Automated edge-driven Markov random field segmentation of *ex vivo* mouse brain MRM images

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Introduction The automated segmentation of MRM images of the *ex vivo* mouse brain is a challenging task, mostly due to artefacts, noise or deformations. Besides annotation purposes, segmentation of the mouse brain is essential for quantitative phenotyping of (transgenic) mouse models, which is done by volumetric measurements or 3D shape analysis of brain regions. In our previous work[1], manual segmentations of the brain were used for registration to single histology sections. The aim of this work is to develop a fast automated segmentation method that can be used for the registration. Ali et al. presented a segmentation method where mouse brain scans of different imaging protocols were combined with statistical prior information[2]. We chose for an atlas-based segmentation combined with extended Markov random field (MRF) clustering to avoid multiple, time consuming scanning protocols. For human brain segmentation, MRF clustering was previously extended with mutual information[3], probabilistic atlases[4] or deformable models[5]. Although these methods work correctly on human brains, the algorithms encounter problems on mouse brains due to the poor signal-to-noise ratio. We found that mouse brains can be segmented accurately when the MRF clustering is extended with edge information.

Methods For the experiment we used 7 mouse brains, which were perfusion-fixed with paraformaldehyde, after which the skull was removed. The MRM images were acquired with a Bruker 9.4 Tesla scanner with a T1W 3D-GE protocol, resulting in a 256x256x256 volume with an isotropic resolution of 78.125 µm per voxel. The proposed algorithm is split up in two parts: First, an affine atlas-based registration is performed to obtain an initial segmentation, which is then refined by an extended MRF clustering method. The atlas-based registration is used to find a rough initial segmentation for the clustering algorithm and to extract prior information on the intensity distributions for each class. The affine registration uses mutual information combined with an optimizer that is set to a fast convergence. The clustering is used for the refinement of the segmentation near the borders of the various structures, where the atlas-based segmentation alone is not accurate enough. To incorporate the edge information, combined with the prior knowledge from the atlas, we propose to use the following function as extended MRF clustering:

$$p(c \mid x, n \in N) = w_1 P_{posterior}(c \mid x) + w_2 P_{intensites}(c \mid x) + w_3 P_{neightbors}(c \mid x, n \in N).$$

The formula returns the probability that voxel x belongs to class c, given its direct neighbours N, and is composed of three factors which influence the segmentation: the posterior probability, the intensity distribution for all classes and the neighbourhood influence. The weights w_1, w_2 and w_3 are used to tune the algorithm and must sum up to 1, since the three components are probabilities on their own. The components are formulated as:

$$P_{posterior}(c \mid x) = \frac{p(x \mid c)p(c)}{\sum_{c \in C} p(x \mid c)p(c)}, \quad P_{intensities}(c \mid x) = 1 - \frac{(x - \bar{x}_c)^2}{\sum_{c \in C}(x - \bar{x}_c)^2} \quad \text{and} \quad P_{neighbors}(c \mid x, n \in N) = \frac{S(x)}{N+1} + \sum_{n \in N} \frac{S(n_c)}{N+1}.$$

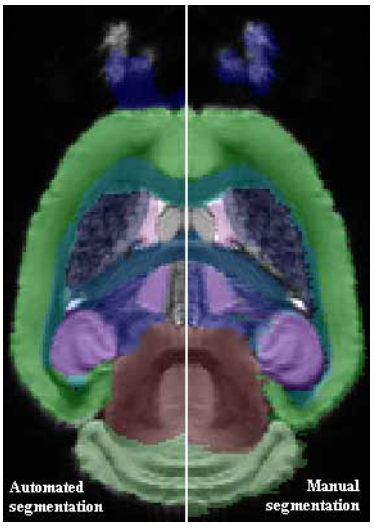
In the formulas above, p(x|c) denotes the ratio of the number of voxels belonging to c, p(c) the random change at class c and $\bar{x}_c$ the mean intensity of class c. The n_c in the last formula symbolises that for each class c, the neighbours can only contribute if they are also classified to c. These neighbours are weighted by the underlying edge information obtained by a Sobel edge detection filter S(x). This weighting causes that neighbours lying on or near an edge have less influence than the neighbours that lie inside a structure.

Results and discussion Since an accurate average *ex vivo* brain atlas was absent, one of the brain images was assigned as atlas before the algorithm was evaluated. However, one volume is not representative for the whole dataset. Therefore, an average atlas was approximated by selecting one mouse brain as atlas and subsequently evaluating the algorithm on the other six mouse brains. This process was repeated seven times, so all mouse brains were used once as atlas. The final results were averaged over all experiments.

We compared the volumes of the automated segmentation to the results of the manual segmentation, which was guided by the LONI atlas[6], according to the kappa index: $\kappa = \frac{2(V_a \cap V_m)}{V_a + V_m}$

The kappa indexes ordered by their volume and a segmented slice are displayed on the right. The good κ results are displayed in bold. The poor result for the olfactory areas is likely caused by experimental errors, since it is difficult to extract the brain from the skull without damaging or deforming the olfactory bulbs. These deformed areas cannot be correctly registered and cause the segmentation to fail. Furthermore, one can see in the segmented image that the automatic segmentation outperforms the manual segmentation on the borders of various structures, e.g at the cerebellum and the thalamus.

segment	kappa
cerebral cortex	**0.85**
midbrain - hindbrain	**0.86**
cerebellum	**0.89**
olfactory areas	0.58
thalamus	**0.82**
hippocampal formation	**0.85**
caudoputamen	**0.80**
corpus callosum	**0.71**
hypothalamus	**0.76**
fornix system	**0.56**
corticospinal tract	0.48
ventricles	0.42
globus pallidus	**0.50**
anterior commisure, olfactory limb	0.25
substantia nigra	**0.55**
anterior commisure, temporal limb	0.15



Conclusion We demonstrated a fully automated and accurate segmentation method. The presented method will be further improved by the use of an average atlas, which is created from a set of *ex vivo* mouse brains. These brains will be imaged when they are still inside the skull, thereby preventing damage and deformation to brain structures like the olfactory areas. A less deformed and damaged atlas will likely generate a more accurate initial segmentation that results in a better clustering. Finally, the *ex vivo* segmentation will be incorporated into our previous work[1] on the automated registration of the *ex vivo* mouse brain MRM images with a single histology section and, eventually, with the *in vivo* mouse brain.

References [1] A.E.H.Scheenstra *et al.*, *in* proc. Intl.Soc. Mag. Reson. Med, pp 2012 (2006) [2] A.A. Ali *et al.*, NeuroImage 27:425–435(2005). [3] S.P. Awate *et al.*, Medical Image Analysis, 10:726–739 (2006) [4] S. Bricq *et al.*, *in* International Symposium on Biomedical Imaging, pp.386–389 (2006) [5] H.R. Underhill *et al.*, *in* proc. Intl.Soc. Mag. Reson. Med, pp 829 (2006) [6] A. MacKenzie-Graham *et al.*, Journal of Anatomy 205:71-149 (2004)