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Comment

Comment on "Structure-Correlated Magnetic Resonance Transverse Relaxivity Enhancement in Superparamagnetic Ensembles with Complex Anisotropy Landscape"

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ABSTRACT: In a recent article, Konwar et al. [*Langmuir* **2022**, *38*, 11087−11098.] reported a new relationship between the structure of clusters of superparamagnetic nanoparticles and the proton nuclear magnetic resonance transverse relaxation they induce. In this comment, we would like to express reservations concerning the adequacy of the new relaxation model proposed in this work.

INTRODUCTION

Water nuclear magnetic resonance (NMR) relaxation caused by superparamagnetic particles has been studied for more than 35 years. The first attempts to use iron oxide particles as contrast agents[2] and to theoretically model the corresponding NMR relaxation[3] were done in the late 1980s. Many papers later, it is now accepted that the water relaxation in the presence of such nanoparticles is caused by the dipolar interaction between the water protons and the superparamagnetic moment of the particle, with a time modulation either by water diffusion or by the fluctuation of the superparamagnetic moment caused by the Néel and/or rotational Brownian relaxation. A relaxation model, which considers the dependence of the particle's magnetic moment with the external magnetic field as well as the effect of magnetic anisotropy and Néel relaxation, has been developed by Roch et al. in 1999.[4] As usually done in the field of magnetic contrast agents, the model was tested and validated through the successful fitting of the curves characterizing the field dependence of the relaxation rates $1/T_1$ and $1/T_2$, the so-called nuclear magnetic relaxation dispersion (NMRD) profiles. Another model that neglected anisotropy[5] was discarded because it did not allow a proper fitting of the NMRD profiles. This illustrates the fundamental necessity of the comparison between experimental results and theoretical predictions for the validation of a theoretical relaxation model. Clustering of superparamagnetic nanoparticles, that could be observed in vivo after the internalization in cells, was shown to have a dramatic impact on relaxation.[6] This explains why clusters were also synthesized as potential contrast agents: in some conditions, the transverse relaxation of the clusters is much more efficient than the relaxation induced by the single particles. In this context, the samples presented in ref 1 are interesting: they are constituted of arrangements of superparamagnetic particles with different distributions of anisotropy axis. From the NMR relaxation point of view, these samples could be seen as very large clusters. Their magnetic characterization is complete and meticulous. However, we have reservations concerning the proposed modification of the superparamagnetic relaxation model.

THE DIFFERENT RELAXATION REGIMES AND THEIR VALIDITY DOMAINS

The work of Roch et al.[4] is accepted in the community as the first satisfying model of the relaxation induced by superparamagnetic particles. More recent papers also contributed to the understanding of the relaxation, for example for particles presenting a strong anisotropy.[7,8] These different models were developed for systems respecting the Redfield condition:

$$\Delta\omega\tau_D << 1 \tag{1}$$

with

$$\Delta\omega = \frac{\mu_0 \gamma M_V}{3} \tag{2}$$

and

$$\tau_D = \frac{R^2}{D} \tag{3}$$

where $\mu_0 = 4\pi\ 10^{-7}$ H/m is the vacuum magnetic permeability, $\gamma = 2.675 \times 10^8$ T^{-1} s^{-1} the proton gyromagnetic ratio, R the particle radius, D the water diffusion coefficient, and M_V the volume magnetization of the magnetic particles. The condition (eq 1) corresponds to the "motional averaging regime" (MAR): indeed, it implies that the motion of water molecules during the relaxation time is fast enough so that the water protons, as time evolves, "encounters" a lot of different magnetic fields. The field "felt" by the protons is "averaged" by the motion.

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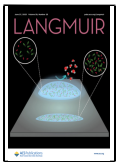

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At large magnetic fields, $1/T_2$ tends to a constant value called the secular term. The eq 8 of Konwar et al.[1] corresponds to the secular term of the equation predicting $1/T_2$ in the motional averaging regime. It should, however, be noted that, if in MKS units, a multiplicative ${\mu_0}^2$ factor is missing in eq 8. This factor appears when the origin of relaxation is the dipolar interaction between two spins I and S.[9]

When the Redfield condition is not respected, other models must be used to evaluate the secular term:

- if $5 < \Delta\omega\tau_D < 20$, the static dephasing regime (SDR) allows to estimate the transverse relaxivity;
- if $\Delta\omega\tau_D > 20$, the partial refocusing model (PRM) provides an estimation of the T_2 measured by a CPMG sequence for a given interecho time.

The validity domains of the different models and their adequacy were tested thanks to numerical simulations[10−12] and comparison with experimental data.[13]

THE MODEL PROPOSED IN KONWAR ET AL.

So, the model used by the authors (eq 8 of ref 1) is valid in the MAR, but they did not check if their samples respected the Redfield condition. To do so, one must evaluate $\Delta\omega$ and τ_D thanks to eqs 2 and 3. Our aim is not to determine exact values of those parameters, which would be impossible since there are several samples with different characteristics. However, global but realistic estimations of $\Delta\omega$ and τ_D can allow one to determine if the Redfield condition is respected. Moreover, with clusters, one must use caution: it is the cluster radius that must be used to calculate τ_D :

$$\tau_D^{\text{cluster}} = \frac{(R_{\text{cluster}})^2}{D}$$

For all the samples in ref 1, the radius seems to be around 200 nm. This value is larger than the value obtained by neutron scattering but smaller than what is observed on the electron microscopy images and much smaller than the hydrodynamic radius reported in the SI. As the relaxation measurements were performed in solution, the hydrodynamic radius is therefore more relevant from the relaxation point of view. Considering $D = 2.3 \times 10^{-9}$ m/s^2 at room temperature, one can estimate a global value for τ_D^{cluster}:

$$\tau_D^{\text{cluster}} = 1.710^{-5}\ \text{s}$$

Similarly, one cannot simply use the magnetization of the primary cores to evaluate $\Delta\omega_{\text{cluster}}$

$$\Delta\omega_{\text{cluster}} = \phi_{\text{intra}}\Delta\omega = \phi_{\text{intra}}\frac{\mu_0\gamma M_V}{3}$$

where ϕ_{intra} is the fraction of the total volume of a cluster that is occupied by the magnetic materials, zinc ferrite cores in our case. M_V is the volume magnetization of the magnetic material (zinc ferrite), and it can be obtained from the magnetic measurements presented in Figure 4 of ref 1. At 300 K all the samples present a mass magnetization larger than 10 emu/g at 3 T (the magnetic field of the imaging device used for the relaxation time measurements). Assuming as a first approximation the same density for the zinc ferrite and magnetite (5200 kg/m^3), this corresponds to a volume magnetization larger than M_V = 52 000 A/m. For dense clusters, if the ferrite crystals are in contact with each other, as what is observed on the TEM pictures, one could estimate ϕ_{intra} to be at least 0.25. Spheres on a cubic lattice and in contact with each other would correspond to $\phi_{\text{intra}} = 0.5$. This allows us to estimate a lower limit for $\Delta\omega_{\text{cluster}}$:

$$\Delta\omega_{\text{cluster}} = 1.510^6\ \text{rad}\ s^{-1}$$

Finally, one obtains a rough estimation of $\Delta\omega_{\text{cluster}}\tau_D^{\text{cluster}} = 25$. This is probably an underestimation since, for some samples, the radius and/or the magnetization is larger.

This is far beyond the validity domain of the MAR, and therefore we think that eq 8 of Konwar et al.[1] is not suited to describe the relaxation of the clusters presented in their article. With such a value for $\Delta\omega_{\text{cluster}}\tau_D^{\text{cluster}}$, the PRM model must be used. However, this would not be straightforward since the T_2 values were measured with a spin echo sequence, while the PRM assumes a more classical CPMG sequence (that properly "kills" the SDR relaxation) for the measurement of T_2. Even for the spin−echo sequence, a suited theoretical model exists[14] and could be used.

Finally, even in the MAR validity domain, we think that the modification of the MAR equation proposed by Konwar et al. is not consistent. There is first a confusion between the relaxation rate $1/T_2$ and the relaxivity r_2 in eq 9 of Konwar et al.[1] These are not equal and, in the equation predicting the transverse relaxivity, the volume fraction V^* should not be present anymore.

Moreover, why should this specific multiplicative term ($\frac{K^2}{M_s^2\mu_0^2}$) be used? A dimensional analysis shows that it cannot be correct: $\frac{K^2}{M_s^2\mu_0^2}$ should be dimensionless, to keep $1/T_2$ in s^{-1}. However, it has units: it is in A^2 m^{-2}. Finally, the second expression given in eq 9 does not depend of M_s anymore. This is in complete contradiction with all the published data (experimental, computer simulations, and theoretical modeling), which showed the importance of the core magnetization. To validate such a new model, a comparison of the theoretical predictions with experimental results (ideally with NMRD profiles) is required, but such a comparison is not made, even for the studied samples.

CONCLUSION

For all these reasons, and even if the samples described in ref 1 are interesting and their magnetic characterization complete, we think that, without further developments, the NMR relaxation model proposed in this work is not suited to describe the relaxation of magnetic nanoparticles or clusters of magnetic nanoparticles. The model needs to be extensively modified and must be validated through a comparison with experimental results and/or computer simulations.

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Notes

The authors declare no competing financial interest.

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