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 T2-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 delivery 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 T2*-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. T1 and T2 relaxivity measurements using Resovist® were performed on a clinical 1.5T system (Siemens) and an experimental 9.4T scanner (Varian). The T1 and T2 values for GM on both field strengths were used from literature. To discriminate between negative and positive contrast sequences, an un-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), T1 contrast sequence at 3mM. Secondly, a large increase in sensitivity was seen when decreasing the field strength from 9.4T to 1.5T.

Results: The relaxivity values measured (R2 > 0.98) for Resovist® were: r1 = 12.2 mM-1s-1, r2 = 256 mM-1s-1 on 1.5T and r1 = 1.2 mM-1s-1, r2 = 258 mM-1s-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, 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 [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 T2-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 T2-decay during acquisition, considering that at high values for D300, the contrast values are the same as in Fig. 1. The effect of T2 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.

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 T2, which allows for a shorter second echo time and improvement of tissue cancellation. It also profits highly from the T1-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 r1 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 the 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.

Conclusions: 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.