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Spatio-Temporal Segmentation and Characterization of Active Multiple Sclerosis Lesions in Serial MRI Data

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Abstract. This paper presents a new approach for the automatic segmentation and characterization of active MS lesions in 4D data of multiple sequences. Traditional segmentation of 4D data applies individual 3D spatial segmentation to each image data set, thus not making use of correlation over time. More recently, a time series analysis has been applied to 4D data to reveal active lesions [3]. However, misregistration at tissue borders led to false positive lesion voxels.
Lesion development is a complex spatio-temporal process, consequently methods concentrating exclusively on the spatial or temporal aspects of it cannot be expected to provide optimal results. Active MS lesions were extracted from the 4D data in order to quantify MR-based spatio-temporal changes in the brain. A spatio-temporal lesion model generated by principal component analysis allowed robust identification of active MS lesions overcoming the drawbacks of traditional purely spatial or purely temporal segmentation methods.

1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). MS lesions consist of areas of inflammation, myelin loss, axonal degeneration and gliotic scar formation. Magnetic resonance (MR) is the primary paraclinical modality to monitor the natural history of the disease and to evaluate the efficacy of treatment in long-term therapeutic studies.

In recent years several segmentation techniques have been developed to quantify brain MRI lesion load. Manual segmentation is not only time consuming but also tedious and error prone. The possibility to acquire multi-echo image data stimulated several attempts to apply classical statistical pattern recognition techniques. But purely intensity based segmentation has strong limitations and does often not provide satisfactory results. Different techniques have been developed and tested to incorporate anatomical knowledge into the segmentation procedure. As $90-95\%$ of MS lesions occur in white matter tissue, prior identification of the white matter area can be used to reduce the number of false positive lesions [8]. However, delineation of lesions is often not accurate enough. Tissue class distributions overlap and therefore voxels are misclassified. This is especially true for MS lesions.

The chronological course of MS lesions can be investigated by looking at significant changes in MR scans at two different time points. By examining temporal changes in consecutive MR scans, rather than to measure absolute intensity

values, active MS lesions can be segmented and characterized in a straightforward manner. A simple approach to detect changes in time series MR data is to subtract two consecutive, registered MR images. Other methods to detect and quantify active lesions in image sequences have been introduced in [7] and [6]. Both approaches rely on calculating a non-rigid deformation field between two consecutive images to express the changes of brain tissue appearance due to pathology. Unfortunately this approach cannot always capture the complex behavior of lesion development, because luminance changes can always be traded for deformation and vice versa.

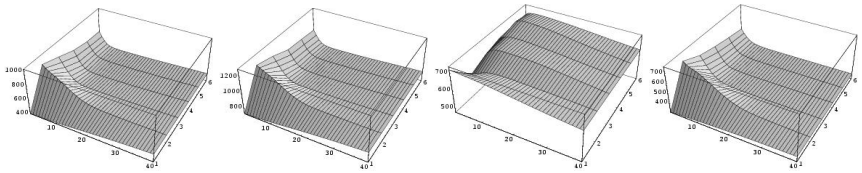
A new method to segment active MS lesions has been introduced in [3]. After preprocessing serial MR data including normalization of the brightness and precise registration of serial volume data sets to 4D data, the hypothesis can be established that intensities in static regions remain unchanged over time, whereas local changes in tissue characteristics cause typical fluctuations in the voxel's time series. A time series analysis has then been applied to reveal active lesion voxels.
The described algorithm is highly sensitive to rigid registration, brightness normalization and noise reduction. Whereas successful algorithms are available for the latter two preprocessing steps, the quality of the rigid registration is strongly dependent on the axial resolution of MR scans. Especially at tissue borders, misregistration leads to fluctuations of intensities over time.

Lesion development is a complex spatio-temporal process, consequently methods concentrating exclusively on the spatial or temporal aspects of it cannot be expected to provide optimal results. The goal is therefore to characterize lesion evolution by quantitative characterization of MR-based spatio-temporal changes. A spatio-temporal lesion model can be used to improve the segmentation results of the time series analysis described above. False positive lesions should be clearly distinguishable from true lesions considering the expected spatio-temporal behavior of active MS lesions.

2 Model Generation

In order to perform temporal and spatio-temporal analysis of MS lesions, we first acquired time series of data in multiple sequences. 11 patients with definite MS underwent monthly MR scans for one year. Proton-density-weighted (PD), T2-weighted (T2), Flair (FL), and T1-weighted images before and after the application of Gadolinium contrast agent (T1 resp. GD) were acquired with an axial resolution of 2mm. Bias-field correction and brightness normalization of the images was obtained using the method described in [1]. Due to unavoidable misregistration during repeated acquisition, an intensity based rigid registration algorithm (described in [4]) was used to create intensity-corrected multichannel 4D data.

Up to now, data collections were compiled using complete, segmented MRI sequences of MS patients. In order to extract a spatio-temporal model of MS lesions, this patient based view was replaced by a lesion based view. Active lesions were extracted manually from 4D data to form a lesion database. The



a b c d

Fig. 1. Spatio-temporal evolution of one lesion in different pulse sequences: T2 (a), PD (b), T1 (c), FL (d). The three axes indicate radius, time and intensity.

complete gray-value information of the lesions and their surrounding tissue in all MR sequences at all time-points was stored.

In order to characterize the spatio-temporal development, we first looked for a spatial model to describe the lesions at a specific time. As they can have varying shape and size we must normalize them in our database in order to robustly characterize changes of the spatial appearance over time. Lesions can very often be described as radially-symmetric structures, therefore a 1D model of radial intensity changes can be used to compactly describe their spatial structure [2].

This approach describes the structure of a lesion as a collection of layers with specific intensities (onion-skin model). Intensities resp. gray-level values at equidistant isosurfaces provide a one-dimensional characterization of a lesion. Adapting the methods applied in [2] to 3D, we used mean curvature evolution to obtain a 1D characterization.

Applying mean curvature flow to 3D images of MS lesions, the corresponding (convex) isosurfaces of the lesion first become asymptotically spherical before evolving into a point at the center of the lesion. Consequently, the intensities at the (fixed) center correspond to the intensities of the original isosurfaces. By collecting these values, a 1D radial intensity profile can be obtained.

Non-convex surfaces will eventually split into convex parts [5]. However, MS lesions are usually rather ellipsoidal with a more or less clearly defined center. Therefore, even if small parts of the lesion would be splitted during the flow, the corresponding intensity evolution at the center will capture most of the internal structure of the lesion. For complex-shaped lesions this kind of normalization might be too strong. We therefore also experimented with more detailed spatial lesion descriptions. However, the low number of active lesions in our database forced us to use the highly simplified 1-dimensional description scheme.

To cover the spatio-temporal development in multiple sequences, we chose to observe the lesion over a period of six months. The appearance of a MS lesion is coupled with a steep rise of intensities in the FL sequence. Therefore, for temporal localization, we determined the maximal gradient for each voxel in the FL sequence and used it for the extraction of the time slot on all pulse sequences. Observation started one month before we could identify the lesion in the FL sequence and finished four months after the appearance. However, it is not possible to extract the defined time slot for lesions appearing at the end of the observation period, resp. those already visible in the first examination. Therefore, such lesions were discarded from further analysis. 23 active lesions remained in

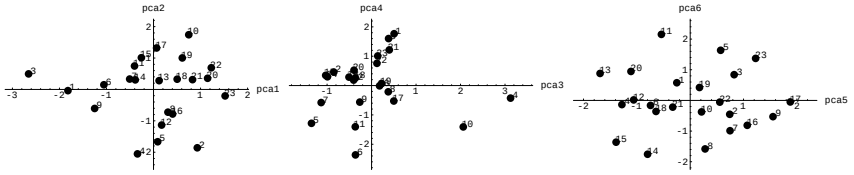


Fig. 2. Projection of the sample points to the first and second (a), to the third and fourth (b) , and to the fifth and sixth (c) principal component.

the database. The center of the lesions was determined by first applying a few steps of mean curvature flow to the maximum intensity image projected over time in the FL sequence followed by a search for the brightest voxel in the lesion's image. The spatial extent was given by the manually extracted region of interest. The evolution was followed in four different sequences: T2, PD, T1, FL (Figure 1). For further analysis the extent of each lesion was normalized to a standard size.

To determine the variation of the spatio-temporal behavior of MS lesions, a principal component analysis (PCA) was applied to the normalized descriptors in the database. The considered vectors $\mathbf{x_i}$, describing one lesion as shown in Figure 1, consist of the normalized intensity profiles (with a length of 40 voxels each) of all considered time points (6 time points) on all pulse sequences (4 sequences). As we have extracted 23 active lesions, we consider a 23×960-dimensional matrix X consisting of the vectors $\mathbf{x_i}$. From the covariance matrix Σ_X of X, the eigenvectors $\mathbf{c_i}$ and eigenvalues λ_i were calculated. The first four components account for about 90% of the sum of the eigenvalues. These components, resp. the corresponding spatio-temporal evolution, define our lesion model. In order to verify that the resulting model can be used as a reference for a "typical" lesion development, the samples were projected to the resulting normalized Eigenspace. In Figure 2 the projections of the 23 samples to the first six principal components are shown.

3 Spatio-temporal Segmentation

Results of the time series analysis provide the starting point of our segmentation process [3]. To capture the spatio-temporal aspects of the evolution of voxels in multiple sequences, we extracted for each active voxel (detected by the time series analysis) the same local spatio-temporal evolution characteristics as for the model generation. Mean curvature flow was applied to each 3D image of the 4D data in all sequences. Snapshots of the diffused 3D images were taken at regular time intervals. By observing the intensities at an arbitrary fixed position during the diffusion process, we can extract the hypothetic radial spatial distribution of intensities at that point. Doing this for each time point and for all pulse sequences results in a description of the spatio-temporal evolution in multiple sequences of each active voxel. Heuristics was applied to extract the size of the hypothetical lesion based on the gradient along the radial intensity profile in

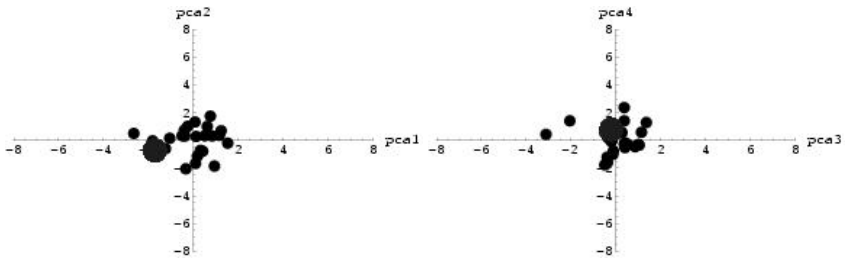


Fig. 3. The projection of the spatio-temporal evolution of a lesion voxel to the first four axes of the Eigenspace.

the FL sequence. The spatial extent was normalized according to the procedure applied during model generation.

As our lesion model was defined using a fixed number (6) of time points, we had to extract the appropriate temporal part of the considered evolution, in accordance with the time spread of the lesions in the database. Again, the maximal gradient in the FL sequence was used to define the time point of appearance. Voxels having their maximal gradient at the end of the observation period resp. their minimal gradient at the first time point (voxel "activated" before the first examination) were excluded from the analysis.

By characterizing voxels including their local neighborhood over time, an instrument is provided to reject voxels having a spatio-temporal development dissimilar to the one of MS lesions. We therefore compared the local spatio-temporal evolution of each active voxel with the spatio-temporal evolution of the generated model. The lesion samples are rather homogeneously distributed around the mean value (Figure 2). Therefore, the mean spatio-temporal evolution of all lesions in the database can be regarded as a characteristic model of a "typical" MS lesion. To measure the deviation of the evolution of an unknown candidate voxel from the generated model, the Mahalanobis distance was used.

In Figure 3 the spatio-temporal evolution of a lesion voxel (large filled circle) projected to the first four axes of the mentioned Eigenspace is shown. The lesions from the database are represented by the small circles to visualize the range of valid evolution. In Figure 4 the evolution of a voxel near the CSF (large circle) projected onto the Eigenspace is shown. This voxel has been wrongly identified as a part of an active lesion by the time series analysis. The extracted spatio-temporal behavior is quite different from the model, which is well visible on the projections.

As mentioned before, only voxels resulting from the time series analysis were considered for the spatio-temporal analysis, which were "active" in the valid observation period (month 2-8). In Figure 5 the Mahalanobis distances of all these voxel candidates on one slice are shown. Low distances are coded as bright intensities. It can be seen that it is easy to choose a threshold to discriminate between lesions and false positive voxels.

In Figure 6 the segmentation results of the time series analysis and of the new, spatio-temporal approach are shown. The color reveals the time point of appearance by taking the maximal gradient of each voxel's time course into ac-

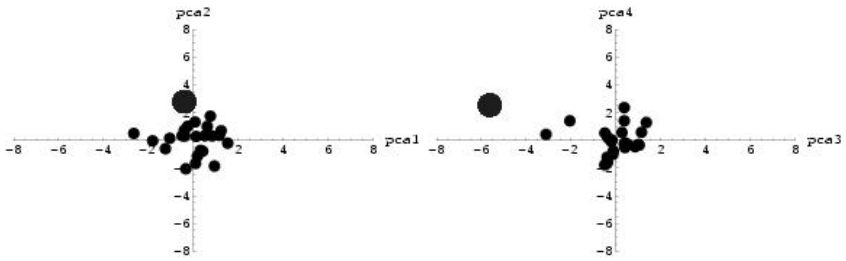


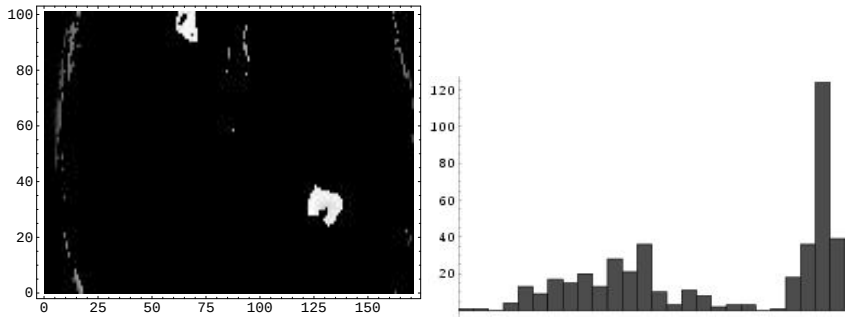
Fig. 4. The projection of the spatio-temporal evolution of a false positive CSF voxel onto the first four axes of the Eigenspace.

count. Most active voxels wrongly identified as lesions in the temporal approach were successfully eliminated by the spatio-temporal segmentation.

4 Conclusions

A new spatio-temporal approach has been introduced to segment and characterize active MS lesions. Deficiencies of a time series analysis with respect to registration errors are successfully rectified. The spatio-temporal model derived from a manually created lesion data base by PCA has been successfully used to characterize and segment active lesions from 4D data in multiple MR sequences. The statistics of the extracted lesion descriptors in our database seems to be reasonably described by a multivariate Gaussian distribution. This was essential for the applied simple characterization of a "typical" lesion evolution and the deviations from this mean. However, it has to be realized, that the number of collected active lesions is much too small to support a reliable statement about the "true" distribution. Eventually, the distribution of the applied descriptors of MS lesions is much more complex than what we have found, which may make the application of more sophisticated algorithms for the identification of the expected spatio-temporal pattern necessary. On the other side, it would be very interesting to find clearly separated distinctive lesion classes in the data.

More advanced methods like ICA could be applied to the data to compensate for the clear limitations of the selected simple PCA-based analysis and to pro-



a b

Fig. 5. Mahalanobis distances for all voxel candidates revealed by the time series analysis (a), and the corresponding histogram (b).

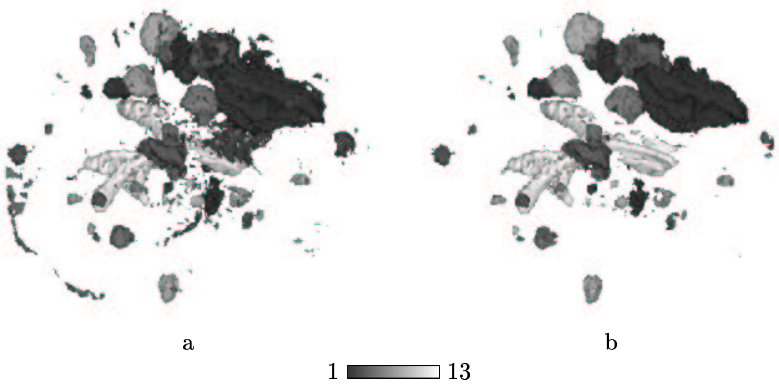


Fig. 6. Results of the purely temporal-based approach (a), and of the newly proposed spatio-temporal method (b).

vide better means for the analysis of clustered distributions. First experiments demonstrated slight improvements as compared to PCA-based analysis. The low number of active lesions in our database, however, did not allow us to reliably estimate the potential of the approach. Accordingly, a significantly larger database of active MS lesions is needed in order to eventually find a classification that can distinguish between different lesion behaviors.

References

1. Brechbühler, C.: Compensation of spatial inhomogeneity in mri based on a multivalued image model and a parametric bias estimate. Visualization in Biomedical Computing (1996) 141–146
2. Gerig, G., Székely, G., Israel, G., Berger,M.: Detection and characterization of unsharp blobs by curve evolution. In Information Processing in Medical Imaging - IPMI'95 (1995)
3. Gerig, G., Welti, D., Guttmann, C., Colchester, A., Székely, G.: Exploring the discrimination power of the time domain for segmentation and characterization of lesions in serial mr data. In Medical Image Computing and Computer-Assisted Intervention - MICCAI'98 (1998).
4. Maes, F., Collignon, A., Vandermeulen, D., Marchal, G., Suetens, P.: Multimodality image registration by maximization of mutual information. IEEE Transactions on Medical Imaging **16** (1997) 187–198
5. Olver, P.J., Guillermo, S., Tannenbaum, A.: Invariant geometric evolutions of surfaces and volumetric smoothing. SIAM J. APPL. MATH. **57(1)** (1997) 176–194
6. Rey, D., Subsol, G., Delingette, H., Ayache, N.: Automatic detection and segmentation of evolving processes in 3D medical images: application to multiple sclerosis. In Information Processing in Medical Imaging - IPMI'99 **1613** (1999) 154–167
7. Thirion, J.P., Calmon, G.: Deformation analysis to detect and quatify active lesions in 3d medical image sequences (Technical Report 3101). Institut National De Recherche En Informatique Et En Automatique (1997)
8. Warfield, S. et al.: Automatic identification of grey matter structures from mri to improve the segmentation of white matter lesions. J. Image Guided Surg. **1** (1996) 326–338