Detectability Threshold of Single SPIO Loaded Cells Using FIESTA

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Introduction

MRI of superparamagnetic iron oxide (SPIO) tagged cells has become a useful tool for studying cell trafficking in vivo in animals and humans. Little is known, however, about the detectability threshold of SPIO labeled cells. Recently, we have demonstrated that single SPIO labeled cells can be detected using the SSFP pulse sequence FIESTA (Fast Imaging Employing Steady State Acquisition) [1]. In the current abstract, we utilize the single cell imaging paradigm to develop a relationship between image resolution, SNR, and minimum SPIO required for single cell detection with the FIESTA pulse sequence.

Methods

Simulations: Numerical simulations of FIESTA signal amplitudes, for voxels containing a single SPIO loaded cell, were performed using the dipolar field offset surrounding a SPIO loaded cell [2], and the known off-resonance signal response for balanced SSFP imaging [3]. FIESTA signal amplitude, estimated from numerical integration of the complex magnetization within the voxel, was predicted for different masses of Fe contained within the cell (m_{Fe}) and resolution.

Cell Culture: THP-1 cells, a human macrophage cell line, were labeled with SPIO nanoparticles (SHU 555A, Schering AG). SPIO uptake into THP-1 cells was varied by incubating at different SPIO concentrations (279, 112, 45, 11, 3μgFe/ml) for 24 hours. To assess cellular Fe uptake, inductively coupled plasma (ICP) mass spectrometry was performed. To facilitate MR and optical imaging, cells were placed in a single plane sandwiched between two layers of 8% w/w gelatin in an optically transparent plastic micro-well (inner diameter 7mm).

MR and Optical Imaging: MRI was performed on a 1.5T GE CV/i MR using a custom-built gradient coil (inner diameter 12cm, maximum gradient strength 600mT/m and peak slew rate 2000T/m/s) and a customized solenoidal radiofrequency coil (1cm diameter, 1cm length). Samples were scanned using 3DFIESTA (TR/TE 7.8/3.9ms, flip angle 60°) at three different resolutions (100x100x100μm, 100x100x200μm, 200x200x200μm). Optical imaging was performed on an Olympus IX50 inverted microscope equipped with a Sony 3CCD color digital camera. 25 bright field photomicrographs of each cell sample were taken using a high-powered objective in order to distinguish between single cells and clusters of two to three cells. The complete field of view was reconstructed by overlapping the photomicrographs to produce a collage.

Correlative MR and Optical Imaging: For each cellular Fe loading, MRI cell patterns (created by SPIO induced signal loss and visualized as discrete "black holes" on FIESTA images) were overlaid onto cell patterns from optical collages. For each discrete area of signal loss corresponding to a SPIO labeled cell or multiple cells, the signal difference between the signal from the central voxel of the void (S_{cell}) and signal from gel containing no cells (S) was calculated ($\Delta S = S - S_{cell}$) and correlated with the amount of Fe in the voxel.

Results

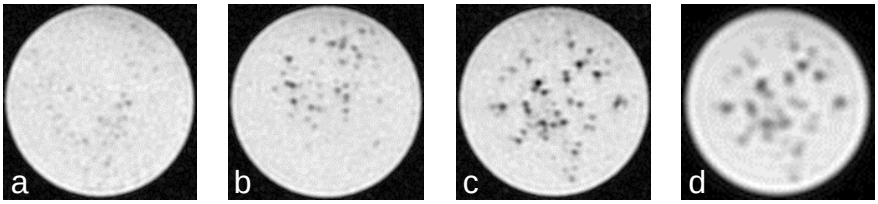

FIG. 1

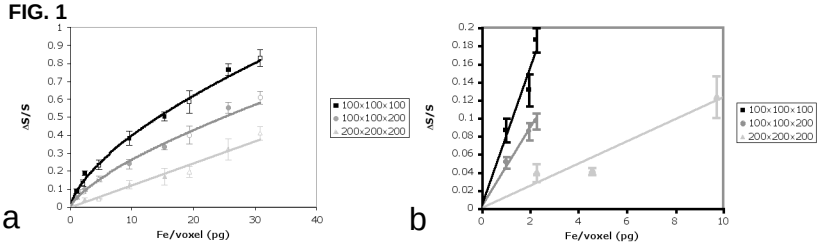

FIG. 2

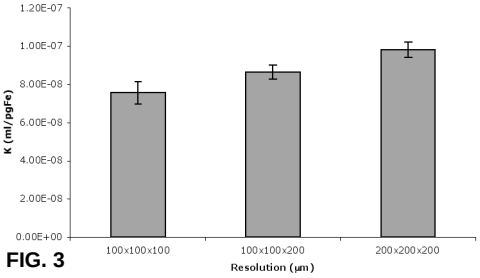

FIG. 3

Numerical simulations of the FIESTA signal amplitude for voxels containing a single SPIO loaded cell predict an initial linear increase in fractional signal loss (ΔS/S) with increasing m_{Fe}, and eventual deviation from linearity as ΔS/S saturates toward unity at higher m_{Fe} (data not shown). The slope of the linear region is inversely related to the voxel volume. Figure 1 (a)-(c) show FIESTA images of phantoms containing cells with increasing m_{Fe} (2.3, 9.7, 25.6 pgFe/cell respectively). Voxels containing both single and multiple cells appear as discrete signal voids which become more evident as m_{Fe} increases. Figure 1 (c) and (d) are scans of the same phantom at two resolutions (100x100x200μm and 200x200x200μm respectively) and demonstrate the effect of resolution on cell detectability. Figure 2 (a) is an experimental plot of ΔS/S versus m_{Fe} for various resolutions derived from analyzing voxels containing one (solid symbols) and two (open symbols) SPIO loaded cells/voxel. Figure 2 (b) is an enlargement of Figure 2 (a) showing the linear region for all three resolutions which occurs at low m_{Fe}. The slopes in Figure 2 (b) are inversely proportional to the voxel volume, as illustrated in Figure 3 through comparison of the slopes, which have been normalized by the voxel volume.

Discussion and Conclusions

Both numerical simulations and experimental results indicate that a linear relationship exists between ΔS/S and m_{Fe}, provided that the mass of SPIO iron within the cell is sufficiently small. Furthermore, signal loss within voxels containing either single or multiple cells per voxel produced the same fractional signal loss, indicating a dependence of ΔS/S on the total mass of iron, but not the distribution of iron, within the voxel. For small m_{Fe}, the linear relationship between ΔS/S and m_{Fe} is inversely proportional to the voxel volume. This can be expressed as: $\frac{\Delta S}{S} = K \frac{m_{Fe}}{\Delta x^3}$, where K is the normalized slope from Figure 3, calculated to be $8.68 \times 10^{-8} \pm 4.6 \times 10^{-9}$ ml/pgFe and Δx^3 is the voxel volume in ml. Given that CNR can be obtained from the product of ΔS/S and image SNR, and that a CNR of 5 is required for detection according to Rose's criterion, the minimum m_{Fe} can be calculated for any given resolution and SNR. We believe this work will greatly simplify the design of single cell detection experiments, since the optimal resolution and required SPIO loading levels may be derived using only a measure of tissue SNR for any specific combination of RF coil and field strength.

References: [1] Foster-Gareau, MRM 49:968 (2003), [2] Bowen, MRM 48:52 (2002), [3] Freeman R, Hill HDW, JMR 4:366 (1971)