Corresponding Author: Sune Nørhøj Jespersen.

Mail: sune@cfin.au.dk

Incorporating white matter microstructure in the estimation of magnetic susceptibility in ex-vivo mouse brain

Anders Dyhr Sandgaard¹, Valerij G. Kiselev², Noam Shemesh³, Sune Nørhøj Jespersen¹,⁴

¹Center for Functionally Integrative Neuroscience, Department of Clinical Medicine, Aarhus University, Denmark

²Medical Physics, Department of Radiology, Faculty of Medicine, University of Freiburg, Freiburg, Germany

³Champalimaud Research, Champalimaud Centre for the Unknown, Lisbon, Portugal,

⁴Department of Physics and Astronomy, Aarhus University, Denmark

Keywords

1) Magnetic susceptibility, 2) Larmor frequency, 3) Magnetic microstructure, 4) Modelling, 5) Quantitative susceptibility mapping, 6) Mesoscopic Lorentz sphere
### Abstract

**Purpose:** To extend Quantitative susceptibility mapping (QSM) to account for local white matter (WM) microstructure and demonstrate its effect on ex-vivo mouse brain at ultrahigh field.

**Methods:** Previous studies have shown that the MRI measured Larmor frequency also depends on local magnetic microstructure at the mesoscopic scale. Here we include effects from WM microstructure, by using our previous results for the mesoscopic Larmor frequency of solid cylinders with arbitrary orientations to describe WM axons in terms of concentric cylinders. We demonstrate how to combine multi-gradient echo (MGE) and diffusion MRI (dMRI) images of ex-vivo mouse brains acquired at ultrahigh field (16.4T) to estimate an apparent scalar susceptibility without impractical sample rotations.

**Results:** We find the induced mesoscopic Larmor frequency due to WM microstructure to be substantial, with a magnitude up to 70% of the total frequency shift in highly anisotropic WM. This in turn changed the estimated susceptibility values by up to 56% in WM.

**Conclusion:** Microstructural field effects impact susceptibility estimates, and should not be neglected when imaging anisotropic tissue such as brain WM.
Introduction

Quantitative Susceptibility Mapping\(^1-^4\) (QSM) is a highly utilized MRI modality for mapping tissue susceptibility, with increased level of specificity compared to previous related modalities\(^5\). Its application in disease is highly promising for imaging changes in tissue iron, calcium and myelin\(^6-^9\). By exploiting that microscopic magnetic fields measured in systems such as isotropic liquids can be computed as a simple product between the elementary Lorentz-corrected dipole kernel\(^10\) and magnetization in Fourier space, a voxel-specific tissue magnetic susceptibility can be estimated from the gradient-recalled echo (GE) signal phase. However, one of the shortcomings of the current QSM framework is assuming that mesoscopic field effects associated with microstructure and anisotropic susceptibility are negligible. This assumption is especially challenged for white matter (WM), where field perturbations from WM axons depends on the orientation to the external field due to its magnetic and structural anisotropy\(^11-^14\). Revealing such effects typically requires active rotation of the sample with respect to the applied external magnetic field \(B_0\), which may not be practical in most biomedical scanners. In addition, WM orientation dispersion greatly affects mesoscopic frequency-patterns\(^15\), and can account for a substantial part of the total Larmor frequency\(^16\). This begs for QSM models incorporating microstructural effects of WM.

Recently, we outlined a framework describing the MRI measured Larmor frequency shift (MMLF)\(^15\). In the present work, we extend the framework towards accounting for mesoscopic contributions to capture effects from explicit magnetic microstructure surrounding each sampling point, as well as a macroscopic QSM-like contribution describing frequency effects from across the sample (see Figure 1 for an overview). We investigated microstructural effects for a population of infinitely long solid cylinders with scalar susceptibility and arbitrary orientation dispersion and found that the mesoscopic contribution depends on \(l = 2\) Laplace expansion coefficients, \(p_{2m}\), of the fiber orientation distribution function (fODF). These findings bridge an important gap between fully parallel or uniformly dispersed cylinders, previously used to describe microstructural field effects from cylinders\(^11-^14\), without the need to assume a low volume fraction\(^11\).

Here we address one of the shortcomings of QSM by incorporating mesoscopic frequency effects from WM microstructure. We extend our model\(^15\) for cylinders to multi-layered cylinders, and use it as a minimal biophysical model for WM microstructure, i.e., susceptibility anisotropy is assumed to be
subdominant and hence is neglected, just like in QSM. Next, we employ our framework for the MMLF to describe the voxel averaged Larmor frequency based on GE signal phase. We demonstrate our model by acquiring multi-echo GE (MGE) and diffusion MRI (dMRI) signals at ultrahigh field (16.4 T) of an ex-vivo mouse brain. Using structural information obtained from dMRI measurements to estimate the fODF, an apparent scalar susceptibility is extracted from the phase of the MGE signal without the need for impractical sample rotations. From this, a WM specific local mesoscopic contribution to the MRI Larmor frequency is estimated, representing a novel contrast based on combined information from susceptibility and fODF.

Theory

We start by outlining the system being considered, along with a brief summary of the framework for the MRI measured Larmor frequency\textsuperscript{15} (MMLF) based on the principle of coarse graining and by using a mesoscopic Lorentz sphere construction\textsuperscript{17–20}. Then we extend our solution for the Larmor frequency from infinite solid cylinders with arbitrary orientation dispersion to include multilayer cylinders (MLC) as can be seen in Figure 2.

System of consideration

We described the macroscopic sample of volume $V$ as a porous medium consisting of impermeable microscopic magnetic inclusions, e.g., myelin lipid bilayers. The spatial organization of the inclusions is represented by the microscopic indicator function $v(r)$, which is 1 inside inclusions and 0 otherwise. This defines the microstructure (depicted as cylinders in Figure 1D). We assume inclusions are weakly dia- or paramagnetic, and uniformly magnetized along the applied field $B_o = B_0 \hat{B}$, where $\hat{B}$ is a unit vector (as are all hatted vectors in what follows). The magnetization response is characterized by a microscopic scalar magnetic susceptibility $\chi(r) \propto v(r)$ ($|\chi|$~ ppm), given relative to the susceptibility of water. The magnetic susceptibility defines the magnetic microstructure\textsuperscript{15} in a similar manner.
**Figure 1: Model of the MRI Larmor frequency.**  
* A: Myelin-stained coronal slice of mouse brain.  
* B: The MRI measured Larmor frequency \( \Omega_{\text{MRI}}(\mathbf{R}) \), coarse grained on the mesoscopic scale and sampled at discrete points \( \mathbf{R} \). Sampling is described by the point-spread-function (PSF), here shown as a blue sinc-function, whose width is macroscopic. For a slowly varying magnetic microstructure, \( \Omega_{\text{MRI}}(\mathbf{R}) \) can be approximated by the following two contributions:  
  
* C, The macroscopic contribution approximated at the scale of the sampling resolution capturing contributions at macroscopic distances; and  
* D, the contribution from nearby magnetic microstructure within a mesoscopic Lorentz sphere. The latter contains here randomly placed multi-layered cylinders, one of which is depicted in E. Mouse brain image is reproduced from © 2011 Allen Institute for Brain Science, Allen Mouse Brain Connectivity Atlas, https://connectivity.brain-map.org.

**Modeling a population of multilayered cylinders**

As shown in previous studies\(^{18-22}\), the MMLF \( \Omega_{\text{MRI}}(\mathbf{R}) \) can be decomposed into two contributions

\[
\Omega_{\text{MRI}}(\mathbf{R}) = \Omega_{\text{Meso}}(\mathbf{R}) + \Omega_{\text{Macro}}(\mathbf{R}).
\]  

(1)
\( \Omega^{\text{Macro}}(R) \) captures the frequency induced by distant sources on the macroscale (Figure 1C), and depends on the given sample shape. \( \Omega^{\text{Meso}}(R) \) is the frequency induced by magnetic microstructure in the mesoscopic vicinity of \( R \) and depends on the local microstructure (Figure 1D). \( \Omega^{\text{MRI}}(R) \) is valid as long as the MRI measured Larmor frequency can be described by the first signal cumulant, which is valid in either static dephasing regime or diffusion narrowing regime\(^{23} \). Assuming that the magnetic microstructure varies slowly compared to the imaging resolution, with a locally uniform magnetic susceptibility (as shown in Figure 1A), then

\[
\Omega^{\text{Meso}}(R) \approx -\gamma B_0 \hat{B}^T \mathcal{X}(R) \mathcal{N}(R) \hat{B}, \quad \text{(Slowly varying microstructure).} \tag{2}
\]

Here \( \mathcal{N}(R) \) is the mesoscopic demagnetization tensor\(^{15} \) and depends only on structural correlations near \( R \). We previously derived \( \mathcal{N}(R) \) for a population of solid and infinitely long cylinders exhibiting arbitrary orientation dispersion\(^{15} \). In WM fibers, water resides not only outside cylinders, but also in the intra-axonal space and myelin bilayers. In appendix A1 we derive the extended cylinder model to include MLC (as shown in Figure 2) and show that \( \mathcal{N}(R) \) is in fact identical to the result for solid cylinders. This means that the mean Larmor frequency in each water compartment is indistinguishable from each other for this magnetic microstructure. The model-specific MRI Larmor frequency \( \Omega^{\text{MRI}}(R) \), Eq. (1), finally becomes

\[
\Omega^{\text{MRI}}(R) = \gamma B_0 \left( -\mathcal{X}(R) \frac{1}{3} \sum_{m=-2}^{2} p_{2m}(R) Y_{2m}(\hat{B}) + \hat{B}^T \sum_R \mathcal{Y}(R-R') \mathcal{X}(R') \hat{B} \right). \tag{3}
\]

Here \( \mathcal{X}(R) \) defines the mesoscopically averaged magnetic susceptibility, and \( \mathcal{Y}(R-R') \) the voxel-averaged dipole field centered at every sampling position \( R' \). The orientation dependence is captured by the \( l=2 \) Laplace expansion coefficients \( p_{2m}(R) \) of the fiber orientation distribution (fODF), measurable with dMRI\(^{24-26} \), and the \( l=2 \) spherical harmonics \( Y_{2m} \). Equation (3) differs from QSM by the presence of a mesoscopic contribution from local magnetic microstructure\(^{14,15,22} \), and by using a voxel averaged dipole field \( \mathcal{Y} \) as opposed to the elementary field\(^{4} \) \( \mathcal{Y} \). We have previously shown with simulations\(^{15} \) that both can have a substantial effect on estimating Larmor frequencies.
Next we demonstrate inverting Eq. (3) to output $\mathcal{P}(\mathbf{r})$ from real MRI measurements of an ex-vivo mouse brain, where $\Omega_{\text{MRI}}$ is estimated from the MGE signal phase, and $p_{2m}$ from dMRI.

**Figure 2:** Structural model of the WM mesoscopic environment. Each fiber is modelled as $M$ concentric cylinders of radii $r_j$ to $R_j$ (small/capital letters indicate inner/outer radii) with $j = 1, \ldots, M$. The cross-sectional volume fraction of the $m$'th fiber is $\zeta_m = \pi \sum_j \left( R_j^2 - r_j^2 \right)$. The mesoscopic environment consists of $N$ fibers with overall cross-sectional volume fraction $\zeta = \sum_m \zeta_m$ and a given orientation dispersion assumed to be independent of fiber positions and radii. Cylinders are impermeable with water uniformly distributed intra- and extra-cylindrical, and in between bilayers.

**Methods**

**Ex-vivo brain imaging**

All animal experiments were preapproved by the competent institutional and national authorities and carried out according to European Directive 2010/63.
**Animal preparation**

Animal experiments were performed on a perfusion-fixed C57BI6 mouse brain. Briefly, the mouse was euthanized prior to the experiment with pentobarbital, transcardially perfused with phosphate-buffered saline (PBS) followed by a 4% paraformaldehyde (PFA) solution. The brain was then extracted and stored in 4% PFA. Before imaging, the brain was washed with PBS to minimize relaxation-effects induced by the fixative\textsuperscript{27}. The brain was subsequently placed axially in a 10 mm NMR tube and filled with Fluorinert (Sigma Aldrich, Lisbon, Portugal).

**MRI experiments**

Experiments were performed on a 16.4 T Bruker Ascend Aeon (Bruker, Karlsruhe, Germany) interfaced with an Avance IIIHD console and a 10 mm Micro5 probe equipped with gradients capable of delivering up to 3 T/m in all directions. Remmi sequences (Remmi) were used to acquire 3D gradient-recalled multi-echo images (MGE) and 3D dMRI images. For all acquisitions, repetition time was kept at 20 ms, flip angle at 20 degrees and bandwidth of 150 kHz. The Field-Of-View for these 3D acquisitions was 10.2×17.0×10.2 mm\(^3\), matrix size 102×170×102 which resulted in an isotropic resolution of (100 µm\(^3\)). For MGE, the echo times were 1.75, 3.5,…, 35 ms, while dMRI was acquired at 11, 12.55,…, 19.75 ms. Two experiments with four averages were acquired for the MGE, while one experiment with 1 average was performed for dMRI. dMRI was acquired with b-values ranging from 1 to 3 ms/µm\(^2\), with 30 directions. In another experiment with identical acquisition parameters, the diffusion parameters were set to b=5 ms/µm\(^2\) and 10 ms/µm\(^2\) measured along 75 directions. Diffusion times for all dMRI experiments were \(\delta / \Delta = 3/6\) ms. The sample was kept at 37° C during acquisition. Acquisition time was 2 hours for MGE and 53 hours for dMRI.

**Data processing**

Data processing was done in Matlab (The MathWorks, Natick, MA, USA). All complex MRI images were denoised using tensor MP-PCA\textsuperscript{28,29} with a window size of [7 7 7], and subsequently Gibbs-unrung\textsuperscript{30} using the complex denoised images.
**MGE pipeline**

The signal phase was unwrapped using SEGUE\textsuperscript{31}, and the Laplacian Boundary Value method (LBV) was utilized for background field removal\textsuperscript{32}. The first 5 echo times of the pre-processed phase was then fitted to a straight line, and the slope was used to approximate the Larmor frequency $\tilde{\Omega}_\text{MRI}$. Figure 3 gives an overview of the MGE pipeline showing both raw images, and the different processing steps for the phase.

![Figure 3: Overview of pipeline for MGE processing. All the complex MGE images were MP-PCA denoised, and Gibbs-unrung. The complex phase was extracted, unwrapped and background-field corrected, and subsequently fitted to extract $\tilde{\Omega}_\text{MRI} \cdot \tilde{\Omega}_\text{Background}$ shows the subtracted background frequency. Representative signal magnitude (left plot) and unwrapped and background-field corrected phase (right plot) are plotted for a white matter (cingulum in blue) and gray matter (thalamus in orange) voxel, respectively. Magnitude is shown in semi-log scale to illustrate the mono-exponential behavior of both signals are predominantly mono exponential. The phase behaves linearly in both WM and GM.](image)

**dMRI pipeline**
Figure 4 gives an overview of the dMRI pipeline. We averaged the dMRI across all echo times using singular value decomposition (SVD), to extract the diffusion-weighted signal component. After this we used the signal magnitude for fODF fitting. Due to sample drift between acquiring dMRI and MGE signals, a rigid co-registration of the dMRI signal to the MGE signal was found and used after fitting to align the fODF with the MGE signal.

**Figure 4: Overview of dMRI pipeline for data processing.** The Complex dMRI images were tensor MP-PCA denoised for each echo time individually followed by Gibbs-unringing. The signal magnitudes were then averaged over echo times using SVD, and the resulting images were then fitted with DKI or FBI for tensor or fODF estimation. Color-coded FA maps from diffusion tensor ($\hat{F}_{AD}$) and scatter matrices ($\hat{F}_{AT}$, cf. Eq. (4) in appendix A) from FBI are shown for various protocols. $S(b, \hat{g})$ denotes the dMRI signal with b-value along $\hat{g}$, here the in-plane direction $\hat{z}$ (green on sphere).

*fODF fitting algorithms*
The fODF Laplace coefficients $p_{lm}$ were estimated with Fiber Ball Imaging\textsuperscript{25} (FBI) which is based on the "Standard Model" of diffusion in WM\textsuperscript{24} (SM) and assumes the extra-axonal water signal is negligible for high gradients. We set the intra-axonal diffusivity to 3 $\mu$m$^2$/ms equal to free diffusion of water at 37 degrees. However, the effect of using a lower diffusivity on the fODF is small\textsuperscript{25}. We used $l_{\text{max}} = 6$ for all methods.

**Susceptibility fitting algorithm**

Here we used an iterative least squares algorithm (LSMR)\textsuperscript{33} to solve the inverse problem:

$$
\arg\min_{\mathbf{\chi}} \left\| \mathbf{\Omega}_{\text{MRI}}(\mathbf{R}) - \gamma \mathbf{B}_0 \mathbf{M}(\mathbf{R}) \left( \frac{1}{3} \sum_{m=2}^{2} p_{2m}(\mathbf{R}) \mathbf{Y}_{2m}(\hat{\mathbf{B}}) \mathbf{M}(\mathbf{R}) \mathbf{\Phi}(\mathbf{R}) + \hat{\mathbf{B}}^{\top} \sum_{\mathbf{R}'} \mathbf{Y}(\mathbf{R} - \mathbf{R}') \mathbf{M}(\mathbf{R}') \mathbf{\Phi}(\mathbf{R}') \hat{\mathbf{B}} \right) \right\|_{\ell_2}.
$$

(5)

$\mathbf{M}(\mathbf{R})$ is the sample mask enforcing both measurements and susceptibility sources to reside inside the brain, following background field removal\textsuperscript{34}. We regularized Eq. (5) by selecting the number of iterations that maximized curvature of the L-curve\textsuperscript{35,36}, which depicts the trade-off between the least squares norm and the norm of the solution. We found the optimal iteration number to be 9. This was optimal both with and without including the mesoscopic contribution. Susceptibility was not post-referenced as only one brain was analyzed.
Results

Ex-vivo brain imaging

Here we present the susceptibility maps from fitting using the MMLF, $\tilde{\Omega}_{\text{MRI}}$, and $p_{2m}$ from the fODF.

Magnetic susceptibility $\chi$

Figure 5 shows the susceptibility maps from two different coronal slices of the mouse brain. $\chi_{\text{QSM}+}$ denotes the susceptibility fit without mesoscopic contribution (i.e. $\tilde{\Omega}^{\text{Meso}}(R) = 0$). “+” is used to set it apart from standard QSM as we are using the voxel-averaged dipole field (6). $\chi_{\text{FBI}}$ denotes susceptibility fit including mesoscopic contribution estimated using the $p_{2m}$ of the fODF. The last 2 rows show the susceptibility difference $\delta \chi$ of $\chi_{\text{FBI}}$ at different $b$ compared to $\chi_{\text{QSM}+}$. We observed increased hyperintensity in highly anisotropic WM parallel to the main field (cf. Figure 4) such as the anterior commissure olfactory limb (ac), mammalithalamic tract (mtt), cerebral peduncle (cp) and the cingulum (cg) and dorsal fornix (df). In Table 2, we list differences between $\chi_{\text{FBI}}$ and $\chi_{\text{QSM}+}$ as the normalized root-mean-squared-error (RMSE), normalized to the susceptibility range of $\chi_{\text{QSM}+}$, for the ROIs shown in Figure 6. We also list the average fractional anisotropy $\text{FA}_T$ of the scatter matrix (cf. Eq. (7) in appendix A), reflecting the amount of orientation dispersion. Here the differences in WM susceptibility compared to QSM+ are found to be substantially different in highly anisotropic WM. This is especially clear in ac, cg and cp. These are all regions with high $\text{FA}_T$, which from Eq. (3) corresponds to a high positive mesoscopic contribution. Figure 6A illustrates the sorted susceptibilities for each ROI. Here it is evident that the susceptibility is increased by the mesoscopic contribution. The medial corpus callosum (cc2) showed a decrease in susceptibility as it is perpendicular to the main field, which produced a negative mesoscopic contribution.
Figure 5: Susceptibility maps of mouse brain at 100 µm isotropic resolution. Coronal slices from the medial and anterior parts of the brain are shown. $\overline{\chi}_{QSM+}$ corresponds to zero mesoscopic contribution (analogous to QSM), and $\overline{\chi}_{FBI}$ corresponds to a non-zero mesoscopic contribution calculated using this method.
Figure 6: Overview of susceptibility and Larmor frequency for different ROIs: cg: cingulum bundle, cp, cerebral peduncle, cc1: external capsule and corpus callosum, cc2: medial corpus callosum, ac: anterior commissure olfactory limb, fa: anterior forceps of corpus callosum, GM: anterior gray matter from primary motor area and primary somatosensory area. A gives a similar illustration of the susceptibility values in each ROI for each algorithm, sorted in ascending order with respect to $\chi_{\text{QSM+}}$. B gives an overview of the total Larmor frequencies $\Omega$ and its mesoscopic contribution $\Omega^{\text{Meso}}$. 

Sorted ROI Values
Table 2: Overview of normalized RMSE between susceptibility $\chi_{\text{FBI}}$ and $\chi_{\text{QSM+}}$. Mean and standard deviation of the fractional anisotropy of scatter matrices are also shown. The deviation reflects both noise and biological variation. RMSE is calculated in the ROIs shown in Figure 6, and normalized by the range of $\chi_{\text{QSM+}}$ in the ROI.

| ROI/Method | FBI (b=5) RMSE (%) | FA_T | FBI (b=10) RMSE (%) | FA_T |
|------------|---------------------|------|----------------------|------|
| cg         | 32                  | 0.47(0.09) | 33                  | 0.45(0.09) |
| cp         | 12                  | 0.66(0.07) | 12                  | 0.67(0.07) |
| cc1        | 28                  | 0.53(0.05) | 32                  | 0.54(0.05) |
| cc2        | 17                  | 0.50(0.08) | 20                  | 0.47(0.08) |
| ac         | 50                  | 0.78(0.06) | 56                  | 0.79(0.05) |
| fa         | 27                  | 0.52(0.07) | 30                  | 0.52(0.07) |
| GM         | 8                   | 0.22(0.06) | 9                   | 0.22(0.05) |

Larmor frequency contributions

Since the mesoscopic Larmor frequency is neglected in conventional QSM, it is of interest to evaluate the magnitude of this contribution to the measured Larmor frequency. By using the estimated susceptibility and $p_{2m}$ of the fODF as input, the macroscopic and mesoscopic contributions to the Larmor frequency were calculated using the forward relation in Eq. (3) and the result is shown in Figure 7. Table 3 summarizes the average values and their standard deviations in the ROIs shown in Figure 6C.
Figure 7: Macroscopic and mesoscopic Larmor frequencies (using $\chi_{\text{FBI}}$ at $b = 5 \text{ ms/µm}^2$). A: The frequencies are calculated using the forward relation in Eq. (3). The biggest mesoscopic contributions to the Larmor frequency are found in regions of highly anisotropic WM. This is especially visible near the cingulum and corpus callosum (green), cerebral peduncle (light blue), and anterior commissure olfactory limb (red) and mammalithalamic tract (dark blue), cf. Figure 6. B: 3D rendition of mesoscopic frequency $\Omega^\text{Meso}$ at $b=10\text{µm}^2/\text{ms}$ based on the maximum intensity projection. Color-coding reflects different the WM regions in A:
Table 3: The absolute mean of the average Larmor frequency from various ROIs. The mesoscopic contributions are shown for the fODF estimated at $b=5$ and $10\mu m^2/ms$. Frequencies are listed in hertz and calculated using the forward relation in Eq. (3). The difference in sign for $\Omega^{\text{Meso}}$ is because $\hat{B}^\top \mathbf{N}\hat{B}$ is positive, when axons are parallel to the main field $\hat{B}$, and negative if perpendicular.

| ROI/Method | FBI (b=5) | FBI (b=10) |
|------------|-----------|------------|
|            | $\Omega$  | $\Omega^{\text{Meso}}$ | $\Omega^{\text{Meso}}$ |
| cg         | -3.28(0.59) | 1.21(0.78) | 1.40(0.80) |
| cp         | -3.81(1.75) | 2.13(1.01) | 2.20(1.00) |
| cc1        | -3.53(0.78) | 0.12(0.36) | 0.10(0.41) |
| cc2        | 0.25(0.59)  | -0.13(0.08) | -0.13(0.07) |
| ac         | -7.60(1.21) | 5.44(1.55) | 5.20(1.36) |
| fa         | -2.51(0.57) | -0.56(0.21) | -0.58(0.23) |
| GM         | -0.77(0.26) | 0.07(0.07) | 0.08(0.08) |

Figure 7 and Table 3 clearly show that the mesoscopic contribution is non-zero in white-matter regions. For cp and ac, the magnitude of $\Omega^{\text{Meso}}$ was found to be around 60% and 70% of the total frequency, respectively. In comparison, $\Omega^{\text{Meso}}$ in gray matter (GM) was only attributed a small contribution around 10%. This is reasonable given that $p_{2m}$'s are found to be close to zero in the relatively isotropic GM. Figure 7B shows a 3D maximum intensity projection of $\Omega_{\text{MRI}}$, $\Omega^{\text{Meso}}$ and $\Omega^{\text{Macro}}$ (at $b=10\mu m^2/ms$). $\Omega^{\text{Meso}}$ has been color-coded to highlight the different WM tracts that appear more clearly, compared to $\Omega^{\text{Macro}}$. This demonstrates that $\Omega^{\text{Meso}}$ provides a novel contrast by combining information of both $p_{2m}$ and $\chi$. 
Discussion

Incorporation mesoscopic field effects into QSM

Estimating magnetic susceptibility is challenging for many reasons. For example, the MRI measured Larmor frequency shift $\tilde{\Omega}_{\text{MRI}}$ (MMLF) depends on the local organization of magnetized tissue at the mesoscopic scale. This particular contribution has so far not been included in standard QSM models, but can potentially be responsible for a frequency shift on the same order of magnitude as the contribution from neighboring voxels, the only contribution considered in QSM$^{15}$.

In this study we utilized our previously presented framework$^{15}$ for $\tilde{\Omega}_{\text{MRI}}$. This assumed the mesoscopically averaged (coarse-grained) Larmor frequency varied more slowly than the MRI sampling resolution. While this can be a reasonable assumption in many voxels, it is less valid at the interfaces between tissue types where the microstructure is not statistically homogenous. Our model also assumes that the measured signal phase is well described by its first cumulant. As the phase was found to be predominantly linear to an initial echo time of 1.75ms, we believe this to be a reasonable assumption. However, reaching such low echo times is challenging on clinical scanners.

Magnetic Microstructure Model

Previous studies have found evidence of macroscopic susceptibility anisotropy$^{37,38}$ in WM originating from an axial symmetric molecular susceptibility tensor of the myelin sheaths$^{18}$. This makes WM of particular interest as it also exhibits structural anisotropy$^{39,40}$, and since the Larmor frequency is sensitive to both types of anisotropy. Conveniently, the microscopic WM magnetic susceptibility can be written as a sum of isotropic and anisotropic susceptibility components$^{13,41}$, and so their contributions can be considered individually and added sequentially to the forward model between the Larmor frequency and susceptibility. The purpose of this study was to tackle the first of these two susceptibility contributions: namely the effect of a WM microstructure with a microscopic isotropic susceptibility. This was done by extending our analytical solid cylinder model to include multilayer cylinders. As a model for WM, this accounts for intra-axonal, extra-axonal, and myelin water between the myelin sheaths. The model presented here also incorporates an important microstructural feature into WM susceptibility estimation,
namely the effects of fiber orientation dispersion which can deviate substantially from fully parallel axons.

In isotropic tissue, e.g. randomly oriented WM axons or GM, the mesoscopic contribution is small as was indeed seen in GM tissue, cf. Table 3. In this case, no assumptions on the type of inclusions are made, as the Larmor frequency in such a voxel only depends on the macroscopic contribution, and the bulk susceptibility can thus represent any type or distribution of inclusions. However, in the case a WM voxel contains multiple sources, for example highly aligned myelinated axons and high levels of extraxonal iron, the model will incur an error on $\chi$. An error will also occur due to the presence of WM susceptibility anisotropy as this was not incorporated at this stage.

**Future extensions of the biophysical model**

The purpose of this study was to take a step towards explicitly incorporating microstructure in susceptibility estimation and demonstrate its estimation in real data. Hence, our model represents a minimal extension of a QSM-like model that incorporates mesoscopic effects associated with WM structural anisotropy and voxel averaging. The next step will be to include the contribution from microscopic WM susceptibility anisotropy. Additional model extensions could be effects from various randomly oriented magnetic inclusions with scalar susceptibilities to model the effect of non-myelin lipids, proteins, organelles etc., or anisotropic structures such as microtubules and unmyelinated axons. Such inclusion types could also be included in a potential model for gray matter.

**Fitting Algorithm**

In order to estimate susceptibility from Eq. (3), an LSRM algorithm iteratively solved the linear least squares problem. Optimal number of iterations was found using the L-curve heuristics. Since extracting $\vec{r}$ from $\vec{D}_{\text{MRI}}$ involves deconvolution with the dipole field, the problem is ill-posed in a similar manner as conventional QSM, due to the nature of the underlying elementary dipole field. This means that the linear system we aimed to solve was underdetermined. Combined with the presence of noise, this resulted in a very low iteration number. From Figure 6 we see that introducing a mesoscopic
contribution from WM microstructure increases the susceptibility in anisotropic white matter parallel to the main field (e.g., cingulum, cerebral peduncle and anterior commissure olfactory limb). As a low iteration number will penalize the norm of $\chi$, it also minimizes the effect of the mesoscopic contribution to $\chi_{\text{FBI}}$, and the solution will be closer to $\chi_{\text{QSM+}}$. Hence, reducing noise and/or overdetermining the fitting procedure by, e.g., acquiring images at multiple sample orientations, could reveal an even greater effect from WM microstructure.

Various preconditioning approaches exist to reduce the condition number. Incorporating the mesoscopic contribution acts as such a preconditioner and decreased the fitting time. The mesoscopic contribution also makes the problem more well-posed by adding a non-zero local contribution in WM, which is zero in standard QSM. However, the model is still singular due to a negligible mesoscopic contribution in GM, and since $\chi(k)$ has a zero cone along the magic angle, which is a known problem in QSM. Numerous QSM fitting algorithms and experimental approaches have also been proposed to improve the visual quality of the estimated susceptibility and reduce various fitting artifacts like streaking. Such protocols could potentially be utilized in fitting Eq. (3) to reduce artifacts from deconvolution of the dipole field $\chi(R - R')$. However, the purpose of this study was not to develop novel fitting procedures to mitigate potential artifacts, but instead to demonstrate the performance and quality of the simplest fitting algorithm for this particular problem.

Ex-Vivo Brain Imaging

Susceptibility and frequency contributions

We estimated the bulk scalar magnetic susceptibility with and without including mesoscopic frequency contributions from WM (Figure 5). The susceptibility maps (cf. Figure 5) revealed noticeable differences in contrast and large quantitative differences (Table 2). For example, in regions of highly anisotropic WM approximately parallel to the main field, as in the cingulum (cg), or anterior commissure (ac), the RMSE in magnetic susceptibility was almost 30-60% across the ROIs, when mesoscopic contributions from WM are not considered. Here the magnitude of the mesoscopic frequency contribution was also found to be around 40-70% of the total frequency shift. This underscores the impact of including
microstructural field effects when quantifying magnetic susceptibility, even without including tensor $\chi$. It is thus important to understand these mechanisms better in the future, before attempting to achieve robust susceptibility estimations and resolve multiple types of inclusions in a single voxel. While our WM model is simple compared to actual magnetic tissue microstructure, the model’s apparent susceptibility gives an important first insight into the relationship between mesoscopic and macroscopic frequency contributions in real data.

$fODF$

Differences in susceptibility across the fODF estimation methods can be understood by examining the fractional anisotropy $FA_T$ computed for each method (see $FA_T$ in Table 2). FBI at $b=5$ ms/µm$^2$ and 10 ms/µm$^2$ are found to be in good agreement with each other, with a slight increase in $FA_T$ for higher $b$. This is reasonable since a higher $b$ should decrease the amount of extra-axonal signal. The reason for using a diffusion weighted MGE signal was to ensure a 1-1 correspondence between the sampling voxels for dMRI and MGE. Since we assumed only a single signal component, namely intra-axonal water, the phase is independent from the diffusion weighting, which made removing the phase an easy task. This enabled us to effectively average across multiple echo times to increase SNR instead of averaging multiple experiments. However, if we had used a lower b-value, or wanted to fit the full standard model$^{24}$ using diffusion weighted MGE signals from multiple b-shells, phase and relaxation should be included in the kernel$^{47}$ for each compartment.

Fixation effects

As imaging was performed on ex-vivo mouse brains, effects related to fixation may also affect parameter estimation$^{27}$. Susceptibility values have earlier been found to be numerically smaller in-vivo compared to ex-vivo$^{48}$. Secondly, whether orientation dispersion of WM differ between ex-vivo and in-vivo remains an open question, and so the mesoscopic contribution may differ between them.

Can we avoid sample rotations?

Estimating the parameters of the WM model presented in this study does not require sample rotations, as every structural degree of freedom is captured by the fODF which was determined by dMRI. This leaves
only a single scalar susceptibility to be determined from the Larmor frequency in each voxel. Introducing an anisotropic WM susceptibility tensor and other inclusions would introduce additional degrees of freedom relating to susceptibility rather than to mesoscopic structure, and would thus require additional information. One approach would be to acquire MGE for a range of sample orientations, which may not be a viable solution from a clinical perspective. The transverse relaxation rate $R'_2$ has already been proposed as an additional source of information to distinguish iron from myelin susceptibility$^5$; thus modelling $R'_2$ for cylindrical networks with orientation dispersion could clarify whether it can provide sufficient additional information. Alternatively, the missing information could potentially be obtained from e.g. compartmental diffusion-weighting, or other MRI modalities. Another example is measuring and modelling internal gradient distributions which could provide rotation-free mapping of magnetic tissue properties, as they can be probed using diffusion gradients$^{49}$.

**Conclusion**

We developed a novel framework for including mesoscopic Larmor frequency contributions in quantitative susceptibility mapping (QSM). This was done by modelling the frequency induced from white matter (WM) magnetic microstructure as organized in infinite multi-layered cylinders with orientation dispersion and scalar susceptibility. Our experimental results show that local WM microstructure account for up to 70% of the induced frequency in WM. Thus, induced frequency from local magnetic microstructure can be substantial and should not be ignored in QSM. We believe our results will advance the pursuit of a full characterization of magnetic microstructure of nervous tissue, with the end goal of faithful parameter estimations that can be used actively in clinical research.

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Abbreviations

**fODF**: Fiber Orientation Distribution Function. **WM**: White Matter. **FID**: Free Induction Decay Signal. **dMRI**: Diffusion MRI. **QSM**: Quantitative Susceptibility Mapping. **STI**: Susceptibility Tensor Imaging. **SWI**: Susceptibility Weighted Imaging. **GE**: Gradient-recalled Echo Signal. **STF**: Symmetric Trace Free Tensor. **SO(3)**: Group of all Rotations about the Origin in Three Dimensional Euclidian Space $\mathbb{R}^3$. **PBS**: Phosphate-buffered Saline. **PFA**: paraformaldehyde. **MGE**: Multi Gradient Echo-Recalled Signal. **MP-PCA**: Marchenko-Pastur Principal Component Analyses. **FBI**: Fiber Ball Imaging. **SM**: Standard Model of Diffusion. **DKI**: Diffusion Kurtosis Imaging. **LSMR**: Least Squares Minimal Residual Method. **CSF**: Cerebral Spinal Fluid. **eg**: Cingulum Bundle. **df**: Dorsal fornix, **mtt**: Mammillothalamic tracts, **cp**: cerebral peduncle. **cc**: Corpus Callosum. **ac**: Anterior Commissure. **fa**: Anterior Forceps of Corpus Callosum. **GM**: Gray Matter. **RMSE**: Root-mean-squared error.

Appendix A

**A1) Indicator function for multilayer cylinder**

In this section we derive the mesoscopic demagnetization tensor$^{15}$, $\mathbf{N}$, for multi-layer cylinders (MLC) with arbitrary orientations (see Figure 2) to extend our model for solid cylinders.

The mesoscopic demagnetization tensor$^{15}$ $\mathbf{N}$ depends only on structural correlations

$$\mathbf{N} = \frac{1}{(1-\xi)} \int \frac{dk}{(2\pi)} \mathbf{Y}(k) \Gamma''(k).$$ (8)

$\Gamma''$ is the structural correlation function, whose generic form in Fourier space is

$$\Gamma''(k) = \frac{\nu(k)\nu(-k)}{|\mathbf{M}|}, \quad k > 0,$$ (9)

and zero for $k = 0$. When susceptibility is uniform, the product $\mathbf{L} = -\chi \mathbf{N}$ defines the mesoscopic Lorentzian tensor$^{15,22}$ and characterizes $\mathbf{\Omega}^{\text{Meso}}(\mathbf{R})$ (cf. Eq. (2)). The indicator function $\nu(k)$ for an infinitely long cylinder consisting of $M$ concentric shells is a superposition of $2M$ solid infinite cylinders$^{15}$

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\[ v(k) = e^{i k \hat{n}} \frac{4 \pi^2}{k} \sum_{q=1}^{M} \left( R_q J_q \left( R_q k \right) - r_q J_q \left( r_q k \right) \right) \delta \left( k \cdot \hat{n} \right). \]  \hspace{1cm} \text{(Multi layer cylinder)} \tag{10}

\[ = 2 \pi e^{i k \hat{n}} v^{2D} (k) \delta \left( k \cdot \hat{n} \right). \]

Here \( v^{2D} (k) \) defines the indicator function in the 2D plane transverse to the orientation \( \hat{n} \), where \( R_q, r_q \) denotes the outer and inner radii of the \( q \)'th layer. Consider \( N \) MLCs as conceptualized in Figure 2. They are randomly positioned and exhibit arbitrary orientation dispersion independent of their size. Summing over all \( N \) MLCs, the total correlation function \( \Gamma^{vv} (k) \), Eq. (9), splits into a sum over autocorrelation \( \Gamma^{Auto} (k) \) and cross-correlation \( \Gamma^{Cross} (k) \)

\[ \Gamma^{vv} (k) = \Gamma^{Auto} (k) + \Gamma^{Cross} (k), \] \hspace{1cm} \text{Eq. (11)}

where

\[ \Gamma^{Auto} (k) = \sum_m \Gamma_m (k) \] \hspace{1cm} \text{Eq. (12)}

and

\[ \Gamma^{Cross} (k) = \sum_{m \neq w} \Gamma_{mw} (k). \] \hspace{1cm} \text{Eq. (13)}

Using Eqs. (9) and (10), we find for \( \Gamma_m (k) \) in Eq. (12)

\[ \Gamma_m (k) = \Gamma^{2D} (k) \delta \left( k \cdot \hat{n}_m \right), \] \hspace{1cm} \text{Eq. (14)}

where the 2D correlation function \( \Gamma^{2D} (k) \) is

\[ \Gamma^{2D}_m (k) = \frac{8 \pi^2}{k^2} \sum_{q,p=1}^{M} \zeta \left( R_q, R_p \right) J_q \left( R_q k \right) J_p \left( R_p k \right) - \]

\[ - \frac{\zeta \left( r_q, R_p \right) J_q \left( r_q k \right) J_p \left( R_p k \right)}{k} - \]

\[ - \frac{\zeta \left( R_q, r_p \right) J_q \left( R_q k \right) J_p \left( r_p k \right)}{k} + \]

\[ + \frac{\zeta \left( r_q, r_p \right) J_q \left( r_q k \right) J_p \left( r_p k \right)}{k} - \]

\[ 4 \pi^2 \zeta \zeta \frac{\delta (k)}{k}. \] \hspace{1cm} \text{Eq. (15)}
Here \( \zeta^\circ(R_p, R_q) \equiv \min(\zeta_{R_p}, \zeta_{R_q}) \max(R_p, R_q) \) is introduced, for convenience, to denote the volume fraction of the smallest cylinder weighted by the ratio between the largest and smallest radii. The last term of Eq. (15) ensures \( \Gamma_2^{2D}(k = 0) = 0 \).

Notice that autocorrelation for the \( m \)'th MLC is itself a sum of autocorrelations \( (m = w) \) and cross-correlations \( (m \neq w) \) over its constituent solid cylinders. In addition, we find for the cross-correlation between two non-parallel MLCs \( \Gamma_{mw}(k) \) in Eq. (13)

\[
\Gamma_{mw}(k) = e^{ik\Delta_{mw}} \frac{16\pi^4}{k^2} \sum_{p,q=1}^{M} (R_p R_q J_1(R_p k) J_1(R_q k) - r_p R_q J_1(r_p k) J_1(R_q k)) \delta(k \cdot \hat{n}_w) \delta(k \cdot \hat{n}_w).
\]

Equation (16) corresponds to a sum of \( 4M \) cross-correlations from solid cylinders, which we previously found not to contribute\(^\text{15} \). We can thus set \( \Gamma_{mw}(k) = 0 \) which results in \( N^{\text{Cross}} = 0 \). Upon calculating the mesoscopic demagnetization tensor \( N \), Eq. (8), we only have to consider the contribution from autocorrelations \( N = N^{\text{Auto}} \). Using Eq.(12), the contribution from autocorrelation becomes

\[
N^{\text{Auto}} = \frac{1}{1 - \zeta} \sum_m \int \frac{dk}{(2\pi)^3} \Psi(k) \Gamma_m(k).
\]

Using GR(6.574.2) from Gradshteyn and Ryzhik\(^\text{50} \) (Where the number refers to the identity in the original tables)

\[
2 \int \frac{dk}{k} \frac{1}{J_1(R_m k) J_1(R_w k)} = \frac{\min(R_m, R_w)}{\max(R_m, R_w)}
\]

with the previous result\(^\text{15} \)

\[
\int \frac{dk}{2\pi} \Psi(k) \delta(k \cdot \hat{n}) = \frac{1}{3} \left( I - \frac{1}{2} (1 - \hat{n}^T \hat{n}) \right),
\]

and that the sum of minimum volume fractions yields the cylinder volume fraction
we obtain for the autocorrelation contribution to $N^{\text{Auto}}$

$$N^{\text{Auto}} = \sum_m \xi_m \left( \frac{1}{3} I - \frac{1}{2} (I - \hat{n}_m^T \hat{n}_m) \right)$$

$$= \xi \left( T - \frac{1}{6} I \right)$$

$$= \xi \frac{1}{3} \sum_{m=-2}^{2} p_{2m} \mathcal{Y}_{2m}.$$  \hspace{1cm} (21)

Here $T = \langle \hat{n}^T \hat{n} \rangle$ is the scatter matrix, which was rewritten in terms of $p_{2m}$, the Laplace expansion coefficients of the fODF. $\mathcal{Y}_{2m}$ is the symmetric trace-free tensors (STF) corresponding to an irreducible rank-2 representation of SO(3). This then yields the same mesoscopic dipole tensor as for solid cylinders

\[ N^{\text{Meso}} = N^{\text{Auto}} = \xi \frac{1}{3} \sum_{m=-2}^{2} p_{2m} \mathcal{Y}_{2m}. \quad (22) \]

**A2) Compartmental Average Larmor frequency $\overline{Q}_C^{\text{Meso}}$**

Here we briefly outline why Eq.(22) also corresponds to the mesoscopic dipole tensor in each of the three major water compartments. This means that the mesoscopic contribution to the average field in the extracylindrical compartment is the same as the intra-cylindrical compartment, and across bi-layers. Each major water compartment can be characterized by their total indicator functions $\nu_l(k)$, $\nu_b(k)$ and $\nu_e(k)$, respectively
\[ v_i(k) = \sum_m e^{\mathbf{k} \cdot \mathbf{a}_m} \frac{4\pi^2}{k} r_i J_0(kr_i) \delta(\mathbf{k} \cdot \hat{n}_m), \quad \text{(Intra-cylindrical)} \]

\[ v_B(k) = \sum_m e^{i\mathbf{m} \cdot \mathbf{a}_m} \frac{4\pi^2}{k} \sum_{q=2}^M \left( R_{(q-1)} J_1(q^{-1}r_q) - r_q J_0(q^{-1}r_q) \right) \delta(\mathbf{k} \cdot \hat{n}_m), \quad \text{(Bi-layers)} \]

\[ v_E(k) = (2\pi)^3 \delta(\mathbf{k}) - v_i(k) - v_B(k) - v(k), \quad \text{(Extra-cylindrical)}. \]

Hence, the structural correlation function is
\[ v(k) = (2\pi)^3 \delta(\mathbf{k}) - v_i(k) - v_B(k) - v_E(k). \]
From this we can define the mesoscopic contribution to the compartmental Larmor frequency \( \overline{\Sigma}_C^{\text{Meso}} \):
\[ \overline{\Sigma}_C^{\text{Meso}} = -\gamma B_0 \chi \hat{\mathbf{B}}^\top N_C^{\text{Meso}} \hat{\mathbf{B}}, \quad (24) \]

where the compartmental mesoscopic demagnetization tensor \( N_C^{\text{Meso}} \) depends on the compartmental correlation functions \( \Gamma_C(k) \)
\[ N_C^{\text{Meso}} = -\frac{1}{\zeta_C} \int \frac{dk}{(2\pi)^3} \Upsilon(k) \Gamma_C(k), \quad \Gamma_C(k) = \frac{v_C(k) v(k)}{|M|} - \zeta_C \zeta \frac{4\pi^3}{3} \delta(k). \quad (25) \]

\( \Gamma_C(k) \) is a cross-correlation as it describes correlations between the water compartment defined by \( v_C(k) \) with volume fraction \( \zeta_C \) and the microstructure with indicator function \( v(k) \), Eq. (10), with volume fraction \( \zeta \). Using the results Eqs. (18)-(20) in Eq. (25) yields identical mesoscopic dipole tensors for all compartments:
\[ N_C^{\text{Meso}} = \zeta \frac{1}{3} \sum_{m=2}^2 P_{2m} \mathcal{Y}_{2m}. \quad (26) \]

Thus every compartment experiences the same average magnetic field, and the weighted sum
\[ N^{\text{Meso}} = \sum_C \frac{\zeta_C}{1-\zeta} N_C^{\text{Meso}} = N_C^{\text{Meso}} \] corresponds to Eq. (22) as expected. This means that if we filter the signal through diffusion weighting to isolate intra-cylindrical signals, we do not gain any new information about the magnetic microstructure.
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