# Intrinsic Field Homogeneity Correction in Fast Spin Echo based Amide Proton Transfer MRI

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**Introduction** - Amide proton transfer (APT) is a novel technique for MR-based molecular imaging of endogenous cytosolic proteins or peptides [1] and reflects protein concentrations as well as local pH via the exchange rate. Promising clinical applications of APT-MRI are envisioned in oncology (enhanced protein concentrations in tumors [2]) and in neurology (ischemic acidosis in stroke [1]). Detection of amide protons is based on a magnetization transfer (MT) asymmetry analysis with symmetric RF saturation frequency offsets around the water resonance, which is strongly biased in the presence of local magnetic field inhomogeneity $\delta B_0$ and needs precise correction methods. Separate $B_0$ mapping, as typically used for this purpose, is prone to inaccuracy, since the actual $\delta B_0$ distribution and $f_0$ (reference value to the water resonance) must not change before/during the actual APT acquisition. $B_0$ mapping integrated within the APT acquisition would be preferable for the precision of $B_0$ correction, for scan time efficiency and for the clinical workflow. Previously, it was proposed to use multi-gradient echo APT acquisitions with intrinsic Dixon-type [3] $B_0$ mapping and correction [4]. On the other hand, fast spin-echo (FSE) and driven equilibrium sequences [5] were shown to provide a superior contrast-to-noise ratio for APT [6]. Thus, intrinsic Dixon-type APT should be translated to FSE sequences. We propose to acquire APT-MRI using an FSE-Dixon-based APT technique and to efficiently derive $\delta B_0$ by an iterative Dixon reconstruction [7] across different saturation frequency offset images. Feasibility of FSE-Dixon-APT MRI in the human head is demonstrated using a clinical 3T scanner.

**Methods** - The study was performed on a 3.0T clinical whole-body scanner (Achieva, Philips Healthcare, NL) using a transmit/receive head coil. Acquisition software was modified to shift the timing of the acquisition window (echo-shift $\Delta$TE) and the readout gradient during the scan series, which is different but equivalent to time-shifting of the refocusing pulse as in [3]. The low-power mode of the RF amplifier was used to enable long saturation pulses [4]. A 2D single-shot FSE sequence with driven-equilibrium refocusing control [6] was used: matrix $128^2$, resolution $1.8\times1.8\times5.0$ mm$^3$, TR=4090 ms, TE=4.8 ms, 3 echo-shift variants with water/fat in phase (IP) or out of phase (OP): $\Delta$TE= -1.15/ 0/ +1.15ms (OP-/IP/OP+ at 3T), pixel bandwidth 1550 Hz, 6 saturation frequency offsets in steps of 0.4ppm around $\Delta\omega=\pm3.5$ppm and one off-resonant ($S_0$, $\Delta\omega$=-160 ppm), saturation pulse-train $T_{sat}$=2 s ($40\times50$ ms, Sinc-Gaussian shapes), $B_{1,rms}$=2.0 $\mu$T, 1½ minutes total scanning time. From the full dataset ($3\times7$ images), a $\delta B_0$ map could be calculated for each saturation frequency offset by iterative Dixon reconstruction [7]. Alternatively, a "mixed" $\delta B_0$ map was calculated by selecting only one echo-shift variant per positive saturation frequency offset (3.1ppm: $\Delta$TE =+1.15ms, 3.5ppm: 0ms, 3.9ppm: -1.15ms), to demonstrate the possibility of a time efficient acquisition. Maps of the asymmetric MT ratio $MTR_{asym}=(S[-\Delta\omega]-S[+\Delta\omega])/S_0$ were calculated based on $\delta B_0$ corrected, point-by-point interpolated water-only images $S[-\Delta\omega]$ and $S[+\Delta\omega]$. *In vivo* feasibility was tested in a human volunteer, from whom informed consent was obtained.

**Results and Discussion** - From the full dataset, water and fat separation could be performed successfully for all 7 saturation frequency offsets, and the $\delta B_0$ maps obtained were consistent within a standard deviation of 0.015 ppm. An example $\delta B_0$ map is shown in Fig.1a, water/fat images in Fig.1d/e. The "mixed" $\delta B_0$ map (Fig.1b), obtained from 3 images with different positive saturation offset and varied echo-shift, is very similar. A difference evaluation (Fig.1c) shows an almost spatially constant offset of about 2 Hz, which is negligible for a precise APT field correction. The signal amplitude $S[\omega]$ varies only by a few percent for $\omega=+3.5\pm0.4$ ppm in brain tissue and typical tumor cases [2]. Furthermore, the $\delta B_0$ reconstruction is robust to variations of the signal amplitude using the "OP-/IP/OP+" echo scheme. Hence, the quality of the iterative Dixon-type $\delta B_0$ mapping is not compromised by the moderate amplitude variations across positive saturation offsets. Nevertheless, for APT-MRI, negative saturation frequency offsets should be avoided for "mixed" $\delta B_0$ estimation, because the saturation pulse may cause strong signal variations by partly cancelling the fat signal at -3.4 ppm. MT asymmetry analysis on the water-only images shows a strong offset without $\delta B_0$ correction (Fig.1g), while the corrected $MTR_{asym}$ is low and homogeneous over the volunteer brain (Fig.1f), for any of the obtained $\delta B_0$ maps. While 21 images were acquired in this study to analyze the precision, the technique can be implemented with efficient data sampling using only 7 different images (e.g.: $+3.1\text{ppm}_{OP-}$; $+3.5_{IP}$; $+3.9_{OP+}$; -3.1; -3.5; -3.9 and $S_0$). With the $\delta B_0$ information available, water/fat separation may still be obtained for all images e.g. by a single-point Dixon approach [8]. For a stable water/fat separation, the negative frequency offsets and $S_0$ should be acquired in quadrature (90° phase difference between water and fat) in this case.

**Conclusion** - A precise APT measurement in the human brain is demonstrated on a clinical MRI scanner using FSE-Dixon-APT MRI with intrinsic $\delta B_0$ correction. $\delta B_0$ could be precisely obtained from 3 images with different positive frequency offsets and varied echo-shift. This technique may enhance precision in a simplified clinical workflow without extra $B_0$ calibration scans, while maintaining the scan time efficiency of the APT examination.

**References**

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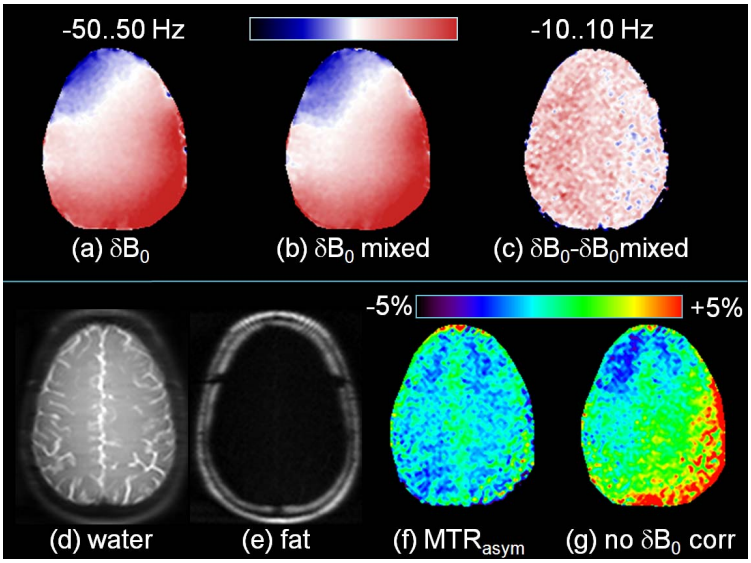


**Figure 1**: APT measurement obtained in a healthy volunteer using FSE-Dixon based water/fat separation and intrinsic $B_0$ homogeneity correction. Equivalent $\delta B_0$ maps are obtained from different echo-shifts for a single saturation offset (a) or from "mixed" positive saturation frequency offsets (b) – the difference is uniformly low (c). At each offset, water (d) and fat (e) images are obtained and $MTR_{asym}$ ("APT image") (f) is interpolated from the water images. Uncorrected MTR images show a strong $B_0$ homogeneity bias (g).