as preprocessing. Then we construct base kernel from selected voxels and combine them as final kernel for SVM training. Lastly, SMDM of test subjects are derived as margin of test sample from decision boundary learnt by SVM. Intuitively, the farther away the subject is from decision boundary, the more typical it is in the group.

2.3 Preliminary image-processing

Preprocessing of raw imaging data is necessary before we apply SVM. T1 MRI images are processed by using Voxel-Based Morphometry (VBM) toolbox in Statistical Parametric Mapping software (SPM8). It integrate tissue segmentation, warping, normalization to MNI space and smoothing into one function.

2.4 Kernel matrices

It is shown that linear kernel perform on par or even better then quadratic and Guassian kernels. Only linear kernels are used here. Base kernel matrices used in the experiments were computed from different set of voxels intensity from smooth warped registered T1 images. Each voxel's intensity value in T1 image can be thought of as a random variable, upon which we performed a t-test, and ranked the voxel by the resulting **T values**. P value is not used here because we do not have know the T value is positive or negative. To exclude voxels that are non-informative (outside the brain) in t-test, we do a thresholding on the intensity value. Both 0.25 and 0.4 are used and analysed and results are shown in Complete.xls. Set of voxels used in constructing the kernel are first 500, 1000, 2000, 5000, 10000, 20000, 50000, and 100000 voxels ranked top in the t-test.

To improve the performance, a combined kernel is computed by nomalizing each base kernel and take the average of the base kernel. This construction of kernel is a surrogate to MKL methods. Advantage of this method is no choice of number of voxels and threshold need to be choosed. Information from different base kernel can be intergrated. In the experiment, base kernel are set of voxel number from 2000 to 9000 with increment of 1000 and from 10000 to 100000 with increment of 5000 coupled with different threshold levels at 0.1,0.15,0.2, 0.25,0.3,0.35 and 0.4. A reasonable range of number of voxels used here is to utilize most information.

We attempted to include the age kernel and gender kernel in the combined kernel. However, the difference is marginal and not included in final experiments.

After using the kernel to train the SVM, we get the support vectors. We can calculate the decision boundary. For each incoming test subject, the distance from the the decision boundary is derived as single module disease marker (SMDM) score. All the AD and CN subjects from ADNI-1 are used in training. MCI from ADNI-1 and Asymptamatic groups are used in testing. Normalizing the kernel is necessary here because when constructing linear kernel $x^T x$, kernels with more voxels will have larger value and thus dominate other kernels at averaging step. First step is to process the subjects to have zero mean and standard deviation 1. Then a linear kernel K is constructed. Second step is to normalize the kernel so that the diagonal of the kernel is one. Each entry in normalized kernel is $\bar{K_{ij}} = K_{ij}/\sqrt{K_{ii}K_{jj}}$

2.5 Implementation

All the analysis experiment is implemented in MATLAB R2012 and lib-svm.