Qualitative and Quantitative Impact of the Dynamic Viscosity on Magnetic Particle Imaging

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Abstract

Magnetic particle imaging (MPI) is an imaging modality utilizing the non-linear magnetization curve of magnetic nanoparticles to measure their spatial distribution using static and dynamic magnetic fields. One aim is to be able to distinguish between the signal of different particle types or states of the particles. The magnetization characteristic of the particles is influenced by numerous different factors e.g. the particles’ size and shape or the hydrodynamic properties of the particles’ surrounding. This work analyses the influence of the dynamic viscosity on the particles’ signal and on the resulting reconstructed images. Severe changes of the spatial signal distribution of the measured system functions are shown and quantified. The influence of the mixing factors is examined and the influence of viscosity on the results of the multispectral reconstruction approach are shown. Furthermore a method is presented to compute a sample’s unknown viscosity from a grid of measurements with varying viscosity using images obtained from multispectral reconstruction. The method is verified to yield proper results and its applicability is enhanced by additionally using a segmentation-based approach, making the sample’s position inside the field of view irrelevant.

Abstrakt

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Chapter 1

Introduction

The progress of medical knowledge, and the capabilities of diagnosis and treatment have always largely profited from advances in natural sciences and engineering. Especially when it comes to medical imaging discoveries, other fields of science like physics, chemistry, mathematics or computer science often triggered new methods that gave physicians new diagnostic tools. Therefore medical research has become one of the most interdisciplinary fields in science.

The discovery of X-rays by Wilhelm Conrad Röntgen in 1895 [Rö95] is marking the birth of medical imaging. Even though this discovery was of physical nature, a new age in medical history was triggered by one of the first experiments with this new kind of radiation: the irradiation of his wife’s hand (see fig. 1.1). The photography of this first radiograph showed physicians around the world the enormous potential of X-rays. Up to that point in time the only way to look into a body was to cut it open. That way often diagnosis fell together with surgery, what led to long lasting surgeries with often unknown outcome. With the new radiographs a broken leg for example can be examined first, and a decision can than be made whether a surgery is necessary or not. Due to this advantage radiographs became a widespread tool in hospitals shortly after the publication of Röntgen’s findings.

Since that first point on the timeline of medical imaging further developments allowed better and better diagnosis. E.g. the rise of computational power was the key to step from projectional to tomographic imaging, which yields three dimensional data of the bodys anatomy. In the late 1970s CT scanners, which were first developed by Sir Godfrey Hounsfield and Allan McLeod Cormack [Bec06], got widely available and became one of the standards of medical imaging.

Another milestone in medical imaging was set by Paul C. Lauterbur who published the
working principle of magnetic resonance imaging (MRI) in 1973 [Lau73], after the basic principle of nuclear magnetic resonance has been under investigation by physicists several decades before, starting with the work of Isidor Rabi in 1938 [RZMK38]. Due to the good contrast between different types of tissue, MRI soon became one of the gold standards in medical imaging.

All the imaging modalities mentioned so far share the characteristic that they image anatomical informations. A different branch of imaging modalities originates in the work of George de Hevesy done in the early 1920s [Mye79]. De Hevesy was the first one to administer radioactive isotopes to plants and animals to monitor their metabolism by measuring the radioactive decays in different parts of the plants and the bodies. With these studies he built the foundations of what we know today as the tracer principle and functional imaging. In contrast to anatomical imaging, we don’t get anatomical information from functional imaging modalities. Instead we measure the spatial distribution of the tracer administered, which indirectly contains anatomical information but also functional information e.g. blood flow and metabolism, which can be derived from the measurement of the tracer’s spatial distribution.

Further developments in functional imaging were triggered by the development of the gamma camera by Hal Anger in 1957 [Ang57]. With the gamma camera it was possible to detect gamma photons emitted by radionuclides contained in tracers. This allowed new modalities like scintigraphy. Also in functional imaging it was a goal to not just get two-dimensional projection images, but three-dimensional data which was achieved with single-photon emission computed tomography (SPECT), and advanced with positron emission tomography (PET). In the new millennium more and more devices were built that combine anatomical and functional imaging modalities, e.g. PET-CT and PET-MRT.

In 2005 Bernhard Gleich and Jürgen Weizenecker published a new method called magnetic particle imaging (MPI), which allows to measure ferromagnetic tracers with an outstanding spatiotemporal resolution [GW05]. In MPI the nonlinear response of magnetic particles is used to measure their distribution. With rapidly changing magnetic fields, the magnetization in one point of the measured volume is flipped, while the magnetization of particles in the rest of the volume stays in saturation due to a constant gradient field. An electric voltage is induced into the coils of the scanner, due to the change of the particle ensemble’s magnetization, which can be measured. By varying the spatial position, the distribution of tracer particles in the volume can be obtained. Due to the the spatial and temporal resolution achieved by this imaging principle, several applications were proposed since the publishing of the first measurements by Gleich and Weizenecker. The most obvious one is the real-time visualization of the blood flow without the drawbacks of e.g. the need of contrast agent or the deposition of radiation dose in the patient [WGR+09]. Also the monitoring of stroke patients by measuring the perfusion of the brain would be a possible application [LGS+16].
Especially in vivo the tracer particles and their magnetization characteristics are influenced by a lot of different parameters of the surrounding, e.g. temperature or density. By changing the behaviour of the particles, the signal that is obtained may be changed as well. This on the one hand leads to the question whether or not the obtained data is quantifiable without further knowledge of the system the particles are situated in. On the other hand it yields the chance of discriminating one or more of those parameters, and thus gaining additional information. In magnetic particle spectroscopy (MPS), which can be thought of as zero dimensional MPI, the influence of viscosity [RW10] and temperature [RHW09] on the signal spectrum have been investigated, yielding promising accuracy for estimation of both quantities. Since the range of different viscosities in the body is enormous, when obtaining information about the viscosity of the particles surrounding one could draw conclusions whether the particles are situated in the blood flow, are bound in tissues e.g. the liver, or are immobilized by blood coagulation [MSH14]. It already has been shown that it is indeed possible to distinguish particles with dissimilar characteristics using a multispectral approach in reconstruction [RHG+15]. Another application which could be improved by this multispectral approach is the discrimination of particles in blood flow from particles immobilized on the surface of a catheter [HPC+16].

The goal of this masters thesis is to further investigate the influence of viscosity on MPI, and to quantify the results, whether or not it is possible to determine the value of viscosity from MPI measurements.
Chapter 2

Theoretical Background

2.1 Magnetic Particles

As the name magnetic particle imaging already implies, MPI is about imaging the distribution of magnetic particles, in final application injected into the body of a patient or an object that should be examined. One material with appropriate properties is iron oxide in the form of nanoparticles. These consisting of two parts: The core and the coating. The core, which is 1 to 100 nm in diameter, contains the magnetic material. The coating serves as a protection from agglomeration of the particles. Furthermore it ensures the bio-compatibility of the particles. The tracers for MPI are often used in the form of ferrofluids. These contain magnetic nanoparticles solved in water or organic solvents.

Due to the small size of the particles, we do not measure individual particles but a concentration $c$ of particles

$$N = \int_V c(r) \, d^3r,$$

where $N$ is the number of particles in the volume $V$ which is measured. The higher the measured signal is, the higher is the concentration of the particles in the volume.

2.1.1 Magnetization

The magnetization of magnetic nanoparticles is a process which is highly non-linear. Despite the fact that it doesn’t accurately reassemble the real process, the underlying principle can be illustrated with the Langevin theory, which mathematically depicts the magnetization of the particles with the Langevin function:

$$L(\xi) = \begin{cases} 
\left( \coth(\xi) - \frac{1}{\xi} \right), & \text{for } \xi \neq 0 \\
0, & \text{for } \xi = 0
\end{cases}.$$
The magnetization is the sum of all nano particles’ magnetic moments \( \mathbf{m}_j \)

\[
M = \frac{1}{\Delta V} \sum_{j=0}^{N_{\text{p}}-1} \mathbf{m}_j .
\]  

Without an external magnetic field the directions of the magnetic moments are distributed equally, hence the magnetization sums up to zero. If we apply an external magnetic field the averaged magnetic moment of the particles starts to align with the direction of the external magnetic field.

\[
\text{saturation region} \quad \text{dynamic region} \quad \text{saturation region}
\]

\[
M
\]

\[
H
\]

Figure 2.1: Visualization of the magnetization \( M \) of the particles as a function of the external magnetic Field \( H \), as described by the Langevin function (eq. (2.4)). For a small magnetic field strength the majority of the particles’ magnetic moment can flip to align with the external field and the magnetization curve shows a rapid increase. For higher field strengths nearly all particles are aligned and the magnetization is saturating.

With eq. (2.2) the dependency of the magnetization from the external magnetic field can be written as

\[
M(H) = cmL(\beta H) \tag{2.4}
\]

with

\[
\beta = \frac{\mu_0 m}{k_B T_P} \tag{2.5}
\]

where \( \mu_0 \) denotes the permeability of free space, \( m \) denotes the single particle magnetic moment, \( k_B \) denotes the Boltzmann constant and \( T_P \) denotes the particle’s temperature. The single particle magnetic moment can be calculated from the particle cores volume \( V_C \) and the saturation magnetization of the core’s material \( M_{S,\text{core}} \):

\[
m = V_C M_{S,\text{core}} . \tag{2.6}
\]
As we can see in the Langevin function, with increasing strength of the external magnetic field the magnetization of the particle distribution rises until a saturation is reached (see fig. (2.1)). Saturation appears due to the fact that at some specific field strength of the external magnetic field nearly all magnetic moments are aligned with the external magnetic field. To reach complete saturation one would theoretically need an infinite field strength. For a reasonable definition of the saturation field strength one could define that the dynamic region as given by the full width at half maximum (FWHM) of the magnetization’s derivative. For the Langevin function this corresponds to a value of $\xi_s = 4.16$ [KB11, p. 19]. Hence we can write the saturation magnetization as

$$M_S = \frac{\xi_s}{\beta} = \frac{4.16k_B T_p}{\mu_0 m}.$$  \hspace{2cm} (2.7)

### 2.1.2 Particle Size

If a spherical shape of the particles is assumed, due to eq. (2.6) the magnetic moment of the particles scales with $1/r^3$. This means, that small particles need a higher field strength to reach saturation. As a consequence large particle sizes are favourable for MPI. Since the iron concentration and not the particle concentration is the limiting factor for applications of MPI, one can take a look at a fixed iron concentration where the particle concentration and the particle core volume scale inversely. With this dependence the factor $cm$ in eq. (2.4) is independent of the particle size, and therefore also the saturation magnetization is independent of the particle size.

Till now we have assumed that all particles have the same size. In reality most of the particles used in MPI have a size distribution that can be described with a log-normal
distribution [KSNG99]

\[
\rho(D) = \begin{cases} 
\frac{1}{\sigma D \sqrt{2\pi}} \exp \left( -\frac{1}{2} \left( \frac{\ln(D) - \mu}{\sigma} \right)^2 \right) & D > 0 \\
0 & D \leq 0
\end{cases},
\]  \quad (2.8)

where \( \mu \) and \( \sigma \) are related to the expectation value \( E(D) \) and the standard variation \( \sqrt{\text{Var}(D)} \), and are given by

\[
\mu = \ln(E(D)) - \frac{1}{2} \ln \left( \frac{\text{Var}(D)}{E^2(D)} + 1 \right),
\]  \quad (2.9)

and

\[
\sigma = \sqrt{\ln \left( \frac{\text{Var}(D)}{E^2(D)} + 1 \right)},
\]  \quad (2.10)

### 2.1.3 Relaxation Effects

So far we have only considered particles in a static magnetic field. If the external field changes its direction, the magnetic moment of the particles will follow, albeit not instantaneous but with a certain delay. The delay in the change of magnetization can be described by the relaxation time \( \tau \). The magnetic moment of the particles can follow the direction of the external magnetic field in two different ways: The Brownian rotation and the Néel rotation (see fig. 2.3).

The Brownian rotation is a hydrodynamic rotation of the whole particle, aligning it with the external magnetic field. The relaxation time in this case can be calculated with

\[
\tau_B = \frac{3\eta V_H}{k_B T_P},
\]  \quad (2.11)

where \( \eta \) denotes the dynamic viscosity and \( V_H \) denotes the hydrodynamical volume of the particle [Bro63].

In contrast to the Brownian rotation the Néel rotation is a rotation of the particles magnetic moment while the particle itself is being static. The relaxation time of the Néel rotation can be calculated with

\[
\tau_N = \tau_0 \exp \left( \frac{K_A V_C}{k_B T_P} \right),
\]  \quad (2.12)

where \( K_A \) denotes the anisotropy constant and \( V_C \) denotes the volume of the particle core [Né55].

As one can see in eq. (2.11) and eq. (2.12) the relaxation time of the Néel rotation depends on the volume of the particles magnetic core, whereas the relaxation time of Brownian rotation depends on the hydrodynamical volume of the particle. Furthermore only the
Brownian rotation is influenced by the viscosity of the medium the particles are situated in. Both types of rotation are influenced by temperature, but where there is a linear dependency for the Brownian rotation, it is an exponential dependency for the Néel rotation. From this we can conclude that the ratio of Brownian and Néel rotation is heavily depending on the particle type and the properties of the medium the particles are situated in.

![Diagram](image_url)

Figure 2.3: Depiction of the Néel rotation and the Brownian rotation by which particles align to an external magnetic field. Here the blue ellipse is the particle’s coating and the red ellipse is the particle’s core. The arrows arising from the particles’ center represents the magnetic moments of the particles. While the Brownian rotation is a geometrical rotation of the whole particle, the Néel rotation only affects the particle’s magnetic moment and the particle itself is static.

The total relaxation time can be defined as a combination of the relaxation times of Brownian and Néel rotation:

$$\tau = \frac{\tau_B \tau_N}{\tau_B + \tau_N}.$$  \hspace{1cm} (2.13)

If the relaxation time is sufficiently lower than the period of the external magnetic field’s change, which means $f_E \ll \frac{1}{\tau}$, the magnetic moment of the particles can follow the external magnetic field. In the case that for either $\tau_B$ or $\tau_N$ this is not true the respective rotation is suppressed and only the other one occurs changing the direction of the magnetic field. If both relaxation times exceed the period of the magnetic field change the particles magnetic moment can’t follow the change of the external magnetic field. This yields a limit for the frequency of the external magnetic field in MPI.

As we have seen in section 2.1.2 a large particle size is beneficial, allowing low saturation field strength. Regarding a low relaxation time small particles are favourable, since the
equations (2.11) and (2.12) show us that the relaxation time rises with particle size.

2.2 Signal Generation and Measurement

2.2.1 Faraday’s Law of Induction

The basic foundation of how the signal is generated and acquired is built by Faraday’s law of induction. It states that a change of magnetic flux generates an electric field, and can be written as

\[ \nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} , \]

where \( \mathbf{E} \) denotes the electric field and \( \mathbf{B} \) denotes the magnetic field. Faraday’s law of induction can also be written in an integral form:

\[ \oint_{\partial S} \mathbf{E}(l) \cdot d\mathbf{l} = -\frac{d}{dt} \Phi_{B,S} \]

Here \( \Phi_{B,S} \) denotes the magnetic flux through the surface \( S \). This can be applied to a receive coil, where the electric field which is generated can be measured due to the voltage it induces into the coil. For this case we obtain

\[ u(t) = \oint_{\partial S} \mathbf{E}(l,t) \cdot d\mathbf{l} = -\frac{d}{dt} \Phi_{B,S}(t) . \]

With the definition of the magnetic flux

\[ \Phi_{B,S} = \int_S \mathbf{B} \cdot d\mathbf{A} , \]

where \( d\mathbf{A} \) denotes one element of the surface \( S \), we get

\[ u(t) = -\frac{d}{dt} \int_S \mathbf{B}(r,t) \cdot d\mathbf{A} . \]

As we can see, the change of the magnetic field is directly connected to the voltage measured in the receive coil, by Faraday’s law of induction.

2.2.2 Signal Generation

As we know by now we need to change the magnetization of the particles to generate a signal we are able to measure. To flip the direction of the particles’ magnetic moment a coil can be used to generate the so called excitation field. Typically a sinusoidally modulated voltage is given onto a coil, that subsequently generates a magnetic field

\[ H_E(t) = -A_E \cos(2\pi f_E) \]
with the amplitude $A_E$ and the frequency $f_E$.

Due to the non-linear behaviour shown in fig. 2.1 the magnetization of the particles first changes due to the magnetic moments aligning with the excitation field. Once most of the particles magnetic moments have aligned, the magnetization saturates, which means that the magnetization isn’t changing significantly any more. Since we are only able to detect the changes of magnetization this behaviour results in a peak, which is the sharper the faster the magnetization reaches saturation. As the excitation field changes its direction the magnetization follows and due to the change of magnetization a second peak is generated. As can be seen in fig. 2.4 during one oscillation of the excitation field two peaks are generated by the particles. These peaks can be distinguished from the sinusoidal signal of the excitation field, which is essential as we will see in the next section.

The amplitude $A_E$ must be chosen high enough to safely reach saturation. In practice amplitudes up to 20 mT $\mu_0^{-1}$ are used for the excitation field. Higher field strengths can be critical as more energy is deposited in the patients body, and the tissue may warm up to much. This correlation is described by the specific absorption rate (SAR). Furthermore to high field amplitudes can cause unwanted magnetostimulation of the nervous system [SGZC13]. The frequency $f_E$ is typically in the range of a few to over hundred kHz.

### 2.2.3 Measurement of the Particle Signal

One problem that arises if one wants to measure the signal of the particles is, that one automatically also measures the signal induced by the excitation field. Hence the signal measured is always a superposition of excitation signal and the particle signal. From a theoretical point of view one could first measure the excitation signal without particles present, and then subtract this signal from the superposition of both signals to obtain the particle signal. In practice this won’t work out due to the fact that the signals need to be measured with infinite precision. Since the particle signal is several orders of magnitude lower than the excitation signal, an analogue to digital converter (ADC) with an extreme dynamic range would be needed. Indeed there is no ADC available covering the whole dynamic range with a sufficient precision.

The solution to the problem of separating the signals lies in the different shape of the signals. For this to become apparent we have to look at the signal in frequency space instead of time space. As both, the excitation signal and the particle signal, are being periodic we can expand them into a Fourier series

$$u(t) = \sum_{k=-\infty}^{\infty} \hat{u}_k e^{2\pi ik f_E t},$$

(2.20)
with the Fourier coefficients

\[ \hat{u}_k = \frac{1}{T_R} \int_0^{T_R} u(t)e^{-2\pi ik_f t} dt, \quad k \in \mathbb{Z}. \]  

(2.21)

![Diagram](image)

Figure 2.4: Visualization of the magnetization characteristics and the signals involved. The top left plot (a) shows the non-linear magnetization curve of the particles. The bottom left plot (c) shows the Magnetization of the particles over time reaching a saturation plateau before the change of the external fields direction. The upper right (b) and bottom right (d) plots show the signal of the particles and of the excitation field respectively. While the excitation field produces a sinusoidal signal, the particles’ signal contains two sharp spikes when their magnetization changes.

The spectrum isn’t continuous but consists of discrete lines

\[ f_k = k f_E, \quad k \in \mathbb{Z}, \]  

(2.22)

which are called the harmonics. As the excitation signal is sinusoidal its spectrum consists of a single line, the fundamental frequency (see fig. 2.5). The particle signal on the other hand additionally consists of higher harmonics, which make the signals’ spectra distinguishable. As said before, we always measure a superposition of both signals. As the signal of the fundamental generated by the excitation signal exceeds the fundamental signal of the particles by some orders of magnitude, it can’t be used for measurement of the particles. Hence the fundamental is filtered out and only the higher harmonics are used, since they can only be generated by the particles.
The top row shows the signal of excitation coil, while the middle row shows the particle signal and the bottom row shows the superposition of the signals. While the sinusoidal excitation only contains the fundamental frequency, the particle signal additionally contains higher harmonics.

2.3 Spatial Encoding

Until now we have only looked at the generation and measurement of a signal, but have not regarded the spatial position of the particles generating the signal. To obtain a spatial distribution of the particles it is necessary to know from which part of a volume the measured signal originates. In the following we want to outline how spatial encoding is achieved in MPI.
2.3.1 Selection Field

Due to the excitation field being nearly homogeneous over the complete volume, all particles contribute to the signal, since the magnetic moments of all particles are flipped. To achieve spatial encoding one needs a way to restrict this change of magnetization to one point in space. If it is known that the signal is generated solely by the particles of one point, it is possible to map the particle distribution by moving this point through space. To obtain such a situation one again utilizes the non linear behaviour of the magnetic particles. If everywhere but in one point the particles’ magnetization is in saturation we know that the signal we measure must be from the one point where the particles are not in saturation, since it is the only point where the magnetic moments can flip. By applying a static gradient magnetic field such a situation can be realised, where nearly all particles are in deep saturation and will be less affected by the excitation field. This field is called selection field. Only in one point, the field-free point (FFP), the static gradient field vanishes completely and the particles magnetic moments can be flipped by the excitation field. Of course not only the particles in the FFP contribute to the signal, but also the surrounding area. As long as the field strength of the selection field is smaller than the saturation field strength the particles will contribute to the signal. Hence the higher the gradient of the selection field is the smaller is the area around the the FFP that contributes to the signal.

Naturally the selection field has to fulfil the Maxwell equations which bring the condition that the divergence of the magnetic field has to vanish:

$$\nabla \cdot \mathbf{H} = \frac{\partial H_x}{\partial x} + \frac{\partial H_y}{\partial y} + \frac{\partial H_z}{\partial z} = 0 .$$ \hspace{1cm} (2.23)

In practice this means that the field gradients can’t be equal. In MPI the gradients are chosen in a way that the gradient strength in one direction is twice the value as in the other directions. When choosing the z-axis this would mean

$$-2G_x = -2G_y = G_z .$$ \hspace{1cm} (2.24)

As the size of the area excited by the excitation field is directly related to the gradient strength, this would result in a spatial resolution that is twice as high in the z-axis as on the x- and y-axis.

2.3.2 Drive Field

Due to the static nature of the selection field the sample has to be moved after every measurement to measure the distribution of the magnetic particles. This can cause problems since the measured object must be much smaller than the area the object is placed in. Otherwise it might be not possible to reach the FFP with every point of the object.
Furthermore this procedure would take an amount of time that precludes real-time applications.

An alternative procedure would be to not keep the FFP on one position, but to move it during the measurement. This can be done by replacing the excitation field with a drive field which has got a higher amplitude. As always the superposition of the fields, which is

\[ H(r_{\text{FFP}}) = H_S(r_{\text{FFP}}) + H_D, \]  

has to be considered, we see that the position of the FFP changes with the strength of the drive field:

\[ r_{\text{FFP}} = -G^{-1}H_D. \]  

Here \( G^{-1} \) denotes the inverse gradient matrix:

\[ G^{-1} = \begin{pmatrix} \frac{1}{G_x} & 0 & 0 \\ 0 & \frac{1}{G_y} & 0 \\ 0 & 0 & \frac{1}{G_z} \end{pmatrix} \]  

Hence if the drive field strength changes, the position of the FFP changes as well. When the FFP passes a point in space the magnetic moment of the particles in this point will be flipped. Thus all points in space that are passed by the FFP generate a signal.

As we know from section 2.2.3 if the excitation caused by the drive field is sinusoidal its induced signal is separable from the particles signal. Hence the movement of the FFP should be performed in a sinusoidal pattern. Considering a drive field of the form

\[ H_D(t) = -A_D \cos(2\pi f_E t), \]  

the position of the FFP is given by

\[ r_{\text{FFP}}(t) = \frac{A_D}{G} \cos(2\pi f_E t). \]  

As one can see, also the speed of the FFP isn’t constant but modulated periodically.

As we are now measuring the signal of several points in space in one measurement cycle, the question arises if the signal of those different points can be distinguished from one another. In one movement period of the FFP it is located at every point in space twice. Therefore every point generates two peaks in the measured signal. But due to the different distances between the points of inflection the time lag between those two peaks is depending on the spatial position. We here ignore the spatial positions that mark the points of inflection since they only yield one peak per cycle. This is reasonable as they just generate negligible signal due to the vanishing velocity of the FFP in these points.

So far we looked at the drive field in an one dimensional situation. In practice we want to measure a three dimensional volume. Hence a three dimensional movement of the FFP
is needed. A three dimensional trajectory can be realised by using the superposition of three separate drive fields, one for each dimension. While the trajectory in the one dimensional case is limited to a simple line, a variety of different trajectories are possible in three dimensions. In the following we will restrict ourself to the Lissajous trajectory as it is the one realised in the scanner used. A Lissajous trajectory is generated by applying a sinusoidal frequency to each drive field. The frequencies are chosen similar but not equal. If the quotient of the frequencies is a rational number the trajectory is closed. This is necessary to achieve a finite repetition time. To generate a Lissajous trajectory that uniformly covers the volume, frequencies are used which fulfil the condition

\[ \frac{f_x}{f_y} = \frac{n}{n+1}, \quad n \in \mathbb{N}. \quad (2.30) \]

For three dimensions all combinations of the three frequencies should yield rational numbers to form a closed trajectory. A simple way to achieve this is to follow the rules depicted in the equations

\[ f_y f_x = \frac{n}{n+1} \quad \text{and} \quad \frac{f_z}{f_x} = \frac{n}{n-1}. \quad (2.31) \]

The repetition time of the drive field in this case is given by

\[ T_R = \frac{(n+1)(n-1)}{f_x}, \quad (2.32) \]

and represents the time it takes for the FFP to complete the trajectory.

Figure 2.6: Two dimensional Lissajous trajectory generated with \( n_x = 10 \) and \( n_y = 9 \).
2.3.3 Focus Field

Due to the limits for energy deposition in a patients body, the maximum field strength for the drive field is limited. Hence it is only possible to cover a volume of a few centimetres in every dimension. For medical applications a larger field of view (FOV) is needed. Due to this reason the focus field was introduced [GWT+10].

The focus field forms a superposition with the selection field and the drive field, and hence influences the position of the FFP. With a static higher field strength it is possible to move the drive fields FOV in space and thus achieve a larger overall FOV. After the Lissajous trajectory of the FFP is completed, the field strength of the focus fields can be changed to shift to another patch that can now be measured. In that way one patch after another can be measured until every point of the volume is covered by at least one patch. An alternative way of scanning the complete volume is to slowly change the focus field strength during the measurement. This way the complete volume can be measured at once instead of merging several small patches.

2.4 Set-Up of a MPI-Scanner

In the previous section we saw that different kinds of magnetic fields are needed to realise a MPI-Scanner. We now want to take a look at how magnetic fields can be generated, and how a generic set-up in practice looks like.

2.4.1 Generation of Magnetic Fields

The easiest way of achieving a magnetic field is to make use of a permanent magnet. The characteristics of the magnetic field generated by a permanent magnet are determined upon manufacturing and can’t be changed easily afterwards. Hence they are only suitable for static fields, e.g. the selection field. With modern material like neodymium iron boron high field strength are achievable without any loss of power. However one has to keep in mind, that the field of a permanent magnet can’t be switched off and is present all the time. This can make additional safety precautions necessary in practice.

Magnetic fields can also be generated by electromagnetic coils. The magnetic field at a position \( \mathbf{r} \) generated by electric voltages is described by the Biot-Savart law:

\[
\mathbf{H}(\mathbf{r}) = \frac{1}{4\pi} \int_V \mathbf{J}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV'
\]

Here \( \mathbf{J} \) denotes the current density and \( \mathbf{r}' \) denotes the position of the conductor. From this it is obvious that if the current density changes with, the generated magnetic field also changes with time. Thus electromagnetic coils are not only suitable for static magnetic fields, but also for dynamic ones.

Homogeneous magnetic fields can be generated using two electromagnetic coils of the same
specifications, with current flowing in the same direction. If the distance between the coils equals their radius the field between the coils is nearly homogeneous. This configuration of coils is called Helmholtz configuration.

When changing the direction of the current in one of the coils one obtains a gradient field between the coils. This configuration is called Maxwell configuration.

2.4.2 Configuration used for MPI

Now that we know how different kinds of fields can be generated, we want to take a look at how this is done for a MPI scanner. The first thing to mention is that we want to measure three-dimensional objects and gather full three-dimensional information. For this every point of the object needs to be reachable for the FFP. To achieve this we need fields on every axis. With the superposition of these fields reaching every point is possible. Nevertheless one axis has to be spatially free since a patient must be inserted into the scanner. This yields additional challenges to the geometrical design of the set-up.

As we have seen in the previous section the selection field can be generated either by permanent magnets or by electromagnetic coils. In MPI-scanners for this task mainly electromagnetic coils are used, due to two reasons. First, for a scanner design capable of being used for humans the volume on which the field has to be applied is defined by the size of a human torso. Hence the permanent magnets must be accordingly large and
thus would be very heavy. Another advantage of using coils is that one can use the same coils for selection field and focus field, as the frequency of the focus field is low compared to the drive field. By applying the voltages needed for the selection field and the focus field to the coils, they directly induce the superposition of selection field and the focus field. Hence only three pairs of coils are needed for the combination of selection and focus fields. Two pairs can be realized in a classical spherical shape. For the third axis a different design is needed due to the requirement of the orifice for the patient. Here a cylindrical coil can be used as can be seen in figure 2.7.

The drive field is generated with separate coils. Due to the high frequency of the drive field the skin effect isn’t negligible compared to coils for selection and focus field. Hence litz wire has to be used for the drive field coils whereas solid copper can be used for the coils generating the excitation and focus fields. For a compact set-up the drive field coils are placed in between the selection and focus field coils. Two pairs are saddle-shaped whereas the one for the third axis is cylindrical due to the needed orifice.

With the same geometrical layout the receive coils can be placed as the innermost layer. The properties of the receive coils are very similar to those of the drive field coils. Hence the drive field coils can be used to also receive the signal. This benefits in a simpler set-up with more space for the patient. The drawback of this combination is that the sensitivity is not as the high as it is with dedicated receive coils.

2.5 The System Function

As the aim of MPI is to measure the distribution of magnetic particles, one may notice that in the previous section we mainly looked at how to generate an electromagnetic signal, using the particles, that we can measure. The question arises how the voltages we measure and the distribution of particles are linked in detail. This knowledge is inevitable to not just verify the presence of magnetic particles but to quantify their amount, and subsequently obtain their distribution.

In this section we want to take a closer look at the connection of measured signal and present particles, given by the signal equation. In this context we will get to know the system function, which plays a key role in the understanding of the connection of particles and measured signal.

2.5.1 The Signal Equation

As we know by now the particle concentration and the induced voltage are related. In general this can mathematically be formulated as

\[ u_p(t) = \int_{\text{FOV}} s(\mathbf{r}, t)c(\mathbf{r})d^3r, \]  \hspace{1cm} (2.34)
where \( u \) is the measured voltage and \( c \) is the particle concentration. \( s \) denotes the system function which is given by
\[
s(r, t) = -\mu_0 p_R \frac{d\vec{m}(r, t)}{dt}.
\] (2.35)

Here \( p_R \) denotes the sensitivity of the receive coil. One can think of the system function as a spatial map of sensitivity for the different frequencies [RWGB09].

For ideal fields the signal equation is shift-invariant and thus can be formulated as a convolution:
\[
u_p(t) = (s \ast c)(r'(t)) = \int_{\text{FOV}} s(r'(t) - r)c(r)d^3r
\] (2.36)

While this representation yields several benefits like high redundancy, efficient reconstruction methods and knowledge of the existence of a solution, it isn’t further investigated here. This is due to the facts, that ideal magnetic fields are not achievable in practice. Furthermore the relaxation effects cause a spatial dependency inhibiting shift-invariance. Also it would need information of the full spectrum, which is not achievable due to the filtering of the excitation frequencies.

More convenient it is to look at the signal equation in frequency space, which is achieved by applying a Fourier transform. Doing so we obtain
\[
\hat{u}_{P_k}(t) = \int_{\text{FOV}} \hat{s}_k(r)c(r)d^3r
\] (2.37)

with the system function in frequency space
\[
\hat{s}_k(r) = -\hat{a}_k \frac{\mu_0}{T_R} \int_0^{T_R} p_R(r) \frac{d\vec{m}(r, t)}{dt} e^{-2\piikt/T_R} dt.
\] (2.38)

Here we already added the transfer function \( \hat{a}_k \) which does not originate from the Fourier transform, but contributes to the fact that due to the filtering of the excitation frequencies, these are not present in our spectrum. Hence the transfer function in practice is normally set to take very small values when close to the excitation frequencies.

To analyse the contribution of individual frequencies and to be able to define the signal-to-noise ratio (SNR) it is helpful to define the energy of a frequency:
\[
\tilde{\omega}_k = \sqrt{\int_{\text{FOV}} |\hat{s}_k(r)|^2d^3r}
\] (2.39)
2.5.2 The System Function in 1D and 2D

In one dimension and for the fields \( H_D(t) = -A_{D,x} \cos(2\pi f E t) \) and \( H_S(t) = G_x x \) the system function can be formulated like

\[
\tilde{s}_k(x) = \frac{2i}{T_R} \left( \tilde{m} * \sin \left( k \arccos \left( \frac{G_x}{A_{D,x}} \right) \right) \right)(x)
\]

\[
= \frac{2i}{T_R} \left( \tilde{m} * \left( U_{k-1} \left( \frac{G_x}{A_{D,x}} \right) \sqrt{1 - \left( \frac{G_x}{A_{D,x}} \right)^2} \right) \right)(x)
\]

as has been shown in [RWGB09]. Here \( U_k(x) \) are the Chebyshev polynomials of second kind and order \( k \):

\[
U_k(x) = \frac{\sin((k + 1) \arccos(x))}{\sin(\arccos(x))}
\]

This means that for ideal particles with a step function as magnetization curve the Chebyshev polynomials describe the system function. For real particles the system function is described by the convolution of the the Chebyshev Polynomials and the derivative of the mean magnetic moment. When visualising the 1D system function one can recognise the patterns of the Chebyshev polynomials depicted in fig. 2.8.

![Figure 2.8: Plot of the Chebyshev polynomials of second kind of order 1 to 5.](image)

The two dimensional system function yields distinct similarities to the tensor products of Chebyshev polynomials in its spatial structure. They have to be weighted with \( \sqrt{1 - x^2} \) and can be expressed as

\[
\tilde{U}_{k,l} = \sin(k \arccos(x)) \sin(l \arccos(y)) .
\]

(2.42)
Due to intermodulation theory a function with excitations caused by sinusoidal functions of different frequencies has components at all linear combinations of these frequencies:

\[ f_k = m_x f_x + m_y f_y, \quad m_x, m_y \in \mathbb{Z} \]  

(2.43)

Here \( m_x \) and \( m_y \) are called the mixing factors. One can now plot the different frequency components ordered by the mixing factors, which is shown in fig. 2.9. One can see the structures similar to the Chebyshev polynomials, with the mixing factors taking the role of the Chebyshev polynomials’ order.
2.6 Reconstruction

Since the result of a MPI measurement is basically a vector containing the measured voltages, visualization of the raw data won’t yield much insight. To gather information about the spatial distribution of the signal reconstruction is necessary.

2.6.1 Measurement of the System Function

As we know from the signal equation, the acquisition of the system function is essential for reconstruction of the particle distribution from the measured voltages. To acquire the system function two different approaches can be taken: Either simulate the system function or measure it. Since the simulation of the system function has only obtained sufficiently accurate results in 1D the system used for this thesis, like most systems, uses the measuring approach. Hence we will now concentrate on the measurement approach. For measuring the system function a small delta sample with a known concentration of tracer particles is used. If the sample if infinitesimally small its distribution can be described by a Dirac delta function:

\[ c_{\text{Dirac},r'} = c_0 \delta(r - r') \]  

(2.44)

Inserting this into the signal equation yields

\[ \hat{u}_{k,r'} = c_0 \int_{\text{FOV}} \hat{s}_k(r) \delta(r - r') d^3r = c_0 \hat{s}_k(r') . \]  

(2.45)

By dividing this by the known concentration of the delta sample \( c_0 \) one obtains the system function. While in theory \( r \) is continuous, it has to be discrete in practice due to limited time for the measurement and limited precision in positioning of the sample. Hence the FOV is subdivided into voxels whose size is defined by the chosen step size for the system function.

Also in practice the sample is not infinitesimal small. When the volume of the delta sample is smaller than the volume of a voxel, the approximation

\[ \hat{s}_k(r') \approx \frac{\hat{u}_{k,r'}}{c_0 \Delta V_{\text{Delta}}} \]  

(2.46)

Since this only yields the necessary information for one voxel, the delta sample has to be moved to the next voxel where another measurement is done. This is done until for every position of the delta sample in the FOV one complete measurement has been made.

The system function is highly dependant on the parameters it was measured with, e.g. voxel size, gradient field strength and the tracer used. Hence every system function can only be used for reconstruction of measurements which match these parameters. If a measurement is done with different parameters or with a different tracer a new system
function has to be measured.

### 2.6.2 General Reconstruction

The mathematical problem that has to be solved for reconstruction we already know as the signal equation in frequency space:

\[
\hat{u}_k = \int_{\text{FOV}} \hat{s}_k(\mathbf{r})c(\mathbf{r})d^3\mathbf{r}
\]  

(2.47)

Here the voltages \( \hat{u} \) and the system function \( \hat{s} \) are known, and the concentration \( c \) is the quantity of interest. Hence this is an inverse problem which can be approached in several different ways. These approaches can be categorized into analytic methods and algebraic methods. While there have been several promising approaches in the field of analytic methods, e.g. x-space reconstruction [GC10], we will now focus on algebraic methods as they are currently used for reconstruction.

Due to the fact that the continuous form of the signal equation can’t be processed properly using analytical methods it first needs to be discretized to apply numerical methods. We then obtain the discretized signal equation

\[
\hat{u}_k = \sum_{n=0}^{N-1} \hat{s}_{k,n}c_n.
\]  

(2.48)

Here the index \( k \) denotes the number of the frequency component. Eq. (2.48) can also be written in matrix vector form, which yields

\[
\hat{\mathbf{u}} = \mathbf{S}\mathbf{c},
\]  

(2.49)

where \( \mathbf{S} \) denotes the system matrix, \( \hat{\mathbf{u}} \) denotes the voltage vector and \( \mathbf{c} \) denotes the concentration vector.

As in practice neither the receive coils and the signal chain nor the measurement environment are perfect the problem of noise has to be accounted since it complicates the process of reconstruction. One way to reduce influence of noise is to do a preselection of the used frequency components. With the definition of the energy of frequency components (eq. (2.39)) and an additional background measurements the SNR for every frequency component can be calculated. Frequency components with a SNR value below a specific SNR threshold are then erased from both the system function matrix and the voltage vector to reduce the influence of noise. This way we obtain the reduced system matrix \( \mathbf{S}_r \) and the reduced voltage vector \( \hat{\mathbf{u}}_r \).

The problem that has to be solved can be formulated as a minimization problem:

\[
\|\mathbf{S}_r\mathbf{c} - \hat{\mathbf{u}}_r\|_2^2 \xrightarrow{\mathbf{S}_r\mathbf{c} = \hat{\mathbf{u}}_r} \text{argmin}
\]  

(2.50)
Here $\| \cdot \|_2$ denotes the euclidean norm. If one tries to solve this least squares problem, due to the system matrix being ill conditioned \[ \text{KS}B08 \] the results may not be adequate if the noise is still to high. Therefore the Tikhonov regularization is used, which introduces a penalty term to penalize terms with a large $L_2$ norm:

$$\|S_r c - \hat{u}_r\|_2^2 + \lambda \|c\|_2^2 \rightarrow \text{argmin}$$

The regularization parameter $\lambda$, which is a positive real number, has impact on the noise level and the spatial resolution of the reconstruction’s result. For a low value of $\lambda$ the noise is reduced only slightly. As $\lambda$ rises the noise is more and more suppressed, while the spatial resolution is impaired due to blurring of the image. Often $\hat{\lambda} = \lambda/\lambda_0$ is reported with $\lambda_0 = \text{trace}(S_r^H S_r)N^{-1}$. In practice one has to find a value for $\lambda$ which is a compromise between the level of noise and the spatial resolution.

Solving the minimization problem can yield negative values or even values with a non-zero imaginary part, as the approach is completely mathematical. This means, that a concentration vector with negative values may be existant which is the best solution for the problem. In practice negative concentrations are physically not reasonable. Hence one can add a constraint to the Tikhonov regularization which only allows positive real values for the solution. Such a constraint can improve the image quality as has been shown in \[ \text{WGR}^+09 \].

To find the solution several different solvers can be used, which can be categorized into direct solvers and iterative solvers. As has been shown iterative solvers are the favorable approach in the aspect of computational performance \[ \text{KRS}^+10 \]. Especially the Kaczmarz method showed satisfying results and is now widely used for reconstruction. This method is basically given by the fixed-point iteration

$$c_{l+1} = c_l + \frac{u_j - s_j^H c_l}{\|s_j\|_2^2} s_j^H,$$

where $s_j$ denotes the $j$-th row of the reduced system matrix. To also account the regularization addressed previously one has to apply the Kaczmarz method to the linear system

$$\begin{pmatrix} S_r & \lambda \frac{1}{2} I \end{pmatrix} \begin{pmatrix} c \\ v \end{pmatrix} = \begin{pmatrix} u_r \end{pmatrix},$$

with the auxiliary vector $v = -\lambda \frac{1}{2} S_r c - u_r$.

### 2.6.3 Multispectral Reconstruction

If the measurement contains particles whose magnetization characteristics differ from those used for the acquisition of the system function, the mathematical result of the reconstruction will only depict the real distribution inadequately due to the mismatch of
the particles signal and the system function. By using several different system functions for the different particles their signal can be distinguished and thus the distribution of different particle types can be achieved [RHG+15].

To do so all the system functions have to be included in the reconstruction. The signal equation in matrix form then becomes

$$\sum_{i=1}^{\Theta} S_i c_i = \hat{u}.$$  \hspace{1cm} (2.54)

Here $i$ is the index of the used sample and $\Theta$ is the absolute amount of samples used. With this modification the reconstruction can be performed as before:

$$\begin{pmatrix} c_1 \\ c_2 \\ \vdots \\ c_n \end{pmatrix} = \hat{u}$$ \hspace{1cm} (2.55)

For a single measurement, meaning a single vector $u$, several concentration vectors are obtained, one for each system function used. These can be visualized in separate pictures or in one picture using different colors for the different channels.

In this context the particles don't necessarily have to be of different type. More general one can speak of particles with different signal characteristics. Therefore it is also possible to use the principle of multispectral reconstruction for particles of the same type, but in different environment, as several characteristics of the environment, e.g. viscosity and temperature, can influence the signal characteristics.

## 2.7 Viscosity

The viscosity of a fluid is a measure characterizing its resistance to deformation or flow. This resistance is caused by different mechanisms. Between molecules close to each other electromagnetic forces apply causing attractions of the molecules. These forces are known as Van der Waals forces and only apply to liquids, since in a gas the mean distance between to particles is to large. Another cause of viscosity is the exchange of momentum of different layers or parts of a fluid. When we consider two layers of a fluid, where one is static and one is moved by a force, the moved layer won't slide perfectly on the static layer. Instead the particles of both layers will collide exchanging momentum, causing the moving layer to slow down.

While it is easy to qualitatively distinguish the viscosity of two liquids, e.g. comparing water and honey, for the purpose of this work it is necessary to quantify the viscosity of different liquids. For this we again consider a stack of different layers of a fluid as shown in fig. 2.10. While all layers move in the same direction, they all move at different
Figure 2.10: Visualization of the effect of viscosity on a liquid. A force \( \vec{F} \) acts on a liquid, consisting of several layers. The force accelerates the whole liquid, but the layers reach different velocity since the lower part is in contact with the static ground. This way a velocity gradient forms that is depending on the viscosity of the liquid.

velocities. When the layers are linearly distributed by velocity we can see that the sample of our fluid changes its shape over time. One can in this case define the velocity gradient as \( \partial v / \partial y \). If we now consider two adjacent layers, due to the previously regarded effects a force is acting between the layers causing shear stress \( \tau \) which is proportional to the velocity gradient [MWS11]:

\[
\tau = \frac{F}{A} \propto \frac{\partial v}{\partial y}
\]

(2.56)

This can also be written introducing a material specific constant \( \eta \):

\[
\tau = \eta \frac{\partial v}{\partial y}
\]

(2.57)

The constant \( \eta \) is called dynamic viscosity. In this work we will only consider Newtonian fluids, which means that the viscosity is independent of the amount of shear stress. Besides the dynamic viscosity for some applications the kinematic viscosity is used, which is the dynamic viscosity divided by the density:

\[
\nu = \frac{\eta}{\rho}
\]

(2.58)

In this work with the term viscosity the dynamic viscosity is meant unless otherwise stated.
Chapter 3

Data Acquisition

3.1 The Scanner

The scanner used is the preclinical system built by Bruker under license of Philips. The magnetic fields are completely generated by copper coils, hence no permanent magnets are obstructed. Gradient field strengths of up to 2.5 T/m can be generated. As a maximum drive field strength amplitude 14 mT can be obtained. The excitation frequencies are 2.5/102 MHz, 2.5/96 MHz and 2.5/99 MHz in the x-, y- and z-direction respectively. They are different for the three axes to achieve a Lissajous trajectory (see section 2.3.2). A focus field strength of 18 mT in the x- and y-direction and 42 mT in the z-direction can be reached. The scanner does not have a dedicated receive coil, it instead uses the drive field coils for receiving the signal with a detection bandwidth of up to 1.25 MHz.

Figure 3.1: Image of the used preclinical scanner built by Bruker and Philips. In front of the scanner a movable mouse bed is positioned.

In front of the scanner a mouse bed is installed which can be used for in vivo mea-
measurements. In the back of the scanner a robot is installed to move samples into the FOV, e.g. to measure a system function. The stepwidth of the robot is 6.25 µm.

![Figure 3.2: Robot used to position samples in the scanner bore. The installed rod is made of glass-fiber reinforced plastic.](image)

### 3.2 First Series of Samples

The first series of samples was manufactured and provided by Dr. Thilo Viereck of the technical university of Braunschweig. The aim of the cooperative measurement of these samples was to create a standard set of system functions and measurements for multispectral reconstruction, using a set of samples with varying viscosities.

#### 3.2.1 Properties of the Samples

The set consists of nine different samples made of transparent plastic with a cavity for the tracer of about $1.5 \times 1.5 \times 4 \, \text{mm}^3$, resulting in a tracer volume of 9 µL (see fig. 3.3). Eight of the samples contain a mixture of water and glycerol and FeraSpin XL of the company Miltenyi Biotec as a tracer. To keep the tracer concentration constant throughout the series amount of tracer was the same for all samples, and only the ratio of water and glycerol was varied to achieve different viscosities. This way a range of viscosities from about 1 mPas to about 180 mPas with a tracer concentration of 30 mM was obtained. The ninth sample contains of the tracer in a freeze-dried sugar matrix. This way the particles are immobilized resulting in an "infinite" viscosity. The particles contain an iron oxide core, and have a mean hydrodynamic diameter of 50 to 60 nm. For further information on the tracer particles please refer to the data sheet in appendix A.
3.2. First Series of Samples

Figure 3.3: First set of samples viewed from two different angles.

Figure 3.4: End of the rod with the mounting. Left: Angled view from the side with one sample in the mounting. Right: View from top.

3.2.2 Measurements

To perform the measurements the samples were placed in a mounting on one end of the robot’s rod, as can be seen in fig. 3.4, which was then placed inside the scanner bore. For every sample a single measurement in the center of the FOV was performed. Additionally for every sample a system function was measured. All measurements were performed with a gradient field strength of 2 T/m and a drive field amplitude of 14 mT. The drive field FOV was $28 \times 28$ mm and the resolution was set to $21 \times 21$ voxels. For each sample an averaging of 5000 measurements was applied.

<table>
<thead>
<tr>
<th>Name of Sample</th>
<th>Viscosity [mPas]</th>
</tr>
</thead>
<tbody>
<tr>
<td>f3</td>
<td>179.8</td>
</tr>
<tr>
<td>f4</td>
<td>84.8</td>
</tr>
<tr>
<td>f5</td>
<td>40.0</td>
</tr>
<tr>
<td>f6</td>
<td>18.5</td>
</tr>
<tr>
<td>f7</td>
<td>8.9</td>
</tr>
<tr>
<td>f8</td>
<td>4.2</td>
</tr>
<tr>
<td>f9</td>
<td>1.9</td>
</tr>
<tr>
<td>fa</td>
<td>0.9</td>
</tr>
<tr>
<td>fb</td>
<td>infinite</td>
</tr>
</tbody>
</table>
3.3 Second Series of Samples

Due to the analyses performed on the first set of samples a second set was prepared. The aim was to approve the findings of the first analyses with a different tracer and to additionally prove the feasibility of computing the viscosity of an unknown sample. For this reason three samples were prepared acting as samples of potentially unknown viscosity.

3.3.1 Calculation of the Viscosities

To achieve different viscosities for the samples, as in the first series mixtures of distilled water and glycerol were used. As the effect of mixing two liquids is a highly non-linear process in terms of viscosity, and no adequate theoretical description is available, models have to be used for the calculation of the viscosity of these mixtures. The model used here is the one published by N.S. Cheng in 2008 [Che08], which is summarized in the following.

Cheng’s model takes the equation

\[ \eta = \eta_w^\alpha \eta_G^{1-\alpha} = \eta_G \exp \left( \ln \left( \frac{\eta_w}{\eta_G} \right) \alpha \right) \]  

(3.1)

as a basis for the viscosity \( \eta \) of a mixture of water \( \eta_w \) and glycerol \( \eta_G \). Here \( \alpha \) is a weighting factor depending on the glycerol concentration in mass \( C_m \):

\[ \alpha = 1 - C_m + \frac{abC_m(1-C_m)}{aC_m + b(1-C_m)}. \]  

(3.2)

\( a \) and \( b \) are parameters given by

\[ a = 0.705 - 0.0017T \]  

(3.3)

and

\[ b = (4.9 + 0.036T)a^{2.5}. \]  

(3.4)

The viscosities of water and glycerol are depending on the temperature \( T \) and are modelled with

\[ \eta_w = 1.790 \cdot \exp \left( \frac{(-1230 - T)T}{36100 + 360T} \right) \]  

(3.5)

for water, and

\[ \eta_G = 12100 \cdot \exp \left( \frac{(-1233 + T)T}{9900 + 70T} \right) \]  

(3.6)

for glycerol. By inserting the equations (3.2) to (3.6) into equation (3.1) one can calculate the viscosity of a mixture of water and glycerol for a given temperature and mixing ratio. As we want to calculate the concentrations of glycerol to achieve a specific viscosity, we
have to solve the equation for $C_m$, what can be done with a mathematical computation program, e.g. Mathematica. The visualization of the result is depicted in fig. 3.5. With this model the mixing ratios for the chosen viscosities of the second series of samples were calculated.

![Graph](image)

Figure 3.5: Plot of the relative concentrations of glycerol needed in a glycerol water mixture to obtain viscosity ranging from 1 to 1000 mPas. The data was calculated Cheng’s model depicted in section 3.3.1 for a temperature of 23°C.

### 3.3.2 Preparation of the Samples and their Properties

#### Properties

For the second series of samples eight different viscosities were chosen, which are exponentially spaced between 1 and 100 mPas (see table 3.2). Additionally three viscosities were chosen which lie between those exponentially spaced samples in terms of viscosity. These act as potentially unknown samples whose viscosities should be computed with the informations gathered from the regular eight samples. As a tracer 10 Vol.-% of Resovist was used for each sample. The mean hydrodynamic diameter of Resovist particles is 62 nm, and the iron concentration is 500 mmol (Fe)/l [RB03], resulting in a concentration of 50 mmol (Fe)/l for the samples.

#### Preparation

An important requirement for the samples is that all samples contain the same concentration of tracer. As the tracer can be seen as part of the water fraction in terms of viscosity and density, the calculated mixing ratios have been converted from mass fraction to volume fraction. Due to pure glycerol’s high viscosity of 1412 mPas, precise pipetting of specific volumes is not possible. Therefore an analytical balance with a precision of 0.1 µg
was used to weigh out the needed quantities for the samples. With a pipette the glycerol was than mixed with the calculated amount of distilled water. Afterwards the amount of tracer needed to achieve the chosen concentration was pipetted. By using a borosilicate glass micropipette the mixtures were then pipetted into glass capillaries of 1.3 mm inner diameter. The capillaries were then closed with silicon and Parafilm.

Table 3.2: Viscosities of the samples of the second series.

<table>
<thead>
<tr>
<th>Name of Sample</th>
<th>Viscosity [mPas]</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>1.0</td>
</tr>
<tr>
<td>G2</td>
<td>1.9</td>
</tr>
<tr>
<td>G3</td>
<td>3.7</td>
</tr>
<tr>
<td>G4</td>
<td>7.2</td>
</tr>
<tr>
<td>G5</td>
<td>13.9</td>
</tr>
<tr>
<td>G6</td>
<td>26.8</td>
</tr>
<tr>
<td>G7</td>
<td>51.8</td>
</tr>
<tr>
<td>G8</td>
<td>100.0</td>
</tr>
<tr>
<td>U1</td>
<td>2.8</td>
</tr>
<tr>
<td>U2</td>
<td>20.4</td>
</tr>
<tr>
<td>U3</td>
<td>75.9</td>
</tr>
</tbody>
</table>

3.3.3 Measurements

As for the first series of samples each sample was attached to the rod of the robot one after another. For the samples G1 to G8 system functions were measured as well as single measurements in the FOV’s center, using an averaging of 5000 frames. For the samples U1 to U3 only the single measurements were done, but no system functions were measured. Due to technical problems the y-channel was not available for measurement. Hence the samples were oriented such that the measurements were performed in the x-z-plane. Due to the different gradient strength depicted in section 2.3.1 the resolution of the measurements is dissimilar in the x- and z-direction.

All measurements were performed with a gradient field strength of 2.0 T/m and a drive field strength of 12 mT. The size of the FOV was 24×12 mm² resulting in a resolution of 26×12.
Figure 3.6: Filled capillary attached to the rod.
Chapter 4

Analysis and Reconstruction

4.1 Analysis of the System Functions

4.1.1 Visualization of the System Function

After measurement the system functions can be accessed, visualized and analysed. The system function contains the information how the signal induced by the magnetic particles is spatially distributed. This means that the system function yields a complete spectrum per receive channel containing all frequency components for every voxel. As for the first series of samples the FOV was discretised to a grid of $21 \times 21$ points in space, the obtained system functions yielded $21 \times 21 \times 1$ spatial entries. The number of frequency components arises from the Bandwidth of the Scanner and the spectral width $\Delta f = 1/T_R$, with the repetition time $T_R$ given in eq. (2.32). With the used scanner and its full bandwidth of 1.25 MHz the number of frequency components in the $x$-$y$-plane is 817, and 1684 in the $x$-$z$-plane. The amount of receive channels is three, as one receive channel for each spatial dimension is available.

The frequency components can be visualized by plotting the according entries for all voxels. In our case all the system functions have two spatial dimensions, hence every entry corresponds to an intensity value of one pixel of a matrix plot, as can be seen in fig. 4.1. Due to the entries being complex values in general, usually the absolute values of the entries are visualized, sometimes with an additional plot for the phase angle. Alternatively the real or imaginary parts can also be visualized. In the following, unless otherwise indicated, the absolute values are plotted.

4.1.2 Spatial Signal Distribution

Since the range of values might change for different samples it can be difficult to directly compare the spatial distribution of signal. To achieve a better comparability the images can be normalized to the maximum values.

The differences of the absolute values as well as the differences in spatial distribution can
be visualized by subtracting the matrices and plotting the result. If this is done with the normalized matrices the values can be interpreted as the relative differences referred to the maximum of the distributions.

The first visual inspections of the system functions suggested a change of the spatial signal distribution. One way to analyse the spatial distribution of a frequency component’s signal quantitatively is to calculate the ratio of the values in the center of the FOV and those in the surrounding area:

\[
R_{\text{Out/In}} = \frac{\sum_{\text{Out}} a_{i,j}}{\sum_{\text{In}} a_{i,j}}.
\]  

(4.1)

Here the \(a_{i,j}\) are the absolute values of the voxels. \(\sum_{\text{In}}\) is the area in the center of the FOV which is defined by the values for \(i\) and \(j\). These are chosen individually for the two series of samples, but stay constant within one series and for different frequency components.

Figure 4.1: Visualization of the frequency component 116 \((m_x = 4, m_y = 3)\) in the \(x\)-channel. The upper plots show the absolute values (left) calculated from the real parts (bottom left plot) and the imaginary parts (bottom right plot), and the phase angle (right). The intensity depicted in the colorbars besides the plots is given in arbitrary units.
\[\sum_{\text{Out}} \text{is the absolute complement of } \sum_{\text{In}}.\]

To compare the signal distribution of the measured system functions this ratio was calculated for all system functions using various chosen frequency components. The results were normalized to the maximum value for each frequency component and compared qualitatively. To achieve a more general result, this was done for the set of frequency components yielding a SNR of over 10 for all system functions. For all system functions the values for the individual frequency components were summed up obtaining an accumulated ratio. These were again normalized to the maximum values.

### 4.1.3 Energy of Frequency Components

Using eq. (2.39) the energy of the system functions' components can be calculated. This can be used to achieve further insight on which frequency components contribute the most to the observed changes in signal distribution. Therefore eq. (2.39) was applied to the measured system functions. For this, the absolute values were squared and summed up, obtaining one value for each frequency component. The square root of these was calculated and due to the wide range of values the common logarithm was taken. These calculations were done for the both receive channels with the results being summed up afterwards. For each system function these values were ordered as a matrix, sorted by the mixing factors. These matrices can then be plotted as done before with the frequency components of the system functions, with the axes depicting the mixing factors instead of the spatial position.

To compare the results for different system functions the relative difference was calculated by subtracting the matrices and divide the values by those of the lower viscosity system function.

It was then investigated if for specific ranges of the mixing factors the relative change in energy was remarkably higher than for other ranges. For this

\[R_{\text{MF}} = \frac{\sum_{k \in \Theta_1} \tilde{\omega}_k}{\sum_{k \in \Theta_2} \tilde{\omega}_k} \quad (4.2)\]

was defined, where \(\Theta_1\) and \(\Theta_2\) denote sets frequency components. If the energy of the frequency components contained in \(\Theta_1\) develops differently under the change of viscosity than those of \(\Theta_2\) one will see a change in \(R_{\text{MF}}\) under variation of the viscosity.

### 4.1.4 Error Measure

While the analyses in the previous sections examined changes of specific characteristics, it is also possible to evaluate the general change of the system function. This can be done
using an error measure which we define as

\[
\sigma_n = \frac{1}{|\Theta|} \sum_{j \in \Theta} \frac{\|s_j - s_{n,j}\|_2}{\|s_j\|_2},
\]

where \( s_j \) is a frequency component of the base system function, \( s_{n,j} \) is a frequency component of a second system function and \( \Theta \) is a set of frequency components. This error measure uses one system function as ground truth. It calculates the norm of the base system function's frequency component and of the corresponding second system function's frequency component. These is then divided by the norm of the base system function's frequency component to obtain the relative change. This is done for all frequency components of the set \( \Theta \) and the values are summed up. For the values to be comparable it is important to choose the same set of frequency components for all system functions.

### 4.1.5 Spectra

The frequency spectrum of a system function is given by the measured signal of each frequency component. Due to eq. (2.39) the signal of the frequency components is closely related to their energy, and hence to the SNR. While one obtains a plot where the SNR of the frequency given in Hz is linearly plotted, eq. (2.47) can be used to identify these frequencies with the mixing factors. For different samples the signal strength and hence the level of SNR can differ. To achieve better comparability also the normalized spectra were calculated and plotted, allowing to evaluate the differences in the progression of the spectra. The drawback of the normalization is that the information about the absolute signal strength and hence the attenuation due to viscosity is lost. On the other hand to use the information about attenuation it is required to know the tracer concentration for all samples, as a lower concentration also yields less signal. A constant concentration is a severe constraint in practice, and it is more feasible to concentrate on effects independent of the absolute signal strength.

### 4.2 Evaluation of the Measurements

For reconstruction the method of multispectral reconstruction described in chapter 2.6.3 was used. Using two system functions this method yields one image for each system function. The superposition of these images would be the final result of the reconstruction. To preserve the information of the individual channels, RGB colors can be assigned to them. This way the amount of the signal from the respective channels is decoded in the pixels’ color. As for the evaluations of this work the differences of the channels' results are crucial, the independent depiction of the channels is chosen as visualization.

As a solver the Kaczmarz algorithm introduced in chapter 2.6.2 was used, with \( \lambda = 0 \).
five iterations, a SNR threshold of two and a positivity constraint. Due to the filter characteristics of the scanner all frequencies below 80 kHz were neglected for reconstructions.

4.2.1 Analysis of the Multispectral Reconstruction

To quantify the correlations found in the qualitative analysis, the contributions of the different system functions in a multispectral reconstructions were compared numerically. A region of interest (ROI) was defined in the center of the FOV where the signal of the sample can be seen. For the contributions of both system functions the values of the pixels inside the ROI were summed up. The resulting values were divided by one another to obtain the ratio of the contributions for the used system functions:

\[ R_{SF} = \frac{\sum_{ROI} c_1}{\sum_{ROI} c_2} \]  

(4.4)

Here \( c_1 \) and \( c_2 \) denote the results of the multispectral reconstruction as in eq. (2.55). This was done with all measurements, obtaining a vector of values which can be visualized as a graph. This evaluation was performed for several combinations of system functions, which were selected due to good results in a qualitative preselection.

Valuation of the System Function Combinations

In a further step the viscosities of the samples U1, U2 and U3 should be computed from the values \( R_{SF} \). Hence a measure to value the different combinations of system functions for this task is needed.

As it is known from qualitative preinvestigations a linear correlation of the viscosity and \( R_{SF} \) is found in a logarithmic coordinate system. Hence a linear interpolation model is used as further described in the next section. To prove how well the data fits to a linear model a linear regression is applied to the data points and the coefficient of determination, denoted \( R^2 \), was calculated. A value of 1 constitutes the optimum value for \( R^2 \) as it states that the differences of the data and the linear model can be completely explained by the data's standard deviation. As a second measure of quality the slope of the regression line can be taken into account. Higher values of the slope are preferred as they state that a change of viscosity corresponds into a severe change of \( R_{SF} \), while a value of 0 would correspond to a constant \( R_{SF} \) over the range of viscosities.

Determination of the Viscosities from \( R_{SF} \)

The viscosities of the samples U1, U2 and U3 should be determined from the ratios \( R_{SF} \) of selected system function combinations. Due to the linear correlation between viscosity and \( R_{SF} \) in a logarithmic coordinate system, found in qualitative preinvestigations, the
common logarithm of both \( \eta \) and \( R_{SF} \) was calculated. For the samples U1, U2 and U3 the values of \( \log(R_{SF}) \) were calculated with the same combination of system functions. To identify the value \( R_{SF} \) of one of these samples with a viscosity, a continuous function is needed. Hence a function \( R_{\text{tip}}(\eta_{\log}) \) was obtained by performing a linear interpolation between the discrete values \( \log(R_{SF}(\eta)) \). The task is then to find the value of \( \eta_{\log} \) for which \( R_{\text{tip}} \) and \( R_{SF,\log} \) are equal. This problem can be formulated as

\[
0 \triangleq R_{\text{tip}}(\eta_{\log}) - R_{SF,\log},
\]

which is then solved for \( \eta_{\log} \) with a root finding algorithm. From this it becomes apparent that \( R_{\text{tip}}(\eta_{\log}) \) needs to be an injective function as otherwise more than one solution may be existent. In that case it would not be possible to determine the viscosity with the described procedure without any further information.

### 4.2.2 Segmentation Approach

For the procedure described in the previous section a fixed mask is used to define the ROI. Hence the sample’s position has to be known and similar for all samples. To overcome this requirements a segmentation approach was realised. The aim is to automatically detect the ROI and calculate \( R_{SF} \) for it.

After the process of reconstruction a cut-off filter is applied to both channels. It determines the maximum individual pixel value and sets all values below a certain threshold to zero. This threshold is given as a pre-defined fraction \( t \) of the maximum value, and constitutes a variable of the segmentation process.

![Visualization of a exemplary mask generated after applying the cut-off filter in segmentation approach. The white squares represent non-zero values while the black squares represent zero values.](image-url)
After the application of the cut-off filter a binary mask was created containing a value of one for every pixel with a non-zero value. An example for such a mask is depicted in fig. 4.2, where the white squares represent entries with a non-zero value, and the black squares represent entries with a value of zero. The non-zero entries of the mask were then arranged into connected components, where all spatially connected entries are put into the same connected component. Fig. 4.3 shows the entries labelled for their connected component, as these are numbered to address them. Every connected component can now be taken as a ROI. For a perfect measurement only one connected component is existing. Due to a high level of noise or other disturbances in some cases more than one connected component could be existing. To address this problem, the values of all entries of connected components are summed up and the one with the maximum sum is defined as the ROI. After this procedure the value of $R_{SF}$ is calculated as before.

\[ R_{SF} = \sqrt{\sum_{i=1}^{n} R_i^2} \]

\[ \sum_{i=1}^{n} R_i^2 \]

Figure 4.3: Visualization of the connected components. All non-zero entries are labelled with the number of the connected component they belong to.

### 4.2.3 Variation of Reconstruction Parameters

As already mentioned the process of reconstruction is dependent of several parameters. The influence of these parameters on the capability to compute a sample’s viscosity should also be investigated. As the values $R^2$ and the slope of the linear model fitted describe the suitability of the configuration for our calculations, their change is observed for the variation of the reconstruction parameters.

In a first step the regularization parameter $\lambda$ has been changed. As the range of possible values for $\lambda$ is extensive, they were spaced in logarithmic steps starting from $10^{-6}$ and rising up to $10^{0}$. In a second step the number of the kaczmarz algorithm’s iterations is evaluated, testing several values with 3 being the lowest and 20 being the highest.
As a third parameter the SNR threshold for the frequency components included in the reconstruction was varied. Additional to these values the positivity constraint can be set on or off and was also evaluated.
Chapter 5

Results

In the first part of this chapter we look at selected system functions of the first set of samples, particularly how they are influenced by viscosity. Several effects can be observed of which some are quantified using the system functions of both sets of samples. In the second part the images obtained from multispectral reconstruction and the analysis of these are presented. Furthermore the results of the approach to compute viscosities introduced in in section 4.2.1 are shown.

5.1 Analysis of the System Functions

5.1.1 Shapes of the Patterns for Immobilized Sample

When comparing the system functions’ patterns of the first series of samples, it becomes apparent that the patterns of the immobilized sample look significantly different to those of the other samples. This can be seen especially for frequency components where $m_x = m_y \pm 1$ is fulfilled. One example is depicted in fig. 5.1, where the frequency component with the mixing factors $m_x = 5$ and $m_y = 4$. As can be seen in the left image, the edges of the maxima in the outer regions are rounded. For the immobilized sample on the right side, the edges appear sharper and more rectangular. In the bottom plot one can see the smoothed profiles of the blue and red lines in the images. As the peak signal of the f9 sample is more than a factor of six higher than the one of the fb sample, both profiles are normalized to the maximum values of their respective images. One can see that the relative energies of these off-center profiles are generally on a higher level for the fb sample. The exception here are the local maxima next to the one in the center of the profile. These take low values compared to the maxima which are in the center of the either the $x$ or the $y$ axis.
Figure 5.1: Frequency component with the mixing factors $m_x = 5$, $m_y = 4$ (frequency component 149) taken from the x channels of the f9 (1.9mPas) and fb (immobilized) sample system functions. The bottom plot shows the smoothed profiles of the pixels marked by the blue and red lines normalized to the maximum values of their respective image.

### 5.1.2 Spatial Signal Distribution

When comparing the patterns of the not immobilized samples it becomes apparent that the distribution of signal intensity changes with viscosity as can be seen exemplary in fig. 5.2.

For samples with a low viscosity the maximum signal is in the center of the FOV and the signal quickly decreases towards the edges. With increasing viscosity the difference between the maximum signal in the center and the surrounding area drops. For the sample f6 with a viscosity of 18.5mPas the difference between the maximum in the center and those next to it has vanished. For sample f4 with a viscosity of 84.8mPas the maxima left and right of the center reach even higher values than the one in the center, as can be seen in the bottom plot of fig. 5.2. Even though it is shown here for one specific frequency component, this change in signal distribution occurs for nearly all frequency components of the spectrum.
Figure 5.2: Frequency component with the mixing factors $m_x = 5$ and $m_y = 4$ for the samples $f9$ (1.9 mPas), $f7$ (8.9 mPas), $f6$ (18.5 mPas) and $f4$ (84.8 mPas). As the viscosity rises the signal distribution changes in a way that the difference in signal between center of the FOV and the surrounding area decreases. The bottom plot shows the smoothed profiles of the pixels marked by the blue and red lines normalized to the maximum values of their respective image.
Figure 5.3: Frequency component with the mixing factors $m_x = 4$ and $m_y = 3$ from the system functions of the samples f9 (1.9 mPas) and f4 (84.8 mPas). The top row shows the pattern with the absolute values normalized to the maximum. The bottom row shows the difference of the not normalized absolute values (left) and difference of the normalized values (right). The color red corresponds to higher values of the sample f9 and the blue color corresponds to higher values of the sample f4.

In fig. 5.2 the pure values for the different samples are shown, which can be seen based on the different maximum values. Figure 5.3 shows an example with normalized values, where a different frequency component with coarser structure was chosen to make the changes more apparent. The top row shows the frequency component with the mixing factors $m_x = 4$ and $m_y = 3$ taken from the system functions of the samples f9 (1.9 mPas) and f4 (84.8 mPas). It is apparent, that the amount of signal from the outer regions of the FOV is higher for high viscosity samples, reaching up to about 70% of the maximum value in this example. This effect is further supported by the differences shown in the bottom row of fig. 5.3. On the left side the difference of the unnormalized frequency patterns is depicted, by using red representing higher values of the sample f9 and blue representing higher values of the sample f4. The biggest difference can be seen in the central part of the FOV where the pattern of the sample f9 contains values nearly twice
Figure 5.4: Normalized ratios of the signal in the center of the FOV and in the surrounding area for different frequency components (top) and different particles (bottom). The plot on top depicts the ratios of different frequency components for FeraSpin XL. The bottom plot depicts the ratios cumulated over all frequency components with a SNR above 10.

as high as those of the sample f4’s image. The differences in the outer parts of the FOV are much smaller than in the center, and even though the values are generally higher for low viscosity samples, we can see areas with even higher values for the sample f4 near the edges of the FOV. In the bottom right image in fig. 5.3 the difference of the normalized images is depicted, visualising the change in the signals’ spatial distribution. It can be seen that the relative signal of the sample f9 is higher in the center than for the more viscous sample f4. Furthermore the values in the outer areas of the sample f4 reach significantly higher relative values than those of the sample f9. We can conclude, that while the general structure of the system functions patterns are not influenced by viscosity, except for immobilized particles, the spatial distribution of the signal shows distinct differences comparing the signal of the central region with the signal of the outer region for several different viscosities.

To quantify this observation, the ratios of signal from the center area and of the signal
from the surrounding area $R_{\text{Out/In}}$ were calculated as depicted in eq. (4.1), and is shown in fig. 5.4. The center area was chosen to contain the values of pixels fulfilling $7 < x, y < 15$. In the top plot the ratios are depicted for single frequency components. For better comparability of the progression all graphs were normalized using the values of the sample f9 due to it yielding the highest ratios. This approves the visual impression that the relative amount of signal contributed by the surrounding rises with increasing viscosity. The major change in the ratios happens from the samples f8 to f5 corresponding to viscosities of 4.2 mPas to 40 mPas. Above or below these values the changes are also present, but less distinct. For very high viscosities the graph even seems to join saturation. When comparing the values of the samples fa (0.9 mPas) and f9 (1.9 mPas) it becomes apparent that for some frequency components ($m_x = 4, m_y = 5$ and $m_x = 5, m_y = 7$ of those depicted in fig. 5.4) the ratio slightly drops from fa to f9. Furthermore it can be seen that the difference of the ratios for high and low viscosities increases with frequency. While the range of values for $m_x = 4, m_y = 3$ is 24.4% it is 63.9% for $m_x = 5, m_y = 7$.

The bottom plot of fig. 5.4 shows a comparison of the ratios $R_{\text{Out/In}}$ for the tracers Feraspin XL and Resovist. The values were calculated and summed up for all frequency components which yield a SNR of above 10 for all system functions. For the samples containing Resovist the center was chosen to be $5 < x < 10$ and $9 < z < 18$. For FeraSpin XL the graph of the accumulated frequencies reassembles the s-shape of the single frequency graphs. Alike a drop from the sample fa to f9 can be observed. The range of values is 31.7%. The graph obtained from the measurements using Resovist describes a different shape. While the graph proceeds flatter and the range of the ratios is smaller being 21.3%, the graph does not saturate in the range of measured viscosities.

![Figure 5.5: Visualization of the frequency components' energy ordered by mixing factors, ranging from 0 to 7. In the left plot the energies of the sample f9 (1.9 mPas), and in the middle of the sample f3 (179.8 mPas) are depicted. In the right plot the difference of these values is visualized. The values shown are the sum of both receive channels.](image-url)
5.1.3 Energy of the Frequency Components

The energy of the frequency components was calculated using eq. (2.43) and sorted by the mixing factors $m_x$ and $m_y$. The results for the samples f9 (1.9 mPas) and f3 (179.8 mPas) are depicted in fig. 5.5. In general it can be seen that, except for the very low values of below 3 which are influenced by the filter, the energy decreases with the sum of $m_x$ and $m_y$. While for the general structure no alteration between the samples are apparent, the difference on the right of fig. 5.5 shows deviations concerning high mixing factors, similar for both axes. As indicated by the red color, the energy of this high mixing factor frequency components reaches higher values for samples of lower viscosities. Frequency components where one of the mixing factors is below two are not showing such significant differences. For the range depicted in fig. 5.5 between the samples f9 and f3 a maximum difference in energy of 9.7% was calculated.

To further quantify this effect the ratios $R_{MF}$ were calculated as described in section 4.1.3. For the high mixing factors the energies of the frequency components accomplishing $4 < m_x < 8$ and $4 < m_y < 8$ were summed up for both receive channels, as these show the highest difference in energy. For the low mixing factors the energies of the frequency components accomplishing $m_x < 2$ and $4 < m_y < 8$, as well as $4 < m_x < 8$ and $m_y < 2$ were summed up for both receive channels. The ratios for both FeraSpin XL and Resovist are plotted in fig. 5.6. For Feraspin XL one can see that the ratio is rising monotonically from sample f9 (1.9 mPas) to sample f3 (179.8 mPas). The same behaviour can be seen for Resovist from sample G3 (3.7 mPas) to G8 (100 mPas). This means that the energy of the frequency components with high similar mixing factors decreases with rising viscosity. As seen before, the samples containing no glycerol (fa and G1) do not fit in the monotone,

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![Figure 5.6: Ratios $R_{MF}$ for FeraSpin XL and Resovist, calculated from the energies of frequency components with high combined mixing factors and low combined mixing factors.](image-url)
or nearly monotone in case of Resovist, progression of the graph. The range of ratios covered by the series of samples is slightly higher for FeraSpin XL (8.8%) as for Resovist (7.8%).

A different way to analyse the energy of the frequency components is to plot their values ordered by frequency. This is shown in fig. 5.7 for the samples f9 (1.9 mPas), f7 (8.9 mPas) and f3 (179.8 mPas). It is observed that the peaks of the pure harmonics, meaning \( m_y = 0 \) in case of the \( x \) channel, reach the same energy values for different samples. While the pure harmonics’ energy values seem not to be influenced by the viscosity of the samples, differences can be seen for frequency components fulfilling \( m_x = m_y \pm 1 \), where samples with lower viscosities as f9 (1.9 mPas) in fig. 5.10 reach higher values than samples of lower viscosities as f3 (179.8 mPas). To quantify these observations the ratios \( R_E \) were calculated by dividing the energy of the frequency component \( m_x = 13, m_y = 0 \) by the energy of the frequency component \( m_x = 7, m_y = 6 \) for samples containing FeraSpin XL. These correspond to the frequencies of 320 kHz and 329.3 kHz respectively. For the samples containing Resovist the corresponding values for \( m_z \) instead of \( m_y \) were used.

![Energy spectrum for the samples f9 (1.9 mPas), f7 (8.9 mPas) and f3 (179.8 mPas) obtained from the x receive channel.](image)

The results of these calculations are depicted in fig. 5.8. For both series of samples a monotone change of the ratios with viscosity is observed. The only exception are again the samples containing no glycerol as they reach higher ratios than expected from the values of the other samples. These results approve our findings from the 2D depiction of
the mixing factors (fig. 5.5) and show that they are also applicable to single frequencies.

### 5.1.4 Error Measure

With the error measure introduced in section 4.1.4 the differences of the system functions were calculated using various system functions as base system function. Three for each series of samples are depicted in fig. 5.9. For FeraSpin XL the intersection of frequency components with a SNR above the threshold of 10 for all system functions resulted in a total of 154 frequency components used for the calculations. For Resovist 75 frequency components were taken into account.

As can be seen in fig. 5.7 every graph takes the value 0 at one point. This is expected since at this point the system function $S_n$ is also used as base system function $S$. In the top plot of fig. 5.7 the graphs for the samples $fa$ (0.9mPas), $f9$ (1.9mPas) and $f3$ (179.8mPas) as base system function are shown as examples. One can see that the more the viscosity of the variable system function differs from the one of the base system function the higher $\sigma$ rises. This is due to the system functions becoming more and more diverse for a rising difference in viscosity. While the individual graphs show linear segments, no general regularity can be seen. Especially using $fa$ as base system function no significant change over the range of viscosities can be seen.

For the samples containing Resovist a more regular behaviour is observed. In the bottom plot of fig. 5.7 the graphs for the sample $G1$ (1.0mPas), $G2$ (1.9mPas) and $G8$ (100mPas) are depicted. As one can see the values are nearly linear in a range from 1.9mPas up to 51.8mPas and show similar behaviours over the whole range of viscosities.

In all graphs it can be seen that again the samples containing no glycerol ($fa$ and $G1$) do not fit into the progression of the graphs and cause segments which are not monotonic.
Figure 5.9: Error measure as defined in eq. (4.2) for FeraSpin XL (top) and Resovist (bottom). For FeraSpin XL, the system functions of the samples fa (0.9 mPas), f9 (1.9 mPas) and f3 (179.8 mPas) were used as base system function, while for Resovist the system function of the samples G1 (1.0 mPas), G2 (1.9 mPas) and G8 (100 mPas) were used.

5.1.5 Spectra

Analysis of the spectra obtained from SNR showed that the general level of SNR is higher for samples of low viscosity, yielding higher signal strength. This can be observed in fig. 5.10 where the spectra of the samples f9 (1.9 mPas), f4 (84.8 mPas) and fb (immobilized) are depicted. For the whole range of frequencies the SNR of the f9 sample reaches higher levels compared to f4 and fb, until the signal finally vanishes in noise at about 750 kHz. The sample of the immobilized particles (fb) achieves the lowest levels of SNR and its highest measurable signal above noise level at about 500 kHz. For a better visibility of differences in the progress of the spectra they were normalized to their maximum values, as can be seen in fig. 5.11. By comparison of the f9 and f4 samples’ peaks one can see that the decrease of the pure harmonics for both is nearly similar. Only for the last maxima above 500 kHz the values of the f9 sample reach significantly higher values. In contrast the decrease of the immobilized particle sample is accelerated compared
to the not immobilized samples.

Figure 5.10: SNR of the samples f9 (1.9 mP as), f4 (84.8 mP as) and fb (immobilized) obtained from the x receive channel.

Figure 5.11: Spectrum of the normalized SNR for the samples f9 (1.9 mP as), f4 (84.8 mP as) and fb (immobilized) obtained from the x receive channel. The range of frequencies was limited to values between 50 and 650 kHz for better visualization of the details.
5.2 Evaluation of the Measurements

5.2.1 Qualitative Comparison

In a first step the influence of viscosity on the reconstruction was qualitatively examined using multispectral reconstruction with system functions of various viscosities. A selection of the reconstructed images is shown in fig. 5.12. The reconstruction was performed with the system functions of the samples f9 (1.9 mPas) and f4 (84.8 mPas). The image of the f9 system function’s channel is depicted on the left, the one of the f4 system function on the right. Exemplarily the measurements of samples f9, f7 and f3 where reconstructed with this combination of system functions. The results are depicted in fig. 5.12. One can see that in both channels signal is present in the center of the FOV, where the sample was placed. The image of the f9 channel yields more signal than the one of the f4 system function. Hence in the image of the f4 channel the noise around the center, which is existent in all images becomes more apparent. In the middle row the results for the sample f7 (8.9 mPas) are shown. Both images show signal of approximately the same level, what suggests that the sample f4’s viscosity is between those of sample f9 and sample f4 as neither of the system functions is dominating the result in this case. In the bottom row the f3 (179.8 mPas) sample’s reconstruction results are shown. Here the image of the f4 channel yields more than twice the signal compared to the image of the f9 channel.

From these results it becomes apparent that a correlation of the measured sample’s viscosity and the viscosities of the used system functions’ samples is existent. If the measurement of a low viscosity sample (in this case f9) is reconstructed, the image of the low viscosity system function (f9) yields the most signal. Conversely, for a high viscosity sample (f3) the image of the high viscosity system function (f4) yields the most signal. For intermediate viscosity samples (f7) these cases merge into one another.

5.2.2 Reconstruction Ratios

The reconstruction ratios should now be calculated as depicted in chapter 4.2.1. For this several combinations of system functions were selected and the ratios were the calculated for measurements. After the calculations of the channel’s ratios $R_{SF}$ they were plotted in log-log plots, for a good visualization over the whole range of values. The best results for both series of samples are depicted in fig. 5.13. For the first series of samples (FeraSpin XL) all combinations show only minor changes above the sample f5 (40 mPas). For the samples f9 (1.9 mPas) to f5 (40 mPas) the values seem to fit to a linear model. To prove this the data points were transferred into a logarithmic coordinate system where a linear regression was performed using the values of the samples from f9 (1.9 mPas) to f5 (40 mPas). The coefficient of determination for the combination of system functions f3 & f9 was the highest for this range of samples with 0.992 (see tab. 5.1). The combination f3 & f9 yielded the lowest value with 0.977. The highest value for the slope of the regression
5.2. Evaluation of the Measurements

Figure 5.12: Reconstructed images of the samples f9 (1.9mPas), f7 (8.9mPas), and f3 (179.8mPas). The reconstructions were done using the system functions of the samples f9 and f4 in a multispectral reconstruction. The images of the f9 (1.9mPas) channel are depicted on the left while the images of the f4 (84.8mPas) channel are depicted on the right.
line was achieved by the combination $f_3$ & $f_9$ with $-0.84$, compared to $-0.82$ for the combination $f_5$ & $f_9$ and $-0.64$ for the combination $f_3$ & $f_a$.

Table 5.1: Calculated values of the slope and $R^2$ for the logarithmised data sets of the ratio $R_{SF}$ for a selection of system function combinations.

<table>
<thead>
<tr>
<th>System Functions</th>
<th>Slope</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_3$ &amp; $f_a$</td>
<td>-0.64</td>
<td>0.992</td>
</tr>
<tr>
<td>$f_3$ &amp; $f_9$</td>
<td>-0.84</td>
<td>0.977</td>
</tr>
<tr>
<td>$f_5$ &amp; $f_9$</td>
<td>-0.82</td>
<td>0.983</td>
</tr>
<tr>
<td>$G_1$ &amp; $G_8$</td>
<td>-0.94</td>
<td>0.989</td>
</tr>
<tr>
<td>$G_2$ &amp; $G_8$</td>
<td>-1.18</td>
<td>0.991</td>
</tr>
<tr>
<td>$G_2$ &amp; $G_7$</td>
<td>-1.40</td>
<td>0.984</td>
</tr>
</tbody>
</table>

For all graphs the values of the sample $f_a$ (0.9 mPas) does not fit the trend of the other samples’ values. This also applies to the G1 (1.0 mPas) ratios for the combinations of system functions $G_2$ & $G_8$ and $G_2$ & $G_7$ depicted in the bottom plot of fig. 5.13. For the combination $G_1$ & $G_8$ this behaviour is not observed. Generally the graph of this combination provides an almost linear progress, resulting in $R^2 = 0.989$ using all values except the one of $G_8$, since it is on the same level as $G_7$ and does not follow the progression of the values so far. For the other combinations the sample $G_1$ was not used in the linear regression. The value of the slope for the combination $G_1$ & $G_8$ is $-0.94$, and thus, as can be seen in tab. 5.1, is the smallest of the three combinations depicted. Here the highest value is reached by the combination $G_2$ & $G_7$ yielding a slope of the value $-1.40$. By comparing the values obtained from the first series of samples with those of the second series of samples one sees, that in general for the second series of samples higher values for the slope are reached. This can be translated into a potentially better performance of Resovist for the computation of viscosities.

**Determination of Viscosities**

The values of $R_{SF}$ were calculated for the second series of samples ans used to compute the viscosities of the control samples U1 (2.8 mPas), U2 (20.4 mPas) and U3 (75.9 mPas), as described in chapter 4.2.1. The control samples’ viscosities lie between those of the other samples. Hence these samples are not covered by the used system functions. For these computations the system function combinations $G_1$ & $G_8$, $G_2$ & $G_8$ and $G_2$ & $G_7$ were used, on which we have looked closely in the prior section. The errors where calculated with the values’ standard deviations from the linear model used. By comparing the computed values with the true ones (see tab. 5.2) one can see good conformity for the values of the samples of U1 and U2. For both combinations of system
functions $G_2 \& G_8$ and $G_2 \& G_7$ the calculated values for $U_1$ are located less than 8% off of the true value. For the sample $U_2$ all the combinations yield values meeting the true value within the calculated uncertainties. The combinations $G_1 \& G_8$ and $G_2 \& G_8$ even yield values differing less than 5% from the true value. In contrast to that, the computed values for the sample $U_3$, ranging from 32.6 mPas to 37.6 mPas, differ strongly from the true value of 75.9 mPas. A comparison of $U_3$’s $R_{SF}$ with those of the samples building the grid shows that the values of $U_3$ do not fit the curve at the right position for any combination of system functions. This implies the invalidity of the sample, due to which the sample $U_3$ won’t be regarded in the following.

For the combination $G_2 \& G_7$ a problem occurred during computation caused by the non-injectivity of $R_{\text{fit}}$, which linearly interpolates between the points of the grid. For the sample $U_1$ two solutions were found due to the non-injectivity in the regime of low
Table 5.2: Comparison of the true and the computed viscosities of the samples U1, U2 and U3.

<table>
<thead>
<tr>
<th>$\eta$ [mPas]</th>
<th>U1</th>
<th>U2</th>
<th>U3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.8</td>
<td>20.4</td>
<td>75.9</td>
</tr>
<tr>
<td>G1 &amp; G8</td>
<td>2.37 ± 0.17 (1.27 ± 0.09)</td>
<td>19.5 ± 1.4</td>
<td>32.9 ± 2.3</td>
</tr>
<tr>
<td>G2 &amp; G8</td>
<td>2.61 ± 0.16</td>
<td>19.7 ± 1.2</td>
<td>37.6 ± 2.3</td>
</tr>
<tr>
<td>G2 &amp; G7</td>
<td>3.02 ± 0.25</td>
<td>18.1 ± 1.5</td>
<td>32.6 ± 2.7</td>
</tr>
</tbody>
</table>

viscosities (see fig. 5.13). In table 5.2 the apparently wrong value is put in brackets.

5.2.3 Results with Segmentation Approach

With the segmentation approach described in section 4.4.2 the viscosities of the samples U1, U2 and U3 were computed as well. The ratios $R_{SF}$ for the used system function combinations are depicted in fig. 5.14. In the top plot it can be seen that with the segmentation approach similar results can be achieved compared to those with a fixed ROI. For G1 & G8 and G2 & G8 even between the ratios of G7 (51.8 mPas) and G8 (100 mPas) a difference can be seen. For G1 & G8 the data is homogeneous and linear over the full range of samples resulting in a coefficient of determination of 0.99 (see tab. 5.3). The values of the slopes for the depicted combinations are in the same range as well, yielding values from $-0.99$ to $-1.36$.

Table 5.3: Calculated values of the slope and $R^2$ for the ratio $R_{SF}$ using the segmentation approach.

<table>
<thead>
<tr>
<th>System Functions</th>
<th>Slope</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 &amp; G8</td>
<td>-0.99</td>
<td>0.992</td>
</tr>
<tr>
<td>G2 &amp; G8</td>
<td>-1.23</td>
<td>0.994</td>
</tr>
<tr>
<td>G2 &amp; G7</td>
<td>-1.37</td>
<td>0.974</td>
</tr>
</tbody>
</table>

In the bottom plot of fig. 5.14 the influence of the threshold factor $t$ for the cut-off filter is depicted. As described in section 4.4.2 all values below the value of this factor times the maximum value are set to zero. One can see a nearly linear progress for $t = 0.3$ and $t = 0.5$, but an inhomogeneity for $t = 0.4$, which that can be seen between G2 (1.9 mPas) and G5 (13.9 mPas). It is caused by values close to the threshold at the edges of the ROI. Whether these pixels have values slightly above or below can cause such inhomogeneities in some cases. Thus the value $t$ must be chosen individually for every combination to avoid this case. This obstructs the target of simplifying the usage of our method.
Figure 5.14: Ratios $R_{SF}$ calculated using the segmentation approach. In the top plot the combinations used for the computation of the viscosity values are depicted. For the system function combinations G2 & G8 and G2 & G7 a threshold factor of $t = 0.5$ was chosen, while for G1 & G8 a factor of $t = 0.4$ was chosen. In the bottom plot the influence of the cut-off filter's threshold factor is shown for the combination G2 & G8.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>$\eta$ [mPas]</th>
<th>U1</th>
<th>U2</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 &amp; G8</td>
<td>$2.35 \pm 0.14$</td>
<td>$16.5 \pm 1.0$</td>
<td></td>
</tr>
<tr>
<td>G2 &amp; G8</td>
<td>$2.02 \pm 0.10 (1.5 \pm 0.06)$</td>
<td>$30.6 \pm 1.5$</td>
<td></td>
</tr>
<tr>
<td>G2 &amp; G7</td>
<td>$2.67 \pm 0.30 (1.49 \pm 0.18)$</td>
<td>$25.7 \pm 2.7$</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.4: Values of the viscosities of the samples U1 and U2, computed using the segmentation approach.

The computed values for the samples U1 and U2 using the segmentation approach are listed in tab. 5.4. For U1 the estimated values lie on a lower level than for the fixed ROI approach. For U2 the estimated values are more scattered compared to the fixed ROI approach. This might be due to the fact that even so a linear grid is given, still for the measured sample the problem of values close to the threshold, described in the previous paragraph, can occur. Nonetheless the values are in the right order of magnitude.
5.2.4 Influence of Reconstruction Parameters

To examine the reconstruction parameters’ influence, the system functions G1 & G8 were used as these yielded the best results in terms of linearity over the whole range of samples.

For variation of the regularization parameter $\lambda$ from $10^{-6}$ up to about $10^{-4}$ no severe changes for the coefficient of determination or the slope are observed. For higher values, the slope decreases as depicted for the system functions G1 & G8 in fig. 5.15.

![Slope values for different regularization parameters $\lambda$ with fixed ROI (blue) and segmentation approach (red). The system functions used for reconstruction are G1 & G8 in both cases. The SNR threshold was set to two and the SNR threshold was two.](image)

This is due to the fact, that the results for the different system functions in a multispectral reconstruction become more and more similar for high regularization parameters. As this applies generally, the effect can be seen for a fixed ROI as well as for variable ROI of the segmentation approach. Hence for the computation of viscosities a low regularization factor is favourable to achieve large difference between the reconstruction results of different system functions. The results for the variation of the kaczmar algorithm’s iterations is depicted in fig. 5.16. Especially for the fixed ROI a relationship between the number of iterations and the slope values can be seen. For reconstructions with less than ten iterations every further iteration yields a significant improvement. Above the values of the slope transition into saturation. For the variable ROI of the segmentation approach a similar, but more irregular effect can be seen. Especially for 5 iterations the value seems to exceed the expected progression. This is due to the effect of values being close to the threshold of the cut-off filter that can occur and was described before. The SNR threshold of the reconstruction was varied between one and six and, as for the number of iterations and the regularization parameter, a correlation for the slope of the fitted graphs can be seen, as depicted in fig. 5.17. For both the segmentation approach high thresholds result in higher slope values than low ones. For the fixed ROI there seems to be an maximum
value between an SNR threshold of three and four. A decline of the values at a distinct point is not surprising, as with a rising SNR threshold the number of used frequency components for reconstruction decreases. Thus for too high values the meaningfulness of the results is questionable. The calculation of the coefficients of confident shows that for the high threshold values our linear model does not apply properly to the data any more.
of the parameter combinations, it dropped when irregularities appeared which caused the model to fail.

The combination of these parameters, meaning a regularization parameter of zero, a SNR threshold of four and a number of iterations of 20, did not further improve our results but worsened them slightly. This is due to the fact that all the reconstruction parameters influence our calculations and hence a variation of one parameter yields varying outcomes for different values of the other parameters.
Chapter 6

Conclusion and Discussion

In this work the influence of the dynamic viscosity on magnetic particle imaging was investigated. The impact on the system function as well as on the reconstruction of measurements was illustrated and quantified. For this two series of samples were measured. The first one, containing FeraSpin XL as tracer particles, was used for qualitative analysis and first quantifications. Based on the findings drawn from these measurements a second series of samples was prepared, using Resovist as tracer particles, for further analysis. This series contained three samples of which the viscosity lies not on the logarithmically spaced grid but in between of the other samples. The viscosities of these three samples has been computed in the course of this work.

The comparison of the system functions’ patterns for a sample of low viscosity and one with immobilized particles showed distinct changes in the structure of the patterns. For the immobilized sample the pattern seemed to be more of rectangular and the edges were less rounded. This shapes of the immobilized sample are similar to those obtained from simulations using Langevin magnetization curves and tensor products of the Chebyshev functions as system function pattern [RWGB12]. Hence we can suspect, that Néel relaxation, which present solely in an immobilized sample, matches the model of the Langevin magnetization curve and the Chebyshev tensor products better then the Brownian rotation. These structural changes of the system function patterns were first published by Rahmer et al. [RHG+15] and can be confirmed by our investigations. Further more the frequency components’ signal distributions were examined for different system functions. It was found, that while for low viscosities in the center of the FOV very high signal values are reached compared to the surrounding area, the signal is more equally distributed for higher viscosities. This observation was then quantified yielding the result that the ratio of signal in the center and signal in the surrounding regions changes monotonous with viscosity. A comparison of the tracers FeraSpin XL and Resovist showed that this effect occurs for both tracers. While the differences are more evident for FeraSpin XL, the saturation occurring for high viscosities does not appear for Resovist. This allows the assumption that Resovist yields a higher potential for distinguishing high viscosities than
FeraSpin XL. This may be due to structural differences of the tracer particles, as they are not perfectly spherical in reality. Their shape is an important factor especially as the Brownian rotation is a hydrodynamic phenomenon. Furthermore tracers tend to differ in their affinity to agglomerate. This can cause more severe differences in the hydrodynamic behaviour than the shape of the single particles.

The energy of the frequency components was calculated and sorted for the mixing factors \( m_x \) and \( m_y \). This showed that the relative change of energy is most significant for frequency components with similar mixing factors. Again the frequency components fulfilling the relation \( m_x = m_y \pm 1 \) can be defined as the quantity for which this effect is most apparent. This is also approved by the analysis of the full spectrums’ energies. In the depiction of this we saw that the energies of the pure harmonics \((m_x = 0 \text{ or } m_y = 0)\) were nearly constant for different system functions, whereas the energy of highly mixed harmonics decreases with viscosity. This ratio was quantified for two chosen frequency components and a monotone relationship was found for both tracer particles.

The overall change of structure for the system functions’ frequency components was investigated with an error measure and it was shown, that the changes in the system function are substantial in the regime of low viscosities, while in the regime of high viscosities the differences per mPas are comparatively small.

In summary it can be said, that the viscosity influences both, the general signal strength and the spatial distribution of the signal. The difference in signal strength can be explained with the obstruction of the Brownian rotation by higher viscosities. A possible explanation for the structural change is that speed of FFP is higher in the center of the FOV than near the edges. As the viscosity increases the relaxation time of the particles rises (see eq. (2.11)) and a part of the signal is not assigned to the central area since the relaxation time is too high, and hence the signal "too late". In nearly all of the examinations it was apparent, that the samples containing only water and tracer provide system functions yielding results differing from what was expected based on their viscosity. For reconstruction of the measurements a multispectral reconstruction with two system functions was used. It shows that for a sample of low viscosity the contribution of the low viscosity system function is higher than the contribution of the high viscosity system function and vice versa. This difference was used to calculate a ratio of the system functions’ contributions for all samples. For several combinations of system functions a linear correlation was found using a logarithmic coordinate system. Hence a linear model was used to define a function linking the ratios with the viscosity. To prove the legitimacy of the linear approach the coefficient of confidence was calculated for a linear regression using the ratiosion was calculated. The values for the combinations of system function which were used for calculations lay between 0.977 and 0.992. This validates our assumption of a linear model as nearly all of the deviations from our linear model can be explain by the standard deviation of the data itself.

Additionally for three control samples not covered by system functions the ratios \( R_{SF} \)
and from them the viscosity was calculated using the linear model. Using a sample of 2.8 mPas the best result yielded a value of 2.62 ± 0.16 mPas, which corresponds to a relative deviation of 6.4%. For a sample of 20.4 mPas viscosity the best result yielded a value 19.7 ± 1.2 mPas, corresponding to a relative deviation of 3.4%. In both cases these results were achieved using the combination of the system functions of the samples G2 (1.9 mPas) & G8 (100 mPas). In this case the viscosities of both samples lie between those of G2 & G8, but if the viscosity should be computed for a sample exceeding this range the results may not be reliable any more. If for example the viscosity of a sample of 1.3 mPas is computed with this combination of system functions two solutions are given due to non-injective regions if including values below the viscosity of G2. This is the case due to the G2 measurement matching perfectly with the G2 system function, which hence yields very high values in the reconstruction. For the sample with 75.9 mPas viscosity no combination yielded results which come close to this value. Since the values of this sample strongly deviate from what we would expect by its viscosity in any analysis, we assume that the sample is flawed.

The previous results were obtained with a fixed ROI, and hence the position of the sample needs to be known for the calculations. Additionally for every new position of the sample a new ROI has to be defined. For a better applicability a segmentation approach was realised which automatically defines the ROI. The computed values for the 2.8 mPas sample still were close to the true value, with an relative deviation of 4.6 % as best case. The values for the 20.4 mPas sample worsened with 16.5 ± 1.0 mPas as the best result, corresponding to a relative deviation of 19.1 %. Also the coefficients of determination decreased in general, still yielding values of 0.99 to the best combinations.

The influence of the reconstruction parameters was investigated to the best combination of system functions in terms of linearity over the whole range of viscosities. It was found that the range of ratios is nearly constant for a relative regularization parameter of up to 10^−4. For larger values the differences in the distributions of the system functions were reduced and are thus unfavourable. For the number of iterations the highest slope values were reached for high amounts of iterations. While the best slope values are reached for high SNR thresholds of 4 for a fixed ROI and up to 6 for the segmentation approach, in practice such values yield worse results since the data does not fit the linear models in that cases.

With calculations and computations done it became distinct that the difference caused to the signal by a change of viscosity is larger in the regime of low viscosities. From 1 to 40 mPas the differences between the signal of the samples was high enough to reliably distinguish between the samples. For higher viscosities the differences were noticeable only for selected analyses. Despite the insights our analyses yields, and the capabilities of our approach to compute the viscosity a sample’s viscosity provides, our methods are not free of potential for error. One example for this is the sample U3 for which all analyses and reconstructions of the measurement indicate that its viscosity strongly differs from
the one desired. Our assumption is that human error in the preparation of the sample
caused this strong deviation. In general the preparation of the samples poses an error
source as there was no possibility to measure the viscosity after preparation to achieve a
ground truth. Especially for high viscosities, where the amount of glycerol is high com-
pared to the amount of water, small deviations in the ratio of water and glycerol causes
remarkable differences in viscosity. Hence a tool to measure the viscosity of a fluid would
be a way to minimize the potential of human error in the sample preparation. Also the
calculated ratios of water and glycerol themselves contain errors since they are calculated
from a model based on empirical data. For the computations of viscosities we assume
a linear model and hence perform linear interpolation between our data points. While
this is a good assumption for a large range of viscosities, as proved by the coefficient
of confidence, it is not exact and thus adds error to our calculations. This error can be
minimized by increasing the number of data points used to generate the interpolation
function. This on the other hand means a higher effort as more samples must be prepared
and measured, as well as a rising computation time. The segmentation approach with
its ROI of variable size causes error in combination with the cut-off filter needed for seg-
mentation. For cases where on the edges of the ROI the values of the pixels are close to
the cut-off threshold errors can arise when these pixel take values below the threshold for
one system function and values above the threshold for a different system function. Here
further improvements may be possible by using a more advanced thresholding procedure,
e.g. Otsu’s method [Ots79]. For samples of a constant and known size a compromise
could be chosen where the size of the ROI is static but its position is variable to prevent
this error. Another possible error could be caused by temperature, since the viscosity of
glycerol is highly dependant on the temperature. In our calculations a temperature of
23°C was assumed since this is the air temperature in the scanner room.

As this work is one of the first steps in the field of multispectral MPI it should also pave
the way for further advances of the introduced methods and new ideas in this field. Possi-
ble ideas would be to use several system function combinations for the computation of the
viscosity. One covering the whole range of viscosity can be used for a rough calculation
of the viscosity and to further decide which combination is the best for the computation
in this regime. Furthermore one could think of possible ways to compute the viscosity
from a measure including the results of a multispectral reconstruction with more than
two system function. Due to the strong dependency of glycerol’s viscosity from the tem-
perature, measurements performed under controlled variation of the sample temperature
would mark a next step in this field. This is especially interesting as the temperature not
only influences the viscosity but also the relaxation times of the particles as can be seen
in eq.(2.11) and eq.(2.12). From the measured data the question arises how the signal
depends on whether the particles are solved in pure water or in a mixture of water and
glycerol with a similar viscosity. The results of our analysis showed differences which are
larger than expected from the difference of viscosity. This allows the assumption that
there are also chemical effects influencing the signal which need further investigation.
Appendix A

Datasheets

On the following three pages follows the data sheet of FeraSpin XL, the tracer used for the first series of samples. As no official data sheet for Resovist is available the reader is referred to [RB03].
Contents
1. Description
  1.1 Background information
  1.2 Applications
  1.3 Physico-chemical properties
  1.4 Requirements
2. Protocol
  2.1 Preparation
  2.2 Injection
  2.3 Imaging
3. References
4. Related products

1. Description

Components
- 850 µL FeraSpin™ XL MRI contrast agent (superparamagnetic iron oxide nanoparticles)
- or
- 5×850 µL FeraSpin™ XL MRI contrast agent (superparamagnetic iron oxide nanoparticles).

Capacity
- 5×100 µL injections
- or
- 25×100 µL injections.

Product format
FeraSpin XL is supplied as a sterile isotonic solution with an iron concentration of 10 mM.

Appearance
Clear, amber liquid.

Storage
Store at 2–8 °C. Do not freeze. The expiration date is indicated on the vial label.

For laboratory and animal research use only. Warning: Not for human or animal therapeutic or diagnostic use. Make sure to comply with all laws and regulations governing research on animals.

1.1 Background information
FeraSpin XL is a nanoparticulate superparamagnetic iron oxide contrast agent specifically formulated for pre-clinical magnetic resonance imaging (MRI).

FeraSpin XL belongs to the FeraSpin Series, which encompasses size-selected, narrowly distributed nanoparticulate agents with well-defined particle sizes derived from FeraSpin R (for details refer to the product portfolio at www.miltenyibiotec.com/viscover). The FeraSpin Series includes FeraSpin XS, FeraSpin S, FeraSpin M, FeraSpin L, FeraSpin XL, and FeraSpin XXL. Their identical composition allows for exclusive size-dependent studies and selection of the most suitable contrast agent for the intended application.

FeraSpin XS, S, M, L, XL, and XXL are agents of high relaxivity. They enhance the contrast in T2- and T2*-weighted MRI due to a shortening of the spin-spin relaxation time (T2) and increase the signal intensity in T1-weighted MRI due to a shortening of the spin-lattice relaxation time (T1). The T2-effect increases with increasing particle size whereas the T1-effect increases with decreasing particle size. On accumulation in cells, the T1-effect diminishes and the T2-effect increases.

Upon intravenous injection, all agents of this series circulate in the bloodstream and are taken up by macrophages. They accumulate in the liver and spleen and are degraded within a few days with their iron being transferred into the physiological iron stores. The macrophage uptake varies in dependence of particle size. Increased uptake by the Kupffer cells (macrophages of the liver) with increasing particle size leads to a rapid accumulation in the liver and spleen and a short blood circulation time. With decreasing particle size, the uptake by the Kupffer cells is reduced leading to a prolonged circulation time and increased uptake by other macrophages.

The following schematic diagram shows the characteristics of the FeraSpin contrast agents in dependence of their particle size.

![Characteristics of the FeraSpin Series in dependence of particle size.](image-url)
1.2 Applications

The FeraSpin Series is an innovative research toolbox that offers solutions for a wide range of imaging applications. It provides the possibility for selection of the MR contrast properties, the pharmacokinetic properties as well as the iron oxide load and, thus, allows a tailoring of the contrast agent to customer needs. FeraSpin XS, S, M, L, XL, and XXL are indicated for use in MRI of small animals, for example, mice. They can be used in various applications, such as ex vivo cell labeling or in vivo macrophage labeling for inflammation imaging. Principally, all agents of this series can be used to facilitate the visualization of the liver and spleen as well as visualization of the vasculature.

Note: For liver and spleen imaging the use of FeraSpin R is recommended. In applications where a long blood circulation time and a strong T1 effect are favorable, for example in MR angiography, the use of FeraSpin XS is most suited. For more details refer to the product portfolio at www.miltenyibiotec.com/viscover.

Note: The contrast agents of this series are provided with equal composition for reasons of comparability. For custom-tailored concentrations please contact the customer support.

1.3 Physico-chemical properties

<table>
<thead>
<tr>
<th>FeraSpin</th>
<th>Mean particle size*</th>
<th>Relaxivity, r2/r1**</th>
</tr>
</thead>
<tbody>
<tr>
<td>XS</td>
<td>10–20 nm</td>
<td>3–5</td>
</tr>
<tr>
<td>S</td>
<td>20–30 nm</td>
<td>5–9</td>
</tr>
<tr>
<td>M</td>
<td>30–40 nm</td>
<td>9–22</td>
</tr>
<tr>
<td>L</td>
<td>40–50 nm</td>
<td>22–32</td>
</tr>
<tr>
<td>XL</td>
<td>50–60 nm</td>
<td>32–39</td>
</tr>
<tr>
<td>XXL</td>
<td>60–70 nm</td>
<td>39–46</td>
</tr>
</tbody>
</table>

* hydrodynamic diameter, ** in water, 37 °C, 1.41 T

Figure 2: Schematic diagram of small, medium, and large-sized nanoparticles of the FeraSpin Series.

1.4 Requirements

- Sterile syringes and needles (27G–30G)
  ▲ Note: To allow sufficient volume for 5×100 µL injections per vial, the syringe/needle dead volume should be kept below 70 µL. Tip: Use insulin or tuberculin syringes.
- 70% ethanol

2. Protocol

2.1 Preparation

▲ Read the entire protocol before starting.

▲ Tip: For optimum device settings perform initial studies in a suitable imaging phantom.

▲ The contrast agent is ready for injection as provided.

▲ Standard animal-handling procedures and local regulations must be followed.

▲ The dosing varies in dependence of the intended application as well as the selected FeraSpin contrast agent and, thus, has to be adapted accordingly. For a mouse weighing 20–30 g an injection volume of 100 µL corresponds to a dose of 40 µmol Fe/kg body weight (for a 25 g mouse).

2.2 Injection

▲ FeraSpin XL contains no preservatives. Avoid microbial contamination and discard any unused material after 24 hours.

1. Vortex the vial to ensure thorough mixing.
2. Disinfect the septum with 70% ethanol. Let septum dry.
3. Warm the mouse tail to dilate the veins and enhance their visibility.
4. Inject FeraSpin XL via the lateral tail vein of the mouse.

2.3 Imaging

▲ Imaging can be performed in a multitude of devices at all commonly used field strengths including high-field MRI.

▲ FeraSpin XL can be detected by T1- as well as T2- and T2*-weighted sequences.

▲ The time interval between injection and imaging depends on the application. For applications involving imaging of the vasculature begin imaging immediately after injection. For other applications imaging over an extended time period after injection, for example 24 hours, is recommended.

Find examples of FeraSpin-enhanced MR images at www.miltenyibiotec.com/viscover.

3. References

4. Related products

FeraSpin™ R # 130-095-138, # 130-095-139
FeraSpin™ XS # 130-095-140, # 130-095-141
FeraSpin™ S # 130-095-166, # 130-095-167
FeraSpin™ M # 130-095-168, # 130-095-169
FeraSpin™ L # 130-095-170, # 130-095-171
FeraSpin™ XXL # 130-095-174, # 130-095-175
GadoSpin™ M # 130-095-134, # 130-095-135
GadoSpin™ P # 130-095-136, # 130-095-137
GadoSpin™ F # 130-095-162, # 130-095-163
GadoSpin™ D # 130-095-164, # 130-095-165

A comprehensive product portfolio for the imaging modalities MRI, CT, US, OI, SPECT, and PET is available at www.miltenyibiotech.com/viscover.

Warranty

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Bibliography


