Published in final edited form as:

Magn Reson Med. 2014 May ; 71(5): 1906–1911. doi:10.1002/mrm.24837.

Dispersion of Relaxation Rates in the Rotating Frame Under the Action of Spin-Locking Pulses and Diffusion in Inhomogeneous Magnetic Fields

John T. Spear^{1,2}, Zhongliang Zu^{1,3}, and John C. Gore^{1,2,3,4,5,*}

¹Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, USA

²Departments of Physics and Astronomy, Vanderbilt University, Nashville, Tennessee, USA

³Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee, USA

⁴Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee, USA

⁵Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee, USA

Abstract

Purpose—A method is described for characterizing magnetically inhomogeneous media and the spatial scales of intrinsic susceptibility variations within samples. The rate of spin-lattice relaxation in the rotating frame, $R_{1\rho}$, is affected by diffusion effects to a degree that depends on the magnitude of an applied spin-locking field. Appropriate analysis of the dispersion of $R_{1\rho}$ with locking field may be used to characterize susceptibility variations in inhomogeneous tissues.

Theory and Methods—The contribution of diffusion to $R_{1\rho}$ is quantified by an analytic expression derived by analyzing the effects of diffusion through periodic variations of magnetic susceptibility and is used to predict the effects of inhomogeneities in simple phantoms. The theory is further applied to imaging to derive parametric images that portray the dimensions of susceptibility inhomogeneities independent of their magnitude.

Results—Significant dispersion of $R_{1\rho}$ with locking field was predicted and measured experimentally for suspensions of microspheres ranging from 1 to 90 μm in diameter. For scales of practical interest, these dispersion effects occur at much lower locking fields than the range in which chemical exchange effects cause similar dispersion.

Conclusion—There is good agreement between theory and experiment, and the method has potential for quantitative tissue characterization and functional imaging.

Keywords

$T_{1\rho}$; dispersion; diffusion; spin-lock; susceptibility

INTRODUCTION

The overall purpose of the work reported here was to develop a novel imaging approach for characterizing inhomogeneous biological tissues distinguished by intrinsic spatial variations of magnetic susceptibility. Such variations arise in several contexts, notably within trabecular bone, in the presence of vasculature containing paramagnetic agents or deoxyhemoglobin, or in tissues that accumulate iron-bearing proteins. Methods for quantifying the scales and magnitudes of intrinsic magnetic inhomogeneities have several practical applications for tissue characterization. Here we consider the potential role of measurements of spin-lattice relaxation rates in the rotating frame ($R_{1\rho} = 1/T_{1\rho}$) and demonstrate how these may be used to derive novel information about the spatial scales of inhomogeneities.

The variation of $R_{1\rho}$ under the action of spin-locking fields of different magnitudes ($R_{1\rho}$ dispersion) has been previously exploited for studies of chemical exchange and for quantitative measurements of exchange kinetic parameters (1–4). In biological samples, exchange between labile protons in various metabolites or macromolecules and solvent water may make major contributions to measured relaxation rates of water, especially at high fields, but their significance generally decreases under increasingly stronger locking fields. This variation with locking field provides a basis for estimating the exchange rates (5). Similar to the jumping of nuclei from sites of different discrete chemical shifts (and hence resonance frequencies), diffusion of mobile nuclei among intrinsic magnetic field gradients produced by variations in magnetic susceptibility may also lead to spin dephasing and alter measured relaxation rates (6). Again, the variation of $R_{1\rho}$ with locking field can provide insight into the time-scale of the variations of the resonant frequency, and thereby their spatial extents.

Where susceptibility variations within a sample volume or image voxel are produced by discrete inhomogeneities or inclusions, such as the presence of paramagnetic particles, or deoxyhemoglobin within the microvasculature, the magnitude and spatial extent of the field perturbations depend on the nature and sizes of the inhomogeneities (7). The influences of diffusion among such inhomogeneities on transverse relaxation rates R_2 and R_2^* have been previously extensively analyzed by theory and computer simulations and studied experimentally in vitro and in vivo (8–19), and various regimes have been defined for how diffusion affects relaxation in spin echo and gradient echo imaging. However, the corresponding effects on $R_{1\rho}$ have been much less considered previously. Lammentausta et al. (20) reported measurements of $T_{1\rho}$ for water within trabecular bone but noted “to our knowledge there is currently no theoretical formalism considering $T_{1\rho}$ relaxation during diffusion in local field gradients.” Moreover, they measured increases of $R_{1\rho}$ with respect to the locking field amplitude for water in bone, contradictory to what would be expected. They noted that “a more complete theoretical formalism... is required to better understand the behavior of $T_{1\rho}$ relaxation under these kinds of experimental conditions.” Others, e.g., Kettunen et al. (21), examined the effects of changes in intravascular susceptibility from the use of iron oxide contrast agents but saw little change in $R_{1\rho}$ at a single (relatively high) locking field. However, they did not measure the dispersion at other fields, although they did

confirm that $R_{1\rho}$ decreases when blood is oxygenated because of changes in exchange-mediated relaxation by deoxyhemoglobin.

Here, a new simple analytic relationship is derived between the dispersion of $R_{1\rho}$ measurable by spin-locking methods and the rate of diffusion within spatially varying gradient fields. We subsequently use this theoretical result to predict how $R_{1\rho}$ may be used to quantify aspects of diffusive behaviors and intrinsic susceptibility variations in inhomogeneous media. Although the expression for the ideal case we analyze is only an approximation to realistic situations, we show how reasonable estimates may be obtained of novel material properties that can be used for quantitative tissue characterization.

THEORY

The approach of Deverell et al. (22) was adopted for analyzing the behavior of a system of spin-1/2 nuclei subject to a static magnetic field $H_0 = \omega_0/\gamma$ and an on-resonance rotating field of frequency ω_0 and amplitude $H_1 = \omega_1/\gamma$. They considered the effects of a time varying perturbation field $\delta\omega(t)$ that fluctuates with an average correlation time τ_c and which can induce relaxation of the magnetization aligned with H_1 . If $\delta\omega\tau_c \ll 1$ and $\delta\omega \ll \omega_1 \ll \omega_0$, Deverell et al. show that the contribution to $R_{1\rho}$ from time-varying field perturbations depends on the spectral content of the autocorrelation of field variations experienced by the nuclei at the relevant locking frequency.

$$R_{1,\rho} = \frac{1}{2} \int_{-\infty}^{\infty} \overline{\delta\omega(t)\delta\omega(t-\tau)} \cos\omega_1\tau d\tau. \quad [1]$$

We use this result to describe the behavior of nuclei diffusing in a spatially varying field $b(x)$ such that

$$\delta\omega(t) = \gamma b(x) = \gamma b(x(t)). \quad [2]$$

We consider the special case where the field varies sinusoidally in one dimension. Cowan (23) has analyzed the correlation of displacements and fields experienced by spins diffusing in such a medium. In this case,

$$b(x) = A \sin qx \quad [3]$$

where q is the spatial frequency of the variation. Then

$$\frac{\partial b(x)}{\partial x} = Aq \cos qx \quad [4]$$

The mean squared gradient is g where

$$g^2 = \frac{A^2 q^2}{2} \quad [5]$$

so that

$$b(x) = \sqrt{2} \frac{g}{q} \sin qx \quad [6]$$

A linear gradient corresponds to the case $q = 0$. Substituting for the correlation of the frequency variations,

$$\overline{\delta\omega(t)\delta\omega(t-\tau)} = \gamma^2 \langle b(0)b(\tau) \rangle = 2 \left(\frac{\gamma g}{q} \right)^2 \langle \sin(qx(0)) \sin(qx(\tau)) \rangle \quad [7]$$

The position $x(t)$ changes with time and we may write the displacement

$$\Delta x(t) = x(\tau) - x(0) \quad [8]$$

so that

$$\overline{\delta\omega(t)\delta\omega(t-\tau)} = 2 \left(\frac{\gamma g}{q} \right)^2 \left\{ \langle \sin^2(qx(0)) \cos(q\Delta x(\tau)) \rangle + \langle \sin(qx(0)) \sin(q\Delta x(\tau)) \cos(qx(0)) \rangle \right\} \quad [9]$$

The displacement and the starting position are not correlated for random diffusion, so the second term on the right is zero, while the average of the term $\sin^2(qx(0))$ is 1/2. Thus

$$\overline{\delta\omega(t)\delta\omega(t-\tau)} = 2 \left(\frac{\gamma g}{q} \right)^2 \left\langle \frac{1}{2} \cos(q\Delta x(\tau)) \right\rangle \quad [10]$$

For random Brownian motion, the probability distribution of $x(t)$ for unrestricted diffusion is Gaussian so that

$$P(\Delta x) = \frac{1}{\sqrt{2\pi\langle\Delta x^2\rangle}} \exp \left[-\frac{\Delta x^2}{2\langle\Delta x^2\rangle} \right] \quad [11]$$

Then

$$\left\langle \frac{1}{2} \cos(q\Delta x(\tau)) \right\rangle = \int_{-\infty}^{\infty} \frac{1}{2} \cos(q\Delta x(\tau)) P(\Delta x(\tau)) d\Delta x = \frac{1}{2} \exp \left[-\frac{q^2 \langle \Delta x^2(\tau) \rangle}{2} \right] \quad [12]$$

where

$$\langle \Delta x^2(\tau) \rangle = 2D\tau \quad [13]$$

and D is the usual self-diffusion coefficient. Putting this together with [12] we obtain

$$\overline{\delta\omega(t)\delta\omega(t-\tau)} = 2 \left(\frac{\gamma g}{q} \right)^2 \frac{1}{2} \exp(-q^2 D \tau) \quad [14]$$

Substituting into [1],

$$R_{1\rho} = \frac{1}{2} \int_{-\infty}^{\infty} \left(\frac{\gamma g}{q} \right)^2 \exp(-q^2 D \tau) \cos \omega_1 \tau d\tau \quad [15]$$

or

$$R_{1\rho} = \frac{\gamma^2 g^2 D}{(q^2 D)^2 + \omega_1^2} \quad [16]$$

Equation (16) states that the values of $R_{1\rho}$ will disperse for different locking fields and are strongly dependent on the gradient strength and the spatial frequency. We can define a characteristic locking field frequency ω_c for a specific spatial frequency q , $\omega_c = (1/\tau_c) = Dq^2$, so that

$$R_{1\rho} = \gamma^2 g^2 D \frac{\tau_c^2}{1 + \omega_1^2 \tau_c^2} \quad [17]$$

This curve has an inflection (i.e., steepest part of the curve where the second derivative $d^2 R_{1\rho} / d\omega_1^2 = 0$) when $3\omega_1^2 = 1/\tau_c^2$. The interval τ_c is an intrinsic characteristic of the medium that depends on the spatial scale of the inhomogeneities but not the magnitude of the susceptibility variations.

Equation [17] provides a useful starting point for the interpretation of $R_{1\rho}$ measurements of media with quasiperiodic distributions of nonuniform susceptibility at different locking fields. For example, spherical objects in a magnetic field produce an internal field that differs from the external field according to their susceptibility difference. Field gradients are generated external to the surfaces and decrease with distance (24,25). Both R_2^* and $R_{1\rho}$ will depend on the applied field (B_0), the magnetic susceptibility between the particle and the surrounding material (χ), and the object radius (R) (26). For an array of small particles in relatively close proximity the field will vary across space and the characteristic spatial frequency will be of the order of $q \approx \pi/R$. $R_{1\rho}$ will then show an inflection in the dispersion when $\omega_1 = \pi^2 D / \sqrt{3} R^2$, i.e., when the period of spin nutation about the locking field matches the time to diffuse the characteristic dimension of the inhomogeneity. For $D = 2.5 \times 10^{-5} \text{ cm}^2/\text{s}$, dispersion over the range of 23–363 Hz is expected for inhomogeneities of diameters 20–5 μm , respectively.

Our derivation started by assuming that the locking field is on resonance, but in the presence of large susceptibility variations the effective field will no longer lie in the transverse plane and the dispersion will potentially be influenced by off-resonance behaviors. However, this range of locking frequencies is convenient and accessible for practical implementation on imaging systems including clinical scanners and corresponds to locking field amplitudes roughly in the range of 0.5–9 μT , well within the capacity of common radiofrequency coils. It suggests that appropriate measurements of $R_{1\rho}$ vs. ω_1 may be used to infer characteristic dimensions of inhomogeneities. From knowledge of the scale of intrinsic gradients and the magnitude of their effects on $R_{1\rho}$, additional insight may be gained into the size of the susceptibility mismatch.

METHODS

Although pure sinusoidal field variations do not occur naturally, the above expression provides useful insights as an approximate theoretical description of more realistic arrays of structures. To demonstrate this, a series of samples consisting of closely packed polystyrene spheres (Polysciences Inc., PA) in water with diameters ranging from 1 to 90 μm were prepared. Spectroscopic measurements of $R_{1\rho}$ were performed at 7 T (Varian Inc., Palo Alto, CA) using a 10-mm loop gap coil and a spin-locking sequence consisting of an adiabatic 90° excitation followed by half of the spin-lock time (SLT), a 180° refocusing pulse, then the second half of the spin-lock pulse with reversed phase (27). We acquired signals using 10 logarithmically spaced spin-lock amplitudes for each sample that varied across a portion of the range from $\omega_1/2\pi = 0$ to 1000 Hz (0–23.5 μT), each with six SLTs logarithmically spaced from 20 ms to 1 s. Temperature was monitored by the use of a thermocouple attached to an animal physiologic monitoring system (SA Instruments, Stony Brook, NY) and maintained at 20° C. Dispersions were obtained by calculating $R_{1\rho}$ values at each locking amplitude from least squares fitting of the signal values at different SLTs to a monoexponential decay. Subsequently, the $R_{1\rho}$ values were fit to Eq. [16] in a least squares manner to extract the parameters g^2D and q^2D . Assuming a value for D (such as $2.5 \times 10^{-5} \text{ cm}^2/\text{s}$), we can then estimate the internal gradient strengths and spatial frequencies. Here we report values of g^2D and q^2D only.

The packed samples were subsequently imaged (128×128 matrix, $24 \text{ mm} \times 24 \text{ mm}$ field of view) using a spin-lock prepped fast spin echo acquisition with a fixed locking time (150 ms) and three different spin-lock amplitudes (0 Hz, 300 Hz, 1000 Hz) spanning an appropriate range that was derived by inspection of the measured dispersion curves. The spin-locking prepulse was the same as the spectroscopic sequence with the addition of a reverse adiabatic 90° pulse followed by a crusher gradient to spoil residual transverse magnetization before the fast spin echo acquisition. The three images acquired with different values of the locking amplitude were then combined on a voxel by voxel basis as

$$I = \frac{1}{\omega_m} \sqrt{\frac{\log I_h - \log I_l}{\log I_h - \log I_m} - 1} \quad [18]$$

where I_l , I_m , I_h are the measured image intensities, proportional to $\exp(-R_{1\rho}\text{SLT})$, at $\omega_1 = \omega_l$, ω_m , ω_h , the lowest, middle, and highest spin-lock amplitudes, respectively. If $(\omega_l\tau_c)^2 \ll 1 \ll (\omega_h\tau_c)^2$, the corresponding rate contributions are

$R_{1\rho} = \gamma^2 g^2 D / (q^2 D)^2$, $\gamma^2 g^2 D / ((q^2 D)^2 + \omega_m^2)$, and 0, respectively. The combination in Eq. [18] thus produces parametric images which, depict directly the characteristic interval $\tau_c = 1/Dq^2$, the time required for diffusing the spatial scale of inhomogeneity within the sample, and an intrinsic property of the medium. Finally, the four samples were imaged twice more after being dispersed in larger volumes of water to increase the average spacing between spheres. Each of the original samples were packed in 20 μL of water, partially filling 0.6 mL tubes to start, and 100 μL of water was added to each bringing the total amount of water in each sample to 120 μL . The spheres were evenly dispersed in a BR-2000 vortexer (Bio Rad, Hercules, CA) so the average space between the spheres was $d \approx \sqrt[3]{V/N}$ where V and N are

the total volume of water and number of spheres, respectively. The samples of larger beads contained fewer spheres with larger spacing between them. During the time of measurement, only the spheres 45 μm diameter and larger showed small signs of settlement, and others maintained a reasonably uniform suspension. The samples were imaged using the same method to depict how the correlation time changed with sphere spacing. This was repeated after adding another 100 μL of water to each of the samples bringing the total volume of water to each of the samples bringing the total volume of water to 220 μL for the last images.

RESULTS

Significant dispersion of $R_{1\rho}$ with increasing locking field was apparent for all samples. Figure 1 depicts the dispersion curve for one such sample (red) along with a plot of the second derivative of the fitted curve (black). The resultant curves were analyzed to derive the inflection frequencies at $\omega_i = Dq^2 / \sqrt{3}$ for each sample, from which values of τ_c were calculated. Figure 2 reveals how τ_c increased with bead radius R . The shift of the inflection points to higher frequencies with smaller bead sizes in Figure 2 confirms that stronger locking power was needed to overcome the dephasing effects of more rapidly changing internal gradients. From these dispersion curves, we also fit for estimates of g^2D to evaluate the intrinsic gradient strengths between spheres. When close packed, larger beads produce weaker field gradients at their surfaces, and so the contribution to relaxation might be expected to decrease with size, but this effect is more than overcome by the strong inverse dependence on spatial frequency predicted by Eq. [17], and so larger beads show greater dispersion over the range of our measurements. Figure 3 confirms how the internal gradients decrease for larger bead sizes as roughly R^{-1} , as expected. Figure 4 shows an image calculated using Eq. [18] for four of the samples in which the image intensity represents $\tau_c = 1/Dq^2$, depicting the average spatial scale of the inhomogeneous internal fields. The average correlation time, τ_c , was also shown to increase with increasing sphere spacing as depicted in Figure 5. Even though all the samples were polystyrene microspheres, the samples 10 μm and larger were crosslinked with divinylbenzene during the manufacturing process. This may explain why the magnitude of dispersion and asymptotic limits of the dispersion for the smallest samples deviated from the trend of the larger samples, but the trend of the shift in inflection frequency was not altered. Measurements of the inflection frequency, and hence the calculations of correlation times, were not affected by the gradient strengths and solely depended on the average spacings of the spheres.

DISCUSSION AND CONCLUSIONS

Although the effects of chemical exchange on the behaviors of relaxation times in the rotating frame have been extensively described before, there have been relatively few previous studies that explicitly examine how values of $R_{1\rho}$ are affected by diffusion through internal field gradients. Lammintausta et al. (20) reported diffusion effects of water in trabecular bone, but their results show a different behavior to ours and behave contrary to theoretical expectations. The cause of the discrepancy is unclear, but it may be noted that the gradients they studied may have been stronger and they studied mainly stronger locking fields and worked at lower main field. Others (28,29) have reported measurements of $R_{1\rho}$

but not the dispersion with locking field. The theoretical expression for the diffusion contribution to $R_{1\rho}$ suggests a novel approach for the characterization of inhomogeneous media. The expression given by Eq. [17] may be compared to the results for the contribution of diffusion dephasing to apparent transverse relaxation rates. In a linear gradient ($q = 0$) signals decay as $S = S_0 \exp[-(\gamma^2 g^2 D t^3)/12]$ (30), which is nonexponential but reasonably well approximated by an effective decay rate $R_{2,\text{diff}}$. In a gradient of spatial frequency q , when $q^2 D t \gg 1$ (rapid diffusion), $R_{2,\text{diff}} = \gamma^2 g^2 D / (D q^2)^2$ (23). We therefore see explicitly what spin-locking achieves: in the absence of other contributions to relaxation, taking reciprocals we find $T_{1,\text{diff}} = T_{2,\text{diff}} + \omega_1^2 / \gamma^2 g^2 D$. The effective relaxation time corresponding to diffusive losses can be lengthened using locking pulses, to a degree that is independent of the spatial scale of the intrinsic gradients but dependent on their strength. On the other hand, measurements of the dispersion behavior and identification of the inflection frequency provides an explicit indication of the spatial scale of the inhomogeneities, independent of the internal gradient strengths.

Spin-echo and gradient-echo measurements have previously been shown to characterize susceptibility variations within tissues, and appropriate comparisons between these have been used to infer spatial scales, e.g., vessel size imaging (15,31–34). Here we show an alternative approach using a spin-locking imaging method to derive parametric images characterizing the dimensions of inhomogeneities that, at high field, cause dephasing via diffusion. Note that for scales of practical interest these dispersion effects occur at much lower frequencies than the range in which chemical exchange effects between labile protons and water cause dispersion in $R_{1\rho}$ with locking field, allowing for separate analysis of each relaxation mechanism (2). Further imaging studies examining the behavior of different media and the influence of microvasculature will be of particular interest. Tissue microvasculature may be considered as producing susceptibility inhomogeneities within tissues with a characteristic scale and separation. However, the simple theory outlined here, while providing a useful pragmatic guide to the interaction of rotating frame relaxation and diffusion in inhomogeneous materials, may need to be refined for accurate practical applications in more complex media. For example, more complex and realistic correlation functions may be required to properly describe vasculature in which multiple scale parameters and modified assumptions must be incorporated, as have previously been considered for transverse relaxation effects (16–19).

One potential application of interest is the detection of changes in blood oxygenation levels resulting from neural activation. For example, performing a conventional functional MRI acquisition is equivalent to using a spin-lock preparation with locking amplitude = 0, and the relaxation rate $R_{2,\text{diff}}$ will vary $\approx q^{-4}$ and be dominated by large-scale structures such as draining veins. However, at high values of the locking field, the contribution of diffusion to $R_{1\rho}$ is reduced. For example, in the presence of a locking field of 80 Hz, $R_{1\rho}$ will show maximal rate of change (largest contrast effects) to susceptibility variations for which $q \approx 3950 \text{ cm}^{-1}$, corresponding to structures whose radius is $\approx 8 \text{ }\mu\text{m}$. Compared to their contributions when the locking field is 0, the contributions to $T_{1\rho}$ from diffusion around objects of dimension $\approx 1000 \text{ }\mu\text{m}$ should decrease by a factor of more than 10^8 , for $100 \text{ }\mu\text{m}$ by a factor of more than 10^4 , whereas for $10 \text{ }\mu\text{m}$ by a factor of less than 10. Therefore, the

contribution of diffusion around microvasculature structures of interest may be dramatically enhanced relative to larger structures by appropriate selection of the locking frequency. Preliminary demonstrations of the merits of spin-locking for assessing brain activity in functional MRI have recently been reported by Rane et al. (35), who used a spin-lock prepared fast spin echo imaging sequence to derive activation maps with higher spatial resolution, reduced spatial distortion and reductions of the influence of large veins compared to conventional functional images. Further efforts to exploit these predictions in functional MRI and other studies appear justified.

Acknowledgments

The authors thank Dr. J.P. Xie for help with sample preparations.

Grant sponsor: NCI; Grant numbers: 1R25CA136440-01 and EB000214-15.

REFERENCES

1. Cobb JG, Xie J, Gore JC. Contributions of chemical and diffusive exchange to T1 ρ dispersion. *Magn Reson Med*. 2013; 69:1357–1366. [PubMed: 22791589]
2. Cobb JG, Xie J, Gore JC. Contributions of chemical exchange to R1 ρ dispersion in a tissue model. *Magn Reson Med*. 2011; 66:1563–1571. [PubMed: 21590720]
3. Jin T, Autio J, Obata T, Kim SG. Spin-locking versus chemical exchange saturation transfer MRI for investigating chemical exchange processes between water and labile metabolite protons. *Magn Reson Med*. 2011; 65:1448–1460. [PubMed: 21500270]
4. Chopra S, McClung RED, Jordan RB. Rotating-frame relaxation rates of solvent molecules in solutions of paramagnetic ions undergoing solvent exchange. *J Magn Reson*. 1984; 59:361–372.
5. Davis DG, Perlman ME, London RE. Direct measurements of the dissociation-rate constant for inhibitor-enzyme complexes via the T1 ρ and T2 (CPMG) methods. *J Magn Reson B*. 1994; 104:266–275. [PubMed: 8069484]
6. Majumdar S, Gore JC. Studies of diffusion in fields produced by variations in susceptibility. *J Magn Reson*. 1988; 78:41–55.
7. Li L, Leigh JS. Quantifying arbitrary magnetic susceptibility distributions with MR. *Magn Reson Med*. 2004; 51:1077–1082. [PubMed: 15122694]
8. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. *Magn Reson Med*. 1995; 34:555–566. [PubMed: 8524024]
9. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. *Magn Reson Med*. 1994; 31:9–21. [PubMed: 8121277]
10. Ye FQ, Allen PS. Relaxation enhancement of the transverse magnetization of water protons in paramagnetic suspensions of red blood cells. *Magn Reson Med*. 1995; 34:714–720.
11. Weisskoff RM, Zuo CS, Boxerman JL, Rosen BR. Microscopic susceptibility variation and transverse relaxation: theory and experiment. *Magn Reson Med*. 1994; 31:601–610. [PubMed: 8057812]
12. Majumdar S, Zoghbi S, Pope CF, Gore JC. A quantitative study of relaxation rate enhancement produced by iron oxide particles in polyacrylamide gels and tissue. *Magn Reson Med*. 1989; 9:185–202. [PubMed: 2716504]
13. Zhong J, Kennan RP, Gore JC. Effects of susceptibility variations on NMR measurements of diffusion. *J Magn Reson*. 1991; 95:267–280.
14. Kennan RP, Zhong J, Gore JC. On the relative importance of paramagnetic relaxation and diffusion-mediated susceptibility losses in tissues. *Magn Reson Med*. 1991; 22:197–203. [PubMed: 1812346]
15. Kiselev VG, Posse S. Analytical model of susceptibility-induced MR signal dephasing: effect of diffusion in a microvascular network. *Magn Reson Med*. 1999; 41:499–509. [PubMed: 10204873]

16. Jensen JH, Chandra R. NMR relaxation in tissues with weak magnetic inhomogeneities. *Magn Reson Med*. 2000; 44:144–156. [PubMed: 10893533]
17. Sukstanskii AL, Yablonskiy D. Gaussian approximation in the theory of MR signal formation in the presence of structure-specific magnetic field inhomogeneities. *J Magn Reson*. 2003; 163:236–247. [PubMed: 12914839]
18. Sukstanskii AL, Yablonskiy D. Gaussian approximation in the theory of MR signal formation in the presence of structure-specific magnetic field inhomogeneities. Effects of impermeable susceptibility inclusions. *J Magn Reson*. 2004; 167:56–57. [PubMed: 14987599]
19. Fröhlich AF, Østergaard L, Kiselev VG. Theory of susceptibility-induced transverse relaxation in the capillary network in the diffusion narrowing regime. *Magn Reson Med*. 2005; 53:564–573. [PubMed: 15723392]
20. Lammentausta E, Silvast TS, Närviäinen MT, Gröhn OHJ. T₂, Car-Purcell T₂ and T_{1ρ} of fat and water as surrogate markers of trabecular bone structure. *Phys Med Biol*. 2008; 53:543–555. [PubMed: 18199901]
21. Kettunen MI, Gröhn OHJ, Silvennoinen MJ, Penttonen M, Kauppinen R. Effects of intracellular pH, blood, and tissue oxygen tension on T_{1ρ} relaxation in rat brain. *Magn Reson Med*. 2002; 48:470–477. [PubMed: 12210911]
22. Deverell C, Morgan RE, Strange JH. Studies of chemical exchange by nuclear magnetic relaxation in the rotating frame. *Mol Phys*. 1970; 18:553–559.
23. Cowan, B. Nuclear magnetic resonance and relaxation. Cambridge: Cambridge University Press; 1997.
24. Glasel JA, Lee KH. On the interpretation of water nuclear magnetic resonance relaxation times in heterogeneous systems. *J Am Chem Soc*. 1974; 96:970–978.
25. Haacke, EM.; Brown, R.; Thompson, M.; Venkatesan, R. Magnetic resonance imaging: physical principles and sequence design. 1st ed.. Hoboken, NJ: John Wiley & Sons; 1999.
26. Stables LA, Kennan RP, Gore JC. Asymmetric spin-echo imaging of magnetic inhomogeneous systems: theory, experiment, and numerical studies. *Magn Reson Med*. 1998; 40:432–442. [PubMed: 9727947]
27. Witschey WRT, Borthakur A, Elliot MA, Mellon E, Niyogi S, Wallman DJ, Wang C, Reddy R. Artifacts in T_{1ρ}-weighted imaging: compensation for B₁ and B₀ field imperfections. *J Magn Reson*. 2007; 186:75–85. [PubMed: 17291799]
28. Gröhn OH, Lukkariinen JA, Silvennoinen MJ, Pitkänen A, Van Zijl PC, Kauppinen RA. Quantitative magnetic resonance imaging assessment of cerebral ischemia in rat using on-resonance T₁ in the rotating frame. *Magn Reson Med*. 1999; 42:268–276. [PubMed: 10440951]
29. Menezes NM, Gray ML, Hartke JR, Burstein D. T₂ and T_{1ρ} MRI in articular cartilage systems. *Magn Reson Med*. 2004; 51:503–509. [PubMed: 15004791]
30. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. *Phys Rev*. 1954; 94:630–638.
31. Dennie J, Mandeville JB, Boxerman JL, Packard SD, Rosen BR, Weisskoff RM. NMR imaging of changes in vascular morphology due to tumor angiogenesis. *Magn Reson Med*. 1998; 40:793–799. [PubMed: 9840821]
32. Packer KJ. The effects of diffusion through locally inhomogeneous magnetic fields on transverse relaxation in heterogeneous systems. Proton transverse relaxation in striated muscle tissue. *J Magn Reson*. 1973; 9:438–443.
33. Tropès I, Lamalle L, Péoc'h M, Farion R, Usson Y, Décorps M, Rémy C. In vivo assessment of tumoral angiogenesis. *Magn Reson Med*. 2004; 51:533–541. [PubMed: 15004795]
34. Tropès I, Grimault S, Vaeth A, Grillon E, Julien C, Payen JF, Lamalle L, Décorps M. Vessel size imaging. *Magn Reson Med*. 2001; 45:397–408. [PubMed: 11241696]
35. Rane, S.; Spear, JT.; Zu, Z.; Donahue, MJ.; Gore, JC. Functional MRI using spin-locking pulse sequences to modulate BOLD activation. Proceedings of the 21st Annual Meeting of ISMRM; Salt Lake City, Utah, USA. 2013; p. 3265Abstract 1414

FIG. 1.

$R_{1\rho}$ dispersion curve (red) for the 45 μm diameter bead sample calculated using a least squares fitting algorithm to Eq. [16] with the error bars representing one standard deviation. The second derivative (black) is shown to cross through zero at $\omega_1/2\pi \approx 7$ Hz (circled), which was used to calculate the corresponding correlation time. The inflection frequencies for the 1–90 μm diameter samples varied from $\omega_1/2\pi \approx 4$ to 390 Hz, respectively.

FIG. 2.

Correlation time, τ_c , as a function of sphere radius R for packed bead samples at 7 T calculated from spectroscopic data with error bars representing one standard deviation. The correlation time monotonically increases with sphere radius, and hence space between sphere centers, without being affected by the internal gradient strength.

FIG. 3.

Fitted parameter g^2D vs. sphere radius for spheres ranging from 0.5 to 45 μm with error bars representing one standard deviation. The gradients are expected to fall off as R^{-1} , close to our fitted dependence of $R^{-0.915}$.

FIG. 4.

Correlation time map, τ_c , for 1–20 μm diameter packed sphere samples at 7 T calculated using the image combination technique with three fast spin echo acquisitions described in Eq. [18]. The correlation time increases in the same manner as the spectroscopic measurements and tracks the change in the average space between the spheres.

FIG. 5.

Average correlation time, τ_c , for 1–20 μm diameter sphere samples with 20, 120, and 220 μL of water calculated from imaging data. The correlation time is shown to significantly increase in all samples with increasing sphere spacing, and hence decreasing density.