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Are nanocubes more efficient than nanospheres to enhance the nuclear magnetic relaxation of water protons? A Monte Carlo simulation study 📀

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J. Chem. Phys. 162, 124111 (2025) https://doi.org/10.1063/5.0251512



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Cite as: J. Chem. Phys. 162, 124111 (2025); doi: 10.1063/5.0251512 Submitted: 3 December 2024 • Accepted: 18 February 2025 • Published Online: 26 March 2025

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ABSTRACT

Iron oxide superparamagnetic nanoparticles have been extensively studied as T_2 contrast agents in magnetic resonance imaging. The theory of nuclear magnetic relaxation induced by superparamagnetic nanoparticles has been validated by numerous experimental studies in the case of spherical particles. Recently, several studies focused on the synthesis of cubic nanoparticles. Some of them reported significantly higher relaxivities compared to their spherical counterpart and attributed this increase to their specific shapes. This work investigates the impact of cube-shaped nanoparticles on nuclear magnetic relaxation through Monte Carlo methods. Transverse relaxation at high static magnetic field is simulated by modeling the proton diffusion in the magnetic field generated by a cubic or a spherical nanoparticle. The results indicate that, in the case of magnetite nanoparticles, there is no significant difference between both shapes for sizes above 30 nm when particles are compared at equal volumes and magnetization. Below this size, a -40%-15% variation of the relaxation rates is predicted for the cubic case compared to the spherical case. These results are explained using general relaxation models that incorporate the distribution of the magnetic field generated by the nanoparticles. The simulation predictions are compared to some experimental results from the literature, revealing that, in some cases, the magnetic field specific to the nanoparticle shape alone cannot explain the observed increase in the relaxation rate of cubic nanoparticles.

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NOMENCLATURE

		MR	magnetic resonance
B_z	z-component of the magnetic field	MRI	magnetic resonance imaging
\vec{B}_0	external magnetic field, supposed to be parallel to	NP	nanoparticle
	the z axis	PRM	partial refocusing model
С	nanocube edge length	R	spherical nanoparticle radius
С	NP concentration	R_2	transverse relaxation rate
CA	contrast agents	r_2	transverse relaxivity
CPMG sequence	Carr-Purcell-Meiboom-Gill sequence	SDM	static dephasing model
D	proton diffusion coefficient	SPM	superparamagnetic
f	volume fraction of the sample occupied by the	T_2	transverse relaxation time
	particles	V	NP volume
M	superparamagnetic nanoparticle saturation	$V_{protons}$	volume occupied by the protons in the sample or
	magnetization		the simulation space

MAR

motional averaging regime

γ	proton gyromagnetic ratio
μ	magnetic moment of the superparamagnetic
	nanoparticle
μ_0	vacuum magnetic permeability
$ au_D$	proton diffusion correlation time
$ au_{IE}$	CPMG inter-echo time

I. INTRODUCTION

Nuclear magnetic relaxation times T_1 and T_2 are known to impact the image contrast in magnetic resonance imaging (MRI).¹ To ease the diagnosis, contrast agents (CAs) are often used to highlight regions of interest (such as tumor cells) in the MR image. CAs are magnetic compounds that interact with nuclear spins and shorten their relaxation times. There are two main categories of CAs: T_1 and T_2 agents. T_1 agents are usually gadolinium-based compounds, while T_2 agents mainly comprise superparamagnetic iron oxide nanoparticles.

Superparamagnetic (SPM) nanoparticles (NP) were first studied by Néel² who discovered the superparamagnetism phenomenon: below a given size limit, typically at the nanoscale, these NPs present no hysteresis and no remnant magnetization. Their magnetization saturates at high external magnetic fields, reaching a very high saturation value. Indeed, each SPM NP is composed of a single magnetic Weiss domain in which all the electron spins are aligned with each other. The most used SPM NPs in MRI are iron oxide NPs because of their non-toxicity, ease of synthesis, and functionalization. These properties make them suitable for a wide range of biomedical applications, in addition to MRI, such as magnetic hyperthermia, magnetic particle imaging, magnetic separation, and drug delivery.^{3–5}

Iron oxide NPs are usually synthesized as spherical NPs. However, for more than 15 years, numerous studies have focused on the synthesis of NPs with exotic shapes, such as cubes, rods, stars, or nanoflowers.^{6–8} Experimental studies have shown that NP shapes have a crucial impact on their efficiency in applications such as hyperthermia,^{9–11} photothermal therapy,^{11,12} or drug delivery.⁶ Several experimental studies measured relaxation times for different NP shapes^{13–22} and sometimes reported very high relaxivities (i.e., relaxation rates normalized by the iron content). Thus, exotic-shaped NPs appear to be promising efficient MRI CAs. A fine understanding of the underlying relaxation mechanisms could help define the parameters that optimize their efficiency.

The influence of SPM NPs on water nuclear magnetic relaxation can be explained by the interaction between proton spins and the large dipolar magnetic fields produced by the NPs.²³ The main relaxation mechanism comes from the bulk diffusion of water protons around the NPs (the so-called "outer-sphere mechanism"). In most relaxation models, SPM NPs are considered as impenetrable spheres: there is no quantitative prediction about the potential influence of their shape on the relaxation times. The observed experimental increase in relaxation rates for NPs with non-spherical shape is often attributed to proton diffusion in intense magnetic field gradients around sharp corners of the nanoparticles.^{13,15} Nevertheless, this hypothesis has never been fully quantitatively verified from the theoretical point of view.

In this work, the influence of the NP shape—cubic vs spherical—on the relaxation rate will be studied using Monte Carlo

simulations. A cube is a simple shape that allows a straightforward adaptation of the original simulation designed for spherical shapes.^{24–26} This shape is thus chosen as a proof of concept demonstrating that relaxation simulations can be adapted to other NP shapes. Moreover, nanocubes have been widely synthesized and studied in the literature.^{13,14,17,20,22,27–33} They are efficient agents for magnetic hyperthermia⁶ in combination with photothermal therapy.³⁴ To our knowledge, despite some semi-quantitative attempts, there has been no study that completely simulates the proton relaxation induced by SPM nanocubes. Indeed, the existing studies^{13–15} only evaluate the magnetic field produced by such cubes without simulating proton diffusion.

The aim of this work is to investigate the effect of NP cubic shape on NMR relaxation (more specifcally, the effect of proton diffusion in the magnetic field specific to the NP shape) and compare it to spherical NP using Monte Carlo simulations. The proposed simulation method accounts for proton diffusion and for the magnetic field produced by these particles. This article is organized into the following sections: (a) A theoretical section that outlines the three different relaxation size-dependent regimes and their associated relaxation models. (b) A description of the Monte Carlo simulation methodology used in this work. (c) A presentation and interpretation of simulation results using established relaxation models. (d) A comparison between the simulation predictions and some experimental results reported in the literature.

II. THEORIES

Theories of water nuclear relaxation induced by SPM NPs will be only briefly described in this section as they have already been detailed in the literature (for example, see Refs. 23, 25, and 35). Their derivation from more general models will be discussed to allow a more quantitative interpretation of simulation results in Sec. V.

In the case of colloidal suspensions of nanoparticles in water, relaxation occurs due to the interaction between proton spins and magnetic fields generated by the SPM NPs. In the classical approach, each proton carries a vectorial magnetic moment $\vec{\mu}_i(t)$ and their movement is modeled by a diffusion equation or a random walk. As this study focuses on the transverse relaxation time T_2 at high external static magnetic field B_0 , only the equations that satisfy this specific condition will be presented in this section.

At high B_0 , the relaxation rate $R_2 = 1/T_2$ reaches a plateau whose value is given by the so-called "secular term."³⁶ This plateau is reached when the B_0 values satisfy the following condition:

$$\gamma B_0 \tau_D = \gamma B_0 \frac{R^2}{D} \gg 1, \tag{1}$$

where γ is the proton gyromagnetic ratio, R is the spherical SPM radius (more precisely, the minimum approach distance between the proton and the SPM center), D is the proton diffusion coefficient (equal to water diffusion coefficient as this study focuses on water protons), and the diffusion correlation time $\tau_D = R^2/D$. For example, for an SPM radius of 5 nm and a water diffusion coefficient of 3 × 10⁻⁹ m²/s (value at 37 °C), the secular term is reached for $B_0 \gg 0,37T$, which is the case for usual MRI magnetic fields. Thus, the results and models presented in this work are valid for the magnetic fields used in MRI.

Three relaxation models exist for SPM NPs, each characterized by their own range of validity:²⁵ the motional averaging regime (MAR) model for low NP radii, the static dephasing model (SDM) for "medium" sizes, which provides the maximum achievable relaxation rate, and the partial refocusing model (PRM) for larger sizes. For magnetite nanoparticles, diameters less than around 30 nm, in the 30–120 nm range and larger than 120 nm, respectively, correspond to the MAR, static and PRM "regimes." These three models assume a spherical nanoparticle shape. To the best of our knowledge, no analytical model exists for cubic particles.

A. Motional averaging regime

The MAR model assumes that each proton encounters many different SPM NPs during relaxation. In the MAR, relaxation times are obtained using the quantum Redfield formalism.³⁷ In this formalism, relaxation times depend on the Fourier transform of the correlation functions of the proton Hamiltonian, called the "spectral densities." It has been shown that, in the particular case of proton relaxation induced by superparamagnetic nanoparticles, a classical formalism in which proton spins are modeled as classical vectors interacting with their local magnetic field is equivalent to the quantum formalism.^{38,39} In the MAR model, the transverse relaxation time is given by^{38,40}

$$\frac{1}{T_2^*} = R_2^* = \gamma^2 \int_0^\infty \langle B_z(0) B_z(\tau) \rangle d\tau,$$
(2)

where B_z is the *z* component of the magnetic field experienced by the protons and the applied field \vec{B}_0 is assumed to be parallel to the *z* axis. The star indicates that the relaxation time is measured without the use of 180°-refocusing pulses. In this study, the static magnetic field of the NMR device is assumed to be perfectly homogeneous. The model only considers the magnetic field inhomogeneities produced by the particles. The brackets indicate an average over all the proton trajectories within the sample. This general equation is valid for any magnetic field fluctuations and is thus applicable to any arbitrary NP shape.

In the specific case of protons diffusing in the dipolar magnetic field of the superparamagnetic nanoparticles, Eq. (2) gives

$$R_{2}^{*} = \frac{64\pi}{135} \left(\frac{\mu_{0}}{4\pi}\right)^{2} \mu^{2} \gamma^{2} \frac{C}{RD},$$
(3)

where $\mu = MV$ is the magnetic moment of the SPM NP, *V* is the volume of the NP, *C* is the NP concentration (number of NPs per unit volume), *M* is the SPM saturation magnetization, and μ_0 is the vacuum magnetic permeability. In this equation, *R* is rigorously the minimum distance of approach between the proton and the particle. This quantity corresponds to the NP radius considering a permeable coating and the water molecule bearing the proton spins is much smaller than the NP. In the case of magnetized spheres, the equations of the MAR are only valid when the Redfield condition is obeyed,

$$\frac{\gamma\mu_0}{3}\frac{MR^2}{D} \ll 1. \tag{4}$$

In that regime, the 180° -echo pulses used in the spin-echo or the Carr-Purcell-Meiboom-Gill (CPMG) sequences do not influence the relaxation rate and thus $R_2 = R_2^*$. It can be shown⁴¹ from

Eq. (3) that R_2^* is proportional to R^2 when *M* is constant: Thus, the relaxation rate increases when the NP size gets larger.

B. Static dephasing model

In the static dephasing regime, the proton movement is small compared to the NP size and its position can be considered as fixed during the relaxation time. In this case, the SDM predicts⁴²

$$R_2^* = \frac{2\pi\mu_0}{9\sqrt{3}}C\gamma\mu.$$
 (5)

This model is obtained by computing the statistical distribution of the z component of the magnetic field B_z that the protons experience. In the spherical case, it is the B_z -distribution associated with the dipolar magnetic field. The nanoparticle is considered impenetrable so the B_z -distribution does not include the magnetic field inside the nanoparticle. Brown demonstrated that, in the case of the dipolar magnetic field of an impenetrable sphere, B_z follows a Cauchy distribution,⁴²

$$p(B_z) = \frac{K}{B_z^2 + \pi^2 K^2},$$
 (6)

where $K = 2C\mu_0\mu/(9\sqrt{3})$. In this model, a variation of the B_z distribution leads to a different time evolution of the spins and thus impacts the relaxation time. For a CPMG sequence, previous studies^{25,41} showed that Eq. (5) provides an upper limit of the maximum achievable relaxation rate R_2 induced by superparamagnetic NPs (with equal SPM magnetization and NP volume fraction).

C. Partial refocusing model

1

When spherical SPM NPs are very large and when a CPMG sequence is used, R_2 is given by the partial refocusing model,²⁵

$$R_2 = 3\pi x^{1/3} CDR \left[1.34 + \frac{4\pi CR^3}{3} x \right]^{5/3},$$
(7)

where

$$x = \sqrt{\frac{1}{80}} \gamma \mu_0 \frac{\mu}{\pi R^3} \tau_{IE},\tag{8}$$

where τ_{IE} is the inter-echo time, i.e., the time duration between two consecutive 180°-pulses. This model predicts a decrease in the relaxation rate when the NP size increases. At constant magnetization M and volume fraction f [defined by Eq. (10)], it can be shown that Eq. (7) is inversely proportional to R^2 and that the relaxation rate decreases with the NP size.

In this model, space around the nanoparticles is divided into two spherical regions centered on the NP: the inner and the outer regions are indicated by red and green, respectively, in Fig. 1. It has been demonstrated that the NMR signal from the protons, which get in the inner region is completely lost: only the protons that diffuse in the outer region contribute to the relaxation.²⁵ The radius of the inner region is given by

$$R_{inner} = R \left[\frac{x}{1.34 + VCx} \right]^{\frac{1}{3}}.$$
 (9)



FIG. 1. Two regions of the PRM model. Any proton passing through in the red region does not contribute to the transverse relaxation. The green region corresponds to the "outer-region" whose protons predominantly contribute to the relaxation.

D. Relaxivities

The efficiency of a negative contrast agent depends on its effect on the transverse relaxation rate R_2 : the higher the relaxation rate, the more efficient the contrast agent becomes. To compare the efficiency between two different contrast agents, their relaxation is usually normalized by the amount of magnetic compound: The corresponding quantity is called "relaxivity." In the case of iron oxide, relaxivities r_2 are expressed in s⁻¹(mM[Fe])⁻¹.

When studying different NPs composed of the same material, working at constant iron concentration is equivalent to working at constant volume fraction f. Volume fraction f is defined as the ratio between the volume occupied by nanoparticles and the sample volume. This is why Eqs. (3), (5) and (7) are usually expressed in terms of volume fraction rather than NP concentration. These two quantities are related through the following expression:

$$f = \frac{V_{tot SPM}}{V_{sample}} = \frac{N_{SPM}V}{V_{sample}} = CV,$$
 (10)

where V is the volume of a single NP, $V_{tot SPM}$ is the total volume of all sample NPs, V_{sample} is the volume of the whole sample, and N_{SPM} is the total number of NPs in the sample.

III. METHODS

Methods simulating the transverse relaxation have been thoroughly described in previous publications (see Refs. 24–26 for example). They were always applied to spherical nanoparticles. This work proposes an adaptation of the simulation protocol to the case of cubic nanoparticles.



FIG. 2. Two types of simulation configurations studied in this work, with $\vec{B_0}$ as the external magnetic field. In both cases, the simulation space (blue) is cubic and protons (yellow) diffuse within it. The NP (brown) is at the center of the simulation space and is either spherical or cubic. These simulation spaces only contain one single nanoparticle while the proton diffusion is subject to periodic boundary conditions.

A. Monte Carlo T₂ simulations

Monte Carlo T_2 simulations are composed of the following steps: (1) initialization of the simulation space, (2) diffusion and dephasing of proton spins, and (3) NMR signal computation.

1. Initialization of the simulation space

In this work, the simulation space in which protons diffuse is cubic—this eases the implementation of the periodic boundary on the proton diffusion (see the next step). The simulation space contains a single NP in its center (Fig. 2). In some studies,^{24,25} several NPs are introduced in the simulation space. However, a previous study³⁹ showed that, if the volume fraction *f* is small enough, a single NP provides similar results and allows a substantial decrease in the computation time. The simulation space size is determined from the volume fraction *f* and the NP volume.

In the case of a cubic NP, the external magnetic field is chosen perpendicular to two cube faces (Fig. 2). At large magnetic field in a colloidal suspension, the NP magnetic moment is supposed to be aligned with the magnetic field and with the anisotropy axis of the particle. This means that for cubic nanoparticles, we consider that the anisotropy axis is perpendicular to two faces of the cubic NP while it is known to be usually along the longest diagonal of the cube.⁴³ However, the configuration of Fig. 2(b) is more easily adaptable to our simulations. The work presented in this paper aims at providing a proof of concept about the simulation of an NP shape different from the sphere and a semi-quantitative comparison between these two shapes: the system that was the easiest and the fastest to adapt was chosen. The potential influence of the orientation of the magnetic moment of the NP will be detailed in Sec. V.

2. Diffusion and dephasing of proton spins

In this step, proton diffusion within the simulation space and their spin dephasing are simulated. As water molecules are at least 100 times smaller than the considered nanoparticles, the simulated protons can be considered punctual. This work focuses

on the contribution of the SPM NP to relaxation, proton-proton interactions are, therefore, not considered. It greatly simplifies the simulations: the protons can be simulated independently from each other.

Each proton *i* starts at an initial position $\vec{r}_i(t=0)$ randomly generated inside the simulation space with the constraint that it cannot penetrate the NP. The applied magnetic field \vec{B}_0 is assumed to be parallel to the *z* axis. The proton starts with a spin vector $\vec{s}_i(t=0)$ initially aligned with the *x* axis, which corresponds to an initial phase $\phi_i(t=0) = 0$. This simulates the proton spin state immediately after a 90°-pulse excitation, at the beginning of the CPMG sequence.

At each time increment Δt , proton diffusion is simulated by a random walk,

$$\vec{r_i}(t + \Delta t) = \vec{r_i}(t) + \Delta r \vec{\delta}(t), \qquad (11)$$

where $\vec{\delta}(t)$ is a vector randomly oriented on a unit sphere and $\Delta r = \sqrt{6D\Delta t}$ is the proton step size. The newly generated position is then tested.

- (1) If the new position is inside the NP then a new position $\vec{r_i}(t + \Delta t)$ is regenerated from $\vec{r}(t)$ until it is outside the NP.
- (2) Periodic boundaries of the simulation space are applied: if the new position is outside the simulation space, it is relocated to the opposite face of the simulation cube.

The spin phase is also updated at each time step and its evolution is computed using the *z* component of the magnetic field $\vec{B}(\vec{r})$ generated by the NP,

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$$\phi_i(t + \Delta t) = \phi_i(t) + \gamma B_z(\vec{r}_i(t))\Delta t.$$
(12)

The (normalized) proton spin vector at time t is then given by³⁹

$$\vec{s_i}(t) = (\cos\phi_i(t), \sin\phi_i(t), 0).$$
(13)

In this work, the main difference between simulations for spheres and cubes lies in the computation of the magnetic field $B_z(\vec{r})$ generated by the SPM NP. In both cases, as the magnetic field B_0 is assumed to be very high, the SPM magnetic moment can be assumed to be parallel to it, i.e., to the *z* axis. For spherical particles, the generated field $B_z(\vec{r})$ is given by the dipolar magnetic field,

$$B_{z}(\vec{r}) = \frac{\mu_{0}}{4\pi} \frac{\mu}{r^{3}} [3\cos^{2}\theta - 1], \qquad (14)$$

where *r* is the distance between the NP center and the proton spin and θ is the inclination angle of the vector joining the proton spin to the SPM particle. This expression is exact for a spherical NP but in the case of an arbitrary NP shape, Eq. (14) is only valid for large values of *r*.

For a magnetized cubic particle, if we assume that the magnetic moment is oriented along the z axis (Fig. 3), the generated magnetic field is given by⁴⁴

$$B_{z}(\vec{r}) = -\frac{\mu_{0}}{4\pi} \frac{\mu}{V} \sum_{k,l,m=1}^{2} (-1)^{k+l+m} \operatorname{atan}\left(\frac{\left(y+(-1)^{k} \frac{c}{2}\right)\left(x+(-1)^{m} \frac{c}{2}\right)}{\left(z+(-1)^{l} \frac{c}{2}\right)\sqrt{\left[y+(-1)^{k} \frac{c}{2}\right]^{2}+\left[z+(-1)^{l} \frac{c}{2}\right]^{2}+\left[x+(-1)^{m} \frac{c}{2}\right]^{2}}}\right),\tag{15}$$

where $\vec{r} = (x, y, z)$ is the position at which the magnetic field is computed, *c* is the edge length of the cubic NP, and $V = c^3$ its volume. The cube is supposed to be centered at(0,0,0). This field converges to the magnetic field of a punctual dipole, i.e., to the dipolar magnetic field (14) when large distances *r* are considered.

The CPMG sequence is simulated by including 180°-pulse every inter-echo time τ_{IE} . The simulations assume that pulses perfectly refocus proton spins: if such a pulse is applied at time *t*, the reversal of the spin $\vec{s_i}(t)$ is carried out by changing the sign of its phase, i.e., $\phi_i(t) \rightarrow -\phi_i(t)$.

3. NMR signal computation

When all the spins have been simulated, the transverse NMR signal $M_{xy}(t)$ can be computed by averaging the proton spins,

$$M_{xy}(t) = \frac{1}{N} \left| \sum_{i=protons} \vec{s}_i \right|$$
$$= \frac{1}{N} \sqrt{\left(\sum_{i=protons} \cos \phi_i(t) \right)^2 + \left(\sum_{i=protons} \sin \phi_i(t) \right)^2}, \quad (16)$$

where *N* is the number of simulated protons. The signal is then fitted to an exponential decay, which provides the relaxation rate R_2 . If the first fit is bad (reduced chi-square larger than 10^{-4}), a biexponential expression is used for the fitting and the relaxation rate corresponding to the greatest exponential amplitude is considered.

B. Physical and simulation parameters

As in a previous work,²⁴ the volume fraction f is fixed at 3.14 × 10⁻⁶ corresponding to an iron concentration of 0.211 mM. The edge length of the cubic simulation space is then given by $L_{\rm sim} = \sqrt[3]{V/f}$. Considering the magnetite magnetization value (382 000 A/m), the corresponding relaxivities (expressed in s⁻¹mM[Fe]⁻¹) are equal to the relaxation rates obtained by our simulations, multiplied by a factor of 4.74. D is fixed at 3×10^{-9} m²/s, which corresponds to water proton diffusion at normal body temperature (310 K). Echo time (time duration between the 90°-pulse and the first 180°-pulse) of the CPMG sequence was set to 1 ms (i.e. inter-echo time of 2 ms).

When the proton is at a distance 5 times larger than the spherical NP radius (or than $c\sqrt[3]{3/4\pi}$ for the cubic NP with edge



FIG. 3. NP cube and its coordinates. The magnetic moment is assumed to be vertical, aligned with the z axis, and the cube center coincides with the origin of the reference frame.

length *c*), the proton step size Δr is set equal to the NP radius *R* in the spherical case (or to $c\sqrt[3]{3/4\pi}$ in the cubic case). When the proton is closer to the NP, Δr is set to *R*/8 and Δt is thus divided by 64, considering the well-known random walk relation $\Delta t = R^2/6D$. This ensures optimal computation times while keeping a sufficient accuracy of the computed proton dephasings. The value of the duration t_{final} of the simulated NMR signal is fixed so that the remaining signal is less than 1% of the initial signal. This value depends on the particle size: for example, for spherical

nanoparticles, t_{final} is set to 0.3 s for a diameter of 10 nm, 0.04 s for 200 nm, and 1 s for 1000 nm.

The number of simulated protons is determined based on R_2 and on the SPM particle sizes, ranging from 5000 protons (for NP sizes below 14 nm) to 75 000 protons (for NPs with a diameter of 1000 nm). This range was found to be optimal for balancing the simulation time and accuracy of the simulated NMR signal. For SPM particle diameters (or cubic edge length) above 15 nm (12 nm), three simulations are conducted whereas four simulations were performed in the other cases. The R_2 values shown in Fig. 4 correspond to the mean of the performed simulations and error bars to the standard deviation.

IV. RESULTS

The main result is shown in Fig. 4: it provides the dependence of the simulated relaxation rates R_2 on the nanoparticle volume for the spherical and cubic cases. NP magnetization, water coefficient diffusion, and volume fraction were kept constant. It is important to note that the abscissa corresponds to the volume of the nanoparticles and not their size: from the relaxation point of view, two different NP shapes must be compared at equal volumes rather than equal size. Indeed, the interaction between protons and nanoparticles occurs mainly through the dipolar magnetic field, which depends on the magnetic moment of the nanoparticle-a quantity directly proportional to the volume of the nanoparticle. This is also equivalent to comparing nanoparticles composed of the same amount of magnetic compound (i.e. iron atoms in the case of magnetite or maghemite). In Fig. 4, the volume range goes from 10^{-25} to 10^{-19} m³, which corresponds to spherical diameters from 5.76 to 576 nm or cubic edge lengths from 4.64 to 464 nm. These diameter and edge length ranges cover the three relaxation regimes as well as the NP sizes that are



FIG. 4. Relaxation rates R_2 obtained by simulations for nanocubes and nanospheres. The different theoretical models and regions MAR [Eq. (3)—red], SDM [Eq. (5)—green], and PRM [Eq. (7)— blue] are also shown for comparison. The x axis represents the nanoparticle volume.

discussed in Sec. V F. These ranges were also chosen due to simulation time constraints: smaller sizes require much more computation times.

Both the simulated curves follow the well-known "bell" shape that has already been detailed in previous studies.^{24,25} The theoretical models using the physical parameters of the simulations (without any fittings) are also shown: for small NP volumes, the simulation points follow the MAR model [Eq. (3)], and then, they reach a plateau upper bounded by the SDR model [Eq. (5)]. Finally, at large NP volumes, they decrease following the partial refocusing model [Eq. (7)].

Figure 4 allows the comparison between both NP shapes: the curves are mostly the same. For larger sizes (volumes larger than 3×10^{-23} m³ corresponding to spherical diameters larger than 40 nm and cubic edges larger than 45 nm) within the SDR and the PRM regime, their relaxation rates are similar within the error bars. Figure 5 shows the relative R_2 difference between both shapes, defined as

$$\varepsilon_{rel} = \left| \frac{R_{2sphere} - R_{2cube}}{R_{2sphere}} \right|. \tag{17}$$

For large NP sizes, this value is below 2%, which is below the typical T_2 uncertainties when using NMR relaxometers or MRI scanners.

Figure 4 shows that below a volume of 2×10^{-23} m³ (spherical diameter of 33.6 nm or cube edge of 27.1 nm), a significant difference (larger than the error bars) between relaxation rates of cubic and spherical NPs appears. Figure 5 quantitatively confirms this trend: the relative difference between relaxation rates of both shapes reaches 10%–15% below a volume of 7×10^{-24} m³ (corresponding to a diameter of 23.7 nm or cube edge of 19.1 nm), while the relative error bars, due to statistical fluctuation of the Monte Carlo simulations, are up to 4%. This difference is thus significant and can be intrinsically attributed to the two different NP shapes. In summary, our main result shows the following:

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- (1) No difference is observed when particle sizes are large enough, i.e., when they are in the SDR or the PRM region;
- (2) In the MAR (small nanoparticle sizes), significant relative differences (relaxation rates difference of a few tens of percent) occur between cubic and spherical nanoparticles. In Fig. 4, relaxation rates associated with cubic NPs are larger than those with spherical NPs. However, it will be shown in Sec. V that our model could also predict smaller relaxation rates for cubic NPs compared to spherical NPs.

These comparisons must be made at equal nanoparticle volume, magnetization, and volume fraction. In the following discussion, different general relaxation models will be used to explain these trends.

V. DISCUSSION

In this section, the obtained results will be interpreted by separating the "bell curve" into the three regions corresponding to the PRM, SDM, and MAR models using their corresponding general relaxation model. This section is intended for readers who wish to theoretically understand the simulation results and are familiar with relaxation models. Readers more interested in this work for experimental purposes can jump to the last subsection of this section.

A. Magnetic field in rescaled coordinates

As a preliminary remark, it should be noted that the magnetic fields (14) and (15) can be re-expressed in coordinates normalized by the corresponding shape size,

$$B_{sphere\ z}\left(\widetilde{\vec{r}}\right) = \frac{\mu_0}{3}M\frac{1}{\tilde{r}^3}\left[3\cos^2\theta - 1\right] \ with\ \widetilde{\vec{r}} \equiv \vec{r}/R, \tag{18}$$

between the transverse relaxation rates associated with the cube and the spherical nanoparticles. The MAR, SDR, and PRM regions are shown in red, green and blue, respectively.

FIG. 5. Relative difference [Eq. (17)]



$$B_{cube\ z}(\tilde{\vec{r}}) = -\frac{\mu_0}{4\pi} M \sum_{k,l,m=1}^2 (-1)^{k+l+m} \operatorname{atan}\left(\frac{\left(\tilde{y} + (-1)^k \frac{1}{2}\right)\left(\tilde{x} + (-1)^m \frac{1}{2}\right)}{\left(\tilde{z} + (-1)^l \frac{1}{2}\right)\sqrt{\left[\tilde{y} + (-1)^k \frac{1}{2}\right]^2 + \left[\tilde{z} + (-1)^l \frac{1}{2}\right]^2 + \left[\tilde{x} + (-1)^m \frac{1}{2}\right]^2}}\right)$$
(19)
with $\tilde{\vec{r}} = \frac{\vec{r}}{c} = \left(\frac{x}{c}, \frac{y}{c}, \frac{z}{c}\right).$

In the following sections, the SPM NP will be assumed to be at the center of a spherical space of radius R_{space} (Fig. 6)—contrarily to the simulations in which the space is supposed to be cubic. The cubic simulation space was chosen to ease the periodic boundary condition of the proton diffusion. In this section, computations are carried out to study the magnetic field distribution and do not imply proton diffusion. The periodic boundary condition is thus no more necessary and another simulation space shape can be chosen. A spherical space will ease the analytical computation of the distribution of the B_z values. Indeed, the integrations will be greatly simplified in spherical coordinates. This does not affect the comparison between spherical and cubic NPs as long as very low volume fractions are considered. Thanks to the normalizations (18) and (19), statistics on B_z will be independent of the nanoparticle size if the magnetization and the ratios R_{space}/R (spherical case) or R_{space}/c (cubic case)—or equivalently, the volume fraction f—are kept constant. These normalizations justify that, in the following discussions, the statistics on B_z are carried out with only one nanoparticle size *R* or *c*.

The quantity $\nabla_{\vec{r}}B_z$ will also be studied in the following. Using the rescaled coordinates, it can be shown that multiplying this quantity by *c* or *R* also makes it independent of the nanoparticle size. Thus, analysis using $\nabla_{\vec{r}}B_z$ was also carried out for only one nanoparticle size.

It is also important to note that when a cubic NP is compared to its spherical equivalent, the volumes of the particles must be equal *and* the simulation space volumes in the two cases must also be equal. This ensures that the NP magnetic moment and the magnetic compound concentration (iron concentration for magnetite/maghemite) are equal in the cubic and spherical cases. Thus, in the next discussions, when the simulation space will be varied,



FIG. 6. Configuration between spherical and cubic nanoparticles (in brown) can be compared only when their volumes are equal $(c^3 = 4\pi R^3/3)$ and when the total simulation volumes (particle volume in brown + volume in blue) are equal.

spherical and cubic cases will always be compared at equal volume fractions. R_{space} can be computed from the volume fraction f and nanoparticle volume V,

$$R_{space} = \sqrt[3]{\frac{3V}{4\pi f}}.$$
 (20)

B. Motional averaging regime

The MAR corresponds to NP volumes less than $\sim 10^{-23}$ m³ (diameter of 26.7 nm, cube edge of 21.5 nm). In this region, the difference of relaxation rates between cubic and spherical shapes is the largest, with a relative difference of up to 15% (Fig. 5). This difference may, *a priori*, be attributed to the difference between the magnetic field of the sphere (14) and cube (15). Since these two magnetic fields converge at large distances from the NP, the relaxation rate difference is likely due to the field variations in the region close to the NP. The MAR is characterized by a short diffusion correlation time: during relaxation, each proton travels a large distance and encounters a great number of nanoparticles. Thus, in the MAR, a difference of relaxation rate between cubic and spherical NP indicates that each proton spends a significant amount of time in the region near the nanoparticles.

This hypothesis can be evaluated using the Redfield formalism associated with the MAR region. In this formalism, relaxation rates can be expressed as the Fourier transform of the autocorrelation functions of the magnetic field experienced by the protons, i.e., by Eq. (2). In this equation, the difference between the cubic and spherical cases is encoded in the autocorrelation functions $\langle B_z(0)B_z(\tau)\rangle$. As $B_z(t)$ is a wide sense stationary process, the autocorrelation function is upper-bounded by its variance,⁴⁵

$$\langle B_z(0)B_z(\tau)\rangle \le \langle B_z^2(0)\rangle. \tag{21}$$

Thus, if we assume that the correlation times associated with the cube and the spherical cases are quite similar, the difference in the MAR region could be roughly evaluated by computing the variance $\langle B_z^2(0) \rangle = \langle B_z^2 \rangle$.

Figure 7 shows the dependence of the quantity $\langle B_z^2 \rangle$ on the volume fraction in the spherical and cubic cases. This quantity was computed using a Monte Carlo integration scheme (see the supplementary material, Sec. A). Moreover, in the spherical case, it can be easily shown that

$$\begin{aligned} \langle B_z^2 \rangle &= \frac{1}{V_{protons}} \int_{V_{protons}} B_z^2 dV \\ &= \frac{3}{4\pi (R_{space}^3 - R^3)} \int_0^{\pi} d\phi \int_0^{\pi} d\theta \int_R^{R_{space}} drr^2 \end{aligned}$$



FIG. 7. Variance of the z component of the magnetic field generated by the spherical and cubic nanoparticles. The points correspond to the variance obtained by using a Monte Carlo integration method. The line corresponds to the theoretical prediction in the case of a sphere. The inset shows the complete data simulated including the highest volume fraction. The error bars are smaller than the point size.

$$\times \sin \theta \left(\frac{\mu_0}{4\pi} \frac{\mu}{r^3} \left[3\cos^2 \theta - 1 \right] \right)^2$$
$$= \frac{4}{45} \mu_0^2 M^2 f, \qquad (22)$$

$$\varepsilon_{rel} = \left| \frac{\langle B_z^2 \rangle_{cube} - \langle B_z^2 \rangle_{sphere}}{\langle B_z^2 \rangle_{sphere}} \right|. \tag{23}$$

The corresponding results are shown in Fig. 8. The relative error seems independent of the volume fraction and reaches values around 10%-15%, which corresponds to the same values associated to the R_2 results.

This confirms the hypothesis that, in this regime, the observed difference can be attributed to the difference between the magnetic field produced by the spherical and cubic shapes, more specifically to the difference between their magnetic field variances. In this regime,



where $V_{protons}$ is the volume occupied by the protons, i.e., the entire volume minus the nanoparticle volume. This analytical expression is also traced in Fig. 7: The variance associated with the cube is always slightly larger than the spherical case. The analytical curve perfectly fits the sphere results.

The relative difference between the spherical and cubic cases can be quantitatively evaluated using the following equation:





FIG. 9. Probability density of the *z* component of the magnetic field produced by a spherical and a cubic nanoparticle in a high volume fraction case (f = 0.2444).

the protons spend a sufficiently long time near the nanoparticle to make the NP shape influence the relaxation rates.

C. Static dephasing region

The "static dephasing region" is defined as the region where the transverse relaxation rate reaches a plateau. Figure 4 shows that this region comprises an approximate volume range from 10^{-23} m³ (diameter of 26.7 nm, edge of 22 nm) to 10^{-21} m³ (diameter of 124 nm or edge of 100 nm). As recalled in Sec. II, the relaxation rate is mainly dependent on the distribution $p(B_z)$ of the magnetic field B_z in this regime. Thus, a change in the relaxation rates can be observed only if this distribution is different.

Since no difference is observed in Fig. 4 between the cubic and spherical cases, it indicates that the magnetic field distribution $p_{cube}(B_z)$ of the cubic NP is comparable with the magnetic field distribution $p_{sphere}(B_z)$ of the sphere. This is expected for sufficiently small volume fractions: magnetic fields of the cubic and spherical NPs differ significantly only at distances close to the particles. They are approximately equal at large distances as they converge to the magnetic field of a punctual dipole. It means that, in this region, the cubic and spherical cases are identical because the great majority of the protons contributing to the relaxation "see" the nanoparticles as a punctual dipole.

To validate this hypothesis, the distributions $p_{cube}(B_z)$ and $p_{sphere}(B_z)$ were computed using a Monte Carlo sampling detailed in the supplementary material, Sec. A. These distributions were computed for different volume fractions. Figures 9 and 10 show the distributions at very high and very low values of volume fractions, respectively (for other volume fractions, see the supplementary material, Figs. B3–B6). In the case of very large volume fractions, the size of the spherical space R_{space} is of the same order of magnitude as the NP size and differences between the magnetic field produced by cubic and spherical NPs are expected to be large. Therefore, the two magnetic field distributions significantly differ in this case. For lower volume fractions (i.e., a space very large compared to the NP size), differences are expected to be very small and both magnetic field distributions coincide.

The difference between $p_{cube}(B_z)$ and $p_{sphere}(B_z)$ can be quantified by computing the surface difference between these distributions (using a bin-to-bin comparison integration, see the supplementary material—Sec. A),

$$\varepsilon = \int |p_{cube}(B_z) - p_{sphere}(B_z)| dB_z.$$
 (24)

This quantity can also be interpreted as a relative difference as, by definition,

$$\int p_{cube}(B_z) dB_z = \int p_{sphere}(B_z) dB_z = 1.$$
(25)

Figure 11 shows the dependence of ε on the volume fraction. As expected, it is high for large values of f (above 10^{-1}) and rapidly decreases for lower and more realistic ones. Below $f = 10^{-2}$, the relative difference drops to a few percent and seems to reach a non-zero plateau for decreasing values of f. However, this difference is expected to theoretically tend to zero for very small f. This observed plateau is explained by the error of the Monte Carlo integration method which was used (supplementary material, Sec. A)



FIG. 10. Probability density of the z component of the magnetic field produced by a spherical and a cubic nanoparticles in a low volume fraction case ($f = 8 \times 10^{-6}$). The distribution is mainly composed of magnetic fields of the order of 10^{-5} T. The inset graph shows that magnetic fields of the order of 0.1 T (which are dominant in the high-volume fraction case) negligibly contribute to the distribution in the low-volume fraction case.

(27)

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where the volume integration corresponds to the blue region in Fig. 12. To evaluate the impact of R_{inner} on the relaxation times, σ^2 was computed for different values of R_{inner} . The values of R_{space} and the NP volume were fixed. A Monte Carlo integration method (see the supplementary material, Sec. A) was used to evaluate the integral (27). An analytical expression for σ^2 can easily be obtained (see the supplementary material, Sec. B3) in the spherical case,

 $=\frac{1}{V_{protons}}\int_{R_{inner}}^{R_{space}} \left|\vec{\nabla}_{\vec{r}}B_{z}(\vec{r})\right|^{2}r^{2}\sin\theta\,drd\theta d\varphi,$

$$\sigma_{sphere}^2 = \frac{9}{20\pi^2} \frac{\mu^2 \mu_0^2}{\left(R_{space}^3 - R_{in}^3\right)} \left(\frac{1}{R_{in}^5} - \frac{1}{R_{space}^5}\right).$$
 (28)

The results of the evaluation of the normalized gradient $\sigma^2 R^2$ are shown in Fig. 13 (*R* is the radius in the case of a spherical NP. In the case of a cubic NP, *R* is proportional to the cube edge length and



FIG. 12. Definitions of R_{in} and R_{space} for the computation of Eq. (27). The blue region corresponds to the region in which the average/integration is computed.

and would tend to zero if the number of points used for the integration was larger. In the simulations of Figs. 4 and 5, the volume fraction was set to 3.14×10^{-6} , which is smaller than the considered *f* values of Fig. 11: this explains why the R_2 difference between the cubic and the spherical NPs are below a few percent in the static region.

D. PRM region

The "PRM region" is defined as the region where the relaxation rate R_2 decreases for increasing NP volumes. In Fig. 4, this region approximately begins at volumes of 10^{-21} m³ (corresponding to spherical diameter of 124 nm or cube edge of 100 nm).

In the PRM, relaxation arises from protons that diffuse far from the particles, i.e., at distances larger than those given by Eq. (9). At these distances, the magnetic field of the cubic NP is approximately equal to that of the spherical NP, i.e., equal to the magnetic field of a punctual dipole. Thus, protons in both cases experience the same magnetic interactions and the induced relaxation times are equal. In other words, protons "see" both cubic and spherical nanoparticles as punctual dipoles, and thus, their shape is expected not to influence the relaxation times.

This hypothesis can be quantitatively validated by computing the gradient of B_z . Indeed, in the PRM, the transverse relaxation rate is given by the mean gradient diffusion theory⁴⁶ through the following equation:

$$\frac{1}{T_2} = \frac{1}{12} D\gamma^2 \tau_{IE}^2 \frac{1}{V_{protons}} \int_{V_{protons}} \left| \vec{\nabla}_{\vec{r}} B_z(\vec{r}) \right|^2 d^3 \vec{r} \equiv \frac{1}{12} D\gamma^2 \tau_{IE}^2 \sigma^2.$$
(26)

In this equation, the relaxation rate is proportional to σ^2 , i.e., the average of the square of the gradient of the magnetic field experienced by the protons. In the specific case of SPM NP in the PRM, the volume $V_{protons}$ corresponds to the volume occupied by the protons at distances larger than R_{inner} that is given by Eq. (9). Thus, the NP-shape effect in the PRM can be evaluated by computing the following quantity in both cubic and spherical cases:

FIG. 11. Quantity ε given by Eq. (24) for different volume fractions. As expected, ε is low for "realistic experimental" volume fraction values (i.e., values below 10⁻⁵).

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 $\sigma^2 \equiv \left(\left| \vec{\nabla}_{\vec{r}} B_z(\vec{r}) \right|^2 \right)$

 $= \frac{1}{V_{protons}} \int_{V} \left| \vec{\nabla}_{\vec{r}} B_z(\vec{r}) \right|^2 d^3 \vec{r}$





FIG. 13. Computation of the $\langle |\vec{\nabla} B_z|^2 \rangle R^2$ in the spherical and cubic cases. R_{space} was kept constant and computed from a volume fraction equal to 8×10^{-6} .

FIG. 14. Relative difference of the quantity $\langle |\vec{\nabla} B_z|^2 \rangle$ between the spherical and cubic cases. The inset shows the results for all the simulated value of R_{in}/R , and the main graph shows the relevant values for the PRM model, i.e., $R_{in}/R > 6$.

is defined as the radius of a sphere with volume equal to that of the cubic NP). The points corresponding to the Monte Carlo integration of the spherical case perfectly follow the analytical prediction. No difference between cubic and spherical nanoparticles is visible for large R_{in} . This is expected since, at these distances, the magnetic fields of the cubic and spherical NPs are approximately equal. For very low R_{in} , a slight difference appears. A more quantitative evaluation is shown in Fig. 14 by the computation of the relative difference between the cubic and the analytical spherical cases,

$$\varepsilon_{rel} = \left| \frac{\left\langle \left| \vec{\nabla}_{\vec{r}} B_z \right|^2 \right\rangle_{cube} - \left\langle \left| \vec{\nabla}_{\vec{r}} B_z \right|^2 \right\rangle_{sphere}}{\left\langle \left| \vec{\nabla}_{\vec{r}} B_z \right|^2 \right\rangle_{sphere}} \right|.$$
(29)

For $R_{in} > 5R$, this quantity is lower than 1%. Using Eq. (9) and the parameters used in the simulations, one finds that $R_{inner} = 6, 8R > 5R$. This is consistent with the R_2 simulation results of Fig. 5, where a relative difference below a few percent between the cubic and spherical cases was observed in the PRM.

It should be noted that the value of R_{space} used for the integral (27) corresponds to a volume fraction is larger than that used in the R_2 simulations of Fig. 4, for computational time purposes. The relative difference between the σ^2 of the cubic and spherical shapes is expected to be smaller when the volume fraction decreases, allowing our conclusions to be extended to the volume fraction used for the R_2 simulations.

E. Orientation of the superparamagnetic magnetic moment

As mentioned in Sec. III, the SPM magnetic moment of the cubic nanoparticle—which is parallel to the magnetic anisotropy axis and to the magnetic field \vec{B}_0 when B_0 is large—was supposed to be perpendicular to two of the cubic NP faces [Fig. 15(a)]. This case is not the most common configuration as the magnetic crystalline anisotropy axis of magnetite NP is usually parallel to the longest diagonal of the cube [see Fig. 15(b)]. Ideally, the dependence of the orientation NP magnetic moment on proton relaxation should be evaluated by a full simulation including proton diffusion and a



FIG. 15. (a) Simulations in this work suppose that the NP magnetic moment (in green, aligned with $\vec{B_0}$) is perpendicular to two faces of the cubic NP. (b) For the magnetite case, the magnetic moment is parallel to the longest diagonal of the cubic NP.

suited orientation of the cube in the simulation space. Such adaptation is beyond the scope of this work that aims at providing a proof of concept of these simulations as a tool to evaluate the influence of the NP shape on relaxation.

However, an estimate of the impact of the orientation of the magnetic moment can be obtained using the field analysis presented in Sec. V (i.e., computing $\langle B_z^2 \rangle$ in the MAR, the magnetic field distribution $p(B_z)$ for the static dephasing region and $\langle |\vec{\nabla} B_z|^2 \rangle$ for the PRM region). In this section, this analysis has been preliminary performed in the case where the NP magnetic moment is parallel to the longest diagonal of the cube [Fig. 15(b)]. The magnetic field generated by the nanoparticle is different from Eq. (19) when the orientation of the magnetic moment is varied and must be computed from expressions given in the supplementary material (Sec. C).

Details of the B_z field analysis are provided in the supplementary material (Sec. C). It shows that, when the anisotropy axis is parallel to the longest diagonal of the cube [Fig. 15(b)], the relaxation rates are not significantly different from their spherical counterpart in the static dephasing and the PRM regions. This is analogous to what was obtained with configuration (a) of Fig. 15 and this is expected as in these regions, the protons that contribute to relaxation are far from the particle, i.e., they experience a magnetic field that converges to the field of a punctual magnetic dipole.

In the MAR, the variance $\langle B_z^2 \rangle$ of configuration (b) of Fig. 15 is lower than that of its spherical counterpart. This indicates that the relaxation rate of cubic NPs is smaller than that of spherical NPs for this orientation of the magnetic moment, contrary to the case where the magnetic moment is perpendicular to two faces of the nanocube [Fig. 15(a)]. This is a surprising result as cubic NPs are generally shown to be more efficient than spherical NPs in experimental studies (see Sec. V F). However, it should be emphasized that the predicted variation remains within a few tens of percent (40%). The influence of NP orientation will be investigated in future work by properly simulating the proton diffusion in such configuration.

F. Comparison with previous experimental studies

Several studies have experimentally compared the relaxivity r_2 of cubic and spherical NPs. Most of the synthesized cubic

nanoparticles are in the MAR, so only NPs in the MAR will be considered in this section. Larger relaxivities for the cube are generally observed. In light of the previous discussion, such comparison only makes sense if the spherical NP and the cubic NP have the same volume and magnetization, which is, of course, never rigorously the case for real samples. In the case of different volumes and/or magnetizations, a normalization is necessary to make the comparison consistent.

We, therefore, propose using a simple normalization procedure that allows to check the predictions of our simulation results and compare different sample conditions (different magnetization, volume, and/or temperature). Let us suppose that $r_{2-s-\exp}^{V_s,M_s,D}$ and $r_{2-c-\exp}^{V_c,M_c,D'}$ are the experimental transverse relaxivities of a spherical (cubic) nanoparticle with volume vs (V_c) and magnetization M_s (M_c). D and D' are the corresponding water diffusion coefficients, which are temperature-dependent. These values will be compared to Eq. (3), which predicts the relaxation rate for the spherical case. This equation can be rewritten as²³

$$R_{2-s-th}^{V,M_{sat},D} = \frac{116}{50\ 625} \frac{\mu_0^2}{\pi} \frac{\gamma^2 V M_{sat}^2 C_{Fe}}{\rho_{Fe_3O_4} D\delta},$$
(30)

where C_{Fe} is the iron concentration of the sample (expressed in mM), V is the nanoparticle volume, and δ is the minimum distance of approach between the proton and the particle. In the case of spherical shape, δ corresponds to the NP radius. In the case of a cubic shape, it can be defined as the root of the mean square distance between the cube center and the surface of the cube, i.e., $\delta = c\sqrt{5/12}$. The value of the relaxivity $r_{2-s-th}^{V,M_{aut},D}$ can be obtained using Eq. (30) and setting $C_{Fe} = 1$ mM and is expressed in s⁻¹mM[Fe]⁻¹. The nanoparticle is supposed to be composed of magnetite and $\rho_{Fe_3O_4} = 5210$ kg/m³ is the bulk density of magnetite. Our previous discussion in the MAR theoretically predicts that

$$\frac{r_{2-c-th}^{V,M_{sat},D}}{r_{2-s-th}^{V,M_{sat},D}} \equiv \alpha \text{ with } 0.60 \le \alpha \le 1.15,$$

$$(31)$$

where $r_{2-c-th}^{V,M_{sat},D}$ and $r_{2-s-th}^{V,M_{sat},D}$ are, respectively, the relaxivity obtained by our simulations for a cubic nanoparticle of volume V and the theoretical relaxivity corresponding to spherical nanoparticles of volume V, with saturation magnetization M_{sat} , and a water diffusion coefficient D. In this equation, the particles parameters (V, M_{sat}, D) are the same in the numerator and the denominator. It is not the case for experimental data. However, one can write, using Eq. (31),

$$\frac{r_{2-c-th}^{V_c,M_c,D'}}{r_{2-s-th}^{V_s,M_s,D}} = \frac{r_{2-c-th}^{V_c,M_c,D'}}{r_{2-s-th}^{V_c,M_c,D'}} \frac{r_{2-s-th}^{V_c,M_c,D'}}{r_{2-s-th}^{V_s,M_s,D}} = \alpha \frac{r_{2-s-th}^{V_c,M_c,D'}}{r_{2-s-th}^{V_s,M_s,D}}.$$
(32)

Thus, one way to compare our simulation predictions to experimental studies is to check that

$$\frac{r_{2-c-\exp}^{V_c,M_c,D'}}{r_{2-s-\exp}^{V_s,M_s,D}} \approx \alpha \frac{r_{c,M_c,D'}}{r_{2-s-th}^{V_s,M_s,D}}$$
(33)

or, equivalently, using Eq. (30),

Study	Shape (name)	r ₂ (s ⁻¹ mM[Fe] ⁻¹)	Cube edge length or spherical diameter (nm)	M _{sat} (A/m)	Diffusion coefficient $(10^{-9} \text{ m}^2/s)$	Computed ratio [Eq. (35)]	Comments
Basini <i>et al.</i> ³⁰	Cube (C8_hex)	26	7.1	218 820	4.26	+29%	Nanoparticles in hexane
	Sphere (S8_hex)	17	8.5	234 450	4.26		diffusion coefficient has been adapted.
Walter <i>et al.</i> ²²	Cube (oxNC16)	221	12.8	222 461	б	+219%	Relaxivity of spherical NP at 60 MHz was chosen
	Sphere (NS10)	78	11	148 182	σ		Magnetization was indi- rectly obtained using a fit of NMRD.
Yang <i>et a</i> l. ¹⁴	Cube	559.3	12	394 397	1.99	+50%	MnIO particles. Magneti- zation was computed sup- nosing magnetite but as
	Sphere	367.3	15	381 372	1.99		Eq. (35) Eq. (35) implies ratios of magneti- zation, this normalization
							has no impact on the final computed ratio.
Zhen <i>et al.</i> ¹⁷	Cube	61.4	8.1	208 400	1.99	+48%	
	Sphere	17.3	8.2	161 510	1.99		
Zhou <i>et al.</i> ⁴⁸	Cube (IO cube 7)	76.4	7	246 433	2.68	+247%	The ratio was com- puted using the sphere
	Cube (IO cube 15)	80.8	15	281 861	2.68	-37%	The ratio was com- puted using the sphere
	Sphere (IO sphere-16)	125.7	16	315 205	2.68		10-splittere-10 uala.

This equation is composed of two factors: one that comes from raw experimental data and the second one that normalizes the relaxation rates and allows to check the theoretical predictions and compare different particles parameters and experimental conditions. This equation can also be rewritten to obtain the relative variation in the relaxation rate of cubic NPs compared to spherical NPs,

$$\beta \equiv (\alpha - 1) \approx \left(\frac{r_{c-M_c,D'}^{V_c,M_c,D}}{r_{2-s-\exp}^{V_c,M_c,D}} \frac{V_s M_s^2}{V_c M_c^2} \frac{D'}{D} \frac{c}{R} \sqrt{\frac{5}{12}} - 1 \right),$$
(35)

where $-40\% \le \beta \le +15\%$.

In summary, the proposed procedure for the comparison between theory and experiments is composed of the following steps:

- (1) Finding experimental studies that consider both nanoparticle shapes: spherical and cubic.
- (2) Collecting the relaxivities related to the cubic and spherical nanoparticles.
- (3) Identifying independent measurements of their corresponding volume and saturation magnetization.
- (4) Finding the temperature and computing the solvent coefficient diffusion (for water, the diffusion coefficient was interpolated using data from Ref. 47).
- (5) Using Eq. (35) and verifying that the obtained value of β falls within the theoretical prediction range of -40% to +15%.

For simplicity, we mainly focus on studies concerning pure magnetite/maghemite nanoparticles. We also only choose studies that synthesize both spherical and cubic shapes to ensure that their characterization methodologies and choices of normalization are similar for both shapes. In addition to the relaxation rates, we only retain articles that also mention the saturation magnetization and explicitly describe how the size of the cubic NPs was measured (edge, longest diagonal etc.). This leads us to the studies referenced in Table I. This certainly does not constitute an exhaustive list of the existing experimental studies. Our goal is not to be comprehensive but to confront a small but still significant number of studies to our predictions and discuss the potential discrepancies.

It is important to note that such a comparison is always very approximate: indeed, in the theoretical models, several important experimental factors are neglected, such as size polydispersity, the effect of coating, measurement errors on the iron concentration, and the temperature dependence of the NP saturation magnetization. Magnetization is normalized by iron concentration or the NP mass, and the bulk density of magnetite has been used to convert it into a volume magnetization. This supposes that the particle is fully composed of magnetite, which is not usually the case: it is often composed of a mix between magnetite and maghemite. These hypotheses can lead to large errors bar on the evaluation of the theoretical relaxivity, up to a few tens of percent and, in some cases, more than +100%.⁴¹

Table I sums up our results. For three studies (Basini *et al.*,³⁰ Zhen *et al.*,¹⁷ and Yang *et al.*¹⁴), the increased ratios β are comprised between +20% and +50%. This is larger than our prediction

of +15%, but, given the mentioned errors, these ratios can be considered in agreement with our interpretation. The IO-cube-15 sample of Zhou et al.48 is the only sample for which relaxation is less efficient than the spherical sample. Its computed ratio β of -37% is in the order of the minimum values of -40% predicted by our simulation. Two samples show great discrepancies compared to our theoretical prediction. The sample oxNC16 of Walter et al.²² has an increased ratio β more than 14 times larger than our predicted ratio of +15%. The sample IO-cube-7 of Zhou *et al.*⁴⁸ has an increased ratio β of +247% that is 15 times larger than our +15% prediction. Notably, for this last sample, the normalization procedure is necessary to properly compare the samples: looking at their relaxivities, the IOcube-7 is apparently less efficient than the IO-sphere-16. However, the spherical NP is four times larger than the cubic NP. After normalization, the IO-cube-7 is shown to be actually more efficient than the IO-sphere-16.

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The discrepancies observed for the oxNC16 and the IO-cube-7 could—at least partly—be explained by experimental conditions. In the case of the oxNC16 of Walter *et al.*,²² the magnetization values come from a fitting of the NMRD (nuclear magnetic relaxation dispersion), a method known to yield less accurate magnetization values compared to those obtained from magnetometry measurement. For the IO-cube-7 of Zhou *et al.*,⁴⁸ NMR measurements were performed at a magnetic field of 0.5 T (whereas in the other studies listed in Table I, the magnetic field is at least 1.5 T), which corresponds to the lower limit for the secular term hypothesis and could lead to a greater gap between the experimental results and our theoretical predictions.

The other samples exhibit a variation in the order of magnitude of the theoretical prediction, i.e., a few tens of percent. However, most of them are characterized by an increase in the relaxation rate (compared to their spherical counterpart). In our model, this increase corresponds to the case where the NP magnetic moment is perpendicular to two faces of the cube [Fig. 15(a)], i.e., the most uncommon case. For the commonly expected case [magnetic moment along the longest diagonal of the cube, Fig. 15(b)], the model predicts a decrease in the cubic relaxation rate. The fact that our model reproduces the experimental results in the case of an unusual orientation of the NP magnetic moment leads us to two hypotheses.

The first hypothesis is that for such small nanoparticles, the anisotropy axis is not aligned with the longest diagonal of the cube. This is plausible as the anisotropy energy of a magnetic particle has several contributions. At this size, the surface NP anisotropy might be important enough to change the orientation of the overall anisotropy axis.

The second hypothesis is that our model does not properly include all the relaxation mechanisms involved in such samples. This would imply that the common assumption—that relaxation is due to the proton diffusion in the *magnetic field specifically generated by cubic NPs*—is not sufficient to interpret the experimental results. In this hypothesis, an increase in the relaxation rates could only be explained by additional relaxation mechanisms that partly depend on the NP shape such as its surface-to-volume ratio. Indeed, a cube has a larger surface-to-volume ratio than a sphere, which could influence a relaxation mechanism that is primarily dependent on the NP surface. This hypothesis might also explain the great discrepancy associated with the IO-cube-7 NPs. Indeed, these NPs are

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characterized by a surface-to-volume ratio of 0.852 nm⁻¹ while the ratio of the spherical NP to which they are compared (IO-sphere-16) is 0.375 nm⁻¹. This difference in ratios is the largest observed among the samples listed in Table I.

VI. CONCLUSIONS

This work studies the influence of the nanoparticle shape on the proton transverse relaxation times using Monte Carlo simulations. Our results emphasize that comparisons between spherical and cubic nanoparticle shapes must be made at equal volumes (and not size) and magnetizations. In this case, our simulations show the following:

- In the MAR (sizes smaller than 30 nm for magnetite nanoparticles), a cubic shape leads to a relaxivity variation ranging from -40% to +15% compared to its spherical counterpart when relaxivities of both cubic and spherical NPs are correctly normalized.
- For larger sizes, no differences in relaxivities are expected between cubic and spherical nanoparticles. For these larger particles, there is no need to synthesize exotic shapes as the effects are predicted to be similar to those obtained with simple spheres.

These effects have been interpreted with the help of general relaxation models and using the statistical computation of the magnetic fields produced by both NP shapes.

We introduced a method that enables the comparison of experimental results with our theoretical predictions. This method allowed us to compare experimental relaxivities of particles with different shapes in the MAR, without requiring equal NP volumes or magnetizations.

Most of the experimental studies showed a relaxivity enhancement—after volume and magnetization renormalization—of a few tens of percent, i.e. the order of magnitude predicted by our simulations. One study showed a reduction in the relaxivity, which is also in the range of our theoretical predictions. The observed great discrepancies for the other samples might be attributed to experimental measurements or conditions (NP magnetization not precisely estimated or measurement at a too low magnetic field).

However, this apparent general agreement with the theoretical predictions should be qualified. Indeed, the model predicts a decrease in the relaxation rate of cubic NPs when the magnetic moment is along the longest diagonal of the cube, which is the most commonly expected configuration at high magnetic field. As a consequence, a decrease in relaxation should be more commonly observed according to the model, contrary to most of the measurements in the experimental studies. This leads to two hypotheses: (a) the effective anisotropy axis may not lie along the longest diagonal of the cube for such NP sizes and (b) the usual claim that "the magnetic field specific to cubic NPs enhances the relaxation" cannot solely explain the measured relaxation rates. Another relaxation mechanism involving the NP surface must be invoked to interpret the experimental results. Further simulations involving different cube orientations and additional experimental studies focusing on the surface-to-volume ratio of SPM NPs as well as surface relaxation

This work lays the foundation for a simulation methodology that could be applied to other particles with more complicated shapes, such as cylinders, nanostars, or nanoflowers. This will ultimately allow predicting which shape would provide the optimal generated magnetic field and would yield the highest relaxivity for a given size and magnetization.

SUPPLEMENTARY MATERIAL

The supplementary material provides a description of the Monte Carlo integration method and tests that validate the method. Additional figures for magnetic field distribution are also included. The results for the field analysis when the magnetic moment is parallel to the longest diagonal of the cube are also detailed.

ACKNOWLEDGMENTS

F. Fritsche, G. Rosolen, B. Maes, Y. Gossuin, and Q. L. Vuong acknowledge support from the Action de Recherche Concertée (Project No. ARC-23/27 UMONS3). Computational resources have been provided by the Consortium des Équipements de Calcul Intensif (CÉCI), funded by the Fonds de la Recherche Scientifique de Belgique (F.R.S.-FNRS) under Grant No. 2.5020.11 and by the Walloon Region.

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Florent Fritsche: Formal analysis (lead); Investigation (lead); Methodology (supporting); Software (lead); Writing – original draft (equal); Writing – review & editing (equal). Gilles Rosolen: Conceptualization (supporting); Funding acquisition (supporting); Methodology (supporting). Alice De Corte: Software (supporting). Bjorn Maes: Conceptualization (supporting); Funding acquisition (supporting). Yves Gossuin: Conceptualization (supporting); Funding acquisition (supporting); Methodology (supporting). Quoc Lam Vuong: Conceptualization (lead); Funding acquisition (lead); Methodology (lead); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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