A geometric approach to separate the effects of magnetic susceptibility and chemical shift/exchange in a phantom with isotropic magnetic susceptibility

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Funding information
National Research Foundation of Korea grant, funded by the Korea government (Ministry of Science and ICT), Grant/Award Number: NRF-2018R1A2B3008445; Creative-Pioneering Researchers Program through Seoul National University; The Institute of Engineering Research at Seoul National University

Purpose: To separate the effects of magnetic susceptibility and chemical shift/exchange in a phantom with isotropic magnetic susceptibility, and to generate a chemical shift/exchange-corrected QSM result.

Methods: Magnetic susceptibility and chemical shift/exchange are the properties of a material. Both are known to induce the resonance frequency shift in MRI. In current QSM, the susceptibility is reconstructed from the frequency shift, ignoring the contribution of the chemical shift/exchange. In this work, a simple geometric approach, which averages the frequency shift maps from three orthogonal B0 directions to generate a chemical shift/exchange map, is developed using the fact that the average nullifies the (isotropic) susceptibility effects. The resulting chemical shift/exchange map is subtracted from the total frequency shift, producing a frequency shift map solely from susceptibility. Finally, this frequency shift map is reconstructed to a susceptibility map using a QSM algorithm. The proposed method is validated in numerical simulations and applied to phantom experiments with olive oil, bovine serum albumin, ferritin, and iron oxide solutions.

Results: Both simulations and experiments confirm that the method successfully separates the contributions of the susceptibility and chemical shift/exchange, reporting the susceptibility and chemical shift/exchange of olive oil (susceptibility: 0.62 ppm, chemical shift: −3.60 ppm), bovine serum albumin (susceptibility: −0.059 ppm, chemical shift: 0.008 ppm), ferritin (susceptibility: 0.125 ppm, chemical shift: −0.005 ppm), and iron oxide (susceptibility: 0.30 ppm, chemical shift: −0.039 ppm) solutions.

Conclusion: The proposed method successfully separates the susceptibility and chemical shift/exchange in phantoms with isotropic magnetic susceptibility.

Keywords
chemical exchange, chemical shift, magnetic susceptibility, quantitative MR, quantitative susceptibility mapping
1 | INTRODUCTION

With the development of ultrahigh-field MRI systems, phase shift or resonance frequency shift has become a vital contrast for high-resolution anatomy.\(^1\)\(^-\)\(^3\) The origins of the resonance frequency shift have been attributed to the effect of magnetic susceptibility,\(^4\)\(^-\)\(^6\) chemical shift,\(^7\) chemical exchange,\(^8\)\(^-\)\(^11\) and complex tissue microstructure.\(^12\)\(^-\)\(^14\) Among them, the magnetic susceptibility effect has been suggested as a primary contributor to the resonance frequency shift. Under this assumption, QSM has been proposed by converting a frequency-shift image to a susceptibility map.\(^15\)\(^-\)\(^19\) The method has been demonstrated to generate great details of anatomical structures and has been applied for various clinical studies.\(^20\)\(^-\)\(^24\) However, the accuracy of QSM degrades when other sources of frequency shift exist. For example, in abdominal QSM, the chemical shift from fat introduces substantial artifacts in QSM images if it is reconstructed without consideration of the chemical shift of fat.\(^25\)\(^,\)\(^26\) Efforts were made to design models that separated the susceptibility and nonsusceptibility sources, but they required specific conditions to hold (eg, a piece-wise constant assumption).\(^27\)\(^,\)\(^28\)

The magnetic susceptibility and chemical shift/exchange are the properties of a material (eg, vegetable oil has the magnetic susceptibility of 0.65 ppm and chemical shift of −3.46 ppm\(^28\) bovine serum albumin solution [100 mg/mL] has the magnetic susceptibility of −0.068 ppm and chemical exchange of 0.008 ppm\(^29\); see section 5). Hence, understanding the contribution of the two sources is important not only for the reliable reconstruction of QSM, but also for the separate measurements of the two sources. In a few previous studies,\(^8\)\(^-\)\(^10\) efforts have been made to separate the effects of the magnetic susceptibility and chemical exchange by mixing a material of interest with a reference chemical (eg, dioxane). However, a more recent study has suggested a nonnegligible level of interactions between the reference chemical and the material under investigation.\(^30\) As a result, further research is necessary to determine the validity of the reference chemical-based measurements.

In this study, we present a geometric method that separates the susceptibility and chemical shift/exchange without requiring a reference chemical that is mixed with the sample of interest. A mathematical formulation that uses multiple \(B_0\) orientation data has been developed to achieve the separation. Numerical simulation and phantom experiments were performed to validate the method.

2 | THEORY

2.1 | Resonance frequency shift

When the effect of the susceptibility and chemical shift/exchange coexist in an isotropic medium (ie, no anisotropic susceptibility, no anisotropic microstructure, and no orientation-dependent chemical shift/exchange) with no additional sources for the frequency shift, the total frequency shift can be written as

\[
\Delta f(\vec{r}) = f_c(\vec{r}) + f_s(\vec{r}),
\]

where \(\Delta f\) is the total resonance frequency shift; \(\vec{r}\) is a position vector; \(f_c\) is the chemical shift/exchange-induced frequency shift; and \(f_s\) is the susceptibility-induced frequency shift. The susceptibility-induced frequency shift has been shown to be modeled as follows\(^31\)\(^,\)\(^32\):

\[
f_s(\vec{r}) = d * \chi(\vec{r}),
\]

where \(d\) is a dipole kernel; \(\chi\) is susceptibility; and \(\theta\) is an angle between the position vector and \(B_0\) orientation. Because \(d\) is a function of \(B_0\) orientation, the susceptibility-induced frequency shift is also dependent on the orientation of \(B_0\).\(^4\)\(^,\)\(^33\)

2.2 | Separation of chemical shift/exchange from susceptibility

When \(B_0\) is applied to an object along the three orthogonal axes (ie, \(x\)-, \(y\)-, or \(z\)-axis), the three susceptibility-induced frequency shifts can be written as

\[
\begin{align*}
f_{sx}(\vec{r}) &= d_x(\vec{r}) \ast \chi(\vec{r}) = \frac{1}{4\pi} \cdot \frac{3\cos^2\theta_x - 1}{r^3} \ast \chi(\vec{r}), \\
f_{sy}(\vec{r}) &= d_y(\vec{r}) \ast \chi(\vec{r}) = \frac{1}{4\pi} \cdot \frac{3\cos^2\theta_y - 1}{r^3} \ast \chi(\vec{r}), \\
f_{sz}(\vec{r}) &= d_z(\vec{r}) \ast \chi(\vec{r}) = \frac{1}{4\pi} \cdot \frac{3\cos^2\theta_z - 1}{r^3} \ast \chi(\vec{r}),
\end{align*}
\]

where subindex \(x\), \(y\), and \(z\) indicate the orientation of \(B_0\); and \(\theta_x\), \(\theta_y\), and \(\theta_z\) represent the angle between the position vector and \(B_0\) field along the \(x\)-, \(y\)-, and \(z\)-axes, respectively.

When we sum the three frequency shifts of the orthogonal orientations, it results in a null frequency shift:

\[
f_{sx}(\vec{r}) + f_{sy}(\vec{r}) + f_{sz}(\vec{r}) = \left\{ \frac{1}{4\pi} \cdot \frac{3(\cos^2\theta_x + \cos^2\theta_y + \cos^2\theta_z) - 3}{r^3} \right\} \ast \chi(\vec{r}) = 0.
\]

because \(\cos^2\theta_x + \cos^2\theta_y + \cos^2\theta_z\) equals to 1 for the three orthogonal axes (see Supporting Information Section 1).

Using this property, we can measure the chemical shift/exchange-induced frequency shift by averaging the frequency shifts from the three orthogonal \(B_0\) orientations, as follows:
\[
f\text{average } \langle \mathbf{r} \rangle = \frac{1}{3} \left\{ f_x \langle \mathbf{r} \rangle + f_y \langle \mathbf{r} \rangle + f_z \langle \mathbf{r} \rangle \right\} = \frac{1}{3} \left\{ 3f_x \langle \mathbf{r} \rangle + \{f_{xx} \langle \mathbf{r} \rangle + f_{xy} \langle \mathbf{r} \rangle + f_{xz} \langle \mathbf{r} \rangle \} \right\} = f_x \langle \mathbf{r} \rangle.
\]

Then, the susceptibility-induced frequency shift can be calculated by subtracting the chemical shift/exchange-induced frequency shift from the total frequency shift:

\[
f_x \langle \mathbf{r} \rangle = f \langle \mathbf{r} \rangle - f_x \langle \mathbf{r} \rangle.
\]

From this susceptibility-induced frequency shift, one can measure the susceptibility using a QSM algorithm.

This approach of separating the susceptibility and chemical shift/exchange requires data acquisition of three different \( B_0 \) orientations that are orthogonal to each other. If an object has geometric symmetry, however, the number of scans can be reduced. For example, a cylindrical phantom has the geometric symmetry in the two short axes; therefore, only two acquisitions, one with \( B_0 \) along the long axis of the cylinder and the other with \( B_0 \) along one of the short axes, are necessary. The missing frequency-shift map can be generated by the 90° rotation of the frequency-shift map acquired with \( B_0 \) along the short axis. Similarly, a spherical phantom can be scanned once to apply our method. The idea can be generalized for arbitrary \( B_0 \) orientations using a least-squares minimization method (see Supporting Information Section 2).

### 3 | METHODS

#### 3.1 | Numerical simulation

A numerical simulation was designed to demonstrate that the summation of the three susceptibility-induced frequency shifts results in a null field (Equation 5). Four numerical phantoms in the shape of heart, cylinder, sphere, and brain were constructed in a 2563-voxel grid each. For the heart, cylinder, and sphere phantoms, the susceptibility of 0.1 ppm was assigned. For the brain phantom, the following susceptibility values were assigned to subregions: caudate nucleus = 0.04 ppm, putamen = 0.07 ppm, globus pallidus = 0.12 ppm, gray matter = 0.02 ppm, and white matter = −0.02 ppm. The background had zero susceptibility. No chemical shift/exchange was assumed. Then, the susceptibility-induced frequency shifts of the three orthogonal \( B_0 \) orientations were generated using a Fourier-based frequency-shift calculation method. After that, the three susceptibility-induced frequency shifts were summed to demonstrate that the result was a null field.

Another numerical simulation was performed to illustrate the process of the proposed method. A cylindrical phantom of the 30-voxel radius was embedded at the center of a 256 × 256 × 40-voxel grid. The material inside the phantom was assumed to be fat with a chemical shift of −3.5 ppm and susceptibility of 0.65 ppm. The background was assumed to have zero susceptibility and chemical shift. A susceptibility-induced frequency-shift map was calculated for each of the three orthogonal \( B_0 \) orientations using the Fourier-based method. Then a chemical shift–induced frequency-shift map, which was confined to the cylinder with a −3.5 ppm frequency shift, was generated. The two maps were summed to yield a total frequency-shift map for each \( B_0 \) orientation. Our method of separating the susceptibility and chemical-shift sources was applied to the three total frequency-shift maps. As the first step, the three total frequency-shift maps were averaged to produce a chemical shift–induced frequency-shift map (Equation 6). Then, this map was subtracted from each of the total frequency-shift maps, providing the susceptibility-induced frequency-shift maps (Equation 7). From these frequency-shift maps, susceptibility maps of each orientation were reconstructed using a QSM method with a regularization factor of 10. For comparison, susceptibility maps were reconstructed from the total frequency shifts, which contained the chemical-shift effect, using the same QSM method.

#### 3.2 | Phantom experiment

Olive oil (O1514; Sigma-Aldrich, St. Louis, MO), bovine serum albumin solution (100 mg/mL; A7906; Sigma-Aldrich), ferritin solution (0.43 mg/mL; F4503; Sigma-Aldrich), and iron oxide solution (2.5 × 10⁻³ mg/mL; PMC1N; Bang’s Laboratories, Fishers, IL) were used to test the proposed method. Each solution filled out two identical plastic cylinders (inner diameter = 28 mm, outer diameter = 30 mm, and height = 110 mm). Then, the two cylinders were positioned in a large container such that one cylinder was parallel to \( B_0 \) and the other was perpendicular to \( B_0 \). The container was filled with distilled water. In a separate scan, a sphere phantom (diameter = 40 mm) filled with the olive oil was also constructed and tested.

All scans were conducted on a 3T MRI scanner (Siemens Tim Trio, Erlangen, Germany) with a 12-channel array coil. The scan started with a three-plane localizer. Then, shimming was performed to reduce field inhomogeneity. For the main scan of the bovine serum albumin, ferritin, and iron oxide solutions, data were acquired at room temperature using a 3D multi-echo gradient-echo sequence with the following parameters: FOV = 192 × 192 × 64 mm³, voxel size = 2 × 2 × 2 mm³, TR = 64 ms, TE = 5 to 23.75 ms with an echo spacing of 3.75 ms, number of echoes = 6, bandwidth = 330 Hz/pixel, flip angle = 12°, GRAPPA factor = 2, monopolar readout gradient, and total acquisition time = 2.03 minutes. For the olive oil, the readout gradient was modified from monopolar to bipolar, to achieve shorter
echo spacing, because of the large chemical shift of the olive oil when compared with the others. The scan parameters were also modified to TR = 40 ms, TE = 1.5 to 9.78 ms with an echo spacing of 0.92 ms, number of echoes = 10, bandwidth = 2000 Hz/pixel, and total acquisition time = 1.6 minutes. To compensate for the artifacts in the bipolar gradient, the sequence was repeated with the opposite gradient polarity. After scanning each solution, the two cylinders (or a sphere) were replaced by cylinders (or a sphere) with distilled water. Then, the scan was repeated to acquire a reference for a background field.

For data processing, the k-space data of each solution were reconstructed to multi-echo complex images using GRAPPA reconstruction and multichannel image combination. For the olive oil data, the two same TE complex images of the opposite gradient polarity were averaged to generate a complex image. The background field was removed by dividing the complex image of the main scan by that of the reference. Then, a frequency-shift map was derived using a linear least-squares fitting from the multi-echo complex images. The resulting map was registered to the other maps. After that, the third orientation frequency-shift map was generated by a 90° rotation of the frequency-shift map whose cylinder was perpendicular to \(B_0\). The resulting map was registered to the other maps. For the spherical phantom, the frequency-shift map was rotated by 90° in two orthogonal orientations. Then, the two rotated maps were registered to the original map. Next, our method was applied to separate the susceptibility-induced frequency shift and chemical shift/exchange-induced frequency shift. From the susceptibility-induced frequency-shift maps, susceptibility maps were reconstructed using the QSM method with two different regularization factors (10 and 100). During the QSM reconstruction, voxels that contained the cylinder wall had low SNR and were excluded to avoid partial volume–induced errors. For comparison, susceptibility maps were also reconstructed from the total frequency-shift maps. To quantify the results, a region of interest was chosen at the central eight slices of the cylinder. Then, the mean and SD of the susceptibility and chemical shift/exchange were measured in the region of interest.

All data processing was performed using MATLAB (2014b; MathWorks, Natick, MA).

4 | RESULTS

The simulation results of the four numerical phantoms in the shapes of the heart, cylinder, sphere, and brain confirm that the sum of the three orthogonal frequency-shift maps generates a null frequency shift in all phantoms (Supporting Information Section 3), demonstrating the validity of Equation (5).

The process of separating the susceptibility and chemical shift/exchange is shown in Figure 1 for the numerical fat phantom. The total frequency-shift maps of three orthogonal \(B_0\) orientations are illustrated in Figure 1A. When the three frequency-shift maps are averaged to generate a chemical-shift map (Figure 1B), the frequency shift measured inside the cylinder is −3.5 ppm, which is the same as the assigned chemical shift. This map is subtracted from each of the total frequency-shift maps, generating the susceptibility-induced frequency-shift maps, as shown in Figure 1C. When these maps are reconstructed for QSM, they result in consistent susceptibility estimations for all \(B_0\) orientations (Figure 1E; left cylinder: 0.65 ± 0.01 ppm, middle cylinder: 0.65 ± 0.01 ppm, right cylinder: 0.65 ± 0.00 ppm) that are equal to the assigned susceptibility value (0.65 ppm) regardless of the \(B_0\) orientations. On the contrary, when susceptibility maps are reconstructed from the total frequency shifts in Figure 1A, the susceptibility values show significant variations (Figure 1D; left cylinder: 4.16 ± 0.60 ppm, middle cylinder: 4.16 ± 0.60 ppm, right cylinder: −8.97 ± 0.01 ppm). These results demonstrate that the chemical shift/exchange-induced frequency shift produces susceptibility errors and streaking artifacts.

The experimental results using the cylindrical olive oil phantom are displayed in Figure 2. The same trend as in the numerical fat phantom is observed. The frequency-shift maps from the three orthogonal \(B_0\) show orientation dependency (Figure 2A). When the three maps are averaged, the chemical shift–induced frequency-shift map reveals −3.60 ± 0.01 ppm (Figure 2B). This map shows no blooming artifacts, confirming that the chemical-shift effect is localized to the source. After removing the chemical-shift effect, the susceptibility-induced frequency-shift maps (Figure 2C) are reconstructed to generate the QSM maps (Figure 2E). The results report consistent susceptibility for all orientations (left cylinder: 0.63 ± 0.02 ppm, middle cylinder: 0.61 ± 0.02 ppm, right cylinder: 0.63 ± 0.01 ppm). The measurements show robustness to the regularization factors (Supporting Information Table S1). When susceptibility maps are reconstructed from the total frequency-shift maps that include the chemical-shift effect, they result in large susceptibility variations (left cylinder: 11.4 ± 0.8 ppm, middle cylinder: 10.6 ± 1.1 ppm, right cylinder: −10.2 ± 0.2 ppm) and streaking artifacts (Figure 2D). The results of the olive oil using a spherical phantom report the same trend and are summarized in Supporting Information Figure S2.

The susceptibility and chemical-exchange measurements of the bovine serum albumin, ferritin, and iron oxide solutions are listed in Table 1. In all solutions, the susceptibility measurements show more consistent results in the proposed method than in the conventional QSM reconstruction.
DISCUSSION

In this paper, a method that separates the susceptibility and chemical shift/exchange in a phantom without anisotropic susceptibility or microstructure is presented. The method yields quantitative maps of magnetic susceptibility and chemical shift/exchange and is tested in numerical simulations and phantom experiments.

When the susceptibility and chemical shift/exchange measurements from our method were compared to literature values, they showed a good correspondence. The measurements of the bovine serum albumin solution (susceptibility: $-0.059 \pm 0.002$ ppm, chemical exchange: $0.008 \pm 0.001$ ppm) closely matched to the literature values (susceptibility: $-0.068$ ppm, chemical exchange: $0.008$ ppm; these values were scaled from Leutritz et al\textsuperscript{29} for concentration and Lorentz sphere correction). The measurements of the olive oil (susceptibility: $0.62 \pm 0.01$ ppm, chemical shift: $-3.60 \pm 0.01$ ppm) were also well in agreement with the literature values (susceptibility: $0.65$ ppm and chemical shift: $-3.46$ ppm from vegetable oil measured in de Rochefort et al\textsuperscript{28}; susceptibility: $0.75$ ppm from oleic acid in Lide\textsuperscript{41}).

In previous studies\textsuperscript{8-11}, the quantification of chemical shift/exchange of a solution was performed using a reference chemical (e.g., dioxane), assuming no interaction between the reference and solution. In a more recent study, however, a nonnegligible amount of interaction was reported\textsuperscript{30}, undermining the results of previous studies\textsuperscript{8-11}. In other studies, algorithms were proposed to separate susceptibility and non-susceptibility sources, assuming a piece-wise constant condition.\textsuperscript{27,28} Our approach, on the contrary, avoids potential complications from the reference chemical while allowing voxel-wise image reconstruction.

The proposed method requires three scans of orthogonal $B_0$ orientations when an object has an arbitrary shape. The number of scans can be reduced in an object with symmetry (e.g., sphere or cylinder). For example, a spherical phantom can be scanned just once. However, practical issues such as

FIGURE 1  Separation of the susceptibility and chemical shift in the numerical fat phantom. A, The three total frequency-shift maps generated from the three orthogonal $B_0$ orientations include the contributions of both susceptibility and chemical shift. B, The average of the three total frequency-shift maps produces a chemical shift-induced frequency shift map. C, The susceptibility-induced frequency-shift maps are generated by subtracting the chemical shift-induced frequency shift from the total frequency-shift maps. The susceptibility maps reconstructed from the total frequency-shift maps (D) and the susceptibility maps from the susceptibility-induced frequency-shift maps (E) reveal significant differences, with the latter reporting correct susceptibility estimations in all orientations.
positioning the sphere, removing air bubbles, and performing the reference scan were difficult in the spherical phantom. As a result, it was used once to demonstrate the feasibility. Instead, cylindrical phantoms, which require two scans of orthogonal B₀ orientations, are easier to handle. The two phantoms resulted in consistent measurements as demonstrated in Figure 2 and Supporting Information Figure S2.

When the alignment of the three orthogonally oriented data set is not accurate, it may introduce errors in the estimations. This effect is analyzed in Supporting Information Section 6. The results suggest that the measurements are robust (less than 0.5% errors) for a small misalignment (<5°). Additionally, the effects of the noise amplification of the proposed method is analyzed in Supporting Information Section 7.

In our study, a reference scan was acquired to eliminate the background field accurately. Alternatively, one may apply a background field removal method to reduce the scan time from the reference scan.42

Because the olive oil phantom has a large chemical shift–induced frequency shift (~3.58 ppm; 458.24 Hz in 3 T), a shorter echo spacing time (<1.09 ms) was required for the gradient-echo sequence to reconstruct the frequency-shift maps from the phase maps. To reduce the echo-spacing time, we modified the readout gradient of the sequence from monopolar to bipolar. Then, the two data sets with the opposite readout gradient were combined to avoid the phase modulations.37 This modified gradient-echo sequence with the echo spacing of 0.92 ms allowed us to reconstruct the frequency-shift maps of olive oil phantom without any artifacts.

In the phantom experiments, we experienced a B₀ drift, which may induce measurement errors.43 To minimize the B₀ drift–induced errors, we stabilized the B₀ field through a sufficient amount of dummy scans before the main scan. The scan time was also reduced by using parallel imaging.39

Applying our method to in vivo human brain is challenging because of the three orthogonal orientation scans required. Furthermore, the brain has additional sources of frequency shift,
such as tissue compartmentalization\textsuperscript{13} and susceptibility anisotropy.\textsuperscript{6} These contributions have $B_0$-orientation dependency and are not considered in our model. Additionally, a study has suggested that chemical exchange may have $B_0$-orientation dependency in vivo.\textsuperscript{44} All of these will complicate our results when the method is applied directly to in vivo. As a result, further improvement in methodology is necessary, and this work will provide a stepping stone toward future research.

## 6 CONCLUSIONS

In this study, we developed a geometric approach for separating the susceptibility and chemical shift/exchange in a phantom without anisotropic susceptibility or microstructure. The proposed method yields accurate susceptibility and chemical shift/exchange measurements in the numerical simulation and phantom experiments. When susceptibility maps are reconstructed from the total frequency-shift maps that include the chemical shift/exchange effect, they reveal large susceptibility variations and streaking artifacts depending on the $B_0$ orientation. On the contrary, the reconstruction results from the susceptibility-induced frequency-shift maps demonstrate correct susceptibility measurements with no artifacts. The proposed method is useful not only in measuring magnetic susceptibility and chemical shift/exchange, but also in improving QSM reconstruction algorithms.
ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea grant funded by the Korea government (MSIT; NRF-2018R1A2B3008445), Creative-Pioneering Researchers Program through Seoul National University, and the Institute of Engineering Research at Seoul National University.

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FIGURE S1  Susceptibility-induced frequency shifts in the heart-, cylinder-, sphere- and brain-shaped numerical phantoms. The frequency shift maps demonstrate $B_0$ orientation dependency. When the frequency shift maps of the three orthogonal $B_0$ orientations are summed, a null field is generated. The susceptibility and frequency shifts are expressed in parts per million.

FIGURE S2  Experimental results of the olive oil in the spherical phantom. The chemical shift (B, $-3.58 \pm 0.01$ ppm) and susceptibility (E, left sphere: $0.66 \pm 0.01$ ppm, middle sphere: $0.66 \pm 0.01$ ppm, right sphere: $0.62 \pm 0.01$ ppm) measurements are close to those of the olive oil in the cylindrical phantom. When the susceptibility maps are reconstructed from the total frequency shift maps with the chemical shift effect (B), significant susceptibility variations (left sphere: $-5.07 \pm 0.63$ ppm, middle sphere: $-4.02 \pm 1.08$ ppm, right sphere: $-4.23 \pm 0.07$ ppm) and streaking artifacts are observed (D). As compared to the cylindrical phantom, the spherical phantom requires only one scan for the proposed method. However, the spherical phantom is not practical in some ways, and therefore, the cylindrical phantoms are used for the other solutions.

FIGURE S3  Evaluation of the misalignment effects of the cylindrical phantom. The plots of the percentage errors of the chemical shift/exchange (A) and susceptibility (B) measurements for the misalignment w.r.t. $x$- (blue), $y$- (orange), or $z$- (yellow) axis. The errors are small, suggesting the robustness of the method for the misalignment.

TABLE S1  Susceptibility measurements with two different regularization factors ($\lambda = 10$ and $\lambda = 100$).

How to cite this article:  Eun H, Jeong H, Lee J, Shin H-G, Lee J. A geometric approach to separate the effects of magnetic susceptibility and chemical shift/exchange in a phantom with isotropic magnetic susceptibility. Magn Reson Med. 2021;85:281–289. https://doi.org/10.1002/mrm.28408