Quantitative susceptibility mapping for preclinical imaging

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Highlights

- Quantitative susceptibility mapping
- Susceptibility tensor imaging
- Preclinical imaging applications

Target audience

Physicians, imaging scientists, engineers, technologists, and other health care professionals interested in quantitative susceptibility mapping methods for preclinical imaging and beyond

Outcome/objectives

Demonstrate how to obtain quantitative susceptibility maps and provide example applications

Introduction

Magnetic susceptibility is the magnetization response of an object in the presence of an externally applied magnetic field. The response can depend on the content of the material, the function of the tissue, and the disease state. Materials and tissue matter are generally characterized as being paramagnetic (positive susceptibility) or diamagnetic (negative susceptibility). If paramagnetic, the field increases with the applied magnetic field. If diamagnetic, the field decreases with the applied magnetic field. Materials can have a very wide range of susceptibility values ranging from a few parts per billion (ppb) to parts per million

(ppm) of the magnetic field. The ability to quantify this property allows one to determine subtle changes or perturbations to the field.

One tool capable of extracting changes in susceptibility is a method called quantitative susceptibility mapping (QSM) via MR phase imaging (1-7). To obtain QSM, the phase information first needs to be unwrapped and processed. Nonlocal phase variations must be deconvolved. Finally, a matrix inversion is performed to map the local susceptibility information or QSM (5,8,9). Susceptibility information can be orientation-dependent or anisotropic (6,10,11). A method called susceptibility tensor imaging (STI) has been developed to study anisotropic susceptibility (10). STI is considered the tensor or non-scalar form of QSM.

QSM has demonstrated a variety of applications in the central nervous system, and can detect brain injury such as white matter demyelination, iron accumulation, and cerebral microbleeds (4,12-17). While QSM has been used to study diseases in the kidney and liver (18,19), its use beyond the brain and in preclinical imaging has been limited. QSM has the potential of quantifying pathophysiology in animal models of human disease and can be critical in bridging research from benchtop to bedside. In this work, I will demonstrate the use of QSM for small animal imaging. Basic principles, sequences, and data processing will be introduced. Specific examples where QSM surpasses traditional techniques will be shown, and application in several organ systems will be included.

Note: there are several terms closely associated with magnetic susceptibility including susceptibility weighted imaging (SWI), QSM, STI, electromagnetic property of tissue, and dynamic susceptibility contrast (DSC). SWI is a method to weigh phase information on top of magnitude images. Electromagnetic property of tissue is a topic that includes electrical conductivity, permittivity, and magnetic susceptibility. DSC is a dynamic T_2*-weighted imaging method with use of contrast agent. Only QSM and STI will be discussed.

Methods for obtaining QSM/STI

Sequences for phase-sensitive images

The gradient-echo (GRE) sequence with relatively long echo time (TE) is an established technique to assess the field perturbation caused by a susceptibility distribution source (20). Several variations of GRE can be applied including a flow-compensated GRE, a spoiled GRE, echo-planar imaging (EPI), and a multi-echo GRE. Multi-echo GREs can be used to enhance the susceptibility SNR and CNR, when individual echo images are corrected and summed (19,21,22). Acquisitions can be accelerated using non-Cartesian imaging with spiral or radial trajectories (23,24). Non-Cartesian sequences have several advantages including rapid and efficient k-space sampling, SNR efficiency, and refocusing of motion and flow-induced phase error. However, spiral sampling can be prone to off-resonance artifacts. Radial sampling may require an additional off-resonance saturation pulse and is geared towards imaging short T_2 components.

Processing phase data

The phase from certain MRI sequences, e.g., GRE, gives rise to a frequency offset that can be used to calculate the susceptibility image or QSM. Phase is typically wrapped around 2π or 360 degrees. The first step towards obtaining QSM is to unwrap the phase data. Several methods have been used for unwrapping including a path-based approach and a Laplacian-based strategy (5,25). In the unwrapped phase data, the magnetic field inside the object of interest contains susceptibility contributions inherent in the tissue and contributions from outside sources such as field inhomogeneities or air-tissue interfaces. The background information from outside the object of interest is removed using two methods: spherical mean value filtering (known as SHARP) (20,26,27) and deconvolution of the dipole field pattern (known as PDF) (8,28-30).

Quantifying susceptibility as a scalar and as a tensor

Magnetic susceptibility can be computed as a scalar (QSM) or as a tensor (STI). After phase unwrapping and phase background removal, the filtered phase is used for calculating the susceptibility image. The scalar QSM is then calculated with a least squares algorithm using

orthogonal and right triangular decomposition (LSQR) by inverting the following equation (31-33):

$$f(r) = FT^{-1}\left\{\left(\frac{1}{3} - \frac{k_z^2}{k^2}\right)\chi(k)\right\}\gamma\mu_0 H_0$$

where $\chi(k)$ is the susceptibility map in the frequency domain, k is the reciprocal space vector and k_z is its z-component, γ is the gyromagnetic ratio for water proton, μ_0 is the vacuum permeability, H_0 is the magnitude of the magnetic field, $f(r)$ is the frequency offset map, and FT^{-1} is the inverse Fourier transform. The frequency map $f(r)$ is defined as phase θ divided by the echo time t.

Computing STI requires acquisition at several physical orientations, and thus, registration to map each image into a common reference frame. The registration is based on the magnitude of the dataset. The filtered phase (unwrapped and background removed) is then registered to the common reference based on the transformation determined from the magnitude images. The transformation matrix from the registration is also used to determine the magnetic field vector in the new image space. The final registered phase (θ) is used for tensor calculation:

$$\theta = FT^{-1}\left\{\frac{1}{3}\hat{\mathbf{B}}_{\mathbf{0}}^{\mathbf{T}} FT\{\chi\}\hat{\mathbf{B}}_{\mathbf{0}} - \mathbf{k}\cdot\hat{\mathbf{B}}_{\mathbf{0}}\frac{\mathbf{k}^{\mathbf{T}} FT\{\chi\}\hat{\mathbf{B}}_{\mathbf{0}}}{k^2}\right\}\gamma B_0 t$$

where the superscript **T** represents the transpose operation, $\hat{\mathbf{B}}_{\mathbf{0}}$ is the unit vector of the applied magnetic field, FT is the Fourier transform, FT^{-1} is the inverse Fourier transform, $\mathbf{k}$ is the spatial frequency vector, χ is the second-order (rank 2) susceptibility tensor, γ is the gyromagnetic ratio for water proton, B_0 is the magnitude of the applied magnetic field, and t is the echo time.

The susceptibility tensor is assumed to be symmetric, i.e., 6 independent elements from the 9-element tensor matrix, and is computed from the sampled image phase at different orientations. For simplicity, image phase is expressed as normalized phase since each orientation dataset is scaled by the same constants:

$$\theta_s = \frac{\theta}{\gamma B_0 t}$$

Theoretically, only 6 orientations are needed to solve for the 6 susceptibility tensor elements. The accuracy of the tensor can be improved with more acquisitions or orientations. Given *n* datasets, the susceptibility tensor can be estimated by solving the following system of linear equations in the form of matrix multiplication:

$$\left[\theta_{s,j}(\mathbf{k})\right] = \left[A_{jk}\right]\left[\chi_j(\mathbf{k})\right] \quad \text{or} \quad \begin{bmatrix} \theta_{s,1}(\mathbf{k}) \\ \theta_{s,2}(\mathbf{k}) \\ \vdots \\ \theta_{s,n}(\mathbf{k}) \end{bmatrix} = \begin{bmatrix} a_{11}^{(1)} & a_{12}^{(1)} & a_{13}^{(1)} & a_{22}^{(1)} & a_{23}^{(1)} & a_{33}^{(1)} \\ a_{11}^{(2)} & a_{12}^{(2)} & a_{13}^{(2)} & a_{22}^{(2)} & a_{23}^{(2)} & a_{33}^{(2)} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ a_{11}^{(n)} & a_{12}^{(n)} & a_{13}^{(n)} & a_{22}^{(n)} & a_{23}^{(n)} & a_{33}^{(n)} \end{bmatrix} \begin{bmatrix} \chi_{11}(\mathbf{k}) \\ \chi_{12}(\mathbf{k}) \\ \chi_{13}(\mathbf{k}) \\ \chi_{22}(\mathbf{k}) \\ \chi_{23}(\mathbf{k}) \\ \chi_{33}(\mathbf{k}) \end{bmatrix}$$

where $[\theta_{s,j}]$ is n×1 vector of scaled image phase, $[A_{jk}]$ is n×6 matrix of coefficients, and $[\chi_j]$ is a 6×1 vector of tensor elements. The coefficient, $a_{jk}^{(n)}$, is defined as:

$$a_{jk}^{(n)} = \begin{cases} \frac{1}{3} B_j^{(n)} B_j^{(n)} - \mathbf{k}^{\mathbf{T}} \hat{\mathbf{B}}_{\mathbf{0}}^{(n)} \frac{k_j B_j^{(n)}}{k^2} & \text{if } j = k \\ \frac{2}{3} B_j^{(n)} B_k^{(n)} - \mathbf{k}^{\mathbf{T}} \hat{\mathbf{B}}_{\mathbf{0}}^{(n)} \frac{k_j B_k^{(n)} + k_k B_j^{(n)}}{k^2} & \text{if } j \neq k \end{cases}$$

The susceptibility tensor can be solved by inverting the system of equations (10,34). This matrix inversion to compute $\boldsymbol{\chi}$ is an ill-conditioned problem. Instead of direct inversion, $\boldsymbol{\chi}$ can be estimated using a pseudo-inverse with a least-squares algorithm:

$$\left[\chi_j(\mathbf{k})\right] = \left(\left[A_{jk}\right]^{\mathbf{T}}\left[A_{jk}\right]\right)^{-1}\left[A_{jk}\right]^{\mathbf{T}}\left[\theta_{s,j}(\mathbf{k})\right]$$

The susceptibility tensor in the spatial domain is computed by taking the inverse Fourier transform.

Eigenvalue decomposition can be performed on the tensor to define the three principal susceptibility values with corresponding eigenvectors. The major eigenvector points in the direction with the most positive (paramagnetic) susceptibility and the minor eigenvector points in the direction with the most negative (diamagnetic) susceptibility. The three eigenvalues can be summed to produce a susceptibility trace image.

Anisotropy from susceptibility images is defined using two methods. Susceptibility anisotropy (SA) is computed following (34):

$$SA = \frac{\chi_1 - \frac{\chi_2 + \chi_3}{2}}{\chi_1 + \chi_2 + \chi_3}$$

Alternatively, anisotropy can be defined as mean susceptibility anisotropy (MSA) following (13,35):

$$MSA = \chi_1 - (\chi_2 + \chi_3)/2$$

Results and applications

QSM has demonstrated promising application in both physiology and pathology in the brain, heart, kidney, and lungs. QSM also has applications in imaging paradigms including blood-oxygen level-dependent (BOLD) fMRI, susceptibility-based oximetry (SBO), and susceptibility weighted imaging (SWI) (36-40). These methods have the potential to be used in the preclinical domain. This work will present demonstrated applications of QSM and STI for preclinical imaging.

Demyelination in shiver mice

In a mouse brain, QSM has been particularly sensitive to damages in myelin of white matter axons. Liu et al. demonstrated that loss of myelin in the central nervous system of shiverer mice resulted in a dramatic reduction of magnetic susceptibility (16). Susceptibility contrast

between gray and white matter was reduced by 96% in shiverer compared to wild type controls. DTI parameters, on the hand, showed a mild reduction in this disease model (15% reduction in FA and up to 27% reduction in ADC). QSM is a promising tool to study normal brain structure and white matter diseases associated with the critical myelin material.

Imaging tubular and fiber structures

STI can be complementary to DTI in studying the architecture of tubular and fiber structures. In the brain, STI is able to detect white matter, as well as track fiber orientation (10,34). In the kidney, STI can detect tubules with larger diameters where diffusion appears isotropic and DTI fails (41,42). In a recent study, STI showed more sensitivity to cellular damage in kidney disease, while DTI exhibited results similar to a normal kidney (43). STI can detect and track myocardial filaments in the heart (44).

Detecting inflammation and fibrosis

Deposits of lipids and proteins are found during cellular inflammation and fibrosis. Detecting these markers has been challenging for conventional magnitude MRI. Similar to the lipoproteins found in myelin, lipids and proteins in fibrosis have diamagnetic susceptibilities (12,45). QSM has been able to locate and quantify the degree of inflammation and fibrosis by determining the amount of diamagnetic content in fibrotic kidney tissue (19).

Applications for short T_2 components

Structures with very strong susceptibility sources or short T_2 components can be studied with QSM. These components are typically attenuated or contribute minimally to susceptibility contrast using traditional GRE with relatively long TEs greater than 10 ms (24). The brain, for example, can have very strong susceptibility sources (short T_2 components) that are likely due to bounded protons between myelin sheaths. QSM from an ultrashort echo time (UTE) sequence can potentially reveal these structures.

Consequently, short T_2 components can occur during dynamic contrast-enhanced (DCE) studies. For instance, one study demonstrated that a signal dropout and blooming artifact occurred during a UTE based DCE scan (magnitude) of the kidney (46). This suggests that the concentration of the contrast agent was sufficiently high to have a very short T_2* in consideration of an ultrashort TE (20 μs). With QSM, this region was then resolved from an artifact into an area of strong susceptibility contrast and positive enhancement.

Lastly, the tissue-air boundary creates susceptibility artifacts when imaging of the lungs, even with UTE. Besides the large artifacts, SNR can be very low with lung imaging. In this presentation, I will demonstrate the application of QSM to alter this source of artifact into a source of tissue contrast.

Discussion and conclusion

While QSM and STI are promising methods, there are still have a few challenges and unmet needs. One of the challenges is that susceptibility values are relative to the object of interest and are not absolute quantification. Currently, susceptibility values have been defined in relation to homogeneous tissues areas with relatively known susceptibilities such as the cerebral spinal fluid in the ventricles or the pelvic fluid in the kidney.

Obtaining QSM from traditional GRE sequences requires relatively long acquisition times. Methods have been introduced to speed up acquisitions including spiral imaging (23), radial UTE (24,46), and Wave-CAIPI (35). STI requires sampling at different physical orientations and is time-consuming and physically challenging for body imaging. Wave-CAIPI has been demonstrated to alleviate some of the challenges. Imaging the multipole response in p-space can be a potential solution where physical orientations are not needed (47).

In conclusion, QSM and STI offer a promising approach to probe local microstructure and tissue properties based on small susceptibility variations. These methods have demonstrated additional information compared to magnitude counterparts, as well as conventional tensor

imaging methods. The application of susceptibility imaging spans a variety of disease models including demyelination of white matter axons, inflammation and fibrosis, and renal nephropathy. Susceptibility imaging can be used to study the normal physiology of brains, hearts, kidneys, and lungs of small animals.

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