

UNIVERSITY OF TWENTE

MASTER ASSIGNMENT

Searching for the cause of the SuperParamagnetic Quantifier measurement drift

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Abstract

Research into superparamagnetic particles has surged over the last decades. With it comes the need to characterize and quantify these particles for various applications. One device capable of doing so is the SuperParamagnetic Quantifier (SPaQ). With differential magnetometry (DiffMag) it quantifies superparamagnetic iron oxide nanoparticles (SPIONs), and with a related technique it measures the derivative of the magnetization curve dM/dH . These latter measurements present poor reproducibility in the form of drift. This drift prevents comparison of the SPaQ measurements with similar devices and encumbers characterization.

Repeated measurements of Sienna+ and tattle tape have shown that the sample does not play a role in the occurring drift. Temperature measurements have shown that an increasing system temperature does affect the picked-up signal. However, with a reference measurement, this is corrected for. The observed drift can be accounted for by an imbalance of the gradiometric set-up, but the origin of the imbalance remains unknown.

Augmentations to the SPaQ can be made to ensure it is appropriate for its intended applications. The used excitation sequence can be altered to more closely represent the DiffMag approach used in other applications, such that the SPaQ can be used for DiffMag protocol optimization. Sample temperature control might be desired too, for particle characterization. The observed drift remains to be overcome, but other hardware augmentations are less essential.

Samenvatting

Onderzoek naar superparamagnetische deeltjes is sterk toegenomen de laatste decennia. Hierdoor is ook de noodzaak ontstaan om deze deeltjes te karakteriseren en kwantificeren voor verschillende toepassingen. Eén specifiek apparaat dat hiertoe in staat is, is de SuperParamagnetic Quantifier (SPaQ). Met differentiele magnetometrie (DiffMag) kan deze superparamagnetische ijzeroxide nanodeeltjes (SPIONs) kwantificeren, en met een gerelateerde techniek meet het de afgeleide van de magnetizatiecurve dM/dH . Deze laatste metingen zijn matig reproduceerbaar door drift. De drift voorkomt het vergelijken van de SPaQ metingen met vergelijkbare apparaten en bemoeilijkt karakterisering.

Herhaalde metingen van Sienna+ en beveiligingstape hebben laten zien dat de deeltjes geen rol spelen in het ontstaan van drift. Temperatuurmetingen hebben laten zien dat een toenemende systeemtemperatuur het gemeten signaal wel beïnvloed. Echter, hiervoor wordt gecorrigeerd met een referentie meting. De geobserveerde drift kan verklaard worden door een onbalans van de gradiometer opstelling, maar de oorzaak voor de onbalans blijft onbekend.

Aanpassingen van de SPaQ zijn mogelijk om ervoor te zorgen dat deze toepasbaar is voor de bedoelde toepassingen. De gebruikte excitatie sequentie kan aangepast worden om beter te vergelijken te zijn met de DiffMag aanpak die gebruikt wordt in andere toepassingen, zodat de SPaQ gebruikt kan worden om het DiffMag protocol te verbeteren. Controle over de deeltjestemperatuur is ook wenselijk, voor de kwalificatie van de deeltjes. De geobserveerde drift benodigt nog steeds correctie, maar andere aanpassingen aan de hardware zijn minder essentieel.

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Part 1

Introduction

Chapter 1

Introduction

Research into small magnetic particles, specifically magnetic nanoparticles (MNPs), has increased at an exponential rate over the last decades. There is no indication that this trend will not continue. Figure 1.1 displays the increasing amount of results the FindUT search engine of the University of Twente library gives for MNP related searches [1]. Many magnetic particles are superparamagnetic. A large portion of the research into magnetic particles relates to this property, as figure 1.1 demonstrates.

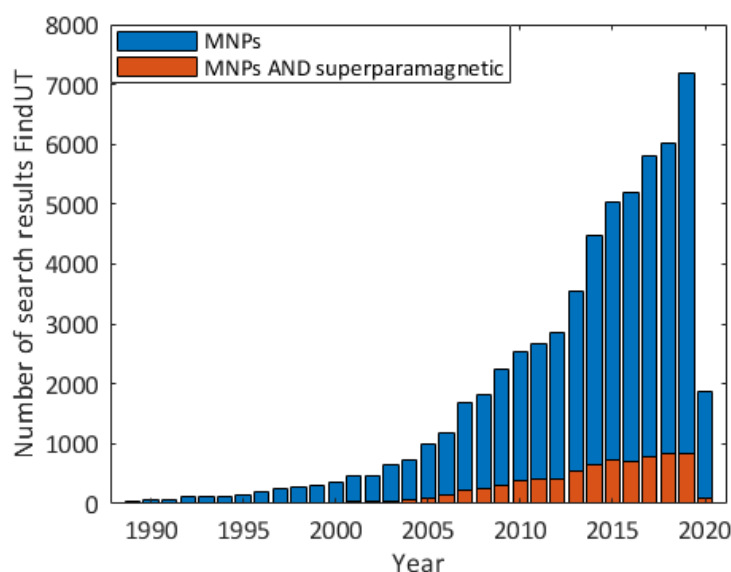


Figure 1.1: The number of search results for magnetic particle related searches of the FindUT search engine of the University of Twente increases over time. A large portion of the search results also relate to the superparamagnetic property. The drop in search results in 2020 is explained by the year not having come to an end [1].

Interest in these magnetic particles relates to their use in various medical applications such as imaging, drug delivery and molecular detection [2]. With the increased interest in magnetic particles comes the necessity to quantify and characterize these. Quantification relates to the ability to count the magnetic particles. Due to their micro- or nanosized nature, counting or even detecting these particles is not trivial, while it is desirable for many applications. Characterization concerns

the anticipation of the particles' behaviour under certain circumstances.

Many devices are capable of detection and characterization of superparamagnetic particles. One of these is the SuperParamagnetic Quantifier (SPaQ). With differential magnetometry (DiffMag) these particles can be detected and quantified. A related technique is used for characterization [3]. Presently, the SPaQ is limited in its application.

The SPaQ measures the derivative of the magnetization curve for superparamagnetic iron oxide nanoparticles (SPIONs). This curve represents the particles response to an externally applied magnetic field. These measured curves are of interest in this report. At the moment, the measurements of these curves are not reproducible. Repeated measurements contain drift; the curves are identical in shape but differ in height. See figure 1.2.

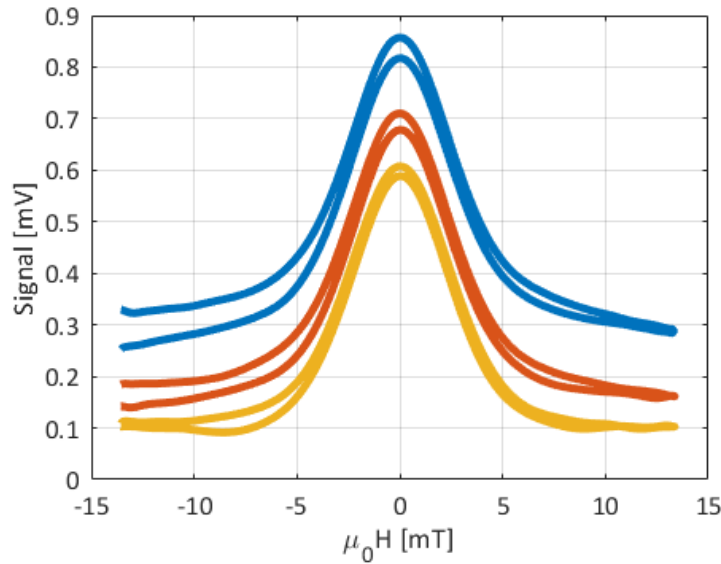


Figure 1.2: The measurement drift of the superparamagnetic quantifier. Measurements of the derivative of the magnetization curve are similar in shape but differ in height. Here, three repeated measurements of 50 μL diluted Sienna are shown.

The drift potentially hinders application of the SPaQ and encumbers comparison of measurements with other systems. As the curve measurements are the derivative of the magnetization curve, integration is required to find the more commonly used magnetization curve. This conversion is hindered by drift. Thus, improved reproducibility of the magnetization curve derivative measurements is desired. Leading to the following research question:

- *What is the cause of the observed drift of the SPaQ measurements?*

Drift hinders the application of the SPaQ, but other augmentations to the SPaQ could be desirable too. Specifically, augmentations ensuring better suitability for specific applications. From specific applications follow specific requirements. If the SPaQ does not meet these requirements, changes are needed. This leads to a second research question:

- *What SPaQ augmentations ensure suitability for its applications?*

Chapter 2

Report structure

This report consists of two main parts. Part 3 and 4 respectively. Each of these treat their own respective research question. These parts are preceded and followed by more general parts. The overall structure can be found in figure 1.3.

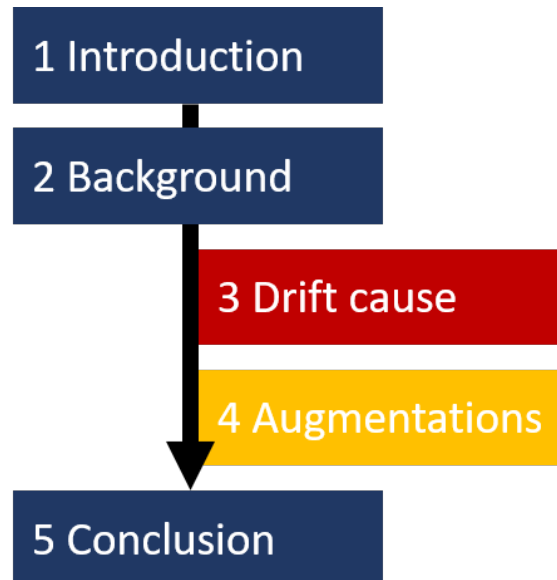


Figure 1.3: The structure of this report is divided into five parts.

Part 1 contains the general introduction. Part 2 contains the general background needed for the following parts. This background mainly considers superparamagnetic particles, their application, and the SuperParamagnetic Quantifier itself.

Part 3 covers the first research question relating to the measurement drift observed in the SPaQ. This part describes performed measurements, and following discussion and conclusions. Part 4 covers the second research question relating to SPaQ augmentations. This part builds on part 3 as it covers possible augmentations to improve upon the SPaQ. Also, it refers to the background in part 2, as the possible applications of the SPaQ play a role in answering the research question. Part 4 also draws its own conclusion.

Part 5 considers the general conclusion and the recommendations.

Part 2

Background

Chapter 1

Magnetic nanoparticles

As figure 1.1 in the introduction showed, research into small magnetic particles has increased at an exponential rate over the last decades. The interest in MNPs stems from their magnetic properties, which allows manipulation of their behaviour through magnetic fields. Furthermore, many MNPs do not agglomerate, which is a desirable property as well [2]. Many Magnetic particles are superparamagnetic. When these are sufficiently small, they are considered superparamagnetic iron oxide nanoparticles (SPIONs). Magnetic beads are many magnetic nanoparticles in a matrix. These form microparticles with superparamagnetic properties as well. This property is of increasing interest too as figure 1.1 also demonstrates.

1.1 Superparamagnetic iron oxide nanoparticles

Although the SPaQ can measure a variety of samples, superparamagnetic iron oxide nanoparticles are the main sample of interest concerning the SPaQ. These particles possess desirable magnetic properties and have many medical applications, as will be covered in section 1.2.

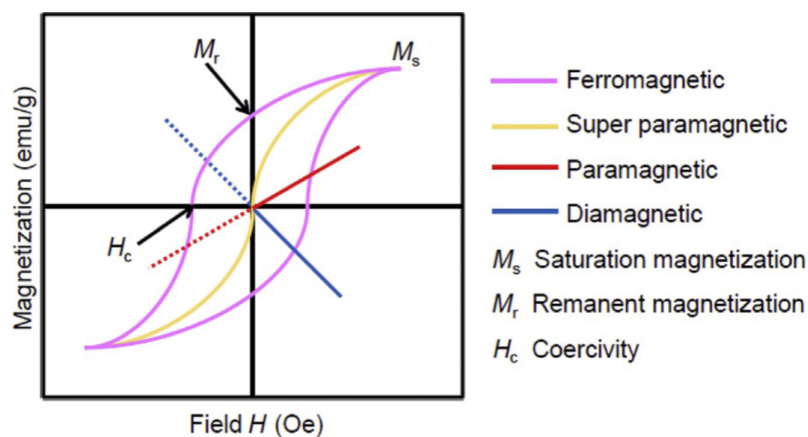


Figure 2.1: Different types of magnetic responses to external magnetic fields. Superparamagnetic magnetization distinguishes itself from other types of magnetization by its non-linearity and lack of memory effect [4].

The superparamagnetic property considers the response of the particles magnetic moment to an externally applied magnetic field; this is the magnetization of the particles. The magnetic moment of dielectric material opposes the external magnetic

field, decreasing its strength. The magnetic moment of paramagnetic material aligns with an external magnetic field, thus increasing its strength [5]. The response of superparamagnetic materials to a magnetic field is nonlinear. Furthermore, while ferromagnetic materials display a memory effect in the form of hysteresis, superparamagnetic particles do not. Different forms of magnetization are shown in figure 2.1.

The SPaQ uses differential magnetometry and related techniques to quantify and characterize superparamagnetic particles. For this, it utilizes the nonlinear characteristic of superparamagnetism.

1.2 Applications of magnetic nanoparticles

Applications of superparamagnetic particles are widespread. This report only considers medical applications. These can be generally divided into imaging, drug delivery, hyperthermia, and molecular detection. See figure 2.2 Especially the latter comprises a large number of sub applications.

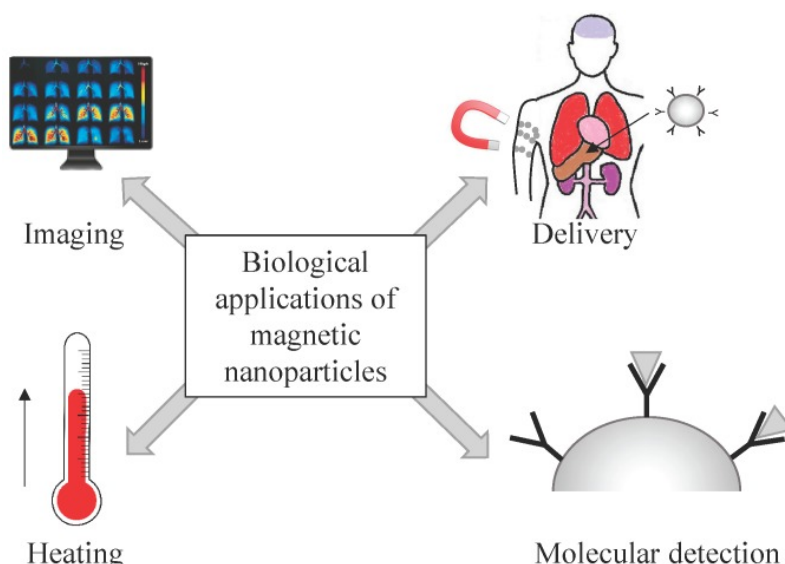


Figure 2.2: The biological applications of magnetic nanoparticles [2].

1.2.1 Imaging

Superparamagnetic particles can be applied as contrast material for magnetic resonance imaging (MRI) [2]. Accumulated Resovist, a medically approved SPION, reduces signal and produces a negative contrast on MRI images [6]. An affinity component attached to the particles allows the contrast agent to be targeted to specific molecules. Thus, enabling molecular imaging. Non-targeted magnetic particles can be used as contrast agent as well. Commonly, gadolinium is used as a contrast agent [7][8].

Another, method of imaging involving SPIONs is magnetic particle imaging (MPI). Here, a tomographic image is generated with static and dynamic magnetic fields. Gradient fields are used to find the distribution of SPIONs in three dimensions [9][10]. Characterization of SPIONs for MPI is usually done through magnetic

particle spectroscopy (MPS).

1.2.2 Hyperthermia

In hyperthermia treatment, cancerous tissue is heated to induce cell apoptosis. Superparamagnetic particles can be used for this purpose [2][6]. The particles are accumulated in the cancerous tissue and heated with an alternating magnetic field. Cell apoptosis is then induced through a number of mechanisms [7][8]. The magnetic particles are used to target the heating to specific areas, to prevent damage to the surrounding tissue.

1.2.3 Drug delivery

The magnetic properties also render magnetic particles suitable for drug delivery [2]. They can be used as substrate to carry drugs to specific locations. Magnetic fields are used to guide the magnetic particles. This is specifically useful whenever targeted drug delivery is desired [8][7]. This is the case whenever non-targeted drugs result in unwanted side effects. Much like in hyperthermia, where heating surrounding tissue results in unwanted side effects.

1.2.4 Lab on a chip

The lab on a chip (LoC) was introduced in 1990 and initiated the increased interest in nanoparticles [2]. Magnetic nanoparticles are to be used in many lab on a chip applications, specifically microfluidic devices. Here, it can be used in bioseparation, cell sorting, enzyme immobilisation, immunoassays, purification, sensing, and transfection. The magnetic particles serve as detection label to samples, allowing those to be manipulated by magnetic fields [8][11][7][6].

1.2.5 Sentinel lymph node biopsy

Magnetic particles could be used to identify the sentinel lymph node (SLN) for cancer detection. The presence of metastasis in these nodes provides essential information for the staging of cancer. Therefore, lymph nodes are excised and examined. To excise as few as possible lymph nodes, the SLN needs to be identified. Now, a radioactive tracer and gamma probe is used for this. Magnetic particles with a magnetic probe are an alternative [6][12].

1.3 Fabrication

Different applications of magnetic particles require different properties. Fabrication of particles with the exact desired properties is therefore crucial. Properties such as size, coating, and surface functionalization are particularly relevant [2][7]. Also, stability and uniformity of the beads is desirable, yet remains challenging [6]. Furthermore, biocompatibility is required for most medical applications.

Chapter 2

Differential magnetometry technologies

The SuperParamagnetic Quantifier can quantify and characterize superparamagnetic iron oxide nanoparticles. For quantification, differential magnetometry is used. For characterization, a closely related technology is used to measure the derivative of the magnetization curve [3]. These technologies are not identical and not exclusive to the SPaQ, and are therefore explored separately in the following subsections.

2.1 Differential magnetometry

Differential magnetometry (DiffMag) is a method to detect and quantify superparamagnetic material. DiffMag is not exclusively used in the SPaQ. A very similar technique was first used in 2002 by Besse et al. to detect a single magnetic microbead [13]. They simply referred to it as "*a detection method exploiting the superparamagnetic behaviour of the bead*". The technique was coined differential magnetometry in relation to its application in the SPaQ and the closely related handheld probe [14]. Whenever it is not referred to as differential magnetometry, the method is usually employed in a Hall magnetometer [15][16][17][18][11][19]. Although the devices DiffMag is used in differ, the method remains nearly identical in all cases.

Differential magnetometry utilizes the nonlinear characteristic of superparamagnetism. Superparamagnetic particles are exposed to an externally applied alternating current magnetic field H_{AC} , superimposed to a direct current magnetic field H_{DC} . As the particles are superparamagnetic, the magnetic moments will align with the field according to the magnetization curve of the particles. An induction coil in the same direction as the external field, or a Hall detector parallel to it, then pick up a signal proportional to the slope of the magnetization curve at H_{DC} according to figure 2.3. The difference between offset H_{DC} and offset $H_{DC} = 0$ is the DiffMag value.

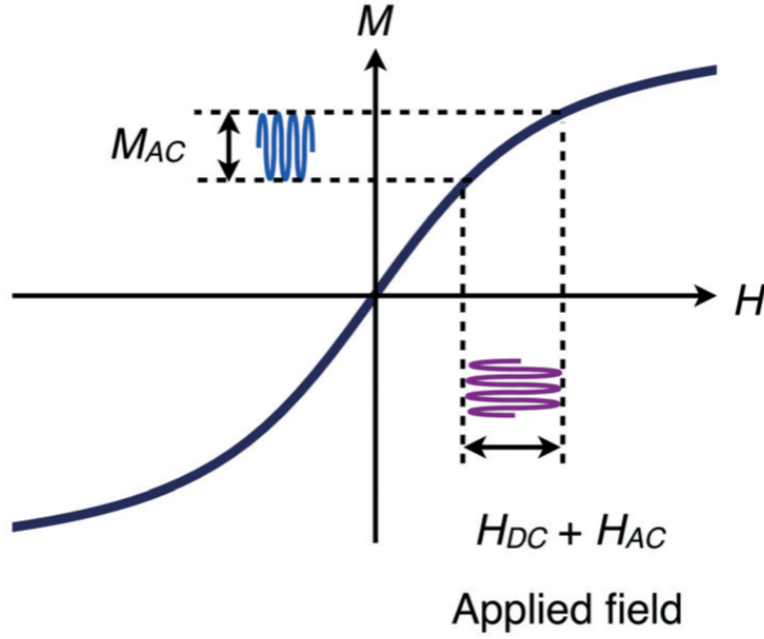


Figure 2.3: Differential magnetometry principle. Superparamagnetic particles are exposed to an AC magnetic field H_{AC} superimposed to a DC magnetic field H_{DC} . With an induction coil or Hall detector a signal proportional to the slope of the magnetization curve at H_{DC} can then be detected. The difference in signal between offset H_{DC} and $H_{DC} = 0$ gives the DiffMag value [19].

2.2 Magnetization curve measurement

The SuperParamagnetic Quantifier cannot measure the magnetization curve directly. Instead, the derivative of the magnetization curve dM/dH is measured. The method to do so is closely related to differential magnetometry.

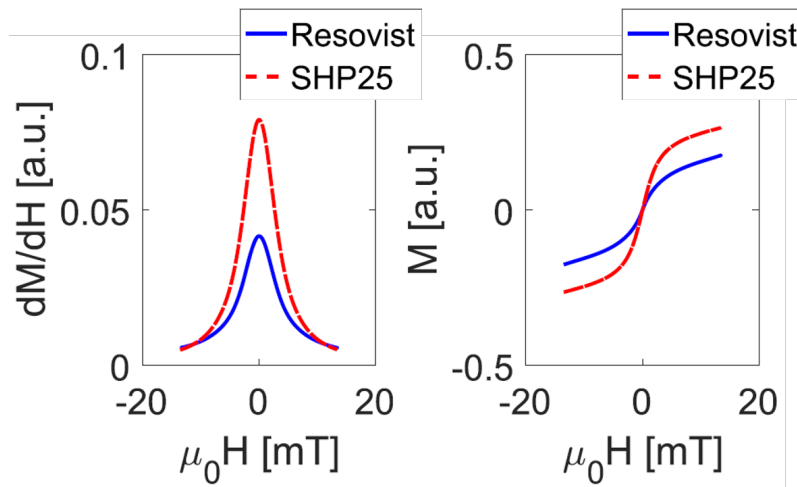


Figure 2.4: SPaQ measurements of superparamagnetic particles Resovist and SHP25 with (left) the detected dM/dH curve, and (right) the found magnetization curve through integration [3].

As for DiffMag, superparamagnetic particles are exposed to an AC magnetic

field H_{AC} superimposed to a DC magnetic field H_{DC} . With an induction coil or Hall detector the slope of the magnetization at H_{DC} is measured. Sweeping H_{DC} then gives the derivative of the magnetization curve [3]. Integration then gives the more commonly used magnetization curve as seen in figure 2.4.

Chapter 3

Magnetometers

With the increasing research into magnetic nano- and microparticles comes an increase in work on magnetic sensors. With the SPaQ as an example of this. Many of these devices concern magnetoresistive or Hall sensors for use with magnetic bead assays [11]. Some of these magnetometers seem very similar to the SPaQ, while others also seemingly incorporate some form of differential magnetometry.

Many of these magnetometers have been designed and researched [20]. Only some will be mentioned here. Specifically, those which are capable of measuring the (derivative of the) magnetization curve or DiffMag related value. This is to gain an understanding of the SPaQs capabilities and applications relative to these other magnetometers.

3.1 Similar magnetometers

The SPaQ has previously been compared to vibrating sample magnetometry (VSM) and magnetic particle spectroscopy (MPS) [3]. Although these devices are similar in many ways to the SPaQ, a clear differentiation can be made.

The VSM vibrates the sample in a static magnetic field H_{DC} inducing a signal proportional to the magnetization curve at H_{DC} in a pick-up coil. A sweep of the H_{DC} then gives the static magnetization curve [21][22].

MPS is closely related to magnetic particle imaging (MPI) and uses a large alternating current excitation field H_{AC} to sweep through the entire magnetization curve each period of the excitation signal. Of course, the entire magnetization curve being only the range in which is measured. This induces a signal proportional to the slope of the curve in the pick-up coils. This is the derivative of the dynamic magnetization curve dM/dH [23][10].

3.2 Differential magnetometers

Although the SPaQs method to measure the dM/dH curve is not labelled DiffMag, it is very closely related. Developed in close relation with the SPaQ is the handheld probe. Other magnetometers exist using slight variations of DiffMag. Most notable are some Hall magnetometers used for magnetic bead detection.

3.2.1 SuperParamagnetic Quantifier

The SuperParamagnetic Quantifier will be discussed in more detail in chapter 4. Here, it is included for completeness. The SPaQ was developed in close relation to the handheld probe mentioned in the following subsection.

The SPaQs sample holder is large enough to fit an entire lymph node, so that the iron content of lymph nodes can be determined with DiffMag. This relates to potential clinical applications of the SPaQ. Other clinical applications of the SPaQ are sparse but will be discussed later.

3.2.2 Handheld probe

The handheld probe uses DiffMag to detect SPIONs in a sentinel lymph node biopsy (SNLB). In this procedure, SPIONs are injected into a known tumour and drained through the lymphatic system. These accumulate in the sentinel lymph node (SLN) to be detected by the handheld probe. The SLN is then biopsied to check for metastasis. In the Netherlands it is now customary to use a radioactive tracer and gamma probe. The DiffMag procedure seems a promising replacement for this technology. In Scandinavian countries, it is more common to employ magnetic detection [24]. For the DiffMag probe, the theoretical advantage over competing magnetic probes is its insensitivity to interference from other instruments [12].

3.2.3 Hall magnetometers

A very similar device to the SPaQ is the Hall magnetometer. Already in 2002 Besse et al. presented a Hall sensor capable of detecting a single magnetic bead with a technology very similar to DiffMag [13]. The Hall sensor presented by Sandhu et al. in 2004 seemingly uses a technology identical to DiffMag [15]. In the following years more devices were developed seemingly employing DiffMag [16][17][25][18].

More recently, a microhall magnetometer was developed capable of characterization like SPaQ as well [19]. The main difference here is the sample size, as the microhall magnetometer is capable of small sample characterization and single cell detection. This allows for its use in lab on a chip devices. Which is the aimed clinical application of most Hall magnetometers.

The technology of these magnetometers has not been compared to DiffMag as of yet. However, as the used methods seem very similar, these devices can be considered DiffMag magnetometers. All use an offset DC excitation field H_{DC} and a superimposed probing AC excitation H_{AC} to measure the slope of the magnetization curve.

These Hall magnetometers obviously differ from the SPaQ in their use of Hall detectors, rather than pick-up coils. The SPaQ uses a gradiometric set-up to remove the signal from the excitation field. Hall magnetometers employ various methods to remove background signal. Many place their sensor parallel to the excitation field. This removes the excitation field signal, but still leaves a signal proportional to the slope of the magnetization curve. Figure 2.5 shows the inversely proportional relation between orthogonal and parallel detection. The recently developed microhall magnetometer solely uses lock-in detection to remove the excitation field.

Hall sensors are much smaller than induction coils can be. As a homogeneous detection coil is desired, this means that the sample size for Hall magnetometers is

much smaller than that of the SPaQ, which can fit an entire lymph node.

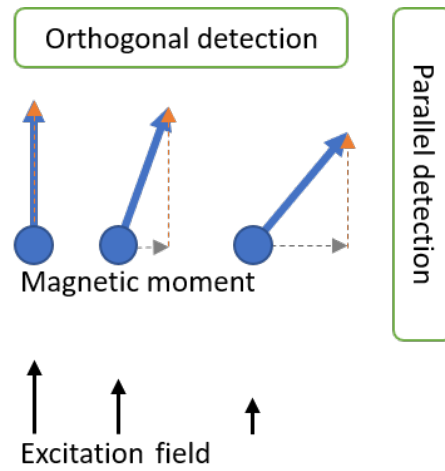


Figure 2.5: The inversely proportional relation between orthogonal and parallel detection. Orthogonal detection requires a gradiometric set-up to remove the excitation field while parallel detection does not. The detected signal by the particles remains proportional to one another.

Chapter 4

SuperParamagnetic Quantifier

This chapter focuses more on the SPaQ itself, as techniques such as DiffMag are not unique to it. Devices such as the handheld probe and Hall magnetometers are similar to the SPaQ [12][25]. Here it is described how the SPaQ quantifies and characterizes SPIONs.

4.1 Hardware

The SPaQ hardware is mainly comprised of its coils and electronics. A schematic overview of the SPaQ can be found in figure 2.6.

4.1.1 Coils

The main components of the SPaQ are the excitation and detection coils. The excitation coil is a solenoid (blue in figure 2.6). An outer field coil (purple in figure 2.6) is wound around the excitation coil for improved homogeneity of the excitation field and shielding. The detection coils are two oppositely wound solenoids to form a first order gradiometric set-up. This effectively removes the excitation field from the detection signal as the sample is placed in the upper coil [3]. The entire coil system is placed in an oil bath to allow cooling of the system.

4.1.2 Electronics

Through a data acquisition (DAQ) card the SPaQ excitation and detection is connected to a personal computer. Hereon, it is controlled with MATLAB. The used sequences for this are discussed in the next section. The DAQ card sends the excitation sequence through a power amplifier to the excitation coils. The detected signal is amplified by a low-noise differential preamplifier and sent back through the DAQ card. The signal is further filtered in MATLAB using a digital lock-in amplifier.

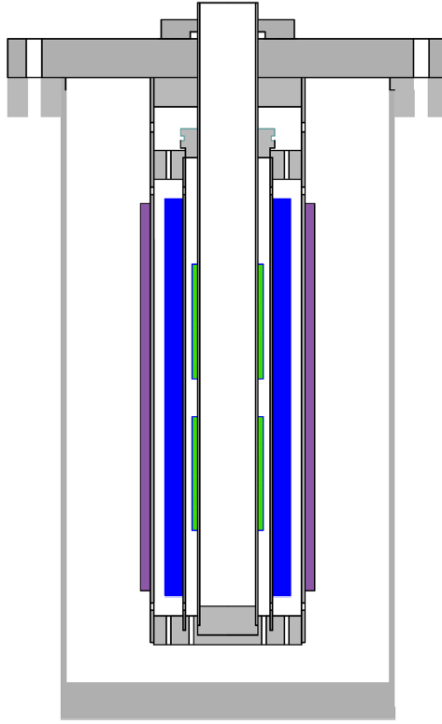


Figure 2.6: Schematic overview of the Superparamagnetic Quantifier with (blue) the excitation coil, (purple) outer field coil, and (green) gradiometric pick-up coils [3].

4.2 Sequences

The SPaQ is controlled in MATLAB. Most commonly, two programs are used; Parcival and LangevinSweep are used for DiffMag and dM/dH curve measurements respectively.

4.2.1 Parcival

Parcival is the sequence used for DiffMag measurements. Therefore, it is also used in the handheld probe. The output of this sequence is a DiffMag value in counts. These counts are proportional to the detected signal. The use of counts ensures closer similarity between the handheld probe and the gamma probe it aims to replace.

In this sequence, an AC excitation field is superimposed to a DC excitation field as DiffMag requires. The AC excitation field is constant. Four DC excitation offsets are measured. First, $H_{DC} = 0$ is measured followed by $H_{DC} = \text{positive offset}$. Then, $H_{DC} = 0$ is measured again followed by $H_{DC} = \text{negative offset}$. See figure 2.7. As mentioned before, the DiffMag value follows from the difference between the detected signal at H_{DC} and $H_{DC} = 0$. In Parcival, the DiffMag value for a negative and positive offset is averaged for increased accuracy.

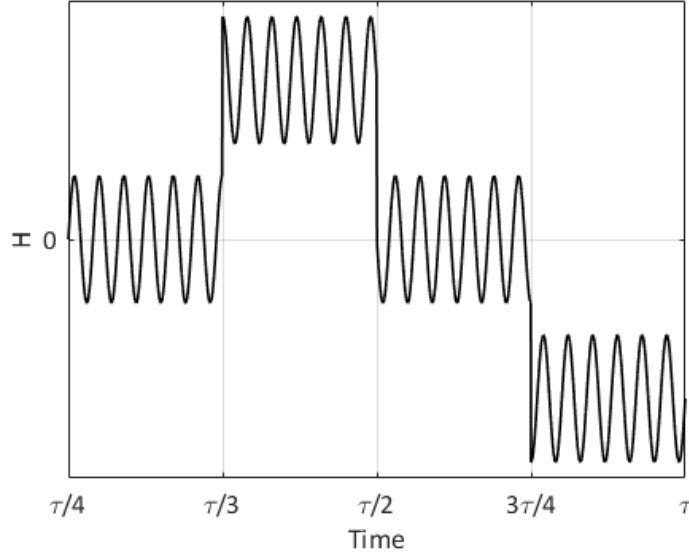


Figure 2.7: Parcival sequence [12].

4.2.2 LangevinSweep

LangevinSweep is the sequence used to measure dM/dH curves. This is the sequence under review in this report and the sequence used for most measurements. Effectively, it is a sweep of the excitation field H_{DC} . This results in a curve which is the derivative of the magnetization curve. H_{AC} is kept constant. The curve is swept hence and forth to measure the curve in two directions. This sequence is displayed in figure 2.8. The sequence starts at $U = 0$, which is representative of $H_{DC} = 0$. This is to remove unwanted effects from the power supply.

AC amplitude	0.4 [V]
DC amplitude	4 [V]
AC frequency	2500 [Hz]
Sample frequency	160000 [Hz]
Sequence length	1 [s]

Table 2.1: Default measurement settings for LangevinSweep.

The sweep is performed two times; once without sample in the sample holder and once with the sample in the sample holder. These are reference measurement Z0 and sample measurement Zs respectively. The reference measurement is subtracted from the sample measurement to remove unwanted background noise. The default settings for LangevinSweep can be found in table 2.1.

The SPaQ uses phase sensitive detection with a digital lock-in amplifier. This gives the output both in the phase domain and the amplitude domain. Usually, the amplitude domain is the output of interest, as it represents dM/dH . These outputs are given for the reference measurement and the sample measurement. These are subtracted to result in the final phase domain plot and amplitude domain plot.

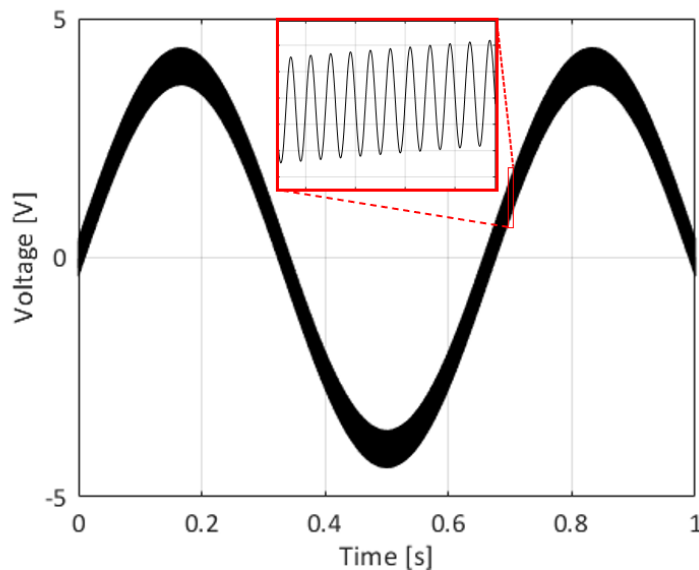


Figure 2.8: Excitation sequence of the SPaQ to measure dM/dH curves. An AC excitation field H_{AC} is superimposed to a DC offset field H_{DC} . A sweep of H_{DC} gives the derivative of the magnetization curve. This sweep is performed with sample and without sample to remove unwanted background noise.

4.3 Applications

The SPaQ is capable of detection and characterization of superparamagnetic particles. Applications for the SPaQ follow from this. Applications can be divided into clinical applications, applications related to the DiffMag optimization, and applications related to the applications of superparamagnetic particles.

4.3.1 Clinical applications

One clinical application is the detection of sentinel lymph nodes for colon cancer patients. For this purpose, the iron content of lymph nodes needs to be detected in vitro. Now, a piece of the colon of colon cancer patients is excised and all found lymph nodes are checked for metastases. This procedure is used for staging of colon cancer. The SPaQ could be used to decrease the required workload for this procedure. In that scenario, SPIONs are injected in the known tumour and drained by the lymphatic system. Subsequently, a piece of the colon of cancer patients is excised. Now, the sentinel lymph node should contain most of the iron. Measuring the iron content then greatly reduces the number of lymph nodes to be checked for metastasis. Unfortunately, preliminary research at the Magnetic Detection & Imaging group at the University of Twente into this application are not promising.

4.3.2 DiffMag optimization

Another application is the characterization of magnetic nanoparticles for use in other DiffMag applications. As described before, the handheld probe can detect iron content of lymph node in vivo, which allows for its use in sentinel lymph node

biopsies. The behaviour of particles used in these procedures can be characterized in the SPaQ since the dM/dH curves measured in the SPaQ are indicative of the signal behaviour of the particles in DiffMag applications [12]. Also, the DiffMag protocol can be optimized with regard to field frequency, amplitude and sequence more easily in the SPaQ. Here, it is beneficial that the sample holder of the SPaQ can hold entire lymph nodes, so that SPIONs can be characterized in biological environments.

4.3.3 Particle applications

Applications of MNPs include imaging, drug delivery, heating, and molecular detection. For none of these the SPaQ can be applied directly. Only the latter application, specifically lab on a chip devices could require the quantification of SPIONs. Currently, it is unclear whether the SPaQ could be applied here. In the process of fabrication of superparamagnetic particles the SPaQ might prove useful too, as the characteristics of the produced particles need testing.

Part 3

Drift cause

Chapter 1

Introduction

In this part, the first research question is analysed: *What is the cause of the observed drift of the SuperParamagnetic Quantifier measurements?* For this purpose, the reproducibility error was quantified, and the cause explored. For this, a series of measurements has been conducted, which will be described and discussed.

Measurements have been conducted to quantify the reproducibility error, to find its relation to temperature, and to find the relation to the imbalance of the coil. These will be discussed separately, although there is some overlap in the measurements. All measurements have been performed with the default measurement settings. In that case the SPaQ operates at $2500[Hz]$, with a sample frequency of $160[kHz]$, as shown in table 2.1. The DC excitation field amplitude is $4[V]$ and the AC excitation field amplitude is $0.4[V]$. The total sequence is $1[s]$ in which the curve is measured in two directions.

1.1 Hypothesis

The cause of the reproducibility error is expected to be the heating of the SPaQ. The excitation coil generates large amounts of heat due to the current flowing through it. This could cause expansion of the coils and thus unbalance the gradiometric set-up of the detection coils. Another cause could lie with the particles. The particles in the SPaQ are heated as well as the system. This could cause the particles to behave differently.

Chapter 2

Reproducibility error

2.1 Measurements

Repeated empty measurements: Fifty measurements were performed without sample. As each measurement consists of an empty measurement and a sample measurement, effectively a hundred empty measurements were performed.

Repeated Sienna+ measurements: 50 $[\mu L]$, 100 $[\mu L]$, and 200 $[\mu L]$ 100x diluted Sienna+ samples are each measured fifty times in close succession. Sienna+ is a typical superparamagnetic particle [26].

Repeated tattle tape measurement: $\sim 6 [mm^2]$ and $\sim 3 [mm^2]$ tattle tape samples are each measured fifty times in close succession. Tattle tape has a linear paramagnetic response which is known to be constant under varying circumstances [27].

2.2 Results and discussion

Repeated measurements detailed: Six measurements series have been conducted, each consisting of fifty measurements. These measurements are all similar in many ways and will therefore not be displayed in full. Usually, only the amplitude domain is of interest. However, the SPaQ also outputs the detected phase domain. The measured curves Z are the difference between the sample measurement Z_s and reference measurement Z_0 , of which the curves are also measured. Figure 3.1 shows a selection of three measurements of the 100 $[\mu L]$ diluted Sienna+ measurements with all output curves.

A couple of observations can be made from these measurements. The first being that Z_0 is not constant as it is expected to be. This indicates that changes in the excitation field are picked up by the detection coil. Secondly, the largest drift occurs in the phase domain. Finally, both the Z_0 and Z_s measurements display large amounts of drift. This is much less so the case for the Z curve, indicating that the reference measurement removes a large amount of drift.

Another observation was made for the full curves produced by the 50 $[\mu L]$ diluted Sienna measurements. This has previously been displayed in figure 1.2 in the introduction. This shows that drift is not only found between separate measurements,

but also within single measurements. This occurrence appeared seemingly random for smaller sample volumes.

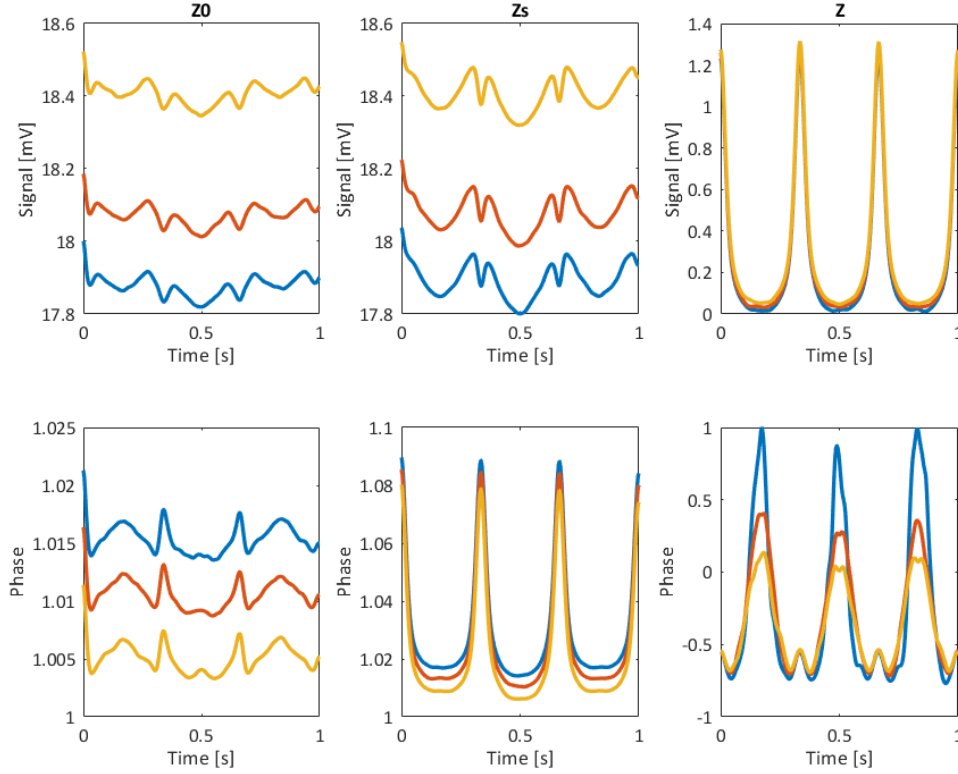


Figure 3.1: Complete output of the SPaQ for three repeated measurements of 100 μL diluted Sienna. The upper three figures display amplitude, while the lower three display the phase. The Z0 and Zs measurements display a large amount of drift which is largely, but not completely, removed in final curve Z.

Figure 3.1 only displays very limited drift. As figure 3.2 will demonstrate, the drift is unaffected by sample volume. Thus, larger samples are affected similarly to smaller samples in absolute values. However, large samples are affected relatively less.

Repeated measurements overview: Although figure 3.1 shows the most complete output of the SPaQ, this can be considered overwhelming for a series of fifty measurements. Therefore, the results of the repeated measurements are summarized using the amplitude curve average. As the curve shape remains largely identical, the average should give a clear indication of the drift. The following figure displays the repeated measurements from the empty measurements, the Sienna+ measurements, and the tattle tape measurements. The measured data is represented in boxplots, as these best display the spread of the data. To better compare the spread among sample data more directly, the average of each measurement series is subtracted from each measurement. Thus this removes the signal amplitude from the comparison. Figure 3.2 shows the compensated boxplots for the Z0, Zs and Z measurements.

Figure 3.2 also shows the unaltered boxplot for the Z data. In these boxplots the red line represents the median, the blue box the 25th and 75th percentile and the black bars the lower and upper adjacents. The red crosses consider outliers.

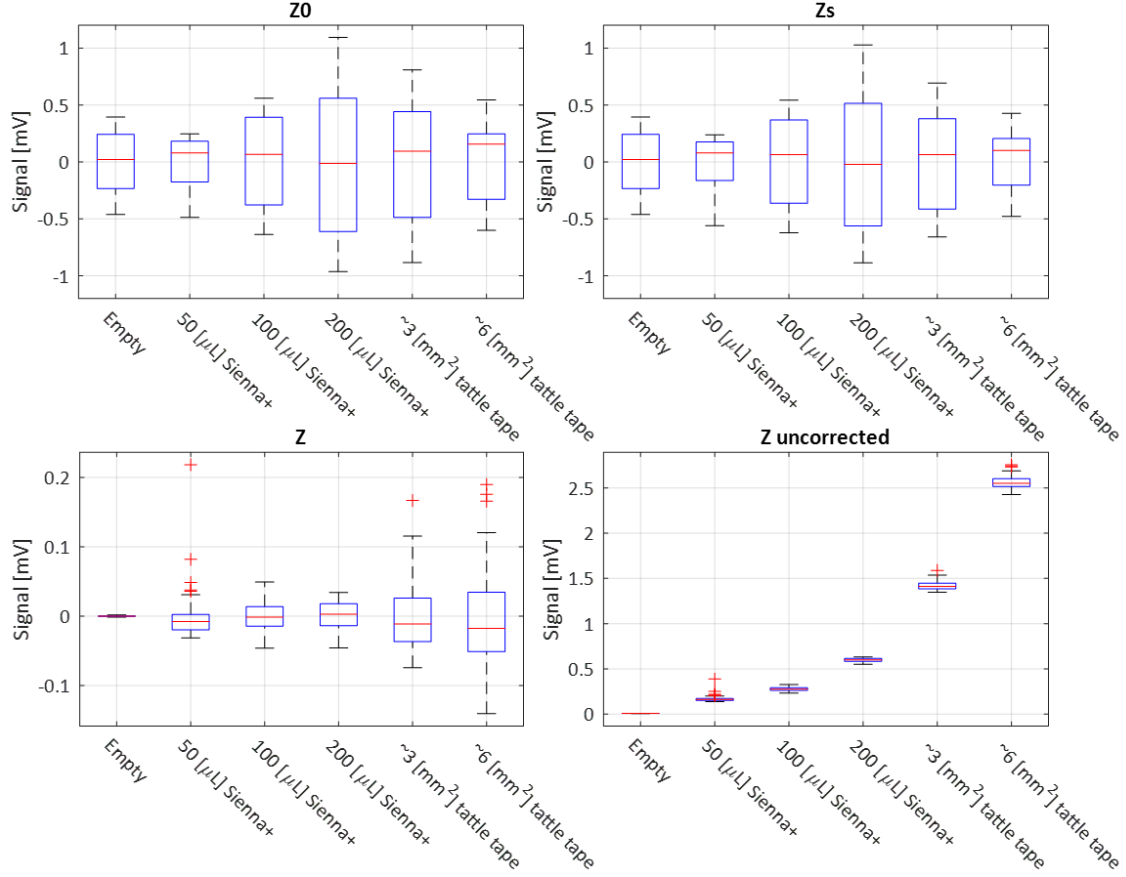


Figure 3.2: Boxplots for the average measurement signals for repeated measurements of different samples. The reference measurement Z0 and sample measurements Zs show near identical drift, while the drift for the difference Z is much smaller. The unaltered boxplot for the difference Z shows a linear relation between sample volume and signal. Note that the reference measurement Z0 shows empty measurements related to the sample measurements.

The uncorrected Z plot in figure 3.2 clearly shows a somewhat linear relation of sample volume with average signal strength, which is as expected. The corrected Z plot in figure 3.2 shows a nearly negligible spread for the empty measurements. This could be related to a somewhat different measurement procedure, where the sample holder was not placed in the SPaQ for each measurement. For the Sienna+ samples, the spread seems unrelated to sample volume, as well as for the tattle tape. This indicates that the error is absolute, rather than relative. The tattle tape does show a much larger spread. All measurements seemingly have a normal distribution, which indicates a random error.

The largest drift is measured for the 6 [mm²] tattle tape. Here, the drift is 0.1897 [mV] from the average. For the Sienna+ measurements the largest drift is 0.049167 [mV]. The maximum drift for the empty measurements is 0.0015834 [mV].

The boxplots of the reference measurements Z_0 show a varying, but similar distribution in all cases. The spread of Z_0 already indicates a large distribution in some cases. Curiously, the spread of Z is occasionally smaller than the spread of Z_0 . Although the boxplots for Z do not indicate a relation to sample volume, this does not take into account the larger Z_0 spread per sample volume. As this is an empty measurement, this cannot be related to the sample. Thus, an increased sample volume seemingly decreases the spread of Z if the spread of the reference measurement is taken into account. For the tattle tape, this does not seem to be the case, nor for the empty measurements.

Chapter 3

Temperature dependence

3.1 Measurements

While conducting the repeated measurements of tattle tape, Sienna+, and without sample in section 2.1, the temperature of the system was measured as well. The temperature is measured three times during the measurement; before the empty measurement, after the empty measurement/before the sample measurement, and after the sample measurement. These measurements aim to find the relation of the detected signal to the system temperature.

3.2 Results and discussion

The measurement signal can be correlated to the temperature increase of the system. The repeated measurement without sample was used for this purpose. The average signal can be plotted against the temperature at the start of each single measurement. This shows a clear linear relation of $0.32582 [mV/K]$. See figure 3.3. The measured temperature of the first measurement is $23.35 [^{\circ}C]$, and of the final measurement $26.14 [^{\circ}C]$. Thus, a single measurement is related to a temperature increase of $0.03 [^{\circ}C]$, or $0.06 [^{\circ}C]$ per complete measurement.

Each measurement consists of a sample measurement and a reference measurement. Measurements have shown that both the sample measurement and the empty measurement are linearly related to the temperature. These measurements are subtracted from one another as shown in figure 3.3 (right). Clearly, this removes the linear relation to the temperature and the distribution seems random. This indicates that the reference measurement compensates for the increase in signal.

A similar relation can be found for the reference and sample measurements of Sienna+ and tattle tape as shown in figure 3.4. This shows that the signal increase with temperature is very similar for all measurements with only minor differences. Also, the slope of the curves is the same for both the reference Z0 measurements as for the sample Zs measurements. This further indicates no effect from the samples on the signal increase. Also, the subtraction of the reference measurement from the sample measurement removes the temperature dependence.

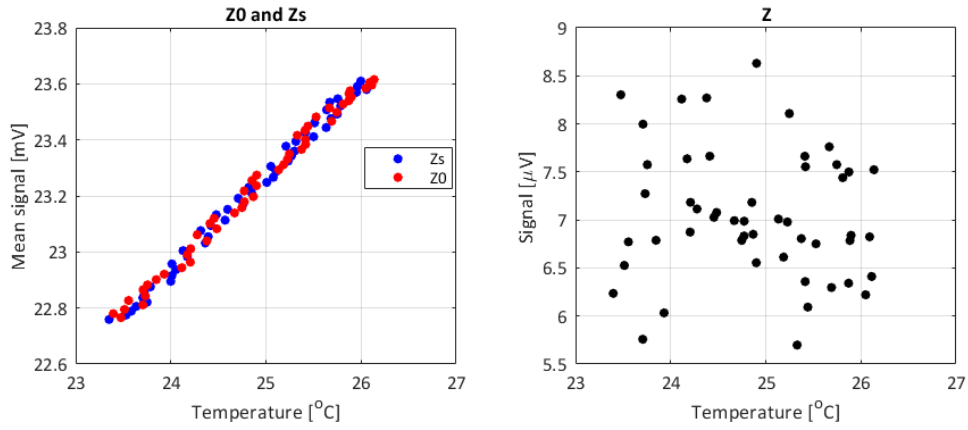


Figure 3.3: The signal amplitude of the SPaQ increases with temperature (left). When the reference measurement Z_0 is subtracted from the sample measurement Z_s , there is no relation to temperature (right). Note that both Z_0 and Z_s are measured without sample holder here.

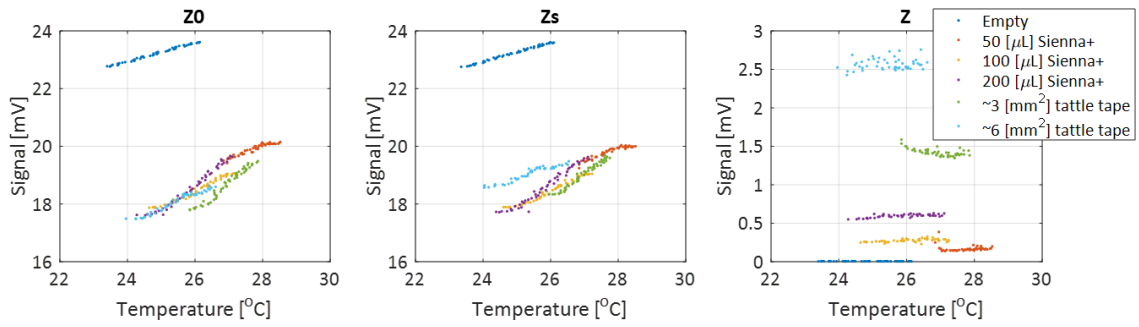


Figure 3.4: The signal amplitude of the SPaQ increases with temperature for sample measurements. The difference signal Z is not related to temperature.

Chapter 4

Coil imbalance

4.1 Measurements

The measurement signal without sample is measured with the excitation coil in three positions. First it is balanced, so that it gives the lowest possible signal. Then it is moved up and down to the most extreme positions. These being only 0.67 [mm] upward and 0.56 [mm] down. In these unbalanced positions the signal received by the gradiometer should increase. With these measurements it is possible to roughly estimate the needed unbalance to cause the measured drift.

4.2 Results and discussion

Imbalance of the gradiometer set-up should increase the picked-up signal. The voltage through the coil heats it, thus expanding it. The expansion of the coil could subsequently unbalance the system. As it is challenging to measure the minimal expansion of the excitation coil directly, the coil was unbalanced purposefully to find the change in signal. 0.0183 [V]. Upward displacement of 0.67 [mm] gives a signal of 0.4095 [V] and downward displacement of 0.56 [mm] gives a signal of 0.3481 [V]. See figure 3.5.

Using the assumption of a symmetric excitation field, both displacements can be placed upon one line, and be used for interpolation. A linear fit is shown in figure 3.5. Then another assumption can be made, that expansion of the coil is similar to displacement of the coil. Although this is obviously erroneous, it will be used for a rough estimation. The thermal expansion coefficient of Tufnol is $1.8 \cdot 10^{-5} [1/K]$, thus resulting in a change of about 0.0027 [mm/K] assuming an excitation coil length of 150 [mm]. A change in temperature of 0.03[K] per single measurement gives a change in coil length of 81 [nm]. The signal increases with 0.58631 [V/mm], thus resulting in an increase of 0.05 [mV] per measurement. This is larger than the observed signal increase per measurement, but is close considering the large amount of assumptions made. A similar calculation can be made where interpolation is performed with a quadratic approximation. This has similar results. See figure 3.5.

Figure 3.5 can also be used to calculate the required displacement of the excitation coil for the measured drift. The largest drift measured is represented by the largest difference seen in figure 3.2. This being $2.7581 - 2.4281 = 0.33[mV]$. Using the linear fit, this would require a displacement of 0.6 [μm]. With the quadratic

fit, the found displacement is 60 [nm]. This indicates that the expansion of the excitation coil could lead to drift.

As only a displacement of 60 [nm] is required, drift could be caused by the placement of the sample holder in the system. this theory is further supported by the absence of drift for the empty measurement series, where the sample holder was not removed for each measurement.

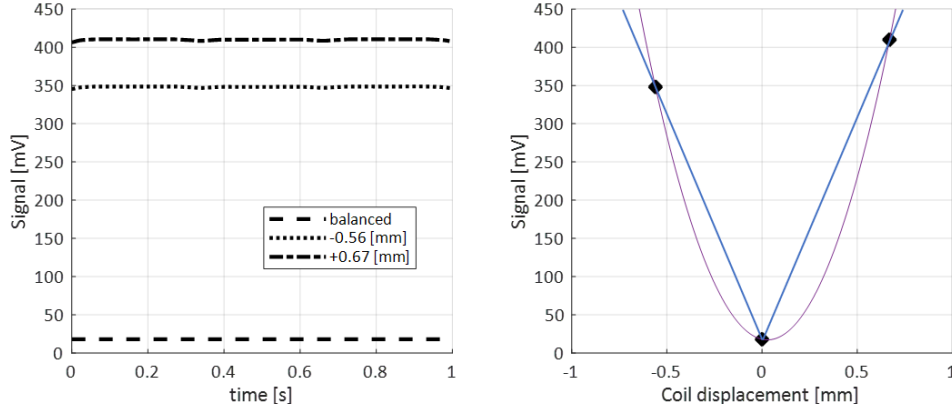


Figure 3.5: Measured signals for different offsets of the excitation coils (left) and average detected signal versus the excitation coil offset (right). An offset results in an increased signal. The data is fitted with a linear fit (blue) and a quadratic fit (purple). The linear and quadratic fit show that displacement with 0.6 [μm] or 60 [nm] respectively could result in the found drift.

Chapter 5

Conclusion

The goal of the performed experiments was to answer the following question: *What is the cause of the observed drift of the SuperParamagnetic Quantifier measurements?*

Changes in the excitation field are detected by the pick-up coils. As these changes should only affect the shape of the curves, these should not be related to the observed drift. See figure 1.2.

The empty reference measurements Z0 show a similar drift as to the sample measurements Zs, indicating that the drift is not sample related. This is further supported by the tattle tape measurements. These show similar drift, while these samples are known to be constant under various circumstances. This also indicates that it is an absolute error, caused by the SPaQ itself. See figure 3.2. As the error is absolute, larger samples will relatively be less impacted by drift.

The signal pick-up by the SPaQ is linearly related to temperature. The reference measurement and the sample measurement signals increase with the temperature. The difference between these signals Z is not related to the temperature and seems random.

Displacement of the coil results in an increased signal as well. A linear and quadratic fit show that displacement with $0.6\ [\mu m]$ or $60\ [nm]$ could result in the found drift. Theoretically, the Tufnol around which the excitation coil is wound expands $81\ [nm]$ per measurement. This indicates a relation between this expansion and the drift.

All in all, the drift causing the reproducibility error of the SPaQ measurements is not caused by the measured particles. Measurements indicate that the temperature increase per measurement expands the Tufnol around which the excitation coil is wound. This could lead to some drift, although other measurements show that this drift is mostly compensated for by the reference measurement. Possibly, placement of the sample holder in the system could cause drift, although more measurements are required to confirm this.

Part 4

Possible augmentations

Chapter 1

Introduction

In this part, the second research question is discussed: *What SuperParamagnetic Quantifier augmentations ensure suitability for its applications?* This research question thus concerns the potential applications of the SPaQ, as discussed in section 4.3 of the background.

Application of the SPaQ mainly concerns optimization of the DiffMag protocol and particle characterization. Particles can be characterized for many applications as discussed in the background. These all consider clinical applications.

The next chapter discusses potential augmentations to improve the measurement drift as discussed in the previous part. As the conclusion of the previous part is not definitive, this part remains somewhat speculative.

The following chapters each discuss one of the possible applications of the SPaQ. To some extent the SPaQ is suitable for these applications. Much of the SPaQs hardware has shown to be working as expected. The overall design of the system seems appropriate. Still, the applications could benefit from certain augmentations, as will be discussed in their respective chapters.

Augmentations to both hardware and sequences are taken into account. This part aims to answer the second research question. Therefore, potential augmentations will be discussed without recommendation. The recommendations in part 5 discuss whether the discussed augmentations should be implemented.

Chapter 2

Drift

Drift encumbers comparison of SPaQ measurements with measurements of other systems. Also, conversion of the measured curve to the often used magnetization curve is hindered. The cause of the drift remains unknown, but is likely caused by unbalance of the gradiometer coils. See part 3. This unbalance could be caused by slight movement of the excitation coil. This chapter discusses potential augmentations improving the reproducibility of the SPaQ.

2.1 Sample holder

Placement of the sample holder into the system could cause the gradiometer coils to become unbalanced. Placement of the sample holder results in a slight tap on top of the system. As displacement of only some nanometers could result in an unbalance of the coils, this tap could cause drift. Ensuring that the sample holder is disconnected from the coil system would prevent displacement due to placement of the sample holder. An added mechanism to place the sample into the system mechanically could also be beneficial, especially when one sample needs repeated measurements as will be discussed later.

2.2 Gradiometer coils

As the drift is likely the result of unbalanced gradiometer coils, it is essential that the gradiometer set-up is easily rebalanced. Furthermore, a second order gradiometer set-up could be considered, as these have shown to be even less sensitive to noise [28]. Therefore, the second order set-up has been employed in similar systems [29][30]. The present first order set-up consists of two oppositely wound coils. A second order set-up consists of three coils, where two coils are oppositely wound and half the size of the third coil. Effectively, a second order coil is a first order coil with the second coil split in two as in figure 4.1 [31].

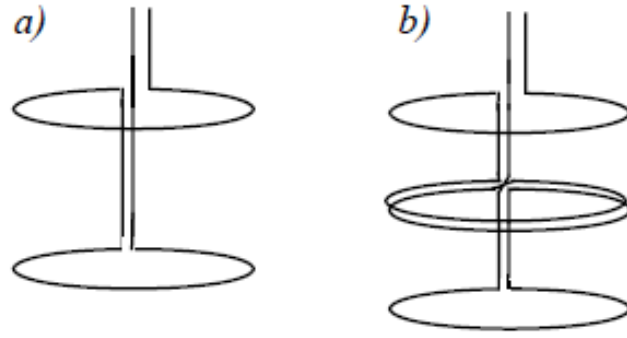


Figure 4.1: The gradiometer set-up of a) first order and b) second order. A first order set-up consists of two oppositely wound coils. In the second order set-up, the second coil is split in two [31].

2.3 Averaging

The boxplots in the results of part 3 indicate a somewhat normal distribution of the measured curves. This means that averaging of the curves should lead to the correct curve. See figure 4.2. That way, no hardware needs to be altered to remove the reproducibility error. Of course, as the sample needs to be removed and replaced in the sample holder for each measurement, this would result in more manual labour.

Other approaches to this method could be considered too. An addition to the current SPaQ would be a device repeatedly placing the sample in the system as is the case for the MPS systems of pure devices [32].

Another approach would be to leave the sample in the system for repeated measurements. However, if the reproducibility error is caused by the sample placed in the system, this would result in a similar error.

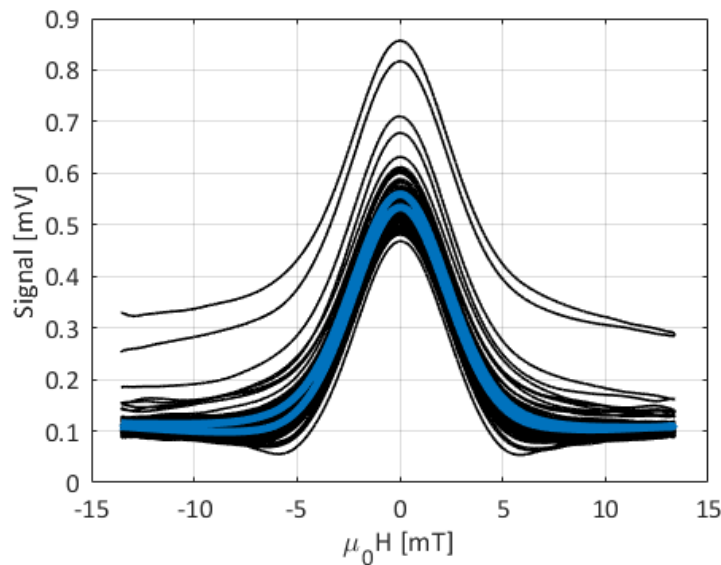


Figure 4.2: The averaging of measurements. Fifty 50 $[\mu L]$ Sienna+ measurements (black) were averaged (blue).

Chapter 3

Particle characterization

The SPaQ can be used to characterize particles for use in other clinical applications such as the sentinel lymph node biopsy. For that purpose, the sample holder is capable of holding an entire lymph node. That way, the particles behaviour can be estimated in the appropriate environment. The appropriate environment can be a lymph node, other tissue, or a phantom. No large augmentations are therefore required for the SPaQ to be applied here.

3.1 Temperature control

The sample environment can largely be controlled, with the exception of the temperature. The previous part has shown that heating of the system does not affect the signal. However, heating of the sample remains undesirable, especially as the magnetic behaviour of many particles is temperature dependent. Also, biological samples might be adversely affected by high temperatures. Insulation between the excitation and detection coil could prevent the detection coil and sample coil from being heated. See figure 4.3.

Currently, an oil bath is used to disperse the generated heat. However, the heating has not directly shown to affect the signal. The effect of removing the oil should be investigated as a system without oil could be more convenient.

Although uncontrolled heating of the sample is undesirable, measurements at controlled temperatures could prove insightful. Specifically, measurements at body temperature would more closely mimic conditions encountered in the handheld probe applications. Temperature control of the sample could therefore be considered. A Peltier element could be used to increase or decrease the sample temperature in a controlled loop [30]. However, placement of the Peltier element should not affect the homogeneity of the magnetic fields. Using the detection coils as heater would not influence the field generation, but would bring along other electrical challenges.

3.2 Excitation coils

The characterization of particles occurs in a research setting. Therefore, patients will not be exposed to stray magnetic fields. Currently, the SPaQs excitation field is generated by a solenoid coil and an outer field coil. This outer field coil serves as shielding. It also improves the field homogeneity. This is done according to the

ICNIRP guidelines [33]. If the SPaQ would only be applied in a research setting, shielding might not be required.

An increase of the solenoid coil would also increase the field homogeneity in the sample region. Only employing a solenoid coil would increase the simplicity of the design as well. More heat would also be generated with an increased coil size. However, previously it was concluded that heating does not affect the measurements.

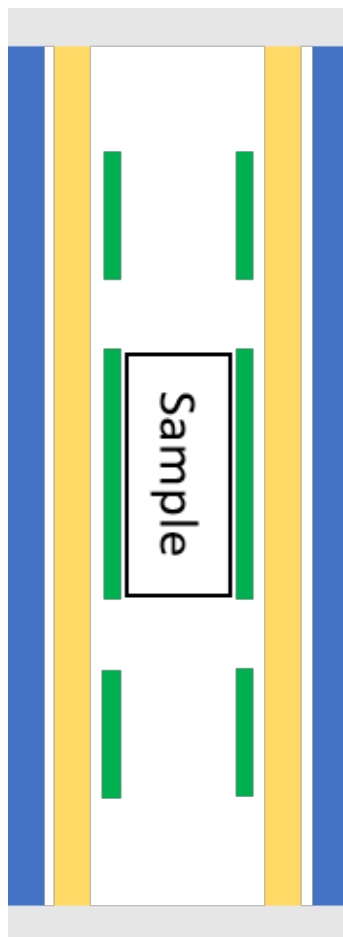


Figure 4.3: Schematic overview of proposed SPaQ augmentations with (blue) the excitation coil, (yellow) isolation, and (green) second order gradiometric pick-up coils.

Chapter 4

DiffMag protocol optimization

The measured dM/dH curve of the SPaQ is closely related to DiffMag measurements. As such, the SPaQ can be used to optimize the DiffMag protocol. Effect of parameters such as AC field frequency can more easily be found with the SPaQ. For this, the dM/dH curve should represent DiffMag values as close as possible. As H_{DC} is swept rapidly, changes in the DC excitation field are detected as well. A more stepwise approach would cause the measured dM/dH curves to be better representative of DiffMag values.

4.1 LangevinStep

Rather than sweeping through the curve in a sinusoidal fashion, each offset for H_{DC} could be measured at a time, resulting in a stepwise sequence. See figure 4.4. Depending on the number of steps taken, this could lead to a longer sequence. More steps would result in more data points, but a longer measurement time.

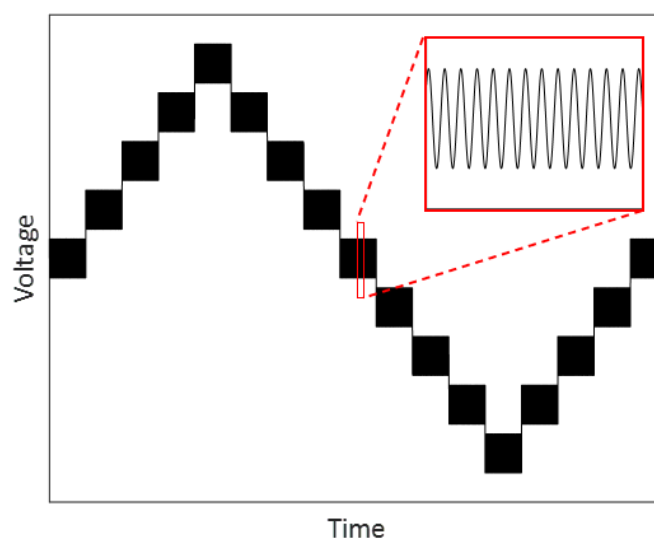


Figure 4.4: Proposed sequence for the dM/dH measurement. A stepwise approach ensures the measured curve is related to DiffMag values more closely. However, the sequence could become longer and result in fewer datapoints.

A stepwise approach would also remove the effect from the excitation sequence as observed in part 3. Effectively, an empty measurement should give no signal. A stepwise approach could provide this as H_{DC} does not change (rapidly) over time.

4.2 Reference measurement

A stepwise approach could ensure that the changing DC excitation signal does not induce a signal in the pick-up coils. Because this is currently the case, the reference measurement needs to contain a complete sweep of H_{DC} as well. With a stepwise approach, another approach to the reference measurement could be taken as well.

The shape of the measured curve is usually identical for repeated measurements. The reference measurement is required to find the correct height of the curve. This height could be found by measuring at a single offset H_{DC} . This is assuming that changes in H_{DC} do not induce a signal in the pick-up coils. See figure 4.5.

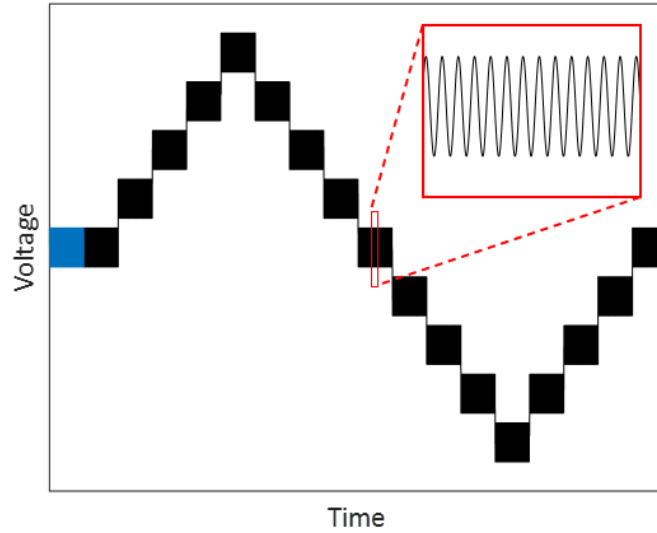


Figure 4.5: A stepwise sweep of the dM/dH curve (black) with reference measurement (blue). The reference measurement is only measured for one offset H_{DC} as the excitation field should not influence measurements.

Measuring the DiffMag value for different offsets H_{DC} would result in a similar curve, albeit inverse to the dM/dH measurement. Inverting the curve and finding the correct height with a reference measurement would lead to a similar result. See figure 4.6. Two reference measurements are conducted. One before and one after the measurement of the sample. These are averaged for increased accuracy.

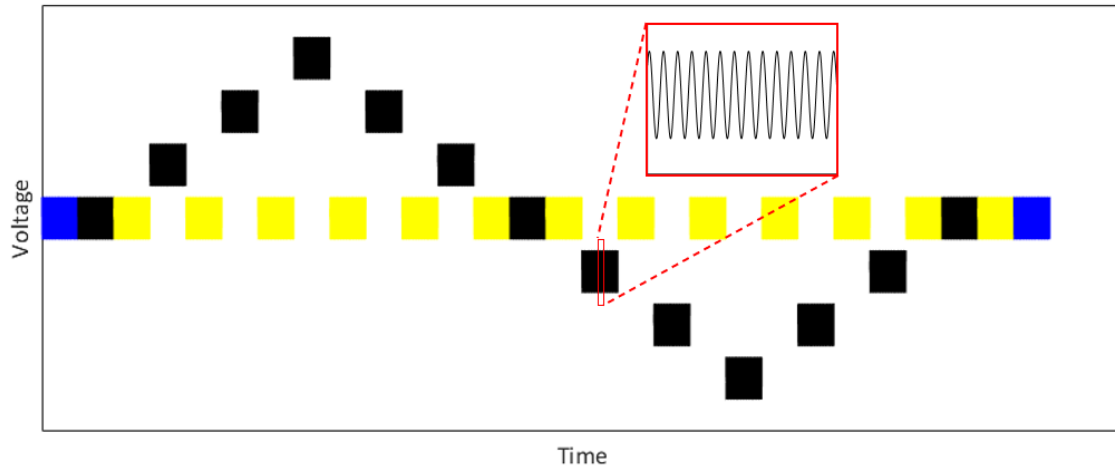


Figure 4.6: DiffMag sequence to find the dM/dH curve. The DiffMag value is measured for multiple offsets H_{DC} (black) paired with $H_{DC} = 0$ measurements (yellow). The reference measurements (blue) are used to find the appropriate height for the curve.

Chapter 5

Discussion and conclusion

In answer to the question: *What SPaQ eugmentations ensure suitability for its applications?* there are many ways to improve upon the existing SPaQ. All in all, the current design does not contain major design flaws and could be used for its intended applications. Still, certain augmentations would improve the system for certain applications.

Correcting the drift of the SPaQ is desired for all applications of the system. Separating the sample holder from the coil system could achieve this, but this has yet to be confirmed. The gradiometer could be more sensitive if changed into a second order coil system. However, improved sensitivity is not necessarily required. The drift could be compensated for by averaging many measurements. This could be a feasible solution even when the exact cause remains unknown. This method would require confirmation before implementation. Also, a protocol for repeated measurement would be needed.

For particle characterization, more control of temperature is desired. Heating of the system does not affect the result, but should be approached carefully nonetheless. Heating of the sample is preferably controlled. That way, particle characterization can be performed at the right temperature. Heating (or cooling) the sample externally and then placing it in the device could be considered as alternative, albeit a less elegant solution.

Shielding of the excitation coil does not seem necessary. However, the current design with outer field coils performs as desired and changes are therefore not needed. Only whenever a simplified design is wanted, a single solenoid coil for excitation could be considered.

For DiffMag protocol optimization a stepwise approach of the excitation sequence would be more suitable. The present sequence (LangevinSweep) results in an unwanted signal from the $H_D C$ sweep. The presented sequences might offer a solution, but have yet to be confirmed.

Part 5

Conclusion and recommendations

Chapter 1

Conclusion

This report aimed to answer two research questions: *What is the cause of the observed drift of the SPaQ measurements?* and: *What SPaQ augmentations ensure suitability for its applications?* Previous parts already discussed their respective research questions and drew conclusions. What remains here is only a brief, general discussion. The following recommendations are treated in the next chapter.

The cause of drift has not yet been fully identified. However, some progress has been made. It is very likely that the drift is caused by unbalance of the gradiometer. Coil displacement of only a few nanometers could cause the observed drift. The origin of the displacement remains unknown and requires further research.

For any application, drift should be removed from the measurements. Ensuring that the gradiometer remains balanced is key here. Averaging repeated measurements of one sample could potentially correct for drift but needs further research.

For the SPaQ to be used for particle characterization, control of the sample temperature is desired. For the SpQ to be used for DiffMag protocol optimization, the excitation sequence should be altered to a stepwise sequence.

Other augmentations could improve the SPaQ, but are not essential for the intended applications of the device. These could be considered whenever a new SPaQ is designed. Overall, the SPaQ performs sufficiently for its intended applications.

Chapter 2

Recommendations

Part 4 discussed potential augmentations to the SPaQ. However, it should not be made a priority to implement these augmentations. These recommendations consider the followings steps relating to the research questions.

2.1 Coil displacement

The drift is very likely to be caused by slight displacement of the coils. Therefore, it should be researched whether vibrations cause increased measurement drift. Measurements where the SPaQ is vibrated purposefully are recommended for this purpose.

2.2 Sample holder

If vibrations could cause drift, the source of vibrations needs confirmation. It should be investigated whether placement of the sample holder in the system is the cause of this displacement. This could be done by repeated empty measurements where the sample holder is placed in the system as is done whenever a measurement is performed with sample. Comparison with the empty measurements previously performed should indicate whether this causes the observed drift of measurements.

2.3 SPaQ comparison to Hall magnetometers

A closer comparison of Hall magnetometers with the SPaQ is required. The methods used by these devices seem very similar to that of the SPaQ. However, slight differences exist. Therefore, measurements should be compared directly, to find if the measured curves are comparable.

2.4 Applications of the SPaQ

Regarding applications of the SPaQ, other applications where SPIONs need to be quantified in vitro should be researched further. LoC applications might prove not particularly suitable as the Hall magnetometers could be better applied here. However, a literature study on this subject should be performed to confirm this.

2.5 Sequence

A stepwise sequence more closely resembles the DiffMag approach and should therefore be incorporated in the SPaQ. Currently, the changing H_{DC} is detected and could thus affect the measurements. Thus, to optimize the DiffMag protocol, a stepwise sequence is required.

2.6 Hardware

It is not recommended to upgrade the hardware of the SPaQ, while the cause of the measurement drift remains unknown. It is recommended that the effect of the oil bath is researched. As the temperature is not related to the drift, the usage of oil might be more cumbersome than beneficial. Therefore, simulation of the heat dispersion with and without oil could provide more insight. Also, measurements without oil could prove as good as without. Overall, the SPaQ performs as intended.

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