Accelerated In Vivo Cell Tracking Using Fluorine-19 MRI with Compressed Sensing

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Introduction

In vivo cell tracking using perfluorocarbon (PFC) labels combined with ^{19}F MRI detection has emerged as a powerful approach for visualizing transferred cells(1-2) and macrophage infiltration at sites of inflammation (3-4). Cell tracking using ^{19}F MRI has the advantage that there is no background signal, and thus has high cell detection specificity. Moreover, signal quantification is straightforward in spin density-weighted images enabling '*in vivo* cytometry' (2) and inflammation quantification (3). ^{19}F nuclei are intrinsically sensitive, 83% relative to ^{1}H, however, the ^{19}F images are often in the low signal-to-noise ratio (SNR) regime due to probe sparsity. Consequently, in certain applications significant signal averaging and long data acquisition times are employed to help boost SNR. Recently, compressed sensing (CS) has been used to significantly reduce MRI acquisition time (5) in applications including dynamic imaging, T_1/T_2 mapping, angiography, and chemical shift imaging. Several studies using ^{19}F MRI and CS have been reported (6-7). CS methods are well-suited for cell tracking studies as the image data often display isolated, punctate signal distributions (5) in the field of view. In the current study, we investigated 3D CS methods to accelerate ^{19}F MRI and evaluated the effect of acceleration on ^{19}F signal quantification. We applied these 3D CS ^{19}F MRI methods to quantify the macrophage burden in a localized inflammation mouse model.

Materials and methods

Phantom studies A ^{19}F phantom was prepared by filling eight capillaries (diameters R, 0.754R, 0.617R, 0.500R, 0.381R, 0.316R, 0.237R, and 0.157R, where R=1.83 mm) with perfluoro-15-crown-5-ether (PCE) oil. The signal from these capillaries in axial images is proportional to their cross sectional areas. Axial images of the ^{19}F phantom were acquired on an 11.7 T microimaging system (Bruker BioSpin, Billerica, MA) using an in-house developed 3D CS-RARE sequence. A predetermined phase encoding gradient table was added to the RARE sequence with a pseudo-random sampling pattern emphasizing the k-space center. The k-space was undersampled by factors of 2, 4, 8, 16, and 32. Image parameters were: TE/TR=11/100 ms, NA=16, a 4×4×4 cm^3 FOV, and a matrix size of 128×128×128. ***In vivo* studies** A female C57BL/6J mouse was anesthetized using isoflurane and a skin incision of 1.5 cm was made near the jugular vein and then sutured closed. After 24 hours, 0.2 ml of perfluoropolyether (PFPE) emulsion (VS-1000H, Celsense Inc., Pittsburgh, PA) was given intravenously. This PFPE reagent is known to be taken up by macrophages *in vivo*, thereby labeling these cells *in situ*; labeled macrophage accumulates at sites of inflammation resulting in ^{19}F signal accumulation at lesioned sites. At 48 hours post-surgery, the mouse was scanned using a 3D CS-RARE ^{19}F MRI sequence at 11.7 T. Imaging parameters were: TR/TE=1000/11 ms, NA=8, a 3.2×3.2×3.2 cm^3 FOV, and a matrix size of 64×64×64. Fully sampled and 8-fold undersampled k-space data were acquired. In addition, a ^{1}H image was acquired as an anatomical underlay using a respiratory-gated spin-echo sequence with parameters: TR/TE=700/11 ms, NA=4, a 3.2×3.2×3.2 cm^3 FOV, and a matrix size of 256×256×64. A reference capillary with a 10% diluted PFPE emulsion in agarose was placed along the animal's torso. **CS reconstruction and signal quantification** CS images were reconstructed offline using the SparseMRI software package (5). Briefly, reconstruction was performed by solving the following equation using a nonlinear conjugate gradient descent algorithm with back-tracking line search (5). Specifically, $\hat{\rho} = arg\ min[\alpha|\rho|_{TV} + \beta|\rho|_{L1}] \quad s.t. \|F\rho - d\|_2^2 \leq \varepsilon$, where $|\rho|_{TV} = \sum_1^p \sqrt{\left|[D^h\rho]_p\right|^2 + \left|[D^v\rho]_p\right|^2}$ and $|\rho|_{L1} = \sum_1^p |\rho_p|$ represents the TV-norm and the L1-norm operation, respectively, F is the Fourier encoding matrix, d is the sampled k-space data vector, ρ is the image of interest to be reconstructed, α and β are weighting parameters, ε is the threshold constraint on data consistency, and D^h and D^v represent the differential operators along the horizontal and vertical dimensions, respectively. The sparsity transform is the identity transform. The total phantom signal intensity in each capillary was normalized by the signal of the largest capillary. *In vivo* ^{19}F signal was normalized by the 10% PFPE reference capillary.

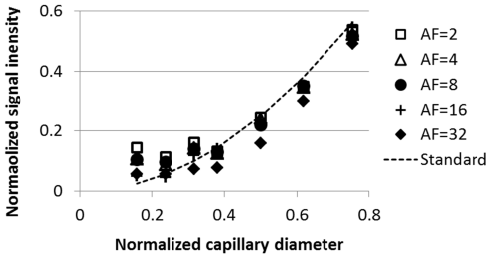

Fig. 1 3D CS acquisition and reconstruction of ^{19}F phantom showed comparable signal intensity to the standard in capillaries with diameter greater than 0.38R. R=1.83 mm. Standard: theoretical ^{19}F signal values calculated using the cross sectional areas of capillaries. AF: acceleration factor. SNR=8.

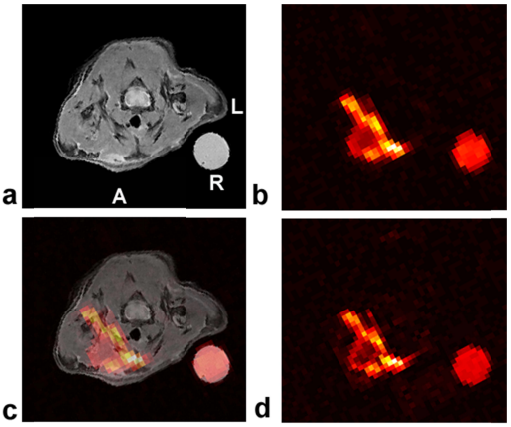

Fig. 2 *In vivo* ^{19}F 3D CS-RARE with 8-fold acceleration shows macrophage accumulation in the region of inflammation in mouse. **a**: anatomical image by conventional ^{1}H spin-echo sequence. **b**: 3D ^{19}F CS-RARE (AF=8) image of **a**; **c**: fused image of **a**&**b**; **d**: ^{19}F RARE (AF=1) image of **a**. Here A=anterior wall, L=left, and R= reference.

Results

With all SNR levels examined (SNR=8, 14, and 58) in the phantom studies, the ^{19}F signal quantification from CS-RARE images showed good agreement to the theoretical values. The quantitative comparison at the lowest SNR level is shown in Fig. 1. When the acceleration factor (AF) was in the range of 2 to 8, less than ±10% signal difference was observed in the capillaries with diameter greater than 0.380R (0.695 mm). With higher AF (16 or 32), the signal difference increases (Fig. 1). The ^{19}F signal estimate in the three smallest capillaries was less accurate. The loss of accuracy was partly due to the partial volume effect.

In the wounding-inflammation mouse model, ^{19}F signal was observed at the right anterior side of animal which coincides with the site of incision (Fig. 2b-d). Such signal indicates the presence of PFPE labeled macrophages. No significant blurring in ^{19}F signal was detected in the 8× accelerated CS-RARE image compared to the conventional RARE image (Fig. 2b&d). The k-space undersampling preserved the spatial variation of fluorine signal (Fig. 2b&d). The intrinsic denoising effect by CS reconstruction (5) was also observed (Fig. 2b&d) which is due to the non-linear nature of CS image reconstruction that enforces a constraint on data consistency. Quantitatively, the total ^{19}F signal at the inflammation site was 1.78 times stronger than that of the 10% PFPE emulsion phantom. The total ^{19}F spins calculated from CS with 8 times acceleration was comparable to the fully sampled k-space; the difference in total spin quantification was only -6.2% (6.22×10^{19} spins for AF = 8 versus 6.63×10^{19} spins for AF = 1).

Conclusions

We show that 3D CS ^{19}F MRI methods enabled accurate and reproducible quantification of ^{19}F signals with a significant reduction of imaging time over conventional ^{19}F MRI. The utility of these methods was demonstrated in a localized inflammation mouse model, and the ^{19}F spins was accurately quantified. These 3D CS methods display great potential in advancing ^{19}F MRI cell tracking.

Reference

1. Ahrens, *Nat Biotechnol*, 2005; 23:983-7.
2. Srinivas, *Magn Reson Med*, 2007; 58: 725-34.
3. Hitchens, *Magn Reson Med*, 2011; 65:1144-53.
4. Flogel, *Circulation*, 2008; 118:140-8.
5. Lustig, *Magn Reson Med*, 2007; 58: 1182-95.
6. Kampf, *J Magn Reson* 2010; 207:262-73.
7. Larson, *Magn Reson Med* 2011; 65:610-9.