Nonlinear Normalization of Magnetization Transfer Ratio Images for Multi-Centre Clinical Trials

Robert Allan Brown[1], Sridar Narayanan[1], and Douglas Arnold[1]
[1]*Montreal Neurological Institute, McGill University, Montreal, QC, Canada*

Introduction

Magnetization transfer ratio (MTR) magnetic resonance (MR) imaging is a non-invasive technique that provides good specificity for myelin in the central nervous system[1]. MTR measurements correlate very well with Luxol fast blue[2], a standard stain for histological assessment of myelin. MTR can also be acquired quickly and is implemented on most recent scanners.

MTR is defined as the percent difference between a T1- or proton density (PD)-weighted scan and an image acquired with the same sequence plus an off-resonance magnetization transfer (MT) preparation pulse. However, although MTR is a quantitative measurement of the effect of the MT pulse, it is not a quantitative measure of myelin: different MTR sequences produce different values for the same tissue. For this reason, MTR measurements from different scanners, literature values, and measurements obtained in longitudinal studies where scanners have been upgraded, are often difficult to compare. This presents a challenge for the use of MTR in multi-site clinical trials and long longitudinal studies.

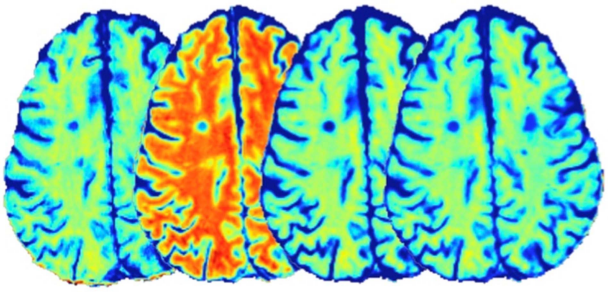

Figure 1: Normalized and unnormalized MTR maps. From left to right: site 1 (reference); site 2 no normalization; site 2 linear normalized; site 2 nonlinear normalized.

MTR measurements are commonly normalized to normal appearing white matter (NAWM) or gray matter (NAGM). This single-point normalization corrects intensity shifts but cannot correct differences in contrast. Additionally, many disease processes, such as multiple sclerosis (MS), have subtle effects on normal appearing tissues, potentially introducing bias. We have previously presented a linear normalization technique that uses white matter and gray matter from one or more normal controls to produce a calibration function[3]. Using two reference tissues, this technique corrects both intensity and contrast differences, maps data from any calibrated scanner onto a meaningful scale and, since the function is determined based only on data from normal controls, avoids bias.

However, MTR is a non-linear contrast and, even with linear normalization, MTR values away from the calibration points may be improperly normalized. In MS, T2 lesions have MTR values below both white matter and gray matter. In this study we propose a non-linear calibration technique and compare it to our previous linear method and no normalization.

Methods

Twenty-five subjects with MS received MTR and conventional anatomical scans at multiple timepoints, at one or both of two sites, a total of 352 scans. One subject was scanned at each site within five days, and this pair of scans was used as calibration data. For each scan, tissue probability maps were constructed for NAWM, NAGM and T2 lesions using a Bayesian classifier.[4] T2 lesion masks were produced by trained readers based on these probability masks. All scans were linearly co-registered to the T2-weighted scan from the first timepoint using minctracc[5] and common high probability NAWM and NAGM masks identifying tissue with > 85% probability at all timepoints were created for each subject.

Using the pair of calibration scans, a linear calibration function was calculated for each scanner using NAWM and NAGM as reference points. To compute a non-linear calibration curve, joint histograms were constructed with the linear normalized MTR calibration scans from each site for the NAWM, NAGM and T2 lesions. Data from these three tissues were weighted equally and fit with polynomials. To assess the performance of each normalization method, MTR values from each of NAWM, NAGM and T2 lesions, normalized with each method, were fit individually with random effects models having elapsed time since baseline as a fixed effect and subject and site as random effects. Inter-site to inter-subject variance ratios were calculated from the models for each combination of site and tissue. Small ratios indicate better normalization, and ratios less than 1 indicate that inter-site variation was reduced below inter-subject variation.

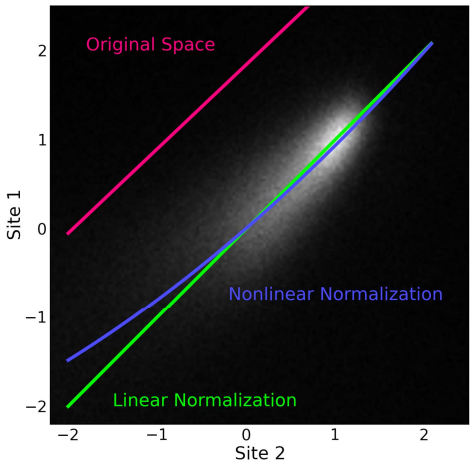

Figure 2: The joint histogram for MTR data from sites 1 and 2, shown in calibrated (WM=1, GM=0) space. The transform back to native MTR space is shown in red, the linear transform in green and the nonlinear transform in blue. The raw images differ in intensity (shift of the histogram) and contrast (rotation), which are well normalized by the linear method. The proposed method detects some nonlinear effects at low MTR values.

Results

Inspection of the images (Figure 1) and joint histograms (Figure 2) showed that linear normalization greatly improved the agreement between scans. A modest additional non-linear effect was observed in the second order polynomial. Higher order polynomials produced unrealistic fluctuations and were not used. The quantitative variance ratios (Table 1) showed dramatic reductions in inter-site variance using linear normalization, and slightly smaller reductions with nonlinear normalization, in all tissues. Both linear and non-linear normalization reduced inter-site variance below inter-subject variance.

Table 1: Inter-site to inter-subject variance ratios. Smaller numbers within a tissue type indicate better normalization.

Tissue Type	No Normalization	Linear Normalization	Nonlinear Normalization
WM	97.5	0.0952	0.403
GM	272	0.208	0.736
T2 lesions	4.36	0.0614	0.326

Conclusion

MTR data acquired on different scanners should be normalized before it is compared. Linear normalization is simple, fast and robust. Despite the non-linear nature of MTR contrast, differences between scanners are sufficiently linear in the range of most interesting tissues that non-linear normalization did not produce any additional benefit and in fact introduced some additional variance.

References

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