Implementation of fast macromolecular proton fraction mapping on 1.5 and 3 Tesla clinical MRI scanners: preliminary experience

V Yarnykh¹,² and A Korostyshevskaya³

¹ Department of Radiology, University of Washington, Seattle, WA, USA
² Research Institute of Biology and Biophysics, Tomsk State University, Tomsk, Russian Federation
³ Institute “International Tomography Center” of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russian Federation

E-mail: yarnykh@uw.edu

Abstract. Macromolecular proton fraction (MPF) is a biophysical parameter describing the amount of macromolecular protons involved into magnetization exchange with water protons in tissues. MPF represents a significant interest as a magnetic resonance imaging (MRI) biomarker of myelin for clinical applications. A recent fast MPF mapping method enabled clinical translation of MPF measurements due to time-efficient acquisition based on the single-point constrained fit algorithm. However, previous MPF mapping applications utilized only 3 Tesla MRI scanners and modified pulse sequences, which are not commonly available. This study aimed to test the feasibility of MPF mapping implementation on a 1.5 Tesla clinical scanner using standard manufacturer’s sequences and compare the performance of this method between 1.5 and 3 Tesla scanners. MPF mapping was implemented on 1.5 and 3 Tesla MRI units of one manufacturer with either optimized custom-written or standard product pulse sequences. Whole-brain three-dimensional MPF maps obtained from a single volunteer were compared between field strengths and implementation options. MPF maps demonstrated similar quality at both field strengths. MPF values in segmented brain tissues and specific anatomic regions appeared in close agreement. This experiment demonstrates the feasibility of fast MPF mapping using standard sequences on 1.5 T and 3 T clinical scanners.

1. Introduction

Macromolecular proton fraction (MPF) is a fundamental biophysical parameter defined within the two-pool model of magnetization transfer (MT) and describing the amount of macromolecular protons characterized by quasi-solid molecular dynamics and involved into magnetization exchange with mobile water protons in biological systems [1]. Over past decade, MPF measurements attracted a substantial practical interest due to the discovery of very close correlation between MPF and myelin content in neural tissues [2-6]. For quite a long time, experimental MPF measurements have been unavailable to clinicians, because existing methods (reviewed elsewhere [1]) required extremely time-consuming data acquisition due to the necessity of determining all two-pool model parameters or their subsets from the multi-parameter fit. A recently emerged fast MPF mapping method [7] overcame this...
difficulty by reducing the number of required images to three by utilizing an optimally constrained model [1], data normalization based on a synthetic (calculated) reference image [7], and an optimal sampling scheme corresponding to an appropriately chosen point in the tissue Z-spectrum [1]. Fast MPF mapping has been successfully tested in clinical studies [8, 9] where it demonstrated a promise as a biomarker of white matter (WM) and grey matter (GM) demyelination in multiple sclerosis [8] and post-concussion syndrome after mild traumatic brain injury [9]. Recently, this method has been histologically validated as a myelin biomarker in the murine cuprizone demyelination model [6] and proposed as a uniform myelin imaging approach for clinical and preclinical studies. The fundamental advantage of MPF is independence of magnetic field strength that enables its application across a range of human and animal imaging platforms [10]. However, the fast MPF mapping method has not been tested on 1.5 T MRI scanners to date, and all published studies utilized MRI equipment with field strengths of 3 T or higher. Implementation of the method for lower fields would considerably extend its clinical availability. Another obstacle to the widespread use of this promising technology is the need in customized pulse sequences to enable optimal saturation of macromolecular protons [1, 7, 8, 9]. Such sequences are difficult or even impossible to implement on each clinical MRI unit. At the same time, the basic acquisition sequence, spoiled gradient echo (GRE) with and without MT preparative module, is commonly available. However, the design of the MT saturation block in manufacturers’ product sequences may be substantially suboptimal relative to that needed for accurate MPF measurements according to the original publication [1]. In this preliminary study, we sought to test the feasibility of fast MPF mapping implementation on a 1.5 T clinical scanner using standard manufacturer’s sequences and compare the performance of this method between 1.5 T and 3 T scanners of the same manufacturer with both product and customized sequences.

2. Materials and Methods
Experimental data were obtained on the two MRI scanners of the same manufacturer (Philips Medical Systems, Netherlands) including 1.5 T Achieva and 3 T Ingenia units. A 16-channel neurovascular coil and a 32-channel head coil were used on 1.5 and 3 T scanners, respectively. The fast MPF mapping protocol was implemented on the 3 T scanner in two variants. The first option included a custom optimized MT-GRE pulse sequence with the following modifications: replacement of the manufacturer’s off-resonance pulse by a more time-efficient one, increased spoiler gradient areas to enable diffusion-based spoiling [11], phase increment for radiofrequency spoiling of 169° [11], standard duration of excitation RF pulse independent of the flip angle, and flexibility in setting MT saturation parameters. The optimized sequence was used for reference measurements and is termed below the “gold standard sequence.” The second option included the protocol design based on the unmodified manufacturer’s sequences. On the 1.5 T scanner, only the manufacturer’s product implementation was used. All protocols included the following sequences required to reconstruct an MPF map using the single-point synthetic reference method [7]:

1) T1-weighted spoiled GRE imaging: repetition time (TR) = 20 ms, echo time (TE) = 2.3 ms for the 3 T and 6.1 ms for the 1.5 T scanners, flip angle (FA) = 20° and 25° the 3 T and 6.1 ms for the 1.5 T scanners;

2) Proton-density (PD)-weighted spoiled GRE imaging: TR = 20 ms, TE = 2.3 ms for the 3 T and 6.1 ms for the 1.5 T scanners, FA = 3° and 4° the 3 T and 6.1 ms for the 1.5 T scanners;

3) MT-weighted spoiled gradient echo (GRE) imaging: TR = 28 ms for the gold standard sequence at 3 T, 50 ms for the product sequence at 3 T, and 32 ms for 1.5 T scanner, TE = 2.3 ms for the 3 T and 6.1 ms for the 1.5 T scanners, FA = 10° for all protocols.

Off-resonance saturation was achieved by the single-lobe sinc pulse in the gold standard sequence and the three-lobe sinc pulse in the product sequence, both with Gaussian apodization. The following saturation pulse parameters were used in the gold standard sequence: offset frequency 4 kHz, effective FA = 560°, and duration 12 ms. In the product sequence, offset frequency was 1.1 kHz, effective FA was 520° and 1040° for 3 T and 1.5 T, respectively, and duration was 16.5 ms and 15 ms for 3 T and 1.5 T, respectively.
Additionally, for reference measurements, correction of $B_0$ and $B_1$ field inhomogeneities was carried out using field maps. For $B_0$ mapping, the dual-TE GRE phase-difference method [12] was used with $TR/TE_1/TE_2 = 20/2.3/3.3$ ms and $FA = 10^\circ$. For $B_1$ mapping, the actual flip-angle imaging (AFI) method [13] was used with $TR_1/TR_2/TE = 40/160/2.3$ ms and $FA = 60^\circ$.

All images were obtained in 3D mode with single signal acquisition, field-of-view (FOV) = 24x20x24 cm and matrix size 192x134x60 (actual voxel size 1.25x1.5x4 mm) zero-interpolated to 240x240x120. The total scan time was 9 min for the gold standard sequence with additional 6 min for field mapping, 12 min for the product sequence at 3 T, and 10 min for 1.5 T.

Data were acquired from one healthy volunteer. The study was approved by the Ethical Committees at the Tomsk State University and at the International Tomography Center of the Siberian Branch of the Russian Academy of Sciences. Written informed consent was obtained from the participant.

MPF maps were reconstructed according to the single-point synthetic reference image method [7] using custom-written C-language software. MPF maps were registered to the map obtained with the gold standard sequence (rigid registration with six degrees of freedom) and skull stripped using MIPAV software (Center for Information Technology, National Institutes of Health, USA). All MPF maps were then segmented into four tissue classes (white matter (WM), gray matter (GM), mixed WM-GM, and GM mixed with cerebrospinal fluid) using FSL software (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, England) as detailed earlier [8]. MPF values were calculated within tissue masks and regions of interest (ROIs) in selected anatomic structures.

### 3. Results
Table 1 summarizes MPF measurements in segmented brain tissues and anatomic structures obtained using the gold standard sequence and product sequences on 3 T and 1.5 T Philips MRI scanners. Figure 1 illustrates MPF maps obtained in the three described above experiments. Overall, there is very good agreement between MPF values obtained at both field strengths. MPF values measured with the product sequence are also similar to those obtained with the gold standard sequence, though they look slightly lower for certain WM structures. Visually, the MPF maps reconstructed from all datasets appear very similar without any signs of image quality degradation at lower field strength (figure 1).

| Tissue, structure          | 3 T, gold standard sequence | 3 T, product sequence | 1.5 T, product sequence |
|---------------------------|----------------------------|-----------------------|------------------------|
| WM                        | 11.7                       | 11.3                  | 11.2                   |
| GM                        | 5.3                        | 5.2                   | 5.3                    |
| Mixed WM-GM               | 8.0                        | 7.9                   | 8.1                    |
| Frontal WM                | 12.2±0.4                   | 12.2±0.3              | 11.3±0.4               |
| Occipital WM              | 12.7±0.4                   | 12.2±0.7              | 12.0±0.7               |
| Corpus callosum, splenium | 13.6±0.4                   | 11.9±0.3              | 12.6±0.5               |
| Corpus callosum, genu     | 14.7±0.5                   | 13.5±0.7              | 13.2±0.8               |
| Pons                      | 11.3±0.4                   | 10.3±0.4              | 10.5±0.5               |
| Caudate nucleus           | 5.8±0.4                    | 5.9±0.3               | 6.1±0.6                |
| Putamen                   | 6.2±0.3                    | 6.5±0.2               | 6.7±0.2                |
| Insular cortex            | 5.3±0.6                    | 5.4±0.8               | 6.0±0.9                |

### 4. Discussion
The product implementation of the MT-weighted gradient echo sequence substantially differs from the optimally designed technique [1, 7]. The off-resonance saturation pulse is applied quite close to resonance (1.1 vs. 4 kHz) thus making possible unaccounted saturation of free water protons. The value of the effective flip angle of the saturation pulse is about two-fold greater than that in the optimal setting. Nevertheless, the MPF values obtained with the gold standard and product sequences are essentially similar. Furthermore, the noted aspects of the MT module implementation theoretically might result in overestimation of MPF, whereas the values obtained with the product sequence seem to slightly lower than reference values. The presented example confirms the fact that the single-point MPF mapping method is robust with respect to variations in sequence parameters, because the reconstruction algorithm [1, 7] takes into account actual values of most important parameters including the offset frequency, power, duration, and shape integrals of the saturation pulse, TR, and excitation flip angle.

![Figure 1. Brain MPF maps of one volunteer obtained using the gold standard sequence on a 3 T scanner and manufacturer’s product sequence on 3 T and 1.5 T scanners. All maps are presented with the same grayscale window corresponding to the MPF range 0-20%.](image)

At the same time, there still is a possibility of MPF measurement errors due to hidden from the user sequence implementation details, which are not accounted for in the MPF map reconstruction algorithm. Examples of such factors include variations in the actual excitation bandwidth of the saturation RF pulse, different implementations of RF spoiling, imperfectness of excitation pulses, variable noise level, and some automatic algorithms intended to optimize advanced clinical sequences, such as automatic adjustment of pulse durations dependent on power calibration. Accordingly, instrumental errors may occur in the case of MPF mapping implementation based on the standard manufacturer’s sequences without user’s control over all relevant parameters. While it is impossible to identify any bias from the single-subject measurements, we speculate that some systematic differences in MPF between the gold standard and product sequences may arise from the suboptimal implementation of radiofrequency spoiling, which is based on the 150° phase increment in the manufacturer’s sequence. As it was demonstrated in the earlier publication [11], this spoiling regime causes effective overestimation of T1 by the variable flip angle method. The error in T1 may propagate into MPF and result in underestimation of MPF measurements according to the theory detailed elsewhere [14]. Our preliminary experience summarized in this report suggests that such errors are small if not negligible.

5. Conclusion
The described proof-of concept experiment demonstrates the feasibility of fast MPF mapping implementation based on product sequences on 1.5 T and 3 T clinical scanners and high consistency of MPF measurements between field strengths and pulse sequence implementations.

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