Reconstruction of Bound Pool Fraction Maps from Subsets of Cross-Relaxation Imaging Data at 3.0 T: Accuracy, Time-Efficiency and Error Analysis

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Introduction: Cross-relaxation imaging (CRI) describes the kinetics between mobile water protons (free pool) and macromolecular protons (bound pool)[1]. CRI has demonstrated a strong correspondence between the bound pool fraction, *f*, and major fiber tracts in the human brain in vivo[2], which make it advantageous for imaging white matter (WM) disease (e.g. multiple sclerosis [MS][3]). Broad clinical utility of CRI has been largely limited by acquisition time. At 1.5T, a time-efficient three-dimensional (3D) whole-brain CRI technique has been enabled by using the pulsed off-resonance saturation method with a limited number (four) of offset frequencies[2]. The key feature of this technique is the determination of the principle kinetic parameters of the two-pool model[1] (*f*; and the rate constant, *k*) by constraining the transverse relaxation time of both the free (T_2^F) and bound (T_2^B) pools to reduce the number of fitted parameters and limit the number of off-resonance measurements. Recently, further reduction in scan time at 1.5T has been proposed by Yarnykh via an algebraic approach that captures both *f* and *k* with only two experimental off-resonance measurements[4]. Alternatively, Lee et al[5] have described a time-efficient approach at 1.5T that reduces acquisition time by applying an additional constraint to *k* in order to solely determine *f*. Whole-brain CRI has been recently demonstrated at 3.0T[6]. Implementation at 3.0T required optimization of parameter constraints at the increased field-strength to accurately determine *k* and *f*, and correction of both B_0 and B_1 non-uniformities[6]. In this study, we sought to identify the effects of time-efficient protocols and reconstruction methodology on the determination of *f* at 3.0 T. In addition, a pathological MS lesion is simulated to determine the error introduced via the application of various parameter constraints during the optimal time-efficient protocol at 3.0T.

Methods: A healthy male volunteer (age 35years) was imaged at 3.0 T (Philips Achieva, Best, Netherlands) with a transmit/receive head coil. Twelve pulsed *Z*-spectroscopic data points with variable offset frequencies (Δ) of the off-resonance saturation pulse (Δ = 1, 2, 4, and 8 kHz; duration 19 ms) and effective flip angles of 700°, 850°, and 990° were acquired with a 3D spoiled gradient echo pulse sequence (TR/TE = 43/2.3 ms, α = 10°) as previously described[2, 6]. A reference image for data normalization was obtained with Δ = 96 kHz (no MT effect is observed at this frequency) for each effective flip angle to ensure that the transmitter operates with identical gain settings. A complementary R_1 map necessary for parameter fitting was obtained using the variable flip angle (VFA) method with a 3D spoiled gradient echo sequence (TR/TE = 20/2.3 ms, α = 3, 10, 20, and 40°). All *Z*-spectroscopic and VFA images were acquired with FOV = 240×180×180 mm, matrix = 160×120×60, resolution 1.5×1.5×3.0 mm (zero-interpolated to 1.0×1.0×1.5 mm), and one signal average. Scan time was 3.33 and 1.55 minutes per point for *Z*-spectroscopy and VFA, respectively. To account for effects of B_0 and B_1 heterogeneity, whole-brain B_0 and B_1 maps were acquired using previously described techniques[7, 8] to establish actual off-resonance of the saturation pulse and determine actual flip angles during parameter fitting. Scan time for B_0 and B_1 maps was 2 and 3 minutes, respectively.

The reference standard for *f* was obtained from 4-parameter fitting (*k*, *f*, T_2^F, and T_2^B) using 12-pt data and a previously described non-linear least squares fitting (NLSF) method[2, 6]. The other reconstruction methodologies included: 1) 2-parameter fitting with 4-pt (990°; Δ = 1, 2, 4, and 8 kHz) data; 2) 1-parameter fitting with 4-pt (990°; Δ = 1, 2, 4, and 8 kHz) data; and 3) 1-parameter fitting with 2-pt (990°; Δ = 4 and 8 kHz) data. For each of these approaches, the NLSF method was used along with recognized parameter constraints (T_2^F=0.024/R_1 and T_2^B=11μs) to determine *f* at 3.0 T. For 1-parameter fitting, the additional constraint of $k = 26 \times (1\text{-}f)^{-1}f$, a ratio derived from previous in vivo data at 3.0T[6], was exploited. Additionally, 1-parameter fitting of *f* was determined separately and independent of *k* using the algebraic approach described by Yarnykh[4], where T_2^F and T_2^B are similarly constrained as in the NLSF method.

Pearson's correlation coefficient, *r*, was used to compare results from a variety of anatomic structures between the reference standard for *f* and the different reconstruction methodologies. Simulation of WM, grey matter (GM), and an MS lesion was done with a previously established model of CRI[6].

Results: Parametric *f* -maps using each methodology are presented in Figure 1. All reconstruction methodologies had a strong concordance with the reference *f*-map, however, the 2-pt, 1-parameter algebraic technique demonstrated increased noise and weaker differentiation of grey and white matter (for example, the external capsule is ambiguous). The reference value of *f* from ROIs taken from within GM and WM structures was most strongly associated with the 2-pt, 1-parameter NLSF method (r = 0.95, p<0.001) and 4-pt, 1-parameter NLSF method (r = 0.95, p<0.001), followed by the 2-pt, 1-parameter algebraic method (r = 0.90, p<0.001) and 4-pt, 2-parameter NLSF method (r = 0.87, p<0.001). Notably, estimation of *f* by the 2-pt, 1parameter NLSF method tended to underestimate *f* in WM, while the 2-pt, 1-parameter algebraic method over-estimated *f* in WM. Errors consequent of parameter constraints in WM, GM and an MS lesion were systematic (Figure 3).

Discussion: The 2-pt, 1 parameter NLSF method demonstrated the strongest agreement (Fig. 2C) with the reference standard and used the shortest scan time. Although the 2-pt, 1-parameter algebraic method was computationally more efficient, scan time was the same and the results were sub-optimal at 3.0T (Figs.1D and 2D). The relatively weaker performance by the 4-pt, 2 parameter NLSF (Fig. 2A) method may have resulted from insufficient data points to accurately determine 2 parameters. Error consequent of parameter constraints during the 2-pt, 1-parameter NLSF method were minor for T_2^F and T_2^B. Notably, error was substantially less than previously reported for the same simulation using the 4-pt, 2-parameter method at 3.0T[6]. Error attributable to *k* was the principal source of error. However, across biological ranges, error was <|20%|, which was consistent with our in vivo observation that the 2-pt, 1-parameter NLSF method underestimated *f*.

Conclusion: Time-efficient, whole-brain parametric *f*-maps at 3.0T may be acquired with reduced experimental measurements using an NLSF approach. The substantially shortened scan time (total scan time: 21 min) while affording a reasonable estimation of *f* may improve the translatability of CRI to clinical medicine.

References: 1. Henkelman *MRM* 1993;29:759-66 **2.** Yarnykh *Neuroimage* 2004;23:409-24. **3.** Davies *Multiple Sclerosis* 2004;10:607-13. **4.** Yarnykh *Proc ISMRM* 2007:1765. **5.** Lee *JMRI* 1997;7:913-7. **6.** Underhill *Neuroimage* 2009;47:1568-78. **7.** Skinner *MRM* 1997;37:628-30. **8.** Yarnykh *MRM* 2007;57:192-200.

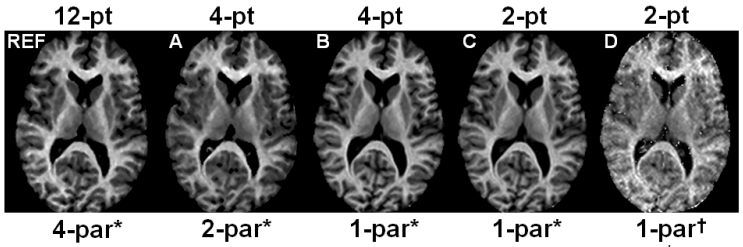

Figure 1. Parametric *f*-maps using each reconstruction methodology (*NLSF, †algebraic method). Notably, the 2-pt, 1-par* method (C) had the strongest agreement with the reference image, while using the shortest scan time.

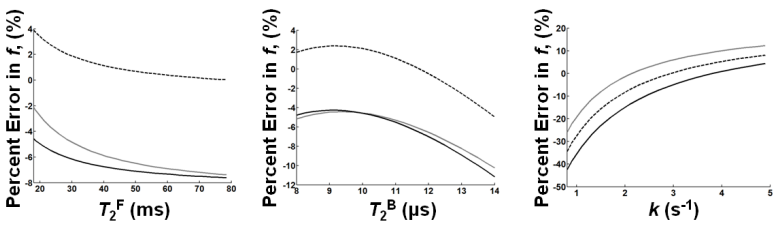

Figure 3. Relative errors for the 2-pt, 1-par NLSF method of determining *f* across serial values of T_2^F, T_2^B, and *k* for GM (gray line), WM (black line) and an MS lesion (dashed).

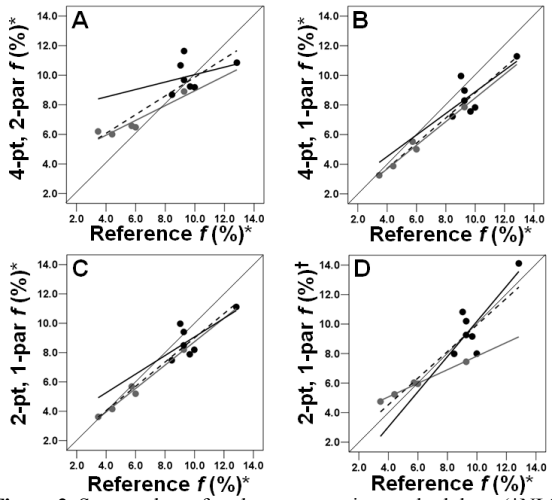

Figure 2. Scatter plots of each reconstruction methodology (*NLSF, †algebraic method) compared to the reference method (12-pt, 4-par*). Grey dots = GM, black dots = WM. Colored regression lines correspond to colored dots. The dashed line is for both GM and WM.