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Effects of Superparamagnetic Iron Oxide Nanoparticles on the Longitudinal and Transverse Relaxation of Hyperpolarized Xenon Gas

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Abstract

SuperParamagnetic Iron Oxide Nanoparticles (SPIONs) are often used in magnetic resonance imaging experiments to enhance Magnetic Resonance (MR) sensitivity and specificity. While the effect of SPIONs on the longitudinal and transverse relaxation time of ^1H spins has been well characterized, their effect on highly diffusive spins, like those of hyperpolarized gases, has not. For spins diffusing in linear magnetic field gradients, the behavior of the magnetization is characterized by the relative size of three length scales: the diffusion length, the structural length, and the dephasing length. However, for spins diffusing in non-linear gradients, such as those generated by iron oxide nanoparticles, that is no longer the case, particularly if the diffusing spins experience the non-linearity of the gradient. To this end, 3D Monte Carlo simulations are used to simulate the signal decay and the resulting image contrast of hyperpolarized xenon gas near SPIONs. These simulations reveal that signal loss near SPIONs is dominated by transverse relaxation, with little contribution from T_1 relaxation, while simulated image contrast and experiments show that diffusion provides no appreciable sensitivity enhancement to SPIONs.

Graphical abstract

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Keywords

Superparamagnetic iron oxide nanoparticles; Hyperpolarized ^{129}Xe ; Longitudinal relaxation; Transverse relaxation; Restricted diffusion

I. Introduction

Hyperpolarized (HP) noble gas MRI has been extensively developed as a methodology to image the lung airspaces in place of conventional proton MRI [1–4]. Proton MRI in the lung, while possible, is difficult for a variety of reasons [5]. The lung provides intrinsically low MR signal because of the low density of water in the lungs and because susceptibility differences between air and tissue create strong, local magnetic field gradients that cause rapid dephasing of the ^1H signal [6].

Hyperpolarized noble gases are much less affected by the highly inhomogeneous magnetic environment of the lungs due to their rapid diffusion [7]. In recent years, thanks to an increase in polarization efficiency, hyperpolarized gas MRI in the lung has been shown to provide anatomical information on ventilation defects caused by asthma, cystic fibrosis, and Chronic Obstructive Pulmonary Disease (COPD) [8–11]. The isotopes ^3He and ^{129}Xe can both be hyperpolarized and used for lung imaging, with ^3He generating a stronger signal due to a larger gyromagnetic ratio and, generally, greater achievable polarization compared to ^{129}Xe . However, high demand and a limited supply have made ^3He less attractive, while lower cost and high tissue solubility have made ^{129}Xe more attractive for lung imaging [12]. Specifically, the high tissue solubility of xenon has allowed HP ^{129}Xe applications in the lungs to be extended from lung ventilation imaging to imaging of gas exchange and tissues and organs outside the lungs [13–16].

Another contrast agent that has been of particular interest for in vivo MR applications is Super Paramagnetic Iron Oxide Nanoparticles (SPIONs). SPIONs demonstrate high compatibility with biological systems and their properties can be easily manipulated by adjusting their size and their surface coating, or by surface functionalization [17–19]. Functionalized SPIONs have been used to target specific cells, like tumor cells, and to enhance the sensitivity of conventional ^1H MRI down to the single cell [20]. This sensitivity enhancement is possible thanks to the SPIONs' large magnetic moment, which affects both transverse and longitudinal relaxation times of nearby ^1H spins in a manner that is fairly well understood [19,21].

While superparamagnetic iron oxide particles and hyperpolarized gases have been used independently, for different applications, very few studies have tried to combine them [22,23]. Vignaud, et al. used SPIONs in combination with HP ^3He to decrease the tissue/air susceptibility mismatch and increase the transverse relaxation time of HP ^3He in the lungs. Years ago, our group proposed combining HP ^3He with SPIONs to increase sensitivity and specificity of MR to detect of cancer cells in the lungs. However, to our knowledge, no studies have yet been performed to systematically evaluate the effects of iron oxide on HP gases, specifically to separate the effects of SPIONs on the longitudinal and transverse relaxation times of hyperpolarized gas spins as well as their effects on image contrast.

The objective of this paper is to characterize the separate effects of SPIONs on the transverse and longitudinal relaxation rates of hyperpolarized xenon under several restricted diffusion regimes and evaluate the effect that SPIONs have on hyperpolarized image contrast in gradient echo sequences. This is accomplished by first computing the field perturbation generated by various amounts of iron oxide nanoparticles. Three-dimensional random walk simulations of spins diffusing and dephasing within the magnetic field perturbation created by SPIONs are then used to analyze the contribution of SPIONs to the longitudinal and transverse spin relaxation at different length scales while the magnetization decay within individual voxels is utilized to generate simulated gradient echo MR images. Experimental work is then performed to validate this approach.

II. Materials and Methods

A. Theory

The effect of magnetic field gradients on the transverse relaxation time of water has been studied for decades [24–27]. Magnetic field inhomogeneities are known to produce a spatial variation of the Larmor frequency, causing a loss of phase coherence between the spins and a decrease in signal intensity. In the presence of uniform gradients, the behavior of the magnetization is often described based on the relative size of three characteristic length scales: the diffusion length, the structural length, and the dephasing length. The diffusion length is defined as the distance that a particle can diffuse in a given time, τ :

$$l_D = \sqrt{D\tau}, \quad (1)$$

where D is the diffusion coefficient of the molecule. This length scale depends exclusively on the diffusion coefficient of the molecule under study and on the time between signal excitation and detection, which for a gradient-recalled echo sequence corresponds to the echo time. The structural length, l_s , is a measure of the dimension of the restriction in which the spin is allowed to diffuse and is defined by the volume to surface ratio (V/S). Finally, the dephasing length is the distance a particle has to diffuse to acquire a total phase shift of 2π . For a linear gradient, this distance is defined as [28]:

$$l_g = \left(\frac{D}{\gamma g} \right)^{\frac{1}{3}}, \quad (2)$$

where γ is the gyromagnetic ratio of the nuclear spin, and g is the strength of the linear gradient.

Depending on the relative size of these length scales, three main regimes of transverse magnetization decay have been identified: free diffusion, localization, and motional narrowing. Free diffusion occurs when the diffusion length is the shortest length scale. In this case, the magnetization decay is described by [29]:

$$\frac{M(g, \tau)}{M_0} = \exp\left(-\frac{2}{3}\gamma^2 g^2 D \tau^3\right). \quad (3)$$

The motional narrowing regime is found when the structural length is the shortest. In this regime, the spins appear to experience a mean dephasing. In this case, the dephasing of the magnetization is described, for restricted diffusion between two planar boundaries by [25]:

$$\frac{M(g, \tau)}{M_0} = \exp\left(-\frac{1}{120} \frac{\gamma^2 g^2 l_s^4 2\tau}{D}\right). \quad (4)$$

Other structural geometries will have a similar expression but with different numerical factors in the exponent. The localization regime occurs when the gradient length is shortest. In this case the magnetization decay at long echo times between parallel plane boundaries is described by [28]:

$$\frac{M(g, \tau)}{M_0} = c \frac{D^{\frac{1}{3}}}{\gamma^{\frac{1}{3}} g^{\frac{1}{3}} l_s^{\frac{1}{3}}} \exp\left(-a_1 \gamma^{\frac{2}{3}} g^{\frac{2}{3}} D^{\frac{1}{3}} \tau\right), \quad (5)$$

where $c = 5.8841$ and $a_1 = 1.0188$.

As can be seen from these examples, for relatively simple geometries in the presence of linear gradients, simple analytical expressions of the magnetization decay can be obtained. However, most of the magnetic field gradients in MRI experiments are non-uniform. Examples are the magnetic field gradients present in the lung airspaces, or those generated by SPIONs. In this case, the dephasing length, l_g , is expected to acquire a spatial dependence, and as previously described by Valckenborg, et al. [30], a fourth characteristic length scale can be introduced: the magnetic-field curvature length. The magnetic-field curvature length, l_B , is a measure of the non-linearity of the magnetic field gradient and is defined by [30]:

$$l_B(x) = \left| \frac{g(x)}{C(x)} \right|, \quad (6)$$

where $g(x)$ is the gradient and $C(x)$ is the curvature of the local magnetic field. When this length scale is larger than l_g , the spins do not experience the non-linearity of the gradient and the above description of the magnetization decay still holds. However, when l_B is comparable to the local l_g , the description of the magnetization decay becomes more complicated [30].

In the presence of non-uniform field gradients, multiple numerical models have been developed to predict the magnetization decay, including the static dephasing regime, the Gaussian phase approximation, and the weak field approximation. In the situation when diffusion is unable to average out the phases of different nuclei faster than the time needed for their dephasing, the static dephasing regime may be utilized [26]. For permeable or impermeable, structure-specific magnetic field inhomogeneities of mesoscopic scale, it is possible to use the Gaussian phase approximation for the magnetization decay [31,32]. The weak field approximation may apply when the field inhomogeneities are non-uniform but still weak in magnitude [27]. It has been shown that these approximation regimes accurately predict the behavior of the magnetization when specific criteria are satisfied.

The static dephasing regime for gradients produced by spherical SPIONs holds true if [26]:

$$\delta\omega \cdot \frac{\zeta^{\frac{1}{3}} R_0^2}{6 \cdot D} \gg 1, \quad (7)$$

where R_0 is the average radius of the iron oxide particles, ζ is the volume fraction of iron oxide, and $\delta\omega$ is the characteristic frequency shift, which for spheres is defined as:

$$\delta\omega = \frac{\gamma(m_0 - m)}{3}, \quad (8)$$

where m_0 and m are the magnetization densities of the iron oxide and medium, respectively. The Gaussian phase approximation can accurately predict the magnetization decay when [32]:

$$\frac{\zeta D d}{\gamma \Delta \chi B_0 R_0^2} > 1, \quad (9)$$

where d is a geometrical factor equal to three for spheres, χ is the magnetic susceptibility difference between iron oxide and the medium, and B_0 is the external magnetic field strength. Finally, the weak field approximation is valid for spherical iron oxide particles when [27]:

$$\frac{\gamma \Delta \chi B_0 R_0^2}{3D} \ll 1. \quad (10)$$

In addition to transverse relaxation, magnetic field inhomogeneities are known to cause increased longitudinal, or T_1 , relaxation rates. For water molecules, this effect is typically small and confined to water molecules that are able to diffuse around the iron oxide nanoparticles and experience a fluctuation of the transverse component of the magnetic field

at the Larmor frequency. However, for rapidly diffusing spins like hyperpolarized gases, whose diffusion coefficient is three orders of magnitude higher than water, the effect can be significant. In addition, while water spins typically experience signal enhancement from field inhomogeneities in T_1 -weighted sequences, diffusion in magnetic field inhomogeneities causes permanent loss of signal in xenon spins due to the non-renewable nature of the nuclear spin polarization. This effect can be described by the following relation [33,34]:

$$\frac{1}{T_1} = D \frac{|\nabla B_T|^2}{B_0^2} (1 + \Omega_0^2 \tau_c^2)^{-1}, \quad (11)$$

where ∇B_T is the transverse component of the spatially-dependent gradient of B_0 . The extra factor, $(1 + \Omega_0^2 \tau_c^2)^{-1}$ accounts for rotation of spins between kinetic collisions, with Ω_0 representing the Larmor frequency and τ_c representing the time between collisions. This factor is nearly unity under the experimental conditions of interest presented here and will be omitted. To this end, one of the scopes of this work was to analyze the conditions under which SPIONs can give rise to longitudinal relaxation.

B. Simulations

To compute the magnetic field perturbation caused by given amounts of iron oxide nanoparticles, COMSOL Multiphysics (COMSOL Inc., Burlington, Massachusetts, U.S.A.) was employed. Although the magnetic field generated by a sphere-like iron oxide accumulation has an analytical expression that can be easily calculated, the use of COMSOL in calculating the magnetic field allows for a large field of view to be analyzed without loss in resolution, as the mesh size of the simulations can be easily decreased with minimal increase in computation time.

Simulations were first performed to characterize the effects, during restricted diffusion, of structural size and iron oxide concentration on the relaxation rates of hyperpolarized xenon. The geometry involved a cubic structure, which represented the region in which the gas was allowed to diffuse, with iron oxide particles placed at its center (Fig. 1). A cubic structure was used to guarantee equal distance between mesh points. Five different side lengths, 0.02 cm, 0.04 cm, 0.2 cm, 0.4 cm and 2 cm, were used for the large cube and the side length of the iron oxide was changed proportionally to maintain a constant volume fraction of iron oxide. To examine the various diffusion regimes, three different iron oxide volume fractions were tested: 1 ppm, 15.625 ppm, and 125 ppm.

The magnetic field perturbation produced by these iron oxide particles was computed assuming an external magnetic field of 9.4 T oriented along the z-direction (Fig. 1). The material chosen, in this case, for the iron oxide was a built-in, non-linear magnetic material with a saturation magnetization of 146,000 A/m, roughly a factor of three less than the saturation magnetization of bare magnetite.

Monte Carlo simulations were performed using a custom MATLAB (MathWorks, Natick, MA, USA) script to determine the depolarization and dephasing of an ensemble of 100,000 spins within the cubic structure. Specifically, for every time step, the instantaneous theoretical T_1 relaxation value for each spin was computed using Eq. 11 while the spin phase for each time step, $e^{-i\gamma B_z t}$, was determined by using the z-component of the magnetic flux density. Temporal resolutions, calculated using the mean square displacement in three dimensions and the average distance to the nearest neighbors, were 14.4 ns, 82.5 ns, 1.44 μ s, 8.37 μ s, and 135 μ s for the 0.02 cm, 0.04 cm, 0.2 cm, 0.4 cm and 2 cm structural lengths, respectively. Spatial resolution was determined by the side length of the diffusion region. Images were then generated, at the specified “echo” time, by summing the magnetization of each spin, with its acquired phase, for each of the 10×10 voxels in which the simulated cubic volume was partitioned.

Water images were produced by assuming a static dephasing regime for water protons, where diffusion is ignored and only T_2^* relaxation contributes to signal loss. For the hyperpolarized xenon gas, where diffusion could not be neglected, the diffusion coefficient was determined using the Fuller-Schettler-Giddings equation at a temperature of 293.15 K and pressure of 100,000 Pa and calculated to be 0.117 cm²/s [35].

Simulations were also performed for a 15 ml conical centrifuge tube (Thermo Fisher Scientific, Waltham, Massachusetts, U.S.A.) with 1.5 mg of ferric oxide taped to the outside of the tube. First, a full-scale, rectangular model of the tube and iron oxide was created using the computer-aided design (CAD) software SolidWorks (Dassault Systèmes SolidWorks Corp., Vélizy-Villacoubly, France). A rectangular model was used instead of a cylindrical model so that a cubic matrix could be used to partition the entire volume for the random walk simulation. The CAD model was imported into COMSOL Multiphysics and used to calculate the field perturbation produced by iron oxide placed in a 9.4 T uniform magnetic field oriented along the longitudinal axis of the tube. The volume magnetic susceptibility of the ferric oxide was taken to be 5300 ppm, giving a magnetization of 39,500 A/m. This value was used to match the field perturbation produced experimentally at 9.4 T by the iron oxide nanoparticles placed on the surface of the centrifuge tube.

The volume magnetic susceptibility of the empty space inside the tube was chosen to be 0 ppm, while the value of the magnetic susceptibility of water placed inside the tube for comparison was chosen to be -9.04 ppm [36]. The volume magnetic susceptibility of the 1 mm thick plastic wall of the phantom tube and the volume surrounding the tube and iron oxide was taken to be zero in all cases. Once the field was generated, the same custom MATLAB script was employed to calculate the longitudinal relaxation rate and magnetization for an ensemble of 100,000 spins with a temporal resolution of 70 μ s. Data from MATLAB was used to generate simulated magnetic resonance images with a spatial resolution of 2 mm by 2 mm and a slice thickness of 1.65 cm (the width of the 15 ml phantom model) to match the experimental imaging parameters.

Finally, simulations were performed on a mouse lung model composed of a matrix of 341 empty spheres with a radius of 40 μ m and a surface thickness of 4 μ m, packed in a face-

centered cubic structure. The airspace of the alveoli were treated as air and had a magnetic susceptibility value of 0 ppm, while the surface was treated as tissue and given a magnetic susceptibility of -7.79 ppm [37]. To simulate cancerous tissue targeted by iron oxide nanoparticles, the central alveolus was filled with iron oxide mixed in water at varying concentrations. Simulations were performed for various molarities of iron oxide nanoparticles with a volume magnetic susceptibility of 5300 ppm.

The field distribution was determined in each case and random walk simulations for an ensemble of 100,000 spins, randomly distributed among the 42 nearest alveoli surrounding the iron oxide, were performed in MATLAB with a temporal resolution of 4 ns. At each time step, the magnetization from each spin was summed and normalized by the total number of spins to determine the overall magnetization decay within the 42 alveoli.

C. Experiments

All imaging experiments were performed on a Bruker Biospec 94/30 USR (Bruker Biospin, Billerica, MA, USA) controlled via a console running ParaVision software. Proton and xenon images were obtained using a 35 mm inner diameter dual-tuned $^1\text{H}/^{129}\text{Xe}$ volume coil (m2m Imaging Corp., Cleveland, Ohio, USA), resonant at 400 MHz and 110.7 MHz, respectively. For xenon images, phantoms were connected to a custom-built, hyperpolarized gas-compatible ventilator that enabled pumping of hyperpolarized xenon into the centrifuge tube at a constant rate. Hyperpolarized ^{129}Xe gas, with a polarization of 16% and with a 26.4% ^{129}Xe isotopic abundance, was produced by using a Polarean 9800 ^{129}Xe hyperpolarizer (Polarean, Inc., Durham, NC).

To generate phantom images, phantoms were placed on a cradle so that the iron oxide was directly at the top of the 15 ml tube and then taped in position. The cradle was placed such that the iron oxide was at the center of the sensitive region of the volume coil. For xenon images, the acquisition was triggered 100 ms after freshly polarized xenon gas was flowed into the centrifuge tube. Proton and xenon images were acquired using a gradient-recalled echo sequence in the sagittal slice orientation with a field of view (FOV) of 6.4×3.2 cm, a matrix size of 64×32 , flip angle (FA) of 30° , and echo times (TE) of 2.7 ms, 5.4 ms, 8.1 ms, 10.8 ms, 13.5 ms, and 16.2 ms.

III. Results and Discussion

Criteria of validity for the static dephasing regime, Gaussian phase approximation, and weak field approximation were tested for relevant parameters of all simulated geometries, including those of the 15 ml centrifuge tube. A summary of calculated values for each approximation regime is shown in Table 1. From these results, it can be seen that none of these theories are sufficient to model the overall magnetization decay for any of the cubic geometries simulated. While the static dephasing regime may describe the overall magnetization decay in the centrifuge tube, it cannot be used to describe the decay within individual voxels. More importantly, at large structural lengths, the signal decay in individual voxels, which ultimately determines image contrast, can vary significantly based on proximity to the iron oxide.

To analyze the effect of diffusion on transverse relaxation, multiple structural lengths and iron oxide volume fractions were simulated. Simulated ^{129}Xe images for two different structural lengths but the same iron oxide volume fraction are shown in Fig. 2. At a structural length of 400 μm , adding a boundary around the iron oxide prevents the xenon from diffusing near the iron oxide and experiencing the strongest dephasing, considerably reducing the relaxation effects of the iron oxide nanoparticles. However, at a length scale of 4000 μm , this is no longer true. At this larger scale, the contrast generated by the iron oxide with and without the boundary is nearly identical.

When the relative contribution of T_1 and T_2^* to the signal decay is analyzed, it is clear that, in both cases, the main contribution to the signal decay is from transverse relaxation (Fig. 3). For both structural lengths, there is a negligible contribution to the magnetization decay from longitudinal relaxation. While the T_1 effect can be decreased slightly with the addition of a boundary, the overwhelming majority of magnetization loss arises from the dephasing of the spins near the iron oxide, which is only slightly enhanced in the absence of a boundary.

Figure 4 shows simulated xenon and proton images for an echo time of 2.7 ms. From this figure, it is clear that structural length plays a major role in the contrast generated by the iron oxide nanoparticles. For the 1 ppm and 125 ppm iron oxide volume fractions, diffusion is only apparent at small length scales (hundredths of centimeters). It is important to note that while the contrast enhancement in both cases is not equivalent, as the color bars vary from image to image, contrast “wash-out” is apparent for both volume fractions. This contrast “wash-out” is the result of spins being in the motional narrowing regime where spins have sufficient time to lose their individuality defined by their initial positions. However, at the largest length scales (centimeters), the effect of diffusion completely disappears. For the intermediate length scale, the effect of spin diffusion is observed only near the edges of the dark spot.

Of course, the type of contrast generated depends on the echo time at which the images are acquired. At very short echo times, the diffusion length can be much shorter than the structural and dephasing lengths. In this case, the spins behave as expected for the free diffusion regime. However, at longer echo times, for very small structural lengths the spins soon move into the motional narrowing regime as shown in Fig. 5.

At larger length scales, similar to those probed by current MRI techniques, xenon spins that are far away from the iron oxide nanoparticles appear to be in the free diffusion regime, whereas spins near the iron oxide nanoparticles appear to be in the localization regime. This behavior is confirmed by an analysis of the magnetization decay (Fig.6). At short length scales, the magnetization decay, near and far from the iron oxide, has a linear dependence on time. According to Eq. 4 and Eq. 5, this could mean that the region is within the motional narrowing or localization regimes. Figure 4 shows that the regime is most likely motional narrowing due to the reduction in magnetization decay for both volume fractions at the smallest length scale. However, at large length scales, the magnetization decay exhibits vastly different characteristics. Far from the iron oxide, the magnetization decay displays a cubic dependence on time, which according to Eq. 3 is indicative of the free diffusion

regime. Near the iron oxide, where the magnetic field gradients are highly non-uniform, and at short time scales, the magnetization decay is linear, indicating that spins have not yet experienced the non-linearity of the gradient and are effectively in the localization regime. At longer echo times, as the spins experience the non-linearity of the gradients, the behavior becomes chaotic and can no longer be defined by any of the restricted diffusion regimes described above.

In order to validate the methodology used to compute the effect of iron oxide on hyperpolarized xenon images, simulations and experiments were conducted on a gas phantom in the presence of a given amount of iron oxide. In this case, the value of the saturation magnetization was chosen based on the field perturbation produced and measured experimentally by the iron oxide on the same phantom filled with water. As can be seen from Fig. 7, the experimental image contrast nicely matches the simulated image contrast.

These simulations also show that, at the large length scales typically probed by MRI, xenon diffusion provides no sensitivity enhancement to iron oxide. The lack of contrast enhancement due to the diffusion of xenon is evident when xenon images are compared to proton images acquired from the same phantom filled with water. The contrast produced by iron oxide in the proton image looks very similar to the contrast produced by the same iron oxide particles in the xenon images acquired at a four-fold longer echo time, as one would expect based on the difference in gyromagnetic ratio between these two nuclei. Figure 8 shows that, in this case, while the dephasing length still has a spatial dependence, voxels far from the iron oxide are still in the free diffusion regime. However, near the iron oxide, where the magnetic field gradients are highly non-uniform and the magnetic-field curvature length is on the order of the diffusion length, the magnetization decay quickly becomes chaotic and cannot be described analytically by any of the restricted diffusion regimes. In addition, Fig. 8 also shows that, while the overall magnetization decay may have an analytical expression, the magnetization decay can vary significantly from voxel to voxel.

Hyperpolarized gases combined with functionalized SPIONs have been proposed to increase the sensitivity of MRI to cancer nodules in the lungs as computed tomography, the imaging modality used most frequently to provide anatomical information on lesions, is often unable to differentiate benign and malignant cells in the lungs [23,38]. The ability of MRI to detect cancer nodules in the lungs depends on the contrast enhancement provided by SPIONs on the hyperpolarized gas. To test the effects of iron oxide on the longitudinal and transverse relaxation of xenon diffusing in the lung airspaces, simulations were performed on a model of the mouse lungs. Figure 9 shows the magnetization decay of the alveoli surrounding the alveolus containing iron oxide nanoparticles and water. Interestingly, at low iron oxide concentrations, the relaxation of the magnetization of nearby alveoli is reduced as the susceptibility mismatch between air and tissue is reduced, similar to results previously obtained experimentally in mouse lungs by Vignaud, et al. using hyperpolarized ^3He [22]. By further increasing the iron oxide concentration in the central alveolus, the susceptibility mismatch is recreated, causing a decrease in the transverse relaxation time and an increased signal decay rate. However, the iron oxide concentration necessary to create an appreciable increase in signal decay is $93.6 \mu\text{mol/L}$ using iron oxide with a saturation magnetization of $39,500 \text{ A/m}$. This corresponds to a concentration of iron oxide in tissue of 15 mg/g , which is

approximately fifty times higher than the achievable concentration of 0.3 mg/g [39,40]. This indicates that in order to create a significant dephasing effect from SPIONs targeting single alveoli filled with cancer cells in xenon lung images, nanoparticle targeting efficiency and saturation magnetization must increase.

In summary, our simulations and experiments together show that iron oxide nanoparticles mainly reduce the transverse relaxation time of hyperpolarized xenon, with little effect on the longitudinal relaxation time. In addition, at the length scales typically probed by MR, hyperpolarized xenon gas diffusion does not provide a sensitivity enhancement to iron oxide nanoparticles and, because of the lower gyromagnetic ratio of xenon, the sensitivity of xenon to iron oxide is reduced compared to that of ^3He or water protons. However, for lung imaging, where the T_2^* effect of iron oxide on water protons cannot be used, as the proton signal is rapidly dephased by the strong magnetic field gradients present in the lungs, a more appropriate comparison would be between the T_1 enhancement of iron oxide on water protons in ultra-short echo time images, and the T_2^* effect of iron oxide on xenon in gradient echo images. We attempted such a comparison experimentally without much success as, when a given amount of iron oxide in solution was injected into the lungs, the signal defect generated in xenon images by the reduction in T_2^* could not be differentiated from ventilation defects caused by the obstruction of the airways. At the same time, a signal enhancement in the water images caused by the reduction in T_1 could not be differentiated from the injected suspension in the lungs.

IV. Conclusions

The effect of SPIONs on the longitudinal and transverse relaxation rates of hyperpolarized xenon during restricted diffusion was analyzed using Monte Carlo simulations. These simulations revealed that xenon signal loss near SPIONs is due mainly to transverse spin relaxation with no appreciable effect on longitudinal spin relaxation at any of the length scales analyzed and for reasonable amounts of iron oxide particles such as those expected in targeted tissues. While the longitudinal relaxation rate does increase with decreasing structural length, the length scales at which a noticeable effect would occur are in the micrometer range. At larger length scales, near the iron oxide particles, simulations showed that xenon appears to be in a regime which cannot be described by conventional restricted diffusion regimes, including approximations for non-uniform gradients, with diffusion adding no sensitivity enhancement. As such, in order to increase sensitivity to iron oxide, one should consider using gases with higher gyromagnetic ratios, such as ^3He or fluorinated gases.

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- Effect of SPIONs on the T_1 and T_2^* relaxation rates of xenon is characterized.
- Various restricted diffusion regimes are tested using FEM and Monte Carlo simulations.
- Simulations are validated in a phantom and with comparison to previous studies.
- SPIONs have negligible effect on xenon gas T_1 .
- Xenon diffusion provides no sensitivity enhancement near SPIONs compared to water.

FIG. 1.

Cubic model used for COMSOL simulations. The large volume highlighted in red shows the region in which spins are allowed to freely diffuse. The purple volume at the center represents the impermeable volume occupied by iron oxide nanoparticles. The side lengths of both regions were changed proportionally to keep the volume fraction of iron oxide constant while increasing the structural length of the region of free diffusion.

FIG. 2. Simulated hyperpolarized ^{129}Xe MR images showing a slice in the XZ plane (modeled by translucent slice in cartoon to the left) at different echo times displaying the effect of a boundary around the iron oxide on image contrast. Top: Diffusion region with a side length of 400 μm and iron oxide with a side length of 10 μm . Adding a boundary causes a noticeable difference in contrast enhancement. Bottom: Diffusion region with a side length of 4000 μm and iron oxide with a side length of 100 μm . Adding a boundary causes no noticeable change in contrast enhancement.

FIG. 3.

Longitudinal and transverse relaxation curves for two different diffusion regions with the same iron oxide volume fraction showing that the overwhelming majority of relaxation arises from transverse spin dephasing. Top: 400 μm side length diffusion region. While only a very small difference is seen in longitudinal relaxation when adding a boundary, a noticeable difference is seen in transverse relaxation. Bottom: 4000 μm side length diffusion region. In this case, the addition of a boundary has a negligible effect on both longitudinal and transverse relaxation.

FIG. 4.

Simulated xenon and water MR images at TE=2.7 ms for two different iron oxide volume fractions, at various length scales. Top: Iron oxide volume fraction of 125 ppm. While the effect of diffusion is noticeable at small length scales, at large length scales it becomes undetectable. Bottom: Iron oxide volume fraction of 1 ppm. While the smaller amount of iron oxide used in these simulations produces a significantly smaller signal decay, the same trend holds true: the effect of diffusion is only apparent at very short length scales. Proton images appear the same at all length scales because diffusion at these length scales can be ignored. Cubes to the left are for reference but are not shown to scale.

FIG. 5.

Simulated xenon MR images at various length scales for an iron oxide volume fraction of 1 ppm. Top: While at extremely short echo times the spins are in the free diffusion regime, as the echo time increases they quickly move into the motional narrowing regime. Center: At intermediate length scales, the effect of diffusion becomes apparent at longer echo times (milliseconds). Bottom: At large length scales, the effect of diffusion is undetectable even at longer echo times (tenths of a second).

FIG. 6.

Simulated xenon magnetization decay for an iron oxide volume fraction of 125 ppm for small and large length scales. Top: For the smallest diffusion region, the magnetization both near and far from the iron oxide exhibits a linear dependence on time, indicating that spins are in the motional narrowing regime and have lost their individuality defined by their initial positions. Bottom: For large diffusion regions, more than one diffusion regime exists. While spins far from the iron oxide are in a free diffusion regime, as indicated by the cubic time dependence on the log of the magnetization, near the iron oxide the log of the magnetization decay is linear for short echo times, indicating a localization regime. However, as the spins continue to evolve they experience the non-linearity of the dephasing gradients and the magnetization decay becomes chaotic.

FIG. 7.

Experimental (top) and simulated (bottom) xenon and water MR images of a 15 ml conical centrifuge tube (shown on left with red outline indicating slice size) with 1.5 mg of iron oxide taped on the outer wall (right side of tube). As the echo time increases, the effect of xenon gas diffusion is unnoticeable in both the simulations and experiments. At large length scales, the contrast generated by iron oxide particles in the xenon images is similar to that observed in water images (far right) at a four-fold smaller echo time.

FIG. 8.

Magnetization decay for the 15 ml conical centrifuge tube with 1.5 mg of iron oxide taped on the outer wall. While the overall magnetization decay may be described analytically using a monoexponential function, individual voxels exhibit very different magnetization decay. Similar to the large length scale cubic simulations, spins far away from the iron oxide nanoparticles are found in the free diffusion regime. This shows that, even though iron oxide generates a non-linear magnetic field gradient, if the field is not too strong, such that the dephasing length is the shortest length throughout the volume, the free diffusion regime is still achievable. Near the iron oxide, at very short echo times, the decay is linear. However, at longer echo times, as spins experience the non-linearity of the gradient, the decay becomes non-linear.

FIG. 9.

Magnetization decay for the 42 alveoli (highlighted in blue) surrounding the central alveolus (highlighted in red) containing a mixture of water and iron oxide at different concentrations. First, the relaxation is relatively small, less than 1% even after 20 ms. Second, the magnetization decay (right) shows a similar trend to the experimental decay observed by Vignaud, et al. [22] for helium gas in the mouse lungs. Initially, at increasing iron oxide concentration, the magnetization decay rate decreases, but for iron oxide concentrations $>47 \mu\text{mol/L}$, there is an increase in signal decay rate.

Calculated values for criteria of validity in the static dephasing regime, Gaussian phase approximation, and weak field approximation. Cubic geometries with iron oxide volume fractions of 1 ppm, 15.625 ppm, and 125 ppm do not meet the criteria for any of the approximation regimes. Only the centrifuge tube meets the criteria for the static dephasing regime.

TABLE 1

	Volume Fraction 125 ppm	Volume Fraction 125 ppm	Volume Fraction 125 ppm	Volume Fraction 15.6 ppm	Volume Fraction 15.6 ppm	Volume Fraction 15.6 ppm	Volume Fraction 1 ppm	Volume Fraction 1 ppm	Volume Fraction 1 ppm	Centrifuge Tube
Structural Length (m)	0.0002	0.002	0.02	0.0004	0.004	0.04	0.0004	0.004	0.04	0.025
Static Dephasing Criterion $\frac{1}{\zeta^3} \frac{2}{R_0^2} \delta \omega \cdot \frac{1}{6 \cdot D} \gg 1$	2.8 E-3	0.285	28.5	1.4E-3	0.142	14.2	9.1E-5	0.00911	0.911	247
Gaussian Approximation Criterion $\frac{1}{\zeta D d} \frac{1}{\gamma \Delta \chi B_0 R_0^2} > 1$	1.5E-4	1.5E-6	1.5E-8	1.9E-5	1.9E-7	1.9E-9	7.7E-6	7.7E-8	7.7E-10	1.8E-8
Weak Field Approximation Criterion $\frac{1}{3D} \frac{1}{\gamma \Delta \chi B_0 R_0^2} \ll 1$	0.424	42.4	4240	0.424	42.4	4240	0.0678	6.78	678	20600