Amide proton transfer imaging with continuous wave dual frequency saturation can detect the amide proton peak in the z-spectrum acquired at 3T

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Introduction: Amide proton transfer (APT) imaging[1] offers a new method for tissue characterization based on protein concentration and pH. Although APT-images show differences in stroke[2], brain tumors[3] and normal tissue, quantifying the amide proton signal in lesions and healthy tissue remains difficult. Because direct water saturation and magnetization transfer (MT) from membranes and macromolecules have a much greater effect on the water signal than saturation transfer from amide protons, in-vivo z-spectra acquired at 3T typically show no features from the amide protons. Even after asymmetry analysis, the intrinsic MT asymmetry competes against the APT signal, leading to APT-weighted maps with negative or near zero values. Recently, we proposed a pulsed saturation with frequency alternating RF irradiation[4] (SAFARI) designed to be insensitive to direct water saturation and MT. In this abstract, we propose a continuous wave (CW) version of SAFARI and demonstrate its ability to measure the amide proton peak in the z-spectrum a 3T.

Theory: The key to the SAFARI technique is the acquisition of an image with RF irradiation applied simultaneously at both the amide proton (ω_s = +3.5ppm) and control ($-\omega_s$) frequencies. On-resonance irradiation of the amide protons will fully saturate the line at relatively low power, while the macromolecular and water lines require larger powers to reach saturation. As a result, there is a range of RF powers for which the amide proton saturation is independent of power, while direct water saturation and MT vary linearly with power. If the standard APT images are acquired with double the power compared to the dual frequency image, the MT and direct water saturation effects at each frequency double, while the APT effect does not change. Subtracting two-times the dual frequency image from the sum of label frequency and control frequency images will yield the APT signal, while both MT and direct water saturation cancel out exactly, even in the presence of B_0 inhomogeneity and MT asymmetry.

Methods: All images were acquired on 3T GE SIGNA EXCITE scanner. The APT imaging sequence consisted of a 250ms CW-RF irradiation followed by a single shot spin-echo EPI acquisition [TR=2s, TE=20.2ms, FOV=24cm, matrix=96x96, slice thickness=8mm]. Dual frequency preparation was achieved by CW saturation on resonance with amplitude modulation: $\mathbf{B_1}(t)=\sqrt{2}B_1\sin(\omega_s t)$. This generates a frequency response with components at $+\omega_s$ and $-\omega_s$. Forty-eight time-interleaved images (12 label, 12 control and 24 dual frequency images) were acquired for each SAFARI scan in 1.5min. To evaluate the robustness of the pulse sequence against B_0 inhomogeneities as a function of power, APT imaging was performed in a control phantom (no CEST, no MT, T_1=600ms T_2=65ms) with B_1=1, 2, 3, 4, 5μT at the frequency pairs $\omega_s+2\pi f$ and $-\omega_s+2\pi f$, where the frequency shift f was varied from -450Hz to 450Hz in steps of 30Hz. Three healthy volunteers were imaged after giving written informed consent. A z-spectrum was acquired at B_1=1μT for frequency pairs from ±200 to ±1500Hz. In addition, single frequency images were acquired between -200 and 200Hz to map the center of the water line for B_0 correction. The APT effect was evaluated by conventional MT ratio asymmetry analysis after B_0 correction: $MTR_{asym}=[S_{sat}(-3.5ppm)-S_{sat}(+3.5ppm)]/S_0$ and by SAFARI with no additional B_0 correction: $MTR_{SAFARI}=[S_{sat}(+3.5ppm)+S_{sat}(-3.5ppm)-2\,S_{sat}(\pm3.5ppm)]/\,S_0$.

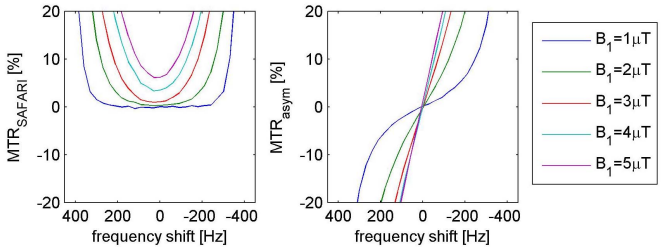

Figure 1: A) MTR_{SAFARI} and B) MTR_{asym} with B_0 correction as a function of frequency shifts simulating B_0 inhomogeneity in the control phantom.

Results and Discussion: Phantom results are shown in Figure 1. As expected in the absence of amide proton exchange, MTR_{SAFARI} (f=0Hz) is zero (<0.5%) at low powers of 2μT and below. In addition, MTR_{SAFARI} remains constant in the presence of frequency shifts up to ±240Hz at 1μT and ±60Hz at 2μT. In other words, direct water saturation is removed as long as the off-resonance irradiation frequency is at least 210Hz from the water line. Assuming the MT line is centered at -1.5ppm[5], it is 255Hz from the control frequency of -3.5ppm and should also be successfully removed by the SAFARI strategy. At powers higher than 2μT, direct water saturation is no longer linear and MTR_{SAFARI} increases. Based on these results, in-vivo experiments shown in Figure 2 were conducted with a power of 1μT. The in-vivo MTR_{asym} map (Fig 2A) is negative due to intrinsic MT asymmetry overpowering the APT effect. Consequently, no amide proton peak is detected in the z-spectrum (Fig 2C) or the MTR_{asym} spectrum (Fig 2D) of a white matter ROI, consistent with previous studies at 3T. The MTR_{SAFARI} map (Fig 2B), in contrast, is positive indicating that intrinsic MT asymmetry has been removed. As a result, the MTR_{SAFARI} spectrum in the white matter ROI exhibits a significant amide proton peak centered at 3.5ppm.

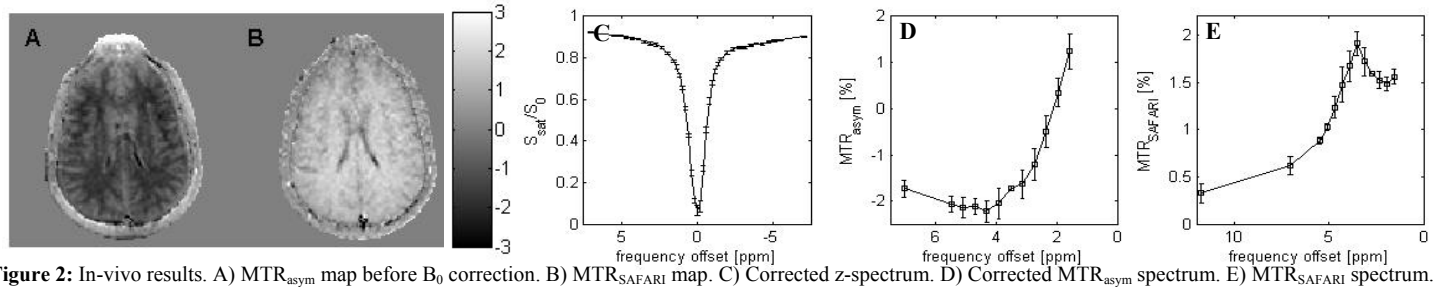

Figure 2: In-vivo results. A) MTR_{asym} map before B_0 correction. B) MTR_{SAFARI} map. C) Corrected z-spectrum. D) Corrected MTR_{asym} spectrum. E) MTR_{SAFARI} spectrum.

Conclusions: This abstracts describes a CW dual frequency saturation scheme for the acquisition of amide proton transfer images. Compared to the pulsed-SAFARI technique described previously[4], the CW sequence has the advantage that the signal depends only on the saturation time and RF power, as opposed to the pulse width, interpulse delay, flip angle, and saturation time of the pulsed sequence[6]. This simplifies sequence optimization, modeling and interpretation of results and facilitates comparison with other results obtained using CW methods. While hardware restrictions limited the irradiation to 250 ms, the short saturation duration minimizes T1 effects that can complicate quantification. Our in-vivo APT results demonstrate that the CW-SAFARI scheme can successfully correct for B_0 inhomogeneity and MT asymmetry, allowing for clear identification of the amide proton peak in-vivo at 3T. Therefore, this technique may enable the quantification of protein concentration, amide exchange rates and pH in the human brain with important applications in stroke and tumor imaging.

References: [1]Zhou et al., Nat Med, 9:2003. [2]Jokivarsi et al. MRM 57:2007. [3]Zhou et al., MRM, 50:2003. [4]Scheidegger et al. ISMRM 5142:2010. [5]Pekar et al. MRM 1996. [6]Scheidegger et al. ISMRM 2987:2010