

PROBING VISCOSITY VIA RELAXATION IN MAGNETIC PARTICLE IMAGING

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By
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Probing Viscosity via Relaxation in Magnetic Particle Imaging

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.



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ABSTRACT

PROBING VISCOSITY VIA RELAXATION IN MAGNETIC PARTICLE IMAGING

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Magnetic Particle Imaging (MPI) is a high-contrast imaging modality with applications such as angiography, stem cell tracking, and cancer imaging. In recent years, MPI was shown to be a potential functional imaging modality through “color MPI” techniques, where responses from different nanoparticles can be distinguished. These techniques can be extended to differentiate environmental conditions or states such as different viscosities. Increased viscosity in vivo was shown to be related with various diseases such as hypertension, atherosclerosis, and cancer. Through color MPI techniques, MPI shows a great promise for mapping viscosity and for helping in the diagnosis of these important diseases. This thesis demonstrates the capability of MPI to map viscosities through an estimation of relaxation time constant of nanoparticles. This capability is verified through an extensive experimental work with a magnetic particle spectrometer (MPS) setup that is custom designed. These experiments are conducted for the biologically important viscosity range between 0.89 mPa·s and 15.33 mPa·s, at four different frequencies (between 250 Hz and 10.8 kHz) and at three different field amplitudes (between 5 mT and 15 mT). The results demonstrate MPI’s viscosity mapping capability in a biological range.

Keywords: magnetic particle imaging, viscosity mapping, relaxation, magnetic nanoparticles.

ÖZET

MANYETİK PARÇACIK GÖRÜNTÜLEMEDE RELAKSASYON YOLUYLA VİSKOZİTE ÖLÇÜMÜ

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Manyetik Parçacık Görüntüleme (MPG) anjiyografi, kök hücre takibi ve kanser görüntüleme gibi uygulama alanlarına sahip, yüksek-kontrastlı bir görüntüleme yöntemidir. Son yıllarda geliştirilen “renkli MPG” teknikleriyle farklı nanoparçacıklardan gelen tepkilerinin ayrıştırılabileceği ve MPG’nin fonksiyonel görüntüleme yöntemi olarak da kullanılabileceği gösterilmiştir. Buna ek olarak, aynı nanoparçacıkların farklı koşul veya ortamlardaki durumlarını ayrıştırmak için de bu yöntemleri kullanmak mümkündür; örneğin farklı viskoziteye sahip ortamlardaki nanoparçacıkları ayırt etmek gibi. Yüksek tansiyon, damar tıkanıklığı, ve kanser gibi birçok hastalık yüksek viskozite seviyesi ile ilişkilendirilmiştir. Renkli MPG teknikleri, MPG ile viskozite seviyesini ölçme konusunda umut vaat etmektedirler. Bu tezde, MPG ile viskozite ölçümünün nanoparçacıkların relaksasyon zaman sabiti hesaplanması yoluyla yapılabileceği gösterilmiştir. Bu teknik, özel tasarlanmış bir manyetik parçacık spektrometre (MPS) düzeneği ile kapsamlı deneyler yapılarak doğrulanmıştır. Deneyler, biyolojik olarak anlamlı vizkozite aralığı olan 0.89 mPa·s ile 15.33 mPa·s viskozite değerleri için dört ayrı frekans (250 Hz ile 10.8 kHz arasında), ve üç farklı manyetik alan şiddetinde (5 mT ile 15 mT arasında) gerçekleştirilmiştir. Bu sonuçlar, biyolojik aralıktaki viskozitenin MPG ile ölçülebileceğini göstermektedir.

Anahtar sözcükler: manyetik parçacık görüntüleme, vizkozite haritalama, relaksasyon, manyetik nanoparçacıklar.

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Contents

1	Introduction	1
2	Background and Theory	4
2.1	Magnetic Particle Imaging (MPI)	4
2.2	Relaxation in MPI	7
2.3	Direct Estimation of Relaxation Time Constant	9
3	Materials and Methods	13
3.1	Magnetic Particle Spectrometer Setup	13
3.2	Viscous Sample Preparation and Experimental Procedures	17
3.3	Data Preprocessing	19
3.4	Relaxation Time Constant Estimation	19
3.5	Influence of Tail Truncation on Estimated Time Constants	22
4	Results	24

4.1	Effect of Viscosity on MPS Signal	24
4.2	Effect of Drive Field Amplitude	25
4.3	Effect of Drive Field Frequency	27
4.4	Comparison of Different Nanoparticles	29
5	Discussion and Conclusion	32
A	Detailed Signal Processing Analysis	43

List of Figures

2.1	(a) Characterization of the magnetization, M , of SPIOs as a function of the applied field, H , which is governed by a Langevin function. The magnetization of SPIOs saturates beyond a threshold external magnetic field. (b) Schematics of an MPI Scanner. Here blue lines indicate the magnetic field lines, red dot is the field-free-point (FFP), and green dot is an example point where the SPIO nanoparticles are saturated. (c) When the nanoparticles in the FFP experience a sinusoidal drive field, the time-varying magnetization of the nanoparticles induce a signal in the receiver coil, as denoted by red. If the nanoparticles are in the saturated area, their magnetization does not change and hence no signal is induced, as denoted by green.	5
2.2	(a) The relaxation mechanisms of the SPIO nanoparticles are illustrated. Brownian relaxation occurs when the magnetic moment of the nanoparticles, M , aligns to the applied field, H (red arrow) through a physical rotation (top). On the other hand, Neel relaxation occurs when the magnetic moment of the nanoparticles aligns to the applied field, H , internally (bottom). (b) The effect of relaxation on the nanoparticle signal is shown. When the nanoparticle signal has relaxation effect (blue), it is delayed and peak signal is decreased as compared to the nanoparticle signal without any relaxation effect (red).	8

2.3	Estimating the relaxation time constant directly from the measured MPS signal. (a) Measured MPS signal for nanomag-MIP nanoparticles at 1.1 kHz and 15 mT drive field, for the case of a low viscosity solution (approximately 1.22 mPa·s). The relaxation effect on the signal is clearly visible. (b) The positive half cycle and the mirrored (i.e., time reversed and negated) negative half cycle are overlaid. If the signal had not contained any relaxation effects, these two half cycles would overlap exactly. Due to relaxation, however, each half cycle is blurred along the scanning direction. The time constant estimation yields $\tau = 32.9 \mu\text{s}$. (c) The measured signal can then be deconvolved by the relaxation kernel with the estimated time constant, which reveals the underlying mirror symmetry.	10
3.1	Mutual inductance comparison between two-section design (a, top) (b, blue) and three-section design (a, bottom) (b, red) when the receive coil is shifted in z direction. Three-section design is more robust in case of any constructional flaws such as off-centered positioning.	14
3.2	Solidworks designs of the MPS setup that consists of a drive coil (a) and a receive coil (b). The two coils are coaxially aligned with each other (c).	15
3.3	Magnetic field maps of the custom-made receive and drive coils. The 95% homogeneity occurs in a 7-cm-long region in the drive coil. The receive coil has a 2-cm long sensitive region where it allows a sample tube of 1.5-cm in length.	16
3.4	The sensitivities of the drive coil and the receive coil are measured with a Hall effect gaussmeter. 1A DC current is applied to the coils and the measurement point was moved in a stepwise manner using a linear actuator. The measured sensitivities almost perfectly match with the simulation results.	16

3.5	Overview of the experimental setup. Arrows in the schematic denote the workflow of the transmit/receive chain for my in-house magnetic particle spectrometer (MPS) setup, which is controlled via a data acquisition card (DAQ) through MATLAB. A fiber optic thermometer and a current probe provide real-time monitoring of the temperature and the magnetic field in the MPS setup, respectively.	17
3.6	Acquired data (a) without baseline subtraction and (b) with baseline subtraction. (c) The resultant signal after choosing the higher harmonics of the drive field frequency in Fourier domain and setting all other frequencies to zero. After that a low-pass filter was applied in time domain. (d) An arbitrary period from the signal in (c) is displayed to show that it contains the nanoparticle relaxation effect. The graphs have the same arbitrary unit.	20
3.7	Influence of tail truncation on the estimated relaxation time constants. If the relaxation model worked perfectly, these curves would be horizontally flat, yielding constant τ estimation independent of truncation percentage. At low drive field amplitude and frequency as in (a), large truncation percentage yields diverging results, whereas zero truncation shows a slight variation from the expected flat response. In contrast, at high drive field amplitude and frequency as in (c), the estimations remain constant up to 35% tail truncation. In all cases, tail truncations between 10%-20% yielded constant τ estimations. Results are for nanomag-MIP nanoparticles.	22

- 4.1 Effects of viscosity on nanoparticle signal. (a) The measured signal of nanomag-MIP nanoparticles at 1.1 kHz and 15 mT drive field are shown for low viscosity (0.89 mPa·s) and high viscosity (15.33 mPa·s) cases. The low viscosity case displays a wider response with reduced peak amplitude. The calculated relaxation time constant for these two cases were $\tau = 33 \mu\text{s}$ and $\tau = 24 \mu\text{s}$, respectively. (b) The same samples were measured at 10.8 kHz and 15 mT drive field, yielding $\tau = 3.5 \mu\text{s}$ and $\tau = 3.6 \mu\text{s}$, respectively. Here, the high viscosity case has a slightly wider response than the low viscosity case. 25
- 4.2 Relaxation time constants as a function of viscosity, at four different drive field frequencies for sample set #1 (nanomag-MIP at 11 different viscosities ranging between 0.89 mPa·s to 15.33 mPa·s). Error bars denote the mean values and standard deviations over three repetition experiments. 26
- 4.3 Relaxation time constants as a function of viscosity, at three different drive field strengths for sample set #1 (nanomag-MIP at 11 different viscosities ranging between 0.89 mPa·s to 15.33 mPa·s). Error bars denote the mean values and standard deviations over three repetition experiments. (a) to (c) The same data as in Fig. 4.2, re-plotted to emphasize the effect of drive field frequency at a fixed field strength. (d) to (f) The results in a unified y-axis, where the estimated time constants are normalized by the period of the drive field at each frequency, multiplied by 100. 28

4.4	Relaxation time constant vs. viscosity for the biologically more relevant range of viscosities, for sample set #2 (nanomag-MIP at 20 different viscosities ranging between 0.89 mPa·s to 3.97 mPa·s), measured at four different frequencies at 15 mT field strength. Error bars denote the mean values and standard deviations over three repetition experiments. (a) Estimated time constants and (b) time constants normalized by that of nanoparticles in water to highlight the percentage change in τ vs. viscosity.	29
4.5	Effects of viscosity on the relaxation time constants of two different nanoparticles. VivoTrax and nanomag-MIP nanoparticles were measured at four different drive field conditions, and at 11 different viscosities ranging between 0.89 mPa·s to 15.33 mPa·s. Error bars denote the mean values and standard deviations over three repetition experiments.	30
A.1	Received nanoparticle signal at the viscosity value of 1.22 mPa·s, under the drive field frequency and amplitude of 1.1 kHz and 15 mT. (a) shows the time domain signal and (b) shows the corresponding frequency domain of this signal. The direct-feedthrough contamination surpass the nanoparticle signal. Red circle in (b) shows from the 3rd to 13th harmonics of the nanoparticle signal. .	44
A.2	Background signal is subtracted from the nanoparticle signal given in Fig. A.1. Now, the direct-feedthrough contamination is highly removed. The nanoparticle harmonics is shown in (b). Also in (b), self-resonance frequency of the receive coil is shown. The self resonance of the receive coil contaminates the higher harmonics of the nanoparticle response at the drive field frequency of 10.8 kHz.	45

A.3	Once the baseline-subtracted signal undergoes a two-stage filtering operation, the remaining direct-feedthrough signal is removed along with the noise in non-harmonic frequencies. The resulting nanoparticle signal shown in (a) has the relaxation effects.(b) shows the frequency domain representation of the time domain signal given in (a).	45
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Chapter 1

Introduction

Magnetic Particle Imaging (MPI) is a novel imaging modality that was first published in 2005 [1]. MPI utilizes the non-linear magnetization characteristics of superparamagnetic (SPIO) nanoparticles to provide spatial localization of nanoparticles. Iron oxide nanoparticles are exploited in MPI as a contrast agent (as opposed to iodine or gadolinium) which makes it a safe imaging method, especially for patients with chronic kidney disease (CKD). MPI has been rapidly developing since it was first published [2, 3, 4] with potential biomedical applications such as angiography [5, 6], stem cell tracking [7, 8, 9], cancer imaging [10], guiding cardiovascular interventions [11], and predicting the effectiveness of magnetic hyperthermia [12, 13]. In MPI, the same pole of two strong magnets face each other to create a zero-field point in between (called the field-free-point, FFP), and this point (FFP) is scanned through the object of interest using a time varying field (drive field). MPI detects the response of SPIO nanoparticles to applied external magnetic fields, without any signal from the background tissue. This response is sensitive to the local environment of the SPIOs such as the viscosity of the medium that they are in or their binding state to chemicals, showing a remarkable potential for functional imaging with MPI.

One potential functional imaging application for MPI is in vivo viscosity mapping. In literature, blood viscosity was shown to change with hematocrit level

[14], and several studies associated high hematocrit levels in the blood plasma with important diseases such as hypertension [15], cerebral infarction [16], angina pectoris [17], ischemic heart disease [18, 19], and extensive coronary artery disease [20]. High blood viscosity levels were also found to be prognostic of certain cancer types [21, 22]. It was further suggested that cancer cells have increased cellular viscosity when compared to healthy cells [23]. Importantly, for cell tracking applications, viscosity in a cell cytoplasm can give information regarding the uptake of external particles into the cell environment as well as activities occurring within the cell. Interactions in the cell environment such as signaling, transportation of molecules, enzymatic activity, binding effect were interrelated with viscosity [24, 25, 26, 27]. Diagnoses of atherosclerosis [28], diabetes [29], Alzheimer’s disease [30], and neurological disorders [31] were found to be related with plasma fluidity, membrane viscosity, and serum viscosity. Given this extensive literature, measuring viscosity in vivo has important diagnostic and prognostic implications, making it a promising functional imaging application for MPI.

The relaxation behaviour of nanoparticles under zero-field (i.e., when an applied magnetic field is removed) is modeled by two different mechanisms: Neel relaxation where the magnetic moment of the nanoparticle aligns itself internally with the applied field, and Brownian relaxation where the nanoparticle physically rotates to align its magnetic moment with the applied field. Extensive simulations showed the influence of particle parameters such as size and shape anisotropy, magnetization dynamics, and the sequence of applied fields [32, 33]. Theoretical modeling for Neel relaxation via Landau-Lifshitz-Gilbert equation and for Brownian relaxation via Fokker-Planck equation were also presented [34, 35]. Due to the physical rotation of the nanoparticle, Brownian relaxation is directly influenced by the external environment, such as the viscosity of the medium. With this fact in mind, the monitoring of viscosity through the ratio of nanoparticle magnetization harmonics was proposed, with potential extensions to system-matrix based MPI reconstruction [36, 37]. The relaxation induced signal delays in x-space based MPI reconstruction were also suggested as a possible tool for estimating the mobility of nanoparticles [38]. Recent color MPI studies have shown the capability of MPI to separate signals from different nanoparticles [39, 40],

which could in potential be applied to differentiate nanoparticles in different viscous environments. In these color MPI techniques, a successful separation relied on extensive calibration acquisitions that essentially characterize the behaviour of the nanoparticles under different settings, or measurements at multiple drive field amplitudes to reveal the differences between the responses of nanoparticles. MPI cell tracking experiments have also shown that nanoparticles internalized into the cells displayed reduced resolution [7] or had altered signal characteristics when compared to nanoparticles in water [9], which could stem from viscosity effects on the relaxation behaviour of the nanoparticles. Hence, understanding the effects of viscosity on MPI signal is vital in developing the viscosity mapping capabilities of MPI for functional imaging purposes.

In this thesis, the viscosity mapping capability of MPI is demonstrated through an estimation of the relaxation induced changes in the nanoparticle response. This estimation does not require any a priori information on the nanoparticles. This functional capability of MPI was verified through a custom-designed magnetic particle spectrometer (MPS) device. Through extensive experiments, the results showed that the relaxation time constant as a function of viscosity is dependent on the drive field strength and frequency. These results provide guidance on MPI imaging parameters that can accentuate the signal differences between nanoparticles in environments with different viscosities. The proposed technique can be extended to imaging applications, facilitating the viscosity mapping potential of MPI.

Chapter 2

Background and Theory

2.1 Magnetic Particle Imaging (MPI)

Superparamagnetic iron oxide (SPIO) nanoparticles are utilized as contrast agent in MPI. The magnetization of SPIOs is characterized by a Langevin function where the magnetization saturates beyond a threshold external magnetic field as shown in Fig. 2.1(a). In an MPI scanner, as depicted in Fig. 2.1(b), two magnets create a zero-field point (called field-free point, FFP) in between, and due to the non-zero static field distribution in the remaining points, the nanoparticles are saturated. When the nanoparticles in the FFP experience a sinusoidal drive field, the time-varying magnetization of the nanoparticles induce a signal in the receiver coil. However, if the nanoparticles are in the saturated area, their magnetization does not change significantly and remain almost constant (i.e., they remain saturated) and hence no signal is induced. The SPIO responses of these points are shown in Fig. 2.1(c).

The static field generated by magnets, which is also called selection field, can be mathematically represented in 1-D as follows:

$$H_s(x) = -Gx \quad (2.1)$$

Here G is the selection field gradient strength [T/m/ μ_0], and $x = 0$ is the location

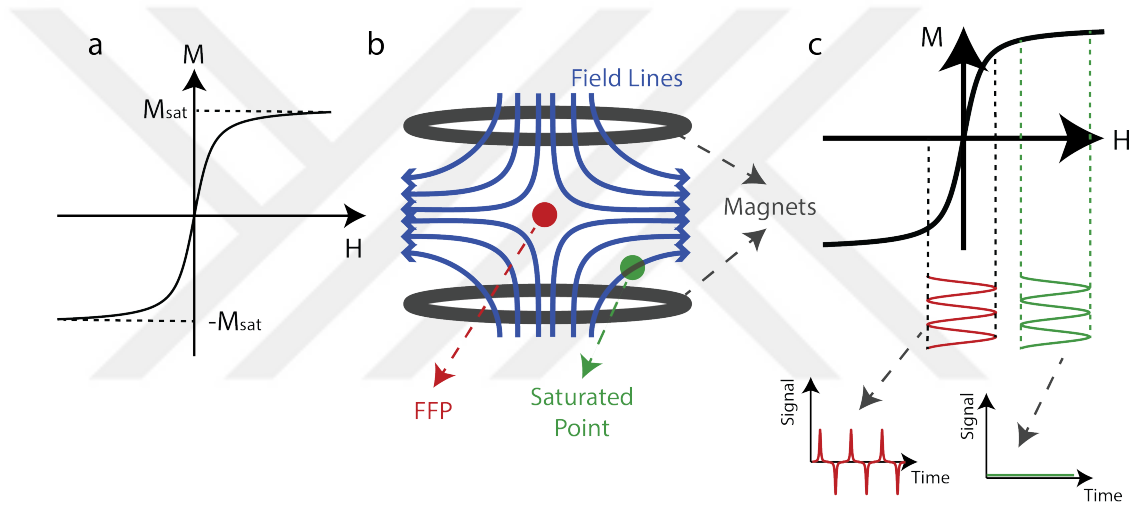


Figure 2.1: (a) Characterization of the magnetization, M , of SPIOs as a function of the applied field, H , which is governed by a Langevin function. The magnetization of SPIOs saturates beyond a threshold external magnetic field. (b) Schematics of an MPI Scanner. Here blue lines indicate the magnetic field lines, red dot is the field-free-point (FFP), and green dot is an example point where the SPIO nanoparticles are saturated. (c) When the nanoparticles in the FFP experience a sinusoidal drive field, the time-varying magnetization of the nanoparticles induce a signal in the receiver coil, as denoted by red. If the nanoparticles are in the saturated area, their magnetization does not change and hence no signal is induced, as denoted by green.

of FFP. The nanoparticles are excited with a time-varying magnetic field, which is called the drive field, and it is typically in the following form:

$$H_d(t) = H_{peak} \cos(2\pi f_d t) \quad (2.2)$$

where H_{peak} [T] is the peak value of the applied sinusoidal field and f_d [Hz] is the frequency of the drive field. The applied magnetic field becomes the summation of the spatial selection field and temporal sinusoidal:

$$\begin{aligned} H(x, t) &= H_d(t) + H_s(x) \\ &= H_d(t) - Gx \end{aligned} \quad (2.3)$$

Note that, the location of FFP is at $H(x, t) = 0$. Solving for the time-dependent position of the FFP, $x_s(t)$ in [m] yields:

$$H_d(t) - Gx_s(t) = 0 \quad (2.4)$$

$$H_d(t) = Gx_s(t) \quad (2.5)$$

$$x_s(t) = \frac{H_d(t)}{G} \quad (2.6)$$

To reconstruct an image from the received signals, there are two main approaches in MPI. One of them is called system-reconstruction method, in which the MPI system is calibrated with a point source before a regular imaging sequence begins. Alternatively, the other approach is called x-space reconstruction method, in which the nanoparticle responses are directly localized with the knowledge of the FFP velocity.

For x-space MPI reconstruction, the 1-D signal equation is derived in [41]. The non-linear magnetization curve of the nanoparticles is described by a Langevin function:

$$M(H) = m\rho\mathcal{L}[kH] \quad (2.7)$$

where m [Am^2] is magnetic moment of the nanoparticle, ρ [particles/ m^3] is density of nanoparticles, k [m/A] is a nanoparticle property, and $H = Gx$ as it

was shown in Eq. 2.1. Assuming the particle distribution is only in x direction, and FFP positon is at $x_s(t)$, the magnetization can be written as:

$$M(x, t) = m\rho(x)\delta(y)\delta(z)\mathcal{L}[kG(x_s(t) - x)] \quad (2.8)$$

Eq. 2.8 can be converted to magnetic flux as given below. Note that, if we assume ρ changes with only x , this equation is a convolution:

$$\begin{aligned} \phi(t) &= -m \iiint \rho(u)\delta(v)\delta(w)\mathcal{L}[kG(x_s(t) - u)] du dv dw \\ &= m\rho(x) * \mathcal{L}[kGx]|_{x=x_s(t)} \end{aligned} \quad (2.9)$$

Finally, the 1-D MPI signal (also called the adiabatic signal) can be expressed as follows:

$$s_{ideal}(t) = B_1 \frac{d\phi}{dt} = B_1 m\rho(x) * \dot{\mathcal{L}}[kGx]|_{x=x_s(t)} kG\dot{x}_s(t) \quad (2.10)$$

where B_1 [T/A] is receiver coil sensitivity.

2.2 Relaxation in MPI

In practice, the received MPI signal is affected by the relaxation behaviour of the SPIOs. The relaxation causes a peak shift in the MPI signal along with a loss in SNR, which blurs the image. There are two relaxation mechanisms that govern the behaviour of SPIOs when the applied field is removed. First one is called Brownian relaxation, in which the magnetic moment of the nanoparticles aligns externally through a physical rotation. Other mechanism is called Neel relaxation, in which the alignment of the magnetic moment occurs internally to the applied field. The combined effects of these relaxation mechanisms result in a delay of the nanoparticle signal along with decreased peak signal. In Fig. 2.2(a), these two relaxation mechanisms are illustrated, and in Fig. 2.2(b) the effect of relaxation on the nanoparticle signal is shown.

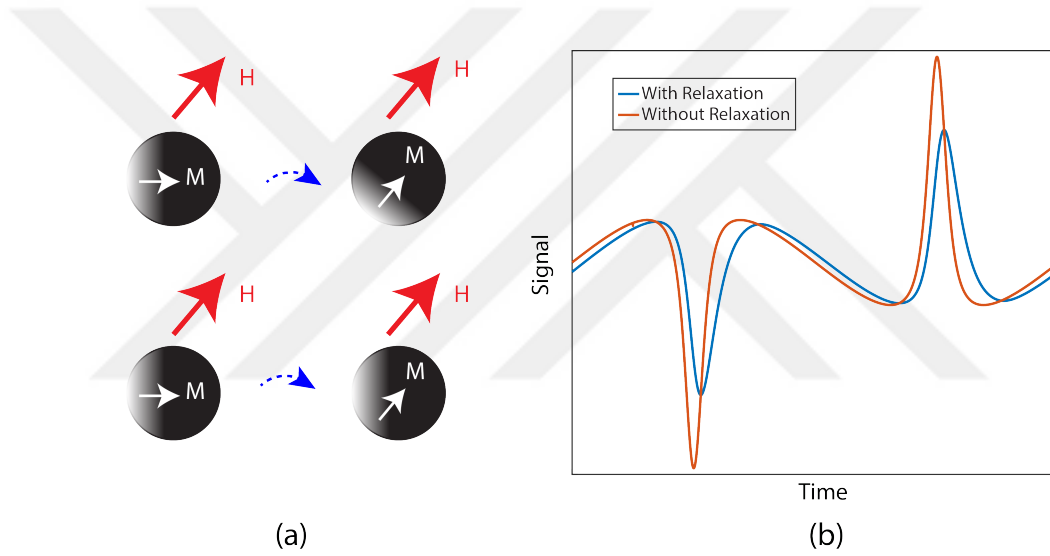


Figure 2.2: (a) The relaxation mechanisms of the SPIO nanoparticles are illustrated. Brownian relaxation occurs when the magnetic moment of the nanoparticles, M , aligns to the applied field, H (red arrow) through a physical rotation (top). On the other hand, Neel relaxation occurs when the magnetic moment of the nanoparticles aligns to the applied field, H , internally (bottom). (b) The effect of relaxation on the nanoparticle signal is shown. When the nanoparticle signal has relaxation effect (blue), it is delayed and peak signal is decreased as compared to the nanoparticle signal without any relaxation effect (red).

The relaxation effect blurs the reconstructed image asymmetrically depending on the scanning direction. Previous studies have modeled this relaxation effect as a temporal convolution of the ideal MPI signal with an exponential relaxation kernel [42, 43]:

$$s(t) = s_{ideal}(t) * r(t) \quad (2.11)$$

where,

$$r(t) = \frac{1}{\tau} e^{-\frac{t}{\tau}} u(t) \quad (2.12)$$

Here, τ is called the relaxation time constant and $u(t)$ is the Heaviside step function. It has been verified via extensive experimental work that this phenomenological model accurately characterizes the MPI response for a wide range of frequencies and drive field amplitudes [42, 43].

2.3 Direct Estimation of Relaxation Time Constant

In MPI, positive and negative half cycles of the drive field move the FFP forward and back across the scanned partial field-of-view (FOV), repetitively. As a result of this back and forth scanning process, the ideal MPI signal acquired during the positive and the negative scanning directions are mirror symmetric, independent of the nanoparticle distribution $\rho(x)$. Here, mirror symmetry refers to the positive half cycle and the time-reversed and negated negative half cycle of the signal being identical. The ideal half-cycle signals can be expressed as follows:

$$s_{pos,ideal}(t) = -s_{neg,ideal}(-t) = s_{half}(t) \quad (2.13)$$

In the case of relaxation, however, the MPI signal is effectively blurred along the scanning direction, which in turn breaks the mirror symmetry between the

two half cycles [44, 45]. To demonstrate this point, Fig. 2.3(a) and Fig. 2.3(b) display the lost mirror symmetry for a measured MPS signal acquired at 1.1 kHz and 15 mT drive field for nanomag-MIP nanoparticles. In theory, the half cycles shown in Fig. 2.3(b) would overlap exactly if the nanoparticles did not exhibit any relaxation behaviour. In theory, the relaxation time constant can be estimated from the half cycles of the MPI signal using the mirror symmetry of the underlying ideal MPI signal, without any a priori information about the nanoparticle type or distribution.

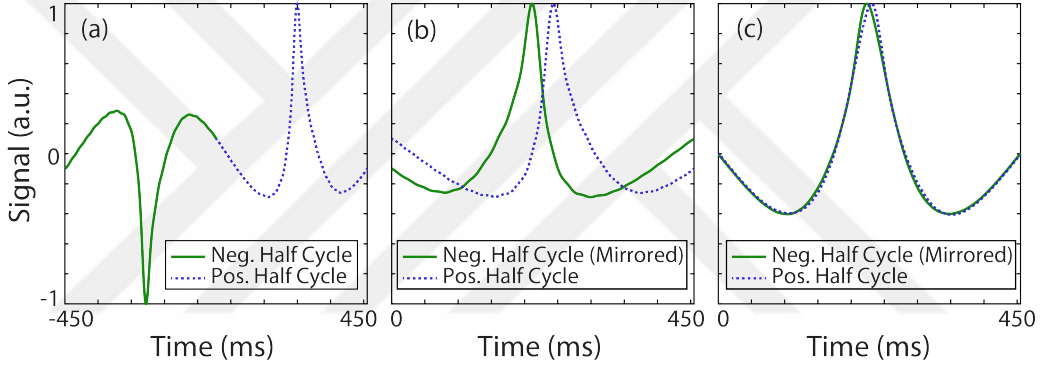


Figure 2.3: Estimating the relaxation time constant directly from the measured MPS signal. (a) Measured MPS signal for nanomag-MIP nanoparticles at 1.1 kHz and 15 mT drive field, for the case of a low viscosity solution (approximately 1.22 mPa·s). The relaxation effect on the signal is clearly visible. (b) The positive half cycle and the mirrored (i.e., time reversed and negated) negative half cycle are overlaid. If the signal had not contained any relaxation effects, these two half cycles would overlap exactly. Due to relaxation, however, each half cycle is blurred along the scanning direction. The time constant estimation yields $\tau = 32.9 \mu\text{s}$. (c) The measured signal can then be deconvolved by the relaxation kernel with the estimated time constant, which reveals the underlying mirror symmetry.

Using the convolution-based formulation for the MPI signal, the half cycles in the case of relaxation can be expressed as:

$$s_{pos}(t) = s_{pos,ideal}(t) * r(t) = s_{half}(t) * r(t) \quad (2.14)$$

$$s_{neg}(t) = s_{neg,ideal}(t) * r(t) = -s_{half}(-t) * r(t) \quad (2.15)$$

Note that $s_{half}(t)$ is the ideal half-cycle signal. Using the exponential model for $r(t)$, these two equations can be solved simultaneously to reveal both τ and $s_{half}(t)$ [44, 45]. Here, the interested variable is the relaxation time constant τ , which can be expressed in closed form in the Fourier domain:

$$\mathcal{F}\{r(t)\} = R(f) = \frac{1}{(1 + i2\pi f\tau)} \quad (2.16)$$

$$\mathcal{F}\{s_{pos}(t)\} = S_{pos}(f) = S_{half}(f) \cdot R(f) \quad (2.17)$$

$$\mathcal{F}\{s_{neg}(t)\} = S_{neg}(f) = -S_{half}(-f) \cdot R(f) \quad (2.18)$$

Here, Eq. 2.16 is the known 1D Fourier transform of an exponential function and Eq. 2.18 follows from time reversal property of Fourier transform. Since $s_{half}(t)$ is real valued, its Fourier transform $S_{half}(f)$ has conjugate symmetry property. Accordingly, the last equation can be re-written as

$$\mathcal{F}\{s_{neg}(t)\} = S_{neg}(f) = -S_{half}^*(f) \cdot R(f) \quad (2.19)$$

where the superscript star sign denotes the conjugation operation. Finally, combining Eq. 2.16 to 2.19, the relaxation time constant can be expressed as follows:

$$\tau = \frac{S_{pos}^*(f) + S_{neg}(f)}{i2\pi f(S_{pos}^*(f) - S_{neg}(f))} \quad (2.20)$$

Once this time constant is estimated, the signal can be deconvolved by the relaxation kernel, $r(t)$, to reveal the underlying ideal MPI signal. In theory, this deconvolution step recovers the mirror symmetry between the half cycles. This process is demonstrated in Fig. 2.3(c). In this work, the relaxation time constant

and system delays were estimated simultaneously (see Section 3.4). The τ, ϕ pair that minimized the RMSE between the deconvolved versions of the positive and the mirrored negative half cycles was chosen as the solution.



Chapter 3

Materials and Methods

3.1 Magnetic Particle Spectrometer Setup

In MPI, the receive coil needs to be in a gradiometer configuration to minimize the mutual inductance between the drive coil and the receive coil. This is because the drive field directly couples into the receive coil and induces a signal that is orders of magnitude larger than the nanoparticle signal. According to our previous simulations, due to the symmetry in the design, an MPS setup that incorporates a three-section receive coil can utilize a shorter drive coil with 23% reduced power consumption to achieve results similar to a design that uses a two-section gradiometer-type receive coil [46]. In a possible constructional flaws, such as off-centered positioning of the receive coil, three-section design is more robust than two-section design. Fig. 3.1 shows the comparison results between these two design types.

In this work, a custom-made magnetic particle spectrometer (MPS) setup (also called an MPI relaxometer) was designed using Solidworks (Dassault Systemes, Canada), which is illustrated in Fig. 3.2. This MPS setup consists of a drive coil that generates 0.97 mT/A magnetic field with 95% homogeneity in a 7-cm-long region down its bore. The drive coil has an inductance of 420 μ H and an internal

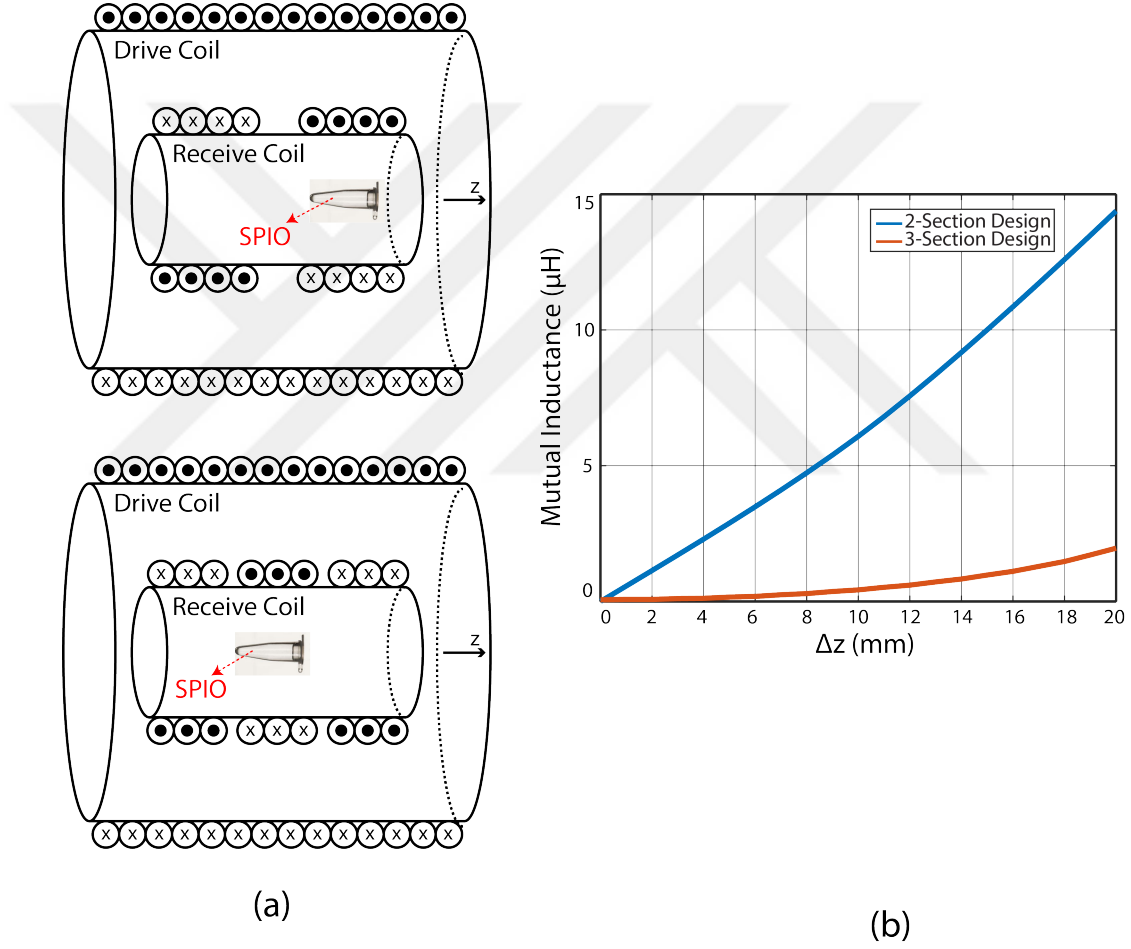


Figure 3.1: Mutual inductance comparison between two-section design (a, top) (b, blue) and three-section design (a, bottom) (b, red) when the receive coil is shifted in z direction. Three-section design is more robust in case of any constructional flaws such as off-centered positioning.

resistance of 2Ω . The inner diameter of the drive coil is 5.6 cm. This MPS setup also utilizes a receive coil which was a three-section gradiometer-type coil that allowed decoupling of the transmit and receive coils [46]. This receive coil design had 7 layers of Litz wire, where each layer contained 41 turns in the middle and 21 turns on both sides. The measurement chamber inside the receive coil allowed a sample tube of 1.5 cm in length and 0.8 cm in diameter. The receive coil has a self-resonance to be around 250 kHz. The magnetic field map simulation for both the drive coil and the receive coil is given in Fig. 3.3.

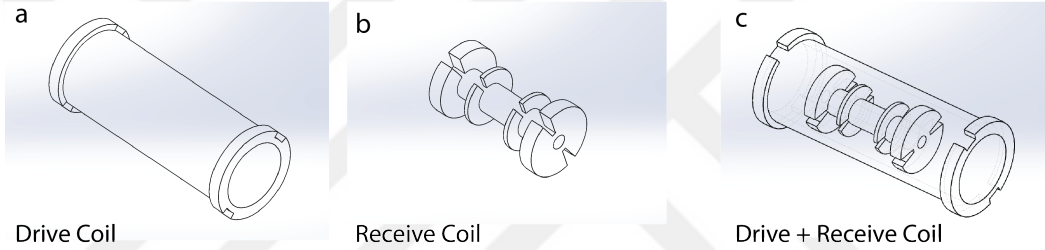


Figure 3.2: Solidworks designs of the MPS setup that consists of a drive coil (a) and a receive coil (b). The two coils are coaxially aligned with each other (c).

The simulated field maps were also tested with hardware. 1A DC current was applied to the coils via a DC power supply and the magnetic field was measured using a Hall effect gaussmeter (LakeShore 475 DSP Gaussmeter). The probe of gaussmeter was moved in a stepwise manner with an actuator (Velmex, BiSlide). The simulation and experimental result of normalized sensitivities of the drive and receive coils are given in Fig. 3.4. The corresponding sensitivities in this figure are the ones measured in the centerline of the coils (i.e., at $r = 0$).

The drive coil was impedance matched to an AC power amplifier (AE Techtron 7224) using a capacitive network, which enabled maximum transfer to the load while low-pass filtering potential higher harmonics of the drive field. On the receive side, the nanoparticle signal was amplified with a low-noise voltage preamplifier (Stanford Research Systems SR560). The MPS setup was controlled with an in-house MATLAB script (Mathworks, Natick, MA). A data acquisition card (National Instruments, NI USB-6363) sent the drive field signal to be amplified to the power amplifier and digitized the signal from the receive chain. The drive field amplitude was calibrated via the Hall effect gaussmeter (LakeShore

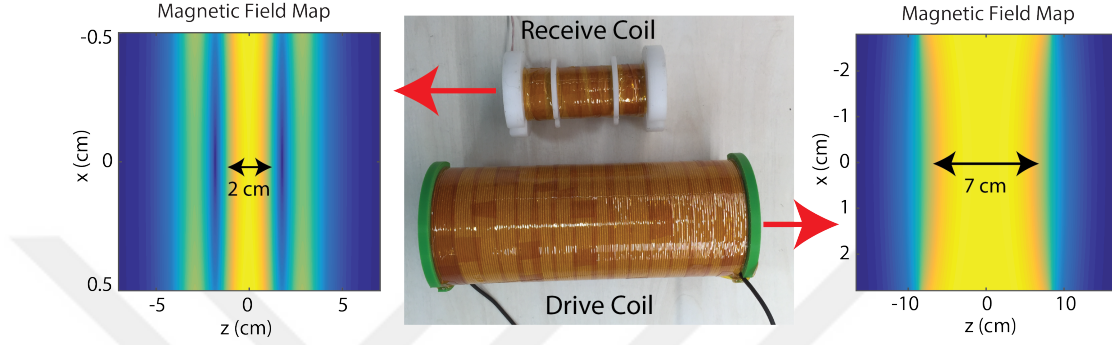


Figure 3.3: Magnetic field maps of the custom-made receive and drive coils. The 95% homogeneity occurs in a 7-cm-long region in the drive coil. The receive coil has a 2-cm long sensitive region where it allows a sample tube of 1.5-cm in length.

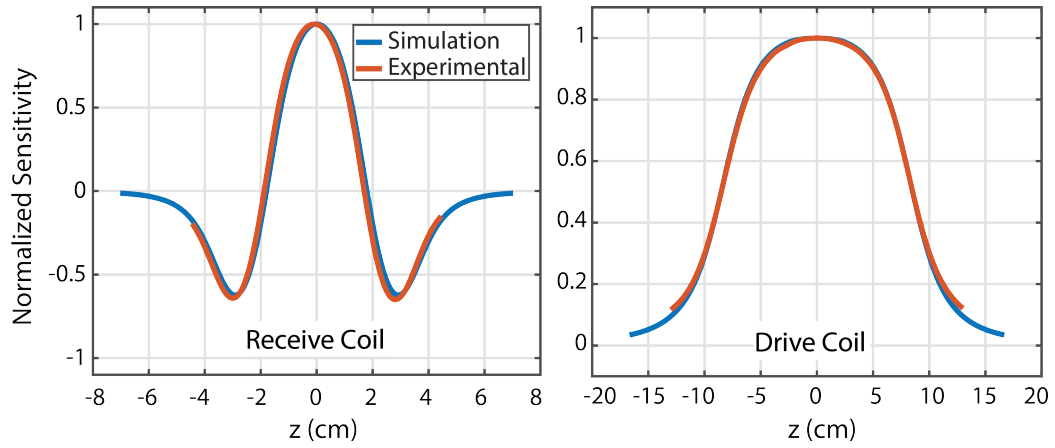


Figure 3.4: The sensitivities of the drive coil and the receive coil are measured with a Hall effect gaussmeter. 1A DC current is applied to the coils and the measurement point was moved in a stepwise manner using a linear actuator. The measured sensitivities almost perfectly match with the simulation results.

475 DSP Gaussmeter) and monitored in real time via a Rogowski current probe (LFR 06/6/300, Power Electronic Measurements Ltd). During the experiments, ambient temperature inside the measurement chamber was monitored using a fiber optic temperature probe (Neoptix Reflex-4). Fig. 3.5 shows the overall experimental configuration.

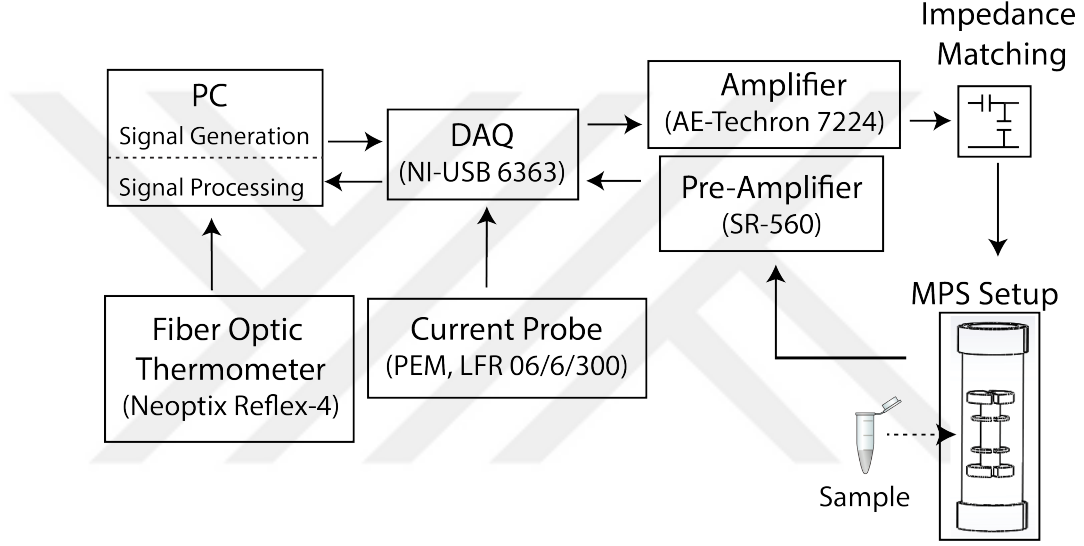


Figure 3.5: Overview of the experimental setup. Arrows in the schematic denote the workflow of the transmit/receive chain for my in-house magnetic particle spectrometer (MPS) setup, which is controlled via a data acquisition card (DAQ) through MATLAB. A fiber optic thermometer and a current probe provide real-time monitoring of the temperature and the magnetic field in the MPS setup, respectively.

3.2 Viscous Sample Preparation and Experimental Procedures

Viscosity in the cell cytoplasm for an aqueous phase is reported to be around 1-2 mPa·s (close to the 0.89 mPa·s viscosity of pure water at 25°C), and this number can become larger as the activity inside the cell increases [47]. Viscosity of the blood, on the other hand, is reported to be in the range of 1.3-7.8 mPa·s for hematocrit percentage in the total blood volume ranging between 14 76% [14].

To provide biologically relevant results in light of this information, three different sets of samples were prepared:

Sample Set #1: 11 samples with viscosities ranging between 0.89 mPa·s and 15.33 mPa·s were prepared. The total volume and nanoparticle amount in each sample was kept identical to avoid any Fe concentration bias in the results. Accordingly, each sample contained 50 μ L of undiluted nanomag-MIP (Micromod GmbH, Germany) nanoparticles with 89 mmol Fe/L concentration. These samples were then diluted to a total volume of 170 μ L, with varying mixtures of deionized water and glycerol to reach the target viscosity levels at 25°C [48]. Here, 0.89 mPa·s corresponds to the viscosity of pure water, whereas 15.33 mPa·s corresponds to 68% glycerol by volume.

Sample Set #2: To investigate the biological range in more detail, I prepare 20 samples with viscosity levels ranging from 0.89 mPa·s to 3.97 mPa·s following a procedure similar to the one described above. For this second set, the total sample volume was 200 μ L, starting from an initial 80 μ L volume of undiluted nanomag-MIP nanoparticles. Here, 3.97 mPa·s corresponds to the viscosity of 45% glycerol by volume.

Sample Set #3: To compare the viscosity effect on different nanoparticles, I prepare 11 samples using VivoTrax ferucarbotran nanoparticles (Magnetic Insight Inc., USA) with 98 mmol Fe/L concentration. Note that this nanoparticle has the same chemical composition as Resovist (which is known to have a well MPI response). For this set, same viscosity levels (i.e., ranging from 0.89 mPa·s to 15.33 mPa·s) and volumes were used as in sample set #1

The samples in set #1 were tested at four different drive field frequencies; 250 Hz, 550 Hz, 1.1 kHz, and 10.8 kHz, and under three different drive field peak amplitudes; 5 mT, 10 mT, and 15 mT. The samples in set #2 were tested at the same four frequencies, but only at 15 mT field amplitude. The samples in set #3 were tested at 550 Hz and 1.1 kHz, under two different drive field peak amplitudes: 10 mT and 15 mT. For each experiment, the amplified signal from the receive chain was digitized with 2 MS/s bandwidth. Acquisition lengths were chosen such that each cosine excitation pulse contained at least 35 periods. For

each measurement, the mean of 16 acquisitions were recorded to increase signal-to-noise ratio (SNR). This step was performed first with no sample inside the measurement chamber to serve as the background measurement, and then with the sample. Overall, each experiment was repeated three times.

3.3 Data Preprocessing

Acquired data sets were processed in MATLAB. For each experiment, the background signal was subtracted from the nanoparticle signal to remove the direct feedthrough and other potential interferences. An initial frequency selection was performed by choosing the higher harmonics of the drive field frequency in Fourier domain and setting all other frequencies to zero. This step removed the remaining direct feedthrough signal at the fundamental frequency (i.e., drive field frequency), as well as the noise in non-harmonic frequencies that would otherwise reduce signal quality. A subsequent high-order zero-phase digital low-pass filter (LPF) was applied in time domain. The cut-off frequency of LPF was determined via comparing the signal power at harmonic frequencies with the noise power at non-harmonic frequencies, which was computed before setting those frequencies to zero. Accordingly, the cut-off frequencies corresponded to 40th, 50th, 50th, and 18th harmonics for 250 Hz, 550 Hz, 1.1 kHz, and 10.8 kHz drive fields, respectively. The usage of fewer harmonics at 10.8 kHz was to avoid the self-resonance frequency of the receive coil, which contaminated signals above 200 kHz. The processing of the received signal is shown in Fig. 3.6. Also the detailed explanation is given in Appendix A.

3.4 Relaxation Time Constant Estimation

The acquired signal contains both the relaxation effects, as well as a phase lag due to inductive/capacitive circuitry. Note that for the ideal MPI signal, the signal peaks would occur at central time points of half cycles, which would trivialize

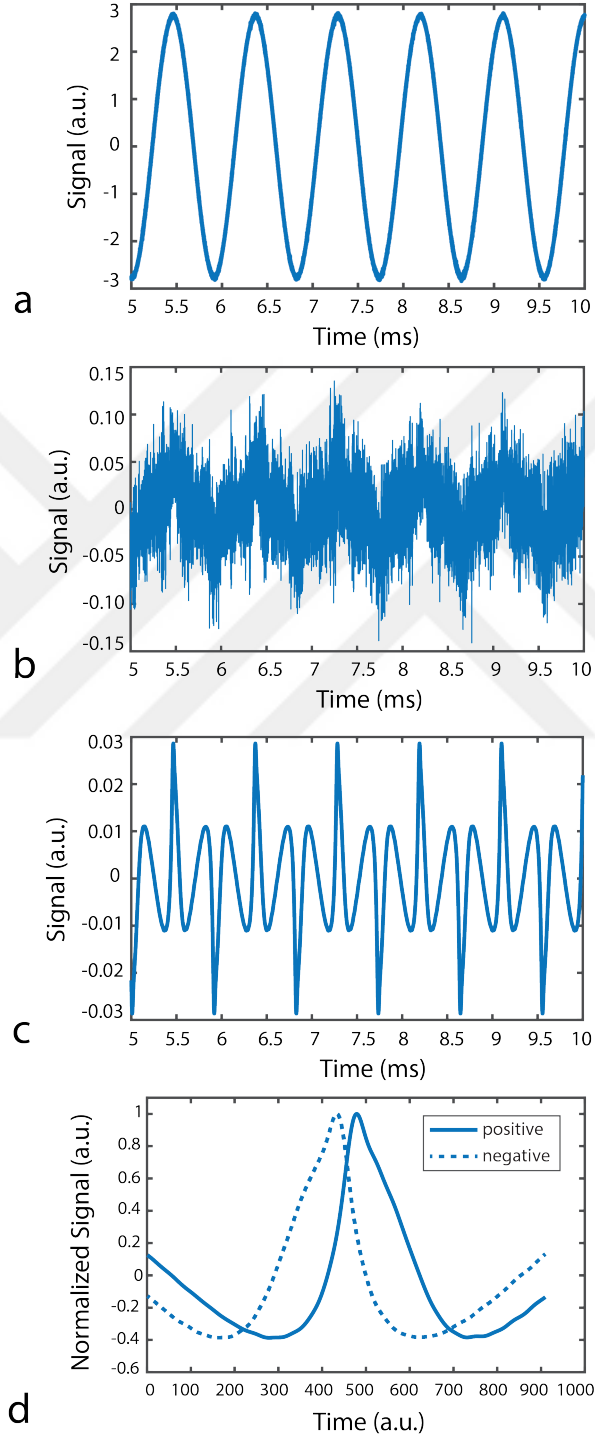


Figure 3.6: Acquired data (a) without baseline subtraction and (b) with baseline subtraction. (c) The resultant signal after choosing the higher harmonics of the drive field frequency in Fourier domain and setting all other frequencies to zero. After that a low-pass filter was applied in time domain. (d) An arbitrary period from the signal in (c) is displayed to show that it contains the nanoparticle relaxation effect. The graphs have the same arbitrary unit.

the phase lag estimation. In the case of relaxation, however, the signal peaks are inherently delayed in time with respect to the half-cycle centers.

Here, the relaxation time constant and the system delays were estimated simultaneously from the received signal, without any prior information. Accordingly, a sweep of phase lags, ϕ , between 0 and π were applied to the received signal and the signal was divided into positive/negative half cycles for each phase lag case. The relaxation time constant, τ , was estimated from these half cycles as described in Subsection 2.3. The signal was then Wiener deconvolved by the relaxation kernel $r(t)$ given in Eq. 2.12. A necessary condition for the successful implementation of the deconvolution step is to have sufficiently high SNR [49], which was achieved via the data processing steps outlined in Subsection 2.3. Next, the root-mean-squared error (RMSE) between the deconvolved positive half cycle, $\hat{s}_{(pos,ideal)}$, and mirrored negative half cycle, $\hat{s}_{(neg,ideal,mirr)}$, was computed. This step was to check whether the mirror symmetry was restored after deconvolution. Finally, the $\{\tau, \phi\}$ pair that minimized RMSE was chosen as the solution, i.e.,

$$\{\hat{\tau}, \hat{\phi}\} = \underset{\{\tau, \phi\}}{argmin} \int |\hat{s}_{pos,ideal}(t) - \hat{s}_{neg,ideal}(t)|^2 dt \quad (3.1)$$

The restoration of mirror symmetry via this technique was confirmed via visual inspection of results on randomly selected experimental data. The tails of the half cycles were excluded from the RMSE calculation step, as they corresponded to the lowest SNR regions of the signal. Accordingly, 15% of the signal was cut from both sides of the half cycles during RMSE calculation. This choice is further explained in Section 3.5. Finally, as each experiment had three repetitions, the mean value and standard deviations across these repetitions were computed for each viscosity level at each drive field strength and frequency.

3.5 Influence of Tail Truncation on Estimated Time Constants

The model in Eq. 2.11 and 2.12 is phenomenological, i.e., it is based on extensive experimental work that demonstrates a good fit to this model [42]. If this model could mimic the relaxation behaviour perfectly, deconvolution with the correct relaxation kernel would restore mirror symmetry completely. As shown in Fig. 2.3(c), the half cycles after deconvolution display close to perfect mirror symmetry, notwithstanding a small region of mismatch at the signal peak locations. The mismatch in the peaks could be avoided by assigning more weight to the goodness-of-fit at the center of half cycles. Doing so, however, would worsen the overlap in the remaining portions of the half cycles.

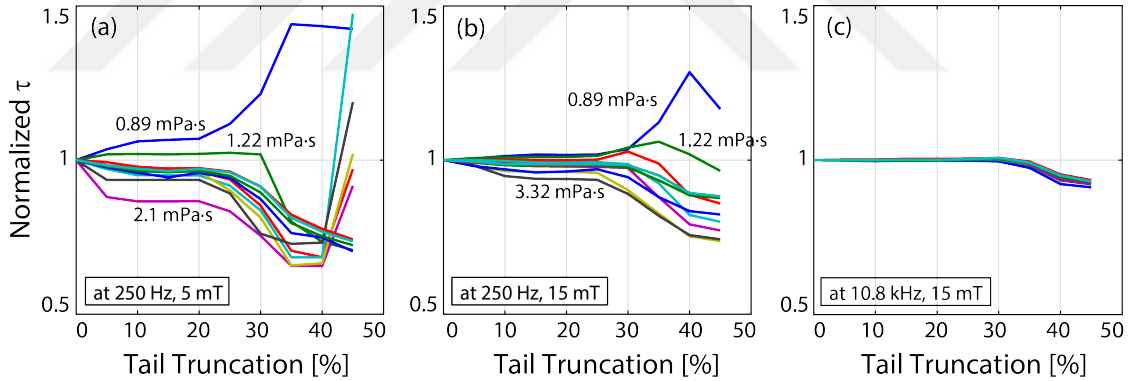


Figure 3.7: Influence of tail truncation on the estimated relaxation time constants. If the relaxation model worked perfectly, these curves would be horizontally flat, yielding constant τ estimation independent of truncation percentage. At low drive field amplitude and frequency as in (a), large truncation percentage yields diverging results, whereas zero truncation shows a slight variation from the expected flat response. In contrast, at high drive field amplitude and frequency as in (c), the estimations remain constant up to 35% tail truncation. In all cases, tail truncations between 10%-20% yielded constant τ estimations. Results are for nanomag-MIP nanoparticles.

The influence of truncating different percentages of the deconvolved half-cycle tails during RMSE calculations was analyzed. For example, when 100% of the half cycles are utilized (i.e., 0% truncation), the RMSE calculation takes into account the overlap of both the tails and the center of the half cycle. Alternatively, one

can truncate a percentage of the tails before calculating the RMSE, such that the overlap of the central regions becomes the main target. Fig. 3.7 shows the effect of tail truncation percentage on the estimated relaxation time constants. The values are normalized to show the overall trends. Here, a 10% truncation indicates 10% of half cycles truncated from both tails, with the remaining central 80% utilized in RMSE calculation. If the relaxation model worked perfectly, one would expect to see a flat τ vs. truncation percent curve, i.e., estimated τ would be independent of the truncation percentage. This is in fact the case at high frequency and high field amplitude, as seen in Fig. 3.7(c). At low frequencies and low field amplitudes, however, a large truncation percentage yields diverging results. These results indicate that the exponential model is a better fit at high drive field frequencies and amplitudes. In all cases considered in this work, estimation remained flat for truncation percentages ranging between 10% and 20%. Accordingly, a truncation percentage of 15% was utilized in all τ estimations presented in this work.

Chapter 4

Results

Overall, 768 distinct experiments were performed. For sample set #1, nanomag-MIP nanoparticles at 11 viscosity levels were measured at 3 different field strengths, at 4 different frequencies, and with 3 repetitions (396 experiments). For sample set #2, nanomag-MIP nanoparticles at 20 viscosity levels were measured at a single field strength, at 4 different frequencies, and with 3 repetitions (240 experiments). For sample set #3, VivoTrax nanoparticles at 11 viscosity levels were measured at 2 different field strengths, at 2 different frequencies, and with 3 repetitions (132 experiments).

4.1 Effect of Viscosity on MPS Signal

First, the effects of viscosity on the MPS signal were investigated at different drive field amplitudes and frequencies. Fig. 4.1(a) compares two cases of MPS signals: at viscosity levels of 0.89 mPa·s (nanoparticles in water) and 15.33 mPa·s (nanoparticles in water/glycerol mixture of 68% glycerol by volume), both acquired at 1.1 kHz and 15 mT drive field. Considering that both samples had the same iron content, one can note that the signal at low viscosity level is reduced when compared to that at high viscosity. In addition, the response at low

viscosity is visibly wider, indicating an increased relaxation time constant. The estimated time constants were $\tau = 33 \mu\text{s}$ and $\tau = 24 \mu\text{s}$ for $\eta = 0.89 \text{ mPa}\cdot\text{s}$ and $\eta = 15.33 \text{ mPa}\cdot\text{s}$, respectively. Fig. 4.1(b) compares the same samples at 10.8 kHz and 15 mT drive field. This time, in contrast to the results at 1.1 kHz, the signal at high viscosity is slightly wider than the one at low viscosity. The estimated times constants were $\tau = 3.5 \mu\text{s}$ and $\tau = 3.6 \mu\text{s}$ for $\eta = 0.89 \text{ mPa}\cdot\text{s}$ and $\eta = 15.33 \text{ mPa}\cdot\text{s}$, respectively.

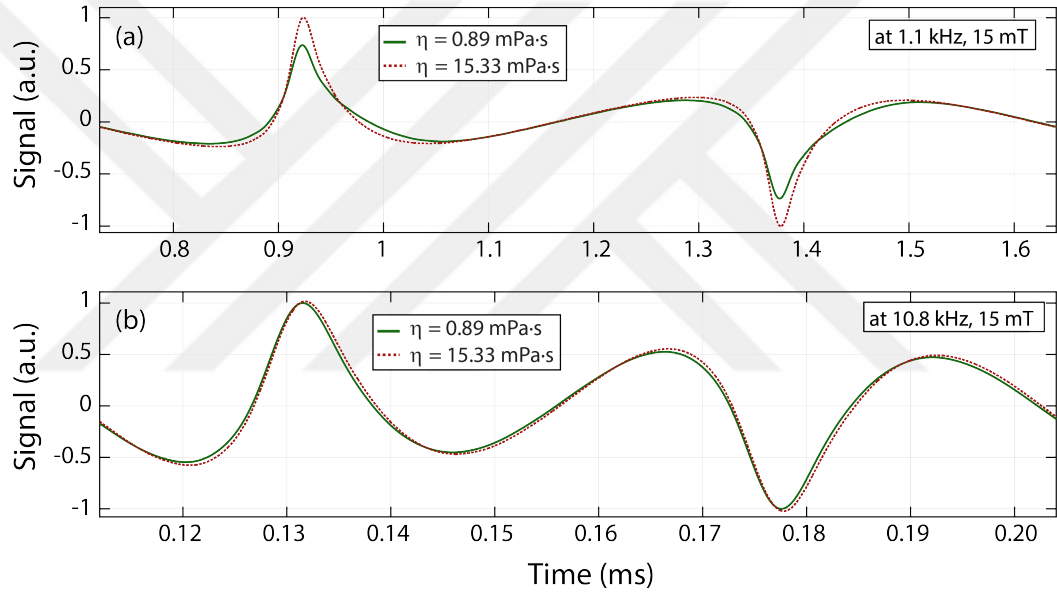


Figure 4.1: Effects of viscosity on nanoparticle signal. (a) The measured signal of nanomag-MIP nanoparticles at 1.1 kHz and 15 mT drive field are shown for low viscosity (0.89 mPa·s) and high viscosity (15.33 mPa·s) cases. The low viscosity case displays a wider response with reduced peak amplitude. The calculated relaxation time constant for these two cases were $\tau = 33 \mu\text{s}$ and $\tau = 24 \mu\text{s}$, respectively. (b) The same samples were measured at 10.8 kHz and 15 mT drive field, yielding $\tau = 3.5 \mu\text{s}$ and $\tau = 3.6 \mu\text{s}$, respectively. Here, the high viscosity case has a slightly wider response than the low viscosity case.

4.2 Effect of Drive Field Amplitude

The relaxation times constants were estimated for all MPS signals acquired. The results for sample set #1 (with 11 different viscosity levels) at four different drive field frequencies and three different drive field strengths are presented in Fig. 4.2

and Fig. 4.3. Error bars denote the mean estimated time constants and standard deviations over three repetition experiments. In Fig. 4.2, for fixed frequency, estimated time constants decrease as field strength increases. The relaxation time constant as a function of viscosity displays a non-monotonic trend. Especially at low drive field frequencies and amplitudes (e.g., at 250 Hz and 5 mT), τ first increases sharply and then decreases with increasing viscosity, finally converging to a roughly constant value. At 10.8 kHz, on the other hand, τ slowly but steadily increases with increasing viscosity.

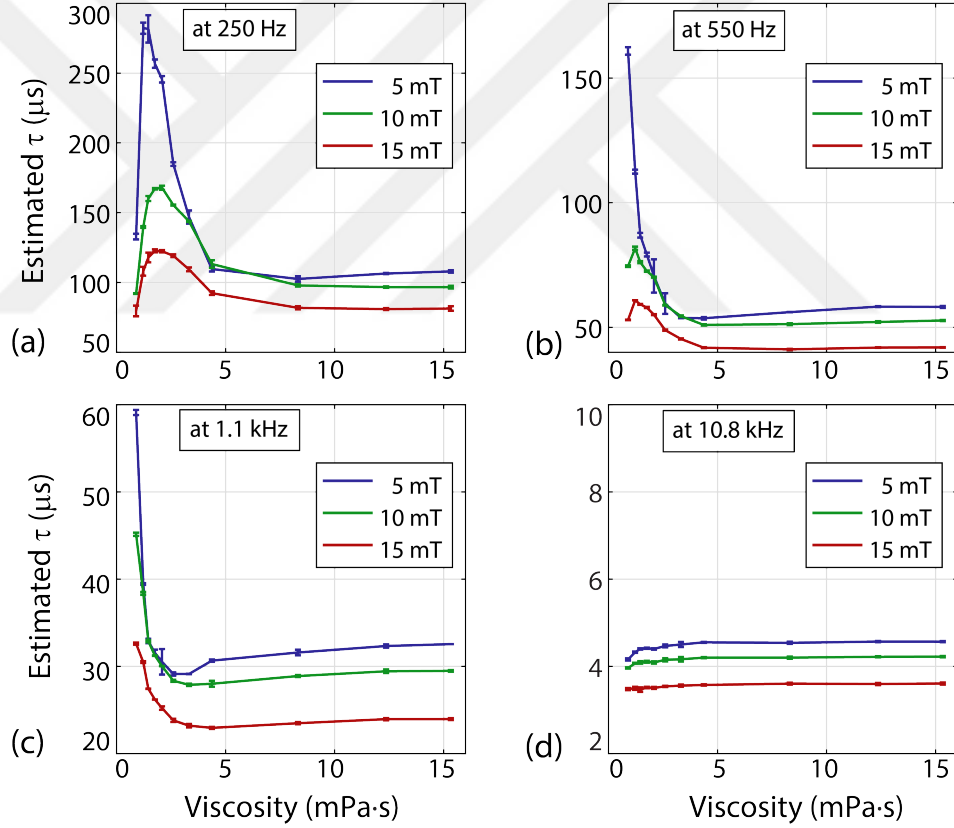


Figure 4.2: Relaxation time constants as a function of viscosity, at four different drive field frequencies for sample set #1 (nanomag-MIP at 11 different viscosities ranging between 0.89 $\text{mPa}\cdot\text{s}$ to 15.33 $\text{mPa}\cdot\text{s}$). Error bars denote the mean values and standard deviations over three repetition experiments.

4.3 Effect of Drive Field Frequency

In Fig. 4.3, the same data are re-plotted, this time to highlight the effect of drive field frequency on estimated time constants. In Fig. 4.3(a) to 4.3(c), the time constants decrease with increasing frequency. Interestingly, one can see that there is a global trend in these curves, such that the same τ vs. viscosity curve is scaled down and shifted towards the left as frequency increases. Fig. 4.3(d) to 4.3(f) present these results with a normalized time axis, where the estimated time constants are normalized by the period of the drive field at each frequency, and multiplied by 100. Effectively, this unified y-axis gives an indication of the percentage effect of relaxation delays at each frequency. Overall, for fixed drive field amplitude, the relaxation effects are more prominent at higher frequencies. Exceptions to this trend are low viscosity and low drive field strengths, where the trends can be reversed (e.g., at 5 mT for viscosities lower than 3 mPa·s).

To investigate the biologically more relevant viscosities of up to 4 mPa·s, the time constants for sample set #2 with 20 different viscosity levels between 0.89 mPa·s and 4 mPa·s were estimated at four different drive field frequencies with 15 mT field strength. Another motivation for this second set of experiments was to ensure that the τ vs. viscosity curves did not exhibit erratic jumps with a slight variation in viscosity. The results given in Fig. 4.4(a) are consistent with the low viscosity portions of the results in Fig. 4.3(c), as no erratic behaviour is observed. Note that the estimated time constants at 2.5 mPa·s and 3.6 mPa·s showed slight deviations from the overall trends. These deviations could stem from pipetting errors during the mixing of water and glycerol, as a small variation in glycerol percentage can significantly alter the viscosity level of the mixture. In Fig. 4.4(b), the relaxation time constants are normalized by that of nanoparticles in water (i.e., the lowest viscosity of 0.89 mPa·s), so that the percentage change in τ can be visualized. At 250 Hz, τ first increases by 40% at around 2.2 mPa·s, then gradually decreases. At 1.1 kHz, τ monotonically decreases, showing a 32% reduction at around 4 mPa·s. At 10.8 kHz, on the other hand, τ increases by only 2% within this viscosity range.

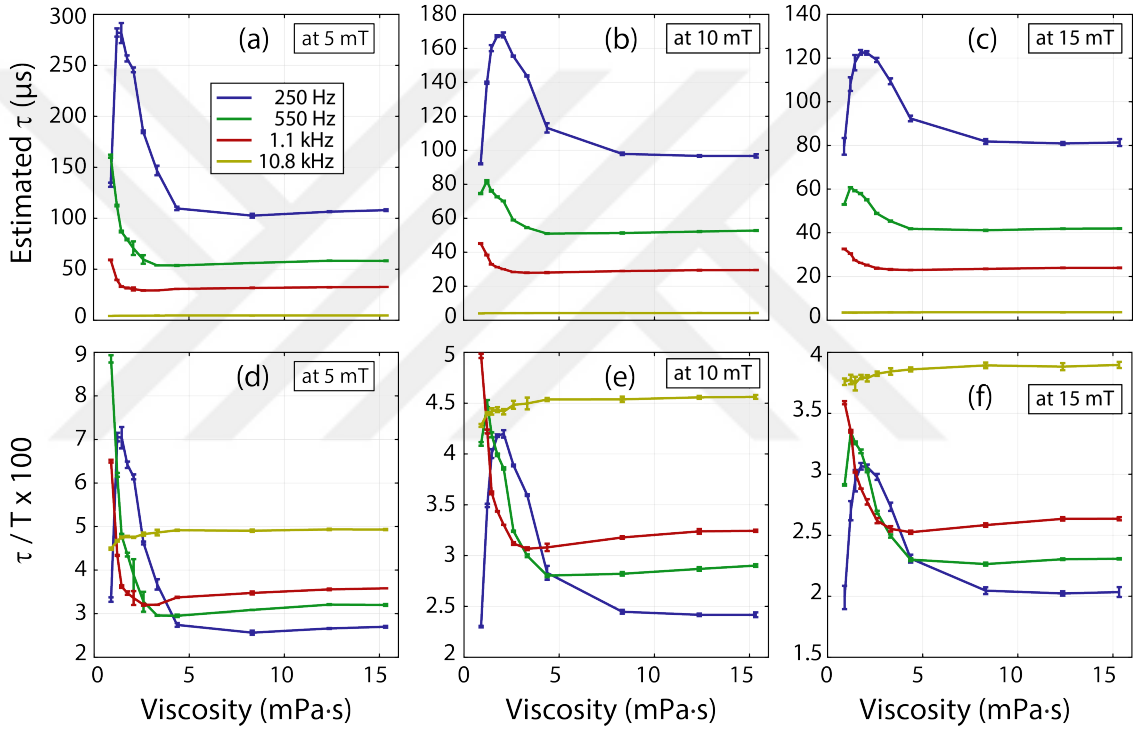


Figure 4.3: Relaxation time constants as a function of viscosity, at three different drive field strengths for sample set #1 (nanomag-MIP at 11 different viscosities ranging between 0.89 mPa.s to 15.33 mPa.s). Error bars denote the mean values and standard deviations over three repetition experiments. (a) to (c) The same data as in Fig. 4.2, re-plotted to emphasize the effect of drive field frequency at a fixed field strength. (d) to (f) The results in a unified y-axis, where the estimated time constants are normalized by the period of the drive field at each frequency, multiplied by 100.

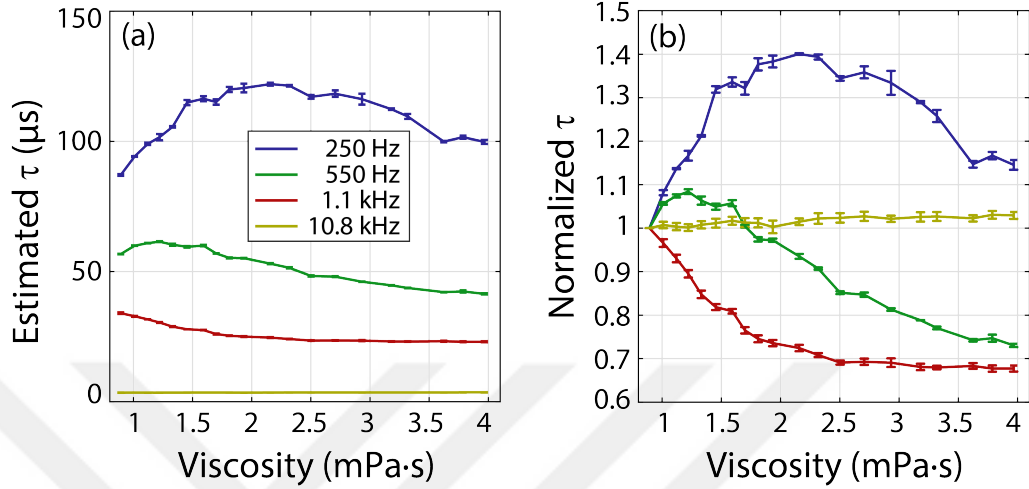


Figure 4.4: Relaxation time constant vs. viscosity for the biologically more relevant range of viscosities, for sample set #2 (nanomag-MIP at 20 different viscosities ranging between 0.89 $\text{mPa}\cdot\text{s}$ to 3.97 $\text{mPa}\cdot\text{s}$), measured at four different frequencies at 15 mT field strength. Error bars denote the mean values and standard deviations over three repetition experiments. (a) Estimated time constants and (b) time constants normalized by that of nanoparticles in water to highlight the percentage change in τ vs. viscosity.

4.4 Comparison of Different Nanoparticles

To provide a better understanding of the effects of viscosity on different nanoparticles, experiments were performed with VivoTrax nanoparticles at 11 different viscosity levels (sample set #3). The results are given in Fig. 4.5, in comparison with nanomag-MIP nanoparticles under the same drive field conditions. Accordingly, the estimated time constants for VivoTrax are larger than those for nanomag-MIP, in general. Importantly, the relaxation time constants for VivoTrax display a non-monotonic trend as a function of viscosity, as was the case for nanomag-MIP. Furthermore, the global trend seen in nanomag-MIP is also observed for VivoTrax: the same τ vs. viscosity curve is scaled down and shifted towards the left with increasing frequency, as can be seen comparing Fig. 4.5(a) with 4.5(c).

During all experiments, the ambient temperature inside the measurement chamber remained between 23-36°C, which corresponds to a minor 4% variation

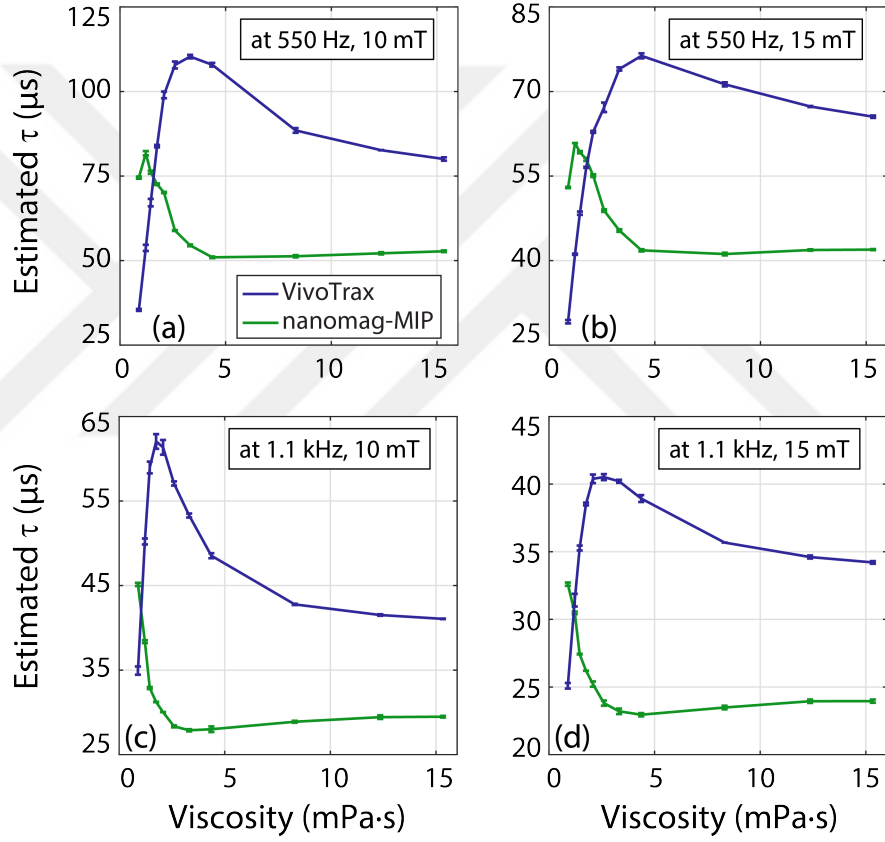


Figure 4.5: Effects of viscosity on the relaxation time constants of two different nanoparticles. VivoTrax and nanomag-MIP nanoparticles were measured at four different drive field conditions, and at 11 different viscosities ranging between 0.89 mPa·s to 15.33 mPa·s. Error bars denote the mean values and standard deviations over three repetition experiments.

in absolute temperature in Kelvins. This variation was due to resistive heating of the drive coil under currents reaching 22 A, which causes a power dissipation of about 350 Watts. Nonetheless, during signal acquisition, each sample tube stayed in the measurement chamber for only 5 seconds at a time. In a separate control experiment, we also measured the temperature inside the sample tubes for the case when the chamber temperature was at 36°C. Accordingly, during the 5-second interval that the sample was exposed to convective heat transfer, its temperature only changed by 0.3-0.4°C. Hence, we do not expect any temperature bias for the results reported in this work.

Chapter 5

Discussion and Conclusion

Viscosity sensing is currently infeasible with ultrasound, magnetic resonance imaging, or other preclinical imaging techniques. This work demonstrated the potential of MPI for viscosity mapping through the estimation of the nanoparticle relaxation time constant. As shown in the results in Fig. 4.2 to 4.4, the trend in the τ vs. viscosity curves strongly depend on the drive field strength and frequency. Ideally, a quantitative viscosity mapping technique should provide a one-to-one mapping of the measured parameter to the viscosity level. Such a technique should also show a sufficiently large variation of the measured parameter as a function of viscosity, such that the viscosity can be determined accurately. For the biologically relevant range investigated in Fig. 4.4, these requirements are best satisfied by the measurements at 1.1 kHz, where the relaxation time constant monotonically decreases with increasing viscosity and displays greater than 30% variation. At 10.8 kHz, on the other hand, the time constant remains almost constant at different viscosity levels. These findings imply that the regular MPI operating frequencies of 25 kHz or 150 kHz are not optimal for viscosity mapping purposes. For the very low drive field frequencies around 250 Hz, on the other hand, τ is a non-monotonic function of viscosity, which would create an ambiguity in viscosity mapping. A potential solution at those frequencies could be to perform measurements at two different field strengths to determine the viscosity level.

The well-known Brownian relaxation time constant of nanoparticles is given as $\tau = 3V\eta/k_B T$, where the time constant increases linearly with viscosity, which is clearly not the case for the results shown in this work. It should be emphasized that the Neel and Brownian time constants are valid for the zero field case only, i.e., when an applied external magnetic field is suddenly removed. Hence, they do not model the more complex cases such as a sinusoidal external field. For those cases, simulation results solving Landau-Lifshitz-Gilbert equation or Fokker-Planck equation were presented [34, 35]. A previous method considered a dynamic magnetization model, where the ratio of 5th to 3rd harmonics of nanoparticle magnetization was utilized to probe viscosity. Accordingly, a non-monotonic trend was observed as a function of viscosity, both in simulations as well as in experiments with Feridex in various gelatin concentrations [36]. Here, the relaxation time constant in Eq. 2.11 and Eq. 2.12 is a lumped parameter that models the blurring effect in the time-domain MPI signal, without considering the underlying physical mechanisms. Still, the result in Fig. 4.1(a) that displays a visibly narrower response at higher viscosity level is counter intuitive, as one would expect a slower nanoparticle response with increasing viscosity. This could potentially be due to the chemical differences between the water solution vs. the high viscosity water/glycerol mixture, which can potentially affect the interaction of the nanoparticles with each other and with the medium. Experiments in solutions with similar viscosities but with different chemical properties could help in understanding this effect.

Previous studies have demonstrated that the MPI signal properties strongly depend on the nanoparticle type [50]. The experiments here were performed using nanomag-MIP and VivoTrax, where both nanoparticles displayed similar non-monotonic trends. Interestingly, the response of VivoTrax at 1.1 kHz and 10 mT was very similar to the response of nanomag-MIP at 550 Hz and 15 mT, as can be seen in Fig. 4.5. These similarities imply that the same physical mechanism is taking place for both nanoparticles, albeit at different strengths. It should be noted that both of these nanoparticles are multi-core nanoparticles with clusters made up of smaller nanoparticles [51]. It remains to be shown whether similar trends are valid for single-core nanoparticles with large diameters.

One important factor to take into account during viscosity mapping with the proposed technique is the homogeneity of the drive field. As seen in Fig. 4.2, for a fixed frequency, changes in drive field amplitude significantly change the estimated relaxation time constant. Hence, to ensure a quantitative mapping of the viscosity during 3D imaging applications, either the drive field needs to be highly homogeneous within the field-of-view (FOV), or one needs to know the field map within the FOV. Another important consideration is the human safety limits of the applied drive fields [52, 53, 54]. According to the results shown in this work, frequencies around 1 kHz have the potential to provide a one-to-one viscosity mapping capability. For 1 kHz, the magnetostimulation safety limit in the human torso can roughly be estimated as 20 mT peak [52]. Hence, the results presented at 1.1 kHz and 15 mT-peak field strength are actually applicable according to the human safety limits of MPI. It should be noted that operating at a lower frequency than the current MPI frequencies (25 kHz, or lately 150 kHz) would have both advantages and disadvantages in terms of image quality. Previous work has shown that peak signal values changed approximately linearly with the drive field frequency and amplitude [55, 43]. Similarly, in our experiments, the received signal strength (before the low-noise preamplifier) at 1.1 kHz was around 10 times lower than that at 10.8 kHz for the same drive field amplitude (results not shown). Hence, the image SNR would decrease when operating at lower frequencies. On the other hand, lower drive field frequencies could yield better resolution images, as previously demonstrated via resolution measurements in a relaxometer setup [43]. Likewise in our experiments, the nanoparticle signal at 1.1 kHz had a narrower peak than that at 10.8 kHz for the same drive field amplitude, as seen in Fig. 4.1.

At all frequencies tested in this work, the relaxation time constants showed an asymptotic convergence for viscosity levels above 5 mPa·s, remaining almost flat above 8 mPa·s. These results indicate that viscosity mapping with this technique may not be feasible at very high viscosity levels. However, there is good evidence in the literature that viscosities below 5 mPa·s are biologically more relevant. For example, it has been previously reported that hematocrit level

exceeding 46% ($> 2.8 \text{ mPa}\cdot\text{s}$) is considered as an important risk factor for cerebral infarction, atherosclerosis in the arteries, and hypertension [16]. In another study, elevated viscosity levels from $1.48 \text{ mPa}\cdot\text{s}$ to $1.71 \text{ mPa}\cdot\text{s}$ due to myocardial infarction was reported [18]. These viscosity levels are within the mapping capabilities of the proposed technique, demonstrating the potential of MPI imaging to provide critical functional information.

To conclude this thesis, the viscosity mapping capability of MPI was demonstrated through proof-of-concept experiments in an MPS device. The technique used to correlate viscosity with the relaxation time constant takes advantage of the underlying mirror symmetry in the time-domain MPI signal. The experimental results at various drive field frequencies suggest that a relatively low drive field frequency of around 1 kHz is promising for a one-to-one viscosity mapping. Future imaging applications exploiting the MPI signals dependence on local viscosity of the nanoparticles will benefit from the results provided in this work.

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Appendix A

Detailed Signal Processing Analysis

In this Appendix, an arbitrary data is selected to show the detailed signal processing analysis. Selected data is at the viscosity level of 1.22 mPa·s, under the drive field frequency and amplitude of 1.1 kHz and 15 mT. Initially, acquired nanoparticle signal is shown in Fig. A.1(a). Here, this signal contains direct-feedthrough signal from the drive field which surpasses the nanoparticle signal. The frequency domain of this signal is shown in Fig. A.1(b). f_0 is the drive field frequency and dashed circle in red shows the higher nanoparticle harmonics.

Acquiring a background signal, and subtracting it from the nanoparticle signal shown in Fig. A.1(a) yields the signal given in Fig. A.2(a). Note that the signal magnitude is dropped from around 4V to 200mV due to the removed direct-feedthrough signal. In Fig. A.2(b), corresponding frequency domain harmonics are shown. Here, at the drive field frequency and amplitude of 1.1 kHz and 15 mT, the spectra of the nanoparticle response has around 50 harmonics (upto 55 kHz). The self-resonance of the receive coil is at around 300 kHz and it does not contaminate the higher harmonics of the nanoparticle response. However, in the case of drive field frequency at 10.8 kHz, it contaminates the signal after 18th harmonic.

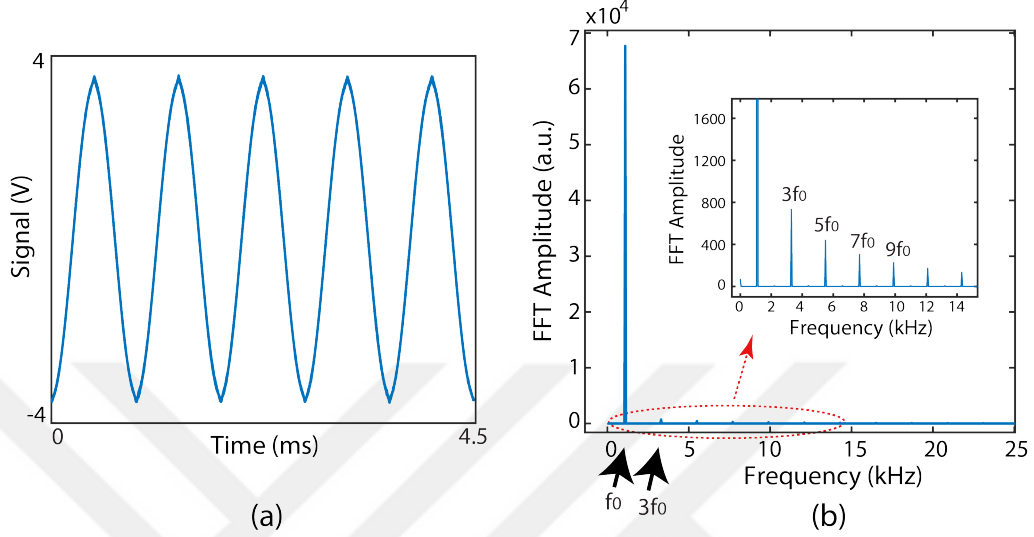


Figure A.1: Received nanoparticle signal at the viscosity value of 1.22 mPa·s, under the drive field frequency and amplitude of 1.1 kHz and 15 mT. (a) shows the time domain signal and (b) shows the corresponding frequency domain of this signal. The direct-feedthrough contamination surpasses the nanoparticle signal. Red circle in (b) shows from the 3rd to 13th harmonics of the nanoparticle signal.

To remove the noise at non-harmonic frequencies and remaining direct feedthrough signal, frequency selection was performed by choosing the higher harmonics of the drive field frequency in Fourier domain and setting all other frequency components to zero. A further high-order zero-phase digital low-pass filter (LPF) was applied in time domain. The cut-off frequency of LPF corresponded to 50th harmonics for 1.1 kHz drive field. The filtered signal in time domain is given in Fig. A.3(a) along with its harmonics in frequency domain in Fig. A.3(b).

Once the signal is filtered, the relaxation effects are visible as previously shown in Fig. 2.3. Recovering the relaxation effect yields the corresponding relaxation time constant which is utilized to map the viscosities.

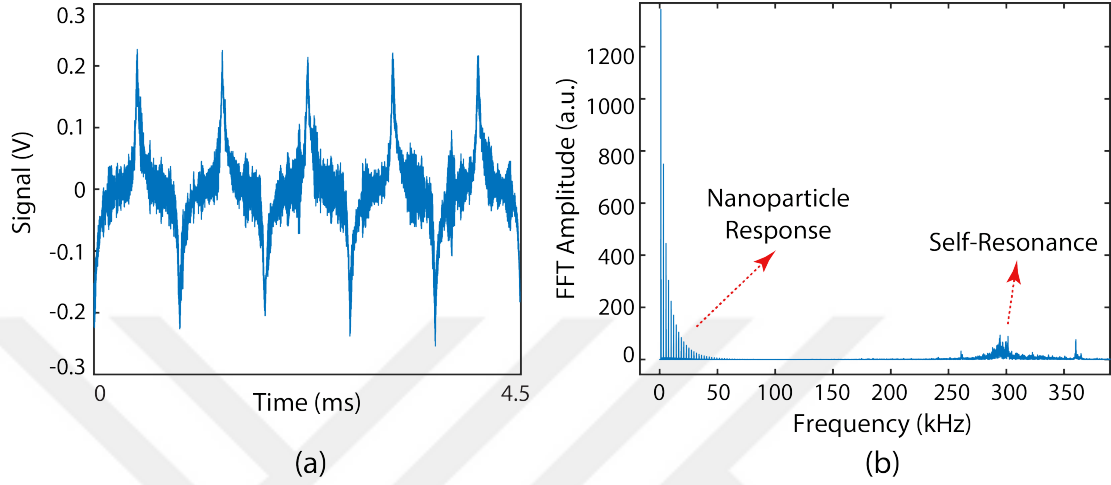


Figure A.2: Background signal is subtracted from the nanoparticle signal given in Fig. A.1. Now, the direct-feedthrough contamination is highly removed. The nanoparticle harmonics is shown in (b). Also in (b), self-resonance frequency of the receive coil is shown. The self resonance of the receive coil contaminates the higher harmonics of the nanoparticle response at the drive field frequency of 10.8 kHz.

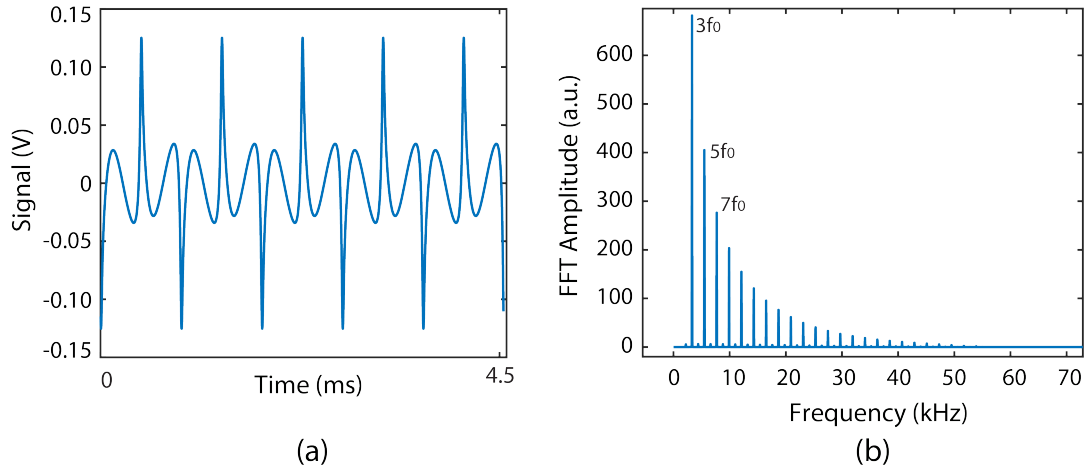


Figure A.3: Once the baseline-subtracted signal undergoes a two-stage filtering operation, the remaining direct-feedthrough signal is removed along with the noise in non-harmonic frequencies. The resulting nanoparticle signal shown in (a) has the relaxation effects. (b) shows the frequency domain representation of the time domain signal given in (a).