On the optimal field strength for detection of targeted Gd-based Contrast Agents in Molecular MR Imaging

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Introduction: Molecular Imaging using targeted Contrast Agents (tCA) is a promising tool for early diagnosis purpose, but optimizing the sensitivity and specificity of CA detection remains a challenging issue. Particularly, the T_1 relaxivity of macromolecular paramagnetic CA's (e.g tCA linked to its target) tends to decrease rapidly above 20-30 MHz which raises the question of their efficiency at high field. The purpose here is to investigate theoretically and experimentally the Contrast-to-Noise Ratio (CNR) obtained with a paramagnetic tCA as a function of the field strength B_0, accounting for Nuclear Magnetic Relaxation Dispersion (NMRD) profiles derived from experimental data. A classical model of MR sensitivity is involved to optimize the contrast of a T_1-weighted sequence. This is applied to differentiate water compartments containing either a diamagnetic solution of the molecular target, a free paramagnetic solution of a specific tCA or a paramagnetic solution of the tCA partially bound to its molecular target as imposed by the finite association constant of the reaction.

Theory: In both compartments we assume the water to be in the Fast Exchange Limit [1] between different pools of protons, leading to mono-exponential relaxations. The general formulation of Signal-to-Noise Ratio (SNR) as given in [2] allows theoretical comparison of MR sensitivity as a function of B_0 using appropriate models to describe radiofrequency sample and coil losses. The CNR of the enhancement between two compartments (I and II) is defined as the SNR difference: $CNR = SNR_{II} - SNR_I$. To compare the efficiency of different MR sequences, SNR or CNR are normalized by the voxel volume and the square root of the total scan time. Considering T_1-weighted imaging, the best efficiency is reached for a spoiled gradient-echo (GE) sequence with repetition time $t_R \ll T_1$'s [3] and echo time $t_E \ll T_2$*'s. This leads to the best differentiation between the two compartments if no synergetic T_1 and T_2-effects are considered, which is generally true based on NMRD profiles observations. For such a sequence and a flip angle α, the analytical expression of the transverse magnetization M_T in steady state is: $M_T = M_0 \sin\alpha\,[(1 - E_1)/(1 - E_1\cos\alpha)]\exp(-t_E/T_2^*)$ where $E_1 = \exp(-t_R/T_1)$. The SNR of each compartment is maximized at corresponding Ernst's angles. The CNR is maximized for a particular angle α_{opt} which depends on relaxometric properties of both compartments. Assuming t_E is short enough, the difference between the T_2* effects in both compartments is not significant, leading to the simplified formulation:

$$\alpha_{opt} = \cos^{-1}\left[\left(E_1^{I} + E_1^{II} - 2(1 + E_1^{I}E_1^{II}) + \sqrt{(E_1^{I} - E_1^{II})^2 + 4(1 - (E_1^{I})^2)(1 - (E_1^{II})^2)}\right) \Big/ \left(2(E_1^{I}E_1^{II} - E_1^{I} - E_1^{II})\right)\right]$$

In the present study the sample losses are assumed to be dominant over the RF-coil losses (i.e. the RF sensitivity term [2] does not depend on B_0) and a thermal equilibrium magnetization M_0 increasing linearly with B_0 is considered. Finally a per-pixel bandwidth is set with a linear dependence on B_0, to keep the image quality constant in terms of T_2* and chemical shift artefacts [4].

Material and Method: *In vitro* experiments were performed at 1.5 T (Achieva, Philips, Netherlands) and 4.7 T (a home-made system) using various concentrations of MS-325 (Vasovist®, Schering/Bayer, Germany) and its target Human Serum Albumin (HSA) at room temperature (293 K). Free MS-325 has a small molecular weight (<1kD) whereas in presence of HSA the bound complex becomes heavier (>40kD) resulting in slower motion and an increased rotational correlation time τ_R. Corresponding NMRD profiles were calculated by fitting the SBM theory onto experimental data sets [5], taking into account the finite association constant of the reaction to extrapolate the profiles corresponding to other species concentrations : 5µM <[MS-325]< 5000µM and [HAS] of 60µM or 600µM. Each tCA concentration was studied in pure water (free form) and in the presence of HSA (partially bound form). The contrast was established in comparison with the corresponding diamagnetic solution, i.e. pure water and HSA, respectively. The expected T_1 contrast was derived as $|(T_{1II} - T_{1I})/(T_{1II} + T_{1I})|$. SNR and CNR were computed as a function of the field strength using the above theory for ideally short t_R and t_E. The expected contrast enhancement, defined as $CNR\% = (SNR_{II} - SNR_I)/(SNR_{II} + SNR_I)$, was also addressed to allow experimental comparisons without absolute SNR calibration. SNR's were measured on the central slices of 3D images acquired by RF-spoiled gradient-echo at various α's with $t_R \approx 15$ms. For each sample, the SNR measured as a function of α was fitted to the analytical function $A\sin\alpha\,(1 - E_1)/(1 - E_1\cos\alpha)$ in order to evaluate T_1. SNR measurements were corrected by the corresponding A in order to account for different T_2* losses affecting some samples. Experimental CNR and contrast enhancement were calculated using corrected SNR. A direct comparison between bound and free forms at the same concentration of MS-325 was also calculated to assess the relative efficiency of both species.

Results:

The bound form of Fig.1. (0.25 mM of MS-325 in 0.6 mM of HSA) corresponds to about 72% of effectively bound MS-325 [5]. Fig.2 displays the different samples used in our experiments, evidencing the varying contrast. Experimental measurements are in good agreement with theoretical expectations based on NMRD profiles and signal modelling of the spoiled-GE sequence (Fig. 3). The partially bound form of the tCA was found to be more efficient than the free one at 1.5 T whereas it appeared to be the contrary at 4.7 T (Fig. 4). This is illustrated by the NMRD profiles (Fig.1.) corresponding to 0.25 mM of MS-325.

Fig. 1: Typical NMRD profiles, T_1 contrast and expected CNR at α_{opt} for 0.25 mM of MS-325 in pure water and in 0.6 mM of HSA

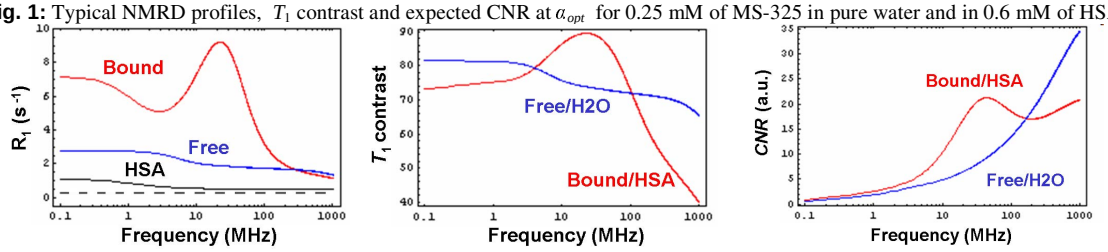


Fig. 2: Typical spoiled-GE image obtained at 4.7 T with α = 12°, t_R = 15ms, t_E = 2.7ms

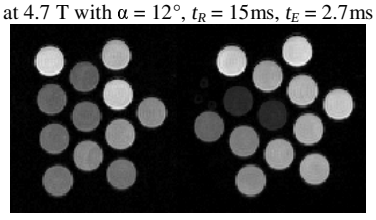
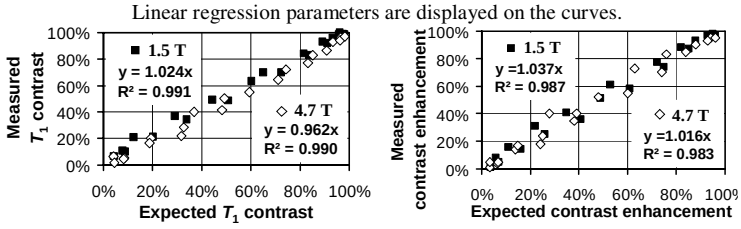
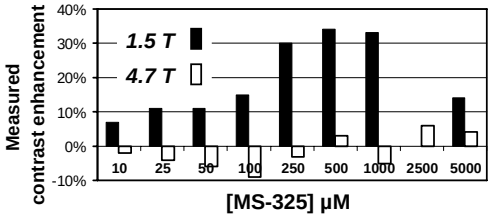


Fig. 3: Experimental T_1 contrast and $CNR\%$ at α_{opt} compared to expected ones. Linear regression parameters are displayed on the curves.



Discussion: The theoretical results of Fig.1 indicate that under some conditions, CE-MRI application on tCA should be done at moderate field strength (~1-1.5 T) rather than at higher field in order to optimize the CNR and benefit from the higher efficiency of the bound form as compared to the free one. This tendency is confirmed for other concentrations of tCA and its target, although limited by the finite association constant which balances in a different manner the free and bound populations in the presence of target. When MS-325 is not efficiently bounded to HSA, leading to a majority of free MS-325 form in the compartment, the corresponding NMRD profile exhibits a less pronounced optimum. Hence the CNR profile is more or less weighted by the free and bound profiles of Fig.1. Finally, absolute evaluation of the CNR gain over field would be possible using simultaneous forward power and flip angle measurements [6]. This would allow a quantitative comparison accounting for different coil geometries and different hardware.

Fig. 4: Bound/Free Experimental $CNR\%$ at α_{opt}



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