B1 Correction for Quantitative in vivo 19F Magnetic Resonance Imaging with Surface Coils

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Introduction: 19F Magnetic Resonance Imaging (19F MRI) has recently received much attention, especially in the field of cell tracking [1]. One of the main advantages of 19F MRI is that the image intensity is proportional to the amount of 19F within a certain region, hence quantification of the number of cells within that region is possible. However, this only holds for the use of volume coils with a homogeneous B1 field for both transmission and reception. Volume coils are often more challenging to construct and other designs such as transcieve surface coils with inhomogeneous B1 profile may be more superior in terms of higher signal to noise ratio (SNR) due to higher filling factor. One solution when using the latter would be to correct the image intensity with a B1 map acquired on the 19F channel. However, this may lead to very long imaging times not applicable to *in vivo* cell imaging due to usually low 19F concentrations, i.e. low SNR. Here we present a scheme that allows correcting for B1 imperfections even in situations of very low SNR in the 19F image by mapping the flip angle (FA) on the 1H channel. The scheme is feasible in all situations when the same coil is used for both the 1H and the 19F imaging at the cost of only ~10 min additional scan time. We evaluated the method *in vitro* and show its applicability *in vivo* in a proof-of-concept experiment of cell implantations into the mouse brain.

Material and Methods: Experiments were performed on an 11.7 T scanner (Bruker BioSpin, Ettlingen, Germany) with a homebuilt, transceive, single-loop surface coil, tunable to both the 19F and the 1H frequency. For *in vitro* and *in vivo* MRI we acquired a background 1H image with a turbo spin echo sequence (TSE) (FOV=2.88x1.92 cm^2, MTX=192x128, 16 slices, slice thickness=0.5 mm, linear k-space encoding, 8 echoes/excitation, TR/TE$_{eff}$=2.2 s/42 ms, 4 averages). In addition FA mapping was performed (based on the double FA method, FA denoted α) [2]. Parameters: FOV identical to 1H TSE, TR/TE=10 s/3.1 ms, MTX=48x32, FA=75°/150° adjusted to a slice parallel to the coil's loop, close to the coil. Afterwards the coil was tuned to the 19F frequency and a spin-density weighted 19F TSE image was acquired (same FOV, MTX=72x48, 8 slices, slice thickness=1 mm, centric encoding, 8 echoes/excitation, TR/TEeff=2.2 s/10.5 ms, 256 averages, FA=90°/180° adjusted to a slice parallel to the coil's loop but through the middle of the phantom/brain to maximize signal there). Neglecting T_1 effects ($TR/T_1>5$) the relative attenuation of the 19F TSE due to an excitation FA β (calculated from the α map) and refocusing FA 2β is $a_{rel} = \sin^3(\beta) \times \alpha/75°$ where the first term denotes the attenuation due to imperfect excitation/refocusing and the second term reflects the reception sensitivity profile of the coil. For quantitative analysis an SNR map (threshold SNR>3) was calculated from the 19F dataset corrected for low SNR in magnitude images [3]. Division through a_{rel} yielded the B1 corrected relative SNR (rSNR) map. To assess if the FA maps of the 1H and the 19F channel are identical we acquired FA maps for both channels separately on a concentrated mixture of trifluoroacetic acid and H_2O. To assess whether a linear relationship of 19F concentration and SNR could be established despite inhomogeneous B1 profile, a dilution series of a commercially available 19F agent (CS1000, Celsense, Pittsburgh, USA) was measured with the protocol above. For *in vivo* experiments NuNu mice (n=2) were implanted with two deposits of 300,000 murine neural progenitor cells labeled with the CS1000 into the striatum (AP: +0.5; L/R ± 2.0; V: -2.5). One day after surgery animals were anesthetized with Ketamine/Xylazine to avoid 19F background from fluorinated gas anesthetics and measured with the MR protocol above. To normalize the rSNR, a reference probe was put next to the animal for *in vivo* experiments. Total experimental time was ~1.5 h. A cell/voxel map was calculated with the linear relationship $cells/voxel = n_{ref}/rSNR_{ref} \times rSNR_{voxel}/n_c$ with the number of 19F spins per voxel in the reference n_{ref}, mean rSNR in the reference/voxel of interest SNR$_{ref}$/rSNR$_{voxel}$, and number of spins per cell n_c. n_c was measured beforehand by comparing peak intensities in spin-density weighted NMR spectra of known number of cells mixed with a KF internal standard. For display purposes all maps shown were interpolated to the 1H image resolution.

Results: The flip angle maps of the 1H and the 19F channel differed by less than 5%, thus rendering the acquisition of a 19F FA map unnecessary The FA mapping produced problems at the edges of the phantom tubes probably due to partial volume effects (Fig. 1). Therefore 25% of the voxels (with lowest and highest rSNR values) were excluded from the rSNR analysis of each tube. With this modification, a linear relationship between rSNR and 19F concentration was found even for low SNR values typical for 19F MRI (SNR<10). MRI of mice together with a reference yielded a mapping of the number of cells/voxel. The map revealed that around 400,000 cells were present on the left hemisphere whereas only 60,000 were found for the right hemisphere, indicating loss of cells during the implantation procedure (Fig. 2).

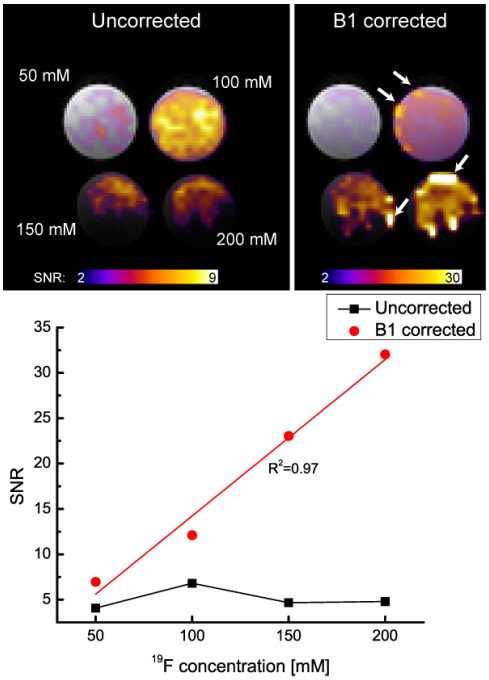

Figure 1 *In vitro* MRI of tubes containing different concentrations of 19F. Top: merged 1H image/19F SNR maps before and after B1 correction. FA mapping often did not properly converge at the edges of the phantom probably due to partial volume effects (white arrows). These voxels were excluded from the analysis. Bottom: SNR increases linearly with concentration after B1 correction whereas no quantitative analysis would be possible for the uncorrected data.

Discussion: To our knowledge this is the first report on how B1 mapping can be used to obtain quantitative maps for *in vivo* 19F MRI in the presence of inhomogeneous coil profiles. Assuming sufficient 1H background signal and absence of 1H partial volume effects, the workflow presented here can be included in all 19F MRI studies for which a coil is used that has the same B1 profile for the 1H and the 19F channel such as very common and easily constructed single-tuned surface coils. With the obtained quantitative maps we were able to control our implantations but this needs to be confirmed by histology. Our results indicate that in many situations a current inherent conflict (sensitivity vs. quantification) in coil design for *in vivo* 19F MRI can be resolved by little time-consuming 1H FA mapping and appropriate post-processing strategies.

Literature: [1] Ahrens *et al*, Nat Biotech (2005), 23(8):983-987; [2] Insko *et al*, JMRI (1993), A(103):82-85; [3] Gudbjartsson et al. MRM (1995) 34(6): 910–914

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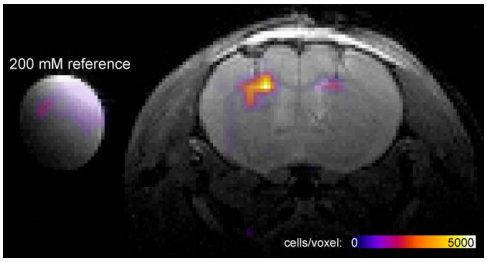

Figure 2 Representative slice of B1 corrected cell/voxel map merged with background 1H image (grey) of a mouse implanted with 300,000 labeled murine neural progenitor cells to the left and right striatum. The same reference tube as in Fig. 1 was used to normalize the B1 corrected rSNR. The map shows the number of cells per 11.3 nL voxel (1H image resolution). The map revealed loss of cells on the right hemisphere either during or after implantation.