Optimized MRI parameters for positive contrast detection of iron-oxide labeled cells using double-echo Ultra-short echo time (d-UTE) sequences

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Introduction: The use of super paramagnetic iron oxide particles (SPIO) has found great applications in single cell detection *in vivo* as it allows detecting their homing in a complete non-invasive way [1-3]. Generally, negative contrast based sequences that make use of the strong T_2-relaxivity of SPIO are employed to track the labeled cells, shown as dark spots on the image. However, many other phenomena will also locally induce local loss of coherence resulting in confounding dark dots hard to distinguish from the labeled cells. Recent studies show that positive contrast can be created by the use of on-resonance saturation of the water line [4,5], off-resonance irradiation [6] or twisted projection reconstruction delivering an ultra-short-echo-time sequence (UTE) [7]. In particular, in the latter one, a double-echo (d-UTE) sequence makes use of the subtraction of two images (called d-image), from which the first is obtained from the free induction decay (FID) and the second is coming from the first echo. In this way, the signal from the tissue can be canceled, which results in bright spots for SPIO-labeled cells. By means of simulations, this study gives quantitative results of the advantages of using a d-UTE sequence over conventional T_2*-based methods for the detection of SPIO labeled particles in the brain at various field strengths. It also establishes optimal parameters to be used at clinical field strength (1.5T) or on an experimental scanner (9.4T).

Materials and Methods: Resovist® was chosen as a SPIO contrast agent and Grey Matter (GM) as the tissue of interest. T_1 and T_2 relaxivity measurements using Resovist® were performed on a clinical 1.5T system (Siemens) and an experimental 9.4T scanner (Varian). The T_1 and T_2 values for GM on both field strengths were used from literature. To discriminate between negative and positive contrast sequences, an RF-spoiled gradient echo (GRE) and d-UTE were considered, respectively. For both sequences, Bloch simulations were performed to calculate steady-state signal intensities of GM with and without SPIO labeling as a function of the repetition time (TR), SPIO concentration ([SPIO]) and echo time (TE). The contrast enhancement (CE) was defined for an optimal TE as the difference between the two calculated signal intensities. In case of the d-UTE, the CE was determined after subtracting the signal intensities calculated from the FID (from 10 µs) and the 1st echo (variable). For the d-UTE and the GRE sequence, the flip angle was chosen as the Ernst angle for the SPIO labeled region and the GM, respectively.

To simulate the effect of the point spread function and particle size, the k-space of 1D-rectangular shapes with diameter D^{GM} = 20 mm and varying diameter D^{SPIO} were calculated through a continuous Fourier Transform (FT), given by S(k) = D*Sinc(D*k). The effect of broadening of the point spread function (PSF) due to T_2-dispersion during acquisition was taken into account by applying a T_2-weighting on k-space ($\exp(-t/T_2)$). Then, 1D-images were reconstructed through a discrete FT with a resolution of 50 µm, which corresponds to 25.6mm FOV and 512 matrix size in k-space. Such resolution can be achieved by means of inserted gradient coils at 1.5T, but it represents an upper limit in terms of SNR. Because typical UTE's have a radial k-space trajectory to shorten the time before the FID can be acquired, the 1D representation was chosen to avoid the need for regridding algorithms that may affect signal intensity.

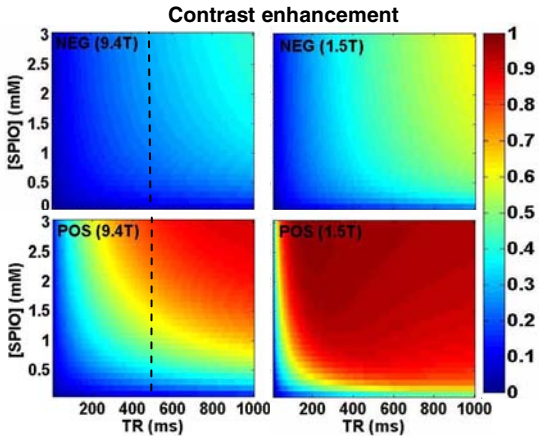

Figure 1: *Contrast enhancement values for negative (NEG) and positive (POS) contrast sequence on different field strengths as function of [SPIO] and TR.*

Results: The relaxivity values measured ($R^2 > 0.98$) for Resovist® were: r_1 = 12.2 $mM^{-1}s^{-1}$, r_2 = 256 $mM^{-1}s^{-1}$ on 1.5T and r_1 = 1.2 $mM^{-1}s^{-1}$, r_2 = 258 $mM^{-1}s^{-1}$ on 9.4T. The difference between 1.5 and 9.4T corresponds very well to findings obtained in theoretical studies [8].

Generally, results show that positive contrast sequences are much more sensitive to slight variations in these parameters (Fig. 1). For instance, when looking along the line TR = 500ms at a field strength of 9.4T, the same contrast is obtained with [SPIO] = 0.3mM in the positive contrast sequence as for the negative contrast sequence at 3mM. Secondly, a large increase in sensitivity was seen when decreasing the field strength from 9.4T to 1.5T.

For TR = 500ms, the true contrast at 9.4T was calculated from 1D-reconstructed images for values of D^{SPIO} between 10 and 500µm. Fig. 2 shows the results for [SPIO] = 0.3, 1 and 3 mM. In contrast to Fig. 1, now the effects of additional T_2-decay during acquisition and the diameter of the SPIO labeled region were taken into account. The contrast obtained in the GRE sequence does not suffer from T_2-decay during acquisition, considering that at high values for D^{SPIO}, the contrast values are the same as in Fig. 1. The effect of T_2 decay in d-UTE is significant (5-10%) for [SPIO] > 1mM. Decreasing the size of the SPIO labeled area has more effect on the contrast when using higher values for [SPIO], as can be seen from the difference in the slopes for the three d-UTE curves at diameters > 200µm. Notice that at a diameter of the SPIO labeled region smaller than 4 times the resolution, the contrast of both sequences decreases rapidly to zero.

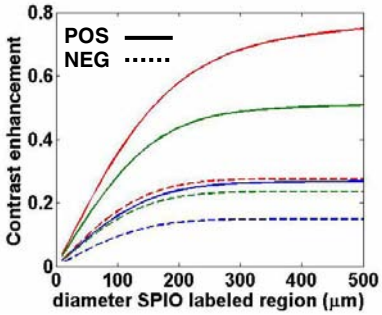

Figure 2: *Contrast enhancement as function of D^{SPIO} and [SPIO] of labeled region at 9.4T. [SPIO] = 0.3 mM (blue), 1 mM (green), 3 mM (red).*

Discussion and conclusion: Bloch-simulations provided a good insight in how contrast in GRE and d-UTE sequences depends on the large variety of parameters involved. Using the d-UTE sequence described in this study as a positive contrast sequence proved to give much better contrast enhancement compared to negative contrast-based sequences. This results from the fact that the d-UTE not only profits from a decrease in T_2, which allows for a shorter second echo time and improvement of tissue cancellation. It also profits highly from the T_1-relaxivity, which causes better contrast in the ultra-short echo images. This also explains the better performance of the d-UTE at 1.5T compared to 9.4T, considering a 10 fold increase in r_1 at the lower field strength. The GRE sequence can reach a similar contrast enhancement, but only for large values of TR. This would however cause a large decrease in contrast efficiency, defined by the contrast enhancement divided by √TR.

The use of a 1D continuous Fourier Transform allowed to simulate both the effect of the diameter of the SPIO labeled region as well as the effect of T_2 decay during echo acquisition. Results showed that although the labeled region is smaller than the image resolution, still contrast enhancement could be obtained, but maximum contrast is only reached for diameters 4 times larger than the image resolution. Because d-UTE uses an echo of the fast decaying SPIO signal to create positive contrast, T_2 decay during acquisition must be taken into account, especially at higher concentrations of SPIO. This effect did not undermine the advantages of using d-UTE over GRE though.

A limitation of this study is that the effect of noise was not taken into account. So far, no difference in contrast-to-noise ratio (CNR) were simulated between field strengths, but the increase in CNR proportional to the field may be an important parameter and could compensate for low values of r_1 at 9.4T. In addition, although off-resonance effects of labeled cells are present beyond the cell boundaries, this effect was left out this preliminary study.

In summary, it has been shown that the use of d-UTE sequences is very promising for the detection of SPIO labeled cells in the brain. Not only does it generate positive contrast which improves detection power, but it also provides better contrast enhancement compared with negative contrast based sequences.

References: [1] Weissleder R, et al. JMRI 1997; 7:258–263. [2] Bulte JW, et al. PNAS 1999; 96:15256–15261. [3] Hoehn M, et al. PNAS 2002; 99:16267–16272. [4] Cunningham CH, et al. MRM 2005; 53:999-1005. [5] Shah SS, et al. ISMRM 2006; 3499.[6] Zurkiya O & Hu X. MRM 2006; 56:726–732. [7] Boada FE & Wiener E. ISMRM 2006; 189. [8] Roch A, et al. J Chem Phys 1999; 110:5403-5411.