Optimization of RF saturation to minimize $B_0$ inhomogeneity effects in pulsed amide proton transfer imaging

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Introduction

Chemical exchange saturation transfer (CEST) of the amide protons present on the backbone of proteins and peptides – dubbed amide proton transfer imaging - has shown promise as an indicator of tissue pH and as a marker for brain tumors. In order to maximize the CEST contrast, RF irradiation power must be optimized to maximize saturation of amide protons resonating at 3.5ppm, while minimizing direct water saturation. Because the applied RF frequency is very close to the free water frequency, strong direct saturation effects are unavoidable and vary quickly with the center frequency of the water line. Thus, APT imaging is strongly dependent on $B_0$ homogeneity and is prone to severe susceptibility artifacts. The goal of this abstract was to optimize the RF irradiation scheme in order to minimize the APT dependence on $B_0$. By using pulsed-RF saturation, the pulse profile, pulse width and interpulse delay can be varied to modulate the frequency selectivity of the irradiation. This allows maximizing the CEST contrast while decreasing RF spillover. In addition, we introduce a new magnetization transfer ratio (MTR) parameter based on a three-way subtraction and show it further decreases the dependence of APT on $B_0$ homogeneity compared to traditional MTR asymmetry analysis.

Methods

The APT contrast was modeled using the Bloch equations for a two-pool exchange model. Numerical simulations were performed in Matlab, with amide proton content $M_{am}=1:1000 M_{aw}$, longitudinal relaxation times $T_{1a}=1.5s$, $T_{2a}=0.77s$, transverse relaxation times $T_{2w}=60ms$, $T_{2w}=33ms$ and chemical exchange rate from amide group to free water $k_{ex}=30Hz$. The RF pulse train consisted of 800 inversion pulses with either Gaussian, Hanning or Blackman profile. Pulse width (pw) was varied from 3ms to 30ms and interpulse delay ($\tau_d$) from 1ms to 100ms. $B_0$ inhomogeneity ($\Delta B_0$) was varied from -2ppm to 2ppm. APT MRI contrast was quantified by the magnetization transfer ratio asymmetry parameter: $MTR_{asym}(3.5ppm) = [S_{sat}(+3.5ppm) - S_{sat}(-3.5ppm)] / S_0$. In addition, a new Saturation with Frequency Alternating RF Irradiation (SAFARI) was evaluated where RF pulses are applied alternating between positive and negative offset ($S_{sat}(\pm 3.5ppm)$). Using this approach the APT MRI contrast was quantified by: $MTR_{SAFARI} = [S_{sat}(+3.5ppm) + S_{sat}(-3.5ppm)] / S_0$. Because the water line is symmetric applying single frequency irradiation at 3.5ppm should be identical to alternating irradiation at frequencies -3.5ppm and +3.5ppm with the same total power. The amide protons however will experience full saturation at 3.5ppm, no saturation at -3.5ppm and saturation at half the power with SAFARI. As a result $MTR_{SAFARI}$ will be zero for direct water saturation effects, but will retain APT contrast.

Results and discussion

1) Pulse shape: To minimize errors due to $B_0$ inhomogeneity we want an RF pulse shape with frequency selectivity approximating a rectangular pulse with bandwidth = 2.5ppm. This pulse would saturate the amide protons in the presence of $\Delta B_0 \leq 1ppm$, without saturating the water line up to $\Delta B_0 = 2ppm$. All three pulses examined had very similar frequency profile for a given pulse width, but the Blackman pulse had decreased sidelobes compared to the Hanning pulse. Fig la,c show the amide proton contrast obtained when off resonance Blackman pulses are applied. For MTR$_{asym}$ (Fig. 1a), 15ms pulses achieve 50% effect at $\pm 1ppm$, however, they do not suppress the signal well outside the desired range. MTR$_{SAFARI}$ (Fig. 1c) shows improved selectivity compared to MTR$_{asym}$ and 10ms to 15ms pulses yields the desired frequency selectivity.

2) Interpulse delay: To optimize the CEST contrast direct water saturation must be minimized while achieving efficient amide saturation (Fig 2). For a given pw water saturation can be decreased by increasing $\tau_d$, however, $\tau_d$ must remain on the order of $-1/k_{ex}$ to saturate the amide protons. Fig. 2a,b show MTR$_{asym}$ and MTR$_{SAFARI}$ for varying pulse widths and interpulse delays. MTR$_{asym}$ was maximized for 30ms pulses with $\tau_d =1ms$ while MTR$_{SAFARI}$ was maximized for 15ms pulses with $\tau_d =1ms$. Note that in practice $\tau_d$ must be at least 2/3 of pw, which still gives close to maximum contrast for 15ms and 30ms pulses.

3) Saturation scheme: In order to minimize the errors due to asymmetric water saturation in the presence of $\Delta B_0$ MTR$_{asym}$ and MTR$_{SAFARI}$ must be zero in the absence of chemical exchange (Fig. 1c,d). MTR$_{asym}$ increases quickly as $B_0$ homogeneity deteriorates (Fig. 1c). MTR$_{SAFARI}$ is much more stable and remains zero with up to $\pm 1ppm$ inhomogeneity for 30ms pulses (Fig. 1d). Including chemical exchange, Fig. 1e,f shows the competing effect between increased MTR parameters due to asymmetric water saturation in the presence of inhomogeneity and decreased amide proton saturation due to off-resonance labeling. For MTR$_{asym}$ 30ms pulses retain CEST contrast the best but direct water saturation still dominates, and the CEST effect is no longer detectable for $\Delta B_0$ greater than a few tenths of a ppm. In contrast, MTR$_{SAFARI}$ has almost no error due to direct water saturation for $\Delta B_0 < 1ppm$ and the CEST contrast is dominated by the ability of the RF pulse to maintain efficient amide proton saturation. This is optimum for the 10ms Blackman pulse.

In summary, MTR$_{asym}$ is maximized with Blackman pulses (pw=30ms, $\tau_d =20ms$) while withstanding $B_0$ inhomogeneity below $\pm 0.3ppm$. MTR$_{SAFARI}$ is maximized with Blackman pulses (pw=10ms, $\tau_d =10ms$) while withstanding $B_0$ inhomogeneity below $\pm 1ppm$.