CREATINE IMAGING USING CHEMICAL EXCHANGE FILTER IMAGING

Zhongliang Zu[1], Junzhong Xu[1], Vaibhav Janve[1], Chad Quarles[1], Mark D Does[1], John C Gore[1], and Daniel F Gochberg[1]
[1]*Institue of Imaging Science, Vanderbilt University, Nashville, TN, United States*

Target audience: Investigators are interested in high spatial resolution imaging of creatine.

Purpose: to demonstrate a novel imaging method's specific sensitivity to creatine (Cre). An imaging method in which contrast reflects tissue creatine levels would provide useful biological information as creatine is a sensitive biomarker of many diseases. MR spectroscopy (MRS) is able to image specific metabolites *in vivo*, including creatine. However, MRS suffers from relatively low resolution, long acquisition times, and has difficulty distinguishing creatine and phosphocreatine (Pcr). Chemical exchange saturation transfer (CEST) has been recently used to image specific metabolites with relatively high resolution and SNR efficiency through the saturation of exchangeable sites[1]. However, CEST suffers from lower spectral resolution, and has difficulty isolating the creatine signal. Here, we present a chemical exchange filter imaging technique based on the recently developed chemical exchange rotation transfer (CERT) approach, that can select specific metabolites based on their exchange rates with water (k_{sw})[2]. Creatine, which is 1.8 ppm from water and with a k_{sw} of about 600 s^{-1} at physiological pH[1], can be selected by the exchange filter imaging, thus mitigating the overlapping and non-specific signals that limit conventional CEST imaging.

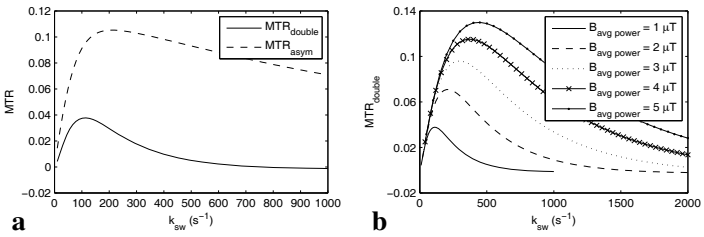

Fig. 1 (a) Simulated MTR_{double} and MTR_{asym} vs. k_{sw} at $B_{avg\ power}$ of 1 μT. (b) Simulated MTR_{double} vs. k_{sw} at a variety of $B_{avg\ power}$.

Methods: The CERT metric MTR_{double} is calculated by the subtraction of signals after pulse-train saturation at two nutation angles (but constant offset frequency and average power $B_{avg\ power}$). The conventional CEST metric MTR_{asym} comes from the subtraction at two frequencies:

$$MTR_{double} = (S_-(2\pi) - S_-(\pi))/S_0\big|_{B_{avgpower}} \quad (1)$$

$$MTR_{asym} = (S_+ - S_-)/S_0 \quad (2)$$

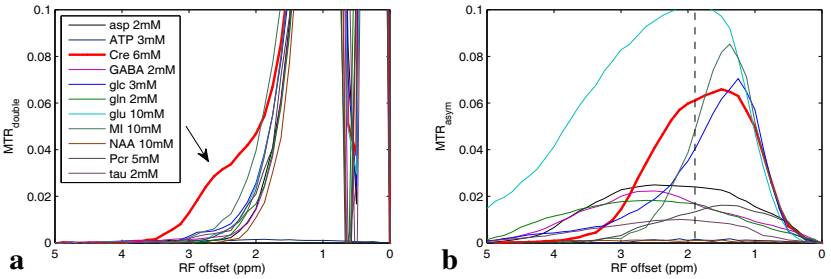

Fig. 2: Experimental MTR_{double} (a) and MTR_{asym} (b) on known phantoms.

MTR_{double} is sensitive to the exchange rate to a greater degree than MTR_{asym} and can effectively function as an exchange low pass filter (Fig. 1a). Fig. 1b shows that the MTR_{double} signal peaks at roughly $k_{sw}=\gamma B_{avg\ power}/2$. Therefore, the pass band can be adjusted by $B_{avg\ power}$. The major metabolites in human brain have a broad range of k_{sw}. By adjusting the $B_{avg\ power}$ and considering the frequency offset and physiological concentration, specific metabolites can be selected.

Simulations in fig. 1 were performed with a 2-pool model (solute and water pool), ignoring direct effects on water. 11 phantoms with different metabolites at their physiological concentration were prepared in 1× PBS and titrated to pH of 7.0. Experiments on phantoms and a rat brain with 9L tumors were performed with $B_{avg\ power}$ of 3.2 μT. The $B_{avg\ power}$ used here selects creatine and was calculated according to the exchange pass band width and the peak position. Anatomy and MTR_{double} images were acquired with 4-shot EPI readout with a 128 × 128 matrix. Also, a T_1 map was acquired with inversion recovery spin-echo EPI with a 64 × 64 matrix. All experiments were performed on a 9.4 T Varian system.

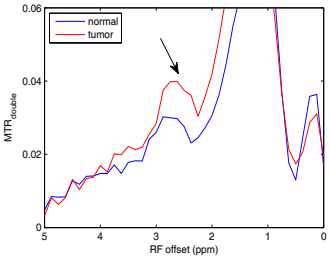

Fig. 3: MTR_{double} on 9L rat brain.

Results: Fig. 2 plots the phantom results. Fig. 2a shows that creatine contributes most of the MTR_{double} signal at 2.5 ppm (arrow), while fig. 2b shows that there is no offset where creatine dominates the MTR_{asym} signal. At the relatively high power used (3.2 μT), the adiabatic condition is not satisfied at low offsets resulting in an artifactual MTR_{double} signal peak due to direct water rotation. This artifact has little effect on isolating the creatine signal. Fig. 3 shows the creatine peak at around 2.5 ppm (arrow) on normal tissue and 9L tumor in a rat brain. The MTR_{double} signal peak at 2.5 ppm is used to image the tumor in fig 4c. Fig. 4 shows the anatomy (T_2 weighted), T_1 map, and MTR_{double} images on a rat brain with 9L tumor.

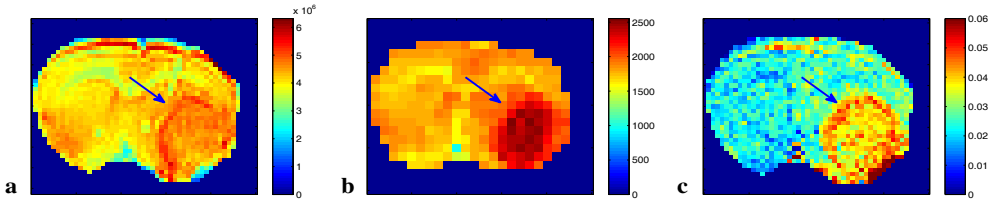

Fig. 4: (a) anatomy (T_2 weighted), (b) T_1 map, and (c) MTR_{double} (creatine) images on a rat brain with 9L tumor at 9.4T. Tumor is indicated by the arrow.

Discussion: Phantom and *in vivo* results indicate MTR_{double}'s specific sensitivity to creatine. Surprisingly, results in the 9L tumor model show elevated creatine. This differs from previous results on total creatine (Cre + Pcr)[3], and this difference may be due to Cre vs. Cre + Pcr changes, contributions from non-metabolite sources such as R_1, R_2, and MT, and the signal quantification method. Also, the creatine imaging in fig. 4c shows clean edge enhancement, which may be due to increased cellular density.

Conclusion: We show how creatine may be imaged *in vivo* using the CERT metric MTR_{double}, exploiting its ability to distinguish metabolites on the basis of both resonant frequency and exchange rate. Initial studies of tumors show heterogeneous contrast.

References:

[1] Cai KJ *et al. nature medicine.* 2012; 18:302-306 [2] Zu, Z. *et al. Magn Reson Med.* in press [3] Doblas S *et al. NMR Biomed.* 2012; 25:685-694