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Review article

Quantitative susceptibility mapping: current status and future directions

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ABSTRACT

Quantitative susceptibility mapping (QSM) is a new technique for quantifying magnetic susceptibility. It has already found various applications in quantifying *in vivo* iron content, calcifications and changes in venous oxygen saturation. The accuracy of susceptibility mapping is dependent on several factors. In this review, we evaluate the entire process of QSM from data acquisition to individual data processing steps. We also show preliminary results of several new concepts introduced in this review in an attempt to improve the quality and accuracy for certain steps. The uncertainties in estimating susceptibility differences using susceptibility maps, phase images, and T_2^* maps are analyzed and compared. Finally, example clinical applications are presented. We conclude that QSM holds great promise in quantifying iron and becoming a standard clinical tool.

1. Introduction

To a large degree, magnetic resonance imaging (MRI) bases its clinical applications on conventional anatomical imaging using spin density, T_1, T_2 and T_2^* type contrasts. The T_2^* contrast is sometimes enhanced with a technique known as susceptibility weighted imaging (SWI) which uses phase as a means to enhance contrast [1–7]. Since its development in the mid-1990s, SWI has served as a precursor to the current focus of using phase [1] for quantitative susceptibility mapping (QSM). Phase information has been used almost since the beginning of MRI especially in chemical shift imaging experiments for water and fat separation techniques [8,9]. The phase information has also been utilized in measuring temperature and pH changes in tissue [10–12]. These approaches were quantitative in nature because the phase depends on both local magnetic fields and chemical shift.

In biological tissues, the major sources of phase contrast include the iron content (heme iron and non-heme iron), calcium, lipid and myelin content [13–18]. For deep gray matter structures, the phase contrast is mainly determined by the amount of iron [13]. As shown in many studies, the amount of iron may be related to many neurological diseases as well as tissue changes with aging [15,19–21]. For the veins in the brain, it is the level of deoxyhemoglobin that determines the MR signal magnitude and phase. The deoxyhemoglobin level is directly related to oxygen saturation, which can provide an indirect assessment of changes in blood flow [1,2,22]. For white matter structures, both the cellular composition and arrangement may affect the magnetic properties of tissues [17]. It is the integration of the microscopic effects that gives rise to the bulk magnetic susceptibility properties [17,23,24]. On the other hand, bulk susceptibility creates non-local phase effects, depending on the geometry and orientation of the object. Therefore, although the phase information at any location is directly related to the local magnetic field of the source, it can be spatially distant to the source of susceptibility changes. Such non-local effects can make it difficult to quantify susceptibility changes using phase images [13]. To avoid such geometry dependence, what one really wants is a source image, i.e., an image that does not depend on object orientation or imaging parameters [25,26]. Efforts over the last decade [27–38] have led to the current tremendous interest in quantitative susceptibility mapping (QSM).

In this review, we will discuss the key issues for robust and accurate QSM processing. These will include the following topics: basic theories of QSM; data acquisition and reconstruction (e.g., resolution, echo time, flow compensation and multi-channel data combination); background field removal (e.g., phase unwrapping and filtering techniques); algorithms for solving the ill-posed inverse problem (using a single orientation approach); propagation of thermal and systematic noise (evaluating the errors in estimating

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susceptibility changes using susceptibility maps, phase images, and T_2^* maps); and applications of QSM (with clinical examples of measuring iron content and estimating venous oxygen saturation, and with a discussion on maximum intensity projection (MIP) and true susceptibility weighted imaging [tSWI]). In addition, susceptibility anisotropy in white matter is discussed briefly.

2. Basics of QSM

For a left-handed system, the phase in the image domain for a gradient echo sequence with an echo time TE can be written as:

$$\phi(\vec{r}) = \phi_o(\vec{r}) + \gamma \Delta B_z(\vec{r}) TE, \tag{1}$$

assuming that the main field is in the z-direction. Here, $\phi_o(\vec{r})$ is a coil-sensitivity dependent phase offset and $\Delta B_z(\vec{r})$ is the z-component of the field variation which can be related to the source magnetization $M_z(\vec{r})$ via [27,31,39]:

$$\Delta B_z(\vec{r}) = \frac{\mu_0}{4\pi} \int_{V'} d^3r' \left\{ \frac{3M_z(\vec{r}')(z-z')^2}{|\vec{r}-\vec{r}'|^5} - \frac{M_z(\vec{r}')}{|\vec{r}-\vec{r}'|^3} \right\}. \tag{2}$$

Eq. (2) can be written as a convolution between $M_z(\vec{r})$ and the point-dipole response $G(\vec{r})$ [25]:

$$\Delta B_z(\vec{r}) = \mu_0 M_z(\vec{r}) * G(\vec{r}), \tag{3}$$

where $G(\vec{r})$ (the Green's function) is given by:

$$G(\vec{r}) = \frac{1}{4\pi} \frac{3\cos^2\theta - 1}{r^3} \tag{4}$$

and θ is the angle between $\vec{r}$ and $\vec{z}$. By using the convolution theorem on Eq. (3), $\Delta B_z(\vec{r})$ can be found easily. The Fourier transform of $G(\vec{r})$ is given by

$$G(\vec{k}) = \begin{cases} \frac{1}{3} - \frac{k_z^2}{k^2}, & for\ k \neq 0 \\ 0, & for\ k = 0 \end{cases} \tag{5}$$

where k_x, k_y and k_z are the coordinates in k-space, and $k^2 = k_x^2 + k_y^2 + k_z^2$. When $\chi \ll 1$, $\mu_0 M_z(\vec{r}) \approx B_0 \chi(\vec{r})$. This is the magnetic field variation induced by the susceptibility source distribution $\chi(\vec{r})$. Finally, $\Delta B_z(\vec{r})$ is found using the forward modeling process:

$$\Delta B_z(\vec{r}) = B_0 \cdot FT^{-1}\left\{ \chi(\vec{k}) \cdot G(\vec{k}) \right\}, \tag{6}$$

where $\chi(\vec{k})$ is the Fourier transform of $\chi(\vec{r})$. Although this prediction will not be perfect, the results are reasonably good for objects much smaller than the field-of-view [26,31]. As an example of this forward modeling process, the susceptibility map and the predicted phase image of a 3D brain model [38] are shown in Fig. 1. The susceptibility values of different structures in this 3D brain model are shown in Table 1.

Table 1
Susceptibility values of different structures in the brain model.

Structure	Susceptibility in ppm	Structure	Susceptibility in ppm
White matter	0	Veins	0.45
Gray matter	0.02	Red Nucleus	0.13
Globus Pallidus	0.18	Substantia Nigra	0.16
Putamen	0.09	Thalamus	0.01
Caudate Nucleus	0.06	Cerebrospinal Fluid	−0.014

Being able to predict local magnetic field opens the door to address a number of key questions. For example, one can now predict the phase changes caused by air/tissue interfaces and, therefore, gain a better understanding of the expected geometric distortions and signal loss from such effects. One can also imagine for simple cases using the predicted phase to compare with the actual phase to extract the susceptibility of the guilty party [40,41].

The critical idea in QSM is to solve Eq. (6) as an inverse problem to provide a pixel-by-pixel estimate of the susceptibility distribution. However, this inverse problem is ill-posed, due to the zero values of $G(\vec{k})$ along the magic angles. Various algorithms have been proposed for solving this ill-posed inverse problem, as will be discussed in the upcoming sections.

3. Data acquisition and reconstruction

Detecting the magnetic field variation is in principle as simple as described in Eq. (1). Unfortunately, there are various sources of phase error ranging from conductivity effects, eddy currents, multiple rf coil combinations and partial volume effects. To further complicate the issue, the digital signal storage system can only store phase values within a 2π range; if the phase passes outside this range, phase aliasing artifacts will appear and the phase data usually need to be unwrapped (see Section 4.2 for more details).

The emphasis on using phase to obtain susceptibility information began with SWI [1–7,42–44]. In order to avoid flow induced phase and to capture as much phase information as possible, a high resolution, flow compensated 3D gradient echo imaging approach was adopted [1–7]. Despite the high resolution used (usually 1 mm^3 or better) there are still partial volume effects for the small veins. It turns out that these partial volume effects are beneficial in SWI for enhancing the small veins [45]. For very high isotropic resolution of 0.5 mm, SWI fails to enhance the veins properly because of the orientation dependence of phase information. This can be improved upon by using susceptibility maps to generate susceptibility weighting masks (see Section 7.6). In this section, a discussion on the optimal imaging parameters is given.

3.1. Imaging resolution

Higher resolution leads to reduced partial volume effects and improved accuracy in the estimated susceptibility values, as demonstrated in Fig. 2. Smaller structures are more affected by partial volume effects than bigger structures. However, the scan time will be increased when high resolution is used. With current fast imaging sequences [46–48] and methods such as parallel and partial Fourier imaging [49–51], achieving a resolution of $0.5 \times 0.5 \times 2$ mm^3 or even higher is applicable in a clinical setting.

Meanwhile, the signal-to-noise ratio (SNR) in the magnitude images will be lower when a higher resolution is used. This corresponds to a larger uncertainty in phase images [22] and susceptibility maps. Consequently, the optimal resolution is dependent on the object of interest, and is a trade-off between the absolute errors and the uncertainties in the estimated susceptibility.

3.2. Optimal echo time

The choice of echo time will depend on the susceptibility of the tissue of interest. Optimizing SNR in phase images usually requires an echo time between $T_2^*/2$ and T_2^* to sustain an acceptable signal level. If optimal contrast-to-noise is favored between two substances with the same T_2^*, then $TE = T_2^*$ is most appropriate and if a specific imaging time is desired (averaging over several acquisitions within a constant imaging time for example) then $TE = T_2^*/2$ is more appropriate [22]. But in the end, the real telltale condition should