SPIO Labeled Cells: Magnetic Resonance Source Quantification by Inverting the Dipole Field

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PURPOSE

An important issue in cell MRI is absolute quantification of magnetic labels. The development of new contrast agents such as superparamagnetic iron oxide (SPIO) particles that can be targeted to specific receptors or internalized into cells[1] could aid new diagnosis and treatment procedures. The local dipole field resulting from the strong magnetic moment surrounding SPIOs creates signal voids (T2* effects) which are very well observed with gradient-echo imaging[2]. Yet, there is no technique available to quantify the amount of label in MRI. Here, we propose the MR-SQUID technique (Magnetic Resonance Source QUantification by Inverting the Dipole field) which combines field mapping and data processing to allow quantification of the magnetic source causing the field shifts.

MATERIAL AND METHODS

Phantom experiments: Ferromagnetic particles were deposited onto paper[3] (Fig. 1-a,b) with a HP-LaserJet 4200n printer and placed into a 1% agarose gel (250 mL). Dictyostelium cells were incubated with anionic SPIO particles for 150 and 60 minutes with an extracellular iron concentration [Fe] of 1 mM and 0.5 mM, leading to an iron load per cell of 5 pg (set 1) and 1.1 pg (set 2) respectively. Cells were dispersed into 3mM Gd doped agarose gel at a concentration of 300 cells for 100µL. Experiments were performed at 1.5T with standard 3D gradient-echo sequences. For the printed dots, data were acquired with a surface copper coil of 13 cm diameter and a matrix size of 100x100x32, a bandwidth per pixel BW of 625 Hz, an isotropic resolution of 1 mm^3, repetition/echo times TR/TE of 50/2 ms, and a flip angle FA of 30°; for the cell experiments, data were acquired with a high temperature superconductive surface coil of 12-mm diameter[4] and matrix size = 135x85x135, BW= 90Hz, isotropic 60 μm^3 resolution, TR/TE=113/13 ms and FA=69°. Full-echo readouts were systematically employed.

Data processing: 1) A high pass filter was applied to the complex data to remove the background field. For each voxel, the mean complex number within a n=7 voxel-diameter sphere was calculated, its phase was removed from the initial phase before conversion into magnetic field shifts. 2) A mask at ~10 times the noise level was applied. 3) For each voxel, the field was fitted to a dipole field $(3\cos^2(\theta)-1)/4\pi r^3$ (θ=orientation along B0, r=distance from sphere center) over the same n=7 voxel-diameter spherical region with weighted linear least squares, considering a weight proportional to the masked signal intensity map, and finally converted either to magnetic moment or iron mass[5]. Error sum-of-square (ESS) and Pearson's R2 coefficient of regression maps were also computed.

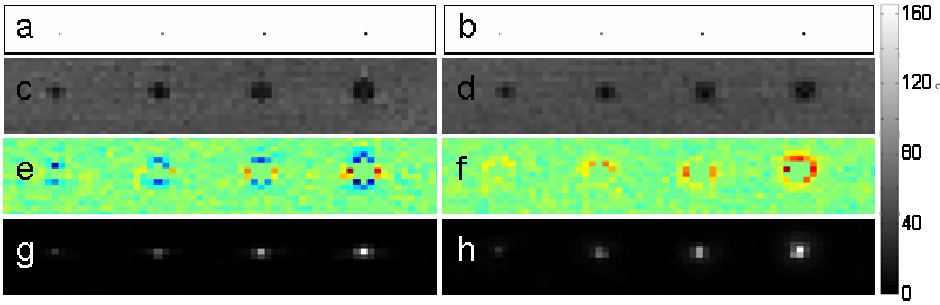

Fig. 1: Printed dots from 2 to 5 pixels square at 300 dpi (a,b); Proton magnetization image (c: coronal, d: axial); Masked filtered field map showing the dipolar pattern (e: coronal, f: axial); Magnetic moment image (g: coronal, h: axial, color bar in $nA.m^2$).

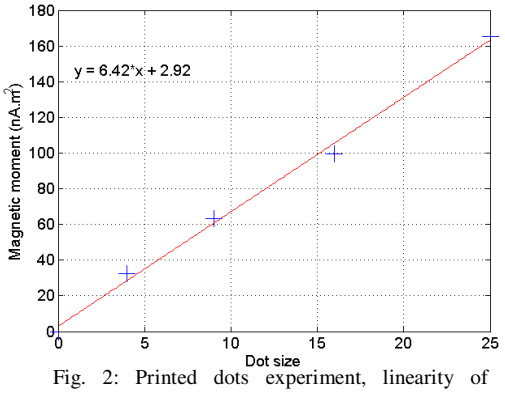

Fig. 2: Printed dots experiment, linearity of magnetic moment as a function of dot size.

RESULTS

A SNR ~30 was obtained for both setups. Proton magnetization images (Fig.1,3) show signal voids at dipole locations as expected. Local field shift maps exhibit a dipolar pattern (both shown for coronal, for which up-down direction is along B0, and axial, normal to B0). Magnetic moment maps display focal hypersignal at dipole locations with zero-background regions. At dipole locations, a fairly good correlation R2 (~0.45) and lower ESS was observed. Fitted magnetic moment values show linearity with the printed dot size (Fig. 2) with a slope of 6.4 $nA.m^2$/pixel printed at 300 dpi.

For 10 manually selected cell locations exhibiting higher local magnetic moment, a mean value of 0.396±0.064 and 0.097±0.041 $pA.m^2$/cell was obtained for sets 1 and 2, respectively, corresponding to 4.98 and 1.14 pg of iron/cell.

DISCUSSION AND CONCLUSION

A novel magnetic source quantification technique based on MRI was presented to measure cell labels. Magnetic field was mapped with gradient-echo images and processed in a 'positive contrast' way for absolute quantification of the dipole magnetic moment. Contrarily to off-resonance visualization techniques[5], a posteriori correction makes the method robust against slow spatial magnetic field variations.

A simple printed phantom was realized to demonstrate linearity of the proposed approach and dedicated hardware was used to obtain high resolution SPIO-labeled cell images with a superconductive RF coil at 1.5T. Consistent iron content was obtained for both tested sets of cells calibrated with single cell magnetophoresis and electron paramagnetic resonance[6]. Both signal intensity and phase were used to fit the magnetic moment. The masking/weighting procedure allowed limitation of signal void regions influence where the measured field suffered from higher uncertainty and non-linear effects with respect to the discretized dipole model used here. The field-deconvolution kernel size covered slightly more than the observed signal voids and larger kernels (n) did not improve the results as the field vanishes quickly with the distance. Spatial resolution was adapted to get isolated dots/cells and apparent signal voids.

The technique should be easily transferable in vivo for focal defect quantification within homogeneous organs. Beyond simple detection, it would allow quantification of labeled cells, monitoring of cell migration and division or quantification of targeted agents.

REFERENCES

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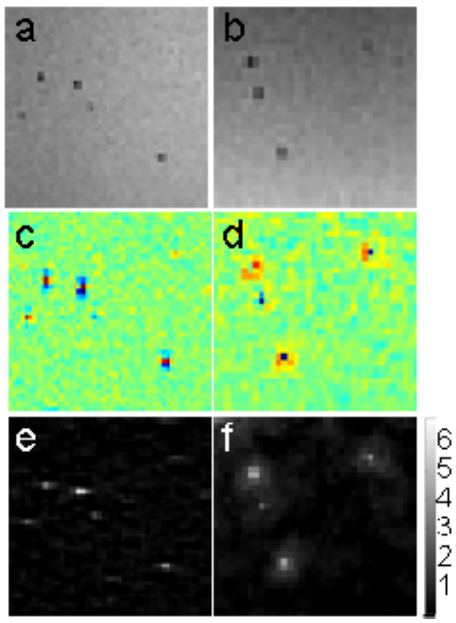

Fig. 3: 5 pg-loaded cells, proton magnetization image (a: coronal, b: axial); Masked filtered field map showing the dipolar pattern (c: coronal, d: axial); Iron mass image in pg (e: coronal, f: axial).