In Vivo Quantification of ^{19}F Molecluar Imaging Agents with improved Accuracy and Sensitivity using Motion Correcting, Simultaneous ^{19}F/^{1}H Radial MRI

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Introduction

^{19}F-labeled diagnostic or therapeutic agents [1] like targeted perfluoro-carbon nanoparticles offer a high potential for quantified molecular MRI [2] with excellent specificity. However, quantitative measurements *in vivo* require long signal averaging (10 minutes or more), because of the limited agent concentration accumulated at target sites. Physiological motion causes anatomical misregistration and blurring of the fluorine signal, which leads to systematic underestimation of the local agent concentration. While ^{19}F-signals are typically too sparse and weak for motion tracking, the proton signal can be used for this purpose, when it is measured at the same time. In phantom studies [3], feasibility of motion compensation using sub-sampled radial k-space acquisitions in simultaneous ^{19}F/^{1}H imaging was shown before. Sub-sampling provides adequate time resolution while maintaining an image quality suitable for motion tracking [4]. In this work, *in vivo* motion correction in a mouse model is demonstrated in 2D and 3D, and improvements for signal quantification are shown.

Methods

The study was performed on four C57BL/6 black mice injected *i.m.* left/right of the thoracic spine with 2-4 × 10 µL of Perfluoro-Crown-Ether nanoparticles (20 vol% $C_{10}F_{20}O_5$), following an institutionally approved animal protocol. Because breathing or pulsation motion of the mice is too shallow and fast to be detected, a model with artificial 1D or 2D irregular translational motion (amplitude ≈ 5 mm) was chosen. A 3T clinical whole-body scanner (Achieva, Philips Medical Systems) with a dual-tuned transmit/receive RF coil (∅ 7cm) and a dual spectrometer system [5] were used. Images were recorded with a 3D stack-of-stars (2D radial & 1D cartesian) gradient-echo sequence, using simultaneous dual-frequency (^{19}F/^{1}H) RF pulses and acquisition windows and in-plane resolutions of 0.55 - 1.46 mm. Exemplary parameters (Fig.1): voxel 1.09×1.09×3.0 mm^3, matrix 128^2, 6 slices, TR/TE = 8.8/4.0 ms, $\alpha = 20°$, pixel bandwidth pBw=197 Hz, 128 time frames of 0.84 s with 96 projections/frame (8 × sub-sampling). For 2D GRE radial simultaneous imaging e.g. (Fig.3): 0.94×0.94×3.0 mm^3, matrix 96^2, TR/TE=10/4.6 ms, pBw=169 Hz, 512 frames of 490 ms, 48 projections per frame. The sub-sampled proton image frames were registered in the spatial domain using the TurboReg algorithm [6]. Subsequently, the measured translations were applied to the ^{19}F image frames by linear phase transformation in k-space. All sub-sampled ^{19}F data were then combined in k-space and reconstructed (3D: 16 sample averages, 2D: 256 averages). For quantitative comparison, the experiments were repeated without external motion and the intensity ratio between motion-corrected and non-moving images (I[motion] / I[static]) was statistically evaluated for all voxels (over all slices), which show signal above a chosen threshold of SNR = 3 in both images.

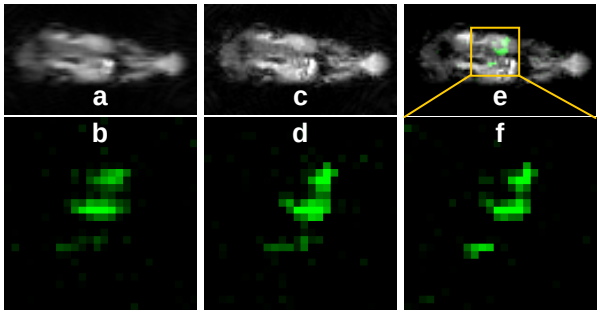

Figure 1: *In vivo* motion correction using a 3D stack-of-stars simultaneous ^{19}F/^{1}H technique on a mouse with PFCE injections: selected ^{1}H slices (a,c,e), magnified ^{19}F slices (b,d,f). Blurring in the uncorrected images (a,b) can be corrected (c,d) to match quality and intensity values of an acquisition without external motion (e,f). Time resolution is 0.84 s for a volume with 6 slices.

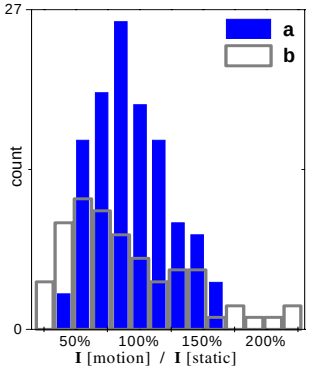

Figure 2: Histogram analysis of intensity values recovered by motion correction. Most uncorrected values (b) show only 65% of the static measurement, and many fall below the chosen noise threshold. Motion correction (a) significantly recovers intensity to 90-100%.

Results and Discussion

All *in vivo* motion compensation experiments were successfully completed. The observed amounts of nanoparticles were varying, because the injection sites differ and the agent is partly diffused. The precision of image registration is found to be about 0.3 voxels for all resolutions. Figure 1 shows an example with 3 visible injections (lower row: magnified ^{19}F images). A green color overlay in (e) shows the ^{19}F signal upon the ^{1}H based anatomy. Motion correction eliminates blurring (c *vs.* a) and recovers the shape and intensity of the fluorine signal (d *vs.* b). Motion corrected images and images without external motion show very similar quality. Statistical evaluation of the corresponding ^{19}F intensity values is shown in Figure 2 as a histogram. The correction improves the signal intensity ratio (most frequent values) from 65% (b) to 90-100% (a) of the signal measured without motion. For the uncorrected images, typically 40-50% less voxels are counted above threshold for the induced motion pattern. Motion tracking found a maximum displacement of 4.7 mm and maximum speed of 0.7 mm/s. These values are considered to be realistic with respect to the required precision of self-navigation for future imaging of larger animals or patients. The presented 3D method is as well applicable to through-plane motion. The single injection visible in Figure 3 showed substantially less signal than the previous example, but was detected without motion (e,f). With 2D translational motion (max. displacement X/Y=7.6 / 9 mm), the ^{19}F signal is no longer visible (b), but can be recovered by the motion correction (d). The corrected (c) and static (e) ^{1}H image quality is similar. To extend the fluorine radial acquisition to agents with multi-spectral lines (like PFOB), spectrally selective RF excitation or multi-echo sequences can be considered.

Conclusion

The results show, that reliable self-navigated motion correction is feasible *in vivo*, improving proton image quality as well as quantitative results of simultaneous fluorine measurements. The presented method is expected to be especially valuable in larger animals and in future clinical trials, where physiological motion will perturb quantification.

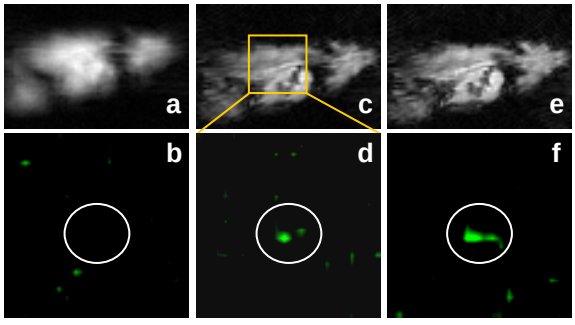

Figure 3: *In vivo* motion correction of 2D external motion using 2D radial ^{19}F/^{1}H imaging: ^{1}H images (a,c,e), corresponding magnified ^{19}F images (b,d,f). Raw images (a,b) show strong blurring and no detectable ^{19}F signal. Correction (c,d) recovers the ^{19}F signal and is comparable to the acquisition without external motion (e,f). 512 image frames with a time resolution of 490 ms were combined.

References

1. Yu JX et al., Curr. Medicinal Chemistry 12:819-848 (2005)
2. Lanza et al., Curr. Topics in Dev. Biology 70:57-76 (2005)
3. Keupp J, Proc. ISMRM 15:874 (2007)
4. Schaeffter T et al., MRM 41:954-963 (1999)
5. Keupp J et al., Proc. ISMRM 14:102 (2006)
6. Thévenaz P et al., IEEE Trans. Image Processing 7:27-41 (1998)