Multiple Sclerosis lesion segmentation using Active Contours model and adaptive outlier detection method

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Abstract. The segmentation of Multiple Sclerosis (MS) lesions on Magnetic Resonance Imaging (MRI) has become a crucial criterion for diagnosis and predicting prognosis in early disease. Automated MS lesion segmentation is highly desirable for its low time computation, cost, e ectiveness and minimum user bias. We proposed to develop and evaluate an automated lesion segmentation method based on Active Contours (AC) model incorporating tissue knowledge issued from T_1-weighted and tissues distribution on Attenuated Inversion recovery (FLAIR) image. The Gray Matter (GM) and White Matter (WM) as well as CerebroSpinal Fluid (CSF) tissue classes issued from from T_1-weighted and the tissues intensities issued from FLAIR are used in order to determine an automatic outlier of each tissue class is used in order to detect outliers. The L_2 metric used an integrated square estimator to detect outlier in order separate MS lesions from the other tissues. The algorithm is evaluated for (T_1-weighted and FLAIR) public datasets of 20 MS patients. Comparing our results with lesion delineation by a human expert and with previously extensively validated results shows the promise of the proposed approach. These results require validation with data from other protocols based on a conventional FLAIR sequence and a T1-weighted sequence. Yet, we believe that our method allows fast and reliable segmentation of FLAIR-hyperintense lesions, which might simplify the quantification of lesions in basic research and even clinical trials.

Keywords: Multiple Sclerosis, Active Contours, Adaptive outlier, Split Bregman

1 Introduction

The segmentation of Multiple Sclerosis (MS) from Magnetic Resonance (MR) imaging is the prerequisite step for performing various quantitative analysis. The MS disease is characterized by unpredictable episodes of clinical relapses and remissions followed by continuous progression of disability over time in most instances [16,11]. Demyelinating lesions within cerebral White Matter (WM) are the hallmark of MS and its detection by T2-weighted MR imaging has become a crucial diagnostic criterion [21]. Moreover, MS lesion (T2-hyper-intense) lesion volume has been demonstrated to correlate with severity of symptoms, progression of disability and Gray-Matter (GM) atrophy [3]. Accordingly, MS lesion volume has been of interest in basic research and has been determined in most pivotal trials on disease-modifying drugs since the late nineties [17]. Automatization of MS lesion segmentation is highly desirable with regard to time and cost e ectiveness but also constitutes a prerequisite to minimize user bias. Several algorithms have been proposed in literature [19,13],but no gold standard has been established. Therefore, in large clinical trials, lesions were manually delineated slice by slice with the help of semi-automated segmentation methods. Such task shows high intra- and inter-rater variability, and high time consuming , which may cause variability in the interpretation by radiologist in the verification phase.

In clinical trials, automatic segmentation should reduce the human interaction and improve reproducibility. However, variability of MR protocols and the heterogeneity (contrast, location, size and shape) of the disease make di cult to develop accurate segmentation for MS lesions with a high levels of reproducibility and reliability. In addition, the anatomical variability between subjects [19] makes MS lesion segmentation results inevitably a ected by intra and inter-expert variability[20]. To reduce this variability, several Methods for automatic MS lesion segmentation have been proposed in [22,12,9,6] and can be split in four categories: Data-depend methods, Model-based methods, Atlas-based methods and Outlier-based methods.

The Data-depend methods extract all the necessary information directly from the patient image datasets. These methods model the distribution of the image intensities using a Gaussian Mixture Model (GMM), where each Gaussian law represents a tissue: e.g. Cerebro Spinal Fluid (CSF), gray matter (GM) or white matter (WM). The GMM enables characterization of the image intensities with a reduced number of parameters.

Model-based methods model the tissues of MS lesion as an independent class to be extracted. A combination of intensity-based k-nearest neighbor classification and template-driven segmentation was designed to segment di erent types of brain tissue. Lesions are modeled as one of the expected tissue types, and the class parameters are obtained through an operator supervised voxel sampling on two randomly selected scans. Since the manual training step is highly data-dependent, it is expected be conducted for each study or data set. Note that in the model-based approaches, a training procedure, to either calibrate the classifier parameters or to choose the tissue class representatives, is normally needed.

In order to obtain desired segmentation results, the testing data sets are also expected to be highly similar to the training sets, ideally from the same group. Atlas-based methods proposed in [16] makes use of the relative consistent continuity and relationship residing in neighboring anatomical structures within the same group of subjects. Lesions are treated as a subclass within the WM tissues, and a topology preservation criterion is used to guarantee the topological equivalence between the atlas and the patient images [24,1]. However, multiple atlases are required to ensure this strict correspondence. In outlier-based methods [8], MS lesions are detected as the outliers to the normal brain tissue distribution (CSF, GM and WM) [8]. Outlier-based models relax the training requirement, but they usually consider a thresholding step. The training step is crucial for the segmentation performance and reproducibility, usually require certain prior to be accurately set up. However the threshold is di cult to be determined.
To overcome this di culty, we proposed to we develop a fully automatic method for MS lesion segmentation based on Active Contours (AC) model that requires no training, atlas, or thresholding steps. Our method can be regarded as a combination of the model based and outlier-based approaches. The core algorithm consists of three steps, and the separation of the lesion class from other normal tissue types is achieved by minimizing L_2 distance. We choose the L_2 distance for measuring similarity between the true Probability Density Function (PDF) and the assumed Gaussian Mixture based PDF, motivated by the following two reasons:

1. The L_2 distance is strongly related to the inherently robust estimator L_2E [7].
2. There exists a closed-form expression for the L_2 distance between Gaussian mixtures, which in turn a ords an e cient implementation of the segmentation algorithm.

The paper is organized as follows. Section 2 provides more details about our methodology; Section 3 presents the data and displays the segmentation results; a conclusion along with future direction is drawn in section 4.

2 Method and Materials

For better understanding, we give a conceptual overview of the three major steps of our algorithm. First, preprocessing is performed with the standard software of SPM8. To surpass smoothing of the individual images by warping, the algorithm operates in the space of the original T_1w image, i.e. in native space. Each pixel of the individual native T_1w image is assigned to one of the three tissue classes of GM, WM, or CSF. The FLAIR image is bias-corrected for MR field inhomogeneity and coregistered to the T_1w image. Second, both T_1w and FLAIR intensity intensity distributions are calculated for each of the three tissue classes to determine adaptive outliers. Third, the MS lesion are segmented and neighboring pixels are analyzed and assigned to lesions under certain conditions. This is done iteratively until no further pixels are assigned to lesions.

2.1 Data

This section presents the MS lesion segmentation challenge 2008 datasets, which is the largest dataset publicly available at `http://www.ia.unc.edu/MSseg/`, aims at evaluating and comparing algorithms in an independent and standardized way for the MS lesion segmentation. Two public datasets can be downloaded through `http://www.ia.unc.edu/MSseg/download.php`.
The first training dataset (labeled MR images) contains 10 cases from the Children's Hospital in Boston (CHB) and the second training dataset contain patient 10 from the University of North Carolina (UNC), which are labeled by a CHB expert rater. UNC cases were acquired on a Siemens 3T Allegra MRI scanner with slice thickness of 1mm and in-plane resolution of 0.5mm The test dataset contains 25 cases, 15 from CHB and 10 from UNC. For each case, the centers provided 3 MR volumes: a T_1-weighted image, a T_2-weighted image and a FLAIR image. These were co-registered and sampled to fit the isotropic $0.5 \times 0.5 \times 0.5 mm^3$ resolution. The data supplied was rigidly registered to a common reference frame and resliced to isotropic voxel spacing using b-spline based interpolation. Multiple sequences were provided, including T1, T2, FLAIR, and DTI.

2.2 Data preprocessing

In our approach, preprocessing includes skull stripping using a model-based level set approach [7] and the N3 inhomogeneity correction []. T1-sequence is used as inputs for the skull-stripping process. T1-W sequences are used because they are able of highlighting the complete structure of hard tissue, such as the skull [], whose intensities are distinct from the intensities of pixels representing other soft tissues present in the MRI datasets. MR images have been considered as more suitable for characterizing the contrast and intensity properties of MS load, as the signal from the cerebrospinal fluid (CSF) is nulled out and only GM and MS load remain brighter than WM, and are used in clinical routine for MS lesion segmentation. MS lesion depends on their contrast with respect to surrounding tissues as well as their location into the WM. Our AC based automated segmentation method takes advantage of these two characteristics. Three preprocessing steps using SPM8 software `http://www.fil.ion.ucl.ac.uk/spm/` were applied before segmenting with our Active contours model:

The selected skull-stripping approach produced better results than those of other well-known skull-stripping algorithms such as those in Refs. [33] and [34]. Subsequently, the inhomogeneity correction method described in [] is then applied to skull-stripped images to correct intensity inhomogeneity. This inhomogeneity correction method has been extensively tested and, in practice, works admirably on our datasets regardless of the lesion load.

The New Segment module of SPM8 was applied on T_1-w images [14]. This combined tissue segmentation, spatial normalization and image inhomogeneity correction approach resulted in probabilistic maps of GM , WM, CSF, meninges and skull in T_1 space as well as bias corrected T_1-w image. The

presence of non-brain tissues in the MRI scans a ects intensity distributions. This is also inherent to the capture process but it is not clear how the probability density function of (GM, WM,CSF) is altered by those external intensities. However, segmentation results are usually improved when those voxels are masked out.

Rigid registration of T_1-w to the FLAIR image. The sub-sampled and cropped so that they all have the same size, $159 \times 207 \times 79$ voxels, and the same resolution, $1 \times 1 \times 2mm^3$. The tissue information obtained from preprocessing steps allows the selection of relevant regions according to their location.

FLAIR image was bias corrected and performs inter-subject intensity calibration [19,23]. Spatial normalization is also performed by aligning the mid-sagittal plane with the center of the images [10]. The average computing time for these preprocessing steps was about 7 mins for each patient.

2.3 Segmentation using Active Contours ISE outlier

Our automatic MS lesion segmentation method was inspired from variational model proposed by Bresson *et al.*[5]. Using total variation formulation for the general image segmentation problem has several well known advantages, e.g. the naturally given possibility to handle topological changes and final solution is independence to the initialization. We proposed to formulate our variational model in characteristic framework as follows:

$$E(\chi) = \underbrace{\int_{\Omega_0} |\nabla \chi| \, d\mathbf{x}}_{E_b(\partial\Omega)} + \underbrace{\int_{\Omega_0} D_{L_2}(\Omega, \theta) \, \chi d\mathbf{x}}_{E_{data}(I,\theta)} \tag{1}$$

where λ is the weighting parameter and χ characteristic function framework defined as:

$$\chi(\mathbf{x}) = \begin{cases} 1 \; \mathbf{x} \in \Omega \\ 0 \; \mathbf{x} \notin \Omega \end{cases} \tag{2}$$

knowledge of the GM, WM and distributions of tissues are incorporated in the formulation of our automatic segmentation method as an additive energy term of the statistical descriptor using the L_2 distance.
has been investigated as an estimation tool for a variety of parametric statistical models and can be treated as a special case of the density power divergence [2]:

$$D_{L_2}(\Omega, \theta) = \lim_{\alpha \to 1} \left(\begin{array}{c} \int \frac{1}{\alpha} p^{\alpha+1}(\Omega|\,\theta) \, d\mathbf{x} + \int p^{\alpha+1}(\mathbf{x}) \, d\mathbf{x} \\ - \int \frac{1+\alpha}{\alpha} p^{\alpha+1}(\Omega|\,\theta) \, p^{\alpha}(\mathbf{x}) \, d\mathbf{x} \end{array} \right) \tag{3}$$

The L_2 distance [7] has been suggested as an alternative to nonparametric penalized-likelihood estimations [4]. The L_2 measures the di erence of an unknown probability density function $p(\mathbf{x})$ and its parametric approximation $p(\mathbf{x}|\,\theta)$.

Note that $p(\mathbf{x})$ doesn't contain any parameter θ, it can thus be dropped from the functional minimized in (3). Assuming that $p(\mathbf{x})$ is a density probability function, $p(\mathbf{x}|\,\theta)\,p(\mathbf{x})$ can therefore be viewed as the expectation of $p(\mathbf{x}|\,\theta)$. Putting these two considerations together, the L_2 distance in (3) can be rewritten as:

$$D_{L_2}(\Omega,\theta) = \log\left(\int p^2(\mathbf{x}|\,\theta)\,d\mathbf{x} - \frac{2}{m}\sum_{i=1}^{m} p^2(\mathbf{x}_i|\,\theta)\right) \tag{4}$$

Where m is the number of channel and $\mathbf{x}_i, ..., \mathbf{x}_N$.

2.4 Adaptive outlier for MS Lesion segmentation

The remaining problem is how to separate the clusters of normal tissues (GM and WM) from the outliers (MS lesions). This is achieved through a 3-step procedure:

1. Based on the one-dimensional histogram of a combined T_{1w} + FLAIR image, model the lesion part with an independent class and make a preliminary separation between lesions and the normal tissues. We adopt an integrated image as the segmentation basis, whose intensity is given by $I_{comb} = \sqrt{I^2_{T_{1w}} + I^2_{Flair}}$. The optimal θ is obtained by minimizing the L_2 distance using Integrated Square Error (ISE) given by:

$$D_{L_2}(\Omega,\theta) = \log\left(\begin{array}{l} \displaystyle\sum_{i=\{WM,GM,MS\}} \alpha_i N\left(I_{comb}|\,\mu_i,\sigma_i^2\right) \\ \displaystyle -\sum_{i=\{WM,GM,MS\}} \beta_i N\left(I_{T_1w}|\,\mu_i,\sigma_i^2\right) \\ \displaystyle -\sum_{i=\{WM,GM,MS\}} \gamma_i N\left(I_{FLAIR}|\,\mu_i,\sigma_i^2\right) \end{array}\right) \tag{5}$$

   Where the parameters $\theta = [v_{WM}, \mu_{WM}, \sigma_{WM}, v_{GM}, \mu_{GM}\ ,\sigma_{GM}, v_{MS}, \mu_{MS}, \sigma_{Ms}]$ is the combined vector representing the portions, means and standard deviations of WM, GM and MS-lesions Gaussian components.
2. Use multivariate Gaussian fitting to capture the GM and WM tissues in T_{1w}/FLAIR 2D-joint histogram to better capture and describe the GM and WM tissues. However, the lesions tissues no longer con-form to a Gaussian distribution, so we only focus on GM and WM and the parametric distribution calculated by GMM is given by:

$$p(I|\,\theta) = \alpha_{WM} N(I|\,\mu_{WM}, \Sigma_{WM}) + \alpha_{GM} N(I|\,\mu_{GM}, \Sigma_{GM}) \tag{6}$$

   Where $\theta = \{\alpha_{WM}, \mu_{WM}, \Sigma_{WM}, \alpha_{GM}, \mu_{GM}, \Sigma_{GM}\}$ represents the weight, means, and covariance matrices of the two Gaussian components. The component $N(x_i|\,\mu_k, \Sigma_k)_{k=1,2}$ represents the multivariate normal density func-

tion. The optimal θ minimizing 2D-joint histogram is assumed as:

$$D_{L_2}(\Omega,\theta)=\log\left(\begin{array}{c}\sum_{k=1}^{2}\sum_{l=1}^{2}\alpha_k\alpha_l N\left(0|\,\mu_k-\mu_l,\Sigma_k+\Sigma_l\right)\\ -\frac{2}{L}\sum_{i=1}^{L}\alpha_{WM}N\left(x|\,\mu_{WM},\Sigma_{WM}\right)\\ -\frac{2}{L}\sum_{i=1}^{L}\alpha_{GM}N\left(x|\,\mu_{GM},\Sigma_{GM}\right)\end{array}\right) \tag{7}$$

where $\alpha_{WM}+\alpha_{GM}=1$.

3. Conduct automatic outlier (MS-lesions) detection based on the Gaussian components from step 2 and the separation line obtained in step 1.

3 Fast Algorithm based on Split Bregman

We employ the Split Bregman method to find a contour minimizing AC energy functional, in the Split Bregman method we replace $\nabla\chi$ by a vectorial variable d [15]. This results in the following unconstrained segmentation problem:

$$(\chi^*,d^*)=\arg\min_{\chi,d}\left\{\int_{\Omega_0}|d|+\lambda\int_{\Omega_0}D_{L_2}(\Omega,\theta)\,\chi+\frac{\mu}{2}\int_{\Omega_0}|d-\nabla\chi|^2\right\} \tag{8}$$

An extra vector b is added to the penalty function in equation (8). Then the two unconstrained steps are iteratively solved by:

$$\left\{\begin{array}{c}\chi^{k+1}=\arg\min_{\chi^k}\left\{\lambda\int_{\Omega_0}D_{L_2}(\Omega,\theta)\,\chi^k+\frac{\mu}{2}\int_{\Omega_0}\left|d^k-\nabla\chi^k-b^k\right|^2\right\}\\ d^{k+1}=\arg\min_{d^k}\left\{\int_{\Omega_0}\left|d^k\right|+\frac{\mu}{2}\int_{\Omega_0}\left|d^k-\nabla\chi^k-b^k\right|^2\right\}\\ b^{k+1}=b^k+\nabla\chi^{k+1}-d^{k+1}\end{array}\right. \tag{9}$$

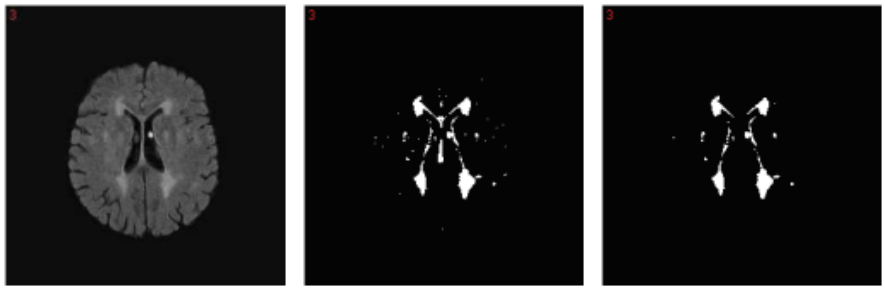
This segmentation problem can be solved when the optimality condition is satisfied:

$$\Delta\chi=\frac{1}{\mu}\left\{\lambda V_{L_2}+\mu div\left(b^k-d^k\right)\right\} \tag{10}$$

Finally, the minimizing solution d^{k+1} is given by soft-thresholding:

$$d^{k+1}=\frac{\nabla\chi^{k+1}+b^k}{|\nabla\chi^{k+1}+b^k|}\max\left(\left|\nabla\chi^{k+1}+b^k\right|-\frac{2}{\mu},0\right) \tag{11}$$

Note that this results in a minimizer which values are between 0 and 1. Then, the final active contour is given by the boundary of the set $\left\{\,\mathbf{x}\in\Omega|\,\chi^{final}>1/2\,\right\}$. Note that the last line is the update of $V_{L_2}^{k+1}$ at each iteration.



(a) First step of MS lesion load segmentation (b) segmentation results before artifact pruning (c) Final lesion segmentation

Fig. 1: segmentation results before artifact pruning

4 Results

4.1 Evaluation

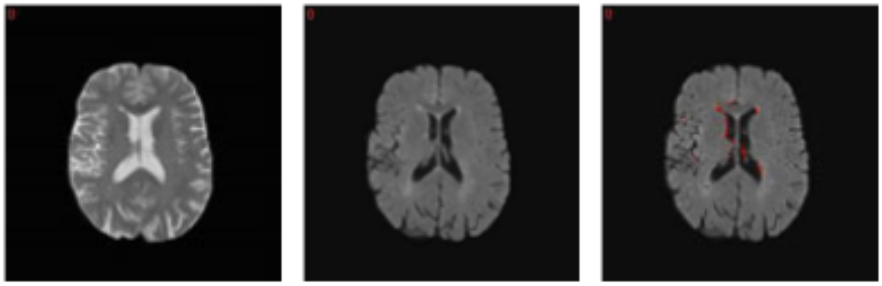
For quantitative analysis of the MS lesions, we perform MS lesion segmentation in cranial MR images using MRI datasets. The accuracy of segmentation can be measured in many ways and is dependent on the objective of the study. The goal of the proposed approach is to quantify the lesion load. However, the exact measurement of lesion load would be challenging. Even in the case of manual segmentation by radiologists, it is a known fact that significant to moderate inter-variability in the results of the segmentation would exist between two or more radiologists. Therefore, a direct voxels-by-voxels comparison between two techniques is not an accepted method of evaluation. In most prior research, several measures such as true-positive fraction (PF), FP fraction (PF), and similarity index are used to provide a robust and accurate evaluation [26,25,18]. The True Positive defined by ($TP = |S \bigcap R|$) pixels, are the pixels common to both S and R. R is the ground truth segmentation and S is the segmentation done by our automated method. True negative pixels are all IC pixels not outlined as lesions by experts ($TP = |IC \bigcap R|$). False positives ($FP = |S \bigcap R|$) are those detected in S but not by R and false negatives ($FN = |S \bigcap R|$) are those identified in R but not in S. The validation measures used include the sensitivity $S_c = TP/(TP + FN)$,the specificity $S_p = TN/(TN + FP)$. Accuracy $A_c = (TN + TP)/(TN + TP + FN + FP)$ and statistics $DSC = 2\frac{|S \bigcap R|}{|S|+|R|}$. ranges from 0.0 to 1.0 (perfect segmentation), with a value of 0.7 generally considered to be a good segmentation [24]. For each experiment, we assessed the scores behavior with varying values of DSC. Table 1. lists several representative results where the rows correspond to DSC = 0.5, 0.64, 0.82, respectively. In the first row, Dice exceeds the value of 0.5, thus the largest possible set of pixels detected as MS lesion is obtained. The last row refers to DSC 0.64 where the maximal value was obtained in both experiments.

Table 1: Quantitative evaluation of MS lesion segmentation for UNC datasets

UNC Datasets	DSC calculated for the method in [15]	DSC of our method
Case01	0,81	0,82
Case02	0,71	0,71
Case03	0,54	0,54
Case04	0,42	0,42
Case05	0,61	0,61
Case06	0,32	0,32
Case07	0,43	0,43
Case08	0,53	0,53
Case09	0,62	0,62
Case10	0,63	0,64

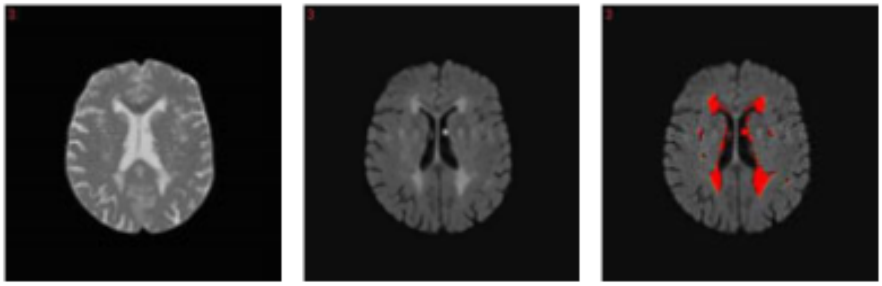
Table 2: Quantitative evaluation of MS lesion segmentation for UNC datasets

Datasets CHB	Dice using [15]	Dice of our method
Case01	0.70	0,71
Case02	0.52	0,62
Case03	0.42	0,51
Case04	0.64	0,79
Case05	0.59	0,61
Case06	0.45	0,67
Case07	0.68	0,78
Case08	0.72	0,76
Case09	0.47	0,61
Case10	0.63	0.71



(a) First step of MS lesion load segmentation (b) segmentation results before artifact pruning (c) Final lesion segmentation

Fig. 2: Segmentation of MS lesion on one MR slice for patient selected from CHB datasets



(a) First step of MS lesion load segmentation (b) segmentation results before artifact pruning (c) Final lesion segmentation

Fig. 3: Segmentation of MS lesion on one MR slice for patient selected from UNC datasets

5 Conclusion

A new method for automatic MS lesion segmentation from FLAIR and T_1 datasets is performed. The proposed method models MS lesion pixels in an additional class to the mixture of the normal brain tissues (CSF/GM/WM). Neither training nor thresholding is needed to performed the fully automatic segmentation based AC and outlier. Another advantage of our approach lies in the fact that it involves no thresholding step. Without explicit modeling, either soft or hard rejection, a predetermined threshold has to be used to decide the separation line/plane between the normal tissue and the outlier pixels. Since the thresholds are often data-dependent, manually chosen values tend to not work consistently across di erent data sets. The proposed segmentation method overcomes this di culty, thanks to the strong capture capability of estimation, and achieves great flexibility and broad applicability. Evaluation was carried out on 20 patients from two public datasets. The accuracy of our method has been

compared with four methods, with considerably better results with respect to two other unsupervised methods, and similar or better results compared with two optimized supervised approaches.

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