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Effect of r_1 and r_2 relaxivity of gadolinium-based contrast agents on the T_1-weighted MR signal at increasing magnetic field strengths

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Most contrast agents for magnetic respnance imaging (MRI) are gadolinium-based T_1 shortening agents. At increasing magnetic field strengths their r_1 relaxivity tends to decrease while the r_2 relaxivity increases. In parallel, at high fields the tissue T_1 times increase and may mitigate the loss in contrast enhancement in T_1-weighted images owing to improved background suppression. In the present work we explored the MR signal for T_1-weighted spoiled gradient echo MRI sequences by simulations at three magnetic field strengths: 3, 7 and 9.4 T. The maximal available contrast enhancement (maxCE) was evaluated in absolute terms with the purpose of assessing how much of the full, underlying magnetization can be exploited, for a wide range of compound properties (r_1, 2–45 $mM^{-1}s^{-1}$; r_2/r_1, 1.2–30). Despite the theoretically predicted loss in r_1 relaxivity at high fields, the same maxCE can be obtained as at low fields if the r_2/r_1 ratio remains unchanged, albeit at the cost of a longer sequence repetition time and 1.5–2 times higher administered doses. For a fixed maximum tissue concentration, there is an optimum field-dependent value for the r_1 relaxivity that yields the greatest maxCE. If the upper bound for the gadolinium concentration is 2 mM, the greatest maxCE is found for compounds with a r_2/r_1 ratio of 1.2 and an r_1 relaxivity of 20.5 $mM^{-1}s^{-1}$ at 3 T, 18 $mM^{-1}s^{-1}$ at 7 T and 16.5 $mM^{-1}s^{-1}$ at 9.4 T. For compounds that do not change their r_1 relaxivity or r_2/r_1 ratios, the necessary dose can be reduced by 10–15% owing to the improved background suppression at higher fields.

Keywords: MRI; gadolinium; signal optimization

1. INTRODUCTION

Gadolinium-based T_1-contrast agents are used in about 30% of all clinical magnetic respnance imaging (MRI) scans at magnetic field strengths of 3 T and below. By use of these agents, areas of blood–brain barrier disruption can be identified in cancer and in active multiple sclerosis lesions, tumor perfusion can be studied by dynamic contrast enhanced imaging, or the tissue contrast of joints can be enhanced, just to name a few of their many clinical uses. Several responsive 'smart' MRI contrast agents that are sensitive to physiological or metabolic tissue status related to local enzyme activity, pH or ion concentrations, are also based on the T_1 shortening effect of gadolinium (1,2).

Although most clinical scanners operate at 3 T and below, clinical high-field MRI systems are becoming increasingly available. Therefore, the question arises whether existing gadolinium (Gd^{3+}) agents will remain as useful as they are at low fields, or if new agents need to be specifically tailored to fully exploit the benefits of high-field MRI. Generally, at increasing magnetic field strengths, the relaxing properties of an agent change. The r_1 relaxivity (expressed in $mM^{-1}s^{-1}$) tends to decrease and the r_2 relaxivity to increase (3–5). In other words, an overall relative signal loss is expected in contrast-enhanced MRI at high field since the agent's capacity to shorten T_1 is reduced and since the agent-induced T_2 decay becomes more pronounced. On the other hand, at higher field strengths, the T_1 relaxation time of the tissue itself is increased (6,7), and may potentially mitigate the lower r_1 relaxivity since the background suppression is improved when using short repetition times.

In the present work we investigated the MR signal in the human brain for T_1-weighted spoiled gradient echo MRI sequences in the absence and presence of T_1 shortening contrast agents by simulations of three magnetic field strengths: 3, 7 and 9.4 T. The maximal available contrast enhancement was evaluated in absolute terms with the purpose of assessing how much of the full, underlying magnetization (proton density) can be exploited for a given combination of compound properties and sequence parameters at various fields. The enhancement was explored for contrast agents with different r_1 values (2–45 $mM^{-1}s^{-1}$) with upper bounds given by theoretical predictions based on physico-chemical modeling (3). Signal loss owing to T_2 decay was also taken into account, and the r_2/r_1 relaxivity ratio was varied between 1.2, which is a typical value at 3 T, and 30, which has been observed at 9.4 T in the presence of human serum albumin (3,5). Since the contrast enhancement depends not only on the relaxivity properties of the compound, but also on the local tissue concentration of gadolinium, theoretically the same maximal

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available contrast enhancement (maxCE) can be observed by simply increasing the dose of the contrast agent. In practice, owing to T_2-related signal decay, maxCE is limited, and therefore a trade-off exists between increasing the contrast owing to T_1-related effects that increase the contrast and T_2 effects that decrease the contrast. Therefore, we performed the optimization of maxCE along three different strategies. The first strategy aims to maximize maxCE for the widest possible range of observable gadolinium concentrations, and hence the efficiency of a particular compound. The MR sequence parameters obtained by this approach minimize the probability of observing 'contrast voids' that occur when T_2 decay at high Gd^{3+} concentrations diminishes the T_1-weighted MR signal. This approach is of particular interest for the pre-clinical development of new contrast agents, including toxicity studies when the highest possible amount of compound needs to be administered and for the development of high-field measurement protocols. The second strategy optimizes maxCE for a fixed range of gadolinium concentrations, and can be used to increase the sensitivity. Hereby the detection of minute changes in the agent concentration is improved and this strategy is also highly relevant for low-dosing regimens in a clinical setting. Finally we also optimized maxCE for a fixed set of MR sequence parameters, in order to make the best use of an agent in the case of a preferred imaging approach or to explore responsive contrast agents with variable relaxivity properties.

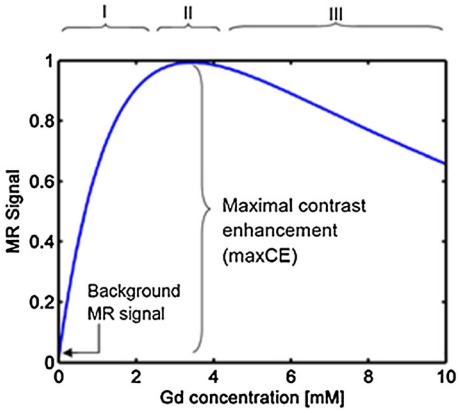

Figure 1. T_1-weighted MR signal as a function of gadolinium concentration. Three ranges can be identified: I, linear and nonlinear signal increase; II, plateau; III, T_2 or T_2*-related signal decay. The maxCE corresponds to the maximal contrast enhancement and is defined as the difference in MR signal between the unenhanced background signal level and the signal level of enhanced tissue at the plateau, II.

2. RESULTS

2.1. The T_1-weighted MR Signal and Contrast Agents

The exact relationship between the observed MR signal in a T_1-weighted gradient echo (GE) sequence and the gadolinium concentration is nonlinear and depends on MR-related factors (magnetic field strength, sequence parameters) and the properties of the contrast agent (r_1 and r_2 relaxivities). Three regimes can be identified for this relationship (Fig. 1). During the first regime, T_1 weighting is dominating and the MR signal increases from it suppressed, unenhanced background level to a plateau value. The increase with the Gd^{3+} concentration is initially linear then becomes nonlinear. In the next regime, the MR signal reaches its maximum value, which depends on the repetition time (*TR*), the flip angle (FA), the Gd^{3+} concentration and the r_1 and r_2 relaxivities of the compound. Beyond this point, the MR signal starts to fall off, owing to T_2*-related signal loss (Fig. 2). How rapid the signal diminishes with increasing Gd^{3+} concentrations depends on the echo time (*TE*), and the tissue T_2* and the r_2 relaxivity of the compound. Only the first two regimes are useful for contrast-enhanced MRI. As shown in Fig. 2, substantial signal loss occurs in presence of signal decay at high Gd^{3+} concentrations. As described in the Experimental section, we approximated the T_2*decay time by T_2 in the present work. This is equivalent to neglecting the dephasing effect of the magnetization that can be refocussed by a spin-echo based MR sequence.

The MR signal difference between fully enhanced tissue at the plateau and the unenhanced background we term the maxCE of the T_1-weighted measurement. It corresponds to the maximal available signal enhancement and captures how much of the full, underlying magnetization (proton density) can be exploited for a given combination of sequence parameters and compound properties. It can be noted that we avoid normalization to the background magnetization that would have given us a measure of the relative signal enhancement. This choice has several

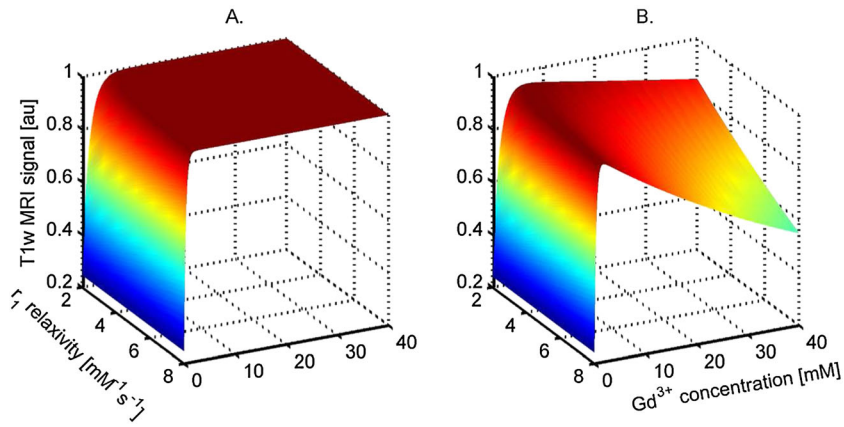

Figure 2. T_1-weighted MR signal (*z*-axis) in the presence of contrast agents with increasing gadolinium concentrations (*x*-axis) and increasing low-range r_1 relaxivity values (*y*-axis). (A) Only r_1 dependence is taken into account. The full MR signal is attained for high [Gd^{3+}]. (B) Both r_1 and r_2 dependency of the MR signal is shown, assuming an r_2/r_1 ratio of 1.2. The MR signal falls off owing to T_2 decay at high [Gd^{3+}].

advantages: it permits the interpretation of the values obtained in terms of MR magnetization; maxCE does not inflate for situations of strong background suppression; and the dependency on the intrinsic tissue T_2* (T_2), which is shorter at higher fields, is maintained.

The maxCE depends on the magnetic field strength, since the intrinsic tissue T_1 is longer and the T_2* and T_2 times are shorter at higher fields. For a fixed triplet of sequence parameters (*TR*, *TE* and flip angle) and unchanged relaxivity properties of the contrast agent, the maxCE increases with increasing field strength since background suppression is more efficient. On the other hand, this boost is limited owing to increased T_2* or T_2 effects at high fields that tend to decrease maxCE.

In the following, we used this measure along three optimization strategies, each one of which may find practical use in different settings: maximization of maxCE in order to observe the widest possible range of Gd^{3+} concentrations, optimization for a fixed contrast agent concentration in order to get the greatest sensitivity for small variations in the Gd^{3+} concentration, and optimization for a fixed MR sequence repetition time, in order to explore contrast agents with different relaxivity properties.

2.2. Maximizing for the Observable Range of Gadolinium Concentrations

In order to observe the widest possible range of Gd^{3+} concentrations, full use of the available maxCE across all concentration levels needs to be ascertained. Different hypothetical compounds with varying relaxivity values were investigated. For each pair of r_1 and r_2 relaxivities, the *TR* and flip angle (FA) were adapted so that the highest possible Gd^{3+} concentration could be measured at the highest available maxCE (Fig. 3). The optimal FA was always 90°, while the *TR* was varied to achieve the greatest available maxCE. The observable range of Gd^{3+} concentrations varied with both r_1 and the r_2 /r_1 ratio, as indicated by the 'triangular' shape of the variation of the maximal Gd^{3+} across the different relaxivity values (Fig. 3A–C). For compounds with high r_2/r_1 ratio, prolongation of *TR* was advantageous to regain the T_2 driven loss in contrast by increasing the T_1 related contribution (Fig. 3D–F). Accordingly, longer *TR* times were required to achieve the highest maxCE at high field strengths. Slightly higher gadolinium concentrations were required at low fields to achieve the highest maxCE due to reduced background suppression.

Using compounds with low r_1 relaxivity, higher Gd^{3+} amounts can be administered without reaching the MR signal plateau. For instance, at 9.4 T compounds with a r_1 relaxivity of 3 $mM^{-1}\,s^{-1}$ and an r_2 /r_1 ratio of 1.2, require that 11.2 mM of Gd^{3+} is present to yield the greatest maxCE, while this value drops to 1.9 mM with an r_1 relaxivity of 18 $mM^{-1}\,s^{-1}$ (Table 1 and Fig. 6C). If on the other hand the r_2 /r_1 ratio increases to 5, the observable, maximal Gd^{3+} concentration drops by more than a factor of 2, from 11.2 to 4.9 mM. It should be noted that high tissue Gd^{3+}

Table 1. Field dependence of the voxel averaged Gadolinium concentration, [Gd^{3+}], and the maximal contrast enhancement, maxCE, for compounds with different r_1 relaxivity values, and r_2/r_1 ratios. Optimal flip angle was always 90°, the echo time (*TE*) 1.5 ms and the repetition times (*TR*) times as listed

		$r_2/r_1 = 1.2$			$r_2/r_1 = 5$		
Field	r_1 ($mM^{-1}\,s^{-1}$)	*TR* (ms)	Gd^{3+} (mM)	maxCE (au)	*TR* (ms)	Gd^{3+} (mM)	maxCE (au)
3 T	45	95	0.9	0.82	170	0.4	0.70
	20.5	95	2.0	0.82	170	0.9	0.70
	3	95	13.7	0.82	170	6.0	0.70
7 T	27	115	1.3	0.84	210	0.6	0.73
	18	115	2.0	0.84	210	0.9	0.73
	3	115	11.9	0.84	210	5.2	0.73
9.4 T	18	125	1.9	0.84	225	0.8	0.73
	16.5	125	2.0	0.84	225	0.9	0.73
	3	125	11.2	0.84	225	4.9	0.73

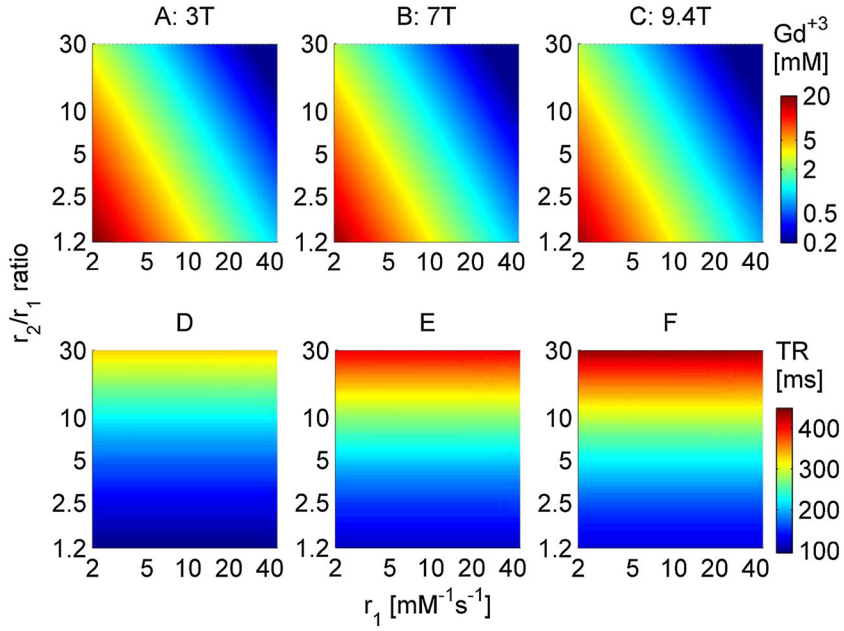

Figure 3. Optimization of the maximum contrast enhancement (see Fig. 1 for definition) to obtain the widest range of observable gadolinium concentrations (A–C) by adjustment of the sequence repetition time (D–F). Compounds with variable r_1 relaxivity (*x*-axis) and r_2/r_1 ratio (*y*-axis) are considered at 3 T (A, D), 7 T (B, E) and 9.4 T (C, F).

concentrations may be toxic, expecially for the kidney during clearance of the agents. Approved agents that have a mean terminal half-life of ca. 1.3-1.6 h (8) typically reach maximal tissue concentrations of ca 10 mM (9). In the following section we will explore maxCE for fixed, nontoxic amounts of Gd^{3+}.

2.3. Optimizing the Conditions for Fixed Amounts of Gadolinium

Important issues in contrast-enhanced MRI at any field strength include how to achieve the highest sensitivity toward changes in local tissue concentrations, and how to minimize the administered amount of agent in order to avoid toxic effects. One way of achieving this goal is to aim for agents with high r_1 relaxivity. In cases of the most widely used clinical agents, the relaxivity is between 3 and 4 $mM^{-1}s^{-1}$, and generally high amounts must be administered in order to achieve the greatest maxCE, as shown in the previous paragraph. Another strategy is to see how far one can get in terms of the maxCE for a fixed Gd^{3+} concentration by matching of the sequence parameters. Also for this optimization strategy, we found that a flip angle of 90° always yielded the highest maxCE. In Figs 4 and 5(B) we show the results obtained if the upper bound for the Gd^{3+} concentration is set to 2 mM. This corresponds to a linear increase of the T_1-weighted MR signal to approximately 1.5 mM followed by a nonlinear increase up to the maxCE plateau. Similar to the previous optimization strategy, the highest maxCE is obtained for the lowest r_2/r_1 ratio, but the decrease in maxCE with increasing ratio is greater (Fig. 5B) because no adaptation of the gadolinium concentration is allowed. The r_1 relaxivity that yields the highest maxCE is field-dependent, and decreases from 20.5 at 3 T to 16.5 at 9.4 T. This is an interesting result, since the highest theoretically achievable r_1

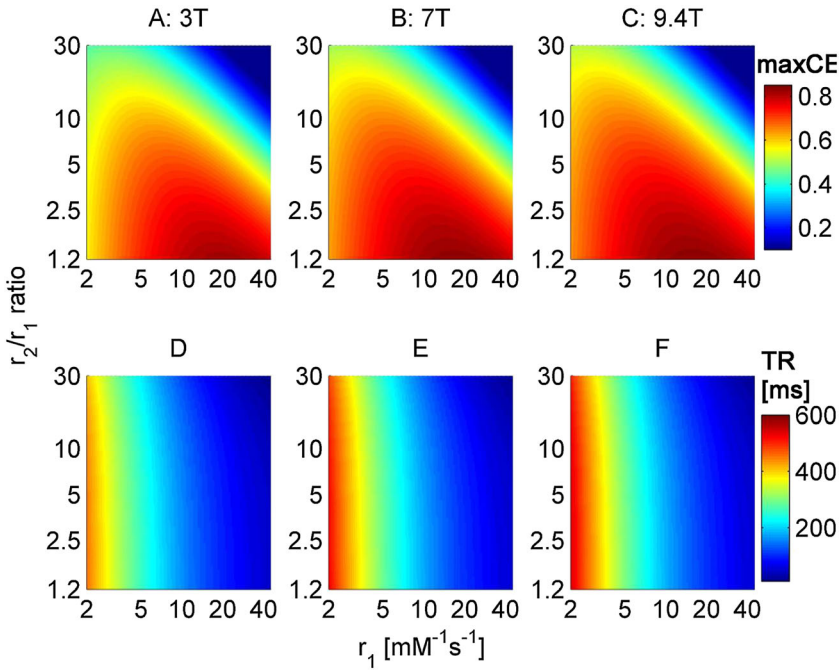

Figure 4. Optimization of the maximum contrast enhancement (A–C) for a 2 mM gadolinium concentration by adjustment of the sequence repetition time (D–F). Compounds with variable r_1 relaxivity (*x*-axis) and r_2/r_1 ratio (*y*-axis) are considered at 3 T (A, D), 7 T (B, E) and 9.4 T (C, F).

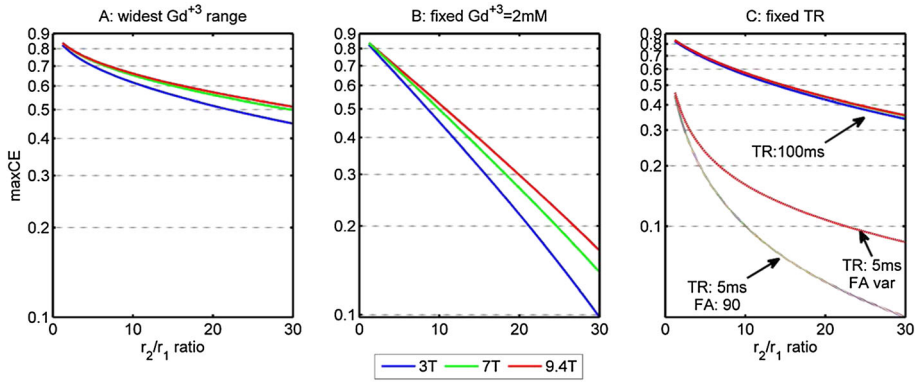

Figure 5. Maximal contrast enhancement, maxCE, as a function of the r_2/r_1 ratio at three magnetic field strengths. Results are plotted for the three strategies used for maximization of maxCE. (A) Widest possible range of observable Gd^{3+} concentrations; (B) a fixed maximal Gd^{3+} concentration of 2 mM; (C) a fixed *TR* of 100 ms (solid lines) or 5 ms with a flip angle of 90° (dotted) or 72° (dashed). The r_1 values are: 20.5 $mM^{-1}s^{-1}$ for 3 T; 18 $mM^{-1}s^{-1}$ for 7 T and 16.5 $mM^{-1}s^{-1}$ for 9.4 T.

relaxivity also decreases with the field (3). In addition, our results suggest that achieving the highest possible r_1 values for a compound may not be required, at least if one wants to capture local tissue concentrations up to a maximum of 2 mM. This strategy can be pursued for lower tissue concentrations, and the smaller the target tissue concentration, the greater the r_1 values at which the greatest maxCE occurs will be.

2.4. Optimization for Fixed MR Sequence Parameters

Smart contrast agents change their r_1 relaxivity dependent on the physiological or metabolic tissue status. Clearly in this case it is impractical to optimize the acquisition strategy to each single level of relaxivity, and therefore optimization for a fixed set of MR sequence parameters is needed. Another example is dynamic contrast-enhanced MRI. Generally, the shortest possible *TR* is used since a high temporal sampling is necessary for pharmacokinetic modeling. The available maxCE is obtained by increasing the gadolinium concentration so that the contribution $1/r_1 \cdot [Gd^{3+}]$ becomes ca. 5 times shorter than T_1. In the case of a *TR* of 100 ms, 20 mM of a compound with an r_1 of 3 $mM^{-1}s^{-1}$ is required to obtain T_1 times on the order of 20 ms, while 1 mM suffices if r_1 is 45 $mM^{-1}s^{-1}$ (Fig. 6B). If the desired *TR* is 5, then substantially higher amounts are required to meet this condition (Fig. 6C). As an alternative, the flip angle can be varied. This reduces the necessary amount and increases maxCE. Since the gadolinium concentration is varied, the optimal flip angle depends inversely on the r_2/r_1 ratio but not on r_1. Low ratios required up to 72° across all fields and for the highest ratios a flip angle of 22–24°, dependent on the field, minimized the T_2-related signal loss. The drop in maxCE for the shorter *TR* depends nonlinearly on the r_2/r_1 ratio and goes from 1.9 to 9.6 when the r_2/r_1 ratio increases from 1.2 to 30 for a fixed FA. Varying the flip angle effectively mitigates the drop in maxCE to 1.2–4 compared with a *TR* of 100 ms.

2.5. Noise Effects

Generally, it is more efficient to use short *TR* times and thereby avoid long, idle periods of time between subsequent excitations. As shown in the preceding paragraphs, we found that rather long *TR* times are required to achieve the highest maxCE. When short *TR*s are used, very high gadolinium concentrations are required to increase maxCE, despite flip angle optimization. We found that the estimated contrast-to-noise ratio per unit time as a function of r_1 relaxivity and r_2/r_1 ratio, calculated according to eqn 6 is relatively high, despite long *TR*. When compared with a *TR* of 5 ms, the loss in CNR is between 5 and 18%. The CNR reduction is greater for compounds with small r_2/r_1 ratios and does not depend on whether or not the upper bound for the gadolinium concentration is kept fixed. This modest reduction of CNR depends on the trade-off between optimizing maxCE, on one hand, and minimizing the noise figure on the other hand.

2.6. Influence of the Magnetic Field Strength on Contrast Enhancement

Since the highest r_1 relaxivity that can theoretically be achieved for Gd^{3+}-based compounds decreases with increasing magnetic field strengths, one may expect that the available contrast is lower at 9.4 T than at 3 T. On the other hand, at higher field strengths, the improved background suppression for a spoiled gradient echo sequence and a high flip angle mitigates this effect owing to prolonged tissue T_1 (Fig. 5). The maximum theoretically predicted r_1 relaxivity at different field strengths is 45 $mM^{-1}s^{-1}$ at 3 T, 27 $mM^{-1}s^{-1}$ at 7 T, and 18 $mM^{-1}s^{-1}$ at 9.4 T (3). Our simulations suggest that this loss in relaxivity can be compensated for by administering higher amounts of contrast agents and increasing the *TR* (Fig. 7A and B). When going from 3 to 7 T (9.4 T) about 1.5 (2.1) times higher Gd^{3+} concentrations are required (Table 1). At increasing field strengths, the paramagnetic effect of any contrast agent is enhanced, leading to a higher r_2 relaxivity associated with a faster T_2 decay, and a reduction of the available image contrast even at the short *TE* times considered here. In line with these observations, we found that the greatest tissue concentration that can be observed without signal loss is limited by T_2-related signal decay. If the r_2/r_1 ratio is 1.2, the maxCE is above 0.82, corresponding to 82% of the available magnetization, while for a r_2/r_1 ratio of 5, this value is reduced to 70%. These values are similar at all three

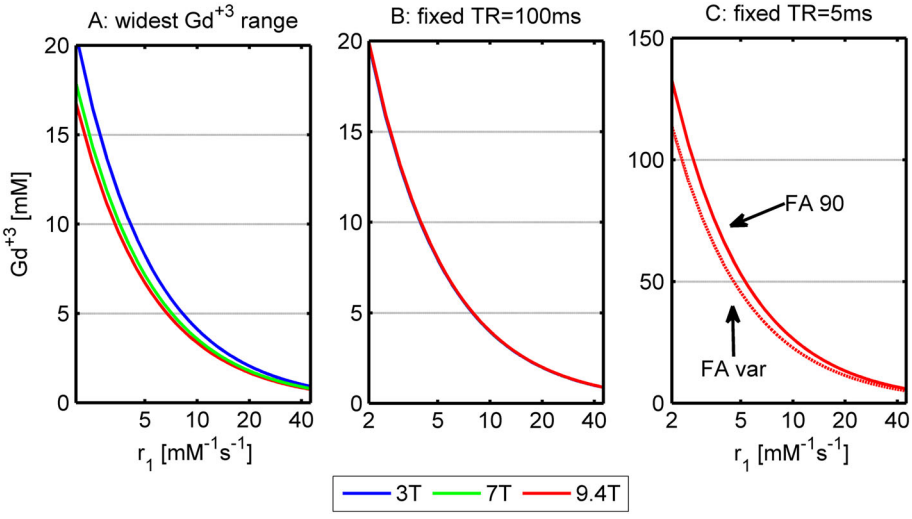

Figure 6. Gadolinium concentration necessary to reach the highest maxCE as a function of the r_1 ratio at three magnetic field strengths for a fixed r_2/r_1 ratio of 1.2. Results are plotted for: (A) *TR* varied freely to achieve the widest possible range of observable Gd^{3+} concentrations; (B) a fixed *TR* of 100 ms – a variable flip angle and fixed flip angle of 90° yielded identical results; and (C) a fixed *TR* of 5 ms for the case of a variable flip angle (dashed) and fixed flip angle of 90° (solid).

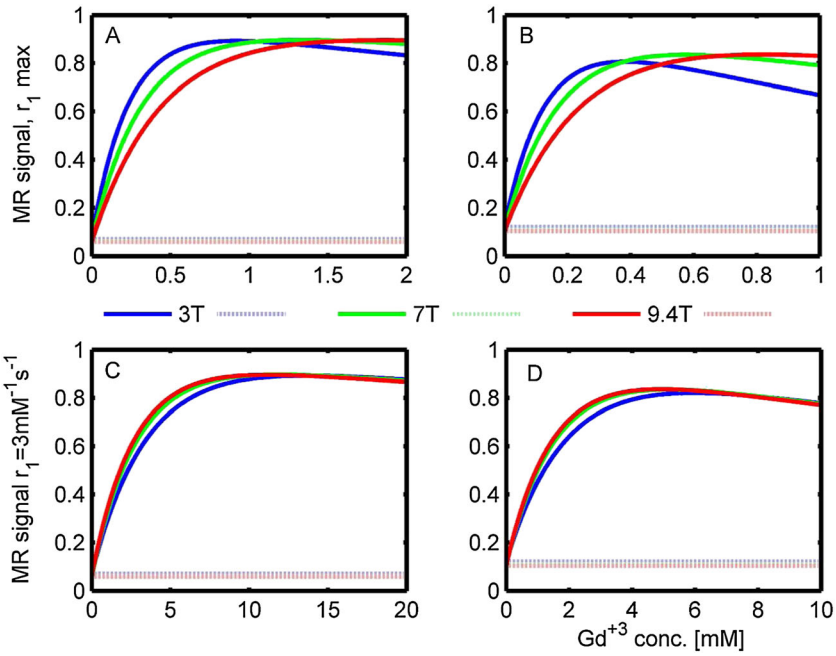

Figure 7. T_1-weighted MR signal in a spoiled gradient echo sequence with a *TE* of 1.5 ms and optimal *TR* at three magnetic field strengths. (A, B) The r_1 relaxivity of the contrast agent at each magnetic field strength was set to the maximum theoretically predicted value, as shown in eqn 3. This value decreases with increasing fields, and therefore the signal maximum occurs at higher gadolinium concentrations. (C, D) The r_1 relaxivity was set to a fixed value of 3 $mM^{-1}\,s^{-1}$. Lower doses can be administered without signal loss by changing the *TR*. The range of gadolinium concentrations at which the plateau is reached depends on the r_2/r_1 ratio, which was set to 1.2 (A, C) and 5 (B, D). The optimal *TR* values are listed in Table 1.

investigated magnetic field strengths (Fig. 5; Table 1). This reduction would have been even greater if not compensated for by lower doses and longer *TR* times. Interestingly, if no change in r_1 relaxivity occurs at higher fields, it is possible to decrease the administered dose by 10–15% (Table 1, Fig. 7C and D).

3. DISCUSSION

The objective of the present study was to investigate the behavior of T_1-shortening, gadolinium-based contrast agents at several magnetic field strengths, with emphasis on explorative studies of new contrast agents and the development of measurement protocols for ultrahigh magnetic fields. The basic idea was to find ways of tailoring the MR sequence to the properties of the compound specifically for each magnetic field strength in order to take full advantage of the available relaxivity. Vice versa, our results could also be used to tailor a compound for specific uses in terms of the desired gadolinium concentration and T_1-weighted measurements at a fixed magnetic field strength.

The issue of optimizing gradient echo sequence parameters to achieve the best contrast in T_1-weighted MRI has been approached in several previous studies (10,11). These have mainly been concerned with optimization for distinguishing between different tissue types, but also for optimizing agent-induced contrast enhancement. In the latter case, a broad range of voxel-specific T_1-, and T_2-relaxation times will be encountered, owing to Gd^{3+} concentration variations. This distribution of relaxation times makes it difficult, if not impossible, to optimize the contrast for single pairs of compartments with and without agent. Instead of trying to obtain a compact expression for the ideal contrast, we here investigate the available maxCE for a wide range of Gd^{3+} concentrations with measurement parameters that were optimized for each pair of r_1-relaxivity values, between 1 and 45 $mM^{-1}\,s^{-1}$, and r_2/r_1 ratios, varying between 1.2 and 30.

Simulations were performed for the spoiled T_1-weighted gradient echo sequence based on the principle of saturation recovery. The inversion recovery technique was not considered, in view of previous reports on low tissue contrast (7,11). For optimization, we chose to evaluate the maximal contrast enhancement, maxCE, which is simply the difference between the observed MR signal at maximum enhancement and the MR signal in the background tissue. The maxCE value thus corresponds to the maximal available signal enhancement and captures the fraction of the full, underlying magnetization (proton density) that can be exploited for a given combination of sequence parameters and compound properties. In the limiting case that the background signal approaches zero, owing to a low steady-state signal in the absence of any contrast agent, and the MR signal in the agent-containing tissue is fully recovered, the value of maxCE is unity. The higher the r_1 relaxivity and the shorter the *TR*, the closer we get to this limiting value. If T_2 effects are neglected, it is possible to achieve the greatest maxCE value at any repetition time, even in case of low r_1 relaxivity, by simply increasing the local tissue concentration. In practice, such an approach requires gadolinium doses that are not physiological and are probably toxic.

If T_2-related signal decay is taken into account, maxCE is limited, especially for high tissue concentrations and for compounds with high r_2/r_1 ratios. In an effort to overcome this T_2-related limitation, three different strategies for optimizing maxCE were pursued: (a) maximizing the range of detected Gd^{3+} concentrations, in order to avoid signal drops in case of high gadolinium concentrations; (b) sequence matching to achieve the best maxCE for a fixed, Gd^{3+} concentration, to achieve the highest sensitivity and minimize toxicity; and (c) maximizing maxCE for an MR sequence with fixed *TR* (100 or

5 ms), to use with smart contrast agents or in case the sequence parameters need to be fixed.

We found that all three optimization strategies are viable in order to make use of 80% (40% in case of the short *TR*) or more of the available magnetization, at least for compounds with the smallest r_2/r_1 ratios. From the viewpoint of optimizing visibility and detection sensitivity of voxels containing the contrast agent, we generally found no advantage of using the tissue Ernst angle. This finding may not always hold true for specific applications. For instance, in 'shutter-speed' imaging, the signal difference between agent-containing, extracellular compartments and agent-free intracellular compartments is maximized. The exchange parameters are best observed using flip angles close to the Ernst angle for the tissue devoid of contrast agent. Hereby the signal in the agent-free intra-cellular compartment is not affected by strong signal suppression (12,13). Concerning pharmacokinetic modeling of dynamic contrast enhancement (DCE) MRI data, an FA that is up to 6 times higher than the Ernst angle for the tissue is recommended (9). These authors also point out that the ideal FA actually depends on the pharmacokinetic parameters that need to be determined. For instance, if wash-out is rapid and low concentrations occur during most of the kinetics, a higher FA is preferred, while if a high equilibrium concentration is achieved within a short measurement time and wash-out is slow, lower FA may be optimal. Our results for a *TR* of 5 ms support these observations. We found that the greatest maxCE is found if the flip angle is varied. In addition to increasing maxCE for compounds with high r_2/r_1 ratios, this choice requires lower gadolinium concentrations than for a fixed 90° pulse. Building upon the work by Pelc (14), De Naeyer *et al*. (15) derive an equation that yields the best flip angle for a specific choice of *TR* and *TE*, for an agent with known r_1 and r_2 relaxivity and concentration, and for a given tissue T_1 time. An analytical expression for the best flip angle is given in their eqn (11). This relation has a singularity when the dimensionless parameter

$$\gamma = \frac{r_2}{r_1} \cdot \frac{TE}{TR}$$

is equal to the ratio

$$\frac{2 - E_1}{1 - E_1}$$

and therefore is not bounded within the expected ±1 limit of a cosine function used to calculate the optimal FA. In practice, for clinically available compounds, the approach proposed by De Naeyer *et al*. yields reasonable flip angle values, but we could not use this relation for our complete search space of r_1 relaxivity values and r_1/r_2 ratios. In contrast, we could apply the equation for the optimal flip angle proposed by Haselhoff (16), and obtained results that were comparable to our reported results, with maximum flip angle deviations $<0.22\%$ (flip angle range $90.11 < \mathrm{FA} < 90.19$) and *TR* deviations $<4.2\%$.

For most of the investigated optimization strategies, the *TR* was relatively long: 95 ms or more across field strengths for different compounds. Such long *TR*s are not optimal in terms of image contrast-to-noise ratio per unit time. The optimal duration of the acquisition is ca. $1.26 \times T_2^*$, while longer durations such as five times T_1 only reduce the signal-to-noise ratio (17). Accordingly, the *TR* should be kept short enough to match the acquisition window and hereby allow for the highest number of acquisitions per unit time. Since the noise decreases inversely with the square-root of *TR* (square-root of the number of acquisitions), a shorter *TR* generally leads to greater contrast-to-noise ratio (CNR) levels. The question is how the final image quality is affected by MR sequence parameters aimed to exploit the highest fractional magnetization, on one hand, and the lowest noise per unit time that the hardware can perform, on the other. Short acquisition windows require high bandwidths and a high duty cycle that may lead to gradient instabilities. Short *TR* times require low flip angles and higher requirements on the stability of the radio frequency transmitter amplifier. We predict that these experimental factors, together with the high gadolinium concentrations that are required in order to boost maxCE for short *TR*s, will tend to decrease the actual contrast-to-noise ratio per unit time.

Generally, r_2 relaxivity is considered to have a negligible effect on the final image contrast in most studies. At low-field strengths and low agent concentrations this is generally true; however, at high field strengths the paramagnetic dephasing effect of Gd^{3+} on the MR signal increases. Therefore the r_2/r_1 ratio will increase with the field strength, even more so for large-sized and protein-binding molecules (5). Compounds with a high r_2/r_1 relaxivity tend to decrease maxCE and an important result in the present study is that this decrease can be mitigated by prolonging *TR* and by administering lower gadolinium doses. Interestingly this brings about a (virtual) increase in sensitivity. For instance, at 3 T our data shows that the Gd^{3+} concentration that maximizes the MR contrast enhancement for a compound with a r_2/r_1 ratio of 5 is three times lower than that for a compound with a relaxivity ratio of 1.2, while the loss in maxCE is only 10%. In other words, despite the fact that we have greater T_2-related signal loss, by prolonging *TR* we can still observe most of the available magnetization.

A limit of our study is that we did not investigate T_2^*-related losses directly, but approximate these by the corresponding T_2 effects. This choice is unavoidable for many reasons. The measurement of T_2 has far greater accuracy, reproducibility and precision than measurements of T_2^*, and consequently the r_2 relaxivity, not the r_2^* relaxivity of contrast agents, is reported. The effective transverse relaxation time, T_2^*, is shorter than T_2, since it is influenced by the field homogeneity in the imaging voxel. Besides paramagnetic compounds that induce field variations within the imaging voxel, the presence of areas with different magnetic susceptibility in the immediate vicinity will influence T_2^*. It is therefore difficult to reliably assess this parameter, especially at high magnetic field strengths where the effects of magnetic susceptibility differences are greater. Only in the limit of an infinitesimal voxel size, T_2 and T_2^* will be the same. In addition to restricting the voxel size, the most effective way to minimize the influence of T_2^* is to use the shortest possible *TE* time in SPGRE sequences. In the present study we set the echo time to 1.5 ms, which is a reasonable value for standard gradient systems, using a pixel bandwidth of 500 Hz and a matrix size of 256.

With regard to local tissue concentrations, 0.1–0.5 mmol/kg is the typical dose for clinical contrast agents. These amounts lead to blood concentrations around 5–10 mM during the first-pass and 1–2 mM at steady state (9), in agreement with a total blood volume of 0.05–0.0.08 L/kg. Higher doses and tissue concentrations than these may lead to toxic effects, as have been shown in several studies, especially in case of reduced kidney function or dehydration (8). Therefore, one of our strategies was to optimize maxCE for a fixed amount of 2 mM Gd^{3+}. This approach is useful to observe the MR signal if the expected tissue concentration is below this limit. Whenever the tissue concentration is greater, T_2-dependent signal loss will yield a lower contrast in

tissues with higher Gd^{3+} concentrations. We found that more than 80% of the available magnetization can be exploited for agents with a r_2/r_1 ratio of 1.2, and more than 70% if the r_2/r_1 is 5, provided that the best *TR* is selected. Interestingly, to achieve these results, it is not necessary to use compounds with the highest possible r_1 relaxivity. For 3 T we found that a r_1 relaxivity of 18.8 $mM^{-1}s^{-1}$ suffices to achieve the highest maxCE.

The r_1 and r_2 relaxivity values of a contrast agents depends on the combined effect of a number of factors, and is a well-described phenomenon (18). The main three factors are (a) the structure of the complex, which determines how close water molecules can get to the Gd^{3+} ion(s); (b) the time constants that govern water exchange between bulk water and bound water, which determines how many water molecules that are effectively influenced by Gd^{3+} per unit of time; and (c) the rotational dynamics of the molecule, which determines the efficiency of the spin–lattice relaxation. Based on relaxation theory, an impressive number of innovative agents that take advantage of the available relaxation mechanisms have been developed pfor reviews see Aime *et al*. (19) and Caravan and Zhang (20)]. At high magnetic field strengths, the relative weights of different relaxation mechanisms are altered, and the overall relaxation effects are physically limited at high fields. From physicochemical modeling of different mechanisms the theoretically predicted, maximal r_1 relaxivity decreases with increasing magnetic field strengths, from 45 $mM^{-1}s^{-1}$ at 3 T to 18 $mM^{-1}s^{-1}$ at 9.4 T (3). In the present work we found that, despite this loss in relaxivity, similar enhancements can be obtained but that longer *TR* times and 1.5–3 times higher concentrations are required, dependent on the r_2/r_1 ratio of the compound. The necessary changes in *TR* and agent concentration are mitigated by the improved background suppression available for longer tissue T_1 times at high fields.

The most widely used clinical agents – gadoteridol, gadodiamide, gadobenic acid, gadopentetic acid and gadoteric acid – have r_1 relaxivity values of 3.7–5.9 $mM^{-1}s^{-1}$ at 1.5 T (4,5). Interestingly, these do not seem to change markedly with increasing field. The r_1 for all of these agents remains above 3 $mM^{-1}s^{-1}$ at 7 T (21). Most probably these compounds will continue to be useful at high fields, although the MR sequence needs to be adapted to achieve the greatest possible contrast enhancement, as we show in the present work. Assuming a constant relaxivity of 3 $mM^{-1}s^{-1}$, we found that increasing the *TR* at high fields allows reduction of the administered dose by 10–15% without loss of maxCE.

4. CONCLUSION

Contrast-enhanced MRI at high and ultra-high magnetic field strengths have to take into account the lower r_1 relaxivity and increased r_2/r_1 ratio. T_2 decay cannot be neglected, since it affects the maximally available contrast enhancement. If the r_2/r_1 ratio remains unchanged, the same contrast enhancement can be achieved despite decreasing r_1 relaxivity at high fields, albeit at the cost of a higher sequence *TR* and 1.5–2 times higher amounts of contrast agent. On the other hand, compounds that maintain their r_1 relaxivity at high fields require 10–15% lower doses, provided that *TR* is optimized. If an upper bound of 2 mM is set for the local gadolinium concentration, the r_1 relaxivity that maximizes contrast is below the theoretically predicted highest r_1 relaxivity values at each magnetic field strength.

5. EXPERIMENTAL

5.1. T_1 and T_2 Relaxation Times

Simulations of expected relaxation times for enhanced and unenhanced conditions were made for Gd^{3+} concentrations, [Gd^{3+}], that varied between 0 and a maximum of 80 mM, in steps of 5 μM. Contrast agents with varying simulated relaxivity values were considered. The r_1 relaxivity was 1–45 $mM^{-1}s^{-1}$, and the r_2/r_1 relaxivity ratio was 1.2–30. Both factors were increased in steps of 0.5. The T_1 and T_2 relaxation times were calculated according to:

$$1/T_1 = 1/T_1^{GM} + r_1 \cdot [Gd^{3+}], \quad (1)$$

$$1/T_2 = 1/T_2^{GM} + r_2 \cdot [Gd^{3+}], \quad (2)$$

The field strength specific $T_1{}^{GM}$ relaxation times for gray matter brain tissue were obtained according to Ref. (6) and was 1.3, 1.8, and 2.0 s at 3, 7 and 9.4 T, respectively. The T_2 times were obtained according to Ref. (7) and were 70, 50 and 40 ms in the gray brain tissue. The relation between the T_2 time and T_2*, that governs decay in the gradient echo sequence is considered below.

5.2. MR Signal in the Spoiled Gradient Echo Sequence

Simulations were performed for the spoiled T_1-weighted gradient echo sequence based on saturation recovery. The inversion recovery technique was not considered, in view of previous reports on low tissue contrast (7,11).

The MR signal for voxels with and without contrast agent was calculated, while varying the sequence parameters: *TE*, *TR* and flip angle. The T_1-weighted signal in a spoiled GE sequence was calculated from:

$$S_{GE} = M_0 \cdot \sin(\alpha) \cdot E2 \cdot \frac{1 - E1}{1 - E1 \cdot \cos(\alpha)}, \quad (3)$$

where $E1 = e^{-TR/T_1}$, $E2 = e^{-TE/T_2}$, α is the flip angle and M_0 is the maximum magnetization set to a value of unity. The spoiled GE sequence actually depends on the effective transverse relaxation time, T_2^* rather than the transverse relaxation time T_2. These two parameters are interlinked via the relation:

$$\frac{1}{T_2^*} = \frac{1}{T_2'} + \frac{1}{T_2}$$

where T_2' describes reversible spin-spin relaxation effects. Since the literature on Gd^{3+}-based contrast agents is based on T_2, we restricted our evaluations to this parameter.

In general, the highest signal is obtained by the Ernst angle, defined as: $\alpha_e = \cos^{-1}(e^{-TR/T1})$, which excites the magnetization just as much as it recovers within one repetition time, when the next excitation occurs. This angle will be different in the presence and absence of the contrast agent. In order to optimize the contrast, the Ernst angle in the presence of the agent should be chosen. However, since [Gd^{3+}] is difficult to estimate, and varies across the measured object and with time, this may be difficult to do in practice. Therefore, for each condition, comprising different field strengths, *TR*, r_1 and r_2 relaxivities, the flip angle for which the maximum maxCE (see below) is achieved was determined.

The minimum *TR* was 5 ms and the maximum 600 ms, in steps of 5 ms, and the minimum (maximum) flip angle was 0 (90°) in steps of 1°. In order to minimize T_2* effects, the echo time was set to 1.5 ms, which corresponds to a per pixel bandwidth of 500 Hz and a matrix size of 256.

5.3. MR Contrast Enhancement

The signal difference between the field-strength-specific, unenhanced, background MR signal and the maximally achievable MR signal in the presence of a contrast agent with known concentration, r_1 and r_2/r_1 ratio was evaluated by subtraction. The signal difference at the plateau of the T_1-weighted MRI signal is termed 'maxCE' and describes the maximal amount of enhancement, while taking into account T_2-related effects in the tissue. It expresses the fraction of the available magnetization (M_0) that can be exploited (Fig. 1). This measure was evaluated according to three different optimization strategies. First, we explored how the properties of the contrast agent determine the MR-sequence parameters that maximize contrast enhancement. Hereby the greatest maxCE is aimed for and the problem of signal drops in structures that accumulate the contrast agent is avoided. To achieve this, we searched for the highest amount of Gd^{3+} that could be detected by the T_1-weighted approach for each pair of r_1 and r_2 relaxivity values. The *TR* and flip angle for which this condition is satisfied were determined. The next strategy was to match a fixed maximally detectable Gd^{3+} concentration (2 mM) to the greatest available maxCE, by searching for the best combination of *TR* and FA. Third, we also evaluated the highest available maxCE across different pairs of r_1 and r_2 relaxivity values for an MR sequence with fixed *TR* (100 and 5 ms).

5.4. Noise Dependence

In MRI, the efficiency ζ, of a sequence is determined by the relation between the time spent sampling the signal T_{ADC}, in relation to the repetition time, *TR*. Therefore, ζ can be defined as:

$$\zeta = \frac{T_{ADC}}{TR}, \tag{4}$$

which has an upper bound of unity, since the sampling duration never exceeds *TR*. The more similar these durations are, the greater the CNR per unit time. On the other hand, it is not possible to prolong T_{ADC} to match the *TR*, since T_2-related signal loss limits the time that a true signal is sampled as opposed to just acquiring noise (17). Therefore we approximate the best sampling duration by:

$$T_{ADC} \cong 1.26 \cdot T_2 \tag{5}$$

The noise figure generated by the sequence is proportional to $\sqrt{1/\zeta}$ so the expected CNR can be approximated by:

$$CNR \cong \frac{\text{maxCE}}{\sqrt{\frac{TR}{1.26 \cdot T_2}}} = \frac{\sqrt{1.26 \cdot T_2} \cdot \text{maxCE}}{\sqrt{TR}}. \tag{6}$$

If endogenous T_2 effects in the tissue are neglected, the relation between CNR and the contrast agent becomes:

$$CNR' \cong \frac{\sqrt{1.26} \cdot \text{maxCE}}{\sqrt{TR \cdot r_2 \cdot [Gd^{3+}]}}, \tag{7}$$

pointing out the importance of keeping the r_2 relaxivity and/or the gadolinium concentrations as small as possible in order to maximize CNR.

5.5. Field Dependence

Magnetic field dependence is explored in the simulations by (a) taking into account tissue T_1 and T_2 relaxation times and (b) specifically evaluating field-relevant r_1 and r_2 relaxivity values from Ref. (3). The first factor affects the background suppression of the tissue, and thereby the available maxCE. The second factor affects the available enhanced MR signal. The maximum theoretically predicted r_1 relaxivity at different field strengths is 45 $mM^{-1}s^{-1}$ at 3 T, 27 $mM^{-1}s^{-1}$ at 7 T and 18 $mM^{-1}s^{-1}$ at 9.4 T.

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