Quantitative CEST with BIRDS

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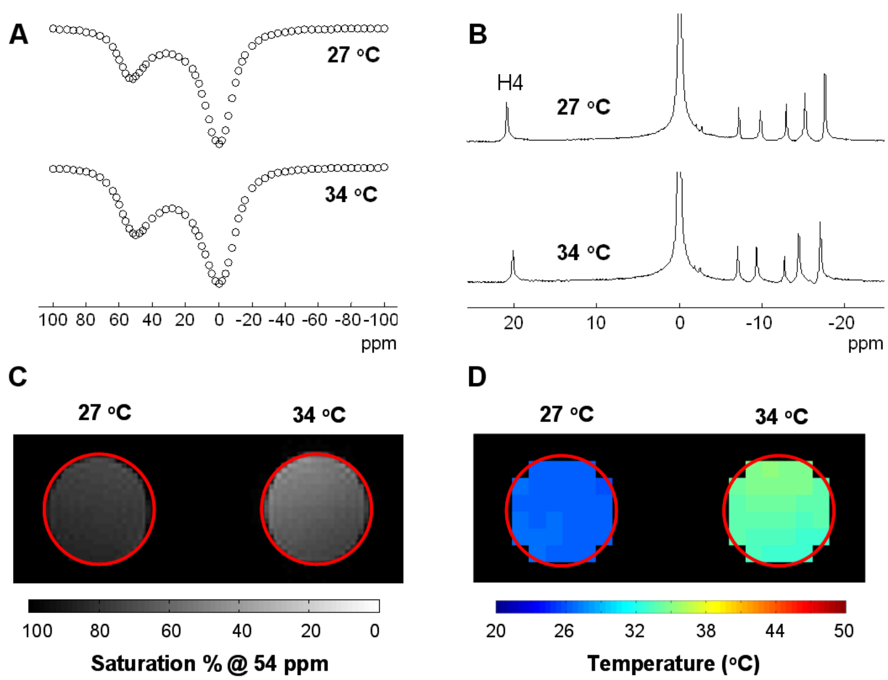
INTRODUCTION **C**hemical **E**xchange **S**aturation **T**ransfer (CEST) generates MRI contrast by probing proton exchange between bound and bulk water **[1]** using paramagnetic lanthanide-based contrast agents (CAs). **B**iosensor **I**maging of **R**edundant **D**eviation of **S**hifts (BIRDS) represents another alternative to CEST imaging, using resonances arising from the CA itself **[2,3]**. Since CEST relies on water, spatial resolution is high. However, CEST data are qualitative because the signal attenuation remains relative, unless the CA concentration is known and furthermore the proton exchange depends on the CA's temperature and pH. Here we demonstrate that quantitative temperature information can be obtained by combining BIRDS with CEST using the complex between the europium (Eu^{3+}) ion and the tetraglycinamide derivative of the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate or EuDOTA-$(gly)_4^-$ **[4]**. This Eu^{3+}-based complex exhibit enhanced CEST characteristics (bound water molecule with a lifetime in the hundreds of μs range) while retaining the high sensitivity to temperature variations specific to BIRDS.

MATERIALS AND METHODS ^{1}H data were obtained at 11.7T from a tube containing 5mM EuDOTA-$(gly)_4^-$ heated to different temperatures (27°C and 34°C). *CEST:* *Z*-spectra were obtained by applying a continuous wave for 1 second, at various frequencies, followed by the acquisition of the water signal. The spectra were acquired at different temperatures to locate the peak of bound water in relation to bulk water (Fig. A). For CEST-based MRI, a single slice spin echo sequence was used in conjunction with saturation at +54ppm ("on") and -54ppm ("off"). Relative maps reflecting the degree of signal loss with saturation were generated from the difference between the image acquired with saturation "off" and the one obtained with saturation "on". *BIRDS:* ^{1}H spectra were obtained at different temperatures to quantify sensitivity of each resonance (Fig. B). For BIRDS-based MRS, a high-speed CSI sequence **[2,3]** was used to image the H4 resonance (δ_4) which shows the highest temperature sensitivity. The temperature (T) was calculated according to the equation:

$$T = 35.3 - 7.74\cdot(\delta_4-\delta_o) + 0.32\cdot(\delta_4-\delta_o)^2$$

where δ_o=20ppm.



RESULTS The *Z*-spectra (Fig. A) showed that the ratio between the bulk water in presence and absence of saturation is ~60% and ~40%, respectively, at 27°C and 34°C. The MRI images show levels of saturation of water signal at the two temperatures investigated similar to those obtained from the *Z*-spectra (Fig. C). The ^{1}H spectra of the CA itself indicate that the H4 resonance (Fig. B) has the highest temperature sensitivity (-0.13ppm/°C). Absolute temperature maps at the two temperatures investigated were generated according to eq.1 (Fig. D).

DISCUSSION A typical BIRDS experiment uses high-speed CSI because of favorable relaxation times for CAs **[2,3]**. Although CSI data of a BIRDS experiment has lower spatial resolution, its quantitative information can enhance qualitative information from the MRI data of a CEST experiment. Future studies should seek variations of Ln^{3+} ions and/or chelates that can combine BIRDS and CEST experiments.

REFERENCES
[1] Zhang S et al., *Acc. Chem. Res.* **36**:783-790, 2003.
[2] Coman D et al., *NMR Biomed.* **22**:229-39, 2009.
[3] Coman D et al., *NMR Biomed.* **(in press)** 2010.
[4] Zhang S et al., *J. Am. Chem. Soc.* **127**:17572-17573, 2005.

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