

Segmentation of Amyloid Plaques in MR images of the APP Transgenic Mouse Brain using SVM

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Introduction

Alzheimer's disease (AD) is linked to increased brain deposition of amyloid-beta peptides in senile plaques. Successful visualization of amyloid deposits in the APP transgenic mouse brain with MR imaging has been reported by several investigators recently. However, there are very few reports of methods for the measurement of plaque burden in the mouse brain. The number of plaques, their size and brain distribution depend on the transgenic mouse line and vary with age. In our previous work, we presented a method based on simulated flooding [1] and data gradient divergence (Laplacian) to segment the AD plaques in mouse MR brain images. The method was fully automatic, but the parameters used for segmentation were based on the Laplacian values observed in a control animal. Here we present an automated selection of the segmentation parameters using support vector machines (SVM) [2] in an unsupervised way. The usual approach for classification is to use the "ground truth", in our case real examples of amyloid deposits in MR images. Obtaining such examples is however very difficult, due to the reduced size and low contrast of plaques. To address this, we employ a "learning by counter-example" approach, by training one class SVM (OCSVM) [3] classifier on control datasets.

Methods

Transgenic Mice: 5XFAD transgenic mice coexpressing a total of five FAD mutations [APP K670N/M671L (Swedish) + I716V (Florida) + V717I (London) and PS1 M146L + L286V] were generated in a collaborator's laboratory [4]. Plaques begin to appear in the 5XFAD mouse brain relatively early, at 2 months, and level off at 9 months.

MR imaging: Brains fixed in 4% paraformaldehyde were used for imaging. During imaging, brains were immersed in Fomblin (a perfluorinated liquid) to prevent dehydration and reduce magnetic susceptibility gradients. All imaging experiments were performed on a Bruker Avance 14.1T imaging spectrometer fitted with a 100G/cm gradient using a10 or 20 mm resonator tuned to proton frequency (600MHz). 3D images were acquired using a fast spin-echo (RARE8) pulse sequence and the following imaging parameters: TR/TEeff 2500ms/40ms; pixel size 35 μ m x35 μ m x35 μ m.

Plaque Analysis: Simulated flooding (watersheds) is used on the MR image I to extract catchment basins (CBs), defined as regions with low intensities completely surrounded by higher intensity neighbors. Then, image Laplacian $L(I) = \text{div}(\text{grad}(I))$ is used to model the plaque cores, defined as regions with small derivatives, surrounded by neighbors with rapidly increasing intensity. $L(I)$ is the degree to which the gradient vector field flow behaves like a source or a sink. Previously, for plaque segmentation, we used a Laplacian threshold, based on the observed CBs in the control data. In this work, we propose a different approach by defining the plaques as an outlier detection problem of the OCSVM. As an extension of the two classes SVM, one-class SVM (OCSVM) estimates a classification function that encloses a majority of the training prototypes in a feature space. We use μ -SVM, an OCSVM implementation that computes a hyperplane to separate a specified fraction $(1 - \mu)$ of data with the maximum distance to the origin. In our case, parameter μ is controlling the outlier ratio that is defined as a ratio of plaques voxels to the volume of the processed brain structure. Kernel methods can be used to project the original data space into a high dimensional feature space, and a linear classification in the latter is equivalent to a nonlinear classification in the former. We use Radial Basis Function (RBF) kernel, $k(x; x_i) = e^{-\gamma \|x - x_i\|^2}$, where γ determines the kernel width [5]. Our method has two steps. First, on OCSVM model is created, by training on the control mouse dataset. This model will classify as plaque any CB that has features different than the CBs in the training dataset. Then, a two class SVM is trained on a 5xFAD 10 months old mouse dataset, using the labels created by the OCSVM classifier. The resulting classifier is then applied to all the other datasets.

Results and Discussion

We applied our algorithm on images of six excised mouse brains: Five 5XFAD mice (age 2 (n=2) and 10 (n=3) months) and a control B6 mouse (7 months). For each dataset the subiculum was segmented manually to assess the plaque distribution within that brain structure. We computed the plaque load PL (ratio between the volume of the segmented plaques and the volume of the structure of interest). The algorithm was evaluated visually (Figure 1), and by comparing the PL values to known plaque characteristics of the mouse strains. Validation with histology data was performed (Figure 2). The plaque load results show a PL increase with age for the 5XFAD mice from 0% at 2 months to 20% at 10 months. The control mouse had a PL of 0% since it was used for OCSVM training.

Our results are consistent with known characteristics of amyloid plaques in the subiculum of 5XFAD mice. The presented method allows the automatic selection of divergence threshold for amyloid deposits segmentation.

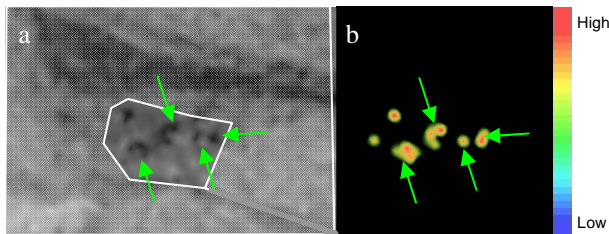


Figure 2
MR image (a) of a 10 month old 5XFAD mouse brain, with the white contour depicting the processed area in the subiculum. Corresponding segmented plaque (b) are displayed in pseudo-color volume-rendering, showing that the Laplacian is higher in the core and lowest in the periphery. Plaque locations and their corresponding detections are indicated by a linked cursor (green arrows)

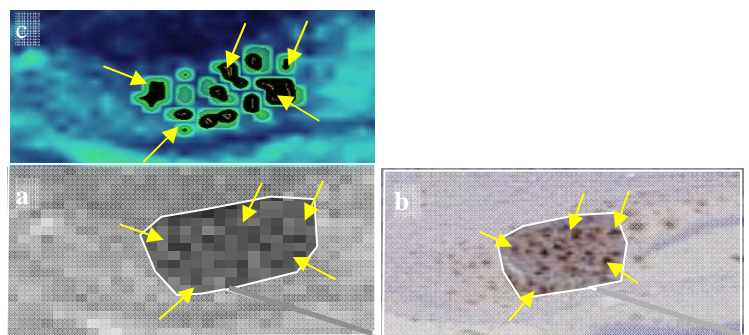


Figure 1
A 35 μ m thick MR slice (a) from a 10 month 5xFAD mouse with the white contour depicting the processed area in the subiculum. A 30 μ m thick histology (b) section stained with 4G8 antibody in the same sagittal plane. Pseudocolored volume rendering (c) of the corresponding segmented plaque contours. Plaques locations and detections and the histology correspondents are indicated by a linked cursor (yellow arrows).

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3. Scholkopf B., et al. Neural Computation, 13(7):1443-1471, 2001
4. Oakley H., et al. J. Neurosci. 26: 10129-140, 2006
5. Chang C. C., et al., LIBSVM: a library for support vector machines, 2001. Software available at <http://www.csie.ntu.edu.tw/~cjlin/libsvm>