Susceptibility quantification for ferritin and Fe_3O_4 nanoparticles: Observation of hyperfine shift in phase images and comparison between phase measurement and CISSCO

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Introduction: Susceptibility quantification in MRI relies on phase values in images. If phase information is purely from the susceptibility differences between tissues, then current quantitative susceptibility mapping (QSM) methods may obtain correct susceptibility maps. However, it is known for a long time that additional frequency shifts (thus extra phase values) can appear inside objects of interest, due to the hyperfine structures of the substances and the interactions between molecules and surrounding protons in water [1]. In this study, we report hyperfine shifts measured from both ferritin and Fe_3O_4 nanoparticle solutions in phantoms. We also compare quantified susceptibility values from phase inside those solutions with the susceptibility values from phase outside those solutions but using our CISSCO method [2].

Material and Method: In this study we used ferritin and Fe_3O_4 magnetic nanoparticles to conduct phantom studies. We made four different phantoms with ferritin in water solution, ferritin mixed with gelled gelatin, Fe_3O_4 nanoparticles in water, and Fe_3O_4 nanoparticles mixed with gelled gelatin. Each phantom consisted of four straws with different concentrations of the samples stated above. The concentrations of each sample were diluted in series with a factor of 2, resulting in 4 corresponding susceptibility values from about 2 ppm down to about 0.25 ppm. We imaged the phantoms with a 2.89T Siemens Verio and with an 11-echo SWI sequence. We oriented the straws perpendicular to the main field and acquired coronal images. We also oriented the straws parallel to the field and acquired transverse images. The imaging parameters are: main field = 2.89 T, resolution = 1 mm isotropic, echo time = 5.68 ms to 29.58 ms with an interval of 2.39 ms, TR = 37 ms, and field of view = 256 × 256 × 64.

We applied FSL to unwrap the phase in images and SHARP to remove the background phase. After this procedure, we applied our CISSCO method to quantify the magnetic moment of the material inside each straw, using phase values outside the straw.

The phase inside a cylindrical object is given by $\varphi = p\,(1\text{-}3\cos^2\theta)/3a^2 + \varphi_{shift}$, where p is the effective magnetic moment, θ is the angle between the axis of the cylinder and the main field, a is the radius of the object, and φ_{shift} is the phase shift due to the hyperfine shift. Since the hyperfine shift is independent of the orientation of the cylinder, by measuring the phase values inside the cylinder from two orientations, one can calculate the magnetic moment and the phase shift for each material. We then converted the magnetic moments to susceptibilities (with the unknown radius of the straw) and compared these susceptibility values with those from our CISSCO method (with the same conversion).

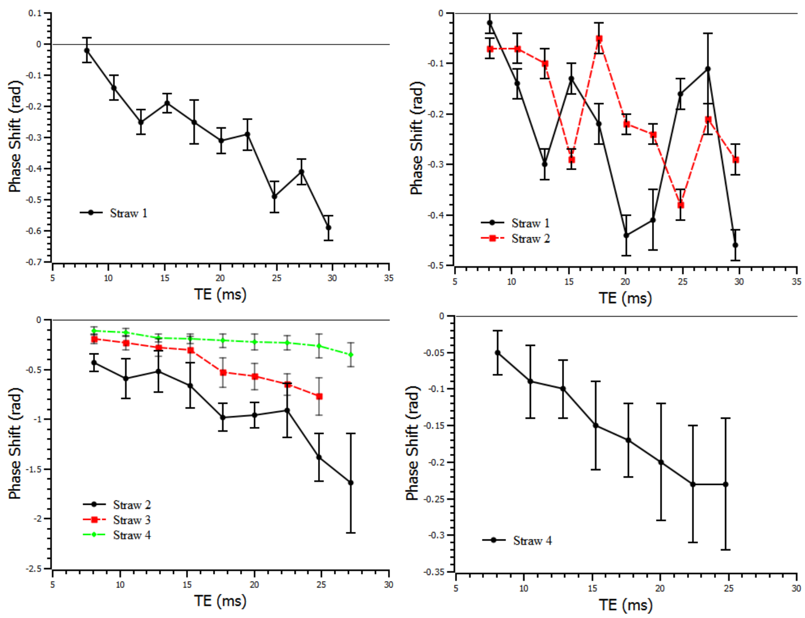

Figure 1. Phase measurements due to hyperfine structures. Top plots are from ferritin (phantoms 1 and 2) and bottom plots are from iron oxide nanoparticles (phantoms 3 and 4). The two figures on the left were from samples in water, and those on the right were from the same substance but mixed with gelled gelatin.

Results: The measured phase shifts due to the hyperfine shift are shown in Figure 1. In general, phase values from most samples indicate linear relation over the echo time, as expected. Note that most phase shifts are not zero. Shifted phase values close to 0 can be treated as unobservable, given the uncertainties in our measurements.

For ferritin samples, the SNR in magnitude images decreases with decreased concentrations. As a result, ferritin samples with lower concentrations have larger uncertainties in phase images. At the meanwhile the hyperfine shifts of lower concentrations can be smaller than the uncertainty we obtained. Thus we are not able to conclusively determine the phase shifts at low concentrations (in straws 2, 3, 4 of phantom 1 and in straws 3, 4 of phantom 2). For the same reason that SMR is lower, phase measurements at longer echo times also have larger errors as indicated in the plots.

For Fe_3O_4 nanoparticle samples, opposite to ferritin samples, the SNR in magnitude images decreases with increased concentrations. Thus, with relatively lower SNR, phase measurements at higher concentrations have larger errors. Similarly, we can only conclusively determine the straws containing phase shifts from relatively lower concentrations, as illustrated in the bottom 2 panels in Figure 1.

We have also calculated the susceptibility of each material from the measured phase value inside each straw. The results are in good agreements with the results measured from the CISSCO method. The results from phantom 1 and phantom 3 are listed in Table 1.

Straw	χ (CISSCO)	χ (Phase_in)
1	2.20 ± 0.05	2.07 ± 0.12
2	1.11 ± 0.02	0.96 ± 0.09
3	0.56 ± 0.01	0.64 ± 0.09
4	0.29 ± 0.03	0.32 ± 0.03

Straw	χ (CISSCO)	χ (Phase_in)
1	2.60 ± 0.07	2.68 ± 0.02
2	1.31 ± 0.04	1.31 ± 0.01
3	0.65 ± 0.02	0.68 ± 0.02
4	0.33 ± 0.03	0.33 ± 0.02

Table 1. Measured Susceptibility (ppm) values from CISSCO and inside phase measurements. The top table lists the results from ferritin in water, and the bottom table shows the results from iron oxide nanoparticles in water.

Conclusion: In this study, hyperfine shifts from ferritin and Fe_3O_4 nanoparticle samples have been observed and measured. Our results suggest that the applications of QSM to *in vivo* tissues containing ferritin may require careful examinations. Comparisons between results also indicate that a method such as CISCCO utilizing phase values outside a given object is a reliable method for magnetic moment quantifications of the object, regardless of the presence of the hyperfine shift inside the object.

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