The effect of the magnetic nanoparticle’s size dependence of the relaxation time constant on the specific loss power of magnetic nanoparticle hyperthermia

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ABSTRACT

Magnetic nanoparticle hyperthermia is a cancer treatment in which magnetic nanoparticles (MNPs) are subjected to an alternating magnetic field to induce heat in the tumor. The generated heat of MNPs is characterized by the specific loss power (SLP) due to relaxation phenomena of the MNP. Up to now, several models have been proposed to predict the SLP, one of which is the Linear Response Theory. One parameter in this model is the relaxation time constant. In this contribution, we employ a macrospin model based on the Landau-Lifshitz-Gilbert equation to investigate the relation between the Gilbert damping parameter and the relaxation time constant. This relaxation time has a pre-factor $\alpha$ which is often taken as a fixed value ranging between $10^{-8}$ and $10^{-12}$. However, in reality it has small size dependence. Here, the influence of this size dependence on the calculation of the SLP is demonstrated, consequently improving the accuracy of this estimate.

1. Introduction

In oncology, hyperthermia refers to the heating of organs or tissues to temperatures ranging from 42 °C to 46 °C where it causes the death of cancer cells [1]. One possible way to locally apply heat to cancerous regions is by means of magnetic nanoparticle hyperthermia [2]. There, magnetic nanoparticles (MNPs) are injected in the body, and subsequently guided towards the cancer cells. This can be achieved by various mechanisms. They can for instance be directed by external fields [3], or, alternatively the particles can be coated with a biological marker which binds them to cancer cells [4]. Once the particles are at the desired location, they are subjected to an alternating magnetic field to induce a temperature increase in the particles and the tumor tissue. The heat generated by MNPs is provided by the dissipated power of the MNPs as they run through a hysteresis loop. This is quantified by the specific loss power (SLP), also known as the specific absorption rate (SAR) which is a measure of power dissipated per unit mass of the magnetic material. The heating properties of the MNPs depend on three major mechanisms. The first is called Néel relaxation [5], where the magnetization within the MNPs is excited by thermal fluctuations and irreversibly jumps over energy barriers due to the anisotropy of the material. Next, in Brownian relaxation the MNPs as a whole rotate due to their Brownian motion in their suspension. Finally, when the externally applied fields are sufficiently large to suppress the energy barriers between different anisotropy directions, a third, temperature independent, mechanism exists [6]. Next to the temperature, the size, the magnetic anisotropy and the saturation magnetization of the MNPs also the amplitude and the frequency of the magnetic field determine the relative strength of each loss mechanism. To gain further insight in the different processes and their combined effect on the SLP, a significant number of measurements have been carried out recently using various experimental setups [3,4,7]. Furthermore, also a number of increasingly complex analytical or numerical descriptions of the physics behind these processes are available [5,8]. Specifically, the theory behind the Néel relaxation mechanism is well established but unfortunately the resulting equations can only be solved analytically in specific limits, e.g. for very large energy barriers, and otherwise one has to rely on numerical calculations. Recently, a macrospin model based on the Landau-Lifshitz-Gilbert (LLG) equation has been employed to investigate the dynamics of the MNPs when subjected to an externally
applied magnetic field [9]. The LLG equation contains a phenomenological damping term, whose size is determined by the Gilbert damping constant [10], which accommodates for all loss mechanisms. The damping constant α is related to τ, which provides a typical relaxation time used in the description of the Néel relaxation process, and is the inverse of an attempt frequency [11]. Usually, τ is described as constant taking values between $10^{-9}$ and $10^{-12}$ s [7]. However, this large range is inconvenient to accurately determine the losses related to the hysteresis loop of MNPs and furthermore, τ has a size dependence which is often neglected. In this contribution, the relation between τ and α is investigated. Based on a macrospin model [12], an empirical relation is determined and subsequently used in the SLP calculations of MNP samples with a lognormal size distribution [13].

2. Methods

2.1. Macrospin model

To investigate the magnetic dynamics of the MNPs, a model based on the LLG equation is used [12]

$$\frac{dm}{dt} = \frac{\mu_0 m B}{1 + \alpha^2} \times (m \times H_{\text{eff}})$$

(1)

where $m$ denotes the magnetization vector of the considered MNP, normalized to the saturation magnetization $m_0 = \frac{N}{A}$, $H_{\text{eff}}$ is the effective field acting on each MNP and takes into account the demagnetizing, thermal, external and anisotropy field contributions [9], $\mu_0$ is the vacuum permeability and $\gamma = 1.7595 10^{11}$ s/T denotes the gyromagnetic ratio.

The LLG equation is numerically integrated for an ensemble of nanoparticles with the simulation tool Vinamax [9]. In all simulations, single core magnetite MNPs are considered with magnetic material properties $M_s=446$ kA/m, $K=25$ kJ/m³, at a temperature of 300 K. The MNP concentrations are assumed to be sufficiently low to neglect the dipolar interactions between the MNPs [11] and that the MNPs are sufficiently small to consider them to be single domain particles [13]. In all simulations an ensemble of at least 10000 MNPs is studied with easy axis orientations being randomly distributed. Either the 5th order Dormand-Prince method or the 7th order Fehlberg method are used to integrate the LLG equation. Both solvers use fixed time steps, which is required for the implementation of the randomly fluctuating thermal field [9]. Finally, for each simulation we carefully checked that an appropriate time step was used.

In real MNP samples, the MNPs often have a lognormal size distribution [13], as dictated by their production process [16]. Such distributions are therefore considered here as well. Eq. (2) shows the probability density function of the MNP radius $r$

$$p(r) = \frac{1}{\sigma r \sqrt{2\pi}} \exp\left[-\frac{\ln(r/\mu)^2}{2\sigma^2}\right]$$

(2)

which can be interpreted as the distribution whose logarithm is normally distributed with $\mu$ and $\sigma$ being the mean radius and standard deviation, respectively.

2.2. Magnetorelaxometry

Magnetorelaxometry is a method to characterize MNPs by measuring the decaying net magnetic moment of the MNP sample after it has been magnetized in an external field [17]. The decaying magnetic signal is described by

$$M(t) = M_0 e^{-t/\tau_0}$$

(3)

where $M_0$ denotes the magnetization of the sample at $t=0$ and $\tau_0$ the effective relaxation time constant given by $1 = \frac{m_0}{\gamma_0} + \frac{1}{\tau_0}$. $\tau_0$ and $\tau$ denote the Néel and Brownian relaxation time respectively.

For immobilized MNPs only the Néel relaxation mechanism is relevant. Since the purpose is to attain the effect of the typical relaxation time $\tau_0$ used in the description of the Néel relaxation process, the Brownian relaxation time will be no longer considered.

The Néel relaxation time

$$\tau_0 = t_0 e^{ varying}

(4)

is mainly determined by the ratio between the energy barrier, given by the product of the anisotropy constant K and the volume $V = 4\pi r^3 / 3$ of the MNPs, and the available thermal energy, which is the product of the Boltzmann constant $k_B$ and the temperature $T$.

As mentioned earlier, $\tau_0$ is typically taken as a constant between $10^{-9}$ and $10^{-12}$ s. However, this quantity is size dependent as can be seen from Eq. (5), derived by Brown [15], in the high barrier limit $KV \gg k_B T$

$$\tau_0 = \frac{1}{\gamma_0} \sqrt{\frac{2\pi r^3}{k_B T}}$$

(5)

With Vinamax, it is possible to simulate MRX experiments [11], and the result of one such simulation is shown in Fig. 1. The green symbols depict the relaxing signal of a sample consisting of MNPs with a fixed radius of 7 nm. The black curve shows a fit to this data with an equation of the form given by Eq. (3), allowing the extraction of $\tau_0$ from these simulations. Because also the energy barrier and temperature are known, $\tau_0$ can thus be obtained with the help of Eq. (4).

When a sample with a lognormal size distribution is considered, the magnetic moment is no longer described by an exponentially decaying function but is given by a weighted sum of such functions [11]:

$$M(t) = \int_0^{\infty} M_0 e^{-t/\tau} p(r) dr$$

(6)

A typical signal for $\mu = 7$ nm and $\sigma = 0.1$ is depicted in Fig. 1 in red. It clearly exhibits a decaying magnetic moment that is no longer described by a simple decaying exponential. Each lognormal distribution gives rise to a characteristic shape, which allows to experimentally recovering the lognormal distribution of MNP samples from MRX data [18].

2.3. Linear response theory

Linear response theory (LRT) is a theoretical model which describes the dynamic response of an ensemble of MNPs to a time-varying external field [14]. When a time-varying magnetic field $H(t) = H_0 \cos(\omega t)$ is applied with angular frequency $\omega$ and amplitude $H_0$ the magnetization response is given as follows:

$$M(t) = M_0 e^{-t/\tau_0}$$

(3)

where $M_0$ denotes the magnetization of the sample at $t=0$ and $\tau_0$ the effective relaxation time constant given by $1 = \frac{m_0}{\gamma_0} + \frac{1}{\tau_0}$. $\tau_0$ and $\tau$ denote the Néel and Brownian relaxation time respectively.
of this curve through the origin is \( \xi \ll 1 \) is the equilibrium susceptibility.

The power loss per cycle, \( \Delta U \), can be expressed as:

\[
\Delta U = -\mu_0 H_0^2 M V \int_0^{\infty} \frac{\alpha}{(1+\omega \tau)^2} d\tau
\]

From Eq. (11), the power loss per unit time \( P \) (W m\(^{-3}\)) can be derived as:

\[
P = \frac{\mu_0 H_0^2}{\rho} \int_0^{\infty} \frac{\omega \tau}{(1+\omega \tau)^2} d\tau
\]

The SLP is then given by the following expression:

\[
SLP = \frac{P}{\rho}
\]

3. Results and discussion

3.1. Size dependence of \( \tau_0 \)

First, the relation between \( \tau_0 \) and \( \alpha \) and their size dependence are investigated. With the help of Vinamax, MRX signals are simulated for MNP samples with radius 5, 6, 7 and 8 nm for 17 different \( \alpha \) values, logarithmically divided between 0.01 and 1. The results of these simulations are shown in Fig. 3 as square dots. The full lines depict the \( \tau_0 \) expected from Eq. (5) and show that, although data points lie 10–30% above the expected value, the dependence on \( \alpha \) scales correctly. The differences between Eq. (5) and the numerical results originate in the fact that Eq. (5) has been derived specifically in the high barrier limit, corresponding to large MNPs. To verify that results get increasingly closer to the theoretical expectation for larger particles, additional simulations are performed for radii between 5 and 8 nm, in steps of 0.25 nm for \( \alpha = 0.01 \).

The results of these simulations are shown in Fig. 4 and indeed prove that the difference between the analytical and numerical results
decrease for larger particles. In the following, these deviations are taken into account by fitting an empirical correction function to the data, see the blue curve in Fig. 4.

$$\tau_0 = (1 + e^{-2.26.10^{-22}r^8})^{1+e^{-2\pi k TM \tau}}$$

(15)

The functional form of $1 + e^{-x}$ with a constant $c$ has no theoretical foundation but is found empirically to be close enough to the numerical data in the considered regime. This correction term allows use of Eq. (5) outside of the high barrier limit. When considering MNPs having different magnetic material properties than those considered here, micromagnetic simulations are again required to solve the correction. Note that when having larger MNP concentrations, the dipolar interactions can no longer be neglected and that the effect of the interactions between particles, being greatly dependent on the concentration and spatial configuration of the magnetic nanoparticles [11], needs to be taken into account next to the size dependence. As in [18], MRX measurements data acquired for a given MNPs ensemble can provide insights on the volume dependence of the $\tau_0$.

3.2. SLP for samples with lognormal size distribution

Now the attention is turned to the effect on the SLP when taking the size dependence of $\tau_0$ into account. To this end, the SLP is calculated using LRT for MNP ensembles with lognormal size distributions with $\mu$ ranging from 4 to 10 nm and $\sigma$ ranging from 0.01 to 0.6 by means of Eq. (14) considering Eqs. (4) and (8) with $\tau(r) = \tau_0(r)$. This calculation is repeated for 2 different $\alpha$ values of 0.01 and 0.1 and in all calculations $H_0=5$ kA/m and $f=200$ kHz are used.

To allow an honest comparison between the results for a fixed $\tau_0$ and the size dependent $\tau_0$ calculations are performed with a size dependent $\tau_0$ determined by Eq. (15), and subsequently used $\tau_0$ fixed to the value it had at the peak of the SLP, situated at $r \approx 6$ nm for $\alpha = 0.01$ and $r \approx 7$ nm for $\alpha = 0.1$. The results of these calculations are presented in Fig. 5.

The results show that the SLP is higher for narrower size distribu-

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Fig. 5. The SLP as function of $\mu$ and $\sigma$ for the material parameters described in the text and $H_0=5$ kA/m and $f=200$ kHz. (a) and (d) show the results for a size dependent $\tau_0$ while (b) and (e) show the results for $\tau_0$ fixed to the values indicated in the figure. (c) depicts the difference between (a) and (b) and (f) between (d) and (e). In panels (a)–(c) $\alpha$ equals 0.01 and in panels (d)–(f) $\alpha$ equals 0.1.

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Fig. 6. The effect of assuming a certain fixed $\tau_0$ value on the corresponding SLP compared to the SLP calculated by means of size dependent $\tau_0$ for $H_0=5$ kA/m and $f=200$ kHz. $\Delta$SLP is the difference between the SLP calculated by means of Eq. (14) with (15) and the SLP calculated by means of Eq. (14) with the assumed fixed $\tau_0$ value. (a) is for the case of $\alpha = 0.01$ and $\mu = 6$ nm, while (b) is for $\alpha = 0.1$ and $\mu = 7$ nm. Results are depicted for three different $\sigma$ values.
tions and peaks at the sizes where the frequency and the relaxation time $\tau_0$ are each other’s inverse [5]. This also explains the shift of the peak towards smaller sizes for $\alpha=0.01$ as compared to its location for $\alpha=0.1$. A lower damping corresponds to slower relaxation mechanisms and thus a longer relaxation time. The optimal size corresponding to the ideal relaxation time, for the considered frequency, is thus found at smaller particles.

When comparing the respective results with a fixed, or size dependent $\tau_0$, no qualitative differences are observed. Therefore, the difference between both results (panels (c) and (f)) is plotted. A small tendency towards larger SLPs is noticed when the size dependence of $\tau_0$ is taken into account, which can amount to 10% of the SLP. However, as only MNPs with a size very close to the optimal volume contribute to the SLP, using a fixed $\tau_0$ in one’s calculations, provided that this value is well chosen, still gives a reliable estimate of the SLP in the light of other uncertainties involved in the MNP characteristics in hyperthermia experiments. Note however that in practice $\tau_0$ is chosen between $10^{-8}$ and $10^{-12}$ s and using for example a value of $10^{-12}$ s in this case results in larger differences for the calculated SLP with this fixed $\tau_0$ value and the calculated SLP taking the size dependency into account.

Fig. 6 shows for instance for a fixed mean radius (in (a) for $\mu=6$ nm, in (b) for $\mu=7$ nm) the effect of assuming a certain fixed $\tau_0$ on the corresponding SLP (i.e. SLP calculated by means of Eq. (14) with fixed $\tau_0$) compared to the SLP calculated by means of Eq. (14) with the size dependent $\tau_0$ determined by Eq. (15) for $r=6$ nm in (a) and $r=7$ nm in (b).

This illustrates that there is a recommended value when using a fixed $\tau_0$ depending on the magnetic material properties of the MNP and its size. One should use, depending on the sizes of the MNP, Eqs. (5) or (15) to obtain a rough estimate of $\tau_0$.

4. Conclusion

The size dependence of $\tau_0$ is investigated by means of micromagnetic simulations using Vinamax. Based on the results, an empirical correction to Brown’s equation is found allowing its use outside its region of validity. The SLP is subsequently calculated using LRT with the size dependent $\tau_0$ and compared to SLP calculated with a well-chosen fixed $\tau_0$. To conclude, although the effect itself can be quite large, taking into account the size dependence of $\tau_0$ is not vital in SLP calculations, as in each size distribution only a limited size range of MNPs contribute to the heat generation. However, a well-chosen $\tau_0$ needs to be used. When this is not the case large differences occur between the calculated SLPs for the fixed $\tau_0$ and the size dependent $\tau_0$. The precise value of $\tau_0$ is most accurate when it is as close as possible to its true value for the radius at the peak of the heating.

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