Diffusion is a Major Determinant of Contrast in SSFP-Based Single Cell MRI: A Theoretical and Experimental Study

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Introduction: Recent work by our group demonstrates the feasibility of detecting single superparamagnetic iron oxide (SPIO) labeled cells, both in vitro [1] and in vivo [2]. Most groups working in this field have used spoiled gradient echo, or SPGR, pulse sequences for iron-based cellular MRI; our group has established the importance of refocused gradient echo, or SSFP, sequences. We have shown that SSFP sequences have greater cellular detection sensitivity than SPGR sequences [3], but the basis for this observation has not been fully understood. Simulations of signal loss in SSFP images due to single SPIO-loaded cells have been based on static dephasing effects and have neglected diffusion effects [1,4]. Here, we hypothesize that the large field distortions surrounding SPIO-loaded cells lead to strong field gradients and non-negligible diffusion effects in SSFP. Using the equations developed by Kaiser [5] to predict the effect of a constant diffusion gradient on the SSFP signal, we simulated the signal loss due to a single SPIO-labeled cell, including both static dephasing and diffusion effects. Previous analyses based on Kaiser's diffusion-weighted SSFP (dwSSFP) theory have made simplifying assumptions, such as only one of the two signals ($S(TR^+)$, $S(TR^-)$) being measured, and uniformly distributed precession angles between 0 and 2π [6,7], but for cellular imaging these assumptions are not valid, and the full Kaiser series expansion is necessary. We developed a full Kaiser dwSSFP simulation, and compared results to experimental contrast due to single SPIO-labelled cells and beads in gel. Results of this comparison indicate that we are now accurately modeling SSFP-based cellular MRI contrast.

Methods: Each voxel was subdivided into isotropic subvoxels of linear dimension 3μm, and the vector sum of the signals from the subvoxels was used to estimate the total complex signal from the voxel. The local magnetic field (B) and gradient (G) of the magnetic field resulting from the field perturbing effect of the SPIO loading were calculated at the centre of each subvoxel. Within a given subvoxel, the local magnetic field was assumed to be uniformly distributed from B-Gdx/2 to B+Gdx/2 (where dx is the subvoxel dimension). The first seven terms (k = -3 to 3) in the Kaiser expansion were used to calculate the signal and a second order Taylor expansion of the F_p term in the Kaiser model was used to avoid divide-by-zero errors. The signal was calculated at an echo time of TE = TR/2 in all cases. We also included the effect of rf pulse chopping, to properly simulate the signal from the SSFP sequence implementation that we used (FIESTA, GE Healthcare, Milwaukee, WI), and we averaged over all possible locations of cell within voxel. The theoretical model was compared with in vitro experiments on SPIO-labeled macrophages loaded with varying amounts of the SPIO-based contrast agent Resovist (SHU 555A, Schering AG, Berlin) and placed in gelatin. An additional experimental study was conducted using 8.4 μm polystyrene-SPIO beads (COMPEL, Bangs Laboratory, Fishers IN, USA), each of which contained a closely controlled amount of iron (9.4 pg). Beads were sparsely distributed in gelatin doped with combinations of Mn and Ni ions to control the R1 and R2 of the gel [8]. Theoretical predictions of contrast between the voxel containing the iron-loaded point perturber and the background signal, (ΔS/S), were compared to experimental measurements made with matching parameters of diffusion coefficient D, relaxation rates R1 and R2, and pulse sequence parameters TR, TE, and flip angle.

Results: Both static and diffusion-mediated mechanisms for signal loss can be seen in Figure 1. Using the static dephasing model, the amplitude of the signal is essentially constant over the voxel and signal loss occurs as a result of alternating phase bands (see Fig 1a: this is referred to as the shell model by Lebel [4]). Using the Kaiser expansion but setting the diffusion coefficient to zero (Fig 1b), the outer regions of the voxel show similar behavior to the shell model, but the inner subvoxels, which contain a large variation in phase within a subvoxel, show substantial reduction in signal magnitude. Despite this obvious difference in intra-voxel detail, the total voxel signal is very similar between the shell model and the Kaiser D=0 model. Introducing non-zero diffusion into the Kaiser model simulation leads to smoother phase transitions and a significantly enlarged region of signal magnitude loss due to diffusion losses (see Figure 1c). The actual diffusion-weighting in the SSFP signal will depend not only on iron mass per cell, but also on D, R1, R2, TR/TE and flip angle, as Kaiser and others have pointed out [5,6,7]. We therefore simulated signal loss due to non-zero diffusion, using the full Kaiser model, for typical gel and brain tissue parameters and sequence parameters. Figure 2 shows that the diffusion influence is significant, accounting for more than a doubling of single cell contrast at typical cell loadings, and that the Kaiser diffusion model fits the experimental data quite well at low SPIO loading levels (<20pgFe/cell), with dramatically better accuracy than the static dephasing model. When simulated signal loss is plotted against experimental signal loss for a single SPIO loading level (~9.5 pgFe) in a fixed 100μm isotropic voxel but varying parameters of R1, R2, D, TR/TE, flip angle, we note a strong correlation with Pearson correlation coefficient of $r^2 = 0.9603$ (see Figure 3).

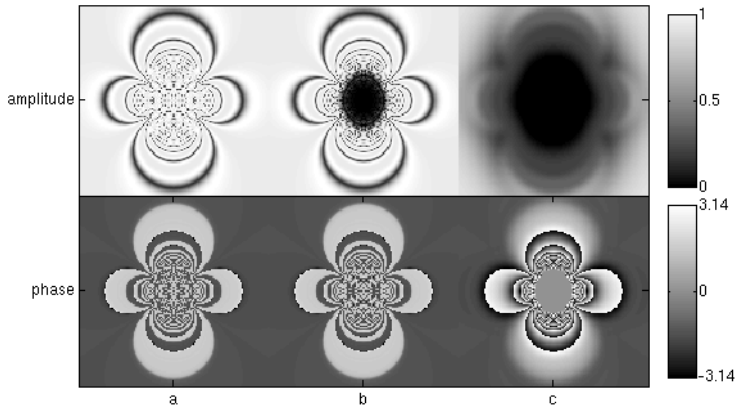

Figure 1: Simulated signal amplitude and phase (0,-3 to 1,3) for a 9.4 pg COMPEL bead at the centre of a 100x100x100 μm voxel, divided into 128x128x128 subvoxels. Taken on a central slice, B_o in the vertical direction. (a) assumes static dephasing, (b) is the zero diffusion Kaiser model and (c) is the Kaiser model with a diffusion coefficient of $1\mu m^2/ms$ ($R1/R2=2/11s^{-1}$, TR/TE=7.6/3.8ms, $\alpha = 30^o$).

Conclusion: We have successfully simulated the diffusion effect in SSFP-based cellular MRI, and our results closely match experimental measurements of single cell contrast in FIESTA images. These results provide a strong theoretical basis for explaining the increased sensitivity of SSFP-based cellular MRI over SPGR-based methods, and for predicting alterations in single-cell contrast due to changes in diffusion coefficients, relaxation rates, sequence parameters and field strength.

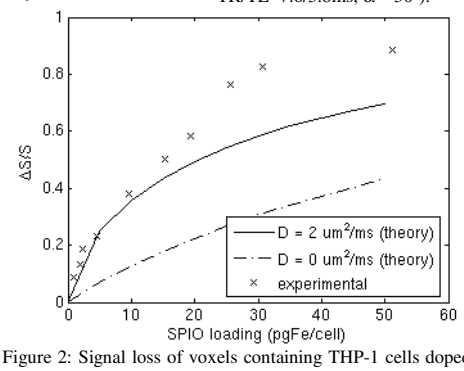

Figure 2: Signal loss of voxels containing THP-1 cells doped with Resovist (in pg of iron) in gelatin imaged at 100x100x100 μm resolution ($R1/R2 = 0.3544/1.3\ s^{-1}$, TR/TE = 7.8/3.9 ms, $\alpha = 60^o$)

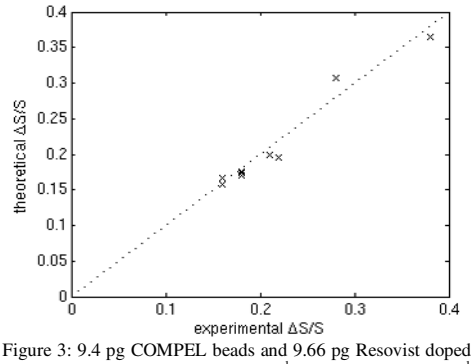

Figure 3: 9.4 pg COMPEL beads and 9.66 pg Resovist doped cells for R1 values ranging 0.5 to 5 s^{-1}, R2 from 1.3 to 18.9 s^{-1} TR/TE from 7.1/3.6 ms to 7.8/3.9 ms and flip angle 35° or 60°

References:

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