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Scaling of transverse nuclear magnetic relaxation due to magnetic nanoparticle aggregation

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ABSTRACT

The aggregation of superparamagnetic iron oxide (SPIO) nanoparticles decreases the transverse nuclear magnetic resonance (NMR) relaxation time T_2^{CP} of adjacent water molecules measured by a Carr-Purcell-Meiboom-Gill (CPMG) pulse-echo sequence. This effect is commonly used to measure the concentrations of a variety of small molecules. We perform extensive Monte Carlo simulations of water diffusing around SPIO nanoparticle aggregates to determine the relationship between T_2^{CP} and details of the aggregate. We find that in the motional averaging regime T_2^{CP} scales as a power law with the number N of nanoparticles in an aggregate. The specific scaling is dependent on the fractal dimension d of the aggregates. We find $T_2^{CP} \propto N^{-0.44}$ for aggregates with $d=2.2$, a value typical of diffusion limited aggregation. We also find that in two-nanoparticle systems, T_2^{CP} is strongly dependent on the orientation of the two nanoparticles relative to the external magnetic field, which implies that it may be possible to sense the orientation of a two-nanoparticle aggregate. To optimize the sensitivity of SPIO nanoparticle sensors, we propose that it is best to have aggregates with few nanoparticles, close together, measured with long pulse-echo times.

1. Introduction

Superparamagnetic iron oxide (SPIO) nanoparticles have been used as nuclear magnetic resonance (NMR) chemical sensors by functionalizing them to aggregate in the presence of a specific small molecule [1]. This aggregation decreases the transverse relaxation time T_2^{CP} of the protons in surrounding water that is detectable by a Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence [1]. SPIO nanoparticles have been functionalized to detect the presence of oligonucleotides [1,2], DNA cleaving agents [1,2], mRNA [1,2], enzymes [1,2], proteins [1,2], viruses [1,2], calcium [3], stereoisomers [4], and block-copolymers [5]. The technique is well suited for *in vivo* sensing because of its bio-compatibility and because it can be read out by magnetic resonance imaging (MRI) [6]. The decrease in T_2^{CP} has been explained theoretically for single nanoparticle systems by inner- and outer-shell theory [7], then refined with chemical exchange [7,8] and partial refocusing models [9]. The current theoretical understanding of NMR relaxation for SPIO aggregates is based on extending the theory of single nanoparticle systems and treating an aggregate as a single magnetic sphere of larger size [10,11]. Monte Carlo simulations have been performed previously to investigate aggregates with up to 15 nanoparticles by varying particle size and average spacing [12]. These simulations reveal that the effect of aggregation on T_2^{CP} depends on nanoparticle size and that T_2^{CP} only decreases for the aggregation of small nanoparticles.

In this work, we perform in-depth Monte Carlo simulations to investigate the dependence of T_2^{CP} on the detailed characteristics of nanoparticle aggregates. We begin by presenting a summary of the theory pertaining to NMR of single nanoparticles. We then describe the random walk simulation used to calculate T_2^{CP} for nanoparticle aggregate systems. The random walk simulation is verified by showing agreement with theoretical results for single nanoparticles. Simulations of two nanoparticles show that T_2^{CP}

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depends strongly on the separation of the nanoparticles and the orientation of the nanoparticles relative to the external magnetic field, an effect that could be used to detect the orientation of nanoparticles aggregates. For larger aggregates, we find that T_2^{CP} scales as a power law with the number N of nanoparticles in an aggregate when the aggregate is in the motional averaging regime. The scaling depends on the fractal dimension d of the aggregate; we find $T_2^{CP} \propto N^{-0.44}$ for aggregates with $d=2.2$, a typical value for diffusion limited aggregation. We find the power law scaling from the random walk simulations to be reasonable in comparison with a simple model. Based on our observations, we propose that the greatest effect on T_2^{CP} will be caused by aggregates with few nanoparticles, that have minimal separation between nanoparticles, and are measured with long pulse-echo times.

2. NMR of single nanoparticle systems

An NMR measurement is performed by initially polarizing an ensemble of nuclear moments, then observing their relaxation in time. For the ensemble of nuclear moments, we consider the nuclear magnetic moment of the hydrogen atoms of water. An external z-directed magnetic field $\vec{B}_e$ initially polarizes the average moment $\vec{I}$ in the z-direction. An NMR measurement begins with an applied radio frequency (RF) pulse rotating $\vec{I}$ to the x-axis. The average moment will relax back to the z-axis with spin–lattice relaxation time T_1 while each individual moment precesses in the x–y plane at the local Larmor frequency $\omega_L = \gamma B(\vec{r})$, where γ is the proton gyromagnetic ratio and $B(\vec{r})$ is the magnitude of the z-directed magnetic field at location $\vec{r}$. The magnitude of $\vec{I}$ will decrease as the moments of the protons lose coherence due to spin–spin interactions and the inhomogeneity of the magnetic field. This transverse decay of $\vec{I}$ is characterized by the effective transverse relaxation time T_2^*. A Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence [13] may be used to cancel the effect of field inhomogeneity in order to measure the true transverse decay time T_2. The CPMG pulse sequence consists of a second RF pulse at time τ_{CP} after the first RF pulse which rotates each moment 180° about the x-axis, and causes the spins to refocus along the x-axis and form a spin-echo at time $2\tau_{CP}$. This process is repeated to obtain a spin-echo train whose envelope decays as [14] $\exp\lfloor -t(T_2^{-1}+T_1^{-1})\rfloor$.

The transverse decay time T_2^{CP} measured by CPMG pulse sequences in systems with diffusion depends on the relationship between the diffusion time τ_D for a water molecule to move between magnetic field fluctuations and the pulse-echo time τ_{CP}. If $\tau_{CP} \gg \tau_D$, water will diffuse far compared to variations in the magnetic field between subsequent pulse-echo pairs making the pulse sequence unable to effectively refocus the moments. This is called the Motional Averaging (MA) regime; in this limit, T_2^{CP} is equal to T_2^* and will remain dominated by the field inhomogeneity. If $\tau_{CP} \ll \tau_D$, water will not diffuse far in between pulse-echo pairs, and thus a CPMG pulse sequence will effectively refocus the magnetic moments and T_2^{CP} will approach T_2. This is called the Echo Limited (EL) regime [13].

There is a good theoretical understanding of the effect of single nanoparticles on the transverse decay time T_2^{CP} measured by a CPMG pulse sequence. We consider a spherical nanoparticle with radius r_P and magnetic dipole moment $\vec{m}$ pinned in the z-direction by an external field $\vec{B}_e$. The external field is typically sufficiently strong such that interactions between nanoparticles can be ignored [15]. The z-component of the magnetic field generated by each nanoparticle is

$$B_z(r,\theta) = \frac{\mu_0 m}{4\pi}\left(\frac{3\cos^2(\theta)-1}{r^3}\right), \tag{1}$$

where $\vec{r}$ is the position relative to center of the nanoparticle, θ the angle to the z-axis, and μ_0 the permeability of free space. The effect of the nanoparticle is characterized by the root-mean-square variation $\Delta\omega$ in the Larmor frequency on the surface of the nanoparticle and the volume fraction Φ occupied by nanoparticles. The diffusion time is given by $\tau_D = r_P^2/D$, where D is the self-diffusion constant of water and r_P is the radius of the nanoparticle. In the EL regime ($\tau_{CP} \ll \tau_D$), the transverse relaxation time T_2^{EL} due to the nanoparticle is given by [7]

$$\frac{1}{T_2^{EL}} = 2.25\Phi(\Delta\omega)^2\frac{\tau_{CP}^2}{\tau_D} \tag{2}$$

In the MA regime ($\tau_{CP} \gg \tau_D$), the transverse relaxation time T_2^{MA} due to the nanoparticle is given by [7]

$$\frac{1}{T_2^{MA}} = \frac{4}{9}\Phi(\Delta\omega)^2\tau_D. \tag{3}$$

These equations are valid for the weak dephasing regime where $\Delta\omega^{-1} \gg \tau_{CP}$ and $\Delta\omega^{-1} \gg \tau_D$, as is typically the case for SPIO nanoparticles. We do not consider decay due to T_1, typically $T_1 \gg T_2^{CP}$ [16]. We set the true transverse decay time $T_2 = \infty$ in order to focus on the effects of the inhomogeneous field [16]. A CPMG pulse sequence is experimentally necessary to cancel relaxation due to inhomogeneous field effects with longer length scales.

3. Methods: random walk simulation

We investigate the dephasing caused by nanoparticle aggregates using a Monte Carlo method to simulate T_2^{CP} for water molecules diffusing in the magnetic field profile created by a nanoparticle aggregate. Monte Carlo methods for calculating T_2^{CP} are well established [9,12,17]. We begin by constructing a nanoparticle aggregate with diffusion limited aggregation (DLA). The aggregate is then placed in a spherical volume in which water molecules are allowed to diffuse. Calculating diffusive trajectories of water allows us to determine the magnetic field experienced by each proton and thus the dynamics of each magnetic moment. An ensemble of such random walks allows us to calculate the average magnetic moment $\vec{I}$ of the ensemble and observe its decay.

We construct aggregates of N nanoparticles by diffusion limited aggregation (DLA) as shown in Fig. 1(a) [18]. A seed nanoparticle is placed at the origin and additional nanoparticles execute random walks until they come into contact with a stationary nanoparticle, at which point they irreversibly stick. Previous simulations of diffusion limited aggregation have shown that variations in the sticking coefficient between 0.1 and 1 do not significantly change the fractal dimension of the aggregate under the circumstances covered in our paper [19]. The size of an aggregate is approximated by its radius of gyration r_G, the root-mean-square distance of the nanoparticles to the center of mass. The fractal dimension d of such aggregates is found to be $d=2.2\pm0.1$ by fitting the aggregates to $r_G \propto N^{1/d}$ over the range $20 < N < 125$. The fractal dimension of aggregates assembled by DLA is typically $d=2.45\pm0.10$ and depends on the details of the DLA technique [18].

To simulate water diffusing in nanoparticle systems, we calculate an ensemble of random walk trajectories for water