Motion of nanometer sized magnetic particles in a magnetic field gradient

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I. INTRODUCTION

Magnetic particles (also called magnetic beads) are very promising for use in biomedical applications such as contrast agents for magnetic resonance imaging, magnetic markers for biosensing, or magnetic carriers in magnetic separation. In the latter application, magnetic particles functionalized with biomolecules (e.g., antibodies) are used for transport and separation of nonmagnetic molecules.

A magnetic separation system typically consists of functionalized magnetic particles in a test tube or a sample region and a permanent magnet generating the magnetic field that magnetizes the particles. The magnet also creates the magnetic field gradient that together with the particle magnetization exerts magnetic forces on the particles. As a result, the particles are transported to the magnet (Fig. 1). When the particle size decreases, the ratio of the particle surface to particle volume increases, and therefore the particles offer a larger specific surface for chemical binding for an equivalent total mass of the particle system. Consequently, there is significant interest in decreasing the size of the particles being used in biomedical separation.

However, when the size of the particles decreases, the induced magnetic moment of the particles decreases as well due to the reduced amount of magnetic material in the particles. Thus the magnetic force exerted on the particle, being directly proportional to the induced magnetic moment of the particle, becomes weaker, which results in a longer separation time. However, it remains unclear to what extent the particle sizes can be reduced and whether the particles can be separated in a reasonable amount of time. Previous research...
related to the motion of magnetic particles in a field gradient has focused on particles in the micrometer range, rather than on nanometer-sized magnetic particles.

In this paper, we report our theoretical and experimental investigation of the behavior of magnetic nanoparticles in the case of magnetic separation in a magnetic field gradient. The particles we have used in this study are so-called multicore particles, i.e., they consist of several single-domains of magnetite (Fe₃O₄) embedded in a polymer matrix. This can be considered a typical magnetic particle system used in biomagnetic separation applications. Our aim is to gain a better understanding of the mechanisms involved in the magnetic separation process of nanometer-sized particles by combining both measurements and simulations.

To simulate the motion of the submicrometer sized magnetic particles in a magnetic field gradient, a numerical model based on a Brownian dynamics algorithm has been implemented. This model takes into account the magnetic forces exerted on the particles as well as the dipole-dipole and hydrodynamic interactions between particles. Simultaneously, an optical measurement setup has been built to evaluate the spatial distribution of the particles in a sample cuvette as a function of time. This method is based on monitoring the change in intensity of a light beam transmitted through the sample volume as the particle concentration changes with time after placing the permanent magnet next to the sample cuvette. We present experimental results on the separation of the magnetic particles as a function of the initial sample concentration, the distance from the magnet, and the strength of the gradient fields. This optical method for quantifying the separation process is a very easy and simple way to study the separation behavior of particle systems with different sizes and magnetic properties. The comparison between the simulations and the measurements has revealed some of the important mechanisms influencing the separation process, for instance the formation of particle aggregates.

### II. THE MAGNETIC PARTICLES

The magnetic particles used in this study are fluidMAG-D nanoparticles from Chemicell GmbH. They are composed of a number of single-domains of magnetite (Fe₃O₄) in a starch coating that consists of a polymer matrix containing terminal hydroxyl groups. The hydrophilic polymer protects the particles from aggregation due to foreign ions, and the terminal functional hydroxyl groups can be used for binding to biomolecules during the separation process. The particles are suspended in de-ionized water. Different particle sizes with the following hydrodynamic diameters have been studied: 50, 100, 150, 200, 250, and 425 nm. These values provided by the particle manufacturer were confirmed by photon correlation spectroscopy measurements.

The initial particle concentration in the sample was diluted to 0.1–0.3 mg/ml (giving a mean distance between the particles of more than ten times the particle diameter). The initial particle concentration was chosen so that the solutions containing the particles had relatively low optical absorption. Lower particle concentrations gave an unstable optical signal when compared to water reference samples. All the optical experiments were conducted with the magnetic particles diluted in distilled water.

The magnetization curves (i.e., magnetization versus field) of the particle systems were measured with a vibrating sample magnetometer from Lake Shore Ltd. The values of the magnetic properties of the particles (see Table I), i.e., the saturation magnetic moment per particle \( \mu_s \) and the intrinsic magnetic moment of the single-domains in the particle \( \mu_d \) were obtained by fitting the magnetization data to the Langevin function \( L \) according to

\[
M = M_0 L = M_0 \left[ \frac{\mu_d B}{k_B T} \coth \left( \frac{\mu_d B}{k_B T} \right) - \frac{k_B T}{\mu_d B} \right],
\]

where \( M \) is the magnetization, \( M_0 \) is the saturation magnetization of the sample, \( B \) is the magnetic field, \( k_B \) is the Boltzmann constant, and \( T \) is the absolute temperature. The result of the fitting for the magnetic particle system with diameter 425 nm can be seen in Fig. 2. From the values of \( M_0 \), the particle concentration and the particle size the magnetic moment per particle \( M_p \) can be calculated for the different particle systems (Table I). The average size of the single-domains in the particles can be estimated from the \( \mu_d \) value and is also given in Table I. The Langevin model does not take into account magnetic interactions between the single-domains in the particle or between particles or magnetic anisotropy of the single-domains. The experimental data points were fitted to Eq. (1) using only one Langevin function meaning that only one size of the single-domains is considered in the fitting. All of these facts imply that the fitting procedure to the experimental magnetization curves gives only approximate values of the size of the single-domains and the number of single-domains per particle.

### TABLE I. The results of the fitting procedure of the magnetization data at 295 K for the different magnetic particle systems: \( \mu_s \) is the saturation magnetic moment per particle and \( M_p \) is the saturation magnetization of the particle (given by \( \mu_s \) divided by the particle volume). The mean diameters of the single-domains are calculated using a typical value of the intrinsic magnetization of small magnetite single-domains (\( M_p = 350 \text{ kA/m} \)) and the number of domains represents the number of single-domains per particle.

<table>
<thead>
<tr>
<th>( D ) (nm)</th>
<th>( \mu_s \text{(Am}^2\text{/m})/\text{particle} \times 10^{-16} )</th>
<th>( M_p ) (kA/m)</th>
<th>( \mu_d/k_B T^{-1} )</th>
<th>Average diameter of single-domain (nm)</th>
<th>Equivalent number of single-domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.016</td>
<td>24</td>
<td>72.2</td>
<td>11.8</td>
<td>5</td>
</tr>
<tr>
<td>100</td>
<td>0.344</td>
<td>66</td>
<td>82.9</td>
<td>12.3</td>
<td>101</td>
</tr>
<tr>
<td>150</td>
<td>0.870</td>
<td>49</td>
<td>91.0</td>
<td>12.7</td>
<td>232</td>
</tr>
<tr>
<td>200</td>
<td>0.662</td>
<td>16</td>
<td>75.0</td>
<td>11.9</td>
<td>215</td>
</tr>
<tr>
<td>250</td>
<td>5.151</td>
<td>63</td>
<td>84.1</td>
<td>12.4</td>
<td>1489</td>
</tr>
<tr>
<td>425</td>
<td>19.35</td>
<td>48</td>
<td>72.1</td>
<td>11.7</td>
<td>6523</td>
</tr>
</tbody>
</table>
interactions, magnetic anisotropy, and single-domain size distributions can be introduced into the magnetization model. However, the results seem reasonable, as seen from transmission electron microscopy images of the particle systems (not shown here).

### III. EXPERIMENTAL SETUP

We perform the experimental measurements by monitoring the absorbance change of the sample volume as the particle concentration varies over time. The experimental setup for the optical measurements consists of the eight following main components [Fig. 3/(Top)]: a light source, a blazed grating, lenses and fibers, a cuvette containing the sample, a magnet, a photodiode, a source measure unit, and a personal computer. The light source is a 250 W tungsten-halogen lamp. The blazed grating with 300 lines/mm is set to get a mean wavelength of 450 nm. This wavelength was found to give the best detection signal. The light is sent through a fiber to the sample chamber (HORIBA Jobin Yvon SampleMAX). In this chamber, two lenses focus the light from the fiber onto the sample and two lenses launch the light passing through the sample back into a fiber connected to a standard photodiode. The current from the photodiode is then measured by the Keithley 237 high voltage source measure unit. Finally, the data is sent to a computer via the GPIB bus of the source measure unit.

The sample is contained in the tapered base (hereafter referred to as sample column) of an Eppendorf UVette, a plastic cuvette with four optical windows (UV and visible transparent between 220 and 1600 nm) and external dimensions of $12.5 \times 12.5 \times 36$ mm$^3$. The length and width of the sample column are 10 and 2 mm, respectively.

The detection volume is limited to a small measuring volume within the sample column defined by the volume of the light beam penetrating through the sample column [Fig. 3/(Middle)]. The light beam has a diameter of about 1.8 mm and the optical path length (i.e., the width of the column) is 2 mm. Thus, the detection volume is about 5 $\mu$l while the total sample volume is 40 $\mu$l. The position of the detection
volume can be changed by adjusting the position of the light beam with respect to the length of the sample column. The sample column is aligned to the focus point of the light with micrometer screws. This arrangement is set such that the light beam crosses perpendicular to the symmetry axis of the magnet.

A neodymium (NdFeB) magnet with a radius of 7 mm and a thickness of 8 mm creates the magnetic field and magnetic field gradient. The sample column, the detection volume, and the cylindrical magnet are illustrated at scale in Fig. 3 (Bottom). The small width of the sample column (2 mm) compared to the magnet diameter (14 mm) guarantees that the whole sample is close to the symmetry axis of the magnet where the magnetic field is mainly directed in the direction of the magnet (x-direction).

We performed a finite-element analysis of the off-axis components of the magnetic field and magnetic field gradient in order to evaluate the longitudinal and transversal components of the magnetic force acting on the particles, \( F_x \) and \( F_y \), respectively. The results show that the ratio \( F_y/F_x \) is around 20 for the particles located where the field lines diverge the most in the sample column (at \( x=11.25 \) mm and \( y=1 \) mm) and higher in the rest of the sample column. This means that the field perpendicular to the symmetry axis in the sample column is negligible in this case, which justifies the use of a one-dimensional approximation in the numerical simulation described in Sec. IV. The magnetic field at the surface of the magnet is about 0.4 T, and its amplitude along the symmetry axis of the magnet is plotted in Fig. 4. Along the symmetry axis, the magnetic field gradient is 52.5 T/m at \( x=1.25 \) mm and down to 7.7 T/m at \( x=11.25 \) mm. The ratio of the magnetic force in the \( x \)-direction to the gravity force of particles (taking the buoyancy into account) is about 77 at \( x=11.25 \) and higher in the rest of the sample column. This means that the separation process due to the magnetic force has a much higher rate than any particle sedimentation of the particles.

By placing the magnet next to the cuvette (as illustrated in Fig. 3) containing a sample of magnetic particles with a homogenous initial particle concentration, the particles start moving toward the magnet due to the magnetic force exerted on them. The particle concentration measured with the optical method represents the actual magnetic particle concentration within the detection volume in the sample column. Usually the degree of separation is defined as the ratio of particles that have reached the magnet to the total amount of particles. In our case, the degree of separation is defined as the ratio of the actual particle concentration within the detection volume to the initial particle concentration. The separation can be evaluated at different positions in the sample by adjusting the position of the detection volume with respect to the length of the sample column. For instance, by positioning the detection volume closer to the magnet, the separation time defined by when all the particles have reached the magnet (the more commonly used definition of separation) can be determined.

A change in particle concentration produces a change in the absorption (or transmission) intensity of the light beam, and thus in the current measured by the source measurement unit. The relation between the particle concentration \( c \) and the measured current \( I \) is given by

\[ I = I_0 e^{-\alpha c}, \]

where \( I_0 \) is the current of a reference sample with no particles (i.e., de-ionized water only), \( I \) is the optical sample length, and \( \alpha \) is the absorption coefficient. The product of the optical sample length and the absorption coefficient can be determined from a calibration procedure with a known particle concentration and no magnet attached to the cuvette, and the particle concentration can then be calculated for every measured current. In the experiments, we use a low initial particle concentration since in this particle concentration range the absorbance coefficient is independent of particle concentration, and therefore the relation between absorbance and particle concentration becomes linear.

In Fig. 5, the absorbance \((-\ln(I/I_0))\) is plotted versus the
particle concentration for the particle systems with different sizes. It is interesting to notice that the slope of the absorbance curves for the different particle systems increases according to the particle size in the following order: 50, 200, 150, 100, 250, and 425 nm. The particle systems are equal with respect to the starch coating holding the single-domains together and single-domain material (magnetite) and size (about 12 nm diameter). According to the Mie theory, the slope of the absorbance curves is expected to increase with increasing particle size. However, the slopes for the particle systems with sizes of 200, 150, and 100 nm are in the opposite order. We believe that this effect can be explained by the fact that the number density of single-domains is larger in the 100 and 150 nm particle systems than in the 200 nm particle system. This can be seen in Table I, where the values of the volume magnetization per particle \( M_s \) for the 100 and 150 nm particle systems are much higher than the value for the 200 nm particle system. In fact, the 200 nm particle system has the lowest \( M_s \) value compared to all the other particle systems in this study. Since the starch coating is transparent in the visible range, the light is mainly scattered by the magnetite single-domains contained in the particles. Therefore, the 200 nm particle system has a lower light scattering effect from the single-domains as compared to the 100 and 150 nm particle systems due to the lower number density of single-domains in the 200 nm particles.

### IV. THEORETICAL MODEL

As explained previously, magnetic particles in a magnetic field gradient are subjected to a magnetic force that accelerates the particles toward the separation magnet. The magnetic force \( F_m \) on a magnetic dipole \( \mu \) in a magnetic field \( B \) is given (in vector notation) by

\[
\vec{F}_m = \nabla(\vec{\mu} \cdot \vec{B}).
\]

If we consider \( \vec{\mu} \) as a pointlike magnetic dipole, then \( \vec{\mu} \) is not a function of the space coordinates and therefore \( (\vec{B} \cdot \nabla) \vec{\mu} = 0 \) and \( (\nabla \times \vec{\mu}) = 0 \). Furthermore, in a source-free space Maxwell's equation gives \( (\nabla \times \vec{B}) = 0 \), and Eq. (3) becomes

\[
\vec{F}_m = (\vec{\mu} \cdot \nabla) \vec{B}.
\]

This equation can be considered as a good approximation for the magnetic particles used in this study, for the following reasons. First, these magnetic particles contain a number of small nanometer-sized \( Fe_3O_4 \) single-domains for which the magnetic dipole approximation holds well. Thus, the total force on the magnetic particle is the sum of the individual forces on each single-domain contained in the particle. Second, the variation in the magnetic field due to the size of the magnetic particle is also assumed to be sufficiently small to be neglected since the particle diameter is small (425 nm and less).

Since in our one-dimensional model we are interested in the motion along the x-direction only, the force on the magnetic particle finally reduces to

\[
F_m = \mu_s \frac{dB_x}{dx}.
\]

where \( \mu_s \) is the induced magnetic moment in the particle due to the magnetic field that the particle is subjected to. The induced magnetic moment in the particle may be approximated by using the Langevin function (as discussed in Sec. II)

\[
\mu_s(B) = n_d M_s V_{ld} \frac{M_s V_d B_x}{k_B T},
\]

where \( M_s \) is the intrinsic magnetization of small single-domains of magnetite (a typical value of \( M_s = 350 \) kA/m is used in the numerical calculations), \( V_{ld} \) is the volume of the single-domain, \( n_d \) is the number of single-domains in the particle, \( k_B \) is the Boltzmann constant, and \( T \) is the absolute temperature. The number of single-domains in the particles depends on the content of iron oxide and on the size of the single-domains. The content of iron oxide is often given for commercial magnetic nanoparticle systems. It is important to note that the magnetic moment of the particle should be used instead of only the magnetic susceptibility of the particle since the intensity of the magnetic field for a typical separation magnet is around 0.4 T close to the pole face of the magnet. In this magnitude range, the magnetization of the particle is far from linear (Fig. 6), and therefore the susceptibility value would lead to a significant error in the calculation of the particle magnetization.

The magnetic field \( B \) along the symmetry axis of a cylindrical permanent magnet is given by

\[
B_r = \frac{M_s V_d}{2 \pi R} \cdot (1 - \cos \theta).
\]

\[
B_\theta = \frac{M_s V_d}{2 \pi R} \cdot \sin \theta.
\]

\[
B_z = \frac{M_s V_d}{2 \pi R} \cdot (1 - \cos \theta).
\]
\[ B_x = \frac{B_r}{2} \left[ \frac{L + x}{\sqrt{(L + x)^2 + R^2}} - \frac{x}{\sqrt{x^2 + R^2}} \right]. \] (7)

where \( R \) and \( L \) are the radius and length of the magnet, respectively, and \( B_r \) is the remnant magnetic field in the magnet.

This magnet gives both the magnetic field magnetizing the particle and the field gradient that together create the magnetic force on the particle. In our calculations, we have used a value of \( B_r = 1 \) T typical for the NdFeB magnet, \( R = 7 \) mm, and \( L = 8 \) mm. Measured values of the magnetic field along the symmetry axis of the magnet agree well with Eq. (7).

As illustrated in Fig. 6, the induced magnetic moment of the particle [calculated from Eqs. (6) and (7)] is not linear with the field for particle positions within the sample cuvette, meaning that a major part of the magnetization curve must be considered (not only the magnetic susceptibility) in the particle separation process.

When moving in a carrier liquid with a specific viscosity, the particle experiences a viscous force \( F_V \) directed opposite to the particle velocity \( \bar{v} \) according to

\[ F_V = -\gamma \bar{v}. \] (8)

As a first approximation, we neglect the particle size distribution and describe our particles as identical hard spheres. In the limit of low Reynolds numbers, the friction coefficient \( \gamma \) of a spherical particle is given by Stokes law

\[ \gamma = 6 \pi \eta a, \] (9)

where \( \eta \) is the dynamic viscosity of the surrounding fluid and \( a \) is the particle radius. When the size of the particle is in the submicrometer range, it becomes important to include the stochastic Brownian force on the particle. Additional forces, such as hydrodynamic, magnetic, and electrostatic interactions between the particles, may also be important if the particles come close to each other. Including all forces acting on the particle, the one-dimensional motion equation of the particle in the \( x \)-direction can be expressed as

\[ m \frac{d^2 x}{dt^2} = \mu_s(B) \frac{dB}{dx} - \gamma \frac{dx}{dt} + F_B + F_I, \] (10)

where \( m \) is the mass of the particle, \( \mu_s \) is the induced magnetic moment of the particle in the \( x \)-direction, \( B_r \) is the magnetic field from the separation magnet in the \( x \)-direction, \( F_B \) is the Brownian stochastic force [with an ensemble average \( \langle F_B(t) \rangle = 0 \)], and \( F_I \) is the sum of all the interaction forces due to (a) neighboring particle flow (pressure disturbance in the liquid), (b) dipolar magnetic interactions, and (c) electrostatic repulsion between the charged particles.

### A. No particle interactions

Let us assume first that the interparticle interactions may be neglected. The equation of motion can then be expressed by (Langevin dynamics)

| TABLE II. Relaxation time \( \tau = m/\gamma \) of the particle motion momentum for the Chemicell fluidMAG-D nanoparticles. |
|-----------------|--------|
| Particle size   | Relaxation time (ns) |
| (nm)            |        |
| 425             | 16     |
| 250             | 6.5    |
| 200             | 4.7    |
| 150             | 1.6    |
| 100             | 0.9    |
| 50              | 0.15   |

\[ m \frac{d^2 x}{dt^2} = \mu_s(B) \frac{dB}{dx} - \gamma \frac{dx}{dt} + F_B. \] (11)

The above particle motion equation has been solved numerically varying (a) particle size, (b) single-domain size in the particle, and (c) the iron oxide content (by changing the number of domains per particle). The numerical model has been compared with the data obtained from the optical measurements described in Sec. III.

In order to solve Eq. (11), we have used the following strategy. In a long-time dynamics, the friction coefficient \( \gamma \) is related to the diffusion coefficient \( D \) of the particle by the well-known Stokes–Einstein relation

\[ D = \frac{k_B T}{\gamma}. \] (12)

For submicrometer particles, i.e., for low Reynolds numbers, inertia effects can be neglected compared to viscous effects. In other words, by restricting the numerical time step \( \Delta t \) to values that are larger than the relaxation time \( \tau = m/\gamma \) of the particle motion momentum (so-called overdamped or long-time dynamics), the acceleration of the particle can be assumed to be essentially zero during the time step. In our simulation, the numerical time step is 1 ms, whereas the relaxation time of the particles with diameter 425 nm is about 16 ns (Table II). This noninertia approximation of the Langevin dynamics model is commonly called Brownian dynamics, and the displacement \( \Delta x \) of the particle can be expressed in this case as

\[ x(t + \Delta t) = x(t) + \frac{D}{k_B T} F_m \Delta t + \Delta x^G, \] (13)

where \( \Delta x^G \) is a random variable of Gaussian distribution with zero mean and variance \( \langle (\Delta x^G)^2 \rangle = 2D \Delta t \). This random displacement represents the Brownian motion due to the stochastic collisions between the molecules of the fluid and the particle. In this approach, the equation of motion is integrated over a time interval \( \Delta t \) that is sufficiently short so that the systematic magnetic force \( F_m \) remains approximately constant during this time interval. The numerical model as described above has been implemented in MATLAB. Figure 7 shows calculated trajectories of three identical 100 nm particles using Eq. (13). The dashed line in this figure shows the particle motion without including the Brownian force while the other three curves show typical irregular particle trajectories due to the Brownian motion.
Since we are using a one-dimensional model of the particle motion and assuming that the particle concentration changes only in the direction of the applied field, the three-dimensional (3D) particle concentration can be directly estimated from the one-dimensional (1D) particle concentration. At the initial time, the particles are assumed to be homogeneously distributed in the sample cuvette. Thus, the average distance between particles in the x-direction $\Delta x$ is calculated from the initial bulk concentration by the following relation:

$$\Delta x = \left( \frac{c_{3D,0}}{\rho_p V_p} \right)^{-1/3},$$

where $c_{3D,0}$ is the initial bulk particle concentration (i.e., the total mass of all the particles in the sample divided by the sample volume), $\rho_p$ is the particle density, and $V_p = 4\pi a^3/3$ is the particle volume, where $a$ is the particle radius. Since the particles are assumed to move only in the x-axis direction, the bulk concentration as a function of time $c_{3D}(t)$ is proportional to the linear concentration along the x-axis $c_{1D}(t)$ according to

$$c_{3D}(t) = \frac{c_{1D}(t)}{c_{1D,0}},$$

where the subscript 0 denotes the concentration value at the initial time.

When we compare the numerical model presented above with experimental results regarding the particle motion, we find substantially different behaviors. This deviation shows that the model based on noninteracting particles is not sufficient to predict the separation time with enough accuracy, even for very low particle concentrations. Hereafter, we extend the model by including dipolar (Sec. IV B) and hydrodynamic (Sec. IV C) interactions between particles.

**B. Magnetic dipole-dipole interaction**

The dimensionless parameter used to estimate the strength of the magnetic dipole-dipole interaction energy between magnetic particles relative to the thermal energy is

$$\lambda = \frac{\mu_0 \mu^2}{4\pi(2a)^3 k_B T}.$$

For instance, the particle system with diameter 425 nm has a value $\lambda$ between 650 and 1100 depending on the position in the sample cuvette. Particle systems with diameters 100, 150, 200, and 250 nm are also characterized by $\lambda$ values significantly larger than unity. This indicates that the magnetic interaction between neighboring particles is significantly larger than the thermal energy $k_B T$ and therefore particle aggregation is expected to occur when the particles are subjected to a magnetic field. Optical microscopy observations confirmed the aggregation of the 425 nm magnetic particles used in this study when applying an external magnetic field (Fig. 8). The particles are contained in a de-ionized water droplet placed on a microscope slide. In the absence of an external magnetic field, the particles are homogeneously distributed [Fig. 8(a)], and as a magnetic field is applied the particles tend to aggregate into linear chainlike structures aligned with the external magnetic field [Fig. 8(b)]. The magnetic field was created by a NdFeB magnet placed next to but slightly above the microscope slide, which explains why the chains appear on the
image with a small out-of-plane tilt. On the other hand, the 50 nm particle system has a λ value below unity even at the closest distance from the magnet (λ=0.46 at x=1.25). This means that the motion of the 50 nm particles is dominated by thermal fluctuations, which prevents the particles from aggregating.

The one-dimensional magnetic dipole-dipole force between two particles is given by

$$F_{dd,ij} = \frac{3\mu_0}{2\pi} \frac{\mu_i \mu_j}{\lvert x_i - x_j \rvert^3}, \quad i \neq j,$$

(17)

where \(x_i\) and \(x_j\) are the positions of particles \(i\) and \(j\) with induced particle magnetic moments \(\mu_i\) and \(\mu_j\), respectively, calculated from the Langevin function [Eq. (6)]. Equation (17) will be used later in the final expression of the particle motion. However, before the particle motion equation can be solved, we must consider the difference in magnetic and hydrodynamic properties of the particle chain compared to single particles.

We assume that the particles aggregate into a chainlike structure that is represented as an ellipsoid of revolution with a total magnetic moment located at the center of the ellipsoid. Dipole interactions between neighboring particles inside the chain increase the total effective magnetic moment of the chain, which can be calculated by iteratively solving the coupled equations of the effective magnetic field \(B_{eff}\) and magnetic moment \(\mu_{eff}\) for all the particles in the chain until convergence is reached (typically, less than ten iterations were needed for convergence with an error of less than 0.1%):

$$B_{eff,i} = B + \frac{\mu_0}{16\pi\alpha^3} \sum_{j=1}^{N} \frac{\mu_{eff,i}}{\lvert i - j \rvert^3}(i \neq j),$$

(18)

where the induced magnetic moment is given by the Langevin expression according to

$$\mu_{eff,i} = n_i M_S V_d L \left( \frac{M_S V_d B_{eff,i}}{k_B T} \right).$$

(19)

We also define a correction factor \(\alpha_M\) as

$$\alpha_M = \frac{\sum_{i=1}^{N} \mu_{eff,i}}{N\mu},$$

(20)

where \(N\) is the number of particles in the chain and \(\mu\) is the induced magnetic moment of the particle when magnetic interactions are neglected [Eq. (6)]. The effective magnetic moments and correction factor are illustrated in Figs. 9 and 10 for the particle system with diameter 425 nm. The correction factor \(\alpha_M\) is at most 1.05 for the chains located furthest away from the pole face of the magnet (where \(B \approx 50\) mT, see Fig. 4) and lower for all the chains closer to the magnet. A subroutine in the program could easily be implemented by using the method described above to compute the correction factor at each time step depending on the position (and thus on the magnetic field) and on the length of the chains. However, since the correction factor is small (less than 1.05), and in order to minimize the computation time, we assume as a first approximation that the total magnetic moment of the chain is equal to the summation of the magnetic moments of the individual particles in the chain. It should be noted that the correction factor \(\alpha_M\) increases rapidly for lower amplitudes of the magnetic field and for instance can reach a value of \(\alpha_M \approx 1.3\) at \(B = 5\) mT, which cannot be neglected for applications in this field range.

Furthermore, the hydrodynamic friction force acting on a chain of particles must be evaluated since it differs from the case of individual particles. A chain of \(N\) particles is represented as an ellipsoid of revolution moving along the \(x\)-axis and the friction coefficient \(\gamma_N\) of the particle chain can be approximated by

$$\gamma_N = \frac{1}{2} \rho \frac{1}{4\pi^{3/2}} \left( \frac{2L}{\pi} \right)^{3/2} \left( \frac{N}{2L} \right)^2.$$
\[ \gamma_N = 6\pi \eta R_{\text{eff}}, \quad (21) \]

where the hydrodynamic effective radius \( R_{\text{eff}} \) is given by

\[ R_{\text{eff}} = \frac{V}{\pi Q + a_x^2 n_x}, \quad (22) \]

where \( a_x \) is the principal radius of the ellipsoid along the direction of motion and \( V = 4\pi a_x a_y a_z / 3 \) is the volume of the ellipsoid where \( a_x \) and \( a_z \) are the principal radii along the \( y \) and \( z \) directions of the ellipsoid. \( Q \) and \( n_x \) can be evaluated analytically for prolate spheroids (i.e., \( 1 = e^2 = 1 - a_z^2 / a_x^2 > 0 \), and \( a_y = a_z \)).

\[ Q = \frac{a_x^2}{2e^2} \ln \left( \frac{1 + e}{1 - e} \right), \quad (23) \]

\[ n_x = \frac{1 - e^2}{2e^3} \left[ \ln \left( \frac{1 + e}{1 - e} \right) - 2e \right]. \quad (24) \]

In the approximation of long chains (i.e., \( a_z \gg a_x \)), the spheroid becomes equivalent to an elongated rod and Eq. (22) can be simplified to

\[ R_{\text{eff}} = a_x \frac{N_e}{3 \ln(2N) - 0.5}, \quad (25) \]

where \( N_e = a_x / a_z \) is the equivalent number of particles in the chain. This result is often referred to as the slender-body theory and was demonstrated to describe the friction coefficient of micrometer-sized superparamagnetic colloidal beads remarkably well, which were aggregated into linear chains by applications of a homogeneous magnetic field. However, as shown in Fig. 11, the slender-body approximation gives a discrepancy of less than 1% compared to the ellipsoid model only for \( N > 10 \). Since we are interested in describing the transition from individual particles (\( N = 1 \)) to chains (\( N > 1 \)), we adopt the ellipsoid model for the calculation of the friction coefficient \( \gamma_N \) (\( \gamma_N = \gamma_1 \), for \( N = 1 \)).

In a long-time dynamics, the mean velocity of a chain of \( N \) particles is given by the ratio of the magnetic force \( F_{m,N} \) to the friction coefficient \( \gamma_N \),

\[ v_N = \frac{F_{m,N}}{\gamma_N}. \quad (26) \]

By combining the results from Eqs. (20) and (21), the velocity of a chain of particles can then be expressed as

\[ v_N = \frac{N \alpha_{m1}}{\gamma} \frac{F_{m1}}{\gamma_1} = \frac{N \alpha_M}{\gamma} v_1, \quad (27) \]

where \( v_1 = F_{m1} / \gamma_1 \) is the mean velocity of a single particle and \( \gamma = \gamma_N / \gamma_1 \) is a normalized friction coefficient for the chain of \( N \) particles. Clearly, the mean velocity of a particle chain compared to a single particle is higher. The velocity enhancement factor \( \alpha_v \) of the particle chain velocity as compared to the velocity of a single particle depends on the number of particles in the chain, on the correction factor for the effective magnetic moment \( \alpha_M \), and on the normalized friction coefficient \( \gamma \). In Fig. 12, \( \alpha_v \) is plotted with \( \alpha_M = 1 \), and in insert with \( \alpha_M \neq 1 \), for different magnetic fields. This clearly shows that in our case the correction factor \( \alpha_M \) has only a marginal effect on the chain velocity, which supports our choice of neglecting this parameter for the reasons discussed previously.

In this case, the mean velocity of a chain of \( N \) particles is enhanced compared to the mean velocity of the \( N \) individual particles by a factor \( \sim N / \gamma \) and, for instance, a chain of 12 particles moves approximately four times faster than the same 12 particles moving individually. Therefore, the aggregation of the particles into chainlike structures gives a faster separation process. However, the overall separation time cannot be simply extrapolated from the velocity enhancement.
factor given above since the chains interact and eventually aggregate to form larger chains as they all move toward the magnet.

C. Hydrodynamic interaction

The numerical model was further improved by considering the hydrodynamic interactions between particles (or chains). A method for simulating the Brownian dynamics of $N$ particles with the inclusion of hydrodynamic interaction was described by Ermak and McCammon. The effects of hydrodynamic interactions mediated by the host solvent are included through a position-dependent interparticle diffusion tensor according to:

$$D_{ij} = \frac{k_B T}{\gamma_i},$$

$$D_{ij} = \frac{k_B T}{8 \pi \eta r_{ij}} \left( I + \frac{r_{ij} r_{il}^2}{r_{lj}^3} \right),$$

where $\eta$ is the viscosity of the fluid, $r_{ij}$ is the vector from the center of particle $i$ to the center of particle $j$ ($r_{ij}^2 = \Delta x_{ij}^2 + \Delta y_{ij}^2 + \Delta z_{ij}^2$), and $I$ is the unit tensor. It should be noted that $D_{ij}$ is independent of the shape of the particles. This relation was derived under the assumption that the particles may be considered to act as point forces on the fluid, i.e., the interparticle distance is considered to be always very large compared to the effective hydrodynamic radius of a single particle. The hydrodynamic interaction on particle $i$ is calculated from the neighbor particles along the same $y$ and $z$ coordinates as particle $i$, and from the neighbor particles at $\pm \Delta y$ and $\pm \Delta z$ as well (Fig. 13) with periodic boundary conditions, but only the $x$-component of the resulting diffusion tensor is taken into account. The lateral spacing $\Delta y$ and $\Delta z$ have fixed values given by

$$\Delta y = \Delta z = \Delta x.$$

Since $\Delta y$ and $\Delta z$ are typically in the range of a few micrometers, we can essentially assume that the magnetic field and magnetic field gradient along the $x$-direction are the same for all the particles.

The reason for using this pseudo-3D approach instead of a real 3D implementation is that the computation time would be drastically increased by the much more intensive calculation routines required to simulate the 3D displacements and interactions of the particles.

D. Electrostatic interaction

At the moment, we are not considering the electrostatic interactions since the optical microscopy observations show that the electrostatic repulsive force does not prevent the particles from aggregating into chains even for low magnetic fields. However, the electrostatic interaction may play a more significant role for other particle systems or magnetic field conditions.

E. Equation of motion including interparticle interactions

After including particle interactions the motion equation for particle $i$ (and neighbor particle $j$) finally becomes:

$$x_i(t + \Delta t) = x_i(t) + \frac{1}{\gamma_i} \sum_j F_{dd,ij}(t) \Delta t + \frac{1}{k_B T} \int_{t}^{t + \Delta t} F_{em,ij}(t) \, dt,$$

$$+ \sum_j \frac{D_{ij}(t) F_{m,ij}(t)}{k_B T} \Delta t + \Delta x_i^D,$$

where the second and third terms on the right side represent the magnetic dipole-dipole interactions and hydrodynamic interactions, respectively.

V. RESULTS AND DISCUSSIONS

In this section, we will present and discuss the particle separation curve, i.e., the time-dependent particle concentration, for different particle sizes under varying experimental conditions. The numerical model described in the previous section will be used to interpret the experimental results.

First, we will present the separation curves for different particle sizes and same initial particle concentration to determine the separation behavior for each particle system. We will also show the results for different particle concentrations of the same particle system to determine whether the separation process depends on the initial particle concentration. Then the influence of the setup alignment on the separation measurement will be demonstrated by changing the position of the light beam crossing the sample volume. Finally, we will show how the separation behavior is influenced by the distance between the sample and the magnet.

Figure 14 shows the separation curves for five different particle systems. The concentration is measured in the middle of the sample column, i.e., 6.25 mm from the pole face of the magnet and along its symmetry axis. The initial particle concentration for all of the particle systems is 0.3 mg/ml. The separation process is faster for larger particles, except for the 100 nm particle system, which separates faster than the 150 nm particle system. In fact, the 100 nm particles sample separates almost as fast as the 200 nm particles.
sample. We believe that this is due to the different magnetic properties of the 100 nm particle system compared to the other particle systems. Indeed, the 100 nm particle system has the highest saturation magnetization when the magnetic moment per particle is divided by the particle volume, see Table I.

The separation curves first exhibit a slow variation of particle concentration with time (Fig. 14). After some time, the particle concentration starts to decrease rapidly. It is possible to observe an inflexion point where the derivative of the separation curve is at its maximum. We interpret this change in the separation behavior as an effect of two different mechanisms that take place in two different time intervals. Initially, the particles move as separate entities. Gradually, particle chains start to form, as discussed previously (Sec. IV). Therefore, we believe that the observed acceleration of the separation process is due to the formation of these chains.

Our numerical model predicts that from the initial configuration (where particles are randomly distributed along the symmetry axis of the magnet), the particles move in the direction of the magnet and collide to form chains when the trajectories of two or more particles coincide (Fig. 15). The formation of chainlike aggregates is due to the attractive magnetic dipole-dipole interaction between the particles after the magnetic particles have been magnetized by the external magnetic field. The chain formation when an external magnetic field is applied to a particle system has been shown in Fig. 8 and in both theoretical\textsuperscript{23} and other experimental work.\textsuperscript{24–26}

Therefore, the sigmoidal shape of the curves in Fig. 14 can be explained as follows. In the beginning of the measurement, the single particles move slowly toward the magnet under the influence of the magnetic field gradient. The chains start to form as the particles come close to each other so that the interparticle magnetic interaction becomes stronger. Larger chains are subject to higher magnetic forces than smaller chains or single particles since the total magnetic moments of such chains grow with the number of particles constituting the chain. As described in Sec. IV, this leads to a higher velocity of the chains and to an acceleration of the separation process, which explains why the rate of changes of the particle concentration increases after some delay (Fig. 14). When most of the individual particles have been agglomerated into the particle chains, there are only small changes in the size of the chains which can further accelerate them. The particle concentration at times longer than 10 min of the 100, 150, and 200 nm particle systems does not fall to zero, which would be the case if all the particles have been moved to the magnet. We believe that for these particle systems, there are still particles in the sample cuvette that cannot be moved to the magnet in reasonable separation times. This explanation is supported by the visual observation of the sample presenting a slightly brownish color typical of iron oxide particles in suspension.

For the 50 nm particles (not shown in Fig. 14), we do not observe any concentration change over time, i.e., the measured particle concentration remains 0.3 mg/ml after more than 30 min. This experimental result agrees well with Eq. (16). As discussed previously, the thermal energy is larger than the dipole-dipole interaction energy (\(\lambda < 1\)) for particles in this size range. This means that the Brownian motion of the particles hinders the formation of particle chains, and as a result the particles cannot be separated in a reasonable amount of time. This illustrates the importance of particle aggregation into chainlike structures to accelerate the separation process.

Figure 16 shows the predicted trajectories of 1210 particles corresponding to a particle concentration of 0.1 mg/ml. As explained in detail in Sec. IV, the theoretical particle trajectories are calculated by considering only the one-dimensional motion of the particles in the sample cuvette as they move toward the magnet.
The separation curve can then be calculated for a specific measurement position in the sample cuvette by counting the number of particles at a specific distance from the magnet over time. A very good fit exists between the experimental and numerical separation curves for the 425 nm particles (Fig. 17). The experimental and the predicted results differ only in the initial stage of the separation process. This difference is probably due to the fact that in our one-dimensional model, the particles are already aligned along the $x$-direction, and therefore they build chains more rapidly than if they were homogeneously distributed in the sample volume.

For smaller particle sizes, the separation time predicted using the numerical model is longer than the measured value. We believe that one reason for this may be that smaller particles build elongated aggregates that are thicker than simply one particle as in our numerical model. This would result in a shorter separation time since particles aggregated into these thick chainlike structures would experience comparatively less friction than the same number of particles grouped into single-particle thick aggregates. We plan to consider extending the numerical model in our future work to take this phenomenon into account and compare the results with the measured separation times for smaller particles sizes.

As explained in the previous section, our theoretical model includes the magnetic interactions between the particles, the hydrodynamic interactions both between the individual particles and the chainlike aggregates, and the Brownian motion of the particles. All of these factors are needed to obtain good agreement between the model and the experimental results.

Since the mean distance between the single particles depends directly on the particle concentration, we repeated the measurements with different initial particle concentrations to evaluate the influence of this parameter on the separation process. As shown in Figs. 18(a) and 18(b) for the 150 and 425 nm particles, respectively, we found that the separation process is approximately the same for samples with an initial particle concentration of 0.1, 0.2, and 0.3 mg/ml. Thus from these results, we can conclude that the separation process is not strongly dependent on the initial particle concentration in this specific particle concentration range.

The fact that we observed the chain building of particles in the presence of a magnetic field and a magnetic field gradient means that even at low particle concentrations, when the distance between the particles is much larger than their diameter, particle chain formation takes place. The small differences between the separation curves for different concentrations (Fig. 18) could mean that at higher particle concentrations the chains are somewhat longer than for low concentrations. Longer particle chains speed up the separation process due to higher magnetic forces on the longer chains compared to shorter chains.

The apparent separation time may also depend on the position of the detection volume, i.e., on the position of the light beam across the sample with respect to the magnet. If the detection volume is close to the magnet, almost all particles have to cross the light beam and the separation is finished when all the particles have reached the magnet. On the other hand, when the detection volume is at the opposite side of the cuvette, the concentration change will only depend on the particles leaving the detection volume. Thus, the measured concentration is expected to decrease faster in the second case than in the first one. To verify this dependence, measurements were conducted with the 425 nm particle system at an initial concentration of 0.1 mg/ml and for two different positions of the light beam, 4 and 6 mm from the magnet. The results are shown in Fig. 19. The differences in the separation curves and the slightly longer separation time observed close to the magnet can be explained by the fact that when the measurement volume is close to the magnet more particles have to pass through the detection volume,

FIG. 16. Trajectories of 1210 particles along the symmetry axis of the magnet vs time, predicted by the numerical model. The cuvette has an inner width $W_{in}=10$ mm and outer dimensions $W_{out}=12.5$ mm (the cuvette walls are indicated by dashed lines). The magnet pole face is located at $x=0$ mm.

FIG. 17. Concentration of the magnetic particles with diameter 425 nm vs time after the magnet has been placed next to the cuvette wall, from the measurements (continuous line) and from the simulation model based on noninteracting particles (open squares) and interacting particles (i.e., magnetic dipole-dipole and hydrodynamic interactions) (open circles). Initial concentration is 0.1 mg/ml.
and therefore there is a longer decay of the light absorbance despite the fact that in this region there are strong magnetic forces on the particles.

The separation time depends not only on the size of the particles and the viscosity of the carrier liquid the particles are placed in, but also on the external magnetic field that magnetizes the particle and the magnetic field gradient that together with the magnetization of the particles determine the magnitude of the magnetic force on the particles. The magnetic forces on the particles have been varied by changing the distance between the permanent magnet and the cuvette. In this case, both the magnetic field and the magnetic field gradient are changed. The influence of the particle diameter is excluded by measuring only one particle system at one concentration. As expected, when the distance from the magnet to the cuvette increases, the magnetic forces on the particles become weaker, and thus the separation time becomes longer. Figure 20 shows the separation curves of the 425 nm particle system at an initial concentration of 0.3 mg/ml for three different distances between the magnet and the measurement volume (9, 15, and 20 mm). It is interesting to note that the shape of the separation curves is similar for the different magnet-to-sample distances, i.e., the different curves are only stretched out in time. In this figure, each

![Figure 18](image1.png)

**FIG. 18.** Normalized particle concentration vs time for magnetic particles of diameters of 150 nm (a) and 425 nm (b) at particle concentrations of 0.1, 0.2, and 0.3 mg/ml. As can be seen from the figure, there is no strong relation between the particle concentration and the separation time.

![Figure 19](image2.png)

**FIG. 19.** Particle concentration vs time for magnetic particles with diameters of 425 nm at particle concentrations of 0.1, 0.2, and 0.3 mg/ml. As can be seen from the figure, there is no strong relation between the particle concentration and the separation time.

![Figure 20](image3.png)

**FIG. 20.** Particle concentration vs time for magnetic particles of diameter 425 nm at different distances between the magnet and the detection volume. The separation curve for 9 mm distance to magnet is as measured while the separation curves for 15 and 20 mm are compressed in time by 4.5 and 10.5, respectively.
separation curve has been scaled in time by a factor that is constant for each distance between the magnet and cuvette. The separation curve for 9 mm distance to magnet is as measured while the separation curves for 15 and 20 mm are compressed in time by 4.5 and 10.5, respectively.

The scaling behavior, as seen in Fig. 20, tells us that the separation process proceeds along similar lines, with the particle chain building in the beginning of the separation process and then the motion of chains later on, irrespective of the magnitude of the magnetic field and gradient from the magnet. The separation curves for different magnetic forces are only scaled in time by a constant factor (4.5 and 10.5) that depends on the distance between the magnet and the cuvette. We found that the scaling factors are directly related to the magnetic force on the particle system, determined by considering both the magnetic properties of the particle system and the magnetic field gradient, as described in Sec. IV.

VI. CONCLUSIONS

In this paper, we have presented our theoretical and experimental investigation of the motion of magnetic nanoparticles in a magnetic field gradient for particle sizes below 500 nm.

A Brownian dynamics algorithm has been implemented and compared with magnetic separation measurements based on an optical detection method. We have shown that the aggregation of particles into chains due to the magnetic dipole-dipole interactions and the hydrodynamic interactions between the chains play a significant role in the separation process as enhancement factors to accelerate the particles toward the magnet and therefore reduce the separation time.

We have observed that particle interactions cannot be neglected even for very low concentrations (down to 0.1 mg/ml), and they have been included in our numerical model. For particle sizes in the range of 425 nm, the simulated separation time agrees well with the experimental data. By using a Brownian dynamics algorithm rather than a continuous approach (i.e., the diffusion equation), the numerical model presented gives an insight on the interparticle interactions during the separation process and allows good prediction of the separation efficiency as a function of the magnetic properties of the particle system and the magnetic gradient.

Using our optical detection method, we have also shown on the one hand that the separation time depends strongly on the size and magnetic properties of the particles as well as on the magnetic field gradients. On the other hand, the separation time depends only marginally on the particle concentration in solution or on the light beam position.

Moreover, the separation curves for different magnetic forces are only scaled in time by a constant factor, which is directly related to the magnetic force on the particles and on the particle chains. Magnetic separation measurements of magnetic particles using the optical detection method presented here provide an easy and simple method for following and to quantitatively characterizing the separation process. This method can be used with all sorts of different magnetic separation configurations with respect to the magnets and the test tube used in the separation setup, and therefore can help in optimizing magnet configurations and magnetic particle systems used in magnetic bioseparation.

These preliminary results have revealed some of the important factors influencing the magnetic separation of submicrometer magnetic particles but additional work is needed to better understand the separation process of magnetic nanoparticles in a magnetic field gradient.

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