Imaging of DIACEST Microcapsules containing Hepatocytes using Length Variation of Saturation and Principal Component Analysis

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Introduction *In vivo* Chemical Exchange Saturation Transfer (CEST) MRI for diamagnetic agents is very challenging due to (i) proximity of exchangeable protons such as –NH, –NH_2 and -OH to the water resonance, and competition with tissue MT; (ii) the inherently low contrast noise ratio(CNR); (iii) the sensitivity to field inhomogeneities. Most methods study saturation as a function of irradiation offset and use spline fitting to correct the saturation contrast on a pixel-by-pixel basis, which requires long scan times, doesn't allow the multiple images to add to the CNR in the resulting maps, and retains motion and fat artifacts, especially in the abdomen with bowel peristalsis and respiratory motion. CEST contrast has a characteristic build-up with saturation length (T_{sat})[1], which is insensitive to B0 shifts provided the saturation pulse is not completely off-resonance with respect to the exchangeable protons of interest. We therefore proposed a method using Length VARiation of Saturation (LVARS), which involves the collection of images with multiple saturation lengths at one frequency ($+\Delta\omega$) to attempt to remove B_0 artifacts in an alternative manner. Principal Component Analysis (PCA) is one of the structure-seeking multivariate statistical techniques, which have been proposed for the detection and characterization of activation in both PET[2] and fMRI[3] time series data[2,3]. As there is similarity in CEST contrast buildup process, we hypothesized that it should be possible to use PCA to extract the build-up property of CEST contrast from images obtained as a function of T_{sat}.

Materials and Methods 2000-2500 hepatocyte-containing alginate microcapsules were transplanted in the lower abdomen of 3 Balb/c female mice, with the CEST contrast agent protamine sulfate as crosslinker integrated in the capsule. MR images were acquired on multiple days after transplantation on a Bruker 9.4T horizontal bore scanner with a 30mm-diameter sawtooth transmit/receive coil. **Image Acquisition:** An axial slice (1-1.5mm thick) centered on the microcapsules was chosen for imaging, and the slice was shimmed to reduce the B_0-shift range to be between -1ppm and +1ppm. Saturation images with an offset of +2.4ppm (the peak frequency of the alginate capsules) were collected with K (K=3-6) T_{sat}'s from 0.5s-4s, $[T_{sat}\#1, T_{sat}\#2, \ldots \ldots, T_{sat}\#K)]_n$, with n cycles to improve CNR and reduce the effects of organ motion. We used the parameters: T_{sat}#1=0.8s, T_{sat}#2=1.2s,T_{sat}#3=2s andT_{sat}#4=3s with n=3; B1=3.6μT, matrix size=128x32, FOV=2.4x1.5cm, TR/TE=5000ms/21.6ms, RARE Factor=8, NA=2. High resolution images (256x128) were acquired for anatomical structure. **Post-processing:** The saturation image series with the different T_{sat} values were first normalized without saturation (S0) and transformed pixelwise along the T_{sat} variation, and PCA was then performed to classify the pixels with different T_{sat}-dependencies. The resulting component scores are displayed in a contrast map. All image analysis was performed using Matlab.

Results and Discussion Fig.1a shows a MT-weighted anatomical image, with the microcapsules highlighted by the orange arrow. The B_0 map is shown in Fig. 1b, leading to the uncorrected MTR_{asym} map at 2.4 ppm (Fig.1c) that displays many artifacts (white arrows) and the CEST contrast that is artificially higher in regions with larger B_0 shifts. However, if the S(+2.4ppm) is examined as a function of T_{sat}, we found the capsule region with(ROI1) and without(ROI2) B_0 shift change to be very similar, while the control ROI has a different trend. When studying the images with 4 different T_{sat} using PCA, we found that PCA component 1 shows a similar contrast to the total signal in saturation weighted images. However, the PCA comp. 2 map (Fig.1e), which is in an orthogonal direction and uncorrelated to PCA comp.1, the capsule region is highlighted while artifacts in Fig.1c are suppressed. Due to the nature of this analysis, each T_{sat} contributes to the component map, and as a result the contrast-noise-ratio in PCA comp 2 is much higher than the CEST contrast map with the Z-spectra corrected using 35 saturation images with offset incremented every 0.2ppm from -3.5ppm to 3.5ppm (Fig.1f). The entire imaging time is only 1/3 (3 repetitions of 4 T_{sat}) of that for the offset increment image time. Moreover, the offset corrected image still has multiple artifacts near the intestines. We further investigated the correlation between PCA component 2 and the conventional MTR_{asym} value, and found that when the PCA comp.2 map drops about 34% relatively from Day 0 (Fig.2a) to Day 6 (Fig.2b) after transplantation, the MTR_{asym} analysis also shows a similar decrease (Fig.2c). The PCA comp. 2 values in the capsule region are correlated with the MTR_{asym} values for the 3 different scans (Fig.2d).

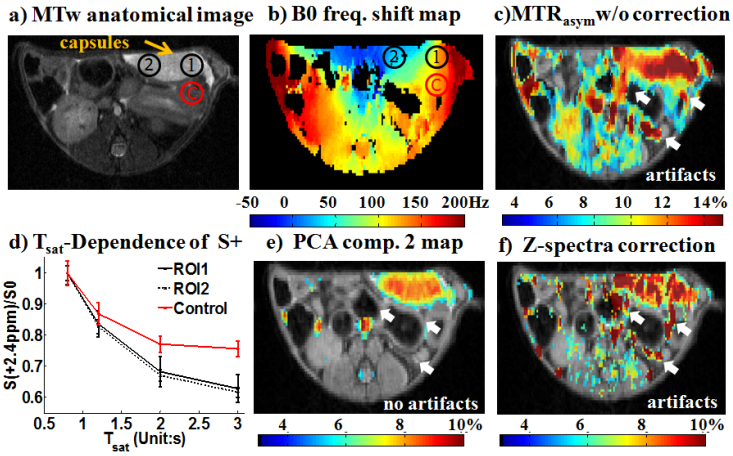

Fig.1 Mice abdomen image and PCA component maps of the T_{sat}-dependence property, comparing with MTR_{asym} map with and without correction.

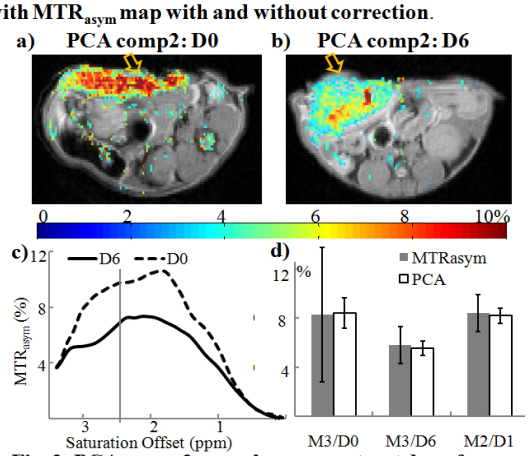

Fig. 2 PCA comp.2 map shows a contrast drop for one mouse from D0 to D6, with a correlation with MTR_{asym}

Conclusion We have demonstrated that Length VARiation of Saturation and PCA can be used to generate high CNR *in vivo* CEST images of hepatocyte-containing microcapsules transplanted into the mouse abdomen which display much less artifacts than CEST images produced using frequency corrected asymmetry analysis. In addition, this method can reduce the scanning time by at least half. Moreover, the PCA comp 2 is found to be correlated with MTR_{asym}, as the drop in MTR_{asym} also reflects in the decrease of PCA comp2. We are now using these methods for CEST pH mapping of the microenvironment of encapsulated cells.

Reference: 1. McMahon MT et al., *Magn Reson Med.* 2006; 55(4):836–847 2. Friston,et.al. J Cereb Blood Flow Metab.1993;13(1):5-14 3.Andersen A.H.,1999;17(6):795-815