Optimized CEST Imaging of Intermediate to Fast Exchanging Agents in In-vivo Situations

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INTRODUCTION

MRI Chemical Exchange Saturation Transfer (CEST) has been extensively used to study protein amide proton transfer (APT) and Magnetization Transfer (MT) and MT Asymmetry (1-3). The estimated exchange rates (k_{ex}) for these phenomena are < 100Hz and fall in the slow exchange regime ($k_{ex} < \Delta\omega$) at typical clinical MR field strengths of 1.5T and 3T. CEST contrast depends on solute exchange rate (k_{exs}), $\Delta\omega$, concentration of molecule with exchanging spins relative to water, T1 and T2 values of water as well as the exchanging molecule, saturation pulse power amplitude (B_1) and duration. With all other parameters being the same, it has been shown that higher B_1 and duration provides higher CEST contrast for solute pools with higher k_{exs} with paramagnetic CEST agents. However, when $\Delta\omega$ is small, such as for endogenous exchanging spins, CEST efficiency is reduced due to direct saturation (DS) of bulk water pool. This situation becomes worse in case of in-vivo situations due to the presence of shorter T2 values and the dominating MT effect of bound water pool. Normalization of CEST contrast by corresponding negative frequency image (S.) instead of the image obtained in the absence of saturation (S_0) can reduce DS contribution (REF) but still the full efficiency cannot be recovered. Here, optimization of pulse parameters for minimizing DS and MT contribution as well as specific absorption ratio (SAR) is demonstrated using full numerical simulations of Bloch-McConnell equations with physiological parameters for a broad range of k_{exs}.

MATERIALS AND METHODS

Simulations: Complete numerical simulations of Bloch-McConnell equations (4) with two pools (free water (fw), bound water (bw)) or three pools (fw, bw and a solute(s)) are used to model z-spectra with physiological parameters at a main magnetic field of 7T. Exchange rate of the solute (k_{exs}) was varied over a range of 50-6000Hz, covering slow to intermediate and intermediate to fast range. The simulations were carried out for two types of saturation pulses, pulse train with Hanning windowed rectangular pulses and continuous wave (cw) rectangular. The bound water pool central frequency was manually shifted by -2.7ppm for mimicking in-vivo MT asymmetry (5). The parameters used in simulations were: T_{1fw}=2s, T_{2fw}=0.06s, T_{1bw}=1s, T_{2bw}=10µs, [M_{fw}]=67M and 73.6M, [M_{bw}]=13M and 6.4M corresponding to white (80% water content and 16% bw fraction)and gray matter(80% water content and 8% bw fraction), k_{exbw} = 50Hz, [M_s] = 30mM, T_{1s} = 1s, T_{2s} = 10ms with k_{exs} being variable.

CEST contrast computation: The CEST contrast is computed using equation(6), CEST=100*[S(-ppm) – S(+ppm)]/S(-ppm). Normalization by –ve ppm instead of S_0 is essential for CEST in order to minimize contribution from DS and MT effect.

RESULTS AND DISCUSSIONS

Figure 1A, shows CEST contrast with $\Delta\omega$ = 500ppm for the solute with 30mM exchanging protons concentration with negligible DS and MT effect for a range of exchange rates and saturation pulse parameters. CEST contrast increases with increase in B1 and duration. In Figure 1B, CEST contrast in the presence of DS and MT pool similar to brain WM situation with M_{0a}=67M, M_{0b} =13M, T_{2fw}=0.06s, with $\Delta\omega$ = 3 ppm for the solute with k_{exs}=2500Hz for a range of B_1 and durations is shown. Figure 1C, mimic in-vivo brain GM situations with M_{0a}=73.6M, M_{0b} =6.4M, T_{2fw}=0.08s. The dependency of CEST contrast on concentration for different B1's and fixed duration (=400ms) is shown in Fig1D. As such the CEST contrast showed linear relation with solute concentration however, maximum contrast was obtained at B1=300Hz. In figure 2 CEST contrast dependence on pulse parameters in the presence of both DS and MT effect is shown for a combination of B_1 and duration for different exchange rates. As shown in Figure 2A, low B_1 and long duration is optimum for slow exchangeable protons, such as amide protons with exchange rate at ~10-50Hz. For intermediate to fast exchangeable protons, high B_1 and longer pulse duration usually provides high contrast in phantoms for intermediate to fast exchanging agents. However, Figure 2 B to D demonstrated that CEST contrast actually start to decrease when saturation duration is too long, such as >1s especially at high B1. This unusual behavior is due to the presence of MT effect, and it becomes more prominent with high B_1 and long duration. However, by using high B_1 and short duration one can improve CEST contrast from in-vivo, in contrast to long duration and low B1. This is mainly due to the fact that exchange rate of bound water pool is very small and it requires longer duration in order to significantly contribute. And in contrast fast exchanging CEST agents can attenuate water signal even in short duration, once they are completely saturated. This observation also opens the possibility of in-vivo imaging of intermediate to fast exchange CEST molecules as SAR deposition will be minimized by this approach. Similar results were obtained with CW saturation pulse. In conclusion, high enough B_1 and short duration can saturate solute pool and it can significantly reduce water signal. This approach minimizes the MT effect as well as contamination from slow exchanging CEST agents and in essence serves as a RF amplitude based filter for selective observation of CEST agents. Since analytical solutions are not possible for these saturation parameters, this strategy requires the use of full numerical simulation to arrive at optimum saturation pulse parameters.

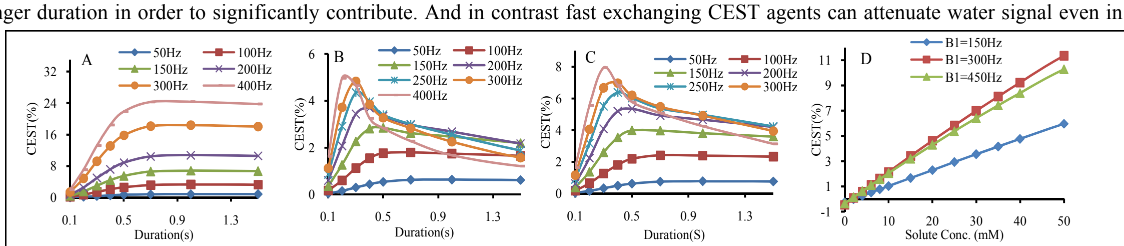

Figure1: Simulation of CEST effect from intermediate exchangeable protons (k_{exs}=2500Hz) with Hanning windowed pulse. For WM mimicking situation (M_{0a}=67M, M_{0b} =13M, T_{2fw}=0.06s), CEST contrast for a range of B_1 and durations at $\Delta\omega$=500ppm (A) and $\Delta\omega$=3ppm (B). In Fig. 1C, parameters similar to GM, with M_{0a}=73.6M, M_{0b} =6.4M, T_{2fw}=0.08s were used to get contrast at $\Delta\omega$=3ppm. Fig. 1D shows CEST contrast dependence at $\Delta\omega$=3ppm, on concentration of solute pool for three B_1's with duration 400ms in GM situation.

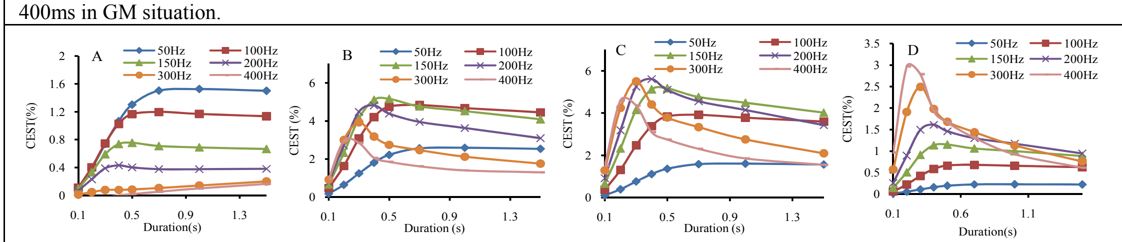

Figure 2. CEST contrast using Hanning windowed at $\Delta\omega$=3ppm with k_{exs} =50Hz (A), k_{exs} =500Hz (B), k_{exs} =1000Hz (C), k_{exs} =5000Hz (D), M_{0a}=67M, M_{0b} =13M, for a range of B_1 and durations.

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