# Partial volume-aware assessment of multiple sclerosis lesions

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## ARTICLE INFO

## ABSTRACT

White-matter lesion count and volume estimation are key to the diagnosis and monitoring of multiple sclerosis (MS). Automated MS lesion segmentation methods that have been proposed in the past 20 years reach their limits when applied to patients in early disease stages characterized by low lesion load and small lesions. We propose an algorithm to automatically assess MS lesion load (number and volume) while taking into account the mixing of healthy and lesional tissue in the image voxels due to partial volume effects. The proposed method works on 3D MPRAGE and 3D FLAIR images as obtained from current routine MS clinical protocols. The method was evaluated and compared with manual segmentation on a cohort of 39 early-stage MS patients with low disability, and showed higher Dice similarity coefficients (median DSC = 0.55) and higher detection rate (median DR = 61%) than two widely used methods (median DSC = 0.50, median DR < 45%) for automated MS lesion segmentation. We argue that this is due to the higher performance in segmentation of small lesions, which are inherently prone to partial volume effects.

## 1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system, characterized by inflammation, demyelination, axonal loss, and gliosis (Noseworthy et al., 2000). Current MS diagnostic and follow-up criteria are exploiting magnetic resonance (MR) imaging metrics of lesion load, i.e. lesion count and location, as well as activity, i.e. gadolinium enhancement due to blood-brain barrier disruption (Rovira et al., 2015). The presence and spatial pattern of focal lesions in MR images ("dissemination in space") and the appearance of new lesions ("dissemination in time") are key components of current diagnosis criteria (Filippi et al., 2016; Polman et al., 2011). The identification of focal pathology and of new lesions as well as their size

changes in follow-up scans are important to perform an early diagnosis, quantifying ongoing disease activity and monitor treatment effects (Filippi et al., 2016). Consequently, one current research focus has been the development of automated MS lesion segmentation (Garcia-Lorenzo et al., 2013; Lladó, Ganiler, et al., 2012; Lladó, Oliver, et al., 2012).

Automated segmentation approaches are either unsupervised or supervised. Unsupervised approaches typically apply clustering algorithms that make use of both image intensity from one or several MR contrasts (T1-weighted, T2-weighted, proton-density-weighted, and/or 2D fluid-attenuated inversion recovery, FLAIR) and spatial information derived from probabilistic atlases of healthy tissues and/or topological constraints (Schmidt et al., 2012; Shiee et al., 2008; Souplet et al., 2008; Tomas-Fernandez and Warfield, 2015; Van Leemput et al., 2001).

Supervised approaches, on the other hand, rely on manually annotated image sets used for training (Anbeek et al., 2004; Brosch et al., 2016; Fartaria, Bonnier, et al., 2016; Morra et al., 2008; Sweeney et al., 2014).

We note that existing automated MS lesion segmentation methods were mostly evaluated on patients in advanced MS stages, who have a high disability, high numbers of lesions, and large lesion volumes (Datta and Narayana, 2013; Sajja et al., 2006; Steenwijk et al., 2013; Sweeney et al., 2013). They, however, showed substantially lower performance when applied to subjects with lower disease burden, i.e. lower lesion load and lesions of smaller size and volume (Anbeek et al., 2004; Cabezas et al., 2014; Fartaria, Bonnier, et al., 2016; Steenwijk et al., 2013; Sweeney et al., 2013). Automated MS lesion segmentation seems to be barely used in clinical practice, where detecting new lesions, particularly of small size, is of key importance for early diagnosis and follow-up of MS patients (Garcia-Lorenzo et al., 2013).

We showed in previous work that small lesions are strongly affected by partial volume (PV) effects, rendering their detection, segmentation and volume estimation challenging (Fartaria, O'Brien, et al., 2017). Taking into account PV could consequently improve the detection of small lesions and the overall lesion volume estimation. This idea was investigated in the mid-90s by (Johnston et al., 1994), who proposed a semi-automated method that takes partial volumes into account using neighborhood and histogram analysis. The same group later added pre- and post-processing steps of image enhancement and mathematical morphology to improve the discrimination between healthy WM and lesions (Johnston et al., 1996). Recently, (Khademi and Moody, 2015) performed image classification using mixed tissue labels as in (Cuadra et al., 2005; Shattuck et al., 2001) and estimated the PV fraction in mixed classes using spatial image gradient analysis. Variants of this approach using hierarchical mixture models are employed in (Galimzianova et al., 2016; Sudre et al., 2015).

Here, we propose a novel method for MS lesion segmentation that relies on a Bayesian PV estimation algorithm inspired by the "mixel" model originally proposed by (Choi et al., 1991), which leads to an ill-posed estimation problem for which (Roche and Forbes, 2014) proposed regularizing priors. We further included spatial constraints to estimate realistic concentration maps of healthy tissues (WM, GM, CSF), and pathological brain tissue. These concentration maps are used to directly compute lesion volumes rather than applying a correction of PV effects in initial hard tissue classification as in previous methods (Johnston et al., 1996; Khademi and Moody, 2015; Wu et al., 2006). Our approach does not rely on edge detection and therefore has the potential to assess PV effects in small lesions without clearly defined boundaries.

## 2. Method

### 2.1. Partial volume estimation

We consider a set of $n_c$ images of a given subject acquired from different MR image sequences and previously submitted to various pre-processing steps including alignment, bias field correction and skull stripping. Consistent with (Choi et al., 1991; Pham and Prince, 2000; Roche and Forbes, 2014; Van Leemput et al., 2003), we assume that the vector of image intensities $y_i$ at a voxel $i$ in the total intra-cranial mask relates to an unknown vector of tissue concentrations $q_i$, with $q_{i,\,t} \geq 0$ (the concentration of tissue $t$ at voxel $i$ is $\geq 0$) and $\sum_t^{n_t} q_{i,t} = 1$ (the sum of the $n_t$ tissue concentrations at a voxel $i$ is equal to one), through the statistical relation:

$$y_i = Mq_i + \varepsilon_i, \qquad \varepsilon_i \sim N(0, V) \tag{1}$$

where $M$ is an $n_c \times n_t$ matrix representing the mean tissue intensities for each channel ($n_t$ is the number of distinct tissues and $M_{ct}$ represents the mean intensity of tissue $t$ in channel $c$), and $N$ represents a multi-variable Normal distribution with zero mean and covariance matrix $V = diag\,(\sigma_1^2, \ldots, \sigma_{n_c}^2)$. We assumed that, in each MR sequence, image intensities are corrupted with independent stationary Gaussian white noise, as a first-order approximation to the non-central chi noise distribution that takes into account the coil combination in MRI (Larsson et al., 2003). In this work, we consider $n_t = 4$ tissues: CSF, GM, WM and lesions, as well as $n_c = 2$ contrasts: magnetization-prepared rapid gradient echo (MPRAGE) and 3D FLAIR.

It was recognized 25 years ago (Choi et al., 1991) that recovering the voxel-wise tissue concentrations $q_i$ from the above multichannel image model leads to an ill-posed inverse problem if $n_t > n_c + 1$, as it is the case in our application. Recently, (Roche and Forbes, 2014) proposed a prior concentration model to regularize the problem when formulated via Bayesian maximum a posteriori (MAP) estimation:

$$\pi(q_1, q_2, \ldots, q_{n_v}) \propto exp\left[ \frac{-1}{2} \sum_i q_i^T A q_i - \frac{\beta}{2} \sum_{i,j \in N_i} \|q_i - q_j\|^2 \right] \tag{2}$$

where $n_v$ is the total number of intra-cranial voxels, $A$ is a symmetric penalty matrix with zero diagonal and positive off-diagonal elements, $\beta$ is a positive constant, and $N_i$ is the neighborhood of voxel $i$ according to the 6-topology (the 6 adjacent voxels connectedness in 3-dimensions). Both the elements of $A$ and $\beta$ are hyperparameters to be tuned in a learning phase. While $\beta$ controls the amount of spatial smoothness of tissue concentration maps, the purpose of $A$ is to disentangle intensity fluctuations due to noise from PV effects. Each non-diagonal element acts as a penalty on the mixing of distinct tissues in a voxel, hence limiting spurious concentration variations when a single tissue is present. For instance, the larger $A_{12}$, the less likely voxels contain both CSF and GM.

We propose to generalize the prior model of (Roche and Forbes, 2014) by allowing voxel-dependent penalty matrices $A_i$ including non-zero diagonal elements in order to penalize tissues locally. This avoids confusing GM and lesions, which have similar intensity signatures in both MPRAGE and 3D FLAIR. Specifically, let $\pi^{GM}$ and $\pi^{WM}$ be a probabilistic atlas-based prior probability map for the GM and WM, respectively. We set the diagonal elements of $A_i$ corresponding to CSF, GM, WM and lesions, via:

$$A_i = \begin{pmatrix} 0 & a_1 & a_2 & a_3 \\ a_1 & a_4(1 - \pi_i^{GM}) & a_5 & a_6 \\ a_2 & a_5 & 0 & a_7 \\ a_3 & a_6 & a_7 & a_8(1 - \pi_i^{WM}) \end{pmatrix}$$

where the parameters $a_1$ to $a_8$ are pre-tuned with the smoothness parameter $\beta$, which are assumed voxel-independent in our particular implementation.

Following (Roche and Forbes, 2014), we estimate the tissue concentrations by MAP, yielding a quadratic programming problem:

$$\min_{q_1, \ldots, q_{n_v}} \sum_i \left[ (y_i - M^T q_i)^T V^{-1} (y_i - M^T q_i) + q_i^T A_i q_i \right.$$
$$\left. + \beta \sum_{j \in N_i} \|q_i - q_j\|^2 \right],$$

where each $q_i$ is searched in the multidimensional simplex. The solution is evaluated using an iterative scheme that loops over the intra-cranial voxels, and solves for the associated concentration vector $q_i$ with all other concentration vectors held fixed using an active set algorithm (Nocedal and Wright, 2006). This method proves very robust in practice, and typically converges in < 25 iterations.

### 2.2. Imaging parameters

The noise variance matrix $V$ is initially assumed to be zero, and is iteratively re-estimated by MAP concurrently with the tissue concentrations (see Section 2.1), yielding the update rule:

$$V = diag\left[ \frac{1}{n_v} \sum_i (y_i - M^T q_i)(y_i - M^T q_i)^T \right] \tag{3}$$