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Magnetic nanoparticles for Magnetic Particle Imaging: from particle characterization to image simulations

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Magnetic nanoparticles for Magnetic Particle Imaging: from particle characterization to image simulations

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Summary

Magnetic Particle Imaging (MPI) is a new medical imaging modality which relies on the visualization of magnetic nanoparticles used as a tracer material, through application of oscillating magnetic fields for detection and field gradients for localization. Magnetic tracer characteristics define the achievable image quality. The goal of this study has been to improve the characterization and understanding of magnetic nanoparticles for use in MPI, and to relate particle characteristics to image quality parameters like sensitivity and resolution. For this purpose, Resovist (a commercially available MRI contrast agent) has been studied. Two important parameters are size and relaxation times of particles. Particle size has been analysed using fractionation techniques, dynamic light scattering (DLS), and vibrating sample magnetometry (VSM). Fractionation experiments indicated a bimodal distribution of particle sizes in Resovist. The distribution of core sizes was determined by fitting a bimodal distribution to the VSM magnetization curve of Resovist, yielding two log-normal peaks with $d_1^* = 8 \pm 1\, \text{nm}$, $\sigma_1^* = 1.9 \pm 0.1$, $d_2^* = 25 \pm 1\, \text{nm}$, $\sigma_2^* = 1.2 \pm 0.1$, a volume ratio between the peaks of $1:0.4 \pm 0.1$ (small to large), and $M_s = (3.5 \pm 0.4) \times 10^5\, \text{A} \cdot \text{m}^{-1}$. Comparison with DLS measurements provided rough estimates for the polymer shell size of $10$-$30\, \text{nm}$. A magneto-optical susceptometer has been developed to study characteristic relaxation times of particles. A magneto-optical susceptibility measurement of Resovist showed relatively good agreement with a magneto-electrical susceptibility measurement. The susceptibility curves needed to be explained by Néel relaxation times. Anisotropy values of either $K_s = (1.9 \pm 0.3) \times 10^5\, \text{J} \cdot \text{m}^{-2}$ or $K_u = (4.4 \pm 1.1) \times 10^3\, \text{J} \cdot \text{m}^{-3}$ were determined from the susceptibility measurements, which can be explained by surface anisotropy or magnetostatic shape anisotropy. It was not possible to determine the relevant type of anisotropy using fractions of Resovist. A model has been proposed to describe the magnetic behaviour of nanoparticles assuming a quasi-fixed orientation of particles. Simulations of spectral components of the magnetization of particles were in good agreement with measured responses of Resovist using Magnetic Particle Spectroscopy (MPS). The proposed model indicates that the optimal size of particles in Resovist is 24-28\, \text{nm} for MPI applications. A tool has been developed to perform image simulations using a simple model to describe Resovist particles. MPI detection levels for Resovist were estimated to be of the order of 0.5\, nmol (Fe) with a resolution of 2\, mm, and 20\, pmol (Fe) with a resolution of 10\, mm, in combination with a temporal resolution of 30\, s. With optimal particles only, sensitivities should be achievable of 50\, pmol (Fe) with a resolution of 1.0\, mm, and 2\, pmol (Fe) with a resolution of 10\, mm.
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Chapter 1
Introduction

Medical imaging techniques are used worldwide in the diagnosis of, among others, cardiovascular diseases and cancer, and have become indispensible tools in today's clinical practice and medical science. These techniques make it possible to “look” inside a human body without cutting the patient open; the methods are thus non-invasive as opposed to the invasive methods such as surgery and endoscopy, which have the potential to cause damage or trauma to the body. Even more important is that medical imaging allows visualization of internal aspects of the body that would not be visible to the naked eye or with a camera. For example functional magnetic resonance imaging (fMRI) makes it possible to obtain images of organ perfusion or blood flow, and positron emission tomography (PET) allows us to obtain images of metabolism or receptor binding. Within the field of medical imaging, molecular imaging is a growing research discipline and is used to follow biological processes at the molecular level.

Magnetic particle imaging (MPI) is a new medical imaging modality invented by scientists from Philips Research and first described in literature in 2005 [1]. MPI offers new possibilities for imaging magnetic tracers with high sensitivity in combination with high temporal and spatial resolution, and may find a variety of applications such as medical imaging, crack detection, polymer processing or fluid dynamics. High resolution and sensitivity of MPI are advantageous for e.g. cardio-vascular imaging and early cancer detection with its fast (real-time) imaging feature, which potentially enables new medical applications. Furthermore, the signal can penetrate tissues virtually unattenuated, allowing the inspection of regions located deeply below the surface. Additionally, MPI does not necessarily require a large scanner. All required magnetic fields may be applied from one side. For a relatively small imaging volume, the scanner itself may be quite small and inexpensive. Finally, the method for localized interaction could be used not only for imaging, but also for therapy by local heating.

The concept of MPI is explained in this chapter after a brief discussion of available medical imaging and of molecular imaging. At the end of this chapter the research goal of this project is stated and an overview of this report is given.

1.1 Medical imaging techniques

Already in 1895, the first medical image was published by Wilhelm Conrad Röntgen; he had made an image of his wives hand using x-rays. The technique Röntgen used is called projection radiography and is still in use nowadays. Since then, more (sophisticated) medical imaging techniques have been developed. Besides projection radiography, the most commonly used imaging modalities are computed tomography (CT), nuclear medicine imaging, ultrasound imaging, and magnetic resonance imaging (MRI). These modalities use different physical principles to perform imaging which are based on, depending on the modality, transmission of x-rays, emission of gamma rays, reflection of ultrasonic sound waves, and spin resonance. A brief overview of the mentioned techniques is presented in appendix A, including the basic principle, applications, advantages, and disadvantages of each technique; more detailed information can be found in literature [e.g. 1.2-1.6].
There exist many applications of medical imaging techniques including imaging of bone injury, dental imaging, brain imaging, imaging of blood arteries and vessels (angiography), imaging of lungs, examination of human breast (mammography), investigation of gastrointestinal and urinary tracks, surgery support, detection of cancer, and visualisation of a foetus during pregnancy. The chosen technique for a certain application depends on characteristics of that technique like imaging performance (for that application), risks, costs, and mobility. Table 1.1 shows a number of these factors for the commonly used imaging modalities, while figure 1.1 provides an indication of achievable sensitivities.

Table 1.1: Comparison of imaging modalities (from [1.4])

<table>
<thead>
<tr>
<th></th>
<th>X-ray</th>
<th>CT</th>
<th>Nuclear</th>
<th>Ultrasound</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial resolution (mm)</td>
<td>0.1</td>
<td>0.25</td>
<td>5-15</td>
<td>1-5</td>
<td>0.3-1</td>
</tr>
<tr>
<td>Examination time</td>
<td>fast</td>
<td>moderate</td>
<td>tracer dependent¹</td>
<td>moderate</td>
<td>long</td>
</tr>
<tr>
<td>Exposure to ionizing radiation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tracer required</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Capital costs</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>moderate</td>
<td>very high</td>
</tr>
<tr>
<td>Mobility</td>
<td>portable</td>
<td>none</td>
<td>none</td>
<td>portable</td>
<td>very limited</td>
</tr>
</tbody>
</table>

Note: (1) Examination time can be lengthy, because of waiting for tracer distribution

![Figure 1.1: Sensitivities of different imaging techniques (from [1.6]).](image)

Image performance parameters also determine the smallest structure (e.g. a tumour or a small blood vessel) which can be visualized. The size of the smallest visible structure is important in the area of molecular imaging, which is discussed in the next paragraph. Important performance parameters which determine this size are sensitivity, spatial resolution, and temporal resolution (the latter being the ability to distinguish two signals in time; this is also related to the required examination time).
1.2 Molecular imaging

Molecular imaging can be broadly defined as the in vivo characterization and measurement of biological processes at the cellular and molecular level. It opens up the possibility of visualizing molecular processes in living organisms without disturbing these processes. While conventional diagnostic imaging produces anatomical or structural images, molecular imaging provides functional or physiological information; therefore, molecular imaging can be used to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these molecular alterations. Molecular imaging should lead to a more fundamental understanding of disease processes, earlier detection and characterization of diseases, and earlier or even direct molecular assessment of treatment effects [1.7]. Nowadays, treatments are often based on the (long term) effects in large populations, and effects for individual patients become clear only after many months. With molecular imaging, treatment effects could be assessed earlier or even during treatment, and the treatment could become more personalized. The multiple and numerous potentialities of this field are applicable to the early diagnosis of diseases such as cancer, neurological diseases (like Alzheimer’s disease), cardiovascular diseases, diabetes, and many others.

To follow biological processes at the cellular and molecular level, specific cells or molecules have to be labelled such that they can be detected with the used imaging modality. These labelled molecules or cells are called probes (or imaging biomarkers) and are able to target specific molecules (“targets”) which are characteristic for a certain disease. Nuclear imaging uses labelling with radionuclides, which is inherent to the technique, and is therefore a typical example of molecular imaging. However, also other techniques can be used for molecular imaging by using contrast agents, which are substances used to enhance the contrast of structures or fluids. Examples of contrast agents are iodine and barium in CT, microbubbles in ultrasound, and gadolinium and iron oxide in MRI. Molecular imaging with MRI is for example used in research to the disease multiple sclerosis (MS), where white blood cells labelled with iron oxide nanoparticles are used [1.8].

To perform successful molecular imaging, several challenges have to be met, both in the area of medicine/biology and in the area of medical imaging techniques. Challenges in the field of biology are: identification of suitable key target molecules for particular diseases; availability of high-affinity probes with reasonable pharmacodynamics; ability of these probes to overcome biologic delivery barriers (vascular, interstitial, cell membrane); and use of chemical or biologic amplification strategies to enhance the image-generating signal [1.7-1.8]. Requirements for molecular imaging techniques are: high sensitivity, high spatial resolution, and high temporal resolution; the latter is needed to prevent motion artefacts, to decrease the time for a patient in a scanner, and to be able to follow the dynamics of biological processes. Nuclear imaging techniques like PET are very sensitive, but the major disadvantages of these techniques is the relatively low resolution and the use of radioactive tracers; these latter expose the patient to ionizing radiation and are also quite expensive due to their short half life time (measured in hours), which requires a short time between production and use. The use of magnetic tracers could be an improvement, since these are in general quite stable and do not expose the patient to ionizing radiation. Detection of magnetic tracers with MRI results in images with high spatial resolution, however, MRI has a lower sensitivity compared to nuclear imaging and it takes a long time to obtain an image. At this point, MPI has a high potency since it is a method for detection of magnetic nanoparticles with high sensitivity and high spatial and temporal resolution.
1.3 Magnetic Particle Imaging

Magnetic Particle Imaging (MPI) makes use of the nonlinear magnetic response of magnetic nanoparticles (used as an imaging agent) to an applied oscillating magnetic field. In general, the challenge of detecting magnetic particles (based on their magnetic moment) is that the field which arises from the magnetic moments of particles is much smaller than the field applied to orient these moments. This problem is circumvented in MPI by application of an oscillating magnetic field with sufficiently high amplitude (the “modulation field”). If the magnetization of the particles is close to saturation in the applied modulation field, the magnetization will exhibit non-linear behaviour, resulting in higher harmonics of the base frequency in the frequency spectrum of the induced magnetization (figure 1.1a). The first harmonic in the frequency spectrum of the measured magnetic induction is mainly due to the applied modulation field, but the higher harmonics provide an indication of the presence of magnetic particles. By means of appropriate filtering, these higher harmonics can be easily separated from the received signal.

After detection, localization of particles is another challenge to be addressed to realize imaging. For this purpose, an additional time-invariant magnetic field is applied. If magnetic particles are exposed to a constant magnetic field with sufficiently large magnitude, the magnetic moment of the particles saturates and thus the harmonics generation is suppressed (figure 1.1b). This suppression can be employed for spatial encoding by superimposing the modulation field on the time-invariant field (“selection field”) that vanishes in the centre of the imaging device, resulting in a “field-free point” (FFP) (figure 1.2a). Magnetic material at the position of the FFP produces a signal containing higher harmonics, but the material outside the FFP does not contribute to signal generation, since this material is magnetically saturated. By steering the FFP through the volume of interest, an image of the spatial distribution of the magnetic material can be generated.

FFP translation across the object could be performed by mechanical movement of the object with respect to the scanner. However, the mechanical movement leads to a low scanning speed and the signal to noise ratio (SNR) is low owing to the weak modulation field. Another way of moving the FFP through the sample is by using two or three (2D/3D image) additional orthogonal homogeneous magnetic fields, called “drive fields” (figure 1.2b). The three components of the selection field can be

![Figure 1.2: Response of magnetic particles to an external field without a field offset (a) and with an offset (b). (From [1.1])](image-url)
cancelled, at any given point in space, by appropriate adjustment of these three fields. By driving each coil pair with a predefined current waveform, the FFP can be moved along a continuous trajectory over the object. This movement of the FFP through the object can be performed at a high frequency. The fast FFP movement leads to a rapid local change in magnetization as soon as the FFP passes a location containing magnetic material. The magnetization change induces a signal that exhibits higher harmonics of the drive field frequencies. This induced signal is detected by recording coils and is sufficient for image reconstruction. The modulation field with low amplitude is now obsolete. The use of drive fields instead of mechanical movement increases both the imaging speed and the SNR.

Typical amplitudes for these drive fields would be 10–20 mT, and a typical frequency of 25 kHz. On the low end, the frequency would be limited due to 1/f-noise. On the high end, field amplitudes up to 20 mT and frequencies up to 100 kHz may be used without harming the patient through heating.

Sensitivity, spatial resolution, and temporal resolution

According to [1.1], the theoretically expected resolution is given by the ratio $2B_k/X_s$, where $B_k$ is the AC field strength at which the material produces substantial higher harmonics, and $X_s$ is the largest spatial derivative of a selection field component. A reasonable value for $B_k$ may be obtained by equating the thermal energy with the Zeeman energy of the magnetic particles; for a 30 nm particle ($M_s=3.4\times10^5$ A·m$^{-1}$) this yields a value of approximately $B_k = 0.9$ mT. In a field gradient of 2.5 T/m a resolution of about 0.7 mm would be achievable. MPI image simulations and experiments have shown comparable values for spatial resolution [1.9-1.10]. Simulations using 30 nm particles showed a resolution of 0.8 mm with an iron concentration in the order of 100 µmol (Fe) L$^{-1}$ for an acquisition time of 40 s or a concentration in the order of 10 mmol (Fe) L$^{-1}$ for an acquisition time of 4 ms. For comparison, for e.g. MRI imaging with Resovist (a commercially available MRI contrast agent) an iron concentration is used of 8 µmol (Fe) kg$^{-1}$ of patient. Assuming that all the iron stays within the blood pool, one would encounter an iron concentration of about 100 µmol (Fe) L$^{-1}$.

Spatial resolution, sensitivity, and imaging speed (or temporal resolution) are interrelated: the sensitivity can be improved by compromising the (spatial) resolution or by using a longer acquisition time. According to [1.1], the sensitivity can be expected to become as low as 20 nmol (Fe) L$^{-1}$ for a resolution of about 1 mm, to be reached by improvements in magnetic tracers and recording.

Figure 1.3: Concept of MPI scanner: the selection field and the FFP are shown in (a); the configuration of the drive field coils is shown in (b) for the case of a 3D scanner. (From [1.2])
electronics. This implies that an amount of $2 \times 10^{-14}$ mol of iron would be detectible. This corresponds to approximately $2 \times 10^4$ iron oxide particles of 30 nm having a total volume of $3 \times 10^{-19}$ m$^3$. As a reference, a cell with a typical size of 10 µm has a volume in the order of $10^{-15}$ m$^3$.

**Magnetic particles**

The achievable image quality depends on the characteristics of the used magnetic nanoparticles. Especially a high susceptibility is important; for particle ensembles with comparable saturation magnetizations, a higher susceptibility implies saturation at lower field amplitudes, and thus a stronger generation of higher harmonics (which implies a better SNR). For nanoparticles (at normal temperatures of 300-310 K), the susceptibility depends mainly on the magnetic moment of a particle, which again depends on the saturation magnetization of the (core) material and on the particle size. Therefore, ensembles with larger particles (of the same material) have a higher susceptibility. Figure 1.4 shows simulated absolute spectral responses for (ensembles of) iron oxide particles of various sizes. The simulations are based on the Langevin function [1.11] and are performed for 10 mT (modulation) field amplitude in combination with a saturation magnetization of $3.4 \times 10^5$ A·m$^{-1}$ (typical for maghemite [1.12]).

So far, magnetic relaxation dynamics have not been considered. However, magnetic nanoparticles have characteristic magnetic relaxation (or remagnetization) times which define responsiveness of particles to a changing magnetic field. The relaxation time varies with particle size and, in general, a larger particle has a longer relaxation time. Therefore, magnetic particles with sizes above a critical size are not able to follow an applied modulation field because of their long characteristic relaxation time. The magnetic moment becomes “blocked” inside the particle and these large particles do not contribute anymore to signal generation. Thus, optimal particles have the largest size at which these particles are still able to follow the applied modulation field.

![Figure 1.4: Simulated absolute responses for iron oxide particles of several sizes.](image-url)
1.4 Research goal & outline

As mentioned above, magnetic tracer characteristics define the achievable image quality for MPI. In particular, a high susceptibility and a short relaxation time are important. Ideally, one would like to employ particles with an optimal particle size. However, in reality a magnetic tracer consists of particles with a distribution in size as well as with distributions of other parameters like shape. Tracer performance could be improved by tuning and optimizing the synthesis of particles and by using fractionation techniques. For tracer optimization, it is very important to be able to characterize the tracer and to understand how these characteristics affect the MPI image quality (in order to provide feedback to the optimization of the tracer).

The goal of this project is to improve the characterization and understanding of magnetic tracers for use in MPI, and to relate particle characteristics to image quality parameters like sensitivity and resolution. For this purpose, Resovist and fractions of Resovist are studied; Resovist is a commercially available contrast agent approved for clinical MRI applications and consists of magnetic iron oxide nanoparticles coated with carboxyldextran (a polysaccharide). The research goal is achieved through several steps. First, fractionation techniques, dynamic light scattering (DLS), and vibrating sample magnetometry (VSM) are used to characterize particle size distribution and magnetic properties; the used characterization techniques are described in chapter 3 together with the analysis results. For characterization of remagnetization dynamics in magnetic particles, a magneto-optical susceptibility setup is developed which provides information on magnetization relaxation and (related) magnetic anisotropy. In chapter 4 this setup is described and magneto-optical experimental results are reported. The non-linear dynamic behaviour of Resovist in typical MPI fields is studied with magnetic particle spectrometry (MPS, in principle a zero-dimensional MPI scanner) and this non-linear behaviour is simulated with (new) particle models in combination with the determined size distribution and anisotropy of Resovist. This work is presented in chapter 5. Finally, the fundamental understanding of magnetization dynamics in magnetic nanoparticles needs to be translated into image quality parameters for MPI. Therefore, simple particle models for Resovist are used in MPI image simulations in order to determine achievable image quality parameters like resolution and sensitivity. Image simulations are described in chapter 6. Conclusions of this work are given in chapter 7. In chapter 2, theoretical aspects of magnetic particle synthesis, their magnetic properties, and magnetization relaxation are considered.
References

Chapter 2
Magnetic nanoparticles

Magnetic fluids (also named ferrofluids) are colloidal suspensions of (ferro- or ferri-)magnetic nanoparticles dispersed in a suitable liquid carrier. The magnetic particles are often stabilized through a coating (or shell) of polymers to prevent the particles from clustering. This core-shell structure is illustrated in figure 2.1A. Figure 2.1B shows two transmission electron microscopy (TEM) images of a ferrofluid. The properties of these particles will be discussed in this chapter, which is divided into three parts: in the first part the synthesis of particles is described, in the second part the magnetic properties will be considered, and the third and last part is devoted to magnetization relaxation mechanisms in magnetic fluids. These relaxation mechanisms are essential to understand how magnetic nanoparticles behave in MPI.

2.1 Particle synthesis

In this part we will consider some general aspects that are related to the synthesis of particles, which are stability requirements, synthesis methods, materials, size distributions, and some clinical aspects.

2.1.1 Stability requirements

A stable colloidal mixture of carrier liquid and magnetic nanoparticles requires both stability against segregation and stability against agglomeration [2.1-2.2]. Gravity tends to pull particles downward which can result in sedimentation of particles, while magnetic field gradients attract particles towards higher-intensity regions of the field which can result in segregation of particles. The larger the sizes of magnetic particles, the more these effects become relevant. However, as long as agglomeration of particles is prevented, sedimentation and segregation are reversible effects. For in vivo applications of nanoparticles these effects are also not very important, since for example blood flow is more important for particle distribution (unless very strong field gradients are applied). Therefore, stability against agglomeration is more important to consider (especially for application of
nanoparticles in-vivo with MPI) and from here, coarse stability criteria against agglomeration are calculated for maghemite ($\gamma$-Fe$_2$O$_3$) nanoparticles at room temperature ($T = 300$ K).

A typical colloidal magnetic fluid contains in the order of $10^{23}$ particles per cubic meter, and collisions between particles are frequent. Hence, if the particles adhere together, agglomeration will be rapid. Particles in a magnetic fluid attract each other because of magnetic dipole and Van der Waals interactions. Agglomeration of particles is opposed by thermal motion, but with increasing particle sizes the attracting forces eventually overcome this thermal motion, and particles start to cluster. The concentration of a ferrofluid determines the average distance between particles and (thus) the rate of collisions; therefore, an increased concentration will accelerate agglomeration.

Van der Waals interactions between particles are only relevant for very short distances between particles relative to their size (the strength of the interaction scales with $r^{-6}$ for distant spheres and $r^{-1}$ for close spheres [2.1]). However, once agglomerated, the energy required to separate two particles is very large. Therefore, it is important that contact between two particles is prevented in order to obtain a stable ferrofluid. Magnetic dipole interactions are also relevant for larger separation distances. Each (single-domain) particle in a ferrofluid has a permanent magnetic dipole moment and maximal attraction between two particles occurs if the moments are aligned. In this case, the energy required to separate two particles with diameter $d$ equals:

$$E_{dd} = \frac{\pi \mu_0 M_s^2 d^3}{9 (l + 2)^3}, \quad (2.1)$$

with $l = 2s/d$ ($s$ is the surface to surface separation distance), magnetic permeability constant $\mu_0 = 4\pi \cdot 10^{-7}$ H·m$^{-1}$, and saturation magnetization $M_s$ [2.1]. As a course stability requirement, $E_{dd}$ should be smaller than the thermal energy $k_B T$ of two particles (with Boltzmann’s constant $k_B = 1.38 \times 10^{-23}$ J·K$^{-1}$). The requirement $E_{dd} \leq 2k_B T$ yields a required separation distance of:

$$s \geq d \left( \frac{3 \pi \mu_0 M_s^2 d^3}{144 k_B T} - 1 \right). \quad (2.2)$$

For maghemite particles ($M_s = 3.4 \times 10^5$ A·m$^{-1}$), the right hand side becomes negative for $d \leq 11$ nm; this implies that magnetic dipole interactions are not strong enough to cause agglomeration between particles smaller than 11 nm in diameter. For particles with diameters of 20 nm and 30 nm, the separation distance $s$ needs to be larger than 17 nm and 52 nm, respectively, in order to prevent agglomeration. The separation distance can be used to calculate a theoretical upper limit for the concentration of a stable ferrofluid, as each particle with diameter $d$ requires at least a volume of $\frac{\pi}{6} (d + s)^3$. For stable ferrofluids containing only particles with a diameter of 20 nm or 30 nm, theoretical concentration limits are, respectively, 12 vol-% and 4 vol-% of maghemite (a density limit of 0.74 for close-packing of spheres has been assumed as well). However, note that this would imply that particles should be perfectly ordered and have no freedom to move. Therefore, realistic concentration limits for stable (monodisperse) ferrofluids are lower.

Thus, in order to limit magnetic dipole and Van der Waals interactions, stable ferrofluids require separation of particles from each other, especially for ferrofluids consisting of relatively large particles (which are interesting for MPI).
2.1. Particle synthesis

2.1.2 Synthesis methods

Two commonly used methods of preparing a magnetic colloid are size reduction and chemical precipitation (which is the formation of a solid in a solution during a chemical reaction) [2.1-2.2]. Size reduction is performed by milling a coarse (micron-sized) powder, often of magnetite, in the presence of a surfactant for long periods of time (~1000 hours). This surfactant consists of polymer chains analogous to soap molecules, one end of which adsorbs on the surface of the magnetic particles while the other end has an affinity with the carrier liquid. The presence of the surfactant makes a large size reduction down to 10 nm possible, and results in each grain being covered by a single polymer layer. This layer stabilizes the magnetic fluid by isolating particles from each other.

There are many chemical methods to prepare a magnetic fluid. In case of chemical precipitation, the process starts with the precipitation of nanoparticles from dissolved salts, normally ferrous chloride (FeCl₂) and ferric chloride (FeCl₃) for the case of iron oxide particles. A possible precipitation reaction for magnetite (Fe₃O₄) particles is

\[ 5\text{NaOH} + 2\text{FeCl}_3 + \text{FeCl}_2 \rightarrow \text{FeO} \cdot \text{Fe}_2\text{O}_3 + 5\text{NaCl} + 4\text{H}_2\text{O}, \]  

(2.3)
in which magnetite is written as FeO · Fe₂O₃ to emphasize the occurrence of divalent and trivalent iron atoms in it. The ratio of the added salts can influence the properties of the precipitated particles like composition and size. After mixing the salts, the mixture needs to be stabilized by separating particles from each other (called peptization). Separation is achieved by steric repulsion through the use of a surfactant, by electrostatic repulsion through charging the surface of the particles, or by a combination of both. After this step, other steps can be performed like magnetic separation, filtration, or concentration/dilution. In general, chemical methods are simpler, faster, and cheaper than mechanical ones. The advantage of size reduction is that it can be applied to more types of compounds.

2.1.3 Materials

The core of magnetic nanoparticles is composed of a magnetic material. The ferromagnetic elements Fe, Co, and Ni can be used as core materials, but more often ferrites are used like γ-Fe₂O₃, Fe₃O₄, CoFe₂O₄, or Zn₀.₅Mn₀.₅Fe₂O₄ (which are ferromagnetic). The iron oxides maghemite (γ-Fe₂O₃) and magnetite (Fe₃O₄) are the most commonly used core materials.

The polymer shell of nanoparticles is used for solubility and stability improvement, but may also influence other properties of ferrofluids like viscosity, distribution of particle sizes (set upon particle synthesis), surface properties of the magnetic cores, or biocompatibility [2.4]. Examples of shell materials used for aqueous solutions are the polysaccharides dextran, starch, chitosan, and ficoll, and the synthetic polymers polyethyleneimine and polyvinylpyrrolidone. Examples of surfactants used for organic solvents are oleic acid, perfluoropolyether acid, and polyphosphoric acid derivates.

Usually organic solvents, like hexane and kerosene, or water are used as a carrier liquid for magnetic fluids. The chosen solvent is related to the used surfactant, and also depends on the application of the ferrofluid. The use of a ferrofluid as an imaging agent requires an aqueous solution with additives to preserve the homeostasis in the human body.
Chapter 2. Magnetic nanoparticles

Maghemite and magnetite

The iron oxides maghemite and magnetite have a similar crystal structure; both crystallize in the inverse spinal structure [2.3]. The large oxygen ions are close packed in a cubic arrangement and the smaller iron ions fill in the gaps. Two types of gaps can be distinguished: a tetrahedral site where the iron ion is surrounded by four oxygen ions (A-sites) and an octahedral site where the iron ion is surrounded by six oxygen ions (B-sites). Magnetite contains both divalent and trivalent iron ions and can be represented as \( [Fe^{3+}]_4 [Fe^{2+}, Fe^{3+}]_8 O_4^2- \). Maghemite contains only trivalent iron and can be represented as \( [Fe^{3+}]_4 [Fe^{3+}_{5/3}, \Delta_{1/3}]_8 O_4^2- \) (\( \Delta \) represents ion vacancies). The similarities in structure between maghemite and magnetite make it difficult to distinguish between both types of iron oxide. A number of properties of maghemite and magnetite are listed in table 2.1.

<table>
<thead>
<tr>
<th>Material: (^{\gamma})-Fe(_2)O(_3)</th>
<th>Magnetite (\text{Fe}_3\text{O}_4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Density (kg/m(^3))</strong></td>
<td>(5.18 \times 10^3)</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
<td>Cubic</td>
</tr>
<tr>
<td><strong>Cell dimensions (nm)</strong></td>
<td>(a = 0.8396)</td>
</tr>
<tr>
<td><strong>Colour</strong></td>
<td>black</td>
</tr>
<tr>
<td><strong>Curie temperature (K)</strong></td>
<td>850</td>
</tr>
<tr>
<td><strong>Saturation magnetization</strong> (at 300 K) (A/m)</td>
<td>4.8-5.2 x 10(^5)</td>
</tr>
<tr>
<td><strong>Critical size SD to PSD(^1) (nm)</strong></td>
<td>30-100</td>
</tr>
<tr>
<td><strong>Magnetic structure</strong></td>
<td>ferrimagnetic</td>
</tr>
</tbody>
</table>

Note: (1) SD means single domain, PSD means pseudo-single domain

2.1.4 Size distribution

Most ferrofluids consist of nanoparticles with different sizes; these ferrofluids are polydispersed, as opposed to monodispersed ferrofluids which would contain particles of only one size. The size distribution of polydispersed particles is in general not well described by a symmetric Gaussian (or normal) distribution, but an asymmetric (or skewed) distribution has to be applied. Both log-normal and gamma distributions are used for fitting, of which the log-normal distribution appeared to fit magnetite particles in hydrocarbon oil somewhat better [2.5]. However, the log-normal distribution seems to overestimate to some extent the concentration of large particles [2.6]. The origin of the log-normal distribution is found in the synthesis process of nanoparticles, which consists of nucleation and growth. This growth can be described by coalescence, a process in which two phase domains of essentially identical composition come into contact with each other and form a larger
2.1. Particle synthesis

A statistical description of coalescence leads to a log-normal distribution of particles sizes [2.7]. The log-normal distribution function can be written as

$$f(x) = \frac{1}{x \sigma \sqrt{2\pi}} \exp\left(-\frac{(\log x - \mu)^2}{2\sigma^2}\right),$$

in which $\mu$ and $\sigma$ are the mean and standard deviation of $\log x$, respectively. Characterization of $x$ is given by the geometric mean (and median) $\mu^* = \exp(\mu)$ and the multiplicative standard deviation $\sigma^* = \exp(\sigma)$. A confidence interval of 68.3% is given by the interval $[\frac{\mu}{\sigma^*}, \mu^* \times \sigma^*]$ [2.8].

2.1.5 Clinical aspects

Medical imaging, hyperthermia, and targeted drug delivery are all (potentially) interesting biomedical applications of magnetic nanoparticles. Even a combination of all named applications might be possible. The use of magnetic fluids for in vivo applications requires addressing a number of clinical aspects like safety, toxicity, biocompatibility, biodegradation, blood circulation time, targeting, pharmacokinetics (i.e. what the body does to the particles or, in general, to the administered substance), pharmacodynamics (i.e. what the particles do to the body), etc. A review of all these aspects is beyond the scope of this report, though, with respect to the capabilities of MPI, it is useful to very briefly discuss targeting, pharmacokinetics, biocompatibility, and allowed doses.

A number of applications (e.g. detection of tumours) require targeting of particles. Targeting can be performed through natural uptake in the body, by coating with recognizing moieties (e.g. antibodies), by incorporation in larger entities (like cells or liposomes), or by using physical stimuli (e.g. magnetic fields) [2.9]. After (intravenous) administration the magnetic nanoparticles need to circulate in the blood long enough to accumulate at target sites, but should be cleared from the body at a reasonable rate to avoid long-term accumulation. The pharmacokinetics of particles are strongly influenced by size and surface properties (e.g. charge) [2.9]. Figure 2.2 gives a qualitative overview of the relation between blood residence time and particles size for iron oxide particles. The relation between pharmacokinetics and particle size may have important implications, since particles with an optimal size to generate a high spectral response in MPI are not necessarily particles with optimal pharmacokinetics.

Other important aspects are biocompatibility and toxicity. Because of their good biocompatibility, often iron oxide particles coated with polysaccharides (e.g. Resovist) are used for in-vivo applications. Toxicity also appears to depend on particle size: a higher cytotoxicity was observed for large magnetic particles than for smaller ones [2.9]. Toxicity and biocompatibility of particles determine the allowed dose for medical applications. The allowed dose is important since this determines the required sensitivity for most imaging applications (e.g. angiography). For Resovist, the allowed dose for MRI applications is 700 $\mu$mol of iron for adults (>65 kg); this corresponds to a dose of approximately 10 $\mu$mol Fe kg$^{-1}$ of body weight. A dose of 20 $\mu$mol Fe kg$^{-1}$ showed no changes in peripheral blood pressure or heart rate in rabbits, while an acute lethal dose in excess of 10 mmol Fe kg$^{-1}$ was determined in mice and rats [2.10]. As a reference, naturally healthy adults contain a total amount of iron (in haemoglobin) between 3 to 5 gram (approximately 1 mmol Fe kg$^{-1}$).
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Overall, key parameters that determine the performance of magnetic particles in clinical applications are surface chemistry, particle size, core material, and magnetic properties. Until here we have been discussing general properties of magnetic nanoparticles, but from this point we will focus on their magnetic properties.

2.2 Magnetic properties

The magnetic properties of magnetic nanoparticles will be described here. Some basic types of magnetism are discussed and the concepts of magnetic anisotropy, magnetic domains, superparamagnetism, and magnetization curves are explained.

2.2.1 Types of magnetism

A material placed in an applied magnetic field \( H \) (SI-unit: A/m) will exhibit a magnetization \( M \) (A/m), which is the sum of all magnetic dipole moments \( m \) per volume \( M = \sum m / V \). The relation between the applied magnetic field and the induced magnetization is characterized by the dimensionless magnetic susceptibility (tensor) of a material, defined as

\[
\chi = \frac{M}{H} \quad (2.5)
\]

The initial susceptibility \( \chi_i \) is \( \chi \) in the limit \( |H| \to 0 \). The magnetic field and magnetization give rise to a magnetic induction \( B \) (Tesla) defined as

\[
B = \mu_0 (H + M) = \mu_0 H \cdot (1 + \chi), \quad (2.6)
\]

with \( \mu_0 = 4\pi \times 10^{-7} \text{H} \cdot \text{m}^{-1} \) the permeability of free space.

Figure 2.2: Qualitative figure of blood residence time of iron oxide nanoparticles as a function of particle size (from [2.9]).
The strength and direction of the induced magnetization depend on the type of magnetism. The most common types of magnetism are diamagnetism, paramagnetism, antiferromagnetism, ferromagnetism, and ferrimagnetism [2.11-2.12]. An overview of these types of magnetism is presented in figure 2.3. The last three mentioned types of magnetism are due to a long-range ordering of atomic spins as a result of strong interactions between neighbouring spins (exchange interactions). If these exchange interactions are positive, i.e. causing neighbouring spins to align parallel, this gives rise to ferromagnetism. Negative exchange interactions cause anti-parallel alignment, which results in anti-ferromagnetism for equal spins, and in ferrimagnetism for spins with different magnitudes. Maghemite and magnetite are examples of ferrimagnetic materials. In magnetite, with structural formula \( [\text{Fe}^{3+}]_A[\text{Fe}^{2+}, \text{Fe}^{3+}]_B \text{O}_4^{2-} \) (see section 2.1.3), spins of iron ions on A-sites are aligned anti-parallel with spins on B-sites. The spins of the trivalent ions cancel and the net magnetic moment of the material results from the ordering of divalent iron ions. Ferrimagnetism exhibits the same macroscopic behaviour as ferromagnetism, and from here we will refer to ferromagnetism for both types of magnetism. The ordered types of magnetism disappear above a certain temperature, which is the Curie temperature \( T_C \) for ferromagnetic materials and the Néel temperature \( T_N \) for anti-ferromagnetic materials. Above these temperatures, materials become paramagnetic. Another type of magnetism is superparamagnetism, which will be discussed later on.

![Figure 2.3: Types of magnetism (from [2.12]).](image)

### 2.2.2 Magnetic anisotropy

In many materials the magnetization has a preferred orientation (called easy axis or easy plane) and therefore not necessarily aligns with the applied magnetic field. In bulk materials this magnetic anisotropy is mainly caused by magnetostatic energy or by the asymmetry of the magnetocrystalline energy, but in magnetic nanoparticles also surface effects that give rise to magnetic anisotropy become important. Magnetic anisotropy plays an important role in the formation of domains and in magnetic relaxation processes; both processes are discussed later on.
Magnetocrystalline anisotropy

Magnetocrystalline energy (due to the crystal structure of a material) can show various symmetries, but uniaxial and cubic forms cover the majority of cases. For uniaxial anisotropy, the anisotropy energy is given by

$$E_{cr} = V(K_0 + K_1 \sin^2 \theta + K_2 \sin^4 \theta + \ldots),$$

while for cubic symmetry

$$E_{cr} = V \left( K_0 + \frac{K_1}{4} (\sin^2 2\theta + \sin^4 \theta \sin^2 2\varphi) + \frac{K_2}{16} \sin^2 \theta \sin^2 2\theta \sin^2 2\varphi + \ldots \right),$$

with volume $V$, anisotropy constants $K_n$, and angles $\theta$ (zenith) and $\varphi$ (azimuth) between directions of the magnetic moment and of the easy axes (or normal to the easy plane) [2.13].

Magnetostatic shape anisotropy

If a magnetic body of finite size is magnetized, free magnetic poles are induced on the outsides of the sample which give rise to a magnetic field in the opposite direction of the magnetization. The demagnetization field can be expressed analytically for a uniformly magnetised ellipsoid:

$$\mathbf{H}_d = \mathbf{N} \cdot \mathbf{M},$$

with tensor $\mathbf{N}$ containing demagnetization constants [2.1]. For axes coincident with the symmetry axes of the ellipsoid, this tensor is diagonal with $N_{xx} + N_{yy} + N_{zz} = 1$. The demagnetization gives rise to shape anisotropy which is expressed for an ellipsoid of revolution (around axis $\mathbf{R}$) as:

$$E_{sh} = V \frac{\mu_0}{2} M_s^2 (N_\perp - N_\parallel) \sin^2 \theta,$$

with $\theta$ the angle between $\mathbf{M}$ and $\mathbf{R}$, and $N_\perp$ and $N_\parallel$ demagnetization factors perpendicular and parallel to $\mathbf{R}$, respectively [2.13]. For a prolate ellipsoidal particle ($\mathbf{R}$ is the major axis) $N_\perp > N_\parallel$ and the magnetization has a preference to align with the major axis; expressions for $N_\perp$ and $N_\parallel$ can be found in [2.14]. For a (hypothetical) spherical particle ($N_\perp = N_\parallel = 1/3$) $E_{sh}$ becomes zero.

Surface anisotropy

The existence of a surface leads to magnetostatic shape anisotropy because of the free poles at the surface. Another type of anisotropy related to the surface is caused by a superficial energy, due to interactions of the atoms at the surface with its surroundings [2.11]. For an ellipsoid of revolution this energy can be expressed as

$$E_{su} = SK_s F(e) \sin^2 \theta,$$

with surface $S$, anisotropy constant $K_s$, and $F(e)$ a function of the ellipticity $e = \sqrt{1 - b^2/a^2}$, with $2a$ and $2b$ the lengths of major and minor axes, respectively [2.11-2.13]. For small $e$ this function is approximately $F(e) = (4/15)e^2 + (32/315)e^4$ [2.13]. Depending on the surface interactions, $K_s$ is either positive or negative, which gives an easy axis parallel to the long axis or a perpendicular easy plane, respectively [2.11-2.12]. $|K_s|$ is generally of the order of magnitude of $10^{-4}$-10$^{-3}$ J·m$^{-2}$ [2.11] and surface imperfection could as well lead to higher order terms [2.13].
2.2. Magnetic properties

Strain anisotropy is another type of magnetic anisotropy which scales with the surface and is due to magnetostriction [2.13]. We will not discuss this type further, because this type is generally less important.

Total anisotropy

Often the anisotropy in materials is characterized by the uniaxial type with one effective (volume related) anisotropy constant:

\[ E_A = VK \sin^2 \theta. \] (2.12)

In actual materials the anisotropy is generally more complex and may involve all mentioned types of anisotropy (thus \( E_A = E_{cr} + E_{sh} + E_{su} \)), including higher order terms. An interesting situation occurs for \( K_s < 0 \) and if magneto-crystalline anisotropy can be neglected (in first instance). The relevant anisotropies in this case are surface anisotropy and magnetostatic shape anisotropy, which are both uniaxial, but (in this case) of opposing sign. At a critical particle size these contributions would cancel each other [2.13]:

\[ \frac{4}{15} e^2 |K_s| S_c = \frac{\mu_0 |m|^2}{2 V_c} (N_\perp - N_\parallel). \] (2.13)

In this situation, the particle would have an easy plane characterized by the surface anisotropy below the critical size and an easy axis characterized by the shape above. Around the critical size the magnetocrystalline anisotropy, which was neglected in first instance, becomes the dominating type of anisotropy.

2.2.3 Magnetic domains

Though ferromagnetism gives rise to spontaneous magnetization, a piece of ferromagnetic material is not necessarily magnetized. This is due to the formation of regions with homogeneous magnetization, called (Weiss) domains, which are separated by domain walls (or Bloch walls). Domains have varying orientations which result in a zero net magnetization of the material in equilibrium. As soon as a (sufficient strong) magnetic field is applied, domain walls start to shift causing a net magnetization in the direction of the applied field. Depending on the magnetic anisotropy, the material may remain in this magnetized state for a very long time even if the applied field is removed; this effect is called hysteresis.

Domain size

Spins gradually change orientation in a Bloch wall, which requires energy because of the change in orientation between neighbouring spins (exchange interaction) and, in case of magnetic anisotropy, deviations from the preferred direction of magnetization. On the other hand, the domain structure lowers the magnetostatic energy (lower demagnetization field) and may also lower the anisotropic energy at the surface or in a multicrystalline structure. Including the energy related to the field \( \langle E = -m \cdot B \rangle \), the domain structure is mainly influenced by these four types of energy. Other contributions could arise from magnetostriction or crystal impurities and imperfections.
In case of a nanoparticle, there exists a critical crystal size below which it is not favourable anymore to form a multi-domain structure. Below this critical size the particle becomes single-domain. For spherical crystals this characteristic diameter is given by

\[ d_{sd} = \frac{18E_\phi}{\mu_0 M_S^2} \]  

(2.14)

with saturation magnetization \( M_S \) and total domain wall energy per unit area \( E_\phi \approx 2\sqrt{K/\Delta} \), with anisotropy energy constant \( K \) and exchange energy density parameter \( \Delta \) [2.13]. Typical values for \( d_{sd} \) are about 30 nm for iron, 70 nm for Co, and 30-100 nm for the iron oxides magnetite and maghemite [2.3,2.13]. Between the single-domain and multiple-domain phase, a pseudo-single-domain phase may exist in which magnetization is not uniform anymore, but neither a two-domain phase has formed [2.3,2.15].

### 2.2.4 Superparamagnetism

Single-domain magnetic nanoparticles have a permanent magnetic moment. In an ensemble of particles, however, individual moments are aligned randomly due to thermal motion, which causes a zero net moment. Upon the application of a magnetic field the individual moments start to align with the field and create a net moment. When the applied field is removed this net moment will drop back to zero again. The timescales of these magnetization processes depend on the size of the particles, and are either due to rotation of the magnetic moment within the particle or due to rotation of the particle as a whole. We will come back to these processes in section 2.3, but for now we note that small particles relax in general faster than larger particles. If the magnetization relaxation occurs within the timescale of a measurement (or often a second is taken), the magnetization of the ensemble behaves like a paramagnetic material, but with magnetization strengths of ferromagnetic materials. Therefore, this type of magnetization is called superparamagnetic. A distinction can be made between intrinsic superparamagnetism due to internal rotation of the magnetic moment and extrinsic superparamagnetism due to external rotation of a particle as a whole. In case the size of particles allows intrinsic superparamagnetism, these particles are called superparamagnetic.

Equilibrium magnetization curves of superparamagnetic (and paramagnetic) materials can be modelled using a quantitative model, developed by Langevin, based on a classical description in which the magnetic moment of each atom (paramagnetism) or particle (superparamagnetism) can take any direction [2.11-2.12]. If a moment \( \mathbf{m} \) has energy \( E(\mathbf{e}) \) for a certain orientation \( \mathbf{e} = \mathbf{m}/|\mathbf{m}| \), the probability of that orientation is proportional to the Boltzmann factor \( \exp(-E(\mathbf{e})/k_BT) \). The thermal average of the magnetization of an ensemble of particles is given by

\[
\mathbf{M} = M_S \frac{\int \mathbf{e} \exp\left(-\frac{E(\mathbf{e})}{k_BT}\right) d\mathbf{e}}{\int \exp\left(-\frac{E(\mathbf{e})}{k_BT}\right) d\mathbf{e}}.
\]

(2.15)

If particles are free to orient as a whole, anisotropy energies can be neglected (these average to zero) and the only relevant energy term is the Zeeman energy [2.11-2.12]:

\[ E_Z = -\mathbf{m} \cdot \mathbf{B} \]

(2.16)
A combination of equations 2.15 and 2.16 leads to:

$$|\mathbf{M}| = M_S \mathcal{L}(\xi) = M_S \left( \coth \xi - \frac{1}{\xi} \right)$$

(2.17)

with Langevin function $\mathcal{L}$ and energy ratio $\xi = mB/k_B T$. The direction of $\mathbf{M}$ is along the direction of the magnetic induction $\mathbf{B}$.

In case particles are not free to orient as a whole, the model can be extended by adding an anisotropy term to the energy. For a single easy axis direction, equation 2.15 can be applied directly; for a distribution of easy axes directions, averaging over all easy axes directions needs to be performed as well. In a similar way, it is also possible to calculate the distribution of easy axes in case particles are free to orient. We will come back to this in chapter 5.

### 2.3 Magnetization relaxation

When the magnetic field applied to a magnetic material is changed, the equilibrium condition of the magnetization in the material is changed as well. At this point the magnetization needs to relax towards a new equilibrium. In a multi-domain structure this relaxation is performed by the movement of domain walls. In a single-domain particle relaxation of the magnetic moment is due to internal relaxation (Néel relaxation) or external relaxation (Brownian relaxation). In this section these last two types of relaxation are discussed. Also dynamic susceptibility will be considered.

#### 2.3.1 Internal relaxation

The magnetic moment $\mathbf{m}$ of an electron is related to (spin and orbital) angular momentum $\mathbf{L}$ of an electron, and this relation is characterized by the gyromagnetic ratio $\gamma = \mathbf{m}/\mathbf{L}$. The value of $\gamma$ for an electron is $1.76 \times 10^{11}$ s$^{-1}$ T$^{-1}$ [2.16]. From equation 2.16 we know that a magnetic moment tries to align with a magnetic field. However, this alignment is opposed by the angular momentum, which causes the magnetic moment to precess around the magnetic field. In a particle the moments of precessing electrons will eventually align with the field due to collisions between precessing electrons. This precession is described by the Landau-Lifshitz-Gilbert equation:

$$\dot{\mathbf{M}} = \gamma \mathbf{M} \times (\mathbf{H}_{\text{eff}} - \eta \dot{\mathbf{M}}) = \gamma \mathbf{M} \times \mathbf{H}_{\text{eff}} - \frac{\alpha}{M_S} \mathbf{M} \times \dot{\mathbf{M}}$$

(2.18)

with $\mathbf{H}_{\text{eff}} = -\partial U/\partial \mathbf{M}$ (in which $U$ is the free energy per unit volume), $\eta = \alpha/\gamma M_S$ and $\alpha$ a damping constant representing alignment due to collisions [2.17]. Reported damping constants for magnetic nanoparticles are in the range 0.05-0.5 [2.18]. Without anisotropy, the characteristic time of the orientation diffusion of $\mathbf{M}$ is given by

$$\tau_D = \frac{V}{k_B T} \frac{M_S 1 + \alpha^2}{\gamma 2\alpha}$$

(2.19)

where $V$ is the volume of a particle [2.14]. The relaxation time $\tau_D$ is minimal for $\alpha = 1$, and in this case for a 30 nm maghemite particle (with $M_S$ is $3.4x10^5$ A/m and at 300 K) $\tau_D = 6.6 \times 10^9$ s. For $\alpha = 0.1$, $\tau_D = 3.3 \times 10^8$ s.
In most cases, however, anisotropy needs to be taken into account. The effect on the relaxation time is illustrated in figure 2.4 for a nanoparticles with uniaxial anisotropy and an easy axis parallel to the field. Suppose that a magnetic field was applied in an equilibrium situation and most particles were aligned with the field. As soon as the direction of the magnetic field is reversed, most particles will have their moments anti-parallel with the field. The anti-parallel state is less energetically favourable than the parallel states, as illustrated in figure 2.4, but to reach the parallel states these particles have to cross an energy barrier $E_B$. The probability of crossing this barrier is proportional to $\exp(-E_B/k_BT)$. For $E_B \gg k_BT$ and for $E_B \gg mB/2$, a characteristic relaxation time for reversal of a magnetic moment along the easy axis (for uniaxial anisotropy) was derived by Néel:

$$\tau_N = \tau_0 \exp \left( \frac{E_B}{k_BT} \right)$$

with $\tau_0 \sim \tau_D$ depending on various parameters including the anisotropy and relaxation paths [2.13]. For $\sigma = E_B/k_BT > 3$ and without applied field, $\tau_0$ is quite accurately described by

$$\tau_0 = \tau_D \left( \frac{\sqrt{\pi}}{2} \right) (\sigma)^{-3/2} \left( 1 + \frac{1}{\sigma} \right).$$

More expressions for $\tau_0$ are found in literature [2.13-2.14], but often a value of $10^{-9}$ s is assumed, since the exponential term in the relaxation time $\tau_N$ is most important.

For the calculation of the Néel relaxation time often $E_B = KV$ is assumed, which is only valid in case of uniaxial (volume) anisotropy and small fields (i.e. $B \ll 2K/M_S$). Expressions for $E_B$ in case of cubic anisotropy are found in [2.13]. Based on the energy barrier three regimes can be distinguished: $E_B \ll k_BT$, the energy barrier is easily overcome due to thermal fluctuations and particles behave superparamagnetic up to very high frequencies (GHz); $E_B \sim k_BT$, whether the barrier will be crossed depends on the measurement time and the magnetization response with some delay to variations of the applied field; $E_B \gg k_BT$, the magnetic moment is “blocked” within the particle and aligned with the easy axis, magnetization relaxation is only possible due to external relaxation (or to a limited extend due to intrawell relaxation [2.19]).
2.3. Magnetization relaxation

Internal relaxation of maghemite nanoparticles in case of crystalline anisotropy only

Maghemite has a cubic crystalline structure with $K_1 = -4.7 \times 10^3 \text{ J/m}^3$ and $K_2 > -(9/4)K_1$, in which situation the energy barrier (due to crystalline anisotropy) approximately becomes [2.13]:

$$E_B = -V \frac{K_1}{4K_2^2}(2K_1 + K_2)^2. \quad (2.22)$$

Since $K_2$ is not exactly known, the limiting situations $K_2 = -(9/4)K_1 = 1.1 \times 10^4 \text{ J/m}^3$ and $K_2 \to \infty$ are considered. The energy barrier therefore ranges between $15V < E_B < 1.2 \cdot 10^3V$. For MPI we are interested in the maximum size of nanoparticles in an ensemble of which the magnetization would still be able to follow the frequency $f$ of the applied field, which is typically 25 kHz. Using equation (2.20) with $\tau_0 = 10^{-9} \text{ s}$ and requiring $2\pi f \tau_N = 1$, the calculated barrier heights indicate a maximum particle size in the range of $38.6 - 167 \text{ nm}$. Note that only in (hypothetical) spherical particles only crystalline anisotropy is relevant, and that for the actual calculation of relaxation times in maghemite nanoparticles also shape and surface anisotropy have to be considered.

2.3.2 External relaxation

The magnetic moment of a particle in a liquid carrier could also become aligned with the magnetic field by rotation of the particle as a whole. The characteristic time of this process is given by the Brownian relaxation time for relative small fields (i.e. $mB \ll k_BT$):

$$\tau_B = \frac{3\eta V_h}{k_BT}, \quad (2.23)$$

in which $\eta$ is the viscosity of the liquid and $V_h$ the hydrodynamic volume of the particle (the size of the particle including the polymer shell and a hydrodynamic layer) [2.14,2.20-2.21]. Equation 2.23 is derived assuming that thermal rotational fluctuations are opposed by viscous forces, and is therefore only valid for small fields [2.21]. For stronger fields, the characteristic relaxation time is determined by magnetic torque opposed by viscous forces.

The actual relaxation time of a magnetic moment is due to a combination of Brownian and Néel relaxation times. An effective relaxation time $\tau_{eff}$ is calculated by [2.17,2.20]

$$\frac{1}{\tau_{eff}} = \frac{1}{\tau_B} + \frac{1}{\tau_N}. \quad (2.24)$$

2.3.3 Dynamic susceptibility

In section 2.2.1 the initial magnetic susceptibility was defined as the ratio between magnetization and applied field (equation 2.5) in the limit $|\mathbf{H}| \to 0$, which for nanoparticles in equilibrium gives a simple ratio depending on particle diameter and on temperature. In a dynamic field, however, the magnetization does not immediately follow the applied field, but rather shows a delay with respect to the field corresponding to the (effective) relaxation time. A complex (initial) susceptibility needs to be used to describe the relation between field and magnetization. A relation between complex
(initial) susceptibility and relaxation time can be derived easily (for $|H| \to 0$, thus for small fields far away from the saturation field).

Assume that an oscillating field $H = H_0 \exp(i\omega t)$ is applied (with angular frequency $\omega = 2\pi f$ in rad·s$^{-1}$), in which case the magnetic response will be $M = \chi H = (\chi' + i\chi'')H_0\exp(i\omega t)$. Further it is assumed that the rate of change of the magnetization is proportional to:

$$\frac{dM}{dt} = \frac{M_{eq} - M}{\tau},$$

(2.25)

with $M_{eq} = \chi_0 H$ the magnetization in equilibrium and $\chi_0$ the (initial) susceptibility in equilibrium. If now the expressions for $H$ and $M$ are filled in and both sides are divided by $H_0\exp(i\omega t)$, this gives:

$$i\omega\chi = \frac{\chi_0 - \chi}{\tau} \Rightarrow \chi(\omega) = \frac{\chi_0}{1 + i\omega\tau}.$$

(2.26)

For applied fields which are not sinusoidal, a Fourier transform of $H$ and a convolution with $\chi(\omega)$ can be applied to calculate the corresponding magnetization [2.1].

To calculate the dynamic susceptibility in a magnetic fluid, the distribution of easy axes orientations (due to anisotropy) has to be taken into account. In a magnetic fluid with rotational freedom of the particles, the easy axes of particles are distributed in all directions due to thermal fluctuations. For the calculation of magnetization or susceptibility in equilibrium (and in the linear regime), the distribution of easy axes can be neglected and calculations are performed using the Langevin function (section 2.2.4) as if there was no anisotropy [2.17]. However, in a dynamic situation this distribution becomes important, because of the difference in energy barrier between particles with their easy axes aligned and perpendicular to the field. This is illustrated in figure 2.5, which shows energy potentials for particles with their easy axes parallel (top-left) and perpendicular (bottom-left) to the field, and magnetization curves corresponding to these potentials assuming uniaxial anisotropy (right); the curves in figure 2.5 (on the right) are calculated using equation 2.15 and by adding an anisotropy energy term to the Zeeman energy (equation 2.16).

An expression for the dynamic susceptibility in weak fields is obtained by:

$$\chi = \frac{1}{3} \left( \frac{\chi_0||}{1 + i\omega\tau||} + \frac{2}{1 + i\omega\tau_\perp} \right) \approx \frac{1}{3} \left( \frac{\chi_0||}{1 + i\omega\tau||} + 2\chi_0\perp \right),$$

(2.27)

with relaxation times $\tau||$ and $\tau_\perp$, and initial susceptibilities $\chi_0||$ and $\chi_0\perp$ for $\omega \to 0$, calculated for particles with their easy axis parallel or perpendicular, respectively [2.14]. Since the magnetic moment in particles with their easy axis perpendicular to the field experiences no energy barrier between energy minima for opposing field directions, the perpendicular relaxation time can be neglected for moderate frequencies ($f<10^6$).
2.3. Magnetization relaxation

2.3.4 Accuracy of relaxation times

The Néel relaxation time (equation 2.20) and the Brownian relaxation time (equation 2.23) are valid only for relatively small fields: the Néel relaxation time requires $B \ll 2K/M_S$, for $M_S = 3.4 \cdot 10^5 \text{ A} \cdot \text{m}^{-1}$ and $K = 5 \cdot 10^3 \text{ J} \cdot \text{m}^{-3}$ the critical field is 29 mT; the Brownian relaxation time requires $B \ll k_BT/m$, for $M_S = 3.4 \cdot 10^5 \text{ A} \cdot \text{m}^{-1}$, $d = 30 \text{ nm}$, and $T = 300 \text{ K}$ the critical field is 0.9 mT. For dynamic susceptibility measurements, which are described in chapter 4, field amplitudes are typically in the order of 0.5 mT and the Brownian and Néel relaxation times are considered to be sufficient accurate. The dynamic susceptibility can be described (for a certain particle size) using equation 2.27 with $\tau_{||}$ an effective relaxation time (equation 2.24) determined by the Néel and Brownian relaxation times.

Because the non-linear behaviour of nanoparticles is of interest for MPI applications, field amplitudes are used of typically 10-20 mT. This implies that the Brownian relaxation time is not valid, and that the use of the Néel relaxation time becomes critical. More accurate calculations of magnetic relaxation processes can be performed using the Fokker-Planck equation [2.13-2.14,2.17,2.21], which allows taking a distribution of easy axes orientation in account as well. However, these calculations are out of the scope of this report.

We will come back to the problem of describing the magnetization relaxation in nanoparticles in chapter 5, were models are discussed to describe the behaviour in magnetic fields characteristic for MPI. In the next two chapters characterization of actual magnetic fluids will be discussed. The measured characteristics will be used for the evaluation of the models described in chapter 5.

Figure 2.5: Left: illustrative energy potentials for particles with easy axis aligned with the field (top) or perpendicular to the field (bottom). Right: magnetization curves for particles, assuming a diameter of 30 nm, $M_S = 3.4 \cdot 10^5 \text{ A} \cdot \text{m}^{-1}$, and $K = 5 \cdot 10^3 \text{ J} \cdot \text{m}^{-3}$ (for uniaxial anisotropy).
References

Chapter 3
Sample characterization

In this chapter characterization of the ferrofluid Resovist (a commercially available MRI contrast agent) using available analysis techniques is presented. Fractionation techniques, dynamic light scattering (DLS), and vibrating sample magnetometry (VSM) are used to characterize the particle size distribution and magnetic properties of Resovist. After a brief description of the studied ferrofluid, the methods to perform fractionation on size are described. In the third paragraph, the analysis techniques DLS and VSM are described. In the fourth and final paragraph, the analysis results of Resovist and fractions of Resovist are described and discussed.

3.1 Resovist

Resovist, also found in literature as SH U555A, is a commercial contrast agent for MRI supplied by Bayer-Schering AG. The agent consists of iron oxide particles coated with carboxyldextran (a polysaccharide). In Resovist buffer, the coating is responsible for negatively charged particles. From Mössbauer spectroscopy it was derived that the core contains mainly Fe\(^{3+}\) and at most 5% Fe\(^{2+}\) \[3\]. This implies that the contribution of Fe\(_2\)O\(_4\) is less than 15% and that the core of the particles therefore mainly consists of γ-Fe\(_2\)O\(_3\) (other iron oxide compounds containing only Fe\(^{3+}\) are not magnetic enough to explain the magnetic properties of Resovist). Also a saturation mass magnetization of 107 A·m\(^2\)·kg\(^{-1}\) Fe (thus per kg of iron) has been specified. Converted into magnetization this becomes 3.8x10\(^5\) A·m\(^{-1}\) (assuming an iron oxide density of 5x10\(^3\) kg·m\(^{-3}\) and a mass ratio iron to iron oxide of 1:1.4). The concentration of the supplied Resovist is 0.5 mol Fe L\(^{-1}\), corresponding to an iron oxide volume fraction of 0.8 vol-%.

In literature the size distribution of Resovist was described as a bimodal distribution \[3\]. Fractions of Resovist acquired with asymmetric flow field-flow fractionation (AF4) were analysed with small-angle X-ray scattering (SAXS). The distribution of core diameters \(d_c\) was approximated with two Gaussian distributions of 10.0±2.4 nm and 19.8±3.2 nm (mean value and standard deviation) with a volume-ratio of 1:2. Further it was stated that >99 vol-% of the particles has a core size between 8 and 26 nm, while <1 vol-% has a size up to 42 nm. Approximations of the shell thickness \(r_s\) were 10 nm and 20 nm for the smaller and larger particles, respectively. Note that the diameter of the particle including shell becomes \(d_t = d_c + 2r_s\).

3.2 Fractionation techniques

In general, magnetic fluids are quite polydisperse. One way to obtain nanoparticles that are less disperse is by the application of fractionation techniques (another way is to optimize synthesis parameters). Fractionation is a separation process in which a certain quantity of a mixture is divided into a number of smaller fractions in which the composition gradually changes. Fractions of magnetic nanoparticles can be collected based on differences in particle properties like size, mass, magnetic moment, or surface charge. Two families of techniques that can be used for fractionation are field flow fractionation (FFF) and chromatography. Illustrations for both type of techniques are shown in figure 3.1. Both with FFF and chromatography the sample flows through a chamber in which particles
have a retention time depending on their properties used for fractionation (the fractionation parameters). The chamber is in general called a channel in FFF and a column in chromatography. Separation in a channel is caused by the action of an externally generated field normal to the flow [3.3]; the type of field determines the fractionation parameter. A column is filled with a material called the stationary phase which is responsible for the difference in retention time (the flowing sample plus buffer are the mobile phase); the type of stationary phase determines the fractionation parameter. In the following (sub-)paragraphs, sedimentation FFF (SdFFF) and size exclusion chromatography (SEC) are described. As a general note, it is important to realize that fractionation may lead to changes in the sample. For example dilution may compromise the stability of particles, especially when another buffer is used than the original one. Also shear forces to the particles may destabilize particles.

3.2.1 Sedimentation field flow fractionation

Sedimentation field flow fractionation (SdFFF) utilizes gravity or a centrifugal force for fractionation [3.3]. Gravitational SdFFF uses a simple channel, but the use of gravity limits the applicable field strength and flexibility of this setup. With centrifugal SdFFF, a centrifugal force is applied by fast spinning of a round belt-like channel; the field strength is more flexible and can be stronger than the gravitational field. For both methods, fractionation is based on differences in effective particle mass, which result from differences in size and density. In normal mode (in general valid for submicrometer particles [3.3]), heavier particles move closer to the wall of the channel where the flow velocity (in a parabolic flow profile) is lower, resulting in a longer retention in the channel. In this work, a number of fractions have been analysed which were fractionated using centrifugal SdFFF. The fractions collected with this technique are not described in this chapter (the fractions are too diluted for VSM analysis), but will be discussed briefly in chapter 5.
3.2.2 Size exclusion chromatography

With size exclusion chromatography particles are fractionated based on their hydrodynamic size [3.6]. This technique is also called gel filtration chromatography (GFC) if an aqueous buffer is used. The column is usually filled with tightly packed porous polymer beads. The pore size of these beads determines the flow of particles: particles smaller than the pore size enter the pores and travel through a larger volume than particles which are excluded by the pores. Smaller particles are therefore longer retained in the column than larger ones. Here, two fractionations with GFC are described, one using a dropping funnel (see figure 3.2) and another using high performance liquid chromatography (HPLC). The fractions from the dropping funnel have been collected for characterization (and from here we speak of the GFC fractions), while only the elusion profile of the HPLC fractionation is considered.

The column for the GFC fractions was prepared in a dropping funnel with a diameter of 20 mm and a height of 40 cm. The flow rate of the buffer through the prepared column was approximately 40 mL per hour (measured at the outlet of the dropping funnel). One millilitre of undiluted Resovist was used for fractionation, while demiwater with 1 wt-% of mannitol ($C_8H_{16}(OH)_6$, a sugar alcohol) was used as a buffer. The mannitol was added to the buffer for stability of the fractions. The fractionation using the mannitol buffer resulted in two ranges of concentrated fractions (see figure 3.1). Analysis of the GFC fractions is described in paragraph 3.4.2.

![Figure 3.2: Column used for gel filtration chromatography with Resovist running through it. The Resovist splits into two parts: a fast part moving fraction (with larger particles) running through the column in one hour, and a slower fraction moving at half the speed. The flow speed of the buffer is $\pm 40 \text{ mL}\cdot\text{h}^{-1}$.](image-url)
Another GFC fractionation has been performed using HPLC, a form of column chromatography using a high pressure pump to move the mobile phase through the column and along a detector that shows the retention time of the particles. The detector measures typically extinction of light in the UV-VIS range, and in this case extinction at a wavelength $\lambda = 254$ nm was measured. The fractionation was performed with 50 $\mu$L of 25x diluted Resovist and a demiwater buffer containing 1 wt-% of mannitol. A flow rate of 1 mL per minute was used at a pressure of approximately 38 bar. Figure 3.3 shows the measured elusion profile for this fractionation. A quantitative analysis of figure 3.3 is not performed since this would require relations between particle size and extinction (due to a combination of light scattering and absorption) and between particle size and elusion time, which are not known. The measured elusion profile shows two peaks which are not clearly separated, however, the peaks can be fitted accurately with two Gaussian peaks. The elusion profile therefore provides a further indication of a bimodal size distribution of Resovist particles.

![Figure 3.3: HPLC elusion profile of Resovist based on extinction detection at $\lambda=254$ nm. Two fitted Gaussian peaks are shown as well.](image)

### 3.3 Analysis techniques

In this paragraph the analysis methods with DLS and VSM are described.

#### 3.3.1 Dynamic light scattering

Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), makes use of Brownian motion of nanoparticles to determine their hydrodynamic size distribution [3.7-3.9]. Nanoparticles illuminated with a laser beam scatter light in all directions and on a screen the scattered light would produce, due to interference, a pattern of dark and light spots. This so called speckle pattern changes in time as a consequence of Brownian motion of particles. The relation between the size of a particle and its speed due to Brownian motion is defined in the Stokes-Einstein equation:

$$D = \frac{k_B T}{3\pi\eta d_h},$$

with $D$ the diffusion coefficient of a particle, $d_h$ the hydrodynamic diameter of a particle (i.e. the size of a particle in solution including the polymer shell), and $\eta$ the viscosity of the ferrofluid [3.2,3.7-3.9].
3.3. Analysis techniques

If the intensity signal of a particular part of the speckle pattern is measured as a function of time, an autocorrelation function of the measured intensity can be determined. For particles with a single size, the first-order autocorrelation function \( g \) would decay exponentially in time as:

\[
g_d(t) = \exp(-q^2 D t)
\]

with wave vector \( q = (4\pi n / \lambda) \cdot \sin(\theta / 2) \) where \( n \) is the refractive index of the sample and \( \theta \) is the scattering angle [3.7-3.9]. For a (normalized) distribution of particle sizes \( \varphi_i(d) \), the measured autocorrelation function becomes:

\[
g(t) = \int g_d(t) \varphi_i(d) \, dd.
\]

If a shape is assumed for the size distribution, for example a log-normal distribution (equation 2.4), the particle size distribution can be determined through a fit of the measured autocorrelation function.

DLS measurements are often characterized by their Z-average and polydispersity index (PDI). These parameters are determined using the cumulants methods which is a fit of a polynomial to the log of the (first-order) autocorrelation function (log \( g(t) = a + bt + ct^2 + ... \)) [3.7]. The Z-average diffusion coefficient \( b \) is converted to a size (using equation 3.1) called the Z-average. The PDI equals \( c/b^2 \). The Z-average is a measure for the (intensity-weighted) mean size, while the PDI is a measure for the width of the size distribution. The Z-average is considered as the most stable number produced by DLS.

The fundamental size distribution determined by DLS is intensity-weighted. For particles smaller than the wavelength of light (\( d \ll \lambda \)), scattering of light can be described by Rayleigh scattering. The scattering intensity from a single particle scales with the particle diameter as \( d^6 \) [3.2,3.10]. Therefore, the volume-weighted distribution \( \varphi_V(d) \) is calculated from the intensity-weighted distribution according to:

\[
\varphi_V(d) = a \cdot \varphi_i(d) / d^3,
\]

where \( a \) is a normalization factor such that \( \int \varphi_V(d) \, dd = 1 \). It is worth to note that after conversion to a volume distribution, measurement and fit errors become relatively more pronounced for the smaller particles in the distribution. Therefore, the larger the ratio between the largest and smallest particles, the less accurate the presence of smaller particles can be determined. In this work, a Zetasizer Nano ZS from Malvern Instruments was used for DLS measurements and data analysis was performed using a supplied software package (Dispersion Technology Software, ver. 4.20).

3.3.2 Vibrating sample magnetometer

A vibrating sample magnetometer (VSM) measures the magnetic moment of a sample by vibrating this sample within a uniform magnetic field. The sinusoidal vibrations of the sample cause an oscillating magnetic flux into nearby pick-up coils. The changing flux induces an alternating voltage in the pick-up coils with amplitude linear to the magnetic moment of the sample. The induced voltage is measured through a lock-in amplifier using the signal that steers the vibrations as a reference signal. By varying the magnetic field it is possible to measure hysteresis curves of samples. In this study a model 10 VSM from DMS-Magnetics which can produce fields up to 2 T was used. Measurements were performed at room temperature. To measure the liquid samples, the samples were sealed in the lid of a PCR-tube with a Teflon tape. Approximately 50 µL of ferrofluid fits into this lid. The actual amount of ferrofluid is determined by weight measurements. The VSM curves are measured in two hysteresis loops in order to improve the sensitivity of the field measurement in the smaller range: one loop between -2 and 2 T with a step size of 100 mT and another loop between -30 and 30 mT with step sizes of 2 mT and 0.5 mT between -10 and 10 mT. The measured curves are corrected for the magnetic moment of the sample holder (PCR-tube) and the solvent of the magnetic fluid. The corrected magnetic moment of the ferrofluid sample is transformed into magnetization through
dividing the moment by the total volume of iron oxide in the sample. The volume of iron oxide is calculated using measured iron (mass) concentrations of samples and it is assumed that all iron present in the ferrofluid is contained in iron oxide (with \( \rho = 5 \times 10^3 \, \text{kg} \cdot \text{m}^{-3} \)).

For monodisperse magnetic nanoparticles which are single domain and non-interacting, the magnetization as a function of magnetic field is described by the Langevin function (equation 2.17). The magnetic moment \( m \) of a single particle is related to the diameter of the magnetic core \( d_c \) (or an effective diameter for non-spherical particles) and the saturation magnetization \( M_s \) as \( m = (\pi/6) d_c^3 M_s \). For a volume-weighted distribution of particle sizes \( \varphi(d_c) \), the magnetization curve is described as

\[
M(B) = \int_0^\infty M_L(B; d_c, M_s) \varphi(d_c) \, dd_c,
\]

where \( M_L \) is the magnetization described by the Langevin function and \( \int_0^\infty \varphi(d_c) \, dd_c = 1 \). If a shape is assumed for the particle size distribution, equation 3.2 can be used to fit the measured VSM magnetization curve of a ferrofluid. Fit parameters are \( M_s \) and the distribution parameters, which are median size \( d^* \) and multiplicative standard deviation \( \sigma^* \) for a log-normal distribution (see paragraph 2.1.4). A bimodal distribution can be described as

\[
\varphi = \frac{1}{1 + r} \cdot (\varphi_1 + r \cdot \varphi_2),
\]

where \( \varphi_1 \) and \( \varphi_2 \) are two normalized volume-weighted distributions and \( r \) is the volume ratio between the two distributions. If a bimodal log-normal size distribution is used to fit a VSM magnetization curve, the total number of fit parameters becomes six (\( M_s, d_1^*, \sigma_1^*, d_2^*, \sigma_2^*, r \)).

The magnetization model described by equation 3.2 requires single-domain and non-interacting particles. Iron oxide (maghemite or magnetite) has a critical single-domain (to pseudo single-domain) size of 30-100 nm (see table 2.1 or [3.11]) and Resovist contains particles with a diameter up to 42 nm [3.2], which seems to justify the assumption of single-domain particles for Resovist. Magnetic dipole interactions between particles can lead to ordering (e.g. string formation) or clustering of particles (see paragraph 2.1.1). It has been verified for undiluted Resovist that the VSM magnetization curve is not altered upon expose of the sample to fields up to 2 T, which arguments against irreversible clustering of particles during VSM measurements. However, this does not exclude (reversible) ordering of particles. In section 2.1.1 it was calculated that dipolar interactions are relevant if particles are separated (from surface to surface) by less than 17 or 52 nm for two particles with diameters of 20 and 30 nm, respectively. Resovist particles have a polymer coating with a thickness of 20 nm for larger particles [3.2] which already provides a separation distance of 40 nm, but especially because of the repelling (negative) coating of particles it is assumed that contributions from dipolar interactions are minor.

A software tool has been developed in MATLAB to perform analysis of VSM magnetization curves based on a discrete version of equation 3.2. This tool and correction of the background signal are described in appendix B.
3.4 Results and discussion

In this paragraph the results of the analysis of Resovist and fractions of Resovist with VSM and DLS are described. The results are discussed at the end of the paragraph.

3.4.1 Analysis of Resovist

![Image of magnetization curve](image)

**Figure 3.4:** Magnetization curve of Resovist measured with VSM. The red line is a fit calculated based on the Langevin function and a bimodal log-normal size distribution.

Figure 3.4 shows a measured VSM magnetization curve of undiluted Resovist. The magnetization has been calculated assuming a concentration $c_{\text{Fe}_{2}\text{O}_{3}}$ of 0.8 vol-% of iron oxide (and assuming that all iron oxide is equally magnetic). The inset in figure 3.4 shows clearly the superparamagnetic behaviour of the particles, since no hysteresis is observed. Two fits of the magnetization curve are shown in figure 3.4 based on a discrete version of equation 3.2 with 200 linearly distribution size points in the range of 0.8 – 100 nm (the lower size limit equals the cell dimension of maghemite [3.11]). A log-normal distribution (with 3 fit parameters) and a bimodal log-normal distribution (with 6 fit parameters) have been assumed. The fitted parameters are found in table 3.1 and figure 3.5 shows the derived size distributions. With both distributions the saturation magnetization is found in the range of $2.9 \text{ to } 3.9 \times 10^5 \text{ A} \cdot \text{m}^{-1}$, as stated in literature for maghemite [3.11]. The magnetization curve is fitted better with the bimodal log-normal distribution than with the log-normal distribution, indicated by a lower root-mean-square (RMS) fit error (see table 3.1) and as can be seen in figure 3.4. Using the log-normal distribution, the contribution of large particles in the sample is overestimated as indicated by the slope of the fitted curve which is too steep around zero field (figure 3.4). The fit with the log-normal distribution is improved (as indicated by the RMS error in table 3.1, the fitted curve is not shown) if the upper limit of the size range is reduced to 40 nm (still 200 size points are used), which is an optimal limit considering the RMS error. The derived size distribution (see figure 3.5) shows a sharp transition near 40 nm, which seems unrealistic since this is not observed with fractionation experiments (see for example the HPLC elusion profile in figure 3.3); the use of a smoother cut-off could of course compensate for this. Although it is obvious that the bimodal distribution provides a more accurate fit since more fit parameters are used, the bimodal distribution seems to be justified by fractionation experiments which showed two (intense) peaks in the measured elusion profiles (see [3.2] and figures 3.2 - 3.3).
Chapter 3. Sample characterization

Table 3.1: Parameters obtained from fits of VSM magnetization curve for Resovist

<table>
<thead>
<tr>
<th>Distribution</th>
<th>$M_s$ (10^5 A/m)</th>
<th>$&lt;d&gt; \pm \sigma$ (nm)</th>
<th>Peak 1 (nm/⁻³)</th>
<th>Peak 2 (nm/⁻³)</th>
<th>Ratio (peak 2/1)</th>
<th>RMS-error (A/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-normal 0.8 – 100 nm</td>
<td>3.13±0.03</td>
<td>15.7±14.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.1±10^3</td>
</tr>
<tr>
<td>Log-normal 0.8 – 40 nm</td>
<td>3.39±0.03</td>
<td>13.1±10.1</td>
<td>$d^*=14.2±0.2$</td>
<td>$\sigma^*=3.74±0.04$</td>
<td>-</td>
<td>1.3±10^3</td>
</tr>
<tr>
<td>Bimodal, log-normal 0.8 – 100 nm</td>
<td>3.15±0.02</td>
<td>14.1±9.7</td>
<td>$d^*=7.8±0.2$</td>
<td>$\sigma^*=1.95±0.04$</td>
<td>$d^*=24.5±0.2$</td>
<td>$\sigma^*=1.19±0.03$</td>
</tr>
<tr>
<td>Bimodal, log-normal for 90% of iron content</td>
<td>3.50±0.02</td>
<td>13.6±9.4</td>
<td>$d^*=7.6±0.2$</td>
<td>$\sigma^*=1.95±0.04$</td>
<td>$d^*=25.4±0.3$</td>
<td>$\sigma^*=1.19±0.03$</td>
</tr>
<tr>
<td>Bimodal, log-normal for 80% of iron content</td>
<td>3.94±0.01</td>
<td>13.1±9.0</td>
<td>$d^*=7.3±0.2$</td>
<td>$\sigma^*=1.95±0.04$</td>
<td>$d^*=23.5±0.2$</td>
<td>$\sigma^*=1.19±0.03$</td>
</tr>
<tr>
<td>Bimodal, log-normal with non magnetic layer</td>
<td>3.21±0.02</td>
<td>15.4±9.6</td>
<td>$d^*=9.1±0.2$</td>
<td>$\sigma^*=1.72±0.03$</td>
<td>$d^*=26.9±0.3$</td>
<td>$\sigma^*=1.19±0.02$</td>
</tr>
</tbody>
</table>

(1) $<d>$ and $\sigma$ are mean size and standard deviation of the fitted size distributions, but are no fit parameters.
(2) Median $d^*$ (in nm) and multiplicative standard deviation $\sigma^*$ (dimensionless).
(3) A non magnetic layer is assumed around the particle with a size $s = 0.83$ nm; the distribution of the total core size is fitted, with the magnetic moment calculated as $m = (\pi/6)(d - 2s)^3 M_s$ with $m = 0$ if $d < 2s$.

Figure 3.5: Volume-weighted size distributions obtained by fitting of the VSM magnetization curve of Resovist.

So far it has been assumed that particles can be described by fully magnetic iron oxide cores with an effective core diameter $d_c$ and a saturation magnetization $M_s$ which is constant for all particles (see equation 3.2). However, in an actual ferrofluid this is not necessarily the case, since the composition of the core may vary between particles. Even the possibility of a relation between particle size and composition cannot be excluded. The core of a particle can contain maghemite ($M_s \sim 3.4\times10^5$ A·m⁻¹) or magnetite ($M_s \sim 5.0\times10^5$ A·m⁻¹), and also non-ferromagnetic forms of iron (hydr)oxide are possible like FeO, FeOOH, or Fe(OH)₂ [3.11]. Further, the outer layer of the core of particle may be non-magnetic due to interactions with the shell or because of a different composition [3.11-3.12]. Both
non-magnetic particles and a non-magnetic outer layer have been considered. Table 3.1 shows the effects of assuming a non-magnetic layer around the particles of one maghemite cell dimension thick (0.83 nm, see table 2.1), and assuming that only 90% or 80% of the particles are magnetic and contribute to the magnetization of the sample (for the latter case, the magnetization curve is now calculated by dividing the measured moment by the assumed magnetic volume of iron oxide and not by the total volume of iron oxide, thus \( c_{Fe_{2}O_{3}} \) becomes 0.72 vol-% and 0.64 vol-%, respectively). These variations have predominantly an effect on the fitted saturation magnetization and to some extent on the size distribution. Based on an upper limit for the expected saturation magnetization of maghemite of \( 3.9 \times 10^5 \) A·m\(^{-1} \), it can be estimated that up to 20 vol-% of the iron oxide is non-magnetic. Confidence margins can be determined from the variations between the different fits with the bimodal distribution, which yield for the magnetic (part of the) core: \( M_S = (3.5 \pm 0.4) \times 10^5 \) A·m\(^{-1} \), \( d_1^* = 8 \pm 1 \) nm, \( \sigma_1^* = 1.9 \pm 0.1 \), \( d_2^* = 25 \pm 1 \) nm, \( \sigma_2^* = 1.2 \pm 0.1 \), and a volume ratio of 0.4±0.1. Note that table 3.1 shows the whole core size of the particles with a non-magnetic layer and that the magnetic part of the core has a diameter which is 1.7 nm smaller. For the distribution of the magnetic core this implies lower values for \( d_1^* \) and \( d_2^* \), and higher values of \( \alpha_1^* \) and \( \alpha_2^* \), which lie within the mentioned confidence intervals.

A Z-average of 56.7±1.6 nm and a polydispersity index (PDI) of 0.176±0.007 were measured for 50x diluted Resovist by DLS. The Z-average corresponds well with the specified hydrodynamic size for Resovist of 57-59 nm [3.1]. The volume-weighted size distribution is shown in figure 3.6 and the volume-weighted mean hydrodynamic diameter is 45.3±19.2 nm. Comparison of the distribution obtained by DLS and VSM provides rough estimates of the polymer shell size. An average core diameter of approximately 15±10 nm found by VSM indicates an average shell thickness in the order of 15 nm. The minimal size of particles found with DLS is approximately 20 nm, indicating a minimal shell thickness of 10 nm. If the largest particles are considered (<\( d \)>+3\( \sigma \): ±45 nm for VSM and ±100 nm for DLS), an estimate for the largest shell size is in the order of 30 nm. These estimates are in the same range as a shell size of 10 and 20 nm for smaller and larger particles respectively, as found in [3.2].

![Figure 3.6: Volume-weighted distribution of particles in (50x diluted) Resovist derived from DLS measurements. The shown graph is the average result of three measurements; the error bars indicate the standard deviation between measurements.](image)
3.4.2 Analysis of fractions of Resovist

Only the analysis of the GFC fractions (fractionated with the dropping funnel) is discussed in this chapter, since only these fractions were concentrated enough to perform VSM analysis. In general, all fractionation techniques showed a clear trend in hydrodynamic particle size between subsequent fractions. The GFC fractions were relatively stable during the first days after fractionation, since no sedimentation of particles was observed and DLS measurements yielded consistent results. Fifty fractions of approximately 1.5 mL have been collected from the onset of particles eluting from the column. Fractions 1-5 and 33-45 were most concentrated. Six fractions have been analyzed with VSM. Iron (mass) concentrations for these fractions have been determined using inductively coupled plasma-atomic emission spectrometry (ICP-AES). The six analyzed fractions contain approximately 27 vol-% of the iron oxide content of Resovist used for fractionation.

Figure 3.7 shows the measured VSM curves of six GFC fractions. The measured curve show a trend with increasing fraction number and especially the difference between the ‘fast’ fractions 2 and 4, and the ‘slow’ fractions 35-40 is clear (see figure 3.2 for the meaning of ‘fast’ and ‘slow’ fractions). The VSM magnetization curves have been fitted using a discrete version of equation 3.2 with 200 linearly distribution size points in the range of 0.8 – 50 nm and assuming a bimodal distribution (all particles are assumed to be fully magnetic). A log-normal distribution was assumed as well, but for all fractions this yielded worse fits (RMS errors were approximately five times larger). The fitted parameters for the bimodal distributions are shown in table 3.2 together with DLS results of the fractions. Also the VSM and DLS results of undiluted Resovist are shown for comparison. Figure 3.8 shows the fitted size distributions. For fractions 2 and 4, the first peak of the bimodal distribution could not be fitted with good confidence. Therefore, the fits have been performed as well for a fixed position and width of the first peak determined by the fitted peak for Resovist, which yielded more reliable results. For all fractions, the fitted distributions from VSM yield peak positions and widths which lie within the confidence margins as determined for Resovist. Mainly the ratio between the peaks appears to vary between fractions.
3.4. Results and discussion

Table 3.2: DLS and VSM analysis results of GFC fractions of Resovist

<table>
<thead>
<tr>
<th>Nr.</th>
<th>DLS: &lt;d&gt; ± σ (nm)</th>
<th>Vol-%¹</th>
<th>Mₘ (10⁵ A/m)</th>
<th>VSM: &lt;d&gt; ± σ (nm)</th>
<th>Peak 1 (nm/-)</th>
<th>Peak 2 (nm/-)</th>
<th>Ratio (peak 2/1)</th>
<th>RMS-error (A/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Res.²</td>
<td>45.3±19.2</td>
<td>7.9x10⁻¹</td>
<td>3.16±0.02</td>
<td>14.0±9.5</td>
<td>d*=8.0±0.2</td>
<td>d*=25.6±0.3</td>
<td>0.34±0.05</td>
<td>5.1x10⁻²</td>
</tr>
<tr>
<td>2</td>
<td>55.5±22.5</td>
<td>1.2x10⁻²</td>
<td>3.85±0.03</td>
<td>21.4±9.8</td>
<td>d*=13.8±10.2</td>
<td>d*=25.6±0.9</td>
<td>1.2±1.3</td>
<td>1.5x10³</td>
</tr>
<tr>
<td>³</td>
<td>-</td>
<td>-</td>
<td>3.88±0.01</td>
<td>21.3±10.1</td>
<td>d*=8.0</td>
<td>d*=24.8±0.1</td>
<td>2.60±0.09</td>
<td>1.7x10³</td>
</tr>
<tr>
<td>4</td>
<td>54.6±22.6</td>
<td>9.1x10⁻³</td>
<td>3.88±0.05</td>
<td>20.4±9.8</td>
<td>d*=10.8±8.9</td>
<td>d*=24.1±0.6</td>
<td>1.6±1.7</td>
<td>1.2x10³</td>
</tr>
<tr>
<td>³</td>
<td>-</td>
<td>-</td>
<td>3.86±0.01</td>
<td>20.6±9.7</td>
<td>d*=8.0</td>
<td>d*=24.0±0.1</td>
<td>2.48±0.07</td>
<td>1.3x10³</td>
</tr>
<tr>
<td>35</td>
<td>46.4±21.1</td>
<td>3.0x10⁻²</td>
<td>3.49±0.01</td>
<td>13.3±9.4</td>
<td>d*=7.4±0.1</td>
<td>d*=25.8±1.0</td>
<td>0.35±0.03</td>
<td>5.3x10⁻³</td>
</tr>
<tr>
<td>36</td>
<td>37.3±17.7</td>
<td>3.5x10⁻²</td>
<td>3.40±0.01</td>
<td>13.6±9.1</td>
<td>d*=8.0±0.1</td>
<td>d*=25.2±0.2</td>
<td>0.33±0.03</td>
<td>3.4x10⁻³</td>
</tr>
<tr>
<td>38</td>
<td>35.3±15.6</td>
<td>3.8x10⁻²</td>
<td>3.42±0.01</td>
<td>12.0±8.1</td>
<td>d*=8.0±0.1</td>
<td>d*=24.0±0.3</td>
<td>0.21±0.03</td>
<td>4.4x10⁻³</td>
</tr>
<tr>
<td>40</td>
<td>31.6±16.5</td>
<td>2.0x10⁻²</td>
<td>3.34±0.01</td>
<td>11.4±8.1</td>
<td>d*=7.0±0.1</td>
<td>d*=24.1±0.3</td>
<td>0.24±0.02</td>
<td>4.1x10⁻³</td>
</tr>
</tbody>
</table>

(1) Volume percentage of iron oxide, calculated from iron concentrations. The maximum inaccuracy of the iron concentrations determined with ICP is considered to be 3% (relative to the measured value).
(2) Resovist: small (non-significant) differences for VSM fit parameters compared to table 3.1 are a result of the smaller size range of 0.8-50 nm used to obtain the results in this table.
(3) The position and width of the first peak were not varied during fitting, four fit parameters were used.

Figure 3.8: Volume-weighted size distributions of GFC fractions obtained by fitting of the VSM magnetization curves. The average distribution is weighted based on the volume concentrations. The distributions with a fixed first peak have been plotted for fraction 2 and 4.
Chapter 3. Sample characterization

In general, DLS data indicates that the fractions are not less polydisperse than Resovist, which limits the determination of size dependent properties using these fractions. The trend in hydrodynamic size (second column) is clearer than the trend in core size (fifth column). This makes sense considering that fractionation is performed on hydrodynamic size and that the core size is not directly related to the hydrodynamic size due to variations in the polymer shell size. The variations in shell size may also explain why fractions still contain particles with both small and large cores, since particles with a small core and a large shell can have the same hydrodynamic diameter as particles with a larger core and a smaller shell.

An interesting observation is that the saturation magnetization decreases with decreasing particle size and is higher for all fractions compared with the value obtained from the fit of Resovist. This can be explained best by the presence of small non-magnetic particles (possibly even without a polymer shell) in Resovist. Non-magnetic (small) particles may occur due to a different composition (e.g. FeO) of the core or due to a non-magnetic layer around the core with size λ, which would cause particles to become non-magnetic for \( d < 2 \lambda \). The latter possibility would thus automatically explain why mainly small particles would be non-magnetic. Non-magnetic particles with a small (hydrodynamic) size would elute after a relatively long time and thus contribute more to the smallest fractions. For the GFC fractionation, the majority of these non-magnetic particles may be present after fraction 40 (note that a total of 50 fractions were collected, but only for the six described fractions the iron concentration has been determined). Note that the HPLC elusion profile (figure 3.3) shows elusion of small particles after the second peak (between 10-11 minutes). If particles are present in Resovist without a polymer shell, these particles are most likely non-magnetic since they would otherwise cluster in a strong magnetic field (which has not been observed during VSM measurements). In the presence of larger particles, these particles without a shell are hard to observe with scattering techniques like DLS (since scattering scales with \( d^6 \)).

3.4.3 Discussion of results

The results from VSM analysis of Resovist and of the GFC fractions of Resovist support the bimodal size distribution model and show consistent results. The fitted bimodal distribution (assuming that all particles are fully magnetic) is however not similar to the bimodal (normal) distribution found in [3.2] (see also paragraph 3.1), as shown in figure 3.9. This figure also shows a magnetization curve based on the described distribution, equation 3.2, and \( M_s = 3.1 \times 10^5 \) A·m\(^{-1}\). This simulated magnetization curve clearly saturates at lower fields strengths than the measured magnetization curve, which can be explained by the absence of the smallest particles. The presence of small particles \( (d < 8 \text{ nm}) \) is however supported by TEM analysis, showing particles with an (number-weighted) average size of 3-5 nm [3.2,3.13]. It was further stated in [3.2] that <1 vol-% of particles is in the size range 26-42 nm, without larger particles present. The maximum size corresponds with the fitted distribution (with only 0.3% above 42 nm), however, the VSM fits with the bimodal distribution show 9-14% of particles between 26-42 nm. A possible explanation for this discrepancy is that the used buffer for the AF4 fractionation destabilizes (the coating of) particles, which could induce clustering and sedimentation of mainly large particles. On the other hand, particle sizes would be overestimated with VSM analysis if some particles have a magnetite core (higher \( M_s \)) or if dipolar interactions would cause particles to align which each other. However, mainly because of the low amount of magnetite in Resovist (<15 vol-% according to [3.1]) and the repelling coating of Resovist, these effects are considered as not sufficient to explain a large overestimation of particle sizes.
3.4. Results and discussion

In this chapter, sample characterisation of Resovist and fractions of Resovist has been described using fractionation techniques, DLS, and VSM. The main goal was to describe the size distribution of Resovist which is required for further analyses performed in this report and which is important for understanding and predicting the behaviour of magnetic nanoparticles in MPI. Fractionation experiments provided indications for a bimodal distribution of particle sizes in Resovist. VSM analysis showed that the measured magnetization curves of Resovist can be simulated accurately using a bimodal distribution. For the remainder of this report, the bimodal log-normal distribution of Resovist will be assumed. Comparison of determined size distributions from DLS and VSM measurements provided a rough estimate for the carboxydextran shell size of Resovist of 10-30 nm.

Further fractionation experiments of Resovist in combination with VSM analysis and iron concentration determination can be used to verify the presence of non-magnetic particles in Resovist and to provide a more accurate description of the size distribution. In general, optimization of fractionation techniques (which are preferably based on core size instead of hydrodynamic size) will be very useful in order to accurately determine size distributions of particles in ferrofluids and in order to obtain less disperse fractions which are of interest to study size dependent properties of nanoparticles. Simulations of particle interactions may be useful in order to verify the used magnetization model.

Besides the size distribution of particles, also a relation of relaxation times to particle size is required for understanding and predicting the behaviour of magnetic particles in MPI. An important parameter which determines the relaxation times is the anisotropy. The characterization of relaxation times (in Resovist and the GFC fractions of Resovist) is considered in the next chapter.

3.5 Conclusions

In this chapter, sample characterisation of Resovist and fractions of Resovist has been described using fractionation techniques, DLS, and VSM. The main goal was to describe the size distribution of Resovist which is required for further analyses performed in this report and which is important for understanding and predicting the behaviour of magnetic nanoparticles in MPI. Fractionation experiments provided indications for a bimodal distribution of particle sizes in Resovist. VSM analysis showed that the measured magnetization curves of Resovist can be simulated accurately using a bimodal distribution. For the remainder of this report, the bimodal log-normal distribution of Resovist will be assumed. Comparison of determined size distributions from DLS and VSM measurements provided a rough estimate for the carboxydextran shell size of Resovist of 10-30 nm.

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Chapter 3. Sample characterization

References

Chapter 4
Magneto-optical susceptometer

In this chapter a magneto-optical susceptometer is described that has been developed during this project in order to study relaxation times of magnetic nanoparticles. Relaxation mechanisms are important in order to understand and predict the behaviour of nanoparticles in MPI. Several experimental methods can be used to measure relaxation times or anisotropies (relaxation time and anisotropy are related properties, see equations 2.20). These methods include magnetization measurements as a function of temperature (zero-field cooled and field cooled), Mössbauer spectroscopy, ferromagnetic resonance measurements, neutron scattering, and AC susceptibility measurements. An overview of these methods is found in [4.1], only the AC susceptibility method is considered here. An advantage of this method is that direct information about remagnetization is obtained in a frequency range which overlaps with frequencies that can be used for MPI.

Susceptibility can be measured using pick-up coils (magneto-electrical) or using magneto-optical effects [4.2]; in this study it has been chosen to use magneto-optical effects. With magneto-optical detection (using Faraday rotation) the measured signal is proportional to the (local) magnetization, whereas with magneto-electrical detection the measured signal is proportional to the magnetic induction \( B \). Magneto-optical detection can therefore be beneficial for the sensitivity since no correction is required for the applied field \( H \). Another potential advantage of the optical method is the possibility to distinguish between orientation of the magnetic moment and orientation of the particle by measuring in different modes (which are discussed in the next paragraph). Further, the optical method could be used in combination with absorption measurements or light scattering. The major disadvantage of using the optical method is that this method is more complex than detection with a pick-up coil, since (for example) the detected signal can depend on particle size and atomic composition [4.1,4.3].

This chapter is organized as follows: First the magneto-optical effects are discussed. After this theoretical part, the used setup and a number of calibration measurements are described. Then the analysis and results of the susceptibility measurements of Resovist and its fractions are presented and discussed. Finally conclusions are drawn and possible future applications of the magneto-optical setup are briefly discussed.

4.1 Magneto-optical effects

Magneto-optical effects are defined as the direct influence on light of the magnetic state, usually characterised by the magnetization, of the material in which the light propagates, or from which it is reflected [4.4]. These magneto-optical effects can show up through a change in the propagation direction, but more sensitively in the polarization, and the intensity of transmitted or reflected light. In numerous materials, including ferrofluids, a linear or circular optical anisotropy is introduced under the influence of a magnetic field (due to magnetization of the material). If the propagation direction of the light is perpendicular to the field (transverse propagation, also called the Voigt configuration), light waves polarized parallel and perpendicular to the field propagate through the material with different phase velocities (called linear birefringence \( \Delta n \), with \( n \) the refractive index)
and with different absorption (called linear dichroism $\Delta k$, with $k$ the absorption coefficient) [4.5]. For propagation parallel to the magnetic field (longitudinal propagation, or called the Faraday configuration) circular birefringence and dichroism occur between right and left circularly polarized waves. Here, for both configurations the origins of the magneto-optical effects are discussed. However, the physical origins of these effects in ferrofluids are still very controversial [4.6].

4.1.1 Longitudinal propagation (Faraday configuration)

Figure 4.1 schematically shows how a linearly polarized light wave is altered when propagating through a ferrofluid parallel to the magnetization (or magnetic field). Linearly polarized light can be resolved into two circularly polarized light waves with equal amplitude, written in Jones vectors as $\begin{bmatrix} 1 \\ 0 \end{bmatrix} = \frac{1}{2} \left( \begin{bmatrix} 1 \\ i \end{bmatrix} + \begin{bmatrix} 1 \\ -i \end{bmatrix} \right)$ [4.7]. The difference in refractive index $n$ and absorption $k$ between left and right circularly polarized light causes, respectively, rotation $\gamma$ and ellipticity $\eta$ (defined as the ratio of the minor to the major axis of the ellipsoid) of the polarized light:

$$\gamma = \frac{l \pi}{\lambda} \Delta n = \frac{l \pi}{\lambda} \text{Re}(\Delta N),$$

$$\eta = \frac{l \pi}{\lambda} \Delta k = \frac{l \pi}{\lambda} \text{Im}(\Delta N),$$

with $l$ the thickness of the sample, $\lambda$ the wavelength of the light, and complex refractive index $N = n - ik$ [4.8]. Both rotation and ellipticity are proportional to the (local) magnetization $M$. The direction of the magnetization thus also determines the direction of the rotation and the sign of the ellipticity. Therefore the circular birefringence and dichroism (called the Faraday effect) can be used to probe magnetization.

The Faraday effect originates from different transition probabilities between electronic energy levels for left and right circularly polarized light [4.5,4.8]. Due to spin-orbit coupling and splitting of energy levels under the influence of (internal) magnetization, the probability to excite certain energy levels differs for left and right circularly polarized light. This is reflected in a difference in refractive index and absorption. Consequently, the Faraday effect is influenced by crystal structure and composition.
4.1 Magneto-optical effects

Measurements at specific wavelengths, being associated with transitions of the different atoms of the material, constitute a local probe of the magnetization at that position in the crystal [4.1]. For example, due to differences in structure or composition between the inner part and the outer layer of the magnetic core of nanoparticles, the magnetization in the core or surface could be measured more sensitively [4.1, 4.9]. In this way the Faraday effect can provide unique information about magnetization processes in magnetic nanoparticles.

An important aspect to consider is that the applied magnetic field used to induce the magneto-optical effect could result in clustering and string formation in (unstable) ferrofluids. Further if the applied magnetic field is not homogeneous, field gradients could cause local changes in concentration. Clustering and concentration changes can alter the scattering and absorption of light transmitted through the samples. Also orientation of clusters or strings causes variations in light intensity. However, these effects are equal for opposite magnetic fields of equal strength (along the direction of light propagation), while the sign of the Faraday rotation depends on the field direction (since the Faraday effect is assumed to be linear to the magnetization). This difference can be used to distinguish the Faraday effect from the other effects.

4.1.2 Transverse propagation (Voigt configuration)

Figure 4.2 schematically shows how a linearly polarized light wave is altered when propagating through a ferrofluid perpendicular to the magnetic field. A linearly polarized light wave can be resolved in two components parallel and perpendicular to the field. Birefringence and dichroism between these two components cause, respectively, ellipticity and rotation of the polarized light (note that this is different from longitudinal propagation, where birefringence is linked to rotation). For ferrofluids, the (so-called) Voigt effect is dominated by other mechanisms than the difference in transition probabilities between polarizations. Multiple explanations exist for the origin of the Voigt effect [4.6, 4.10-4.10], two explanations are frequently put forward: on one hand, (individual) orientation by the applied magnetic field of (non-spherical) single particles or of pre-existing aggregates; on the other hand, induced aggregation under field, which would lead to the formation of anisotropic structures such as strings of magnetic particles. This indicates that the (dominating) origin of the Voigt effect will depend on the stability of the ferrofluid and the applied field strength. The Voigt effect is thus not suitable for AC susceptometry, since the underlying mechanisms are not linear to magnetization. However, if the effect is caused by orientation of single particles, linear birefringence could be applied to gain information about Brownian relaxation.
Measured rotations are typically of the order of $1^\circ$ in Faraday configuration and in the order of 10-100$^\circ$ in Voigt configuration [4.3,4.6,4.11].

### 4.2 Magneto-optical setup

The magneto-optical susceptometer, which has been designed and built during this project, is based on Faraday rotation. With minor adjustments the setup could be made suitable to perform measurements in Voigt configuration as well. Figure 4.3 shows schematically the optical arrangement of the magneto-optical susceptometer.

The light from a laser diode is polarized and propagates through a sample placed in a solenoid, which produces a sinusoidal oscillating magnetic field parallel to the light path. The light, of which the polarization varies due to the Faraday effect, passes through a second polarizer (called analyzer) of which the axis is rotated $45^\circ$ (or $\pi/4$ rad) with respect to the first polarizer. A small Faraday rotation $\gamma$ therefore induces a linear change in intensity (for $2\gamma \ll 1$ rad):

$$\frac{I}{I_0} = \cos^2 \left( \gamma - \frac{\pi}{4} \right) = \frac{1}{2} + \frac{1}{2} \cos \left( 2 \left( \gamma - \frac{\pi}{4} \right) \right) = \frac{1}{2} + \frac{1}{2} \sin(2\gamma) \approx \frac{1}{2} + \frac{1}{2} \gamma,$$

with light intensities $I_0$ before the analyzer and $I$ after the analyzer (see appendix C for a complete derivation including ellipticity). The light is detected with a photo-diode and the induced voltage signal is measured using a lock-in amplifier; the voltage over a resistance in series with the magnetic coil is used as a reference signal for the lock-in amplifier. The intensity variations measured with the lock-in amplifier can be separated into (complex) frequency components $I_x$:

$$I = I_0 + I_1 \cos(\omega t) + I_2 \cos(2\omega t) + \ldots$$

Variations in light intensity due to effects like particle orientation or string formation are independent of the field direction and therefore only cause even harmonics (assuming that there is no field offset). The signal measured at the first harmonic is thus caused by the Faraday rotation which is assumed to be linear to the magnetization $\mathbf{M}$. An illustration is provided in figure 4.4 to clarify these relations. For small field amplitudes, the magnetization is linear to the applied field and the measured frequency component $I_1$ is thus proportional to the (complex) susceptibility. By varying the frequency of the applied field, the susceptibility can be measured as a function of frequency.
4.4. Results and discussion of susceptibility measurements

For a ferrofluid containing CoFe$_2$O$_4$ nanoparticles it was demonstrated for frequencies between 10 Hz and 3 kHz that the AC susceptibility obtained with this optical method corresponds with the AC susceptibility obtained with a magneto-electrical method [4.12]. In the remainder of this paragraph, the setup is explained in more detail. The sample holder, field generation, optical detection, and setup control will be discussed.

4.2.1 Sample holder

A Teflon sample holder has been fabricated which can hold a cuvette containing the ferrofluid and on which one or two solenoids can be mounted (see figure 4.5). An axial hole is drilled in the holder in horizontal direction along the axis of the mounted solenoid(s). The hole allows optical detection through the sample and facilitates the alignment of the laser beam with the applied magnetic field. An additional hole has been drilled in perpendicular direction, which allows measurements in Voigt configuration when using two solenoids. Polystyrene cuvettes, which were cut to fit in the solenoid, are used as a sample holder. The length of the cuvette in the direction of the light path is 10 mm.

Figure 4.4: Illustration of linear relation between applied field and Faraday effect, and quadratic relation between applied field and intensity variations due to orientation of (elliptical) particles or string formation.

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Figure 4.5: Teflon sample holder with the solenoid. The red lines indicate the possible light paths.
4.2.2 Field generation

A schematic overview of the magneto-optical setup is shown in figure 4.6. The sinusoidal signal from the function generator (Agilent 33220 A) is amplified (with Toellner 7610 Power amplifier - DC to 100 kHz or ENI model 240L RF power amplifier - 20 kHz to 10 Mhz) and used to steer the magnetic coil. A resistance (of 1.01±0.01 Ω) is connected in series with the coil and the voltage over this resistance is measured with a multimeter (Keithley 2000) in order to determine the current through the coil. The multimeter is read by a computer which controls the function generator. The magnetic coil is made of Litz wire and creates a field of 0.96±0.02 mT/A (measured using RFL 912 Gaussmeter). At DC the resistance of the coil is 0.1 Ω with a self-inductance of 68.3±0.1 µH (measured with Fluke PM6306 RCL meter). From approximately 100 kHz the resistance and self-inductance start to increase and at 1 MHz the resistance becomes 343±1 Ω and the self-inductance 338±1 µH. With the magnetic coil in combination with the used amplifiers, a field with an amplitude of 0.5 mT can be generated up to 200 kHz. To measure up to higher frequencies a coil with a lower self-inductance and thinner Litz wires would be required (the latter in order to reduce the skin effect which increases the resistance).

![Diagram of magneto-optical setup](image)

*Figure 4.6: Schematic overview of magneto-optical setup. LD is the laser diode and PD the photo diode. The voltage over a resistance (of 1 Ω) is used as a reference signal to the lock-in and is used to measure the current through the coil.*

4.2.3 Optical detection

A laser diode connected to a laser controller (Newport Model 8000 Modular controller) generates the light beam. A laser diode has been used with a wavelength of 670 nm and a light output of 5 mW (SANYO DL-3149-057). The laser diode is mounted in a collimation tube which is focused on the detector such that an almost parallel light beam (slightly converging) is created. A diaphragm is placed in front of the sample holder which reduces the beam diameter to approximately 1.5 mm. Two mirrors are used to separate the optical detection part (laser diode and photo diode) from the field generation part on the optical table (distance approximately 0.5 m). A beam splitter cube is used as the first polarizer, while a linear film polarizer is used as the second polarizer. If the polarizers are crossed, the light intensity is reduced by 99.96% compared with parallel polarizers. An amplified photo diode (Thorlabs PDA10A-EC Si amplified detector, 200-1100 nm) is used as a detector, and is connected to a multimeter (Keithley 2000) and a lock-in amplifier (Signal Recovery 7280 DSP Lock-in amplifier, 0.5 Hz to 2.0 MHz) which are both connected to the computer. The voltage over the
4.4. Results and discussion of susceptibility measurements

Resistance in series with the magnetic coil is used as a reference signal for the lock-in. The multimeter is used to measure the DC signal from the photodiode, while the lock-in measures the AC signal. The lock-in measures an in-phase (real) and out-of-phase (imaginary) component with respect to the reference signal. The AC signal can thus be considered as a complex signal. The Faraday rotation is calculated by dividing the (complex) AC signal ($\sim I_0 \gamma$, see equation 4.3) by two times the DC signal measured with the multimeter ($\sim I_0/2$). The Faraday rotation is thus also complex, which reflects the complex susceptibility.

4.2.4 Setup control

During susceptibility measurements (as a function of field or frequency), the field is switched off before each data point is measured. The DC signal from the photodiode is used to set the laser intensity (by a feedback loop). This step is performed in order to prevent drift of the laser intensity. After this step the field is switch on and a data point is measured. A program is written in Labview to operate the setup from the computer and includes two feedback loops to set the field amplitude and laser intensity. The program automatically measures over a range of discrete frequencies and/or field amplitudes. The signals measured with the lock-in amplifier and the two multimeters are averaged for a number of seconds (most often 30 seconds). The in-phase (real) and out-of-phase (imaginary) signal of the lock-in are averaged separately (note that averaging of the absolute signal will not bring the contribution of the noise down to zero). A flow-chart of the program is found in appendix D.

4.3 Calibration measurements

In this paragraph a number of calibration measurements of the setup are presented, which have been performed to determine how well the measured magneto-optical effect represents the magnetization in the ferrofluid. In the next paragraph the magneto-optical susceptibility measurements are used to determine relaxation times and anisotropy.

4.3.1 Background analysis

At some point during construction of the setup strong signals were measured with the lock-in amplifier without a sample present. This background signal was strongly reduced by improving the grounding of the setup, shielding of the laser diode cable, using the detector instead of the internal photo-diode of the laser to stabilize the laser output, and by averaging of the lock-in signal (separately for in-phase and out-of-phase signals). If an empty cuvette or a cuvette with demiwater is placed in the setup, a signal is measured due to the Faraday rotation in polystyrene and demiwater. These background signals need to be taken into account and determine the achievable sensitivity of the setup.

Figure 4.7 shows measurements of the (absolute) Faraday rotation as a function of field and at a field frequency of 1 kHz without a cuvette, with an empty cuvette, and with a cuvette filled with demiwater. The error bars indicate the standard deviation of the measured signal during averaging (which was performed for 60 seconds). The fitted slopes are presented in table 4.1. Birefringence has been calculated using equation 4.1. The measured birefringence for demiwater of $5.9 \times 10^{-7}$ T$^{-1}$ has the same order of magnitude as a value of $8.1 \times 10^{-7}$ T$^{-1}$ found in literature (for $\lambda=589.3$ nm) [4.7].
If the second harmonic is measured or if the signal is measured without analyzer, for all samples a signal is measured comparable to the signal without a cuvette. Based on the signal measured without a cuvette, the detection limit of the setup can be estimated to be in the order of $10^{-7}$ rad for fields in the order of a mT. As seen in figure 4.7 the intensity of the noise is higher ($10^{-5}$-$10^{-6}$ rad), but this can be compensated by averaging of the (complex) signal.

Table 4.1: Faraday rotation in background measurements

<table>
<thead>
<tr>
<th>Sample</th>
<th>Rotation (rad T$^{-1}$)</th>
<th>Birefringence (T$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without cuvette</td>
<td>$(7.1\pm5.4)\times10^{-5}$</td>
<td>$(1.6\pm1.1)\times10^{-9}$</td>
</tr>
<tr>
<td>Empty cuvette</td>
<td>$(5.59\pm0.07)\times10^{-3}$</td>
<td>$(1.19\pm0.02)\times10^{-7}$</td>
</tr>
<tr>
<td>Cuvette with demiwater</td>
<td>$(3.34\pm0.06)\times10^{-2}$</td>
<td>$(7.11\pm0.11)\times10^{-7}$</td>
</tr>
<tr>
<td>Demiwater</td>
<td>$(2.79\pm0.13)\times10^{-2}$</td>
<td>$(5.93\pm0.27)\times10^{-7}$</td>
</tr>
</tbody>
</table>

4.3.2 Phase calibration

If the magneto-optical signal of demiwater is measured as a function of frequency, a positive phase shift (peak in signal occurs earlier with respect to reference signal) becomes significant for frequencies above 10 kHz and increases with increasing frequency. This phase shift is approximately 45° at 100 kHz (which corresponds to 1.25 µs). The phase shift is independent from the amplifier used. It is assumed that this positive phase shift is caused by a delayed reference signal. All measurements are therefore corrected for this phase shift. More details are found in appendix D.

4.3.3 Calibration measurements with Resovist

If a Resovist sample is analyzed with the magneto-optical setup, an AC signal is measured at the first harmonic (1F) and also a signal of comparable intensity at the second harmonic (2F). The light oscillations at 2F are in the order of 1% of the DC light intensity for field amplitudes in the order of a mT. When the analyzer is removed, an AC signal is measured at both harmonics; for 2F the AC signal divided by the DC signal is equal with and without analyzer, while at 1F the AC/DC signal without analyzer is approximately 10x lower. It is also observed that the DC light intensity measured with the
photodiode increases if an oscillating field is switched on, up to 3% for a field amplitude of 4 mT. The explanation of this behaviour is most probably as follows: the signal with analyzer at 1F is due to Faraday rotation, the signal at 2F is due to orientation of non-spherical particles or clusters of particles and the signal without analyzer at 1F is due to orientation of particles in combination with a small field offset. The latter effect can be corrected for as will be discussed below.

It is known from literature that the ellipticity (long axis over short axis) of maghemite particles can be in the order of 1.25 [4.11]. For an elliptical particle with two equal short axes (prolate spheroid), an ellipticity of 1.25 implies that the projected surface in the direction of the light path is 25% larger if the long axis is aligned with the field compared with the long axis perpendicular to the field. A particle aligned with the field will therefore cause less extinction of light and light intensity fluctuations in the order of 1% of the DC intensity can therefore be explained by orientation of elliptical particles. Also formation of strings in the direction of the applied field can cause oscillations in light intensity; however, for Resovist particles it is assumed that this contribution is minor due to the repelling coating of the particles. The explanation of the light oscillations at 2F by orientation of particles is further supported the frequency dependence of the 1F and 2F signals, as shown in figure 4.8. Orientation of particles can only be due to Brownian relaxation, while orientation of magnetic moments can be due to both Brownian and Néel relaxation. Therefore, it can be expected that the 2F signal drops at lower frequencies than the 1F signal, which is indeed observed.

Since orientation of particles and formation of strings of particles are equal for opposite fields, the intensity oscillations can be expressed as a polynomial containing only even powers of the field:

\[
\frac{I}{I_0} = 1 + aB^2 + bB^4 + \ldots
\]

with constants \(a\) and \(b\). If it is assumed that only the quadratic term has to be considered for small fields, the intensity for an oscillating field with amplitude \(B_1\) and field offset \(B_0\) becomes:

\[
\frac{I}{I_0} = 1 + a(B_0 + B_1 \cos(\omega t))^2 = 1 + aB_0^2 + \frac{aB_1^2}{2} + 2aB_0B_1 \cos(\omega t) + \frac{aB_1^2}{2} \cos(2\omega t).
\]
By measuring the AC/DC signal without analyzer at 1F and 2F as a function of field amplitude $B_1$, $a$ and $B_0$ can be determined.

Field dependence

Figure 4.9 shows the AC/DC signal as a function of the field amplitude measured at 75 Hz without analyzer for a Resovist sample with an iron oxide concentration of $8 \times 10^{-2}$ vol-%. Below a field amplitude $B_1$ of 1 mT, the 2F signal can be approximated reasonably well by a quadratic curve of $5 \times 10^3 B_1^2$. The 1F signal has an initial slope of approximately $0.4 \text{ T}^{-1}$. From equation 4.6 it is found that a field offset $B_0 = 20 \mu\text{T}$ would be required to explain the 1F signal below 1 mT. This field offset is in the same order of magnitude as the earth magnetic field which is approximately $30 \mu\text{T}$ (measured with Gauss meter). Furthermore, it has been verified that this 1F signal can be adjusted by adding an additional field offset.

![Figure 4.9: Measured AC/DC signal without polarizes at 75 Hz. The red points show the signal measured at 1F (inset as well), while the blue points show the signal at 2F. The blue line shows an approximation of the 2F signal at small fields by a quadratic curve.](image)

If the 1F signal is measured with analyzer (including a small field offset which is nearly inevitable), a contribution from the orientation of the particles will be measured as well. The Faraday rotation $\gamma$ will further contain a contribution from the cuvette and demiwater. Therefore to determine $\gamma$ of the ferrofluid, the additional contributions have to be subtracted from the measured signal.

Figure 4.10 shows the corrected Faraday rotation (measured at 75 Hz) of diluted Resovist ($8 \times 10^{-2}$ vol-%) as a function of field overlaid with the magnetization (moment per volume iron oxide) measured with VSM. The range of the axes has been adjusted in order for the curves to overlap. As seen from this plot, both curves overlap quite well within the measured field range. For the used sample a magnetization of $10^5 \text{ A/m}$ corresponds to a Faraday rotation of $4.8 \times 10^{-3}$ rad. If the iron oxide concentration of the sample and the length of the cuvette are taken into account, this implies that the iron oxide in the nanoparticles induces a Faraday rotation equal to $6.0 \times 10^{-3} \text{ rad/m} \cdot (\text{A/m})^{-1}$. For a magnetization saturation of $3.8 \times 10^5 \text{ A} \cdot \text{m}^{-1}$ this would lead to a Faraday rotation of $2.3 \times 10^3 \text{ rad/m}^{-1}$ in saturation with $\lambda=670 \text{ nm}$. This value is close to a value of $2.5 \times 10^3 \text{ rad/m}^{-1}$ measured for maghemite particles in saturation with $\lambda=633 \text{ nm}$ [4.6].

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4.4. Results and discussion of susceptibility measurements

**Wavelength dependence**

Two other laser diodes have been tested with wavelengths of 635 and 650 nm and a light output of 5 mW (SANYO DL-3148-025 and DL-3147-060, respectively). It has been measured that the Faraday rotation at a field of 0.5 mT has the same dependence on frequency (of the magnetic field) for the tested wavelengths.

**Concentration dependence**

From literature [4.3], it is expected that the Faraday effect scales linearly with the (volume) concentration of Resovist. It has been verified using three dilutions of Resovist (with 8x10^{-2}, 1.6x10^{-2}, and 1.6x10^{-3} vol-% of iron oxide) that the measured susceptibility curves as a function of frequency indeed overlap when they are divided by the concentration of the sample. The Faraday rotation measured for the dilution of Resovist with 1.6x10^{-3} vol-% of iron oxide (500x diluted) is in the order of 10^{-5} rad, while the noise level is in the order of 10^{-6} rad, which indicates that the current setup is accurate to concentrations in the order of 10^{-3} vol-% or higher. For concentration above 10^{-1} vol-% in combination with the used cuvettes (l=10mm), measurement of the Faraday rotation will become complicated by the low light transmittance of the ferrofluid. This could be resolved by using a thinner sample holder.

**Size dependence**

It has been assumed so far that the Faraday rotation measured in a ferrofluid is proportional to the magnetization, thus $\gamma = C \cdot M$ with $C$ a proportionality constant. It has been reported that this constant $C$ tends to decrease with increasing particle size, related to the internal field in a particle which is size dependent due to surface anisotropy [4.3]. However, in other (more recent) studies no such size dependence has been considered, and the susceptibility of ferrofluids was assumed to be proportional to the measured Faraday rotation [4.6,4.12]. A dilution of Resovist and the GFC fractions of Resovist, described in chapter 3, are used to analyze the relation between particle size
and the proportionality of the Faraday rotation. It should be noted that the fractions are still quite polydisperse, which limits the determination of the size relation of the Faraday effect. The Faraday rotation was measured as a function of frequency for a field amplitude of 0.5 mT. Between 10 and 100 Hz, the Faraday rotation was more or less constant, and the absolute values of data points in this range (except at 50 and 100 Hz) have been averaged to yield a value for the Faraday rotation. Corrections have been performed for the signal measured without polarizer and for the contribution of demiwater and the cuvette. Table 4.2 shows volume concentration of iron oxide, average particle size (see table 3.2), the susceptibility derived from the fitted VSM magnetization curve (between -0.5 and 0.5 mT), and the measured Faraday rotation for each analyzed sample. The Faraday rotation is divided by the concentration of the sample to yield a comparable value. The last column shows the ratio between the measured Faraday rotation (per volume of iron oxide) and the magnetic susceptibility. As can be seen, the ratio is of the same order of magnitude for all fractions, although variations are considerable. These results show no clear trend as a function of size. A possible explanation for the variations can be related to stability of the fractions. If particles would for example sediment during analysis, fewer particles would be present in the laser beam and thus a lower ratio would be found. This could explain why the signal is highest in Resovist, since this is the most stable measured sample. For susceptibility measurements, the variations in intensity are in principle not relevant as long as they do not influence the relation between frequency (of the applied field) and susceptibility. This is because measured curves can be normalized by susceptibilities measured at low frequencies, and thus only the relation to frequency is relevant.

Table 4.2: Comparison of Faraday rotation with susceptibility in Resovist fractions

<table>
<thead>
<tr>
<th>Fraction</th>
<th>&lt;d&gt;±σ (nm)</th>
<th>( \chi_{\text{vsm}} )</th>
<th>( \gamma ) (10(^{-4}) rad)</th>
<th>( \gamma/c ) (10(^{-1}) rad)</th>
<th>( \gamma/c )/( \chi ) (10(^{-3}) rad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resovist</td>
<td>14.0±9.5</td>
<td>38</td>
<td>1.1±0.1</td>
<td>6.9±0.6</td>
<td>18±2</td>
</tr>
<tr>
<td>2</td>
<td>21.3±10.1</td>
<td>123</td>
<td>0.8±0.2</td>
<td>7.0±1.4</td>
<td>6±1</td>
</tr>
<tr>
<td>4</td>
<td>20.6±9.7</td>
<td>111</td>
<td>0.8±0.2</td>
<td>8.6±1.7</td>
<td>8±2</td>
</tr>
<tr>
<td>35</td>
<td>13.3±9.4</td>
<td>42</td>
<td>1.1±0.2</td>
<td>3.8±0.5</td>
<td>9±1</td>
</tr>
<tr>
<td>36</td>
<td>13.6±9.1</td>
<td>39</td>
<td>1.7±0.2</td>
<td>4.8±0.5</td>
<td>12±2</td>
</tr>
<tr>
<td>38</td>
<td>12.0±8.1</td>
<td>29</td>
<td>1.5±0.1</td>
<td>3.8±0.4</td>
<td>13±2</td>
</tr>
<tr>
<td>40</td>
<td>11.4±8.1</td>
<td>26</td>
<td>0.4±0.2</td>
<td>1.9±0.9</td>
<td>7±4</td>
</tr>
</tbody>
</table>

4.3.4 Magneto-optical versus magneto-electrical measurement of susceptibility

Figure 4.11 shows a (corrected and normalized) susceptibility measurement of Resovist performed with the magneto-optical setup. The graph shows real and imaginary components of the complex dynamic susceptibility (see section 2.3.3). The imaginary part is in principle negative (phase delay), but has been plotted as positive. The curve is measured with two different amplifiers from 100 Hz – 80 kHz (Toellner) and from 20 kHz – 200 kHz (ENI). The curve is compared with a magneto-electrical susceptibility measurement of Resovist, and both curves a normalized based on the first measured data point. Both curves were measured for 0.5 mT field amplitude. As can be seen, the curves show a similar trend, but the susceptibility measured with the magneto-optical setup decreases faster as a
function of frequency than the susceptibility measured with the magneto-electrical setup, up to a
23% lower (absolute) susceptibility at $10^5$ Hz. The difference may indicate that the measured Faraday
effect is not exactly proportional to the measured magnetization for Resovist particles. If for example
the magneto-optical setup would be more sensitive to larger particles, a faster decrease in
susceptibility would be expected. Though, neither deviation between the setups due to the used
electronics can be excluded. In the next paragraph the deviation between the anisotropy found by
fitting both curves is determined.

4.4 Results and discussion of susceptibility measurements

Equation 2.27 shows how the susceptibility of a ferrofluid is related to relaxation times, which are
described by the relations 2.19-2.24. The initial susceptibilities $\chi_{0||}$ and $\chi_{0\perp}$ can be calculated by a
statistical average over all possible orientation of the magnetic moment in the relevant energy
potential (see paragraph 2.2.4), but also closed expressions are found in [4.13]. For a distribution of
particle sizes, the dynamic susceptibility (as a function of frequency $f$) can be calculated as:

$$
\chi(f) = \int_{0}^{\infty} \chi_d(f; d_c, s, E_B) \varphi(d_c) \, d d_c, 
$$

where $\chi_d$ is the susceptibility described by equation 2.27, where $\varphi(d_c)$ is a volume weighted-
distribution of core diameters $d_c$. The thickness of the polymer shell $s$ (which determines the
hydrodynamic diameter $d_h = d_c + 2s$) is used to calculate the Brownian relaxation time (equation
2.23, with $\eta = 10^{-3}$ Pa·s) and the energy barrier $E_B$ is used to calculate the Néel relaxation time
(equation 2.20). The barrier can be described by the magnetic anisotropy energy as $E_B = E_a =
K_V V + K_S S$ (for small fields, i.e. $mB \ll E_a$), with $V$ and $S$ the volume and the surface of the magnetic
core of a particle [4.3]. For $E_B < 0$, the magnetic anisotropy is characterized by an easy plane instead
of an easy axis [4.1]. As the magnetic moment can rotate freely within this plane, this implies that the
relaxation time can be neglected for the frequencies used for the magneto-optical setup. As described
in paragraph 2.2.2, the origin of the volume related anisotropy $K_V$ can be magnetocrystalline and magnetostatic shape anisotropy, while the origin of $K_S$ can be surface
anisotropy (also due to the shape of the particle). Also a time constant \( \tau_0 \) is required to calculate the Néel relaxation time (equation 2.20), for which equation 2.21 is used in combination with equation 2.19 assuming a damping constant \( \alpha = 0.1 \). For maghemite particles, a damping constant between 0.05 and 0.5 has been reported [4.14], but an exact number is not known for Resovist. The influence of the parameter on the fitted anisotropy will be discussed further on. Equation 4.7 will be used in this chapter to fit susceptibility curves, in combination with the bimodal log-normal distributions for Resovist and its fractions derived from the VSM magnetization curves as described in chapter 3 (the values from table 3.2 will be used, with the fixed first peak for fractions 2 and 4, unless stated otherwise). The fit parameters are \( s, K_V, \) and \( K_S \). All curves for Resovist and fractions of Resovist shown in this paragraph are measured with 0.5 mT field amplitude.

4.4.1 Analysis of Resovist

Remagnetization in a ferrofluid can originate from Brownian and Néel relaxation of the magnetic moment of particles. For particles with a strong magnetic anisotropy, only Brownian relaxation is relevant. However, figure 4.12 clearly demonstrates that this is not the case for Resovist. The measured susceptibility curve is compared with curves which were simulated using equation 4.7 and assuming that only Brownian relaxation is relevant (thus \( E_B \to \infty \)). A polymer shell has been assumed of 0, 10, 20, and 30 nm (a shell between 10 to 30 nm was estimated for Resovist, see chapter 3). The simulations indicate that the largest particles in Resovist have a shell of approximately 20 nm or somewhat larger. This is derived from the correspondence of the onset of the decreasing susceptibility and the peak position of the imaginary part of the susceptibility between the measured signal and the signal simulated for a shell size of 20 nm. Note that Néel relaxation would not cause a relative sharp decrease of the susceptibility for a broad distribution of particle sizes, due to the exponential relation to particle size of the Néel relaxation time, except for frequencies in the order of \( 1/\tau_0 \sim \text{GHz} \).

![Graph showing susceptibility curves for Resovist and simulated curves assuming only Brownian relaxation.](image)

*Figure 4.12: Susceptibility curve of Resovist and simulated curves assuming only Brownian relaxation. Particle shells of 0, 10, 20, and 30 nm have been assumed.*
4.5. Conclusions and future applications

To explain the measured susceptibility curves of Resovist, the relaxation should thus be a combination of both Néel and Brownian relaxation (using equation 2.24). The measured susceptibility curve can be fitted using equation 4.7 to determine the anisotropy value(s). Figure 4.13 shows the fitted curves assuming that only \( K_V \) (thus \( K_S \) is set to zero), only \( K_S \), or both are relevant. The fitted values are \( K_V = (4.37 \pm 0.08) \times 10^3 \text{ J m}^{-3} \) with \( s = 20 \pm 2 \text{ nm} \) (RMS error is \( 2.4 \times 10^{-2} \)), \( K_S = (1.89 \pm 0.03) \times 10^{-5} \text{ J m}^{-2} \) with \( s = 24 \pm 2 \text{ nm} \) (error is \( 2.4 \times 10^{-2} \)), or \( K_V = (2.0 \pm 1.0) \times 10^3 \text{ J m}^{-3} \) and \( K_S = (9.9 \pm 4.3) \times 10^{-6} \text{ J m}^{-2} \) with \( s = 22 \pm 2 \text{ nm} \). As can be seen in the graph, the fit with \( K_V \) drops too fast around 1 kHz. This could be related to a distribution of shell sizes which would broaden the contribution of Brownian relaxation. The fitted curve for \( K_S \) starts to deviate from higher frequencies (>40 kHz), which should be compensated by a lower anisotropy value. The fit with both anisotropy constants indicates that a combination is also very well possible. The fits with only one constant can be considered as the limiting situations, and a decrease of one value can be compensated by an increase of the other. A combination of a negative and a positive anisotropy constant yielded no reliable fits of the susceptibility curve, unless one of the two values became so small that it could be neglected. So far it is not possible to conclude what type of anisotropy is dominating. Additional information will be obtained by analysis of the Resovist fractions.

![Figure 4.13: Fitted susceptibility curves of Resovist assuming surface (purple and green line) and volume anisotropy (blue and red line).](image)

Before analyzing the fractions, it is useful to consider the major uncertainties in fitted anisotropy values. Fits have been performed to study three influences: the deviation with the magneto-electrical measurement, the used size distribution, and the damping constant \( \alpha \). Only the influence on \( K_V \) or \( K_S \) is considered (thus not of the combination). Realistic shell sizes found range between 20-26 nm. Fitting of the magneto-electrical susceptibility curve yields anisotropies of \( K_V = (3.73 \pm 0.09) \times 10^3 \text{ J m}^{-3} \) or \( K_S = (1.62 \pm 0.03) \times 10^{-5} \text{ J m}^{-2} \). It should be noted that the relatively abrupt change in slope around \( 10^5 \text{ Hz} \) cannot be fitted accurately with the used model. So far the bimodal size distribution with fully magnetic particles was assumed (from table 3.2). Values determined using the different distributions as stated in table 3.1, yield (reliable) values of \( K_V = 3.3-5.5 \times 10^3 \text{ J m}^{-3} \) or \( K_S = 1.6-2.2 \times 10^{-5} \text{ J m}^{-2} \), with the lower values from the log-normal distribution up to 40 nm and the higher ones from the bimodal distribution assuming 80% of magnetic iron oxide (the log-normal distribution up to 100 nm did not yield realistic results). The determined anisotropy values also depend on the assumed value of the
damping constant. For $\alpha = 0.05 - 0.5$, fitted anisotropies range from $K_V = 3.7-5.1 \times 10^3 \text{ J.m}^{-3}$ or $K_S = 1.7-2.2 \times 10^5 \text{ J.m}^{-2}$. However, the variations due to the damping constant are less relevant since these mainly influence the value of the anisotropy constants and less the fitted relaxation times. A combination of the log-normal distribution (up to 40 nm) with a fit of the magneto-electrical susceptibility curve would yield the lowest anisotropy values, however, the bimodal distributions with less magnetic iron oxide are considered as more reliable and would yield higher anisotropy values. Therefore, the analysis of the variations shows that the anisotropy values can be determined with good confidence as $K_V = (4.4\pm1.1) \times 10^3 \text{ J.m}^{-3}$ or $K_S = (1.9\pm0.3) \times 10^5 \text{ J.m}^{-2}$, for $\alpha = 0.1$, and with $s = 23\pm3$ nm.

4.4.2 Analysis of fractions of Resovist

In figure 4.12 normalized susceptibility curves are plotted for the GFC fractions of Resovist (from 10 Hz to 80 kHz). A clear trend is observed for the large to small fractions: for the fractions containing larger particles the susceptibility drops faster as a function of frequency than for the fractions containing smaller particles. This trend is in accordance with the formulas that describe the size dependence of the Néel and Brownian relaxation times (see equations 2.19-2.24). The susceptibility curves have been fitted using equation 4.7 with the bimodal distributions derived in chapter 3. In table 4.3 the fitted anisotropy values are shown assuming either $K_V$ or $K_S$. For all fractions, the anisotropy values are similar to the values found for Resovist from the magneto-optical susceptibility measurements.

Figure 4.14: Normalized susceptibility curves of Resovist and fractions.
4.4.3 Discussion of results

From the results presented above it is not possible to determine unambiguously the size dependence of the magnetic anisotropy. Taking the possible variations between fitted anisotropies into account, an anisotropy value of either $K_V = (4.4\pm1.1)\times10^3$ J·m$^{-3}$ or $K_S = (1.9\pm0.3)\times10^3$ J·m$^{-2}$ is found. A volume dependence of the anisotropy can be due to magnetocrystalline or magnetostatic shape anisotropy and a surface dependence can be due to surface anisotropy. Maghemite exhibits cubic magnetocrystalline anisotropy characterized by $K_1 \sim -4.7\times10^3$ J·m$^{-3}$ and $K_2 > 1.1\times10^4$ J·m$^{-3}$ [4.1], which implies that $K_V = 1.5\times10^3 - 1.2\times10^3$ J·m$^{-3}$ with $E_B = K_V V$ (using equation 2.22). The measured anisotropies therefore indicate that magnetocrystalline anisotropy is not the dominant type of anisotropy in Resovist particles. Magnetostatic shape and surface anisotropy can be described using equation 2.10 and 2.11 and both effects depend on the (non-spherical) shape of a particle. The shape can be characterized by an ellipticity $e = \sqrt{1 - b^2/a^2}$, with $2a$ and $2b$ the lengths of major and minor axes of the ellipsoidal particle. For surface anisotropy, values of $K_S = 2.7 - 2.8\times10^3$ J·m$^{-2}$ have been reported measured in maghemite particles with ferromagnetic resonance [4.15] and with linear birefringence [4.11]. The anisotropies were related to an (effective) elliptical shape of the particles with $a/b = 1.25$ (or $e = 0.6$). The measured value of $K_S = (1.9\pm0.3)\times10^3$ J·m$^{-2}$ is slightly lower than the reported value, but this can be related to a lower ellipticity of the particles ($e = 0.5$ or $a/b = 1.16$) or to differences in the particles surface for example due to a different coating. For an ellipsoidal particle with $e = 0.5$, the magnetostatic shape anisotropy is $3.6\times10^3$ J·m$^{-3}$ according to equation 2.10 (with $M_5 = 3.4\times10^5$ A·m$^{-1}$ and $N_4 = 1/3 + 1/15 \cdot e^2$ from [4.13]). The measured value of $K_V = (4.4\pm1.1)\times10^3$ J·m$^{-3}$ could thus be explained by magnetostatic shape anisotropy. However, a combination of $K_V = (4.4\pm1.1)\times10^3$ J·m$^{-3}$ and $K_S = (1.9\pm0.3)\times10^3$ J·m$^{-2}$ would yield an anisotropy which is too high. This implies that either both types of anisotropy are of the same order of magnitude but both have a lower value due to less elliptical particles ($e = 0.35$ or $a/b = 1.14$ could already be sufficient), or one of the effects is less relevant. In [4.11] it was assumed that the effect of shape anisotropy in particles will be minor due to a more rock-like shape of particles instead of an elliptical shape. However, based on the

### Table 4.3: Fitted anisotropy values for Resovist fractions

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Only $K_V$</th>
<th>Only $K_S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>$K_V = (4.4\pm0.3)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (1.99\pm0.09)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 20\pm2$ nm</td>
<td>$s = 22\pm2$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 3.4\times10^2$</td>
<td>Error $= 2.9\times10^2$</td>
</tr>
<tr>
<td>04</td>
<td>$K_V = (4.4\pm0.3)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (1.96\pm0.08)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 20\pm2$ nm</td>
<td>$s = 22\pm2$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 3.4\times10^2$</td>
<td>Error $= 2.9\times10^2$</td>
</tr>
<tr>
<td>35</td>
<td>$K_V = (4.4\pm0.2)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (1.90\pm0.05)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 24\pm2$ nm</td>
<td>$s = 27\pm2$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 2.8\times10^2$</td>
<td>Error $= 2.3\times10^2$</td>
</tr>
<tr>
<td>36</td>
<td>$K_V = (4.4\pm0.2)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (1.85\pm0.04)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 20\pm2$ nm</td>
<td>$s = 26\pm2$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 2.7\times10^2$</td>
<td>Error $= 2.3\times10^2$</td>
</tr>
<tr>
<td>38</td>
<td>$K_V = (4.4\pm0.1)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (1.92\pm0.04)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 20\pm3$ nm</td>
<td>$s = 27\pm3$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 2.4\times10^2$</td>
<td>Error $= 2.5\times10^2$</td>
</tr>
<tr>
<td>40</td>
<td>$K_V = (4.4\pm0.2)\times10^3$ J·m$^{-3}$</td>
<td>$K_S = (2.00\pm0.05)\times10^3$ J·m$^{-2}$</td>
</tr>
<tr>
<td></td>
<td>$s = 22\pm4$ nm</td>
<td>$s = 25\pm4$ nm</td>
</tr>
<tr>
<td></td>
<td>Error $= 3.1\times10^2$</td>
<td>Error $= 2.5\times10^2$</td>
</tr>
</tbody>
</table>
measurements performed in this chapter it is not possible to determine whether the latter assumption is justified.

4.5 Conclusions and future applications

In this chapter it was shown how the magneto-optical susceptometer is used to determine anisotropies in ferrofluid samples. Calibration of the setup showed a good agreement with VSM data and magneto-electrical susceptibility data, and anisotropy values derived from magneto-optical susceptibility measurements did not yield significantly different values from values derived using the magneto-electrical susceptibility data. Variations between fractions were observed in proportionality between the susceptibility derived from VSM and the measured (intensity) of the Faraday rotation, which could not be explained unambiguously. However, the anisotropy values derived from the (normalized) susceptibility curves of the fractions were consistent with the values derived from the susceptibility measurement of Resovist, which may indicate that the relation between susceptibility and frequency (of the applied field) is not influenced. In general, also because of the complex origin of the Faraday effect, further calibration measurements focusing on the dependence of the Faraday effect on parameters like wavelength, particle size, and composition of particles would improve the understanding of the Faraday effect and thereby also the reliability of the magneto-optical setup.

Analysis of magneto-optical susceptibility measurements showed that the measured curves can be explained by anisotropy constants of either $K_S = (1.9\pm0.3)\times10^{-5}$ J·m$^{-2}$ or $K_V = (4.4\pm1.1)\times10^{3}$ J·m$^{-3}$. The first constant can be related to surface anisotropy, while the second constant can be related to magnetostatic shape anisotropy. A combination of both types of anisotropy is also possible, but only for lower values of both constants (for example $K_S = 1\times10^{-5}$ J·m$^{-2}$ and $K_V = 2\times10^{3}$ J·m$^{-3}$ are a possible combination). The origin of the anisotropy in the measured samples could not be determined unambiguously. In literature, the surface anisotropy was considered as a better explanation because of the more rock-like shape of particles instead of an elliptical shape. Further, a size of 23±3 nm was determined from the susceptibility measurements for the polymer shell of the (larger) particles.

The full potential of the magneto-optical setup has not yet been employed. The frequency range of measurements can be improved by using other coils. With the developed setup it is further possible to study linear birefringence and intensity oscillations of light, which can provide information about orientation of particles. It is possible to measure at stronger field amplitudes to study non-linear effects of the magnetization. Higher harmonics in the signal can for example be studied as a function of frequency. An interesting potential application is to use the magneto-optical detection method as an in-line detector during fractionation experiments. However, for this application the sensitivity of the setup should be improved, since fractions are in general diluted to a large extend (1000x or more). Possible improvements of the setup can be achieved by focusing of the light beam through the sample, which narrows the volume in which the Faraday rotation is measured, and by reducing the field offset, for example by using an DC current through the coil to compensate for the earth magnetic field. This latter method should reduce the 1F signal measured without polarisers, which also limits the sensitivity of the setup. Finally, the setup could be placed in a better housing in order to reduce background light or other background signals.

In the next chapter the dynamic behaviour of nanoparticles in oscillating magnetic fields typical for MPI is studied, and the anisotropy values found in this chapter will be used, along with the size distributions determined in chapter 3, to explain this behaviour.
4.5. Conclusions and future applications

References

Chapter 5
Magnetic particle spectroscopy

In this chapter the dynamic (non-linear) behaviour is discussed of magnetic nanoparticles exposed to oscillating magnetic fields typical for MPI. As was described in paragraph 1.3, the relevant signal for MPI is obtained by measuring the higher harmonics of the applied frequency in the (time-varying) magnetization of magnetic nanoparticles. In the first section it will be considered how the intensity of these harmonics can be calculated from a known magnetization curve (as a function of field) for a ferrofluid. In the second section particle dynamics are discussed and two models are described which can be used to simulate the magnetization of magnetic nanoparticles in MPI. In the third section, a new analysis technique is described which has been developed at Philips Research called magnetic particle spectroscopy (MPS); the setup is in principle a zero-dimensional MPI scanner and measures the higher harmonics of the oscillating magnetization induced in the measured sample. MPS analyses of Resovist and fractions of Resovist are described and compared with simulations. In the fourth section the phase of the measured harmonics is discussed and compared with simulations (using modified models). The conclusions of this chapter are presented in the fifth and final section.

5.1 Calculation of frequency spectra

In general, a Fourier transform can be used to determine the frequency spectrum of a time-varying signal. For a discrete signal, spectral components can be determined using a discrete Fourier transform (DFT) [5.1]. For a magnetization $M(t)$ measured at $N$ (equidistant) time points $t_n$, the (complex) spectral components $\tilde{M}(k)$ can be determined as

$$\tilde{M}(k) = \frac{2}{N} \sum_{n=1}^{N} M(t_n)\omega_N^{(n-1)(k-1)}, \quad (5.1)$$

where $\omega_N = e^{-2\pi i/N}$. For a sampling rate $f_s$ and $M(t) = A \cos(2\pi(k-1)(f_s/N)t)$, the DFT defined by equation 5.1 yields $\tilde{M}(k) = A$ for $t_1 = 0$ and $k \leq N/2$. For a sine instead of a cosine $\tilde{M}(k) = i \ A$. In equilibrium, the magnetization of a ferrofluid can be described (as a function of field) using the Langevin function (see equation 2.17). For a distribution of particle sizes equation 3.2 can be applied. In an oscillating magnetic field $B = B_1 \cos(2\pi f_1 t)$, these equations remain valid as long as the magnetization relaxes almost instantaneously to equilibrium values. This latter requirement is discussed in the next paragraph. Assuming instantaneous relaxation, frequency spectra can be simulated using the Langevin function as shown in figure 5.1 for particles with a diameter of 10, 20, and 30 nm. As can be seen, the ratio between spectral components for two different particle sizes increases (in approximation) exponentially with frequency (note that the intensities of the spectral components are plotted on a logarithmic scale).

Since the magnetization is an odd function of the field, the frequency spectrum will only contain odd harmonics of the base frequency $f_1$ for magnetic field without an offset, as for odd integers $n$

$$\cos^n x = a_n \cos nx + a_{n-2} \cos(n-2)x + \cdots + a_1 \cos x, \quad (5.2)$$
with constants \(a_n\) [5.2]. The relation is similar for a sine. A comparable relation with even integers \(n\) is valid for even powers of sine or cosine. Therefore, also even harmonics will appear with an additional field offset, as \((b_1 \cos x + b_0)^n = b_1^n \cos^n x + b_1^{n-1} b_0 \cos^{n-1} x + \cdots + b_0^n\). We will come back to this in paragraph 5.3.2.

**Figure 5.1:** Magnetization curves (left), time-varying magnetizations (middle), and absolute spectral components in the magnetization for odd harmonics of \(f_1\) (right), simulated using the Langevin function for particles with diameters of 10, 20, and 30 nm with \(M_S = 3.4 \times 10^5\) A·m\(^{-1}\), \(T = 300\) K, \(B_1 = 10\) mT, and \(f_1 = 25.3\) kHz (immediate relaxation of particles is assumed). A sampling rate of \(f_s = 5\) MHz has been used. The frequency components below \(10^{-10}\) A·m\(^{-1}\) are due to discretization errors.

### 5.2 Particle dynamics in MPI

As can be seen in figure 5.1, larger magnetic particles exhibit a more non-linear response of the (equilibrium) magnetization to the applied magnetic field. This results in higher intensities of the measured spectral components. However, the Néel and Brownian relaxation times (equations 2.20 and 2.23) also increase with increasing particle size and will therefore limit the size of particles useful for MPI. To determine the optimal size of particles for MPI tracers, it is thus required to know how the relaxation of particles influences the magnetization. This is not straightforward because of the non-linear behaviour which is of interest. A correct description would require describing the magnetization processes using the Fokker-Planck equation [2.13-2.14,2.17,2.21]. However, this is out of the scope of this study. In this chapter, a number of simplifications will be applied to obtain compact models which will be compared with spectra measured with MPS. These models can be useful to perform MPI image simulations.

For (almost) instantaneous relaxation, the magnetization of an ensemble of magnetic particles in an oscillating field can thus be described using the equilibrium magnetization curve. The duration of the relaxation processes in these particles should in this case be well below the characteristic time of the field oscillations \(\tau_m = 1/(2\pi f_1)\). If characteristic relaxation times of particles are much above \(\tau_m\), magnetic moments of particles are not able to align with the oscillating field. The magnetization of these particles will thus hardly reach saturation values or even remain zero. Therefore, these particles will have a negligible contribution to the harmonics in the measured frequency spectrum of the magnetization, except for a possible contribution to the first harmonic (since the first harmonic represents the linear response). The magnetization in particles with characteristic relaxation times close to \(\tau_m\) is difficult to describe, and we will come back to this in paragraphs 5.2.1-5.2.4.
Whether Néel or Brownian relaxation determines the characteristic relaxation time depends on the size and anisotropy of particles. A number of regimes can be defined depending on the magnetic anisotropy energy \( E_a = K_s S + K_V V \) and depending on the magnetic energy \( mB \). For \( E_a \ll k_B T \), the magnetic moment of a particle is not coupled to the (external) orientation of the particle, and relaxation is only due to internal orientation of the magnetic moment (Néel relaxation). Relaxation times are in this case of the order of \( \tau_N \sim 10^{-8} \text{ s} \) (see equations 2.19-2.21). Relaxation can therefore be considered as instantaneous in MPI, with typical field frequencies \( f_1 \sim 25 \text{ kHz} \). For \( E_a \gg k_B T \) (or \( E_a > 14 k_B T \)), the moment of a particle can be considered as fixed to the orientation of the particle (at least at time scales typical for MPI). Relaxation is in this case only due to orientation of magnetic moments as a result of orientation of the particle as a whole (Brownian relaxation). The relevant characteristic relaxation time is in this case \( \tau_B \). For \( E_a \sim k_B T \), relaxation is due to a combination of Brownian and Néel relaxation. For \( mB < k_B T \), particles are almost randomly oriented and the characteristic relaxation time is determined by \( \tau_{\text{eff}} \), a combination of both \( \tau_B \) and \( \tau_N \) according to equation 2.24. For \( mB > k_B T \), the orientation of particles is not random anymore and a large fraction of particles are aligned parallel with their easy axis to the applied field. Three (ultimate) situations may occur. The magnetization hardly reaches equilibrium values if \( \tau_{\text{eff}} \gg \tau_m \). The magnetization reaches equilibrium values if \( \tau_B < \tau_m \). An interesting situation occurs if \( \tau_N < \tau_m \) and \( \tau_B \gg \tau_m \). In equilibrium, the distribution of particle orientations (i.e. the orientation of their easy axes with respect to the field) will vary as a function of the applied field. However, for \( \tau_B \gg \tau_m \) particles are not able to orient fast enough in an oscillating field to reach these equilibrium distributions. The larger \( \tau_B \) will be, the more it is likely that the distribution of orientation will not vary and thus can be considered to remain quasi-fixed in an oscillating field. Since \( mB > k_B T \), such a quasi-fixed distribution of orientations will have a relatively large fraction of particles aligned with the field compared with a random distribution of orientations. Since the magnetic moment of a particle both tends to align with the field and with the easy axis of the particle, this quasi-fixed distribution will influence the magnetization values. Thus, even if \( \tau_N < \tau_m \), it cannot simply be assumed that the magnetization reaches equilibrium values in an applied oscillating field. We will come back to this in paragraph 5.2.3, where distributions of orientations are calculated. The discussed situations are summarized in table 5.1.

### Table 5.1: Regimes of magnetization relaxation

<table>
<thead>
<tr>
<th>( E_a )</th>
<th>( mB &lt; k_B T )</th>
<th>( mB &gt; k_B T )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_a \ll k_B T )</td>
<td>Internal relaxation</td>
<td>Internal relaxation</td>
</tr>
<tr>
<td>( E_a \sim k_B T )</td>
<td>Relaxation if ( \tau_{\text{eff}} &lt; \tau_m )</td>
<td>Quasi-fixed orientations if ( \tau_N &lt; \tau_m ) and ( \tau_B \gg \tau_m ) or external relaxation if ( \tau_B &lt; \tau_m )</td>
</tr>
<tr>
<td>( E_a \gg k_B T )</td>
<td>External relaxation if ( \tau_B &lt; \tau_m )</td>
<td>External relaxation if ( \tau_B &lt; \tau_m )</td>
</tr>
</tbody>
</table>
For MPI, the regimes with $mb > k_B T$ are of interest because of the desired non-linear response of the magnetization to an applied field. The search for an optimal particle size implies that $E_a \sim k_B T$ or that $\tau_B \sim \tau_m$. For (the larger) particles in Resovist, a shell size of $s = 23\pm3$ nm was derived in chapter 4 from magneto-optical susceptibility measurements. For particles with a core of $d_c = 20$ nm and a polymer shell of $s = 20$ nm, thus with a hydrodynamic diameter of $d_h = 60$ nm, $\tau_B = 82$ $\mu$s (with $\eta=10^{-3}$ Pa-s) while $\tau_m = 6.4$ $\mu$s for $f_1 = 25$ kHz. The relaxation of (large) Resovist particles in MPI will therefore strongly depend on $\tau_N$. Two models are described in the remainder of this section to simulate the magnetization of particles ($\tau_B > \tau_m$). One model is based on the Langevin function and the other model assumes quasi-fixed particle orientations.

### 5.2.1 Cut-off size

The Néel relaxation time increases exponentially with increasing particle size: $\tau_N \sim \exp[d_h^3]$ for, respectively, surface ($K_s$) or volume anisotropy ($K_V$). The transition from $\tau_N \ll \tau_m$ to $\tau_N > \tau_m$ thus occurs in a relatively small range of particle sizes. Therefore, it seems reasonable to assume a critical particle size above which particles will hardly contribute to the magnetization and below which particles will fully contribute to the magnetization. If the influence of particle orientations on the magnetization is further neglected, the particles below this critical size can be described by the Langevin function. This is in principle the first model, which we will call the ‘Langevin model’. Calculation of the magnetization is performed for a distribution of particle sizes using equation 3.2 in combination with an upper size limit. This upper size limit is thus the critical particle size, which from here will be called the cut-off size to reflect the abrupt transition assumed in the model.

To estimate this cut-off size for Resovist particles, the bimodal size distribution as derived from VSM magnetization curves in chapter 3 and the anisotropy values as derived from the magneto-optical susceptibility measurements in chapter 4 are used. Figure 5.2 shows the bimodal size distribution of Resovist and the susceptibility as a function of size calculated for $f_1 = 25.3$ kHz in one plot. The susceptibilities have been calculated using equation 2.27 and are normalized by $\chi_0 = (\chi_{0||} + 2\chi_{0\perp})$ for each size. The susceptibility curves have been plotted for either $K_s$ (green) or for $K_V$ (red). The dashed curves indicate the error margins. The characteristic time $\tau_m = 1/(2\pi f_1)$ corresponds to a normalized susceptibility of $1/\sqrt{2} \sim 0.7$ (for $|\chi/\chi_0| = |(1 + i\omega\tau)^{-1}| = 1/\sqrt{1 + (2\pi f_1 \tau)^2}$). For the level of $|\chi| = 0.7$, an estimated cut-off is 25 nm for both anisotropies. Because of the complex behaviour of the relaxation around $\tau_m$ it is difficult to predict which susceptibility level would actually provide the best estimate. Taking levels of $|\chi| = 0.5-0.9$ into account and accounting for the error of the anisotropies, an estimate range of 23-28 nm is found.

The inset in figure 5.2 shows the relative contribution of each particle size to the susceptibility of a Resovist sample at 25 kHz. This contribution is obtained by multiplying the non-normalized susceptibility by the volume-weighted distribution per size. This plot indicates that the major contribution to the magnetization is expected from particles between 20-30 nm. However, for a frequency spectrum of the magnetization, the intensities of the highest harmonics in the spectrum increase very fast as a function of size, as can be seen in figure 5.1. This implies that the largest contribution to the spectral intensities for the highest harmonics comes from particles around the cut-off size.
5.2. Relaxation times in MPI

A complication that has not yet been considered is that the Néel and Brownian relaxation times according to equations 2.20 and 2.23, respectively, are valid for \( m_B < k_B T \). For \( m_B > k_B T \), actual relaxation times can be more complicated. In this paragraph these complications are considered, and possible other characteristic relaxation times are discussed.

The Brownian relaxation time is derived assuming that thermal (rotational) fluctuations are acting against viscous forces [5.3]. However, for \( mB > k_B T \) the magnetic torque acting on the particles starts to dominate over the thermal forces. Table 5.1 shows the energy ratio \( \xi = mB/k_B T \) for particle ensembles of different sizes in a magnetic field of \( B = 10 \text{ mT} \) (for \( M_S = 3.4 \times 10^5 \text{ A·m}^{-1} \)).

### Table 5.1: Energy ratios for particles with various diameters

<table>
<thead>
<tr>
<th>Diameter (nm)</th>
<th>( \xi = mB/k_B T ) ((B = 10 \text{ mT}))</th>
<th>( h = mB/2E_a ) ((K_V = 4.4 \times 10^3 \text{ J·m}^{-3}))</th>
<th>( h = mB/2E_a ) ((K_S = 1.9 \times 10^5 \text{ J·m}^{-2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.43</td>
<td>0.39</td>
<td>0.15</td>
</tr>
<tr>
<td>20</td>
<td>3.4</td>
<td>0.39</td>
<td>0.30</td>
</tr>
<tr>
<td>30</td>
<td>12</td>
<td>0.39</td>
<td>0.45</td>
</tr>
<tr>
<td>40</td>
<td>28</td>
<td>0.39</td>
<td>0.60</td>
</tr>
<tr>
<td>50</td>
<td>54</td>
<td>0.39</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Figure 5.2: Bimodal size distribution of Resovist (left axis) and susceptibility values (normalized to equilibrium values) derived from magneto-optical susceptibility measurements for \( f_1 = 25 \text{ kHz} \). The red curves are plotted for \( K_V = (4.4 \pm 1.1) \times 10^3 \text{ J·m}^{-3} \) and the green curves are plotted for \( K_S = (1.9 \pm 0.3) \times 10^5 \text{ J·m}^{-2} \). A shell size of 20 nm was assumed and \( \alpha = 0.1 \). The inset shows the relative contribution for a particle size to the susceptibility. This contribution was calculated by multiplying the size distribution with the non-normalized susceptibilities for \( K_S = 1.9 \times 10^5 \text{ J·m}^{-2} \).
For particles with their magnetic moment fixed to the easy axis (i.e. the magnetic anisotropy effect is very strong), the magnetic torque acting on the particles is equal to $\mathbf{m} \times \mathbf{B}$. In this case, the characteristic time for the relaxation (due to magnetic torque) can be expressed as [5.3]:

$$\tau_{ex} = \frac{6\eta V_h}{mB}. \quad (5.3)$$

This characteristic relaxation time is plotted as a function of particle size in figure 5.3 for a field of 10 mT and assuming $s = 20$ nm. As can be seen for particles up to 50 nm, $\tau_{ex} > \tau_m$ at 25 kHz. In case the magnetic moment is not fixed to the easy axis, the magnetic torque acting on the particle will be smaller and the characteristic time will thus become even longer. Note that in the limit $s \to 0$, $\tau_{ex} \approx 2.5 \mu s$ and thus $\tau_{ex} < \tau_m$.

Also Néel relaxation depends on the field strength. In this case, the energy ratio $h = mB/2E_a$ is of importance. This parameter is presented in table 5.1 for a number of particle sizes, both for volume and surface anisotropy. For $\sigma = E_a/k_B T \geq 5$, $h < 0.5$ and a particle aligned with the field, internal relaxation times become [5.4]:

$$\tau^\pm = \frac{\tau_0}{(1 \pm h)(1 - h)^2} \exp(\sigma(1 \pm h)^2), \quad (5.4)$$

with $\tau_0$ from equation 2.21. The internal relaxation time $\tau^+$ applies to a transition of the magnetic moment from parallel with the field to anti-parallel, while $\tau^-$ applies to the opposite transition. In figure 5.3 both characteristic times are plotted for volume and for surface anisotropy. The plot for $\tau^-$ indicates that even a cut-off up to 34 nm could be possible in case of volume anisotropy, or even higher for surface anisotropy. For surface anisotropy equation 5.4 becomes invalid from ~34 nm.

\[Figure 5.3: \text{Relaxation times as a function of particle size for } B = 10 \text{ mT. To calculate the internal relaxation times, either } K_V = 4.4 \times 10^3 \text{ J} \cdot \text{m}^{-1} \text{ or } K_S = 1.9 \times 10^5 \text{ J} \cdot \text{m}^{-2} \text{ have been assumed (with } \alpha = 0.1). \text{ The relaxation time } \tau_- \text{ for } K_S \text{ has been plotted until } h = 0.5; \text{ above, the used expression is not valid.}\]
The values found for $\tau^-$ may indicate a possible higher cut-off than within the range of 23-28 nm as estimated in paragraph 5.2.1. However, it has to be realized that an accurate description of the internal remagnetization is very complex. Equation 5.4 is only valid for particles with the easy axis parallel to the field, while the probability to find a particle with the easy axis exactly parallel to the field equals zero. A better description requires taking the distribution of easy axes into account. Also, for measurements performed at high frequencies the remagnetization behaviour is not described anymore by a single relaxation time, but requires a more complex path with several characteristic relaxation times [5.3]. In the next paragraph, it is considered how the orientation of particles can influence the magnetization in a ferrofluid.

5.2.3 Orientation of particles

For the second model, the quasi-fixed orientation of easy axis will be taken into account. To study the orientation of particles in a ferrofluid, the magnetic (equation 2.16) and anisotropy energies (equations 2.7-2.8, 2.10-2.12) in nanoparticles need to be considered. The relevant directions are the direction of the field $\mathbf{B}$, the direction $\mathbf{n}$ of the easy axis of a particle, and the direction of the magnetic moment $\mathbf{m}$. In case of uniaxial anisotropy (see paragraph 2.2.2) the energy potential for a particle is given by [5.3]:

$$E = -\mathbf{m} \cdot \mathbf{B} - (\mathbf{e} \cdot \mathbf{n})^2 E_a,$$

(5.5)

where $E_a = K_s S + K_v V$ and $\mathbf{e} = \mathbf{m}/|\mathbf{m}|$. For an angle $\theta$ between $\mathbf{n}$ and $\mathbf{e}$, the anisotropy term can be written as $-E_a \cos^2 \theta = E_a + E_a \sin^2 \theta$, which yields effectively a similar relation as equation 2.12. From here, we define the $z$-axis as the axis along which the field is applied.

If particles are able to orient freely within the relevant time frame, the second term on the right can be neglected in the calculation of the magnetization. The relevant energy potential is in this case described by $E = -\mathbf{m} \cdot \mathbf{B}$ and the magnetization can be described using the Langevin function (see equations 2.15-2.17). However, if particles are not able to rotate freely, the second term needs to be taken into account and the Langevin function is not valid anymore. To calculate the magnetization in Resovist, all possible orientations of $\mathbf{n}$ need to be taken into account as well. The probability (in equilibrium) to find a particle with certain $\mathbf{e}$ and $\mathbf{n}$, with respect to a field $\mathbf{B}$ is proportional to $\exp(-E(\mathbf{B}, \mathbf{e}, \mathbf{n})/k_B T)$. The probability distribution of $\mathbf{n}$ for magnetic particles in equilibrium can therefore be expressed as

$$p(\mathbf{n}) d\mathbf{n} = \frac{\int \exp\left(-\frac{E(\mathbf{B}, \mathbf{e}, \mathbf{n})}{k_B T}\right) d\mathbf{e}}{\int\int \exp\left(-\frac{E(\mathbf{B}, \mathbf{e}, \mathbf{n})}{k_B T}\right) d\mathbf{e} d\mathbf{n}}.$$

(5.6)

Figure 5.4 shows numerical evaluations of this equation. The probability to find a particle with an easy axis at an angle $\varphi$ with respect to the $z$-axis has been plotted. The equation has been evaluated for an ensemble of particles with a diameter of 25 nm, $M_s = 3.4 \times 10^5$ A·m$^{-1}$, $K_s = 1.9 \times 10^{-5}$ J·m$^{-2}$, and for field values from 0 to 10 mT. Note that $\varphi$ is plotted from 0 to $\pi/2$, since anti-parallel easy axes are similar (see equation 5.5). For zero field a random distribution of particles is found. The probability to find a particle with its easy axis exactly parallel to the $z$-axis reduces to zero, while to probability to find a particle in a plane perpendicular to $z$ is largest.
5.2.4 Quasi-fixed particle orientations model

As was discussed in the beginning of section 5.2, in case of $E_a \sim k_B T$, $\tau_N < \tau_m$, and $\tau_B > \tau_m$, the limited Brownian relaxation can lead to an (almost) quasi-fixed distribution of particle orientations. If the shape of this quasi-fixed distribution is known, it is possible to calculate the (time-varying) magnetization assuming that the magnetic moments reach quasi-equilibrium states. A straightforward assumption for the quasi-fixed distribution would be to use the distribution corresponding to the time-average of the magnetic field (the RMS value, which equals $B_0/\sqrt{2}$). This assumption can further be defended by considering the forces acting on (the orientation of) particles during the field oscillations. On one hand, thermal forces ($\sim k_B T$) tend to orient particles towards a random distribution, which is the random distribution as plotted in figure 5.5 for zero field. On the other hand, the misalignment between the magnetic moment and easy axis of a particle causes a torque on the particle. Since moments tend to align with the field, this torque is on average towards the field direction. In the case of a particle with a diameter of 25 nm and with $K_s = 1.9 \times 10^{-5} \text{ J} \cdot \text{m}^{-2}$, the equilibrium distribution of particle orientations clearly deviates from a random distribution, as shown in figure 5.5. This indicates that the torque due to anisotropy is stronger than the thermal forces. Particles perpendicular to the field will therefore on average experience a strong torque towards the field direction, while only smaller thermal diffusion forces act on particles aligned with the field. It is therefore unlikely that the quasi-fixed distribution is close to a random distribution, and a distribution close to the equilibrium distribution for the average field value (of 7.1 mT for the case as shown in figure 5.5) seems more realistic.

For an quasi-fixed distribution of particle orientations $p(n)$ and if magnetic moments reach quasi-equilibrium states, the magnetization can be calculated as

$$M = M_S \int p(n) \frac{\int e \exp\left(-\frac{E(B, e, n)}{k_B T}\right) de}{\int \exp\left(-\frac{E(B, e, n)}{k_B T}\right) de} dn. \tag{5.7}$$

In figure 5.5A, spectra are shown calculated with equation 5.7 for particle sizes from 10-40 nm, $K_s = 1.9 \times 10^{-5} \text{ J} \cdot \text{m}^{-2}$, and $B_0 = 10$ mT. Spectra calculated with the Langevin function are shown for comparison. In figure 5.5B corresponding magnetization curves are shown. Figure 5.5C shows the
assumed distributions of easy axes in the ensembles (calculated with $B = 7.1$ mT). Calculations were performed with a discrete version of equation 5.7 and, for both $e$ and $n$, with steps of $\Delta \theta = 0.05$ from $\Delta \theta$ to $\pi - \Delta \theta$ for the zenith angle and of $\Delta \varphi = 0.05$ from 0 to $2\pi - \Delta \varphi$ for the azimuth angles. The figure clearly shows the influence of assuming a quasi-fixed distribution.

![Figure 5.5: Simulated spectra for $B_1=10$ mT and magnetization calculated with Langevin function (points) or with equation 5.7 (crosses) for $K_s =1.9 \times 10^5$ J·m$^{-2}$ (A), with corresponding magnetization curves (B), and assumed distribution of easy axes (C).]
Chapter 5. Magnetic particle spectroscopy

For the second model, the Langevin function in equation 3.2 is replaced by equation 5.7. For each particle size, the equilibrium distribution for a field of $B_0/\sqrt{2}$ is used as the quasi-fixed distribution. Also for this model a cut-off size is used. This model is called the ‘quasi-fixed orientations model’. The both models are thus similar in the assumption of a cut-off size, but differ in the used equation to describe the magnetization for a single particle size.

5.3 Magnetic particle spectrometer and results

In this section the two models are compared with measured spectra using the magnetic particles spectrometer (MPS). First the MPS setup is described. Then analyses of Resovist, fractions of Resovist, and Resovist with increased viscosity are presented. The cut-off size of the models will be determined based on a comparison with the measured MPS spectra.

5.3.1 MPS setup

The MPS setup is designed to generate a magnetic field oscillating at 25.3 kHz without substantial higher harmonics. The field amplitude can be set up to 25 mT. A sample is placed in the solenoid which produces the magnetic field. The induced field in the sample is measured using a Helmholtz-coil set. The signal induced in the receiving coils is filtered in order to suppress frequencies around the frequency of the generated magnetic field. In this way the higher harmonics in the signal, due to the non-linear magnetization behaviour of the sample, can be measured more sensitively. However, it also implies that the first harmonic of the magnetization is unknown. The measured signal is averaged for 30 seconds and a discrete Fourier transform is performed on the averaged signal (according to equation 5.1). The output is thus a frequency spectrum of the magnetization induced in the sample. The setup is calibrated in order to express the measured intensities as magnetic moment (note that the measured intensity is a voltage). The measured magnetic moment is converted to magnetization (of iron oxide) using the sample volume and iron concentration of the sample (similar as for the VSM magnetization curves in chapter 3). The measured spectral components are complex numbers. In this paragraph only the intensity of the spectra is compared. In paragraph 5.4 the phase of the spectral components is also briefly discussed. All measurements have been performed at room temperature.

5.3.2 Measurements of Resovist

Figure 5.6 shows a measured MPS frequency spectrum of Resovist. The spectrum is compared with the ‘Langevin model’ and the influence of the size distribution is considered as well. Of the measured MPS spectrum of Resovist are shown: spectral components at the odd harmonics ($1f_1$, $3f_1$, ...), at the even harmonics ($2f_1$, $4f_1$, ...), and the average intensity (between two harmonics) of non-harmonic spectral components. The even harmonics can be explained by an additional field offset of 30 µT, which is of comparable strength as the earth magnetic field. This is shown by the curves simulated with the Langevin model including an additional field offset. The simulated curves have been plotted both for a log-normal distribution of particle sizes in Resovist and for a bimodal distribution. The size distributions used in these simulations were determined for a size range of 0.8 – 50 nm. Two simulated curves are shown for the complete range of sizes for both the log-normal as the bimodal (log-normal) distribution. The higher intensities in case of the log-normal distribution reflect the overestimation of particles with a large size as was discussed in chapter 3.
The lower intensities of spectral components (at harmonic frequencies) measured for Resovist compared with the spectrum simulated for the full size range, indicate the relevance of relaxation of particles. With a cut-off at 34 nm, all measured components are below the simulated components until approximately 1.5 MHz where noise sets in. For most components, however, intensities are overestimated, especially for the bimodal distribution. This could reflect a better description of relevant particle sizes by the log-normal distribution, although it could as well be merely a coincidence. Namely, the overestimation can be related well to the sharp cut-off of the used model. If a cut-off of 28 nm is used, the first harmonic components in the spectrum are fitted well. From approximately 1 MHz, the slope of the simulated curve with a cut-off at 37 nm becomes almost parallel to the measured curve. This could be related to 37 nm particles which dominate this part of the spectrum. Two effects can be considered: a fraction of ~10 vol-% of 37 nm particles has a lower anisotropy, for example because they are more spherical; or the relatively long relaxation time for 37 nm particles causes that their contribution to the spectrum, compared with as if they were in equilibrium, is reduced to ~10%. Thus, instead of a sharp cut-off used in the Langevin model, a smoother cut-off range of 28-37 nm can be estimated. This range is above the 23-28 nm estimated (initial) susceptibility values (paragraph 5.2.1), but in accordance with the 34 nm estimated with $\tau^{-}$ (equation 5.4 in paragraph 5.2.2).

![Figure 5.6: MPS spectra of Resovist and simulated spectra for $B_1=10$ mT. Simulations have been performed with the ‘Langevin model’ and the influence of the size distribution is considered. Also the odd harmonics are shown in this plot.](image)
From here, only the odd harmonics are considered. Figure 5.7 shows simulated curves using the ‘quasi-fixed orientations model’ (FM) for the bimodal distribution of Resovist. As shown in the graph, the possible errors due to an inaccurate estimate of the anisotropy are relatively minor. An interesting observation is that similar curves can be simulated as with the ‘Langevin model’ (LM), but in the case of FM the sizes are smaller. This is thus related to the influence of the quasi-fixed distribution of particle orientations. The plot indicates a cut-off range of 24-29 nm. This agrees well with the range of 23-28 nm from paragraph 5.2.1.

5.3.3 Measurements of fractions of Resovist

Figure 5.8 shows MPS spectra measured for the GFC fractions of Resovist as described in chapter 3. Only three fractions are shown: the curve of fraction 4 overlaps with the curve of fraction 2, while the curves for the fractions 36 and 38 are in between the curves of fractions 35 and 40. The curves are compared with both models and the values from table 3.2 have been used for the size distribution. Also here, the curves with a cut-off of 34 nm for the ‘Langevin model’ (LM) are comparable to the curves with a cut-off of 27 nm for the ‘quasi-fixed orientations model’ (FM). An interesting observation is that especially the curves for fraction 2 with cut-offs of 34 nm (LM) and 27 nm (FM) are clearly above the measured curve. While for a cut-off of 24 nm (FM), the simulated spectral components correspond well at the first harmonics with the measured components of fraction 2 and 40. An explanation for the relatively large overestimation for fraction 2 with a cut-off of 27 nm (FM) is the relatively large fraction of particles between 24-27 nm.
The measured MPS curve of GFC fraction 2 shows higher intensities than the curves for the other fractions. However, one could expect based on the increasing relaxation times for larger sizes that intensities would start to decrease at some point for fractions with increasing particle size. This has indeed been observed. Figure 5.9 shows three fractions from an SdFFF fractionation experiment (see paragraph 3.2.1) with (volume-weighted) hydrodynamic sizes determined with DLS. As a reference, this size is $55.5 \pm 22.5$ nm for GFC fraction 2 (see table 3.2). The curves of the SdFFF fractions and of Resovist have been normalized by the intensity at the third harmonic, since iron concentrations were not determined for the SdFFF fractions.

Figure 5.8: MPS spectra of Resovist and GFC fractions including simulated spectra for $B_1 = 10$ mT. Simulations have been performed both with the ‘Langevin model’ (LM) and the ‘quasi-fixed orientations model’ (FM) (with $K_S = 1.9 \times 10^{-5}$ J·m$^{-2}$). Sizes in legend are cut-off sizes.

Figure 5.9: MPS spectra of Resovist and three SdFFF fractions of Resovist ($B_1 = 10$ mT). Sizes have been determined with DLS (and are volume-weighted). Spectra are normalized with the intensity of the 3rd harmonic, since iron content has not been determined for fractions.
5.3.4 Measurements of Resovist in Natrosol

For particles with a core of $d_c = 20$ nm and a polymer shell of $s = 20$ nm, thus with a hydrodynamic diameter of $d_h = 60$ nm, the Brownian relaxation time is $\tau_B = 82 \, \mu$s (with $\eta = 10^{-3}$ Pa·s). This is above the characteristic time of MPS, which is $\tau_m = 6.4 \, \mu$s for $f_1 = 25$ kHz. It is therefore expected that Néel relaxation is dominant. This can be verified experimentally by increasing the viscosity of Resovist, since $\tau_B$ scales linearly with the viscosity (see equation 2.23), while the internal remagnetization time is independent of the viscosity. The viscosity of Resovist has been varied by adding hydroxyethylcellulose (produced by Hercules with trade name Natrosol), which is a water-soluble polymer used to produce solutions having a wide range of viscosities. Two samples of 100x diluted Resovist were prepared with 1 wt-% and 5 wt-% of Natrosol, which had a viscosity of respectively $3.3 \, \text{Pa·s}$ and $500 \, \text{Pa·s}$ (determined with a rheometer). The viscosity of undiluted Resovist is $1.03 \times 10^{-3} \, \text{Pa·s}$ (for $T = 310$ K) [5.5], which is slightly higher than the viscosity of $7 \times 10^{-4} \, \text{Pa·s}$ (for $T = 310$ K) for demiwater [5.6]. Figure 5.10 shows the measured spectra for Resovist with the different viscosities. The curves of Resovist without and with 1 wt-% of Natrosol overlap, which indicates that internal remagnetization is the dominating mechanism. The curve with 5 wt-% of Natrosol deviates up to a factor 2 lower for the highest harmonics shown. The deviation in the latter case can be explained by the assumption of quasi-fixed orientations. The duration of the acquisition of an MPS spectrum is 30 seconds. For $\eta = 3 \, \text{Pa·s}$, $\tau_B \sim 0.1-1 \, \text{s}$ (for $d_h \sim 60$ nm) and particles are able to align towards there quasi-fixed distribution at the onset of the measurement. For $\eta = 5 \times 10^2 \, \text{Pa·s}$, $\tau_B \sim 10-100 \, \text{s}$ and the random distribution at the onset of the measurement only gradually changes towards the quasi-fixed distribution.

![Figure 5.10: MPS spectra of Resovist samples with varying viscosities ($B_1 = 10$ mT).]

5.3.5 Discussion of results

Mainly the results with the varying viscosities support the assumption of a quasi-fixed distribution. The simulations with the ‘quasi-fixed orientations model’ indicated a smooth cut-off range of 24-29 nm to be more appropriate than a sharp cut-off. An optimal particle size for MPI would therefore be within this range. This range corresponds well with the range of 23-28 nm as estimated from the susceptibility curve as plotted in figure 5.2.
5.4 Phase of spectral components

So far, the phase of the spectral components has not been considered. As mentioned in paragraph 5.1, the DFT of a cosine yields a real spectral component equal to the amplitude of that cosine. If a magnetic field $B = B_1 \cos(2\pi f_1 t)$ is applied, the magnetization calculated with the Langevin function or equation 5.7 contains only cosine terms. The phase of the spectral components can therefore only be $0^\circ (+)$ or $180^\circ (-)$. The phase of the spectral components obtained with the simulations so far show indeed alternating $0^\circ$ (for harmonics $1f_1, 5f_1, 9f_1, ...$) and $180^\circ$ (for harmonics $3f_1, 7f_1, 11f_1, ...$). For a real spectrum components can be complex. Due to relaxation, the magnetization starts to lag behind the applied field (hysteresis occurs). This lag in time yields complex spectral components. The phase of the spectral components may therefore provide interesting information about relaxation processes.

To take the dynamic response of the magnetization to the applied field into account, a simple differential equation is assumed here. This differential equation is:

$$ \frac{dM}{dt} = \frac{M_{eq} - M}{\tau}, $$

(5.8)

where $M_{eq}$ is the magnetization calculated with either the Langevin function or equation 5.7 (for one particle size) and $\tau$ a characteristic relaxation time (note that this is the same equation as equation 2.25). The magnetization in a ferrofluid with a distribution of particle sizes can be calculated by integrating over all particle sizes, according to equation 3.2. Using equation 5.8, no cut-off size is required anymore to simulate the magnetization of a ferrofluid in MPS. In figure 5.12, simulated spectra using equation 5.8 are compared with the measured MPS spectrum of Resovist. The bimodal distribution of Resovist was assumed for the simulated spectra. The (quasi)equilibrium magnetization $M_{eq}$ has been calculated either with the Langevin function or with equation 5.7. For $\tau$ the Néel relaxation time is used or $\tau_-$ from equation 5.1 with $B = 7.1$ mT (note that $\tau_-$ depends on the field strength). Figure 5.12B shows the phase of the components for the spectrum of Resovist and figure 5.12C shows the phase for the simulated spectrum assuming a quasi-fixed orientation of particles and $K_s = 1.5 \times 10^5$ J·m$^{-2}$ (just below $K_s = (1.9 \pm 0.3) \times 10^5$ J·m$^{-2}$ as found with the magneto-optical susceptibility measurements). Note that the phase of the first spectral component of Resovist is not reliable, since the first harmonic is filtered with MPS. The phase plots of figures 5.12B and 5.12C do not correspond completely, but at least a similar trend is observed for the phase of the first components in the spectrum.

The results as presented in figure 5.12 indicate therefore that equation 5.8 can be useful both to simulate the actual smoothness of the transition from particle with $\tau_N \ll \tau_m$ to particles with $\tau_N \gg \tau_m$ and to simulate complex spectral components. A more accurate description of the spectrum would require using more time constants to described, as calculation with the Fokker-Planck equations have shown that relaxation mechanisms have a number of characteristic time constants [5.7].
In this chapter measured MPS spectra of Resovist have been compared with simulations. Two models have been used to simulate curves, one based on the Langevin function and the other assuming a quasi-fixed distribution of particle orientations. The model based on the Langevin function in combination with the Néel relaxation time and anisotropy values found with the magneto-optical susceptometer cannot explain the measured spectrum of Resovist, as indicated by the range of cut-off sizes above the range estimated based on the susceptibility for those anisotropy values. It can be assumed that the Néel relaxation time needs to be modified to account for relatively strong fields, which could explain the difference. In the other model the orientation of the particles orientation is assumed to be quasi-fixed for the used field frequency. With this model the spectrum of Resovist and fractions can be explained with the Néel relaxation time and the

Figure 5.12: MPS spectra simulated using differential equation with a constant relaxation time. Intensity spectra are plotted (A), and phase plots for the measured spectrum of Resovist (B), and the simulated spectrum for quasi-fixed orientations with $K_s = 1.5 \times 10^{-5}$ J/m$^2$ (C).

5.5 Conclusions

In this chapter measured MPS spectra of Resovist have been compared with simulations. Two models have been used to simulate curves, on based on the Langevin function and the other assuming a quasi-fixed distribution of particle orientations. The model based on the Langevin function in combination with the Néel relaxation time and anisotropy values found with the magneto-optical susceptometer cannot explain the measured spectrum of Resovist, as indicated by the range of cut-off sizes above the range estimated based on the susceptibility for those anisotropy values. It can be assumed that the Néel relaxation time needs to be modified to account for relatively strong fields, which could explain the difference. In the other model the orientation of the particles orientation is assumed to be quasi-fixed for the used field frequency. With this model the spectrum of Resovist and fractions can be explained with the Néel relaxation time and the
anisotropy values from chapter 4. A combination of the quasi-fixed orientations model with modified relaxation times would lead to much higher intensities of the simulated spectral components than measured (see figures 5.5 and 5.7). It has been shown experimentally that the spectrum of Resovist hardly changes when the viscosity is increased; this result favours the model with the quasi-fixed orientation of particles. Further, it has to be realized that the behaviour for a particle with a Néel relaxation time longer than the characteristic MPS time will show a very complex behaviour: during an oscillating period the relaxation time will be too long if the field is close to zero, while the relaxation time could be short enough when the field is close to its maximum. It also has to be considered that the internal remagnetization time will depend on the orientation of the easy axis with respect to the field. In case that the Néel relaxation time is short enough, the particles moment reorients fast enough during the whole oscillation of the applied magnetic field (and for all orientations) to reach the equilibrium distribution of magnetic moment directions. This consideration favours the model with quasi-fixed easy axis distribution as well. Therefore, the model with the quasi-fixed orientation of particles is considered as the best model to explain the MPS spectrum of Resovist. Of course, a combination of both models can describe a more realistic situation: a reduction in intensity of high harmonics due to some orientational relaxation of particles could be compensated by a reduced relaxation time. Based on the quasi-fixed orientations model the optimal particle size can be estimated to be between 24-29 nm. According to the Langevin model and reduced relaxation times, an optimal size up to 37 nm could be possible.

Also the phase of the spectral components has partly been explained by using a simple differential equation in combination with a constant time constant. However, the actual dynamic situation will be more complex. Simulations could be improved by describing the variations in the distribution of particle orientations and magnetic moment orientations for a field varying in time using (a numerical implementation of) the Fokker-Planck equation. This could provide an accurate description of the behaviour of a particle ensemble. However, it should be realized that this will be a complex task and, to come to a better description of the MPS spectrum of Resovist, also the description of other particle properties should be improved, including the size distribution, the distribution of particles shapes (and thus a distribution of anisotropy values), and other varying properties (between magnetic particles) like magnetization saturation, composition, and shell size.

The quasi-fixed orientation model can be verified further by a number of experiments: MPS spectra can be measured at different frequencies, magnetic particles with various shell sizes can be used, and more monodisperse samples with particles of various sizes could be measured (either obtained through synthesis, fractionation, or a combination of both).

An interesting remark is that the quasi-fixed orientation of particles could be beneficial for the actual application of magnetic nanoparticles in medical imaging. In various parts of the body the viscosity may be different: in case of a quasi-fixed orientation of particles this will not lead to differences in the spectrum of magnetic particles, while this will be the case if external relaxation is relevant.

So far, we have been able to describe the size distribution and relaxation times of particles, and to link these parameters to the behaviour of magnetic particles in oscillating magnetic fields. In the next chapter, it will be considered how the behaviour of magnetic particles influences the achievable image quality in MPI.
Chapter 5. Magnetic particle spectroscopy

References

[5.2] Website:
[5.6] Website (last modification on 8 May 2009):
http://en.wikipedia.org/wiki/Viscosity
Chapter 6
Image simulation

Simulations of MPI images are presented in this chapter. The goal of these simulations is to relate particle characteristics to the image quality parameters resolution and sensitivity. The effects of a combination of particle sizes and of particle relaxation are considered in particular. Although a more accurate model to explain the behaviour of particles in an oscillating magnetic field was described in chapter 5, the simulations here are based on the Langevin function; simulations based on the model with a fixed orientation of particles are complex and calculations require a relatively long time.

This chapter is organized as follows: In the first section image quality parameters are described. The second section is about the image simulation model. In the third section the results obtained with this image simulation model are discussed. The fourth section presents the conclusions of this chapter.

6.1 Image quality

The usefulness of a particular medical imaging technique depends on the achievable image quality. Image quality depends on the imaging modality, on the characteristics and setup of the particular imaging system, but also on factors like the skill of the operator handling the system, patient characteristics, and imaging time. Six (most important) performance parameters can be used to assess the quality of a medical image: contrast, resolution, noise, artefacts, distortion, and accuracy [6.1]. These six parameters are briefly described here with respect to MPI.

6.1.1 Contrast

Contrast refers to the difference in imaging intensity of an object or target and surrounding objects or background. The ability of medical professionals to discriminate among anatomical or functional features in a given image strongly depends on contrast. A human body is in principle free from ferromagnetic substances, and therefore the contrast in MPI arises between regions with and without magnetic particles. For MPI, the achievable contrast is thus mainly determined by the ability to address regions of interest with magnetic tracer material.

6.1.2 Resolution

Resolution is the ability of an imaging system to distinguish and depict two signals that differ in space, time, or energy as distinct; one can speak of spatial, temporal, and spectral resolution, respectively [6.1]. Temporal resolution can be very short in MPI, and it is in principle possible to measure real-time (>46 fps). In paragraph 6.1.3, temporal resolution is discussed in relation to noise. In this paragraph, spatial resolution is considered and from here we will speak about resolution instead of spatial resolution. The ability to distinguish two objects from each other is related to the amount of smearing, or blurring, of an individual object; this is illustrated in figure 6.1. Less smearing of objects implies that the separation between the objects can be smaller before they become indistinguishable. This can be used to determine the resolution of a medical imaging system. The (theoretical) response of an imaging system to a point impulse, or delta function, is called the point
spread function (PSF) [6.1]. For two points to be distinguishable, the separation distance between two neighbouring points should be at least the full width at half maximum (FWHM) of the PSF (see figure 6.1). The FWHM of the PSF is therefore a measure for the achievable resolution.

The resolution in MPI is determined by a number of factors. To obtain an understanding of these factors, it has to be considered how image reconstruction is performed in MPI. After an MPI scan has been performed, the time signals acquired in the receive coils are decomposed into spectral components $U_n$ using a discrete Fourier transform. In general, assuming a linear theory these frequency components can be expressed (for a 2-D scanner) as

$$U_n = \mathcal{G} \hat{C}$$

with $\mathcal{G}$ a vector containing $n$ (real and imaginary) spectral components from one or more receive coils and $\hat{C}$ the concentration at the $p$ positions at which a system function has been acquired. The
size of the system matrix $\mathbf{G}$ is thus $n \times p$. If $\mathbf{U}$ and $\mathbf{G}$ are known, the concentration $\mathbf{C}$ in the imaging plane is reconstructed using the inverse matrix of $\mathbf{G}$. For a well-defined reconstruction of $\mathbf{C}$, it is required that $n \geq p$ and that all system functions are orthogonal. It is still possible to perform a reconstruction for an ill-defined system (which is in general the case with MPI); in this case the achievable resolution will strongly depend on the quality (i.e. number of harmonics and orthogonality) of the system functions matrix and on the used reconstruction method.

First of all, the resolution is thus determined by the number of acquired system functions. For a field of view (FOV) of 20x20 mm with 100x100 acquired system functions, the resolution is at best 0.2 mm. However, to achieve this resolution, more than $100^2$ spectral components should be known (in the obtained signal and in each system function) and all system functions need to be orthogonal. The number of known spectral components is determined by the used drive field frequencies and by the noise level. It is known from previous chapters that the number of harmonics above the noise level is strongly related to particle size; this is one way in which particle size is related to resolution. The orthogonality of the system functions is also determined by the particle size, which was expressed in chapter 1 by the theoretical resolution $2B_k/X_s$. The steeper the magnetization curve of a magnetic tracer and the higher the field gradient, the better distinguishable signals (system functions) are generated by two neighbouring positions. Other factors that can influence the quality of the system functions include the (receive) coil configuration of the scanner, the selection field gradient, and the trajectory of the field-free point [6.2].

### 6.1.3 Noise

Noise is any random fluctuation in an image and generally interferences with the ability to detect a signal in an image. The achievable sensitivity is thus mainly determined by the noise level. For MPI the noise level is mainly determined by the instrumental noise in the receiving coils and recording electronics. As discussed in the previous subsection, the noise level is strongly related to the resolution. A higher noise level implies less usable spectral components. Detection is then still possible based on the lowest harmonics, but the localization of particles becomes more difficult (i.e. the achievable resolution becomes worse). Noise is also related to temporal resolution: a longer signal acquisition time reduces the noise level through averaging of the signal during the acquisition time, but this also implies a longer temporal resolution.

### 6.1.4 Artefacts and distortion

Two types of non-random effects which influence image quality are artefacts and distortion. Artefacts are false signals in an image that do not represent any valid structural or functional signal in the patient. For example movements of the patient in the scanner can lead to motion artefacts. This example is not significant in MPI in case real-time imaging is performed. Distortion is any geometric inaccuracy in size, shape, position, or other geometric characteristics. An example of size distortion would be if (for any reason) objects of the same size located in different regions in the body/FOV appear to have a different size on the acquired image.
Chapter 6. Image simulation

6.1.5 Accuracy

Ultimately, the quality of medical images should be judged on their utility in the context of a specific clinical application. This is expressed by the accuracy of medical images, where accuracy means both conformity to truth and clinical utility. Quantitative accuracy refers to the accuracy, compared with the truth, of numerical values obtained from an image. Diagnostic accuracy refers to the accuracy of interpretations and conclusions about the presence or absence of disease drawn from image patterns.

Of the six described performance parameters, the focus in this study will be on resolution and sensitivity (or noise). Other factors, like for example distortion, could be assessed as well (to some extent) with image simulations. For the eventual determination of (diagnostic) accuracy, (pre)clinical trials with MPI are required.

6.2 Simulation model

The first (detailed) MPI image simulations were described in [6.3], where estimates for resolution and sensitivity were provided for ensembles of iron oxide (magnetite) particles with diameters of 20, 30, 40, and 50 nm of which the magnetization was described by the Langevin function (equation 2.17). It was demonstrated that resolution and sensitivity improve with increasing particle size. The main objective of this work is to study the effect of improved particle models on image simulations. For this purpose a new MPI image simulation tool was developed in MATLAB which can be used to simulate in 2D or 3D, and which can be easily adjusted for different scanner geometries, field settings, or simulation grids. More details on this tool are found appendix E. In this study only 2D simulations are performed and optimization of scanner parameters is not considered. The scanner geometry, applied magnetic fields (or scanning trajectory), the noise model, and reconstruction methods used in this simulation study are adopted from [6.3]. In this paragraph are described: the simulation of the scanner, the simulation of the magnetization (or particle model), the objects and system functions used for simulation, and the reconstruction of images.

6.2.1 Simulation of the scanner

The schematic setup of the simulated scanner geometry is shown in figure 6.2 (along with an example of a scanning trajectory). Two pairs of circular coils are shown which are used for field generation. The diameter of the coils is 0.5 m and the coils of each coil pair are 1 m apart. The coils along the x-direction generate a static field gradient with a field free points (FFP) in the centre of the setup for localization (the selection field, see paragraph 1.3). The currents in the coil assembly are set to create at the FFP a field gradient of 2.5 T/m in the x-direction and therefore 1.25 T/m in the y- and z-directions. On top of this static field, oscillating magnetic fields (drive fields) are generated by both the coils in the x-direction and y-direction. The drive fields are used to simultaneously steer the FFP through the field of view (FOV) and to generate a signal from the magnetic tracer material. The amplitudes of the sinusoidal currents in the coil assemblies are set to create drive fields with amplitudes of 20 mT in both directions. In combination with the applied field gradient, the FFP therefore moves away from the centre up to 8 mm along the x-direction and up to 16 mm along the y-direction. The usable FOV is therefore 16x32 mm. Through the use of different frequencies for the drive fields in the x- and y-direction, the FFP moves along a continuous Lissajous trajectory over the FOV (see figure 6.2 for an example, or [6.2-6.3]). A frequency ratio of 99/98 has been used, and the
frequencies of the drive fields are 25.25 kHz and 25.51 kHz in the x- and y-direction, respectively. With these frequencies one Lissajous trajectory is completed within a time period \( t_p = 3.88 \) ms. To receive the generated signal, two rectangular coils are used. The coils have side lengths of 10 cm, and are placed at 15 and 10 cm from the centre for the coil arrangement normal to the x- and y-direction, respectively. The voltage signals generated in these coils are sampled at 20 MHz.

An important aspect of the simulation of the scanner is the noise model. Here, the noise model as described in [6.3] has been adopted. All noise sources in the system are combined into one noise source, represented by the resistance of the recording coils with a value of \( R_p \approx 0.185 \) m\( \Omega \) at 1 MHz. The noise voltage \( U_{\text{noise}} \) in the recording coils is expressed as

\[
U_{\text{noise}}^2 = 4k_B T \Delta f R_p \frac{t_p}{t_m},
\]

with \( T \) the absolute temperature, the bandwidth \( \Delta f = 10 \) MHz (half the sampling rate), and \( t_m \) the acquisition time. A single run of the Lissajous trajectory is simulated, and the averaging of several runs of the trajectory during the acquisition time \( t_m \) is expressed by the ratio \( t_p/t_m \). With the parameters as described above (and \( T = 300 \) K), the estimated noise levels are \( 5.5 \times 10^{-9} \) V, \( 1.7 \times 10^{-9} \) V, and \( 6.3 \times 10^{-11} \) V, for acquisition times of 3.88 ms, 40 ms (25 Hz), and 30 s, respectively.

Noise is simulated by generating random numbers (between zero and one) which are transformed with a box-Muller algorithm [6.3] to generate a Gaussian distribution of the noise voltage. The noise is scaled to a mean-square value equal to \( U_{\text{noise}}^2 \).

Figure 6.2: Schematic setup of simulated scanner geometry (left). The red circular coils are used for field generation: the coils along the x-direction produce the selection field and the drive fields are produced by both coil pairs. The blue rectangular coils are used to measure the induced signal. On the right an example of a Lissajous trajectory is shown (with \( f_2/f_1 = 21/20 \)).
6.2.2 Simple particle remagnetization models

In this study the simulation of the magnetic behaviour of particles is limited to the Langevin function (equation 2.17) (from here, particles simulated with the Langevin function are called ‘Langevin’ particles). However, the MPS spectrum of for example 25 nm particles assuming quasi-fixed orientations is comparable to the spectrum of 30 nm ‘Langevin’ particles which are free to orient (see figure 5.5). The simulations based on the ‘Langevin’ particles can therefore be considered to correspond in reality to particles with a smaller size. For the particle models in the chapter, a temperature of 300 K and a saturation magnetization of 3.4x10^5 A·m⁻¹ (typical for maghemite) are assumed.

Apart from simulations of particle ensembles with a single particle diameter, two relative simple models are used to study the performance in MPI of a real tracer (Resovist). The first model is based on the combination of two particle sizes as

\[ M = c_1 M_L(d_1) + c_2 M_L(d_2), \]

where \( M_L \) is described by the Langevin function. This model is used to get a first impression of the influence of a particle size distribution on image quality. The particles sizes and relative concentrations are determined by a fit of the MPS spectrum of Resovist acquired at 20 mT field amplitude. The fitted curve is shown in figure 6.3 (the spectrum is calculated from the magnetization curve as described in paragraph 5.1). The fitted particle diameters are \( d_1 = 22.37 \) nm with \( c_1 = 19.8 \) vol-% and \( d_2 = 31.30 \) nm with \( c_2 = 1.24 \) vol-%. Note that \( c_1 + c_2 = 21 \) vol-%, the remaining 79 vol-% is considered as not contributing to the higher (i.e. \( n>1 \)) harmonics in the frequency spectrum. The concentrations \( c_1 \) and \( c_2 \) are considered as relative to the iron oxide concentration in the ferrofluid. Thus, if later on a concentration of e.g. \( c = 0.1 \) vol-% of iron oxide is assumed for the ferrofluid, this ferrofluid contains in total \( c \cdot c_1 = 1.98 \times 10^{-2} \) vol-% of particles with a diameter \( d_1 \).

![Figure 6.3: MPS spectrum of Resovist (at 20 mT) fitted by a two-size particle model. The phase of the spectral components is shown on the right: fitted values are red and measured values blue.](image)

The magnetization relaxation time \( \tau \) of particles has not been taken into account in the first model. The second model is used to study the influence of magnetic relaxation. This model is based on a combination of two particle sizes as well. In this case, the smaller particles are simulated with the
Langevin function as before, which implies the assumption $\tau = 0$. Optimal particles would have a relaxation time close to the characteristic time of MPI, and therefore these particles are simulated using a characteristic relaxation time of $6.3 \, \mu s = 1/2\pi f_x$ (with $f_x = 25.3 \, \text{kHz}$). The magnetization of the relaxing particles is calculated using equation 2.25, for which the equilibrium magnetization is calculated using the Langevin function. The fitted particle sizes are $21.74 \, \text{nm}$ with $c_1 = 21.89 \, \text{vol}-\%$ ($\tau = 0$) and $33.04 \, \text{nm}$ with $c_1 = 14.79 \, \text{vol}-\%$ ($\tau = 6.3 \, \mu s$). The MPS spectrum for this model is shown in figure 6.4. Compared to the first model, the intensities of the simulated harmonics are comparable. The introduction of a relaxation time leads to an optimal fit with large particles with a higher concentration. While the intensities of the fitted spectral components are comparable, the second model leads to a more realistic description of the phase of the spectral components (see insets of figures 6.3 and 6.4).

**6.2.3 Objects and system functions**

Two types of objects are simulated: point functions (or delta probes) and cylinders. Point functions are a single volume element at a single point in space. They are used to determine resolution based on the FWHM of the PSF and are used to acquire the system functions matrix. Cylinders are used in phantom objects to simulate images. These cylinders are composed out of cubic volume elements of $20 \times 20 \times 20 \, \mu m^3$ which are represented by point functions in the centre of each element. For each volume element the magnetic field $B(t)$ at that position is simulated and the particle model is used to calculate the magnetization $M(t)$ for a ferrofluid at that point. Each volume element $\Delta V$ produces a magnetic moment equal to $m(t) = c \cdot \Delta V \cdot M(t)$, with $c$ the concentration of iron oxide (maghemite) expressed as a volume fraction.

For reconstruction of images, a data set of system functions is required (see equation 6.2). In this study two sets of system functions are used. The first set consists of point functions simulated at $100 \times 100$ positions distributed equidistantly over $20 \times 20 \, \text{mm}^2$. This set of system functions covers most of the FOV of $16 \times 32 \, \text{mm}^2$ determined by the field amplitudes and gradients. However, the distance between two neighbouring pixels is $0.2 \, \text{mm}$, which limits the accuracy of studying
resolutions with the PSF. A set of 2000x2000 points would reduce the distance to only 10 µm, but the required data array would be too large to handle within a reasonable time frame with the available computers. Therefore, a second set of 100x100 system functions is used which covers 1x1 mm² (around the centre of the setup). In this case the distance between neighbouring pixels is also reduced to 10 µm.

In the analyses performed in this chapter, no noise is added to the system functions. System functions depend on the scanner setup and on the used tracer, and could be averaged for a long time and be extrapolated using simulations; the acquisition of the signal from an object is more bound to time constraints and it is more difficult to perform extrapolation for an unknown object.

6.2.4 Reconstruction

In one scan of the Lissajous trajectory at a sampling rate of 20 MHz, a total number of 38809 spectral components are acquired per coil. To keep the required calculation time and the required amount of computer memory manageable, the number of harmonics is reduced to 2500 per coil. Selection has been performed by averaging all system functions and selecting the components with the highest average intensity. With 2 components per harmonics (real and imaginary), the resulting system function matrix \( \hat{G} \) is a square matrix with 10⁴x10⁴ components. Only harmonics from 25.8 kHz are taken into account, since in a real scanner the harmonics around 25.3 and 25.5 kHz need to be filtered out in order to improve sensitivity. The remaining components are selected based on the average intensity of the system functions.

Reconstruction of images is performed by the inversion of the matrix \( \hat{G} \) (see equation 6.2) using a zero-order regularization scheme with regularization parameter \( \lambda \) and singular value decomposition (SVD) as described in [6.3]:

\[
\tilde{C} = (G^H G + \lambda E)^{-1} G^H U = V(S^H S + \lambda E)^{-1} V^H G^H U, \tag{6.4}
\]

where the matrix \( S \) contains the singular values, \( V \) is the unitary matrix of the SVD, \( \lambda \) is the regularization parameter and \( E \) is the identity matrix. The superscript \( H \) denotes Hermitian conjugation. The regularization parameter \( \lambda \) is determined manually for each reconstruction by finding a trade-off between noise suppression and resolution. Values of 5x10⁴, 2x10⁴, and 1x10⁴ are tested with \( k \) an integer exponent. The reconstructed images are represented with a colour map ranging from dark blue to dark red for zero to maximal intensity.

6.3 Results and discussion

In this paragraph resolutions determined with the PSF are compared between models and image simulations of a phantom object are performed. Note that an accurate determination of resolutions is complex and may depend on a number of parameters, e.g. the position of an object with respect to the centre of the scanner (especially towards the end of the FOV) or the size of the imaged FOV. Further, it is not straightforward to translate resolutions obtained for these 2D simulations to resolutions achievable for a 3D scanner. The main interest in this study is to compare particle models with each other.
6.3.1 Resolution determined with PSF

In this part, the FHWM of a PSF from a point function positioned in the centre of the setup is used to determine resolution quantitatively. Figure 6.5 shows a reconstructed image and the normalized intensity along the x-axis (see figure 6.2) for an ensemble of 30 nm particles in case of system functions acquired in a plane of 20x20 mm$^2$. No noise (as discussed in 6.2.1) has been added to the signal in the receive coils. The FWHM of the peak is 0.5 mm along the x-direction and 0.8 mm along the y-direction. Note that the plotted intensity contains negative values which cannot be realistic; these values are a result of the applied reconstruction method.

The problem with the PSF described above is that the FWHM has to be determined using only a few data points (note that the distance between neighbouring points is 0.2 mm) and that the top of the PSF is flat. This limits the accuracy of determining the resolution with the FWHM method. For this reason the 1x1 mm system function matrix is used. Figure 6.6 shows a reconstructed image and an intensity plot (along the x-direction) for a point function of a 30 nm particle ensemble without noise. The intensity plot is shown for four values of the regularization parameter $\lambda$, while the image is plotted for $\lambda = 5 \times 10^{-30}$. With this parameter the FWHM becomes 0.26 and 0.34 mm in the x- and y-direction, respectively. The influence of the regularization parameter is illustrated in the intensity plot: with decreasing $\lambda$, first the peak becomes narrower and remains smooth, but at some point discretization noise (this is not the simulated noise in the recording coils!) becomes apparent and the PSF is not smooth anymore. For $\lambda$ below a certain value, the peak cannot be distinguished from the discretization noise anymore. The analyses of the PSF without noise, as presented in table 6.1, are performed with the smallest regularization parameter which results in a smooth curve (as observed by eye). Without noise, the uncertainty in selecting the best suited regularization parameter limits the accuracy of the determined resolution to 0.01-0.02 mm.

Figure 6.5: Reconstructed image of point function (left) and PSF along x-direction (right) for 30 nm particles without noise for an imaged FOV of 20x20 mm.
Chapter 6. Image simulation

For simulations with noise, reconstructed images of a point function gradually change with decreasing lambda from a well defined object with an elliptical shape (figure 6.7 left) to a noisy image (figure 6.7 right). This transition is more difficult to define than without noise. For example, the middle image of figure 6.7 shows still a clear peak in the centre, but the shape starts to be influenced by the noise. At this point, the images are considered as not reliable anymore to determine the PSF. The accuracy at which the FWHM can be determined with noise is limited to 0.02-0.2 mm (more reliable for larger particles and higher concentration).

Table 6.1 shows resolutions determined from the PSF for different particle sizes and models. The resolutions are determined without and with noise. The resolutions without noise are an indication for the influence of particle size on the orthogonality of the system functions matrix and may serve as estimates for the theoretical limits for resolution. For the simulations with noise, the particle size influences the resolution both by intensity as by orthogonality of the system functions matrix. Simulations with noise are performed for an acquisition time $t_m = 30$ s (see equation 6.3). The point function is assumed to represent an iron oxide (maghemite) volume of $1.1 \times 10^{-13}$ m$^3$, which is equivalent to an iron amount of 7 nmol Fe; for comparison, the amount of iron for Resovist administered to patients in MRI is 700 µmol Fe. For illustration, 7 nmol Fe would be contained in $1.3 \times 10^{10}$ iron oxide particles with $d = 25$ nm or in $8 \times 10^4$ cells (e.g. red blood cells) with a diameter of 7 µm and filled with undiluted Resovist.
6.3. Results and discussion

<table>
<thead>
<tr>
<th>Particle model</th>
<th>Relative Concentration</th>
<th>FWHM without noise (x/y in mm)</th>
<th>FWHM with noise (x/y in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 nm</td>
<td>100%κ1a</td>
<td>0.40/0.50 ± 0.02</td>
<td>0.7/0.8 ± 0.1</td>
</tr>
<tr>
<td>30 nm</td>
<td>100%</td>
<td>0.26/0.34 ± 0.02</td>
<td>0.4/0.5 ± 0.1</td>
</tr>
<tr>
<td>40 nm</td>
<td>100%</td>
<td>0.17/0.27 ± 0.01</td>
<td>0.24/0.36 ± 0.03</td>
</tr>
<tr>
<td>50 nm</td>
<td>100%</td>
<td>0.16/0.24 ± 0.01</td>
<td>0.16/0.30 ± 0.02</td>
</tr>
<tr>
<td>60 nm</td>
<td>100%</td>
<td>0.15/0.22 ± 0.01</td>
<td>0.16/0.23 ± 0.02</td>
</tr>
<tr>
<td>Resovist – model 1</td>
<td>21.0%κ1b</td>
<td>0.31/0.39 ± 0.02</td>
<td>0.6/0.7 ± 0.1</td>
</tr>
<tr>
<td>22.37 nm</td>
<td>19.8%κ1c</td>
<td>0.33/0.44 ± 0.02</td>
<td>0.7/0.8 ± 0.1</td>
</tr>
<tr>
<td>31.30 nm</td>
<td>1.24%</td>
<td>0.25/0.33 ± 0.02</td>
<td>0.6/0.8 ± 0.2</td>
</tr>
<tr>
<td>Resovist – model 2</td>
<td>36.7%</td>
<td>0.29/0.38 ± 0.02</td>
<td>0.6/0.7 ± 0.1</td>
</tr>
<tr>
<td>21.74 nm</td>
<td>21.9%</td>
<td>0.35/0.45 ± 0.02</td>
<td>0.6/0.8 ± 0.1</td>
</tr>
<tr>
<td>33.04 nm; τ = 6.3 µs</td>
<td>14.8%</td>
<td>0.26/0.35 ± 0.02</td>
<td>0.6/0.7 ± 0.1</td>
</tr>
<tr>
<td>33.04 nm</td>
<td>14.8%</td>
<td>0.22/0.30 ± 0.02</td>
<td>0.4/0.6 ± 0.1</td>
</tr>
</tbody>
</table>

(1) Relative concentrations as discussed in paragraph 6.2.2. For the simulation with noise a volume of \( V = 1.1 \times 10^{-13} \) m\(^3\) Fe\(_2\)O\(_3\) (maghemite) is assumed, which implies for 1a: 100%-V of 20 nm particles are assumed; 1b: 19.8%-V of 22.37 nm particles and 1.24%-V of 31.30 nm particles are assumed; 1c: 19.8%-V of 22.37 nm particles are assumed.

The results for the single particle sizes show a clear trend of an improving resolution with increasing particle size. From a particle size of 40/50 nm the resolution does not improve considerably anymore, this trend is as expected [6.3]. It is also observed that the noise mostly influences the resolution obtained for the smallest particles; this makes sense considering the lower intensities of the harmonics for smaller particles.

The Resovist models show interesting results: The ultimate resolution (thus without noise) is better for only larger particles than for a combination of particle sizes; this is due to a more non-linear magnetization curve for the larger particles which improves the orthogonality of the system functions matrix. However, as soon as noise is added, the intensity of the harmonics becomes more important. The combination of two particle sizes performs better than only the smaller particles (in terms of resolution and sensitivity), and comparable / slightly better than only the larger particles; this makes sense if it is considered that the sum of the size fractions will always lead to higher intensities than the individual fractions (see figure 6.3). A comparison of the first and second model indicates that image parameters are mainly related to the intensity of the spectrum, and are not significantly influenced by the phase of the magnetization (see also figure 6.3 and figure 6.4).

For an MPI scanner setup as described in this chapter in combination with the used reconstruction method and parameters (like the use of 2500 harmonics per receive coil), the Resovist models indicate that the ultimate resolution for Resovist is 0.3/0.4 mm, while a more realistic achievable resolution is 0.6/0.7 mm for an acquisition time of 30 s and in case it is possible to accumulate an amount of Resovist particles containing 7 nmol Fe at a single target spot. If it is possible to separate the best performing particles from Resovist, which would have an MPS spectrum comparable to 30 nm ‘Langevin’ particles, the ultimate resolution would be 0.2/0.3 mm and a more realistic resolution would be 0.4/0.5 mm. The best obtained resolutions are 0.15/0.2 mm for particles larger than 30 nm.
6.3.2 Image simulations with phantom object

The point function provides quantitative information about resolution, though a single point function does not represent a realistic object. In this subsection, a number of image simulations are presented with a more realistic phantom object. The system functions acquired in a FOV of 20x20 mm are used. The phantom object consists of cylinders which are assumed to be filled with magnetic nanoparticles with iron concentrations of 1 mmol·L\(^{-1}\) to 1 µmol·L\(^{-1}\). These cylinders can be considered to represent for example blood vessels. As a reference, a content of 700 µmol Fe approved for Resovist administration to patients would lead to a concentration in the order of 100 µmol·L\(^{-1}\) for a homogeneous distribution over the blood pool. The phantom object is shown in figure 6.8 and contains 14 cylinders: 2x3 cylinders with diameters of 0.1 and 0.25 mm, and 4x2 cylinders with diameters of 0.4, 0.5, 0.6, and 0.8 mm. The height of the cylinders is 1 mm. The centre of the object lies in the middle between the cylinders of 0.5 and 0.6 mm. With respect to the simulated images, the recording coils are located above and left from the object; the horizontal direction corresponds to the x-direction which is parallel to the field gradient.

Simulated images are shown in table 6.2. The numbers below the images are estimates for the resolutions in the x/y-direction. The estimates are determined from the best distinguishable cylinders. To determine whether cylinders can be distinguished, the intensities along a line through the cylinders (either in the x-direction or the y-direction) have been considered. To consider the cylinders as distinguishable, the intensity between two cylinders should at least drop to half the intensity compared with the intensity of the maximum intensities observed for those two cylinders. The resolution is than estimated by the FWHM of the peak for the smallest cylinder. Those estimates for the resolution in x/y-direction are indicated below the images in table 6.2.
Table 6.2: Image simulations of phantom object for different concentrations and particle models

<table>
<thead>
<tr>
<th>Concentration → Particle model ↓</th>
<th>1 mmol L(^{-1})</th>
<th>100 µmol L(^{-1})</th>
<th>10 µmol L(^{-1})</th>
<th>1 µmol L(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 nm (100 vol-%)</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>Estimated resolutions (x/y):</td>
<td>(1.8/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>30 nm (100 vol-%)</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(0.9/1.3)</td>
<td>(1.0/1.7)</td>
<td>(1.5/-)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>40 nm (100 vol-%)</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(0.8/1.2)</td>
<td>(0.9/1.2)</td>
<td>(1.3/1.7)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>50 nm (100 vol-%)</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(0.6/0.8)</td>
<td>(0.7/1.1)</td>
<td>(0.8/1.3)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>60 nm (100 vol-%)</td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(0.6/0.7)</td>
<td>(0.7/1.1)</td>
<td>(0.7/1.3)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>Resovist – model 1 (21.0 vol-%)</td>
<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(1.6/3.0)</td>
<td>(-/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>31.3 nm (1.24 vol-%)</td>
<td><img src="image25" alt="Image" /></td>
<td><img src="image26" alt="Image" /></td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(2.1/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>Resovist – model 2 (36.7 vol-%)</td>
<td><img src="image29" alt="Image" /></td>
<td><img src="image30" alt="Image" /></td>
<td><img src="image31" alt="Image" /></td>
<td><img src="image32" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(2.3/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
</tr>
<tr>
<td>33.0 nm τ = 6.3 ms (14.8 vol-%)</td>
<td><img src="image33" alt="Image" /></td>
<td><img src="image34" alt="Image" /></td>
<td><img src="image35" alt="Image" /></td>
<td><img src="image36" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>(1.6/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
<td>(-/-)</td>
</tr>
</tbody>
</table>
For an iron concentration of 1 mmol (Fe) L$^{-1}$, the cylinders with diameters of 0.1, 0.25, 0.4, 0.5, 0.6, and 0.8 mm contain an amount of iron of, respectively, 7.9 pmol, 49 pmol, 0.13 nmol, 0.20 nmol, 0.28 nmol, and 0.50 nmol. The amount of iron in all cylinders is 2.3 nmol. For iron concentrations of 100 µmol L$^{-1}$, 10 µmol L$^{-1}$, and 1 µmol L$^{-1}$, the amounts of iron are thus a factor 10, 10$^2$, and 10$^3$ lower, respectively. These numbers in combination with table 6.2 show that the detection level for Resovist is of the order of 0.5 nmol with a resolution of 2 mm, or 20 pmol with a resolution of 10 mm (derived from 10 µmol L$^{-1}$ column). For the 30 nm ‘Langevin’ particles, the detection level is 50 pmol with a 1.0 mm resolution, or 2 pmol with a resolution of 10 mm (derived from 1 µmol L$^{-1}$ column). The 60 nm ‘Langevin’ particles have detection levels of 2 pmol with a resolution of 0.7 mm.

The simulations with the phantom object show similar results for the two Resovist models as described in section 6.2.2. Further, it is observed that the Resovist models compared to the larger fraction of particles in Resovist (31.3 nm / 33.1 nm with $\tau = 6.3$ ms), perform slightly worse for the highest concentration (1 mmol L$^{-1}$) and slightly better for a concentration of 10 µmol L$^{-1}$. These results for the Resovist models obtained with the phantom object are in agreement with the results obtained with the PSF (see table 6.1). In general, resolution values determined with the PSF and with the phantom object show a similar relation between particle model and achievable resolution. The values are, however, not directly comparable, since different concentrations have been used.

The results with the phantom object also indicate that the resolution and sensitivity with Resovist is significantly limited by the relatively small fraction (20-40 vol-%) of particles which contribute to the generated signal. This implies that considerable improvements in resolution and sensitivity can be achieved, for MPI tracers with respect to Resovist, through optimization of synthesis parameters or through fractionation. By improvements on size, resolution and sensitivity comparable to 30 nm or even 40 nm ‘Langevin’ particles could be achievable. To achieve even higher resolutions and sensitivities (comparable to 50-60 nm ‘Langevin’ particles), tracers should be made which contain large particles with lower anisotropies as compared to Resovist; this requires for example to influence the shape of particles (towards more spherical particles).

### 6.4 Conclusions

In this chapter, the achievable resolution and sensitivity in MPI has been studied using image simulations based on two simple particle models validated for Resovist. Resovist spectral response has been modelled using the Langevin function for magnetization in combination with two particle sizes. In one model the larger particles were assumed to respond immediately to the applied field, while in the other model a characteristic relaxation time for the magnetization of the larger particles was assumed (the smaller particles were assumed to respond immediately). Analysis of image reconstruction with a PSF and with a phantom object showed that resolution and sensitivity values were comparable for both Resovist models. The combination of particle sizes indicates that the presence of smaller particles leads to a slightly worse ultimate resolution, but to a somewhat better sensitivity. For the scanner setup and reconstruction parameters used in this chapter, including an acquisition time of 30 s, MPI sensitivities for Resovist were found to be of the order of 0.5 nmol with a resolution of 2.0 mm, and 20 pmol with a resolution of 10 mm. For a tracer which would contain only the best performing particles in Resovist, sensitivities of 50 pmol for 1.0 mm and 2 pmol for 10 mm appear to be achievable based on simulations with 30 nm ‘Langevin’ particles. Sensitivities and resolutions for Resovist models were not studied before in literature. For 30 nm ‘Langevin’ particles,
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A resolution of 0.8 mm for a concentration of 77.4 µmol L\(^{-1}\) was found in [6.3], which is slightly better than the results found here. For shorter acquisition times, e.g. 40 ms (25 fps), the stated detection levels can be multiplied by a factor 27 [6.3].

The imaging tool developed for these image simulations was designed for flexibility to adjust scanner parameters. For further image simulations it would be interesting to study the influence of scanner parameters like coil geometry and scanning trajectory. Further, the tool can be used to perform 3D image simulations. With respect to the particle model, it would be interesting to implement the ‘quasi-fixed orientations model’ from the previous chapter.

In general, the results of this chapter stress the need for the availability of MPI tracers with larger particles which are more monodisperse, in order to achieve good imaging performance with MPI.
References

[6.4] Website:
http://mathworld.wolfram.com/Box-MullerTransformation.html
Chapter 7
Conclusions and recommendations

Magnetic particle imaging (MPI) is a new medical imaging modality invented by scientists from Philips Research and first described in literature in 2005 [7.1]. MPI offers new possibilities for imaging magnetic tracers with high sensitivity in combination with high temporal and spatial resolution, and may find a variety of applications such as medical imaging, polymer processing or fluid dynamics. MPI relies on the direct visualization of magnetic nanoparticles, which are used as a tracer material, through application of oscillating magnetic fields for detection in combination with field gradients for localization.

Magnetic tracer characteristics define the achievable image quality for MPI. In particular, a high susceptibility and a short relaxation time are important; a high susceptibility implies saturation at relatively low field amplitudes, and thus a strong generation of higher harmonics, while a short relaxation time is important to ensure that remagnetization of particles is fast enough at the oscillating field frequencies used in MPI. Susceptibility of magnetic particles is mainly influenced by magnetic core size while the relaxation time depends on magnetic core size and magnetic anisotropy. In general, with increasing magnetic core size, the susceptibility increases while the relaxation time becomes longer. Ideally, one would like to employ particles with an optimal particle size. However, in reality a magnetic tracer consists of particles with a distribution in size as well as with distributions of other parameters like shape and composition (e.g. oxygen content). Tracer performance can be improved by tuning and optimizing the synthesis of particles and by using fractionation techniques.

The goal of this study has been to improve the characterization and understanding of magnetic nanoparticles for use in MPI, and to relate particle characteristics to image quality parameters like sensitivity and resolution. For this purpose, Resovist and fractions of Resovist have been studied; Resovist is a commercially available contrast agent approved for clinical MRI applications and consists of iron oxide magnetic nanoparticles coated with carboxydextran. The research goal was achieved through several steps: First, fractionation techniques, dynamic light scattering (DLS), and vibrating sample magnetometry (VSM) were used to characterize particle size distribution and magnetic properties. In order to obtain information on the relaxation times and the magnetic anisotropy, a magneto-optical setup was developed. In addition, the non-linear dynamic behaviour of Resovist in typical MPI fields was studied with magnetic particle spectrometry (MPS, in principle a zero-dimensional MPI scanner) and this non-linear behaviour was simulated with particle models in combination with the determined size distribution and anisotropy of Resovist. Finally, simple particle models for Resovist were used in MPI image simulations in order to determine achievable image quality parameters like resolution and sensitivity.
Chapter 7. Conclusions and recommendations

Conclusions

Fractionations of Resovist provided indications for a bimodal distribution of Resovist, which has also been described in literature [7.1]. The VSM magnetization curve of Resovist was fitted with a number of size distributions in combination with magnetization curves as a function of size described by the Langevin function. A fit of the magnetization curve assuming a log-normal distribution resulted in a fitted curve too steep around zero field, indicating an overestimation of large particles. The fit was improved by limiting the log-normal size distribution up to 40 nm. An even better fit was obtained with a bimodal log-normal distribution yielding two log-normal peaks with $d_1 = 8\pm 1$ nm, $\sigma_1 = 1.9\pm 0.1$, $d_2 = 25\pm 1$ nm, $\sigma_2 = 1.2\pm 0.1$, a volume ratio between the peaks of $1:0.4\pm 0.1$ (small to large), and $M_s = (3.5\pm 0.4) \times 10^5$ A·m$^{-1}$. Although the exact size distribution of Resovist particles is probably more complex and can only be determined using high-resolution fractionation, the fitted bimodal distribution provides sufficiently accurate distribution for determination of anisotropy and for simulation of MPS curves. This is indicated by comparable anisotropy values determined assuming a single and a bimodal log-normal distribution (as described in chapter 4), and comparable MPS spectra simulated with both distributions. Additionally, comparison with DLS measurements provided rough estimates for the polymer shell size of 10-30 nm, which corresponds to a polymer shell thickness of 10-20 nm as found in [1].

Dynamic susceptibility measurements with the magneto-optical setup have been compared with a VSM magnetization curve of Resovist (susceptibility was plotted as a function of field up to 3 mT for a field frequency of 75 Hz) and a magneto-electrical susceptibility measurement. The dynamic (magneto-optical) susceptibility of Resovist as a function of frequency cannot be explained by external (or Brownian) relaxation only, especially not at 25 kHz (a field frequency typically used in MPI) and thus internal (or Néel) relaxation needs to be taken into account. The susceptibility curves of Resovist and of fractions have been fitted using the bimodal size distribution and a combination of the Néel and Brownian relaxation times, assuming both volume and surface anisotropy. The available data was not sufficient to determine the dominant type of anisotropy, as both types can explain the measured susceptibility curves. Assuming a damping constant of $\alpha=0.1$, the fitted anisotropies are in case of a volume dependent anisotropy, $K_V = (4.4\pm 1.1) \times 10^3$ J·m$^{-3}$ in combination with a fitted shell thickness of $s = 20\pm 2$ nm and in case of a surface dependent anisotropy, $K_S = (1.9\pm 0.3) \times 10^5$ J·m$^{-2}$ with $s = 23\pm 2$ nm. The anisotropy values can be explained by either magneto-static shape anisotropy ($K_V$) or by surface anisotropy ($K_S$). The surface anisotropy value found was comparable to values found in literature.

MPS measurements of Resovist with increased viscosities (using Natrosol) showed no large drop in the intensity of the spectrum for an increased viscosity, which indicates that internal (Néel) relaxation is the dominating relaxation mechanism in particles generating the MPS spectrum (at 25 kHz). The MPS spectrum has been simulated as a first approach assuming a magnetization described by the Langevin function, the determined bimodal size distribution, and a threshold size above which particles do not contribute to the spectrum because magnetization relaxation will take too long. A magnetic core diameter of 23-28 nm is expected for this threshold size, based on the Néel relaxation time and the determined (volume or surface) anisotropy of Resovist. However, a threshold size around 34 nm would be required for the mentioned assumptions to fit the MPS spectrum of Resovist. Two explanations are put forward: one explanation is that the Néel relaxation time has to be adjusted because of the relative strong field values and the other is that the magnetization (as a
function of particle size) cannot be described by the Langevin function since the particles are not able to reorient fast enough. Calculations of adjusted relaxation times showed that a threshold size of 34 nm or even higher could be possible, although these values are quite uncertain as the calculation of accurate relaxation times and relaxation behaviour is very complex. On the other hand, if the magnetization of particles is calculated for a quasi-fixed distribution of particle orientations (determined by the equilibrium distribution at the RMS value of the field), the MPS spectrum of Resovist can be simulated with a threshold size of 24-29 nm. The MPS measurements with Natrosol support the theory of a more or less fixed distribution of particle orientations. Therefore, it is considered that the fixed distribution of particle orientations is the dominating mechanism required to explain the MPS spectrum of Resovist.

MPI image simulations have been performed with two simple two-size particle models based on the Langevin function to describe Resovist. Simulations with these particle models indicated that the MPS intensity spectrum provides a good indication of the expected sensitivity and spatial resolution, while the phase spectrum is of minor importance. For an acquisition time of 30 seconds, MPI detection levels for Resovist were found to be of the order of 0.5 nmol (Fe) with a resolution of 2 mm, and 20 pmol (Fe) with a resolution of 10 mm. For a tracer which would contain only the best performing particles in Resovist, detection levels of 50 pmol (Fe) for 1.0 mm and 2 pmol (Fe) for 10 mm appear to be achievable. For shorter acquisition times, e.g. 40 ms (25 fps), the stated detection levels can be multiplied by a factor 27.

In summary, the results in this study indicate that the optimal size of iron oxide particles in Resovist is approximately 24-29 nm, or up to 34 nm if the Néel relaxation needs to be adjusted. With these optimal particles, detection levels of 50 pmol (Fe) in combination with a resolution of 0.8 mm and a 2 pmol (Fe) in combination with a resolution of 10 mm appear to be achievable for a temporal resolution of 30 s.

Recommendations

The analyses performed in the study stress the importance of the availability of stable ferrofluid samples which are (much) less disperse than Resovist. Mono-disperse samples are useful both for understanding particle behavior (e.g. to determine the type of anisotropy) and for application (e.g. to improve sensitivity per amount of iron in a tracer). Further research should therefore focus on optimization of synthesis methods and/or fractionation methods. The characterization methods and simulations as described in this report can of course be applied to samples other than Resovist. An interesting study would be to find a possible relation between the polymer shell of a sample and the measured anisotropy (as the shell may for example influence surface roughness).

When performing size distribution fits from VSM magnetization curves, it has been assumed that clustering of Resovist particles is not relevant due to their repulsive coating. However, simulations of clustering of particles might be useful in order to determine quantitatively the role of clustering of particles in measured magnetization curves, and possibly in MPI as well.

The developed magneto-optical setup is very flexible and a number of improvements are possible. The field amplitude and frequency range of the setup can be extended relative easily with adequate amplifiers and coils, and as well a broader range of laser wavelengths can be tested. The setup can also be used to measure in linear birefringence mode or without polarizers (thus measuring intensity
fluctuations) in order to study orientation of particles. Further, the setup can be used to study the higher harmonics in the Faraday effect (for example to measure MPS-type spectra). By using multiple coils, even magneto-optical measurements in a simple MPI setup could be performed. More calibrations experiments can be performed to study the linearity between the Faraday effect and magnetization, which may be especially relevant if measurements of higher harmonics are performed. Finally, the magneto-optical detection method can be used in combination with fractionation experiments as an in-line detector to provide direct information about performance of fractions for MPI (especially if higher harmonics are measured).

Future experiments can be performed to validate the model with a fixed orientation of particles, for example by using (almost) identical particles with different shell sizes. Simulations can be improved by using the Fokker-Planck equation to describe variations of particle orientation distribution and magnetic moment distribution as a function of time.

The image simulation tool which has been developed can be used to perform simulations with a whole range of different scanner parameters, objects, and reconstruction methods. It would also be interesting to perform image simulations using a particle model for Resovist (or other samples) assuming a quasi-fixed distribution of orientations.

Finally, most important for the future of MPI as a medical imaging technique is to understand and to apply the behaviour of magnetic particles in vivo. The pharmacokinetics of particles with an optimal size for MPI is very important. The possibility to achieve sufficient accumulation of particles at regions of interest will eventually determine whether certain diseases or ailments can be detected, and thus whether MPI can become an important technique in medical diagnosis.

References

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Tijdens mijn afstudeerproject bij Philips heb ik een leuke tijd gehad, veel ervaringen kunnen opdoen, en veel kunnen leren. Op het laatste heb ik nog wel wat moeite gehad met afronden, maar over het algemeen kijk ik terug op een erg leuke tijd die ik heb gehad. Ik wil hiervoor een aantal mensen bedanken.

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Appendix A
Medical imaging techniques

The most commonly used medical imaging modalities are projection radiography, computed tomography, nuclear (medicine) imaging, ultrasound imaging, and magnetic resonance imaging. These modalities use different physical principles to perform imaging which are based on, depending on the modality, transmission of x-rays, emission of gamma rays, reflection of ultrasonic sound waves, and spin resonance. Detailed information on these techniques can be found in literature [A.1- A.4]. Here, a brief overview of these techniques is presented including applications, advantages, and disadvantages of each technique.

Projection radiography

In radiography the transmission of x-rays through a body is used to produce medical images. X-rays are attenuated more if they travel through dense objects in the body such as bones. In projection radiography a 3D object is projected onto a 2D image. Projection radiography is a rather old technique; already in 1895 Wilhelm Conrad Röntgen published the first radiograph of the hand of his wife, which was also the first medical image. When Röntgen discovered this technique, it was immediately obvious to him that his discovery could have profound impact in medicine. And indeed, the first clinical use of x-rays occurred only two months after the first published image. Soon, the use of x-rays became widespread, and nowadays projection radiography is still used very commonly. Applications of projection radiography include diagnosis of bone injury, dental imaging, imaging of the body’s blood arteries and vessels (angiography), examination of the human breast (mammography), investigations of gastrointestinal and urinary tracks, surgery support etc. Advantages of projection radiography compared with other modalities are low cost and setup simplicity, the possibility of mobile setups (for example lung and breast screening units or dental units), and high bone resolution (spatial resolutions of 0.1 mm are achievable [A.1]). Disadvantages are exposure to ionizing radiation (though in general lower than with CT), poor soft-tissue resolution, and use of projections, which results in overlap of features.

Computed tomography (CT)

In 1972 radiography was extended into transmission computed tomography (or cross-sectional imaging) when the first true CT scanner was produced by Godfrey Hounsfield. Also in this technique x-rays are used for imaging, but now projections are made under different angles and a computer is used to reconstruct a cross-sectional image from these projections. By using several cross-sections it is also possible to create 3D images. With helical CT a whole body scan can be performed in less than a minute, while multislice CT allows near real-time 3D imaging [A.2]. CT is used for several applications, among which are cerebral scans to detect head trauma, detection of pulmonary diseases like lung emboli or emphysema, angiography to study for example coronary artery diseases, detection of cancer (especially to determine the stage of the cancer and to follow the progress), and imaging of complex fractions (especially around joints). An important advantage of CT compared with projection radiography is of course the reconstruction of cross-sections (or slices) from projections; this eliminates the problems of overlap and makes it possible to construct 3D images
which can be viewed from all directions. Another advantage is the high contrast of CT images, which makes it possible to distinguish between tissues that differ in physical density by less than 1% [A.3]. Disadvantages of CT are exposure to ionizing radiation, which is in general higher than with projection radiography, and relatively high system costs.

**Nuclear imaging**

Nuclear imaging makes use of radioactive tracers to study physiology, a concept introduced in 1923 by George de Hevesy. A radiotracer is a drug that mimics a biological compound of interest and is labelled with radionuclides (which emit gamma rays and/or subatomic particles); the distribution of the radioactivity implies the distribution of the drug. Early studies with radiotracers used conventional non-imaging radiation detectors to roughly determine amounts of radioactivity. Around 1950 the first imaging systems were produced. Nuclear imaging includes conventional radionuclide imaging (or scintigraphy), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). The first two methods are analogous to projection radiography and CT, respectively, with the difference that emission of gamma rays is used instead of transmission of x-rays and that an Anger camera is used for detection, which is a special 2D gamma ray detector. Like SPECT, PET also produces images of slices, but the technique works differently. In PET, radionuclide decay produces a positron, which annihilates with an electron to produce two gamma rays emitted in opposite directions. The PET scanner looks for coincident detections from opposing detectors in a ring, thus determining the line that passes through the site where the annihilation occurred. A notable difference of nuclear imaging with other imaging methods is that nuclear imaging provides functional information instead of structural (anatomic) information; the distribution of tracer material is a result of the physiological behaviour within the body. The major clinical applications of nuclear medicine are the measurement of blood perfusion in the brain, the diagnosis of tumours in various organs, and the assessment of cardiac function. An important advantage of nuclear imaging is the functional information provided by this technique, which can be used to assess the uptake of drugs or to monitor behaviour after treatment. Other advantages are the possibility of early identification of skeletal problems and the possibility to perform a whole body scan for example to detect tumours when their site is unknown. Disadvantages are the poor resolution of the technique, the lack of anatomical information, the radiation risk due to the administered radionuclide, radioactive waste, and the relative high costs.

**Ultrasound**

Ultrasound imaging uses electrical-to-acoustical transducers to generate repetitive bursts of high-frequency sound. These pulses travel into the soft tissue of the body and reflect back to the transducer. The time-of-return of these pulses gives information about the location (depth) of a reflector, and the intensity of these pulses gives information about the strength of a reflector. By rapidly moving or scanning the transducer or its acoustical beam, real-time images of cross-sections of soft tissue can be generated. Ultrasound technology progressed through the 1960s from simple A-mode and B-mode scans to today’s M-mode and Doppler two-dimensional (2D) and even three-dimensional (3-D) systems. These modes stand for amplitude (intensity versus time/depth), brightness (2D cross-sectional image), and motion mode (continuous series of A-mode scans). Doppler imaging uses the frequency or phase shift caused by moving objects to generate images that are colour coded by their motion. Doppler flow measurements can be interlaced with B-mode
imaging in order to superimpose the flow maps onto high-resolution anatomical images. This combination is called duplex imaging. Ultrasound is well-known from the visualization of a foetus during pregnancy and is also the only routinely used imaging modality for foetal studies. Other examples of applications are imaging of cardiac diseases, breast imaging, and guiding needles for biopsy. Advantages of ultrasound are its safety (no exposure to ionizing radiation), real-time imaging, mobility of the setup, and its cost effectiveness. Disadvantages are: trade-off between depth of penetration and resolution; no penetration of bone, therefore the adult skeletal system and head cannot be imaged; reflection at air interfaces, making imaging beyond air spaces like lungs difficult; and the clarity of image is poorer than in many other techniques.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging arose from the discovery of nuclear magnetic resonance around 1940. In the 1970s papers from Raymond Damadian and Paul Lauterbur described the use of magnetic resonance in medical imaging. Strong magnetic fields (typically 1.5 T - 3 T) are used in MRI and cause the nuclear spin of hydrogen atoms (i.e. protons) to align either parallel or anti-parallel with the field. Slightly more protons align parallel, resulting in a net magnetization of the body. The protons can thus be seen as little magnets. It is then possible to selectively excite regions within the body, causing groups of these “little magnets” to tip away from the magnetic field direction. While the protons return back into alignment with the field, they precess and generate a radio-frequency electromagnetic signal, which can be sensed with an antenna. MRI is thus sensitive to the hydrogen proton density in different regions of the body, which is again an indication of the tissue type in that region. MRI scanners are incredibly flexible imaging devices, and there are many modes in which they can be used. Next to standard MRI, examples of other modes of operation are: echo-planar imaging (EPI), which utilizes specialized apparati to generate images in real-time; magnetic resonance spectroscopic imaging, which images other nuclei besides the hydrogen atom; and function MRI (fMRI), which uses oxygenation-sensitive pulse sequences to image blood oxygenation in the brain, used to measure brain function. Clinical applications of MRI include brain imaging (e.g. detection of tumours or diagnosis of Parkinson’s and Alzheimer’s disease), imaging of the liver (e.g. diagnosis of liver cirrhoses), imaging of the musculoskeletal system (e.g. hernia detection), and imaging of the cardiac system. MRI is most comparable with CT, since both techniques are able to make 3D images containing anatomical information. Advantages of MRI are that there is no use of ionizing radiation, it is a very flexible technique, it has excellent soft-tissue contrast, and it has a high spatial resolution. Disadvantages are that an MRI system is very expensive, and it has a poor temporal resolution (which means it takes a relatively long time to acquire an image).
Appendix A. Medical imaging techniques

References

Appendix B
Analysis of VSM magnetization curves

Analysis of VSM magnetization curves is performed in three steps: correction of the background signal, calculation from moment to magnetization, and fitting of the magnetization curves. In order to perform analysis of magnetization curves, a software tool with a graphical user interface (see figure B.2) has been developed in MATLAB. The correction step and the tool are described in this appendix.

To measure liquid ferrofluid samples, samples are sealed in the lid of a PCR-tube with Teflon tape. The measured magnetic moment needs to be corrected for the contribution of the solvent, the PCR-tube, and the Teflon tape in order to determine the magnetic moment of the magnetic nanoparticles. The several contributions have been determined by measuring empty PCR-tubes, tubes sealed with Teflon, and by measuring solvents. The measured contributions which are used for correction are listed in table B.1. The value for demiwater is equal to a magnetic susceptibility of \( \chi_v = 9.0 \times 10^{-6} \) (for \( \rho = 10^3 \text{ kg}\cdot\text{m}^{-3} \)), which agrees well with a value of 9.05x10^{-6} as found in [B.1]. The listed values are used in combination with the measured weights of the PCR-tube, Teflon tape, and the sample in order to perform the correction. Small magnetic signals (<10^{-8} Am^2) remain when empty sample holders are measured and corrected, limiting the accuracy of the VSM measurements. For reliable measurements, the magnetic moment of a ferrofluid should be at least >10^{-7} Am^2, which is approximately equal to an iron oxide concentration of >6x10^{-4} vol-% (or 20 µg (Fe) g^{-1}) for a sample of 50 µL. Measured and corrected VSM curves are shown in figure B.2 for Resovist and GFC fraction 2 of Resovist (described in chapter 3).

Table B.1: Contributions from several components

<table>
<thead>
<tr>
<th>Component</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR-tube</td>
<td>-(6.63±0.03)x10^{-9} Am^2 T^{-1} mg^{-1}</td>
</tr>
<tr>
<td>Teflon</td>
<td>-(4.0±0.1)x10^{-9} Am^2 T^{-1} mg^{-1}</td>
</tr>
<tr>
<td>Demiwater</td>
<td>-(7.15±0.05)x10^{-9} Am^2 T^{-1} mg^{-1}</td>
</tr>
<tr>
<td>Demiwater with 1 wt-% of Mannitol</td>
<td>-(7.84±0.05)x10^{-9} Am^2 T^{-1} mg^{-1}</td>
</tr>
</tbody>
</table>

![Graph](image1.png)

**Figure B.1:** Measured and corrected VSM curves for Resovist (left) and GFC fraction 2 (right).
Appendix B. Analysis VSM magnetization curves

After correction, the volume of iron oxide in the sample is calculated from the mass of the sample and the measured iron mass concentration in the sample (using ICP-AES), assuming a mass ratio of iron to iron oxide of 0.7:1 and an iron oxide density of $5 \times 10^3$ kg·m$^{-3}$. The volume of iron oxide is used to calculate the magnetization values from the measured (and corrected) magnetic moments. In the chapters of this report, iron oxide volume concentrations are presented which have been calculated assuming a density of the solvent of $1 \times 10^3$ kg·m$^{-3}$.

The final step is to fit the measured magnetization curve assuming a distribution of particles sizes, which has been described in chapter 3. All three steps are performed using the software tool developed in MATLAB. The user interface of this tool is shown in figure B.2. The user needs to load the VSM data files (if multiple files are loaded, the curves are combined), to enter the sample parameters, and to specify fit parameters. If ICP is unknown, a saturation magnetization is assumed and the iron oxide concentration is fitted. To fit the measured magnetization curve, five types of distributions can be used: a single size (two fit parameters, $M_S$ and $d$, actually no distribution), a normal or log-normal distribution (three fit parameters), or a bimodal normal or log-normal distribution (six fit parameters). Three figures are generated showing uncorrected and corrected magnetic moment, measured magnetization and the fitted curve, and the obtained size distribution. The results of the fit can be stored in a text file which contains all entered values (including start values), all fitted parameters, the VSM data (uncorrected and uncorrected), the fitted magnetization curve, and the size distribution. A complete listing of all the m-files used for this tool would become too long, therefore only the m-file used for fitting (the most essential part) is shown on pages 106-107 for the case of a bimodal log-normal distribution. Explanation of the m-file can be found in the inline comments.

References

[B.1] Website (last modified on 19 May 2009):

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Figure B.2: Graphical user interface of VSM tool.
Appendix B. Analysis VSM magnetization curves

function [ data_fit, fit, output ] = vsm_fit_bmln( data, sizes, d_s, T, input )
% This function is used to fit VSM magnetization curves, assuming a bimodal
% log-normal distribution of particles sizes, and a magnetization curve for
% a single particle size described by the Langevin function
%
% Input parameters:
% - data -> matrix with three columns: field (T), moment (Am^2), and
% magnetization (A/m)
% - sizes -> matrix with two columns: sizes (nm) and size steps (nm)
% - d_s -> assumed thickness of non-magnetic layer (nm)
% - T -> temperature (K)
% - input -> 0 or structure containing start values for fitting
%     if 0, start values are prompted
%     otherwise, two fields: start & vary
%
% Output parameters:
% - data_fit -> column containing fitted magnetization curve
% - fit -> structure containing information about fit: fitted
% parameters, size distributions, errors, averages
% - output -> two fields: start & vary
%
% Load data
B = data(:,1);
M = data(:,3);
%
% Create size grid
d = sizes(:,1)';
d_step = sizes(:,2)';
xd = d-2*d_s; xd(xd<0)=0; % xd is diameter of magnetic part of the core
%
% Boltzmann constant
kb = 1.38e-23;
%
% Define start values
if input.start==0
    parameters = {'Magnetization saturation (A/m): (# = fix)',
                  'Ratio peak2/peak1:',...
                  'Peak 1, d* (nm):',...
                  'Peak 1, s*:',...
                  'Peak 2, d* (nm):',...
                  'Peak 2, s*:'};
    def = {num2str(max(M)), '0.4', '10', '1.8', '20', '1.2'}; % default start values
    in = inputdlg(parameters,'Start values',1,def); % prompt parameters
    start_str = def; vary_str = def;
    vary = ones(1,length(in)); % if 1, vary parameter; if 0, fixed
    start = zeros(1,length(in)); % start values
    % Check for # after entered start value,
    % if # -> parameter remains constant during fitting
    for n=1:length(in)
        start_str{n} = strtok(in{n},'#');
        if strcmp(vary_str{n}, '#'); vary(n) = 0; end
        start(n) = str2double(start_str{n});
    end
else
    start = input.start;
    vary = input.vary;
end
output.start = start;
output.vary = vary;
start(4) = log(start(4)); % start values are prompted as multiplicative sd,
start(6) = log(start(6)); % but internally the sd of log(d) is used
%
% Perform fitting using least-square nonlinear curve fitting
model = @fitfun; % pointer to function at end of file
options = optimset('MaxFunEvals',1e6,'MaxIter',1e5,'TolX',1e-3);
[x,resnorm,residual,exitflag,output,lambda,jacobian] = ...
    lsqcurvefit(model,start,B,[],[],options);

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% 'x' contains fitted parameters
% jacobian is used to determine confidence margins
FittedCurve = model(x,B);

% From here, storing of data
data_fit = FittedCurve;
rms = sqrt(resnorm/length(FittedCurve));
fit.error = rms;
fit.dstep = d_step;

% Determine confidence margins
n = length(find(vary==1));  % check number of varying parameters
fit.conf = tinv(0.95,n)*sqrt(diag(rms^2*inv(jacobian'*jacobian)));

% Obtain fit parameters from 'x'
Ms = abs(x(1));
if vary(1)==0; Ms = start(1);fit.conf(1)=0;end
ratio = abs(x(2));
if vary(2)==0; ratio = start(2);fit.conf(2)=0;end
d1 = 1e-9*abs(x(3));
if vary(3)==0; d1 = 1e-9*start(3);fit.conf(3)=0;end
s1 = abs(x(4));
if vary(4)==0; s1 = start(4);fit.conf(4)=0;end
d2 = 1e-9*abs(x(5));
if vary(5)==0; d2 = 1e-9*start(5);fit.conf(5)=0;end
s2 = abs(x(6));
if vary(6)==0; s2 = start(6);fit.conf(6)=0;end

% Calculate size distributions
D1 = d_step./d.*exp(-log(d/d1).^2/(2*s1^2));D1 = D1/sum(D1);
D2 = d_step./d.*exp(-log(d/d2).^2/(2*s2^2));D2 = D2/sum(D2);
Dv = D1+ratio*D2;Dv = Dv/sum(Dv);
fit.distribution = [d',d_step',Dn',Dv'];

% Calculate mean size and standard deviations
dv = sum(d.*Dv);fit.dv = dv;
dn = sum(d.*Dn);fit.dn = dn;
fit.sn = sqrt(sum(Dn.*(d-dn).^2));

% Save fitted parameters and confidence margins in cell
fit.par = {{'M_s','A/m',Ms,fit.conf(1)};
            {'ratio','','ratio,fit.conf(2)};
            {'d1','nm',1e9*d1,fit.conf(3)};
            {'s1','nm',exp(s1),fit.conf(4)};
            {'d2','nm',1e9*d2,fit.conf(5)};
            {'s2','nm',exp(s2),fit.conf(6)});

% This function is used to fit the data
function FittedCurve = fitfun(par,B)

% Fit parameters, no negative values are allowed
Ms = abs(par(1));if vary(1)==0; Ms = start(1);end
ratio = abs(par(2));if vary(2)==0; ratio = start(2);end
d1 = 1e-9*abs(par(3));if vary(3)==0; d1 = 1e-9*start(3);end
s1 = abs(par(4));if vary(4)==0; s1 = start(4);end
d2 = 1e-9*abs(par(5));if vary(5)==0; d2 = 1e-9*start(5);end
s2 = abs(par(6));if vary(6)==0; s2 = start(6);end

% Calculation of size distribution, two log-normal distributions
% note that 'd' is used to calculate the size distribution
D1 = d_step./d.*exp(-log(d/d1).^2/(2*s1^2));D1 = D1/sum(D1);
D2 = d_step./d.*exp(-log(d/d2).^2/(2*s2^2));D2 = D2/sum(D2);
Dv = D1+ratio*D2;Dv = Dv/sum(Dv);

% Calculation of magnetization curve, note that 'xd' is used to calculate xi
xi = B*Ms*pi/6*xd.^3/(kb*T);
select = abs(xi) < 1e-13;  % below 1e-13 discretization errors occur,
L = Ms*(coth(xi) - 1./xi);  % therefore set to zero
L(select) = 0;

FittedCurve = L*Dv';
end;
Appendix C
Faraday ellipticity

A Faraday rotation \( \gamma \) causes a linear change in the measured intensity for a ferrofluid placed between two linear polarisers with axes at 45°, as was shown in equation 4.3. However, the Faraday ellipticity was not taken into account. It is shown in this appendix that the measured intensity is not influenced by the Faraday ellipticity. The orientation of the axis of the first polariser is defined here as the \( x \)-direction.

The electric field of an elliptically polarized light wave travelling in the \( z \)-direction can be expressed as:

\[
\mathbf{E} = \begin{bmatrix} E_x \\ E_y \end{bmatrix} = A e^{i \delta} \begin{bmatrix} \cos \gamma \cos \varepsilon - i \sin \gamma \sin \varepsilon \\ \sin \gamma \cos \varepsilon + i \cos \gamma \sin \varepsilon \end{bmatrix},
\]

where \( A \) is the field amplitude, \( \delta \) is a phase angle, \( \gamma \) is the angle between the \( x \)-axis and the major axis of the elliptical polarization, and \( \varepsilon = \arctan e \) with \( e \) the ratio of the minor axis over the major axis [C.1]. The intensity of the light \( I_0 \) equals \( A^2 \):

\[
I_0 = \left| E_x \right|^2 + \left| E_y \right|^2 = A^2 (\cos^2 \gamma \cos^2 \varepsilon + \sin^2 \theta \sin^2 \varepsilon + \sin^2 \gamma \cos^2 \varepsilon + \cos^2 \gamma \sin^2 \varepsilon) = A^2.
\]

After the elliptically polarized light wave passes through the second polariser, with its axis at 45° with respect to the \( x \)-axis, the electric field is oriented along the axis of the polarizer with amplitude:

\[
E = \mathbf{E} \cdot \frac{1}{\sqrt{2}} \begin{bmatrix} 1 \\ 1 \end{bmatrix} = \frac{A e^{i \delta}}{\sqrt{2}} (\cos \gamma \cos \varepsilon - i \sin \gamma \sin \varepsilon + \sin \gamma \cos \varepsilon + i \cos \gamma \sin \varepsilon).
\]

The intensity of the light \( I \) becomes:

\[
I = |E|^2 = \frac{A^2}{2} \left\{ (\cos \gamma \cos \varepsilon + \sin \gamma \cos \varepsilon)^2 + (\sin \gamma \sin \varepsilon + \cos \gamma \sin \varepsilon)^2 \right\} = \frac{A^2}{2} (\cos^2 \gamma + \sin^2 \varepsilon) \]

\[
= \frac{A^2}{2} (1 + 2 \cos \gamma \sin \varepsilon) = \frac{A^2}{2} (1 + \sin 2\gamma) \sim \frac{A^2}{2} (1 + 2\theta) = A^2 \left( \frac{1}{2} + \gamma \right),
\]

which yields the same result as equation 4.3.

Reference

Appendix D
Magneto-optical setup details

Two aspects of the magneto-optical setup are discussed in this appendix: the LabVIEW program used to control the setup and a correction of the phase of the measured signal.

LabVIEW program

A program was created in LabVIEW in order to control the magneto-optical setup. As described in chapter 4 (see figure 4.6), the computer is connected (via GPIB) to the laser controller, the function generator, the lock-in amplifier, and two multimeters: one to measure the DC voltage of the photodiode and another to measure to voltage of a resistance in series with the magnetic coil. The computer only reads data from the multimeters and is used to both control and read the other components. Measurement details and settings can be entered using the graphical user interface as shown in figure D.1. Measurements can be performed for a range of frequency points and/or a range of field amplitude points. Each data point is measured according to the flowchart as shown in figure D.1. The field has been switched off before the first step. During the first step, the DC signal of the photodiode is adjusted to a constant value (entered by the user before the measurement) by setting the laser intensity through a feedback loop (with a margin of 0.5%). The operating and measure current of the laser diode are stored. During the second step, the AC field is switched on via the function generator. The RMS level of the voltage over the resistance in series with the magnetic coil is measured with a multimeter and this level is used to set the amplitude of the field through a feedback loop (with a margin of 0.1%). The frequency and amplitude settings of the function generator are stored. During the third step, the lock-in can be set. For the measurements performed in this report these setting were constant during the measurements (manually set before the measurement). However, it is possible to let the lock-in automatically set the sensitivity and gain before each measured data point. The sensitivity and gain of the lock-in are stored. During the fourth step, the signals from the multimeters and the lock-in (in-phase and out-of-phase) are measured and averaged for a number of seconds (set by the user). The mean value and standard deviation for each measured signal are stored. In the final step the field is being switched off. After this step the next data point is measured (or the measurement is finished). After each data point has been measured, all settings and all measured values for each data point are stored in a text file, including a description of the measured sample (entered by the user).
Appendix D. Magneto-optical setup details

Step 1: Set light intensity
Feedback loop

Step 2: Set field
Feedback loop

Step 3: Set lock-in
Auto / manual settings

Step 4: Measure data point
Averaging of signals

Step 5: Switch field off

Figure D.1: Screen shot of GUI of the LabVIEW program.

Figure D.2: Flow chart of magneto-optical control. Multimeters PD and R measure, respectively, the DC voltage of the photodiode and the voltage over the resistance in series with the magnetic coil.
Phase correction

Measurement of the Faraday rotation in demiwater showed that phase of the measured signal (with respect to the reference signal) was not constant as a function of frequency, as can be seen in figure D.3. Since the magnetization in demiwater is a result of diamagnetism, no such phase change is expected. Thereby, the direction of the phase change indicates that the optical signal advances with respect to the reference signal. The phase change is therefore related to a time delay \( \tau \) of the reference signal. The phase of the measured signal \( S_m \) was fitted and used to calculate a corrected signal \( S_c \) in phase with the reference signal. The correction is performed according to:

\[
S_c = S_m \cdot \exp(-i \cdot (a + \tan^{-1}(2\pi f \tau))),
\]

with \( a = 0.0250 \) and \( \tau = 1.3222 \, \mu s \). Figure D.3 shows measured and corrected signals for both demiwater and Resovist.

**Figure D.3:** Measured and corrected signal as a function of frequency for demiwater (left) and for Resovist (right). Measurements were performed with 0.5 mT field amplitude.
Appendix E
Image simulation program

In this paragraph some details on the image simulation program are found.

Simulation of images is performed in number of steps:

- Step 1: definition of object
- Step 2: simulation of scanning of object / system functions
- Step 3: filtering of objects / system functions
- Step 4: perform singular value decomposition for system functions matrix
- Step 5: reconstruction of images
- Step 6: analysis of images

The definition of the objects involves the conversion of objects like spheres or cylinders to points on a grid. The result of the first step is a matrix containing positions and concentrations for each voxel point. The second step is the basis of the simulations. For this step a program was developed with a graphical user interface, as shown in figure F.1. The essential part of the code is found on pages 117 to 120. The third step is in principle averaging and determining which components are used for reconstruction. The fourth step is the singular value decomposition which can be performed with MATLAB. The fifth step can be implemented as described in equation 6.4. Step four can be skipped if another reconstruction is used which does not require a singular value decomposition. Finally, images need of course to be analyzed.
Appendix E. Image simulation program

Figure F.1: Graphical user interface for image simulations.
This script was part of a script used for the GUI of the program. Handles contains the parameters provided to this part of the script.

```matlab
% Load parameters
coils = handles.coils; % Contains information about coil geometry
coils_rec = handles.coils_rec; % Contains information about recording coils
currents = handles.currents.; % Currents used in coils
points_t = handles.timing.points; % Number of samples obtain per coil
ts = handles.timing.t.s; % Time step between samples
points = handles.points; % Number of voxels in object
positions = handles.positions; % Positions at which object is located
select = get(handles.popupmenu2,'Value'); % Load parameters
model = handles.main(select); % Function containing particle model: input
% B(t) (3D vector), output M(t) (vector)
par = handles.help(select)(points_t,ts); % Parameters for model, like Ms and size

% Load parameters
coils = handles.coils;
coils_rec = handles.coils_rec;
currents = handles.currents;
points_t = handles.timing.points;
ts = handles.timing.t.s;
points = handles.points;
positions = handles.positions;
select = get(handles.popupmenu2,'Value');
model = handles.main(select);
par = handles.help(select)(points_t,ts);

% Scan over all positions
n_s = size(positions,1); % Number of positions of object
n_p = size(points,1); % Number of points within object
n_t = n_s*n_p; % Total points of objects including shifts
n_f = floor(points_t/2+1); % Number of harmonics to store
size_gb = 1; % Size of stored signals
p_max = floor(size_gb*1024^3/16/(size(coils_rec,1)*n_f));
p1_end = ceil(n_s/p_max);
for p1 = 1:p1_end
    p2_end = p_max;
    if p1==p1_end && mod(n_s,p_max)==0
        p2_end = mod(n_s,p_max);
    end

% Allocate memory
F = zeros(n_f,size(coils_rec,1),p2_end);

for p2 = 1:p2_end
    n2 = (p1-1)*p_max+p2;
    % Position number
    % Define points
    points_tmp = points(:,1:3) + ones(n_p,1)*positions(n2,:);

% Calculate field at positions for I = 1 A
    field = field(coils,points_tmp);

% Calculate recording sensitivity at positions for m = 1 A.m^2
    rec = rec(coils_rec,points_tmp);

% Calculate magnetization
    U = zeros(points_t,size(coils_rec,1));
    if n_s==1
        for n=1:n_p
            B = currents*grid_field(:,n);
            m = points(n,4)*model(B,par);
            S = m*grid_rec(:,n);
            U = U - (S(2:points_t+1,:)-S(1:points_t,:))/ts;
        end
    else
        for n=1:n_p
            B = currents*grid_field(:,n);
            m = points(n,4)*model(B,par);
            S = m*grid_rec(:,n);
            U = U - (S(2:points_t+1,:)-S(1:points_t,:))/ts;
        end
    end
    tmp = num2str(100*n2/n_s,'%3.2f');
    set(handles.text5,'String',[]Progress: ' tmp % completed...']);
    pause(1e-3);
% Fourier transform
F1 = 2*fft(U,[],1)/points_t;
F(:,:,p2) = F1(1:n_f,:);
end
% Save signals
p_low = (p1-1)*p_max+1;
p_high = (p1-1)*p_max+p2_end;
save([PathName...
'\signals_' num2str(p_low) '=' num2str(p_high) '.mat'],'F','v7.3');
end
set(handles.text5,'String','Progress: done!');
t_time = toc;
t_hours = floor(toc/3600);
t_min = round(mod(t_time,3600)/60);
msgbox(['Total time: ' num2str(t_hours) ' hours ...
' and ' num2str(t_min) ' minutes.']);

% Calculates the grid points and displacement vectors on a field coil
function [X,dL] = field_coil(D,R,theta1,theta2)
% D         distance of coil to centre in m
% R         radius of coil in m
% theta1    azimuth in degrees (x-y plane)
% theta2    zenith in degrees (with respect to z-axis)
theta1 = theta1/180*pi;
theta2 = theta2/180*pi;
P = D*[sin(theta2)*cos(theta1),sin(theta2)*sin(theta1),cos(theta2)];
L = R*[cos(theta2)*cos(theta1),cos(theta2)*sin(theta1),-sin(theta2)];
P(abs(P)<1e-10*D)=0;
L(abs(L)<1e-10*R)=0;
X = zeros(360,3);
dL = zeros(360,3);
for n = 1:360
  X(n,:) = P+L;
dL(n,:) = L*(cos(2*pi/360)-1) + dL./norm(dL)*R*sin(2*pi/360);
  L = L+dL(n,:);
end
X = (X(:,:,)+X([2:360 1],:))/2;

% Calculates the grid points and displacement vectors on a recording coil
function [X,dL] = rec_coil(D,L,theta1,theta2)
% D         distance of coil to centre in m
% L         side length of coil in m
% theta1    azimuth in degrees (x-y plane)
% theta2    zenith in degrees (with respect to z-axis)
theta1 = theta1/180*pi;
theta2 = theta2/180*pi;
P = D*[sin(theta2)*cos(theta1),sin(theta2)*sin(theta1),cos(theta2)];
R = L/2*[cos(theta2)*cos(theta1),cos(theta2)*sin(theta1),-sin(theta2)];
P(abs(P)<1e-10*D)=0;
L(abs(L)<1e-10*L/2)=0;
dL1 = cross(P,R);
dL1 = dL1./norm(dL1)*L/100;
dL1(abs(dL1)<norm(dL1)*1e-10)=0;
dL = cross(P,dL1);
dL2 = dL./norm(dL1)*L/100;
dL2(abs(dL2)<norm(dL2)*1e-10)=0;
dL = cross(P,dL2);
dL3 = dL./norm(dL1)*L/100;
dL3(abs(dL3)<norm(dL3)*1e-10)=0;
dL = cross(P,dL3);
\[
dL4 = \frac{dI}{\text{norm}(dL) * L / 100};
\]
\[
dL4(\text{abs}(dL4) < \text{norm}(dL4) * 1e^{-10}) = 0;
\]
\[
X = \text{zeros}(400,3);
\]
\[
dL = \text{zeros}(400,3);
\]
\[
\text{for } n = 1:50
\]
\[
X(n,:) = \text{P+R};
\]
\[
dL(n,:) = dL1;
\]
\[
R = R + dL(n,:);
\]
\[
\text{end}
\]
\[
\text{for } n = 51:150
\]
\[
X(n,:) = \text{P+R};
\]
\[
dL(n,:) = dL2;
\]
\[
R = R + dL(n,:);
\]
\[
\text{end}
\]
\[
\text{for } n = 151:250
\]
\[
X(n,:) = \text{P+R};
\]
\[
dL(n,:) = dL3;
\]
\[
R = R + dL(n,:);
\]
\[
\text{end}
\]
\[
\text{for } n = 251:350
\]
\[
X(n,:) = \text{P+R};
\]
\[
dL(n,:) = dL4;
\]
\[
R = R + dL(n,:);
\]
\[
\text{end}
\]
\[
\text{for } n = 351:400
\]
\[
X(n,:) = \text{P+R};
\]
\[
dL(n,:) = dL1;
\]
\[
R = R + dL(n,:);
\]
\[
\text{end}
\]
\[
X = \frac{(X(:,1)+X([2:400 1],:))}{2};
\]
\[
\%
\]
\[
\text{Calculates the simulation grid}
\]
\[
\text{function } [\text{grid}] = \text{grid_x}(X,Y,Z,nx,ny,nz,z)
\]
\[
\%
\]
\[
\% X size in x-dimension
\]
\[
\%
\]
\[
\% Y size in y-dimension
\]
\[
\%
\]
\[
\% Z size in z-dimension
\]
\[
\%
\]
\[
\% nx points in x-dimension
\]
\[
\%
\]
\[
\% ny points in y-dimension
\]
\[
\%
\]
\[
\% nz points in z-dimension
\]
\[
\%
\]
\[
\% z selected z-slice
\]
\[
xx = X*(-0.5:1/(nx-1):0.5);
\]
\[
\text{if } nx == 1; xx = 0; \text{end}
\]
\[
yy = Y*(-0.5:1/(ny-1):0.5);
\]
\[
\text{if } ny == 1; yy = 0; \text{end}
\]
\[
zz = Z*(0.5:1/(nz-1):0.5);
\]
\[
\text{if } nz == 1; zz = 0; \text{end}
\]
\[
\%
\]
\[
\text{Calculates the field from multiple coils at simulation grid points based}
\]
\[
\%
\]
\[
\text{on Biot-Savart}
\]
\[
\text{function } [\text{grid_field}] = \text{field}(\text{coils},\text{grid_sim})
\]
\[
\%
\]
\[
\% coils parameters of coils
\]
\[
\%
\]
\[
\% grid_sim points were field is calculated
\]
\[
\text{grid_field} = \text{zeros(size(coils,1),3,size(grid_sim,1))};
\]
\[
k = 1e-7;
\]
for n = 1:size(coils,1)
    [X,dL] = field_coil(coils(n,1),coils(n,2),coils(n,3),coils(n,4));
    for nn = 1:size(grid_sim,1)
        R = ones(360,1)*grid_sim(nn,:)-X;
        C = cross(dL,R,2);
        R3 = (R(:,1).^2+R(:,2).^2+R(:,3).^2).^(3/2)*ones(1,3);
        grid_field(n,:,nn) = k*sum(C./R3,1);
    end
    pause(0.01)
end
lim = max(max(max(grid_field)));
grid_field(abs(grid_field)<lim*1e-10)=0;

function [grid_rec] = rec(coils,grid_sim)
% coils     parameters of coils
% grid_sim  points were field is calculated
grid_rec = zeros(3,size(coils,1),size(grid_sim,1));

k = 1e-7;

for n = 1:size(coils,1)
    [X,dL] = rec_coil(coils(n,1),coils(n,2),coils(n,3),coils(n,4));
    for nn = 1:size(grid_sim,1)
        R = ones(400,1)*grid_sim(nn,:)-X;
        Cy = dot(cross(ones(400,1)*[0,1,0],R,2),dL,2);
        Cz = dot(cross(ones(400,1)*[0,0,1],R,2),dL,2);
        R3 = (R(:,1).^2+R(:,2).^2+R(:,3).^2).^(3/2);
        grid_rec(1,n,nn) = k*sum(Cx./R3,1);
        grid_rec(2,n,nn) = k*sum(Cy./R3,1);
        grid_rec(3,n,nn) = k*sum(Cz./R3,1);
    end
    pause(0.01)
end
lim = max(max(max(grid_rec)));
grid_rec(abs(grid_rec)<lim*1e-10)=0;