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Composite MR Contrast Agents for Conditional Cell-Labeling

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Abstract

Gadolinium-chelates (Gd-DTPA) and superparamagnetic particles of iron oxide (SPIO) are two commonly used MR contrast agents that exhibit inherently different relaxation properties. These two agents have been used to label cells ex-vivo to generate signal contrast with respect to background tissue when introduced to a tissue-of-interest. Assuming minimal mutual interaction between these two agents, we were motivated to investigate the creation of composite relaxation properties by mixing the two in aqueous solutions for conditioning cell labeling. Concentrationdependent relaxivity coefficients were first obtained from each contrast agent, independently, in saline solution at 3 Tesla. These coefficients were then used to predict both the R_1 and R_2 relaxation rates of a composite contrast agent using a linear model combining the effects of both contrast media. The predicted relaxation rates were experimentally confirmed from 25 composite solutions (combinations of SPIO-concentration ranging from 0 to 1 µg/mL and Gd-DTPAconcentration ranging from 0 to 0.20 mM). We show that the combination of SPIO and Gd-DTPA in an aqueous solution exhibits unique and predictable relaxivity properties that are unattainable via the individual use of either agent. The method may be applied to create 'user-tunable' contrast conditions for the visualization of magnetically labeled cells in the context of cell replacement therapy.

Keywords

Relaxation properties; cell imaging; molecular imaging; dual contrast

Introduction

Contrast agents are utilized in magnetic resonance imaging (MRI) to visually exploit and enhance differences in physical structures and/or physiological processes. Gadolinium chelates and superparamagnetic iron oxide particles exhibit distinct relaxation properties that provide a basis for the progressive development of contrast enhanced imaging within the context of MRI.

The gadolinium chelate, gadopentetate dimeglumine (Gd-DTPA; Magnevist, Berlex Inc., Montville, NJ), which primarily shortens T_1 relaxation, has been used for the detection of

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various types of tumor [Huang et al., 2006; Rosen et al., 2003] as well as brain lesions associated with multiple sclerosis [Martino et al., 2002]. On the other hand, the ultrasmall superparamagnetic iron oxide (SPIO) contrast agent, ferumoxides injectable solution (Feridex, Berlex Inc.- hereafter referred to SPIO) is another class of contrast agent that is clinically used to detect alterations in the reticuloendothelial system (RES) associated with hepatic tumors [Kanematsu et al., 2001] or to detect primary site or nodal metastases of various tumors [Mack et al., 2002; Bellin and Roy, 2007]. In low concentration (*i.e.* less than 1 μ g/mL), SPIO exhibits a highly sensitive/selective reduction of T₂ relaxation.

Recently, these two classes of contrast agents were adopted in cellular MRI techniques whereby magnetically-labeled cells (via transfection or binding of contrast materials to surface ligands) can be traced and detected [Bulte et al., 1999, 2001; Hoehn et al., 2002; Shapiro et al., 2004, 2006]. Gd-DTPA has recently been observed to be taken up by atherosclerotic plaques [Barkhausen et al., 2003; Lipinski et al., 2006], thus indicating potential benefits in cardiac imaging. Typically, cells are labeled *ex-vivo*, and are subsequently introduced to the *in-vivo* system to monitor the growth pattern of the labeled cells [Bulte et al., 2001; Shapiro et al., 2006]. The use of a single contrast agent in the context of cellular imaging may provide limited information (for example, hypointense signal from SPIO-labeled cells may be misinterpreted to be a site of hemorrhaging, or vice versa [Dunn et al., 2005]) and thus necessitates the need for more sophisticated methods that allow selective relaxivity/contrast properties to be obtained.

A recent study by Horch and Does [Horch and Does, 2007] provided an important framework for investigating the use of a mixture of MnCl₂ and SPIO to create a model for bi-exponential relaxation. In our study, we investigated the effects of a composite contrast agent, using a mixture of Gd-DTPA and SPIO, on both R₁ and R₂ relaxivity rates. We also formulated the R₁ and R₂ relaxation characteristics of aqueous solutions varying in both Gd-DTPA and SPIO concentrations. By creating different labeling solutions with distinct contrast mechanisms, the cells can be labeled accordingly to exhibit relaxation property that can not be attained using one type of contrast agent. These two contrast agents are hypothesized to exhibit minimal mutual interaction due to their different relative sizes and relaxation properties, and thus they may offer attractive relaxation behavior when they are used collaboratively.

Methods

I. Theory

Contrast agents typically increase transverse and/or longitudinal relaxation in a manner that is linearly proportional to contrast agent concentration. The proportionality constant, or relaxivity coefficient, is specific to a given contrast agent. In this study, two contrast agents, super-paramagnetic iron oxide (Feridex; SPIO) and paramagnetic gadolinium chelates (Magnevist; Gd-DTPA), were used. Saline water (0.9%) was used as a solvent in order to simulate the relaxation properties of SPIO and Gd-DTPA in an aqueous physiological environment. Saline, typically prepared with a phosphate buffer, was used as the main ingredient for the cell-labeling experiment. It is important to note that intra-cellular uptake of the above contrast agents is dependent on the method of transfection, the concentration of exposure to transfection agent) [Bulte et al., 1999, 2001; Hoehn et al., 2002; Shapiro et al., 2004, 2006]. However, once a method to control the amount of contrast materials per cell is determined, the cells containing two contrast agents within its cellular compartment will manifest the composite relaxivity properties. Therefore, the relaxation property of the aqueous mixture of contrast agents was investigated.

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Assuming minimal mutual interactions between SPIO and Gd-DTPA, we modeled the relaxivity rates of the composite contrast agents as linear combinations of the independent relaxivity rates of each contrast media in saline. Therefore, both R_1 and R_2 relaxation rates are expressed as a function of each contrast agent concentration as follows:

$$R_{1}' = \frac{1}{T_{1}'} = \frac{1}{T_{1}o} + \beta_{1,Gd} [Gd] + \beta_{1,Fe} [Fe]$$
⁽¹⁾

$$R_{2}' = \frac{1}{T_{2}'} = \frac{1}{T_{2}o} + \beta_{2,Gd} [Gd] + \beta_{2,Fe} [Fe]$$
⁽²⁾

where T_1° and T_2° are the longitudinal and transverse relaxation times of saline, respectively, in the absence of contrast agents. β_1 and β_2 are the concentration-dependent relaxivity coefficients for R_1 and R_2 , respectively, of Gd-DTPA (noted as Gd) and SPIO (noted as Fe).

II. Relaxivity Coefficient Measurement

All experiments were conducted at 3T using a clinical MRI System (VH, GE Medical Systems) with a standard quadrature head coil for RF transmission and detection. Eppendorf tubes containing 1.5mL sample solutions were placed in a 6×4 tube rack at 17°C. Special care was given to place the phantom in the center of the coil (in consideration for field homogeneity). R₁ and R₂ relaxivity coefficients ($\beta_1 \& \beta_2$) were measured for both SPIO and Gd-DTPA, independently, based on imaging results of two separate sets of phantoms containing seven different concentrations of contrast media (SPIO: 0, 0.1, 0.2, 0.25, 0.5, 0.75, and 1 µg·Fe/mL; Gd-DTPA: 0, 0.01, 0.02, 0.05, 0.1, 0.15, and 0.2 mM Gd) using a conventional spin-echo sequence (128×256, 1 NEX, 20cm field-of-view, 6 mm-thick slices). Two sets of scans, one containing 13 scans with varying TR (TE=8msec; TR range: 100msec–15,000 msec, logarithmically spaced) and the other containing 10 scans with varying TE (TR=3000msec; TE range: 8msec–200msec, logarithmically spaced), were performed to image the samples.

Average signal intensity for each phantom in each scan sequence was then obtained from a circular region-of-interest (ROI), measured in triplicate, and subsequently used to calculate the longitudinal and transverse relaxation times and rates for each concentration [Simon et al., 2006] (e.g. $R_1 = 1/T_1$ and $R_2 = 1/T_2$). Plots of the concentration-dependent R_1 and R_2 values were created for both SPIO and Gd-DTPA (4 sets total: $R_{1,Fe}$, $R_{1,Gd}$, $R_{2,Fe}$, and $R_{2,Gd}$). Subsequently, the corresponding relaxivity coefficients ($\beta_{1,Fe}$, $\beta_{1,Gd}$, $\beta_{2,Fe}$, and $\beta_{2,Gd}$) were obtained from the slopes of linear fits to each plot. The unit of β was (μ g/mL)⁻¹·s⁻¹ for SPIO and mM⁻¹·s⁻¹ for Gd-DTPA.

III. Prediction and Experimental Confirmation

Equations 1 and 2, along with the experimentally obtained β values, were used to predict the R₁and R₂ relaxivity characteristics of aqueous phantom mixtures containing combinations of five Gd-DTPA concentrations and five SPIO concentrations (therefore, 25 combinations were obtained). We then compared these predictions to the experimental results.

In detail, five concentrations (post-mixing) of each contrast agent were chosen for investigation in the study: SPIO (0, 0.25, 0.5, 0.75, and 1 μ g·Fe/mL) and Gd-DTPA (0, 0.05, 0.1, 0.15, or 0.2 mmol·Gd). The range of concentrations were determined based on the scope of clinically recommended dosages (less than ~0.8 μ g·Fe/mL and less than ~0.15 mmol Gd,

assuming 65% water content per body mass). Specifically, stock solutions of SPIO (0.2 mmol·Fe/mL) and Gd-DTPA (0.5 mmol·Gd/mL) were diluted in saline at room temperature (17° C) to prepare 25 phantoms (1.5mL each) for MR imaging: one containing only saline, four containing only SPIO in saline (0.25, 0.5, 0.75, and 1 μ g·Fe/mL), four containing only Gd-DTPA in saline (0.05, 0.1, 0.15, or 0.2 mmol·Gd), and 16 containing all remaining combinations of both SPIO and Gd-DTPA using the chosen concentrations. All 25 phantoms were placed in rows and columns in a small planar rack with equal spacing and were imaged using the same method as was used previously for the measurement of relaxivity coefficients. Additionally, the rack was immobilized in the wrist coil. The same method used to measure both R₁ and R₂ from the samples was applied.

Results

The individual R₁ and R₂ relaxivity curves of aqueous SPIO and aqueous Gd-DTPA (based on seven concentrations each) are shown in Figures 1a and 1b, respectively. Both figures display linearly increasing R₁ and R₂ relaxation rates as contrast agent concentrations increase. Relaxation coefficients were calculated from linear regression applied to the corresponding relaxivity plots (β =slope): SPIO (β_1 =0.06 (μ g/mL)⁻¹·s⁻¹, β_2 =4.02 (μ g/mL)⁻¹·s⁻¹), Gd-DTPA (β_1 =4.49 mM⁻¹·s⁻¹, β_2 =5.60 mM⁻¹·s⁻¹). Additionally, relaxation rates of solutions in Figure 1 containing only saline corresponded to the following relaxation times: T₁° = 2512 msec and T₂° = 1265 msec.

The information presented in Figures 1a and 1b provides a basis for predicting relaxation rates influenced by mixtures of both Gd-DTPA and SPIO contrast agents. The experimental relaxivity data from all 25 phantom solutions is shown in Figures 2b and 2d along with predictions (Figures 2a and 2c). Here, both R₁ and R₂ relaxation rates are verified as maintaining nearly linear relationships with an increase in concentration of either contrast agent, individually, or of both simultaneously. This is further verified by an analysis of the error produced from the predictions based on the experimental results (Figures 2e and 2f). Specifically, the error in the R₁ predictions was less than +/- 8% for all 25 phantoms and the error in the R₂ predictions was less than +/- 8.5% for all 25 phantoms. Figure 3 displays an interpretation of both the experimental and predicted results, overlaid together, in terms of T₁ and T₂, rather than R₁ and R₂, for all 25 phantoms. Experimental results are represented by solid black dots and predicted results are represented by hollow squares.

Discussion

In this study, we presented composite relaxation properties of aqueous solutions, which can be applied to cellular labeling. Using two FDA-approved commercial contrast agents, specifically combinations of the gadolinium-based T_1 contrast agent, Gd-DTPA, and the superparamagnetic iron oxide based T_2 contrast agent, SPIO, we aimed to predict and achieve unique combinations of MRI contrast properties that are otherwise selectively unavailable.

In order to investigate the feasibility of developing a model that can closely predict composite contrast properties using SPIO and Gd-DTPA (i.e. R_1 and R_2 relaxivity rates), we first analyzed the individual MR effects of each media independently in saline using a 3T magnetic field. In comparison to the results for SPIO obtained by Horch and Does (β_2 =4.04 (μ g/mL)⁻¹·s⁻¹ at 7T) [Horch and Does, 2007], our result of β_2 =4.02 (μ g/mL)⁻¹·s⁻¹ at 3T is in reasonable agreement. Additionally, our measurement of β_1 =4.49 mM⁻¹·s⁻¹ for Gd-DTPA at 3T is in good agreement with β_1 =4.94±0.83 mM⁻¹·s⁻¹ from other studies [Liu et al., 2005].

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Using the experimentally obtained relaxivity coefficients, along with equations 1 and 2, we predicted the R_1 and R_2 relaxivity rates of the 25 phantoms (Figures 2a and 2c) and compared them to the original results (Figures 2b and 2d), which produced an error of less than +/- 8% for each R_1 (Figure 2e) and less than +/-8.5% for each R_2 (Figure 2f). Additionally, R_1 and R_2 relaxivity rates were converted to T_1 and T_2 relaxation constants for both the predicted and experimental results from each phantom to help better visualize composite contrast effects (Figure 3). The region bounded by the fitted lines for SPIO and Gd-DTPA in saline water, individually, represents the hypothetical range of available contrast properties using this approach. The error produced in transverse relaxation from the use of a spin-echo sequence can potentially be reduced using alternative methods. For example, optimization of the Carr-Purcell-Meiboom-Gill (CPMG) scan sequence, which reduces magnetic field inhomogeneities by counteracting dephasing echoes, significantly improved the accuracy and precision of T_2 measurements [Pell et al., 2006].

In the current work, we investigated composite contrast properties using specific ranges of contrast agent concentrations. These concentrations were based around recommended dosages for clinical use given by the manufacturer. Accordingly, it has been shown that iron exposure (*i.e.* SPIO) higher than 25pg Fe/cell can be toxic to the cell [de Freitas et al., 2001; Bowen et al., 2002; Cunningham et al., 2005] and is thus not suitable for clinical use. As a result, we are reporting only a fraction of the potential relaxation effects of an MRI composite contrast agent using SPIO and Gd-DTPA. In addition to toxicity, the use of higher concentrations of SPIO would create a drastic reduction in signal intensity due to profound shortening of T_2^* .

There are several known potential applications of a composite contrast agent applicable to contrast enhanced MRI. For instance, the advancement of cell replacement therapies requires the development of long term (i.e. weeks), in vivo cellular imaging techniques [Lindvall and Bjorklund, 2004; Dunnett and Rosser, 2004; Savitz et al., 2004]. Cellular MRI has emerged as a prime candidate to achieve this [Rogers et al., 2006]. However, signal reduction induced by SPIO-based contrast media may deter the unambiguous detection of labeled cells from background tissue comprised of an inherently low signal or signal void [Baklanov, 2004; Cunningham et al., 2005]. The attainment of composite contrast properties, using a mixture of SPIO and Gd-DTPA agents, can greatly aid the elimination of this prospect through the use of differential contrast weightings. As a result, adjustments to contrast weighting might allow for improved monitoring/tracking of magnetically labeled, implanted therapeutic cells. The adoption of dual echo-time imaging and concurrent application of an automatic segmentation algorithm may also help to selectively identify the site of labeled cells [Erickson and Avula, 1998]. Alternative methods may include dual spectroscopic imaging (i.e. SPIO combined with fluorescent nanoparticles containing F19), which has been used to enhance brain tumor delineation for tumor resection [Tréhin et al., 2006]. However, the requirement for multi-nuclear spectroscopic imaging is a potential drawback. The contrast agents based on lipid-shell micro-bubbles used in ultrasound-based molecular imaging [Leong-Poi et al., 2005] may be adopted in conjunction with the use of MR contrast agents for multimodal imaging.

Additionally, temporal progression of MR signals from the acquisition of contrast-enhanced dynamic MRI has previously been used to aid in the determination of the extent of injury from acute myocardial infarction [Kim et al., 1996], the characterization of breast tumors [Yoo et al., 2002], and the determination of hepatic tumor aggressiveness [Pastor et al., 2002]. Contrast kinetics associated with a composite contrast agent may increase the effectiveness of these methods by providing additional information that is unattainable via the use of only one type of contrast agent. However, any potential application requires consideration of the biodistribution of each agent in addition to the basic relaxation

properties. This is because the biodistribution may ultimately affect the tissue signal properties in a manner that is not readily predictable based on the simple formalism of the present study using well mixed phantom solutions.

Conclusion

A composite contrast agent for MRI consisting of an aqueous mixture of SPIO and Gd-DTPA exhibits unique R_1 and R_2 relaxation rates. The observed rates are consistent with the individual use of each material assuming minimal mutual interaction and thus can be well predicted using a linear model within a limited range of media concentrations. The method may be applied to create 'user-tunable' contrast conditions for the visualization of magnetically labeled cells.

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Figure 1.

(a) R_1 and R_2 relaxivity curves for SPIO based on T_1 and T_2 imaging, respectively, using seven phantom solutions containing a range of SPIO concentration in saline. (b) The corresponding relaxivity curves for Gd-DTPA.



Figure 2.

(a) Predicted R_1 of the 25 composite contrast solutions and (b) the actual R_1 from the experimental results. (c) Predicted R_2 of 25 composite contrast solutions and (d) the actual R_2 from the experimental results. Error (percentage) in the predicted R_1 and R_2 results after comparison to the experimental results is shown in (e) and (f), respectively.



Figure 3.

Graph of the experimental T_1 and T_2 relaxation times for each of 25 composite contrast solutions overlaid by the predicted T_1 and T_2 relaxation times. Experimental results are indicated by a solid black dot and predicted results are indicated by hollow squares. A red '+' denotes approximate coordinates (T_1 , T_2), in milliseconds, of white matter (1084, 45), gray matter (1331, 80), and blood (1932, 275) [Wansapura et al., 1999]. Boundaries of relaxation time for both SPIO and GD-DTPA in saline water, individually, are also shown as dotted lines.