Published in final edited form as:

J Magn Reson. 2014 December ; 249: 80–87. doi:10.1016/j.jmr.2014.10.003.

Effects of Diffusion in Magnetically Inhomogeneous Media on Rotating Frame Spin-Lattice Relaxation

John T. Spear^{a,b} and John C. Gore^{a,b,c,d,e}

^aInstitute of Imaging Science, Vanderbilt University, Nashville, TN

^bDepartment of Physics and Astronomy, Vanderbilt University, Nashville, TN

^cDepartment of Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN

^dDepartment of Biomedical Engineering, Vanderbilt University, Nashville, TN

^eDepartment of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN

Abstract

In an aqueous medium containing magnetic inhomogeneities, diffusion amongst the intrinsic susceptibility gradients contributes to the relaxation rate $R_{1\rho}$ of water protons to a degree that depends on the magnitude of the local field variations B_z , the geometry of the perturbers inducing these fields, and the rate of diffusion of water, D . This contribution can be reduced by using stronger locking fields, leading to a dispersion in $R_{1\rho}$ that can be analyzed to derive quantitative characteristics of the material. A theoretical expression was recently derived to describe these effects for the case of sinusoidal local field variations of a well-defined spatial frequency q . To evaluate the degree to which this dispersion may be extended to more realistic field patterns, finite difference Bloch-McConnell simulations were performed with a variety of three-dimensional structures to reveal how simple geometries affect the dispersion of spin-locking measurements. Dispersions were fit to the recently derived expression to obtain an estimate of the correlation time of the field variations experienced by the spins, and from this the mean squared gradient and an effective spatial frequency were obtained to describe the fields. This effective spatial frequency was shown to vary directly with the second moment of the spatial frequency power spectrum of the B_z field, which is a measure of the average spatial dimension of the field variations. These results suggest the theory may be more generally applied to more complex media to derive useful descriptors of the nature of field inhomogeneities. The simulation results also confirm that such diffusion effects disperse over a range of locking fields of lower amplitude than typical chemical exchange effects, and should be detectable in a variety of magnetically inhomogeneous media including regions of dense microvasculature within biological tissues.

Address for correspondence: John C. Gore, Vanderbilt University Institute of Imaging Science, MCN AA1105, 1161 21st Ave South, Nashville, TN 37232, USA, (615) 322-8359, john.gore@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

$T_{1\rho}$; Dispersion; Spin-lock; Diffusion; Simulation; Susceptibility

Introduction

The spin-lattice relaxation rate in the rotating frame, $R_{1\rho} = 1/T_{1\rho}$, typically reports on slow molecular motions and chemical exchange processes. Interest in $R_{1\rho}$ -dependent imaging as a means to study proton chemical exchange processes has recently increased for non-invasively deriving quantitative parametric images and novel information about biological tissues. Although the most widespread method for emphasizing chemical exchange is Chemical Exchange Saturation Transfer (CEST wherein off-resonance RF pulses selectively saturate exchangeable spins that have sufficient chemical shift from water¹), spin-locking methods can also be used to examine exchange processes at high field by analyzing the dispersion in $R_{1\rho}$ with locking field. When the locking field is negligible, excited spins undergo free precession and their $R_{1\rho}$ usually approaches R_2 , but this rate decreases monotonically with increasing locking field in a spin-lock sequence. The locking field induces precession about the effective field which overcomes the dephasing effects of nuclei jumping between two sites with different chemical shifts as long as the precessional period is on the order of or less than the time scale of the exchange process. Several previous studies have demonstrated the effects of exchanging labile nuclei such as amides, amines, and hydroxyls on the dispersion of $R_{1\rho}$ ²⁻⁸. By analogy, the diffusion of nuclei in the presence of intrinsic magnetic field gradients induced by inhomogeneities with susceptibilities distinct from that of the surrounding media also results in $R_{1\rho}$ dispersion. Diffusion-based R_2 dispersions have previously been analyzed⁹⁻¹¹ and $R_{1\rho}$ dispersions have been mentioned in the literature¹², but only recently has a closed form expression been derived explicitly to quantify such effects for $R_{1\rho}$ ¹³.

Our recently derived theoretical expression describes the effects of the fluctuating local fields experienced by randomly diffusing nuclei within a sinusoidally spatially varying gradient, and relates the value of $R_{1\rho}$ to the effective correlation time of those field variations, which in turn depends on the rate of diffusion (D) and the spatial frequency of the field (q). Given that real intrinsic gradients may not be well described with a single spatial frequency, it is of interest to explore whether this simple analysis may be used as an approximate description of more complex media, and used to extract useful characteristics such as the average spatial dimensions of the inhomogeneities in the media. Methods for quantifying the spatial scales of intrinsic tissue variations may have far reaching applications for quantitative characterization of inhomogeneous material, and in biological applications, for the evaluation of pathologies. For example, diffusion effects amongst field inhomogeneities have been identified in trabecular bone, Alzheimer's brain tissue containing amyloid plaques, red blood cells (RBCs) containing deoxyhemoglobin or tissues containing exogenous paramagnetic agents. The effects of diffusion through simple geometries exhibiting intrinsic susceptibility gradients on transverse relaxation rates R_2 and R_2^* have been extensively investigated before through simulation, theory, and experiments¹⁴⁻¹⁸. Simulations of diffusion within vascular networks have also been performed to evaluate

geometry dependent effects on transverse relaxation^{19,20}. However, no previous simulation has quantified the effects of diffusion through susceptibility-induced gradients in the presence of spin-locking fields. Here, finite difference simulations are presented that quantify these effects in gradient fields resulting from different geometries of packed spheres and packed cylinders with susceptibilities distinct from that of the surrounding medium. A specific goal of these studies was to evaluate whether the analysis used previously for sinusoidal gradients of single spatial frequency could be usefully extended to more complex arrays of inhomogeneities.

In the absence of magnetic inhomogeneities, chemical exchange is the process most commonly known to affect $R_{1\rho}$ dispersion in biological media^{6,21}. Spin-locking measurements of $R_{1\rho}$ dispersion can readily probe chemical exchange processes in the range of intermediate ($k_{ex}/\delta \approx 1$, where k_{ex} is the rate of exchange and δ is the chemical shift between the exchanging species) to fast exchange ($k_{ex}/\delta \gg 1$). The effects of diffusion of nuclei through susceptibility gradients depends on the self-diffusion coefficient and the geometry of the perturbing structures, and in practice is characterized as much slower. The disparity in the rates of the exchange and diffusion processes will, in theory, result in separate dispersions occurring over different spin-lock amplitude ranges. The field perturbations should have no effect on chemical exchange rates, so the processes should be completely independent of each other and the dispersions should add linearly without interaction. A second goal of the work presented here is to validate the independent nature of diffusion and chemical exchange effects through simulations while quantifying their individual contributions to $R_{1\rho}$.

Methods

The evolution of net magnetization in the presence of chemical exchange and a spin-locking field is governed classically by the Bloch equations²². To simulate the effects of inhomogeneities, ordered structures of impermeable spheres and cylinders were arranged on $64 \times 64 \times 64$ grids and the field perturbations were calculated in the free space between them by means of superposition. The spherical structures were packed in Body-Centered Cubic (BCC) and Face-Centered Cubic (FCC) unit cell arrangements as shown in figure 1, and their spacings were varied to obtain specific volume fractions.

The z-component of the field shift due to a single sphere in a magnetic field is²²

$$\Delta B_z^{\text{sphere}} = \frac{\Delta\chi}{3} \frac{a^3}{r^3} \left(3 \cos^2(\theta) - 1 \right) B_0 \quad (1)$$

where χ is the difference in susceptibilities of the sphere and the surrounding medium, a is the radius of the sphere, r is the distance from the sphere center, θ is the angle with respect to the z-axis, and B_0 is the magnitude of the static magnetic field. For a second sample, cylindrical structures were packed in a similar manner, as depicted in figure 1. The field shift due to a single cylinder of radius a with its axis perpendicular to the magnetic field is

$$\Delta B_z^{\text{cylinder}} = \frac{\Delta\chi}{2} \frac{a^2}{\rho^2} \cos(2\theta) B_0 \quad (2)$$

where ρ is the radial distance from the cylinder center and θ is the radial angle about the cylinder axis²².

Finite difference simulations were performed using the Bloch-equations shown below.

$$\begin{aligned} \frac{dM_x(t)}{dt} &= \Delta\omega_0 M_y(t) - R_2 M_x(t) \\ \frac{dM_y(t)}{dt} &= -\Delta\omega_0 M_x(t) - R_2 M_y(t) + \omega_1 M_z(t) \\ \frac{dM_z(t)}{dt} &= -\omega_1 M_y(t) + R_1 [M_0 - M_z(t)] \end{aligned} \quad (3)$$

Here $M_{x,y,z}(t)$ are the time-dependent magnetization components, ω_0 is the field offset, $R_{1,2}$ are the longitudinal and transverse relaxation rates, ω_1 is the applied RF amplitude along the x-axis, and M_0 is the equilibrium bulk magnetization. The field deviations, B_z , were calculated everywhere in the spaces between the impenetrable spheres and cylinders using superposition, assuming their volume susceptibility was -8.21×10^{-6} (that of polystyrene), and then incorporated into the terms for ω_0 in the Bloch equations.

All simulations were conducted with the magnetization starting along the x-axis with time steps of 2 μsec and with the parameters $R_1 = 0.385 \text{ Hz}$, $R_2 = 0.833 \text{ Hz}$, with 60 different locking times ranging from 10 to 120 ms, and 12 locking fields ranging from 1 – 2,000 Hz. Some of the smaller radii systems produced dispersions with high frequency inflection points so then the low amplitude locking field was set at 5 Hz rather than 1 Hz to better capture the region of dispersion. A first set of fields was calculated with a constant volume fraction of 60% but with varying radii ranging from $a = 5\text{--}15 \mu\text{m}$. A second set of fields was calculated using a constant radius of $a = 5 \mu\text{m}$ with varying volume fractions from 30 – 60%. The effects of spin diffusion were estimated by discrete sampling of the magnetization on a $64 \times 64 \times 64$ grid, calculating the spin displacement probabilities prior to starting the simulation using $D = 2.5 \mu\text{m}^2/\text{ms}$, and redistributing the magnetization after every time step by multiplying the sparse transition matrix with the vector of magnetization at every position as described by Xu et al²³. Periodic boundary conditions were also implemented in the transition matrix to ensure edge effects at the boundaries of the unit cell did not contribute significant errors to the simulations. The x-axis signal values as a function of time were fit to a monoexponential decay model to estimate the relaxation rates for different locking fields and later used to fit to the expression below. Simulations were performed by changing the susceptibility difference ($\chi = 1 - 6$ times polystyrene) to show that susceptibility will affect only the gradient strength and geometry estimates can still be made from the data. Also, one more set of simulations were executed by changing the grid sizes to achieve various voxel resolutions ($0.171 \mu\text{m} - 0.314 \mu\text{m}$) to show how significant pixelation effects can affect the simulated dispersions.

When the local field experienced by diffusing nuclei is sinusoidal, the contribution of diffusion effects to relaxation depends on the gradient strength and spatial frequency of the field¹³.

$$R_{1\rho} = \frac{\gamma^2 g^2 D}{(q^2 D)^2 + \omega_1^2} \quad (4)$$

Here, γ is the gyromagnetic ratio, g is the mean gradient strength, D is the self-diffusion coefficient, q is the spatial frequency of the spatially varying inhomogeneous field, and ω_1 is the applied spin-locking amplitude. This functional form was derived based on the relationship of the relaxation rate to the spectral content of the frequency perturbations experienced by the nuclei, $\delta\omega(t)$, which themselves are described in terms of a correlation function.

$$R_{1\rho} = \frac{1}{2} \int_{-\infty}^{\infty} \overline{\delta\omega(t) \delta\omega(t-\tau)} \cos(\omega_1 \tau) d\tau \quad (5)$$

Real fields in practice do not vary sinusoidally, but they do fluctuate about a mean value with some deviation that is determined by the gradient strength and the geometry. Therefore as nuclei diffuse they experience a time-varying perturbation $b(t)$. Many physical realistic correlation functions decay exponentially, and such functions are commonly adopted in relaxation theories such as that of the original analysis of Bloembergen, Purcell, and Pound.²⁴ We here assume the field correlations may be described by

$\overline{\sigma\omega(t) \delta\omega(t-\tau)} = \gamma^2 \langle b(0) b(t) \rangle = \gamma^2 \langle b^2 \rangle \exp\left(-\frac{\tau}{\tau_c}\right)$, so that a general lorentzian expression may be written for $R_{1\rho}$.

$$R_{1\rho} = \frac{1}{2} \frac{\gamma^2 \langle b^2 \rangle}{\tau_c} \frac{\tau_c^2}{1 + \omega_1^2 \tau_c^2} \quad (6)$$

If Eq. 6 is compared to the case for a sine wave, one can infer the correlation time is related to the spatial scales of local field variations and the diffusion coefficient by $\tau_c = \frac{1}{q_{\text{eff}}^2 D}$. Here, q_{eff} is an effective spatial frequency that can be used as a parameter to describe the field pattern. The self-diffusion coefficient is relatively constant and known (typically $2.5 \mu\text{m}^2/\text{ms}$). If the $R_{1\rho}$ dispersion values are fit to this model, the parameters $\langle b^2 \rangle$ and $q_{\text{eff}}^2 D$ can be obtained. The precise meaning of q_{eff} will depend on the exact nature of the field distribution but to assist its interpretation we compared derived values of q_{eff} to a characteristic measure of the simulated field distributions, a measure of their variance of spread calculated from the second moment of the spatial frequency power spectrum of the B_z field.

$$\langle q \rangle_{\text{theory}} = \sqrt{\frac{\int \int \int (k_x^2 + k_y^2) |F_{\Delta B}(k_x, k_y, k_z)|^2 dk_x dk_y dk_z}{\int \int \int |F_{\Delta B}(k_x, k_y, k_z)|^2 dk_x dk_y dk_z}} \quad (7)$$

Here, $k_{x,y,z}$ and $F_B(k_x, k_y, k_z)$ are the spatial frequencies and the Fourier transform of the B_z field respectively. Eq 7 is similar to the resolution index used by Van Vleck to calculate a mean squared RF absorption frequency²⁵ and later by Gore et al. to assess the resolution of ultrasound imaging systems with a corresponding transfer function²⁶, but in this context the moment is used to quantify the spatial changes in the local field experienced by diffusing spins. Note that in the spatial domain,

$$\langle q \rangle_{\text{theory}} = \sqrt{\frac{\int \int \int (\nabla \Delta B_z)^2 dx dy dz}{\int \int \int (\Delta B_z)^2 dx dy dz}} \quad (8)$$

In addition to diffusion, chemical exchange was simulated using the Bloch-McConnell equations for two pools, a and b, in exchange. Pool a was assumed to be the solvent and pool b was the small solute pool, each with pool fractions $p_a = 99\%$ and $p_b = 1\%$ respectively for simulations. The exchange between pools was assumed to be first order in nature with the exchange constant k_a describing the rate of transfer of magnetization from pool a to b and k_b describing the transfer from pool b to a, under the stipulation $p_a k_a = p_b k_b$. The Bloch-McConnell equations used are described below in Eq. 9²⁷.

$$\begin{aligned} \frac{dM_x^a(t)}{dt} &= \Delta\omega_a M_y^a(t) - R_2^a M_x^a(t) - k_a M_x^a(t) + k_b M_x^b(t) \\ \frac{dM_y^a(t)}{dt} &= -\Delta\omega_a M_x^a(t) - R_2^a M_y^a(t) - k_a M_y^a(t) + k_b M_y^b(t) \\ \frac{dM_x^b(t)}{dt} &= \Delta\omega_b M_y^b(t) - R_2^b M_x^b(t) - k_b M_x^b(t) + k_a M_x^a(t) \\ \frac{dM_y^b(t)}{dt} &= -\Delta\omega_b M_x^b(t) - R_2^b M_y^b(t) - k_b M_y^b(t) + k_a M_y^a(t) \\ \frac{dM_z^a(t)}{dt} &= -\omega_1 M_y^a(t) - R_1^a [M_z^a(t) - M_0^a] - k_a M_z^a(t) + k_b M_z^b(t) \\ \frac{dM_z^b(t)}{dt} &= -\omega_1 M_y^b(t) - R_1^b [M_z^b(t) - M_0^b] - k_b M_z^b(t) + k_a M_z^a(t) \end{aligned} \quad (9)$$

Simulations were performed using the same structures with locking fields varied from 10 - 5,000 Hz, $k_b = 6,000$ Hz, a solute chemical shift of $\omega_b = 3$ ppm, and a time step $dt = 400$ ns to ensure $k_b dt \ll 1$ in order to keep the simulation stable. When exchange was added, small but significant oscillations were observed in the signal decay with low locking fields caused by off-resonance effects so, rather than fitting to a monoexponential model, the approach of Yaun et al. was adopted to account for these oscillations with a $T_{2\rho}$ term in the following equation²⁸.

$$\text{signal} = S_0 \left[\cos(\alpha) \cos^2(\theta) e^{-\frac{SLT}{T_{2\rho}}} + \sin^2(\theta) e^{-\frac{SLT}{T_{1\rho}}} \right] \quad (10)$$

Here, $\alpha = SLT \sqrt{\omega_1^2 + \Delta\omega_0^2}/2$, $\theta = \tan^{-1}(\omega_1/\Delta\omega_0)$, and SLT was the spin-locking time. With low locking field, $\theta \rightarrow 0$ and the oscillatory $T_{2\rho}$ term becomes significant, but goes to zero as $\omega_1 \gg \omega_0$. The $R_{1\rho}$ values estimated using this model were plotted and fit to a model that incorporated both exchange and diffusion as linearly independent processes. The exchange term was modeled by adding the expression by Chopra et al. to the above diffusion equation³.

$$R_{1\rho} = R_{1\rho}^{Diff} + R_{1\rho}^{Ex} = \left[\frac{\gamma^2 g^2 D}{(q_{eff}^2 D)^2 + \omega_1^2} \right] + \left[\frac{R_2 + \frac{R_{1\rho}^\infty \omega_1^2}{S_\rho^2}}{1 + \frac{\omega_1^2}{S_\rho^2}} \right] \quad (11)$$

In Eq. 11, R_2 is the transverse relaxation rate from exchange at low locking field, $R_{1\rho}^\infty$ is the high locking field relaxation rate, and S_ρ^2 parameterizes the exchange rate and inflection point of the exchange based dispersion. The double dispersions were fit to this model in a least squares manner in MATLAB and compared to pure diffusion and pure exchange cases.

Results

$R_{1\rho}$ dispersion curves for the three types of structures are shown in figure 2 for constant volume fractions with varying radii and for constant radii with varying volume fractions. At constant volume fraction, in all samples the degree of dispersion increased near-linearly with the radius of the perturbors. For these samples, the distance between inhomogeneities increases and the mean gradients decrease as radius increases. The inflection points of the dispersions moved to lower locking field amplitudes with radius corresponding to the field variations having lower spatial frequencies so that the spins experience more slowly varying field fluctuations with longer correlation times. With increasing volume fraction but constant radius, the inflection points moved to higher locking fields, reflecting the increased spatial frequency of the average fields and a corresponding shorter correlation time.

However, while the dispersion magnitudes for the FCC and cylinder structures decreased with volume fraction, the BCC structures displayed the opposite behavior. These differences reflect the manner in which the average field gradients behave for the different geometries as the number density of perturbors increases. Note that the inflection points were not influenced by our choice of χ and the resolution of the grid had only a small impact on the dispersion curves. For example, Figure 3 shows simulations for $R = 5 \mu\text{m}$, 60% volume fraction, BCC structures with various susceptibility differences and matrix sizes. The inflection points for each case do not change by more than 1.5% for the χ plots and no more than 4.5% for the matrix size plots indicating these parameters little influence on the simulated dispersion when compared to the effects of changing the sphere radii or volume fraction of the spheres.

The correlation times (τ_c) derived from fitting are shown in figure 4.

These are inversely related to the locking field at the inflection point of the dispersion curve, i.e. $\omega_1^{\text{inflection}} = 1/\sqrt{3}\tau_c$, and increased with radius and decreased with volume fraction for all structures as expected. The correlation times for the BCC structures are very close to the experimental results found in our previous report on randomly packed polystyrene microspheres of specific radii shown in figure 5.

Assuming that the diffusion coefficient $D = 2.5 \mu\text{m}^2/\text{ms}$, using $\tau_c = \frac{1}{q_{\text{eff}}^2 D}$, values of the effective spatial frequency q_{eff} were derived and compared to the width of the spatial frequency spectrum calculated from Eq. 7 by plotting $\langle q \rangle_{\text{theory}}$ vs q_{eff} as shown in figure 6. Remarkably, there was a strong linear correlation between these different measures of the field characteristics for all structures, suggesting that the derived parameter q_{eff} reliably captures essential features of the fields and that its absolute value may be interpreted as a direct measure of the average spatial scale of the intrinsic field variations.

Finally the dispersion curves for the case of diffusion with chemical exchange are were calculated for radii ranging from 5 – 12 μm . The signal decay curves were no longer monoexponential and needed to be fit to Eq. 10 to account for the off-resonance oscillations. Figure 7 shows an example of the fitting for each case. The case for pure diffusion was fit to a monoexponential decay model in 6a, while the case including chemical exchange was fit to Eq. 10 as shown in 6b. The chemical exchange parameters remained fixed for all simulations so the high frequency dispersion did not change while the lower frequency diffusion-based dispersion displayed the same behavior as the previous pure diffusion simulations. Figure 8a shows the double dispersions for the BCC packed spheres at 60% volume fraction. Figure 8b depicts how the processes are independent of each other and that the double dispersion curve is simply the sum of the pure diffusion and pure exchange cases for the 10 μm case, which was also the case for the other sizes. The individual fitting parameters are plotted and compared to the theoretical chemical exchange and pure diffusion cases in figure 9.

The general discrepancy in the estimated parameters at smaller radii comes from the fact that the double dispersion begins to coalesce and these parameters estimated from a least squares fitting procedure have more uncertainty in them.

Discussion

Few studies have mentioned the effects of diffusion on $R_{1\rho}$ and either reported only a single locking amplitude (not the dispersion) or worked at much lower static fields than 7T^{29–31}. Our previous report showed pure diffusion effects could be measured in model systems of polystyrene microspheres that behaved similar to the simulations described here, and Eq.4 was used to derive quantitative characteristics of the samples¹³. The packing structures were more random in the previously performed experiments but the fitted correlation times displayed striking similarities to those of the simulations for the BCC structures shown in figure 7. Even though the specific R_1 and R_2 relaxation rates were different between the simulations and experiments, which affected the low and high amplitude relaxation rates, the dispersion inflection point is not significantly affected by these parameters and reflects instead an intrinsic correlation time that can be directly related to the spatial scales of field variations relatively well. The simulations reported here were motivated by the need to

further validate this approach. The numerical simulations demonstrate how both diffusion and chemical exchange produce dispersions in $R_{1\rho}$ with separable inflection points that each report on the time scales of the field fluctuations experienced by the ensemble of spins. Water diffusing about inclusions on the scale of microns produced dispersions in $R_{1\rho}$ that occurred at lower frequencies than dispersions from intermediate to fast chemical exchange processes as depicted in figure 8, affording the ability to separate the effects by appropriate analysis. Both effects may be present in realistic in vivo systems of interest, but may not always be separable in very complex systems or if the time scales of the processes are too similar.

The simulation results confirm that larger intrinsic gradients cause greater contributions to relaxation at low locking fields, and that more rapidly varying fields correspond to higher inflection point frequencies in the dispersions. Larger spheres (and cylinders) generate smaller gradients at their surfaces as evident by taking the derivative of Eq. 1, and so diffusion effects on $R_{1\rho}$ dispersion are smaller. On the other hand, larger structures (at constant volume fraction) are spaced further apart and generate more slowly varying fields (lower spatial frequency) so the correlation time of field fluctuations experienced by the spins is longer and the inflection point shifts to lower locking field. Our simulations differ from the traditional two-pool model, which designate free and bound water pools that exchange instantaneously, and incorporate a more continuous transition of the effective field the spins experience. Our model does not take into account the possibility of water adsorption or other interactions at the sphere surfaces. Regardless, the above results demonstrate that free diffusion through susceptibility gradients may produce similar dispersion behavior in $R_{1\rho}$ as chemical exchange mechanisms.

The behavior in the simulations of the BCC structures with varying volume fraction in figure 2d should be noted because the reason they behave differently from the FCC or cylinder structures is not intuitive. The low frequency asymptotic $R_{1\rho}$ values increased with volume fraction for the BCC structures because the correlation time decreased more slowly than the increase in the mean gradient magnitude, whereas the FCC and cylinder structures showed relatively slower increases in their gradient magnitudes reflecting differences in the geometrical properties of the systems. The correlation time, however, is independent of the relaxation rates and the mean gradient strength. It reflects the spatial frequency content of the field variations and not their magnitudes.

Real magnetic field variations from arbitrary arrays of inhomogeneities are likely to be complex and distributed over a range of values. A common approach to capturing salient features of random fields is to compute higher moments of the field distribution, and the second moment or variance of the power spectrum is one such metric. Thus, $\langle q \rangle_{\text{theory}}$ defined above is potentially a parameter for describing and differentiating different field distributions. The fact that it scales linearly with our derived spatial frequency parameter q_{eff} is remarkable and suggests that q_{eff} itself is a robust indicator of intrinsic properties of the sample with a distinct physical interpretation. Mapping q_{eff} via the correlation time in an imaging context may provide a means to characterize the spatial variations of fields produced by perturbing structures without being significantly influenced by gradient strengths. This was shown to be quick and feasible in polystyrene phantoms by combining

just three images¹³. In biological tissues, for example, mapping q_{eff} has potential, for example, for estimating mean microvascular densities and sizes in tumor regions with chaotic vasculature, or helping interpret the nature of fMRI activation maps by identifying the scale of vascular structures. Recently, Rane et al. showed that by adding a spin-lock prep pulse before a turbo spin-echo (TSE) sequence in human fMRI studies of the brain, smaller vasculature could be emphasized over larger venous structures to increase the spatial selectivity of the BOLD effect³². The increase of oxygenated blood upon activation decreases extravascular gradients, but by judicious choice of the locking field the dephasing effects caused by larger structures can be made relatively less influential. This sensitivity to structural geometry in spin-locking methods is not readily available in other exchange sensitive techniques such as CEST. There are also likely to be applications of this approach for the characterization of inhomogeneities in other media in which nuclear spins are able to diffuse.

One limitation of the current study is that some of the results are affected by the discrete pixelation of the structures, which may affect the estimation of spatial frequencies, especially in the volume fraction simulations. Changing the radius with constant volume fraction was the equivalent to keeping the same structure and simply increasing the assigned voxel spacings, but changing the volume fraction meant calculating entirely new structures. The digital resolution of the structures and relative resolution of the B_z fields tended to decrease with smaller volume fractions, and edge effects may cause voxels immediately surrounding the spheres or cylinders to be weighted more as simulated spins spend more time on average in these positions. Lower spatial resolution of stronger gradients may result in a more smoothed gradient field that changes the spatial frequency spectra. However, the simulations with varying matrix sizes in figure 3b show that the resolution had a small effect on the R_2 limit and did not change the calculated inflection frequency by much. The effect should be evaluated but does not change any of the trends of the simulations presented here.

In conclusion, we have verified by simulation how free diffusion in the presence of susceptibility-induced gradients can produce dispersion in measurements of $R_{1\rho}$, that chemical exchange acts as an independent process that typically occurs on a faster time scale, and that the characteristic inflection point in a dispersion plot reflects a measure of the spatial frequency spectral content of the field distribution for complex three dimensional fields. Diffusive effects can be detected in biological tissues and measures of $R_{1\rho}$ dispersion can be used to derive a structural measure of interest. The sensitivity of spin-locking pulse sequences to gradient geometry can be exploited to estimate mean spatial frequencies or be used to emphasize the contributions of smaller inhomogeneities to overall dephasing.

Acknowledgements

We would like to thank Dr. Junzhong Xu for his helpful discussions and assistance with writing the simulation scripts. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE-0909667 and NIH Grants CA109106 and EB000214.

References

1. Van Zijl PCM, Yadav NN. Chemical exchange saturation transfer (CEST): what is in a name and what isn't? *Magn. Reson. Med.* 2011; 65:927–948. doi: 10.1002/mrm.22761. [PubMed: 21337419]

2. Deverell C, Morgan RE, Strange JH. Studies of chemical exchange by nuclear magnetic relaxation in the rotating frame. *Mol. Phys.* 1970; 18:553–559. doi: 10.1080/00268977000100611.
3. Chopra S, McClung RE, Jordan R. Rotating-frame relaxation rates of solvent molecules in solutions of paramagnetic ions undergoing solvent exchange. *J. Magn. Reson.* 1984; 59:361–372. doi: 10.1016/0022-2364(84)90070-2.
4. Trott O, Palmer AG. $R_{1\rho}$ relaxation outside of the fast-exchange limit. *J. Magn. Reson.* 2002; 154:157–160. doi: 10.1006/jmre.2001.2466. [PubMed: 11820837]
5. Cobb JG, Xie J, Gore JC. Contributions of chemical exchange to $T_{1\rho}$ dispersion in a tissue model. *Magn. Reson. Med.* 2011; 66:1563–1571. doi: 10.1002/mrm.22947. [PubMed: 21590720]
6. Jin T, Autio J, Obata T, Kim SG. Spin-locking versus chemical exchange saturation transfer MRI for investigating chemical exchange process between water and labile metabolite protons. *Magn. Reson. Med.* 2011; 65:1448–1460. doi: 10.1002/mrm.22721. [PubMed: 21500270]
7. Cobb JG, Xie J, Li K, Gochberg DF, Gore JC. Exchange-mediated contrast agents for spin-lock imaging. *Magn. Reson. Med.* 2012; 67:1427–1433. doi: 10.1002/mrm.23130. [PubMed: 21954094]
8. Cobb JG, Li K, Xie J, Gochberg DF, Gore JC. Exchange-mediated contrast in CEST and spin-lock imaging. *Magn. Reson. Imaging.* 2013; 32:28–40. doi: 10.1016/j.mri.2013.08.002. [PubMed: 24239335]
9. Hills BP, Wright KM, Belton PS. Proton N.M.R. studies of chemical and diffusive exchange in carbohydrate systems. *Mol. Phys.* 1989; 67:1309–1326. doi: 10.1080/00268978900101831.
10. Hills BP, Babonneau F. A quantitative study of water proton relaxation in packed beds of porous particles with varying water content. *Magn. Reson. Imaging.* 1994; 12:909–922. doi: 10.1016/0730-725X(94)92032-X. [PubMed: 7526110]
11. Hills BP, Duce SL. The influence of chemical and diffusive exchange on water proton transverse relaxation in plant tissues. *Magn. Reson. Imaging.* 1990; 8:321–331. doi: 10.1016/0730-725X(90)90106-C. [PubMed: 2164129]
12. Cobb JG, Xie J, Gore JC. Contributions of chemical and diffusive exchange to $T_{1\rho}$ dispersion. *Magn. Reson. Med.* 2013; 69:1357–1366. doi: 10.1002/mrm.24379. [PubMed: 22791589]
13. Spear JT, Zu Z, Gore JC. Dispersion of relaxation rates in the rotating frame under the action of spin-locking pulses and diffusion in inhomogeneous magnetic fields. *Magn. Reson. Med.* 2014; 71:1906–1911. doi: 10.1002/mrm.24837. [PubMed: 23804212]
14. Majumdar S, Gore J. Studies of diffusion in random fields produced by variations in susceptibility. *J. Magn. Reson.* 1988; 78:41–55. doi: 10.1016/0022-2364(88)90155-2.
15. Yung KT. Empirical models of transverse relaxation for spherical magnetic perturbers. *Magn. Reson. Imaging.* 2003; 21:451–463. doi: 10.1016/S0730-725X(02)00640-9. [PubMed: 12878254]
16. Kurz FT, Kampf T, Heiland S, Bendszus M, Schlemmer HP, Ziener CH. Theoretical model of the single spin-echo relaxation time for spherical magnetic perturbers. *Magn. Reson. Med.* 2014; 71:1888–1895. doi: 10.1002/mrm.25196. [PubMed: 24604710]
17. Jensen JH, Chandra R. NMR relaxation in tissues with weak magnetic inhomogeneities. *Magn. Reson. Med.* 2000; 44:144–156. doi: 10.1002/1522-2594(200007)44:1<144::AIDMRM21>3.0.CO;2-O. [PubMed: 10893533]
18. Weisskoff RM, Zuo CS, Boxerman JL, Rosen BR. Microscopic susceptibility variation and transverse relaxation: theory and experiment. *Magn. Reson. Med.* 1994; 31:601–610. doi: 10.1002/mrm.1910310605. [PubMed: 8057812]
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. doi: 10.1002/mrm.20394. [PubMed: 15723392]
20. Kiselev VG. Effect of magnetic field gradients induced by microvasculature on NMR measurements of molecular self-diffusion in biological tissues. *J. Magn. Reson.* 2004; 170:228–235. doi: 10.1016/j.jmr.2004.07.004. [PubMed: 15388085]
21. Zaiss M, Bachert P. Exchange-dependent relaxation in the rotating frame for slow and intermediate exchange - modeling off-resonant spin-lock and chemical exchange saturation transfer. *NMR Biomed.* 2013; 26:507–518. doi:10.1002/nbm.2887. [PubMed: 23281186]
22. Haacke, EM., Brown, R., Thompson, M., Venkatesan, R. *Magnetic Resonance Imaging: Physical Principles and Sequence Design.* John Wiley & Sons; 1999.

23. Xu J, Does MD, Gore JC. Numerical study of water diffusion in biological tissues using an improved finite difference method. *Phys. Med. Biol.* 2007; 52:N111–N126. doi: 10.1088/0031-9155/52/7/N01. [PubMed: 17374905]
24. Bloembergen N, Purcell E, Pound R. Relaxation Effects in Nuclear Magnetic Resonance Absorption. *Phys. Rev.* 1948; 73:697–712. doi: 10.1103/PhysRev.73.679.
25. Van Vleck J. The Dipolar Broadening of Magnetic Resonance Lines in Crystals. *Phys. Rev.* 1948; 74:1168–1183. doi: 10.1103/PhysRev.74.1168.
26. Gore JC, Leeman S. Transfer functions for describing ultrasound system performance. *Phys. Med. Biol.* 1979; 24:146–156. doi: 10.1088/0031-9155/24/1/012. [PubMed: 432263]
27. McConnell HM. Reaction Rates by Nuclear Magnetic Resonance. *J. Chem. Phys.* 1958; 28:430–431. doi: 10.1063/1.1744152.
28. Yuan J, Li Y, Zhao F, Chan Q, Ahuja AT, Wang YXJ. Quantification of $T_{1\rho}$ relaxation by using rotary echo spin-lock pulses in the presence of B_0 inhomogeneity. *Phys. Med. Biol.* 2012; 57:5003–5016. doi: 10.1088/0031-9155/57/15/5003. [PubMed: 22805278]
29. Lammentausta E, Silvast TS, Närviäinen J, Jurvelin JS, Nieminen MT, Gröhn OHJ. T_2 , Carr-Purcell T_2 and $T_{1\rho}$ of fat and water as surrogate markers of trabecular bone structure. *Phys. Med. Biol.* 2008; 53:543–555. doi: 10.1088/0031-9155/53/3/003. [PubMed: 18199901]
30. Gröhn OHJ, Lukkarinen JA, Silvennoinen MJ, Pitkänen A, van Zijl PCM, Kauppinen RA. Quantitative magnetic resonance imaging assessment of cerebral ischemia in rat using on-resonance T_1 in the rotating frame. *Magn. Reson. Med.* 1999; 42:268–276. doi: 10.1002/(SICI)1522-2594(199908)42:2<268::AID-MRM8>3.0.CO;2-A. [PubMed: 10440951]
31. Menezes NM, Gray ML, Hartke JR, Burstein D. T_2 and $T_{1\rho}$ MRI in articular cartilage systems. *Magn. Reson. Med.* 2004; 51:503–509. doi: 10.1002/mrm.10710. [PubMed: 15004791]
32. Rane S, Spear JT, Zu Z, Donahue MJ, Gore JC. Functional MRI Using Spin Lock Editing Preparation Pulses. *Magn. Reson. Imaging.* 2014; 32:813–818. doi: 10.1016/j.mri.2014.04.001. [PubMed: 24848291]

Highlights

- Diffusion in non-uniform fields causes dispersion of spin-lock relaxation rates
- Spin-lock dispersions can be used to estimate the sizes of susceptibility variations
- Simulations relate dispersions to the spatial frequency content of non-uniform fields
- Spin-lock dispersions can characterize inhomogeneous media and biological tissues

Figure 1.

BCC, FCC, and Cylinder unit cells. Structures were assigned radii and spaced out to have specific volume fractions before the corresponding B_z fields were calculated between the spheres and cylinders. (Color, 2 column)

Figure 2.

Simulated $R_{1\rho}$ dispersions with a 60% volume fraction and radii varying from 5-15 μm for BCC, FCC, and Cylinder structures in a, b, and c (upper). Corresponding dispersions with a radius of 5 μm and volume fractions varying from 30-60% are plotted in plots d, e, and f (lower). (Color, 2 column)

Figure 3.

- a.) Simulated $R_{1\rho}$ dispersion curves for the $R = 5 \mu\text{m}$, 60% volume fraction BCC structure ($64 \times 64 \times 64$ grid size) with the susceptibility increased from 1 to 6 times that of polystyrene.
- b.) Simulated $R_{1\rho}$ dispersion curves for the $R = 5 \mu\text{m}$, 60% volume fraction BCC structure with various grid sizes. (color, 1.5 column)

Figure 4.

a.) Fitted correlation times (τ_c) for each structure type with constant volume fraction and varying radii. b.) Fitted correlation times (τ_c) for each structure type with constant radius and varying volume fractions. (color, 1.5 column)

Figure 5. Correlation times estimated from $R_{1\rho}$ measurements are shown in red and compared to the simulated correlation times for the BCC structures with varying radii. (Color, 1 column)

Figure 6. Theoretical spatial frequencies, $\langle q \rangle_{\text{theory}}$, calculated from Eq. 7 vs. the fitted spatial frequencies from the simulations, q_{eff} . (Color, 1 column)

Figure 7.

a.) Simulated signal decay (blue) and corresponding monoexponential fit (red) for the case of pure diffusion in 5 μm BCC packed spheres with 60% volume fraction. b.) Simulated signal decay (blue) with the corresponding fit to Eq. 10 to account for the observed oscillations (red) for the same structure with chemical exchange. (Color, 1.5 column)

Figure 8.

a.) $R_{1\rho}$ dispersion curves for the case of chemical exchange and diffusion with varying radii but a constant volume fraction of 60%. Chemical exchange induces the dispersion at higher locking fields while diffusion is responsible for the changing dispersions at lower locking fields. b.) $R_{1\rho}$ dispersion curve for the 10 μm radius case (blue) with the dispersion for pure diffusion and pure chemical exchange in red and black respectively. (Color, 1.5 column)

Figure 9.

Fitted chemical exchange parameters are plotted in a.) and b.) and compared to their theoretical values from the simulation input parameters. The fitted diffusion based parameters are shown in c.) and d.) and compared to the simulated values of the pure diffusion case. (Color, 1.5 column)