Relaxometry model for spherical perturbers using balanced SSFP: Application to quantification of iron-oxide labeled cells

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Introduction

Magnetic resonance microscopy using magnetically labeled cells has been used to study a variety of cellular events in medical research including stem and inflammatory cell migration, brain ischemia and cancer. The method uses high resolution MRI to detect either single or groups of cells labeled with super-paramagnetic iron-oxide (SPIO). To date, the majority of studies using a number of imaging strategies involve a qualitative assessment of the hypo- or hyper-intensities observed in tissues containing labeled cells. Qualitative measures of cellular migration have limited use since these preclude assessment of the relative effectiveness of pharmacological interventions, of adequate stem cell homing, or of inflammatory response intensity changes typically associated with the progression of pathology.

In this work, a quantitative theory of the relaxation rate enhancement applicable to SPIO loaded cells is developed for the balanced steady state free precession (b-SSFP) sequence. This sequence (also known as FIESTA or TrueFISP) is investigated since it has previously been shown to provide exceptional sensitivity to SPIO loaded cells [1], high SNR efficiency, and a spin-echo like insensitivity to background off-resonance [2]. An analytic expression of the relaxation rate enhancement from multiple overlapping dipolar fields is first developed, validated using numerical simulations of the b-SSFP signal response, and tested experimentally using a phantom model of SPIO loaded cells. We believe this model will eventually be used to facilitate the generation of quantitative maps of targeted cell populations.

Theory

The NMR signal at the readout time (TR/2) for b-SSFP is well described as a spin-echo, with the spin echo refocusing along either the +y' or –y' axis of the rotating frame [2]. The specific axis for spin-echo formation depends upon the local off-resonance frequency of the NMR signal, and alternates direction for adjacent off-resonance bands having full width defined by 1/TR. Neglecting diffusion, a valid assumption for SPIO loadings in excess of 0.1pg/cell [3], the phase pattern within a voxel containing an SPIO loaded cell will approximate a series of step function phase reversals, or *shells* of magnetization, with signal refocused along opposing directions (see Fig. 1). The off-resonance contour lines that separate shells appear with 1/TR separation at locations defined by the dipolar field equation. Adopting this shell model, and neglecting reduction of the magnetization magnitude at shell boundaries [2], an analytic description of the signal from a voxel containing a single SPIO loaded cell is developed. This involves subtraction of the volume for shells having signal refocused in the -y' direction, relative to that of shells with signal refocused in the direction of the on-resonance signal (+y'). The analytic solution predicts a linear change in the fractional signal decay due to the presence of an SPIO loaded cell, $S/S_0 = 1 - 0.2566\gamma \cdot LMD \cdot TE$, where *TE* is the echo time, and LMD is the local magnetic dose, a quantity proportional the concentration of SPIO [3]. Extending this solution to describe the signal from voxels containing multiple cells, by assuming the independence of signal effects from each dipolar field perturber, the first order differential solution of the fractional signal loss is as follows, $S/S_0 = \exp\{-R \cdot TE\}$, with mono-exponential signal decay occurring at the rate $R = 0.2566\gamma \cdot LMD$.

Methods

Numerical simulations of the b-SSFP signal response to SPIO loaded cells were performed within MATLAB through numerical integration of the intra-voxel magnetization. These were achieved using the diffusion-free b-SSFP steady state solutions [2], and the solution for the dipolar field offset surrounding a SPIO loaded cell [3]. The predictions for multiple perturbers were confirmed experimentally using phantoms with 5µm spherical polystyrene beads uniformly suspended in agar gel, and Gd-DTPA concentrations of 9 and 11 mM. The Gd concentrations were chosen to mimic the dipolar field offsets surrounding SPIO loaded cells for the lower portion of typical loading levels (0.116 pg and 0.130 pg of SPIO respectively). Phantoms containing bead rather than cellular suspensions were used to enable more precise testing of theoretical predictions. All imaging was performed at 4T on a Varian whole body scanner using a 2D b-SSFP sequence. LMD was estimated from calibration of R_2* with theory [3]. R was estimated from multiple acquisitions with varied TE (5-25 ms), and mono-exponential fit to the signal decay.

Results and Discussion

Fig. 2 shows simulations of the fractional signal decay versus echo time for a single SPIO loaded cell (full simulation), with gradient echo simulations shown for comparison (SPGR). The predicted linear signal decay is observed for each curve. Shell model predictions agree within 10% of those from numerical simulation, and have excellent agreement with simulations that discard magnitude information (phase only simulation). This suggests the contrast mechanism for b-SSFP with SPIO-loaded cells is vector cancellation of magnetization between sub-voxel shells, rather than magnitude banding between shells (magnitude only simulation). Fig. 3 shows predictions of the b-SSFP relaxation rate enhancement, R, as a function of LMD for the shell model, simulations, and experimental results. Excellent agreement between simulations and experiment is observed. Deviation from shell model predictions are consistent with that observed in Fig. 2, and result both from neglecting the effects of magnitude banding, and violation of the independent perturber assumption. Simulations of this discrepancy for a range of bead diameters, [Gd] and T1/T2 ratios (not shown) indicate that shell model predictions of R consistently underestimate the measured value by 50%, and so this correction value is adopted.

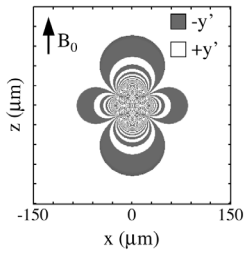

Figure 1: phase shells of refocused magnetization

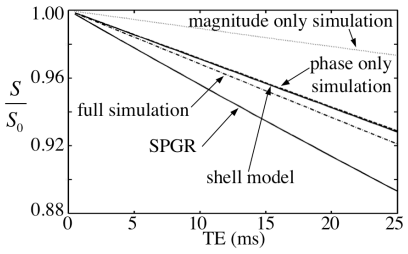

Figure 2: Simulated single particle signal decay

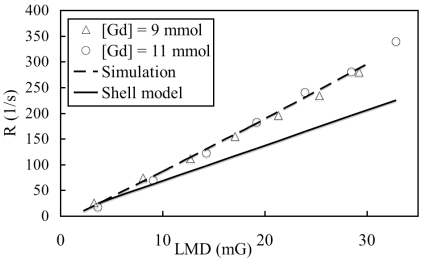

Figure 3: b-SSFP decay rate with varied LMD

Conclusion

A theoretical model describing the b-SSFP relaxation rate enhancement produced by SPIO loaded cells has been developed and validated using both numerical simulation and experimental measures involving phantoms. The dominant contrast mechanism for visualizing SPIO loaded cells has been identified as vector cancellation of magnetization within sub-voxel shells having opposing phase. We believe the application of this theoretical approach to studies involving the migration of SPIO loaded cells will eventually enable the generation of quantitative maps of cellular density, with excellent sensitivity and specificity to SPIO labeled cells.

References

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