Robust intensity standardization in brain Magnetic Resonance images

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Magnetic Resonance images from different sites and scanners are used extensively in medical and clinical research. They bring interesting challenges for image analysis algorithms, as well as diagnosis and development of strategies of various disease treatment. However, many problems can affect the results in a large multi-site clinical study, especially because intensities in MRI do not have a fixed tissue-specific numeric meaning, even within the same MRI protocol, for the same body region, or for images of the same patient obtained on the same scanner in different moments. Madabhushi et al. give an interesting and extensive review, describing various methodologies to achieve intensity normalization and histogram adjustment. An important body of literature, dealing with standardization of MR intensities, based solely on the image characteristics in a post hoc manner, is referable to Nyl and Udupa. They proposed a two-step approach (L4 method) to standardize MR image intensity to a standard intensity scale. The first step (training step) involved finding the parameters of a standardizing transform from a set of images (landmarks). The second step (transformation step) applied a piecewise-linear transform, based on the learnt parameters, to new MRI studies, so as to achieve intensity mapping to a new, standard, greyscale. In this context, we propose a tiSsue-Based Standardization Technique (SBST) of MR brain images (currently tested on T1w scans), mainly inspired by the L4 method. The novelty consists in the use of both histogram and tissue-specific intensity information, which allows to minimize the risk of mixing brain tissues. The procedure was developed and tested on a consistent number (over 500) of MR brain images, belonging to healthy people and to patients with different degrees of neurodegenerative pathology, obtained from public databases and the clinical practice. All MRI volumes were pre-processed before standardization, by performing two steps: global non-linear registration in order to establish spatial correspondence between template tissues and input images, and tissue extraction, i.e. the segmentation of the non-linearly coregistered images of the brain into GM, WM, CSF. Two standard images were used as segmentation templates throughout this study, i.e. MNI152, which is the average of 152 normal T1w MRI scans that have been matched to the MNI305 using a 9-parameter affine transform, and COLIN27, a high resolution (1-mm3 isotropic), high signal-to-noise average of 27 T1-weighted images of a single human brain. For both images, Grey Matter (GM), White Matter (WM), Cerebrospinal fluid (CSF) tissue masks were available. Non-linear registration was performed by using open-source software, both the FMRIB of the Oxford University Software Library (FSL, available at http://fsl.fmrib.ox.ac.uk/fsl) and the Statistical Parametric Mapping (SPM, available at http://www.fil.ion.ucl.ac.uk/spm) tool. In particular, when using FSL, the brain volume is first registered to the standard space (MNI152 or COLIN27) through a priori tissue probability maps, then segmentation into the three tissue classes, based on a hidden Markov random field model and an associated Expectation-Maximization algorithm, takes place. When using SPM, images are non-linearly registered with respect to the template, involving the creation of a mean of all the images. Then they are segmented using a modified Gaussian Mixture Model, extended to include spatial maps of prior belonging probability. It uses Bayes rule to assign the probability for each voxel to belong to each tissue class, by combining the likelihood for belonging to the tissue class and the prior probability. Regardless of the particular software employed in non-linear registration and tissue extraction, an isometric 1 mm voxel-size image of each class (GM, WM, CSF) is obtained.

As to standardization, in the L4 procedure, grey level normalization is obtained by selecting some histogram landmarks for each image of a training-set, averaging the landmarks to obtain a list of reference mean landmarks, to be used as a standard scale. Each training-set image is then standardized, by projecting its landmarks onto the standard ones, while the grey levels between the landmarks are linearly interpolated. Thus a continuous, piecewise linear intensity mapping to a standard scale is achieved. When a new image is acquired, the transformation to the standard scale is used to standardize it. First Nyl and Udupa considered the landmarks as mode-based, i.e. the local maxima of the histogram, but in subsequent works they chose a set of population percentiles instead, in order to make standardization more robust and avoid incorrect scales. But, even when percentiles were used, the risk of tissue mixing

was high. We limited this drawback by separately applying the standardization procedure to the three main cerebral tissue classes, instead of the whole brain, and choosing deciles as the histogram landmarks, so that three standardizing transformations are calculated. As the three transformations do not exactly overlap in the two grey-value ranges shared by different brain matters (i.e. lightest CSF with darkest GM, and lightest GM with darkest WM), interpolation of the overall intensity transformation is performed, so that discontinuities are avoided in the transition regions. This was achieved by polynomial fitting.

This way, when far from discontinuities, the fitting function closely follows the transformation shape, just smoothing angles in the landmark neighborhoods. On the other hand, discontinuities are interpolated and removed. This way the shape of the transformation function is only mildly affected. The final transformation is applied to each member of the considered set of images, and eventually to other Non-Standardized (NS) MRI scans, giving as output the SBST-standardized images. Some histograms before and after standardization, obtained with either the L4 or SBST procedures, with the COLIN27 used as the segmentation template, are shown in Figure 1.

This figure shows (a) that the chosen image was apparently standardized with success by L4. But, once fat, bone, background are removed, and the image is segmented, we observe a different situation by examining boxes b to d. In particular, box (b) compares the template and the image histograms before any standardization: they look quite different in shape, and actually need intensity standardization. In (c) the three matters are shown after L4 standardization (this is the clean equivalent of box (a)): no correspondence exists, even if in (a) standardization looked satisfying. Finally, box (d) shows that SBST correctly and cleanly standardized each tissue, confirming that with SBST the probability of mixing pixels of different tissues during intensity standardization is low. In all of the papers dealing with the subject, standardization is applied to the original image as a whole. For example, in Leung et al. mean GM, WM, and CSF grey values for the images to be standardized were determined by k-means segmentation, and used by linear regression as landmarks for the calculation of the intensity transformation of any brain tissue. On the contrary, in the SBST three standardizing transformations are calculated and separately applied to the GM, WM and CSF images, with only minor corrections to avoid discontinuities in the grey value distributions. Moreover, SBST is convenient compared with other approaches proposing calibration techniques, because it does not require a reference material of known MRI property for calibration, or explicit manual sampling of different tissue regions. Finally SBST can be applied to any MRI protocol in neuroimages, and can be used to correct for intra-/ interpatient, intra-/interscanner, and intra-/intersite MR image intensity variations.

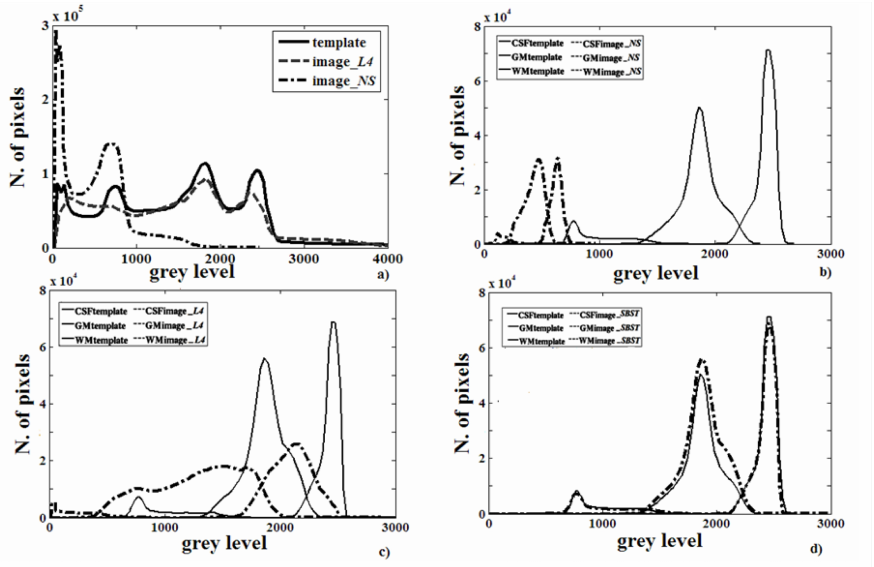

Figure 1. Examples of grey-level histograms in image standardizations (see text).