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Interpreting the magnetorelaxometry signal of suspended magnetic nanoparticles with Kaczmarz’ algorithm

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Abstract
Magnetic nanoparticles in colloidal dispersions are important for biomedical applications like magnetic drug targeting, magnetic particle hyperthermia, and several imaging applications. For a physical understanding of these applications, the particles’ hydrodynamic size distribution should be well characterized. Magnetorelaxometry is a fast method to determine this property, but until now had the drawback that a priori information, like a functional form of the expected size distribution, was necessary. Following recent advances, where Kaczmarz’ algorithm was used to determine the core size distribution from static magnetization curves without any such assumptions, we present a similar study for the determination of the hydrodynamic size distribution. Here, the performance of several implementations of Kaczmarz’ algorithm are investigated for both simulated and measured magnetorelaxometry data. Our results show that this method is able to determine the hydrodynamic size distribution in agreement with either the known input distribution, in the case of simulated data, or other size estimates determined with different methods such as thermal magnetic noise spectroscopy and dynamic light scattering in the case of measured data.

Keywords: magnetorelaxometry, size distribution, Kaczmarz algorithm, magnetic nanoparticles

(Some figures may appear in colour only in the online journal)

1. Introduction

Magnetic nanoparticles are used in increasingly diverse and specialized applications [1, 2]. For example, several imaging applications such as magnetorelaxometry imaging [3, 4], AC susceptibility imaging [5] or magnetic particle imaging (MPI) [6] are currently under development. Another very promising application is magnetic nanoparticle hyperthermia, where an alternating magnetic field is used to increase the particles’ temperature and destroy tumor cells [7, 8]. Typically, magnetic nanoparticles consist of a magnetic core surrounded by a non-magnetic shell. This shell prevents the particles from clustering and oxidation and when equipped with a suitable coating, the particles can be used as biomolecular detector probes [9] or drug carriers [10]. Because a good knowledge of the particle properties is a requirement to ensure a reliable performance of these applications and in some cases even patient safety, particle characterization is becoming increasingly important.

Only a few direct measurement methods exist to obtain the size distribution of magnetic nanoparticles. For instance, the core size distribution can be measured via transmission electron microscopy (TEM) [11]. For the hydrodynamic size distribution, taking into account the volume of both the core
2. Methods

2.1. Magnetorelaxometry

In an MRX experiment, the relaxing magnetic moment of an ensemble of nanoparticles is measured after an externally applied magnetizing field is switched off [21]. Typically, the magnetizing field has a strength of a few mT and is applied for one second. During the relaxation phase, the magnetic moment is recorded for one second with sensitive magnetometers like SQUIDs or fluxgates [25]. When using SQUIDS, as is the case in our setup, the start of the measurement is delayed by 0.1 ms. This dead time is related to recovery effects of the magnetometers. In such samples, the effective relaxation is caused by the Brownian motion so that, except in immobilized samples, the effective relaxation is caused by the Brownian process. When looking at immobilized samples, the exponential volume dependence of the Néel relaxation time implies that only a very small fraction of the particles then contributes to the MRX signal, which presents problems when trying to estimate the size distribution [31]. Therefore, we will limit this study to dispersions with a distribution of particles in which the anisotropy energy barriers are large enough to thermally block the magnetic moments. In such samples, the relaxing ensemble magnetization is described by

\[ M(t) = M_0 \int_0^\infty \exp \left( -\frac{t}{\tau_0} \right) P(D) dD, \]  

(4)

where \( M_0 \) denotes the ensemble magnetization at time 0, when the field is switched off, and \( P(D) \) is the hydrodynamic size distribution, with \( D \) the diameter of the particles. The topic of this paper is to find this distribution from a given \( M(t) \) without making any \textit{a priori} assumptions on the shape of the size distribution.

2.2. Kaczmarz’ algorithm

We can simplify the notation by first estimating the relaxation time distribution, and transforming it into a size distribution afterwards. The measured signal originates in the ensemble magnetization curve [16]. The problem consists in determining the distribution of a superposition of Langevin functions, where each function corresponds to a certain particle size. In a first approach, a lognormal size distribution was assumed in order to simplify this problem. Later, solution methods which make no assumptions on the size distribution were developed. Examples thereof are the regularized singular value decomposition proposed by Berkov [17] or the inversion method proposed by van Rijssel [18]. Recently, also Kaczmarz’ method [19] has been used successfully to reconstruct the size distribution [20].

When interpreting magnetorelaxometry (MRX) [21] data to characterize nanoparticles, a similar problem needs to be solved. Here, however, the signal consists of a superposition of decay ing exponentials. The interpretation of such signals presents a notoriously difficult mathematical problem [22], and until now, size distributions estimated from MRX data always required \textit{a priori} assumptions like e.g. a lognormal size distribution [23].

This assumption is not always valid [24], nor does it have a sound theoretical basis [17]. Therefore, it would be valuable to have a method which does not need \textit{a priori} information on the size distribution. Here, we show that the Kaczmarz method can be used to estimate the hydrodynamic size distribution from the MRX signal of magnetic nanoparticles without making any assumptions on the size distribution. This paper is organized as follows: in the next section, the working principle of MRX is explained, followed by our implementation of Kaczmarz’ algorithm. In the results section, we then validate the proposed method on simulated and measured data.

and the shell, atomic force microscopy (AFM) [12, 13] is a direct measurement method. However, one often has to rely on indirect measurements. Next to non-magnetic methods, like dynamic light scattering (DLS) [14], there exist several magnetic characterization measurement methods [15]. Historically, the first magnetic method which was used to determine the core-size distribution was by interpreting the static magnetization curve [16]. The problem consists in determining the distribution of a superposition of Langevin functions, where each function corresponds to a certain particle size. In a first approach, a lognormal size distribution was assumed in order to simplify this problem. Later, solution methods which make no assumptions on the size distribution were developed. Examples thereof are the regularized singular value decomposition proposed by Berkov [17] or the inversion method proposed by van Rijssel [18]. Recently, also Kaczmarz’ method [19] has been used successfully to reconstruct the size distribution [20].

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\[ \eta = \frac{3\eta_v V_c}{k_B T}. \]  

(1)

In this equation, \( V_c \) denotes the hydrodynamic volume of the identical particles, \( \eta \) and \( T \) are the effective viscosity of the suspending medium and temperature of the sample respectively, while \( k_B \) denotes the Boltzmann constant.

The second process is formed by the jumps of the magnetic moment over the energy barriers originating in the magnetocrystalline or shape anisotropy of the superparamagnetic particles [28, 29]. Assuming an effective uniaxial anisotropy constant \( K \), an ensemble of identical particles with core volume \( V_c \) has a typical Néel relaxation time \( \tau_N \) of

\[ \tau_N = \frac{\tau_0 \exp \left( \frac{KV_c}{k_B T} \right)}{\eta + \tau_0}, \]  

(2)

where \( \tau_0 \) is the inverse of an attempt frequency and is often taken in the range between \( 10^{-8} \) and \( 10^{-12} \) s [30]. In liquid samples, both mechanisms are present and the particles relax with an effective relaxation time constant

\[ \tau_{\text{eff}} = \frac{\tau_N \tau_0}{\eta + \tau_0}. \]  

(3)

However, starting from a certain core diameter \( V_c > \frac{k_B T}{A} \ln \left( \frac{k_B T}{\mu_0} \right) \), the Néel relaxation time is much slower than the Brownian relaxation time so that, except in immobilized samples, the effective relaxation is caused by the Brownian process. When looking at immobilized samples, the exponential volume dependence of the Néel relaxation time implies that only a very small fraction of the particles then contributes to the MRX signal, which presents problems when trying to estimate the size distribution [31]. Therefore, we will limit this study to dispersions with a distribution of particles in which the anisotropy energy barriers are large enough to thermally block the magnetic moments. In such samples, the relaxing ensemble magnetization is described by

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where \( M_0 \) denotes the ensemble magnetization at time 0, when the field is switched off, and \( P(D) \) is the hydrodynamic size distribution, with \( D \) the diameter of the particles. The topic of this paper is to find this distribution from a given \( M(t) \) without making any \textit{a priori} assumptions on the shape of the size distribution.
to the volume weighted hydrodynamic size distribution, some assumptions about the relation between the hydrodynamic and core size of the particles are necessary. We focus on the performance of Kaczmarz’ algorithm to estimate the relaxation time distribution from magnetorelaxometry data. Therefore, we make the simplest possible assumption by assigning each particle only one (hydrodynamic) volume and a magnetization equal to the quotient of its magnetic moment and this volume.

We now turn our attention to how the relaxation time distribution is estimated. First, we assume a sufficient number of discrete relaxation times \( i \) within a suitably chosen lower and upper bound. Subsequently, we estimate the fractions of the ensemble relaxing with each of these relaxation times. To this end, we introduce a vector \( W \) containing \( i \) weights, initialized to zero.

We can then rewrite equation (4) as

\[
M(t) = M_0 \sum_i W_i \exp \left( -\frac{t}{\tau_i} \right).
\]

If we use discretized data points as \( M_j \) corresponding to the value of \( M(t) \) at time \( t_j \), and introducing the matrix \( A \) with elements

\[
A_{ij} = \exp \left( -\frac{t_j}{\tau_i} \right),
\]

we can rewrite equation (5) as

\[
M_j = M_0 \sum_i W_i A_{ij}, \text{ for all time points } t_j.
\]

We aim at finding the values of \( W_i \) which minimize the difference between the calculated and measured \( M_j \). To this end, we use Kaczmarz’ iterative method, where all weights \( W_i \) update each iteration via

\[
W_i^{k+1} = W_i^k + \frac{M_j - (A_j \cdot W_i^k)}{\|A_j\|^2} \overline{A}_j \]

where \( A_j \) denotes the \( j \)th row of the matrix \( A \), \( \overline{A}_j \) is its transpose, \( k \) is the iteration number and one iteration is defined as a sweep over all rows \( j \).

We also implemented Kaczmarz’ randomized algorithm, where instead of iterating over all rows \( A_j \), the probability of choosing a row \( j \) is proportional to \( \|A_j\|^2 \). In one sweep we repeat this procedure \( j \) times in order to be able to compare the total number of iterations with the iterative method.

To exclude the possibility of a negative relaxation, physically corresponding to a spontaneous remagnetization of the particles, this problem can be subject to the constraint that all weights should be positive. This is implemented by putting \( W_i^{k+1} = 0 \) when

\[
W_i^k < \frac{M_j - (A_j \cdot W_i^k)}{\|A_j\|^2} \overline{A}_j.
\]

Figure 1. The input relaxation time distribution together with the reconstructed distributions obtained without ((a) and (b)) and with ((c) and (d)) non-negativity constraint with the randomized Kaczmarz algorithm ((a) and (c)) and the iterative Kaczmarz algorithm ((b) and (d)). Each panel shows the distribution after 1000, 10000 and 100000 iterations. After a sufficient amount of iterations, all reconstructed distributions are in agreement with the input distribution.
In the results section, we will investigate the effect of this extra constraint on the obtained size distributions.

3. Results

In this section, we present the performance of the presented method by comparing estimated relaxation time distributions to a known input distribution in simulated data, discussing the effect of the different implementations, and validating the method against experimental data.

3.1. Simulation results

Using equation (4), we generated the relaxometry signal corresponding to a lognormal relaxation time distribution with $\mu = 0.03$ s and $\sigma = 0.5$. Figure 1 shows this input distribution together with the results of an analysis of the corresponding relaxometry signal, performed using the different implementations described above.

When comparing the reconstructions after 1000, 10 000 and 100 000 iterations, it is clear that the reconstructed distributions do not change significantly after 10 000 iterations, and in the following we will only show the results after 10 000 iterations. Note that this number is valid for all our simulations and experiments where we used 200 logarithmically sampled data points, but should be changed when using a different number of data points, because every iteration, all weights are updated $j$ times.

In contrast, figures 1(a)–(d) show the relaxation time distributions obtained with the non-negativity constraint. The oscillations at small relaxation times are suppressed, but the tails of the distributions are less well reconstructed and show bumps instead of a smooth decay. Although these bumps distort the reconstructed distributions somewhat, we believe the advantage of finding distributions containing only physical values is more important.

Next, we note that the differences between figures 1(a) versus (b) and (c) versus (d) are insufficient to draw any conclusions about the relative advantages of the randomized or iterative implementations.

We continue our investigation with the discussion of figure 2. In this figure, the reconstruction results are shown for two bimodal distributions. One in which both modes are well separated (figure 2(a)) and a case in which they overlap (figure 2(b)). In the case of the overlapping modes, a smoothing effect is visible; the thinnest mode is estimated to be wider than it is in reality and vice versa. The results show that the method is able to reconstruct bimodal distributions. Although the distributions obtained with the random and iterative implementation do not lie on top of each other, there is no significant difference in performance as the quality of the distributions (measured as the relative error norm) lies within 3% of each other.

Before turning our attention to real measurements, we investigate the issue of incomplete information. The used setup measures the magnetorelaxometry signal during a fixed time window. Therefore, the complete relaxation can never be captured. Figure 3 shows how well the algorithm handles partial information. Figure 3(a) shows the simulated magnetorelaxometry signals for six virtual nanoparticle samples with lognormal hydrodynamic size distribution with $\mu = 100$ nm and $\sigma = 0.3$. The colored lines correspond to simulations with different viscosities $\eta$, as detailed in the legend. From equations (1) and (4), it follows that the magnetorelaxometry signals coincide when rescaled with $\eta$, which is confirmed in figure 3(b). It is also visible that, depending on the viscosity, not all measurements contain the same information. Figure 3(c) displays the (simulated) relaxation time distributions for each sample, where the full lines show the part of the relaxation time which gives rise to relaxations visible within the captured signals shown in figure 3(a). The remaining part of the distribution is depicted by a dotted line. Panel (d) shows the reconstructed size distributions together with the distribution used as input to generate the magnetorelaxometry data. For the simulated samples with $\eta = 32$, 16 and 8 mPas, sufficient information about the relaxation times was available to obtain almost perfect reconstructions. In contrast, for the samples with lower viscosities, the incomplete information resulted in size distributions which are systematically shifted towards larger sizes, show a reduced width, show large bumps, and are thus difficult to interpret.
3.2. Measurement results

Based on the results on simulated data, we chose to analyze magnetorelaxometry data using the randomized Kazcmarz algorithm with non-negativity constraint for 10,000 iterations. Although we did not observe significant differences between the iterative and randomized implementation, we prefer the randomized implementation because more weight is given to the part of the relaxometry data with a high signal to noise ratio. In this section, we investigate the performance of this method on measurement data.

We performed two series of measurements on fluidMAG-AS/CF (CFAS) and fluidMAG-HS/CF (CFHS) samples, provided by chemicell GmbH. Particles of both systems show a multicore structure in which the single cores are cobalt ferrite crystallites. The single crystallite size ranges typically between 10 nm and 15 nm, estimated from TEM data of other samples which were produced in a similar way. The single crystallites are embedded/surrounded by Hydroxyethyl starch (CFHS), and acrylic acid (CFAS), with molecular weights of about 130 kDa, and 65 kDa, respectively. Following our simulation study above, six different glycerol-mixtures with viscosities of 1, 2, 4, 8, 16 and 32 mPa s of both particle types were prepared. All CFAS and CFHS samples had an iron concentration of 16 mmol l$^{-1}$ and 13 mmol l$^{-1}$, respectively. The relaxing magnetic moments of these twelve samples were then captured and are shown in figures 4(a) and (b). As expected, the samples with a higher viscosity give rise to a larger signal and relax more slowly. It was checked that even the samples with the highest viscosity are thermally blocked and relax via the Brownian relaxation mechanism [33]. Moreover, we also verified that they are not sensitive to concentration effects. All signals turn to noise at roughly 1 pT. One exception is the CFAS sample with $\eta = 4$ mPa s, which shows unexpected behavior starting at 10 ms, which we attribute to a slight partial aggregation. We want to investigate whether these different relaxation curves give rise to size distributions consistent with each other, and those obtained by DLS and lognormal distributions determined from magnetorelaxometry [23] and thermal magnetic noise spectroscopy [26, 32] data.

As mentioned above, the Brownian relaxation time should scale linearly with the viscosity. We first check if all relaxation curves coincide when properly rescaled. The result of this rescaling is depicted in figures 4(c) and (d), and shows that, above the noise level, all relaxation curves indeed lie on top of each other. Here, one can see again that not all samples contain the same information: the samples with the highest viscosities contain more information about the fastest relaxing (smaller) particles in the distribution. Next, figures 4(e) and (f) depict the relaxation time distribution obtained with Kaczmarz’ algorithm. We allowed the algorithm to look for a relaxation time distribution between 10 ms and 0.1 s, logarithmically divided into 100 relaxation times. However, noting that our measurement data only commences at 0.51 ms, the
Figure 4. The results for the CFHS (left column) and CFAS (right column) samples, the viscosity is indicated with the color code in the legend. (a) and (b) The measured magnetorelaxometry signals. (c) and (d) Magnetorelaxometry data rescaled with the viscosity to show that all signals coincide. (e) and (f) The obtained relaxation time distribution. The full lines show the part of the distribution for which sufficient data was present in the relaxation curves, while the dotted lines indicate that the distribution is unreliable because this information was not available. (g) and (h) The volume weighted size distributions, together with the size distribution estimated from DLS data, and lognormal size distribution estimated for these particles via both magnetorelaxometry and thermal magnetic noise spectroscopy [33].
part of the relaxation time distribution for faster times, indicated with dotted lines, is unreliable. These faster relaxation times were included solely because allowing the distribution to go down to zero improves the convergence of the algorithm. These results illustrate the limitation that only relaxation times larger than approximately 0.3 ms can be discerned.

Finally, we transform the obtained relaxation time distributions to volume-weighted size distributions using equation (1). The resulting distributions are shown in figures 4(g) and (h), together with the distributions obtained with DLS (dotted black lines) and the lognormal size distributions for these particles estimated in [33] (full black lines). Again, the unreliable parts of the distributions are pictured with colored dotted lines. As observed in the simulation results above, the non-negativity constraint gives rise to bumps at the tails of the distribution, which are artifacts of the method and therefore should not be interpreted as real maxima. The results show that the (reliable) parts of the obtained size distributions generally are in reasonable agreement with each other. When accounting for the artificial bumps, the position of the large-particle tail of the distribution coincide well as this information is equally well available for all samples. The part of the distribution for the smallest particles is unreliable for the samples with low viscosities as these do not contain this information and are therefore drawn with a dotted line.

As a reference, also a lognormal distribution estimated from MRX and TMNS data of the same samples is depicted. Contrary to the results obtained with Kaczmarz’ algorithm, the lognormal distribution does not suffer from the bumps at the tails. Nonetheless, the agreement between both estimates is not bad, especially when one takes into account that the small-particle tail of the lognormal estimate is based on a best fit of a functional form of the lognormal distribution on data which does not necessarily follows this form. We believe that extra confidence can be obtained in size distributions by estimating them both with Kaczmarz’ algorithm and from a lognormal fit, because large deviations from a lognormal shape would reliably show up form Kaczmarz’ estimate, while a monomodal distribution would be described better with the lognormal distribution. Finally, also estimated volume distributions obtained with DLS are shown. For the CFAS sample the DLS data confirms the overall position and shape of the size distributions, while the DLS data from the CFHS sample shows a distribution with a peak at significantly lower particle diameters than the other estimates. This might originate in aging effects in the samples during the 6 months time delay between the MRX and DLS measurements. Finally, it might also be possible that non-magnetic components like e.g. excess polymer clews, contribute to the DLS signal.

4. Conclusions

To conclude, we presented the performance of different implementations of Kaczmarz’ algorithm to determine the relaxation time and hydrodynamic size distribution from magnetorelaxometry data. The methods applicability is demonstrated for suspended nanoparticles which are thermally blocked, as it is expected that difficulties will present themselves due to the exponential size dependence of the Néel relaxation time. Based on the presented results, we recommend to use the randomized Kaczmarz algorithm with non-negativity constraint. We validated this method first against simulated data, and in a next step compared the size distributions obtained from MRX data of six dispersions with different viscosities of two particle types. From the resulting size distributions we concluded that the obtained particle size distributions were in agreement with each other. Due to the limitations of the setup, the relaxometry signal does not contain information on the fastest relaxations, and thus does not allow to characterize particles with a diameter smaller than approximately 30 nm. In case the relaxation was so fast that no information on the complete size distribution was available, the algorithm was still able to give a reasonable estimate of the large-particle tail of the distribution apart from artificial bumps caused by the non-negativity constraint. Furthermore, it should be noted that the measurement data only give information on the relaxation time distribution and that theoretical models are used to transform this information to a size distribution. Especially at high concentrations these models are imperfect because they do not take the effect of inter-particle interactions into account [34]. Research is being conducted to also take these effects into account [35, 36], which will give rise to more reliable size estimates in the future.

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