# Simultaneous $^{19}$F and $^{1}$H-CEST technique for improved accuracy and efficiency in quantitative CEST measurements

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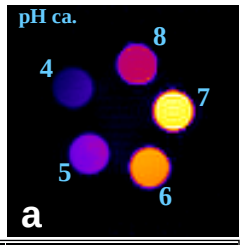
## Introduction

Responsive chemical-shift saturation transfer (CEST) agents [1] have been developed for non invasive mapping of important diagnostic parameters, like local pH for oncology applications. Because the $^{1}$H-CEST signal strength depends on the physiological parameters as well as on agent concentration, a common challenge is the determination of the local concentration for calibrated measurements, which can e.g. be achieved by agents with two different chemical shifts and exchange pools. If a CEST agent is provided, which is additionally labeled by a 19-fluorine marker, the calibration can be performed via $^{19}$F-MRI. This approach also increases specificity, because regions with e.g. native magnetization transfer effects (but no $^{19}$F signal) can be discriminated from the agent. In this work, a novel turbo-spin-echo (TSE) imaging sequence is investigated which, using a dual-tuned spectrometer and coil, allows the truly-simultaneous acquisition of $^{1}$H-CEST and $^{19}$F images, thus improving time efficiency and accuracy of the calibration.




## Methods

The study was performed on a 3T clinical whole-body scanner (Achieva, Philips Medical Systems) with a dual-tuned transmit/receive RF coil (∅ 7cm) and a dual $^{19}$F/$^{1}$H spectrometer system [2]. CEST and fluorine images were recorded simultaneously with a novel TSE sequence applying $^{1}$H only pre-saturation pulses in combination with dual-frequency RF excitation ($\pi/2$), refocusing pulses ($\pi$) and acquisition windows. While visualizing the CEST effect requires two measurements with pre-saturation at $\pm\delta$ (chemical shift), the $^{19}$F signal from the acquisitions, unaffected by the pre-saturation, can be averaged into one image of higher SNR. The resulting $^{19}$F map of the agent concentration can then be used to calculate a calibrated pH map. Two agent types were used for demonstration: (i) a mixture of 30 mM of Yb(III)DOTAM G3 dendritic PARACEST agents [3] with 180 mM (±10%) PFCE ($C_{10}F_{20}O_5$) nanoparticles (NP) at pH levels from 4 to 8. (ii) prototype of a combined CEST/$^{19}$F agent based on europium-chelate coated PFOB-NP ($C_8F_{17}Br$). All experiments were performed at room temperature. The agent probes were contained in 2 mL tubes which were immersed in water. Proton pre-saturation consisted of a train of pulses each with 10 ms length and 1800° flip angle ($B_1$=11.7μT). Imaging parameters (i, Fig.1): 2D TSE single-shot linear, matrix $96^2$, FOV 70 mm, slice 8 mm, TR/TE=13244/274 ms, 180 pulses pre-saturation, $\delta$=±1.9 kHz, excitation BW=1000 Hz , 24 sample averages, scan time 10:49 min. (ii, Fig.2): 2D TSE multi-shot linear, turbo factor 32, matrix $160^2$, FOV 100 mm, slice 3 mm, TR/TE=6357/81 ms, 90 pulses pre-saturation, $\delta$=±7.0 kHz, excitation BW=1450 Hz , 4 averages, scan time 4:27 min. Proton only TSE were taken for comparison with identical parameters except for (ii) TR/TE=6086/77ms.

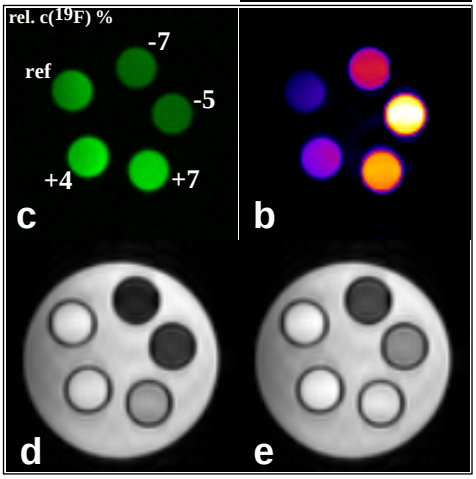



**Figure 1**: Simultaneous $^{19}$F/$^{1}$H Turbo-Spin-Echo (TSE) sequence for calibrated CEST at different pH values (agent mixture: Yb-DOTAM & PFCE nanoparticles): The obtained pH map (b) is similar to a $^{1}$H-only TSE-CEST map (a). A c($^{19}$F) map is provided at the same time (c). CEST images are derived from acquisitions with proton pre-saturation at positive (d) and negative (e) chemical shift offset.

## Results and Discussion

Figure 1 demonstrates feasibility of simultaneous CEST/$^{19}$F imaging on the agent mixture (i). Images with pre-saturation at +$\delta$ (d) and -$\delta$ (e) are subtracted to calculate the CEST signal. The CEST signal (Fig.1a) taken with a proton-only TSE sequence, shows a clear dependence on the pH values. A corresponding pH map (b) is provided by the simultaneous TSE sequence. At the same time, an image (c) is provided, which maps the fluorine concentration c($^{19}$F). The numbers indicate relative concentrations as provided by the agent probes (percent relative to probe labeled "ref"), which correlate well to the measured signal intensities. In Figure 2, the simultaneous TSE sequence was applied to the combined CEST/$^{19}$F agent (ii). The proton image (a) gives an overview on the phantom setup, which contains pure Eu-chelates (no $^{19}$F signal) and the Eu/PFOB-NP. The CEST signal map is very similar when taken in a $^{1}$H only sequence (b) or in the novel TSE sequence (d). Only the Eu/PFOB-NP show up in the simultaneous $^{19}$F image. In comparison to separate serial or interleaved experiments, the simultaneous TSE sequence shows competitive image quality, while eliminating the temporal variability. However, some additional blurring in phase-encoding direction is observed. Because contrast agent dynamics or physiological motion between the CEST and $^{19}$F acquisition may lead to wrong calibration, a significant improvement is expected for quantification due to the same-time calibration. An influence of the pH value on the $^{19}$F signal is not expected, but should be excluded experimentally. The time efficiency gain by the basic sequence is about 10% compared to separate acquisitions of CEST and fluorine. Long TR values, e.g. TR=13 s versus 1.8 s pre-saturation, result from the imposed specific absorption rate (SAR) limit, which is not exceeded due to the introduced wait time. Nevertheless, the wait time can be used for continued $^{19}$F signal acquisition, because the excitation/refocusing pulses have a less significant contribution to SAR than pre-saturation. Thus, time efficiency can be significantly enhanced, which is particularly helpful, when long $^{19}$F signal averaging is necessary for low *in vivo* concentrations.

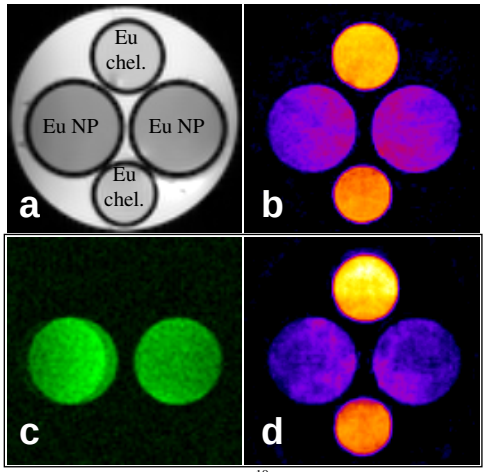



**Figure 2**: Simultaneous TSE applied to a combined CEST/$^{19}$F agent (Eu-chelate on PFOB-NPs, pure Eu-chelates added as reference): Only the NPs show a $^{19}$F signal (c). The $^{1}$H-only TSE (b) and the simultaneous TSE-CEST image (d) are very similar.

## Conclusion

A novel simultaneous CEST and $^{19}$F imaging sequence has been implemented, and basic feasibility was shown in phantom experiments, including first prototype combined imaging agents. It is expected that calibrated CEST measurements with improved accuracy and time efficiency as well as with high specificity can obtained using this technique.

## References

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