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Generalized Lorentzian Tensor Approach (GLTA) as a Biophysical Background for Quantitative Susceptibility Mapping

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Abstract

Purpose—Quantitative susceptibility mapping (QSM) is a potentially powerful technique for mapping tissue magnetic susceptibility from gradient recalled echo (GRE) MRI. Herein we aim to derive the relationships between GRE signal phase and the underlying tissue microstructure and magnetic susceptibility at the cellular level.

Methods—We use Maxwell’s equations and a statistical approach to derive the expression for the magnetic-susceptibility-induced MR signal frequency shift of the GRE signal in single- and multi-compartment systems, in which inhomogeneous magnetic field is induced by the cellular constituents (proteins, lipids, iron, etc.) distributed in intra- and extra-cellular spaces.

Results—We introduce the Generalized Lorentzian Tensor Approach (GLTA) that accounts for both types of anisotropy: the anisotropy of magnetic susceptibility and the structural tissue anisotropy. In the GLTA the frequency shift due to the local environment is characterized by the Lorentzian tensor $\hat{\mathbf{L}}$ which has a substantially different structure than the susceptibility tensor $\hat{\chi}$. While components of $\hat{\chi}$ are simply compartmental susceptibilities “weighted” by their relative volumes, the components of $\hat{\mathbf{L}}$ are weighted by specific numerical factors depending on tissue micro-symmetry and parameters related to the MR pulse sequence. We also provide equations bridging phenomenological and microscopic considerations.

Conclusion—The GLTA provides a consistent background for deciphering phase data.

Keywords

Phase contrast; Generalized Lorentzian Tensor Approach; white matter; magnetic susceptibility; quantitative susceptibility mapping

INTRODUCTION

Quantitative susceptibility mapping (QSM) (e.g. (1–7)) is a potentially powerful technique for evaluating the magnetic susceptibility distribution in a tissue from gradient recalled echo (GRE) MRI phase images. To achieve this goal, certain relationships should be established to link experimental measurements of the GRE signal phase (obtained at the millimeter scale) to the underlying tissue microstructure at the cellular level (micron scale and smaller).

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While definite progress has been achieved by means of phenomenological (8–10) and modeling (11–14) approaches, the issue is still a subject of debate (10,14–16).

To define the problem under consideration, consider tissue as comprised of water and spatially distributed magnetic susceptibility inclusions – biological structures of cellular or subcellular size with magnetic susceptibility different from that of water – cellular membranes, myelin layers, iron stores, neurofilaments, red blood cells, etc. In the external magnetic field $\mathbf{B}_0$, the susceptibility inclusions become magnetized forming “tissue magnetic architecture” (8). For the inclusions characterized by the intrinsic volume magnetic susceptibility tensor $\hat{\chi}_{inclusions}^{(0)}$ (symbol $\hat{\chi}$ denotes tensor), the magnetization distribution is

$$\mathbf{m}(\mathbf{r}) = \hat{\chi}_u^{(0)}(\mathbf{r}) \cdot \mathbf{B}_0 \quad [1]$$

where $\hat{\chi}_u^{(0)}(\mathbf{r})$ is the position-dependent volume magnetic susceptibility tensor, referenced to water:

$$\hat{\chi}_u^{(0)}(\mathbf{r}) = \hat{\chi}^{(0)} \cdot u(\mathbf{r}), \quad \hat{\chi}^{(0)} = (\hat{\chi}_{inclusions}^{(0)} - \hat{\mathbf{I}} \cdot \chi_{water}^{(0)}) \quad [2]$$

where $\chi_{water}^{(0)}$ is the volume magnetic susceptibility of water, $\hat{\mathbf{I}}$ is the 3×3 unit matrix ($I_{ii}=1$, $I_{ij}=0$), and the function $u(\mathbf{r})=1$ inside the inclusions and $u(\mathbf{r})=0$ otherwise. The term “intrinsic volume magnetic susceptibility” means magnetic susceptibility per unit volume of the substance (water or inclusions) and denoted with superscript⁽⁰⁾ to distinguish it from an *average (bulk) volume magnetic susceptibility* (without superscript⁽⁰⁾), i.e. the susceptibility “weighted” by its volume fraction ζ : $\hat{\chi} = \zeta \cdot \hat{\chi}^{(0)}$.

The magnetization $\mathbf{m}(\mathbf{r})$ induces a secondary inhomogeneous magnetic field $\mathbf{h}(\mathbf{r})$, resulting in the magnetic-susceptibility-induced local water MR signal frequency shift. This local shift (with respect to the pure water MR signal frequency) at any given point $\mathbf{r}$ *outside the inclusions* is:

$$\delta f(\mathbf{r}) = \frac{\gamma}{2\pi} \cdot \mathbf{h}(\mathbf{r}) \cdot \mathbf{n} \quad [3]$$

where $\mathbf{n}$ is the unit vector along $\mathbf{B}_0$, and γ is the gyromagnetic ratio (magnetic fields created by external currents are not taken into consideration herein).

Given the distribution of $\mathbf{m}(\mathbf{r})$, the field $\mathbf{h}(\mathbf{r})$ can be found by solving Maxwell equations:

$$\nabla \mathbf{h} = -\nabla \mathbf{m}, \quad \nabla \times \mathbf{h} = 0 \quad [4]$$

A convenient way to solve them for a given distribution of $\mathbf{m}(\mathbf{r})$ and to calculate the magnetic field $\mathbf{h}(\mathbf{r})$ is to use the Fourier transform of the Maxwell equations (e.g., (17), (18)). The local frequency shift $\delta f(\mathbf{r})$ can then be presented in the form:

$$\delta f(\mathbf{r}) = -f_0 \cdot \text{IFT} \left\{ \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{uk}^{(0)} \cdot \mathbf{n})}{k^2} \right\}, \quad \hat{\chi}_{uk}^{(0)} = \text{FT}\{\hat{\chi}_u^{(0)}(\mathbf{r})\} \quad [5]$$

where $f_0 = \gamma B_0 / 2\pi$, FT denotes a standard 3D Fourier transform applied to each component of tensors, and IFT is an inverse FT ($\mathbf{k}$ is a vector in the Fourier domain).

Of course, if the microscopic distribution and angular dependence of frequency shifts $\delta f(\mathbf{r})$ could be measured, we would potentially be able to solve the inverse problem in Eq. [5] and find spatial and orientation dependences of the magnetic susceptibility tensor $\hat{\chi}^{(0)}(\mathbf{r})$. Unfortunately, this problem cannot be solved by means of MRI because a typical scale of magnetic susceptibility inclusions is on the order of microns (cellular and microvascular structures) while the typical resolution of MRI is on the millimeter scale.

Hence, the fundamental question is: what is the relationship between an MR signal that measures an *average phase / frequency* across the imaging voxel and the underlying tissue microstructure at the cellular and sub-cellular levels? In other words, how should one properly define/quantify the influence of numerous magnetic susceptibility inclusions inside an imaging voxel on the MR signal phase measured from a whole voxel? In most QSM papers this issue is addressed *by making two assumptions*:

1. Tissue can simply be characterized by the bulk magnetic susceptibility $\hat{\chi}(\mathbf{R})$ which is a microscopic magnetic susceptibility $\hat{\chi}_u^{(0)}(\mathbf{r})$ averaged across the voxel (hereafter the capital $\mathbf{R}$ labels MRI voxels, while $\mathbf{r}$ in Eq. [5] and earlier stands for the microscopic coordinates on the sub-voxel level); and
2. The effect of the local environment on the MR resonance frequency can be accounted for by using the Lorentzian spherical cavity approach, i.e. assuming that the susceptibility inclusions inside the cavity do not contribute to the local field while inclusions outside the cavity can be considered as a homogeneous medium with the bulk magnetic susceptibility $\hat{\chi}(\mathbf{R})$, creating the magnetic field

$$\frac{1}{3} \cdot \hat{\chi}(\mathbf{R}) \cdot \mathbf{B}_0.$$

For isotropic magnetic susceptibility, $\hat{\chi} = \chi \cdot \hat{\mathbf{I}}$, the well-known and broadly used expression for the frequency shift is (18,19):

$$\delta f(\mathbf{R}) = f_0 \cdot \text{IFT} \left\{ \left[\frac{1}{3} - \frac{(\mathbf{k} \cdot \mathbf{n})^2}{k^2} \right] \cdot \chi_{\mathbf{k}} \right\}; \chi_{\mathbf{k}} = \text{FT}\{\chi(\mathbf{R})\} \quad [6]$$

where the first term in this equation, $\frac{1}{3}\chi_{\mathbf{k}}$, represents the Lorentzian Sphere contribution.

As originally suggested in (7,20), the magnetic susceptibility of White Matter (WM) comprising myelinated axons, can be anisotropic, and the following modification of Eq. [6] was proposed (7):

$$\delta f(\mathbf{R}) = f_0 \cdot \text{IFT} \left\{ \left[\frac{1}{3} \mathbf{n} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n} - \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n})}{k^2} \right] \right\}; \hat{\chi}_{\mathbf{k}} = \text{FT}\{\hat{\chi}(\mathbf{R})\} \quad [7]$$

While the Lorentzian Sphere approach in Eq. [6] represents a reasonable approximation for the case when magnetic susceptibility inclusions are randomly distributed and randomly

oriented in the tissue (8–10,21,22), its usage for the case of anisotropic susceptibility, as in Eq. [7], is problematic (8–10,21,22). Indeed, magnetic susceptibility can be anisotropic only if the underlying biological tissue microstructure is also anisotropic: symmetry of magnetic susceptibility must “follow” structural symmetry. For instance, spherical inclusions can possess only susceptibility of spherical symmetry (unless, of course, such inclusions are artificially fabricated with, e.g., long molecules parallel to each other; however, such “spherical” structures do not exist in real biological systems). Whereas long cylindrical inclusions can possess either spherical (if they are built from homogeneous material) or cylindrical (if they are built from long oriented molecules) symmetry. The latter can be the case with long cells like neurons containing highly ordered and oriented myelin sheath and neurofilaments. As demonstrated in (8), in the presence of longitudinally oriented structures, e.g., axons, the Lorentzian Sphere approach is no longer valid; instead, the Generalized Lorentzian Approach (GLA) was introduced (8). In (10), the GLA was applied to the important case when the tissue has two types of susceptibility inclusions – randomly distributed and randomly oriented inclusions (with isotropic magnetic susceptibility χ_{iso}), and parallel longitudinal structures with cylindrical symmetry (characterized by the radial susceptibility χ_r and axial susceptibility χ_a). Accounting for both, the *structural anisotropy* and the *anisotropy of magnetic susceptibility*, the Lorentzian contribution to the frequency shift is shown to be equal to (10):

$$\delta f_L = f_0 \cdot \left(\frac{1}{3} \cdot \chi_{iso} + \frac{1}{2} \cdot \chi_r \cdot \sin^2 \alpha \right) \quad [8]$$

where α is the angle between the external field $\mathbf{B}_0$ and the longitudinally oriented structures considered as long cylinders. Importantly, the axial component, χ_a , does not contribute to the Lorentzian term in Eq. [8], while it does contribute to the tissue magnetization and the associated magnetic field perturbation.

The goal of this paper is to further extend the GLA to account for magnetic susceptibility anisotropy (hence the term Generalized Lorentzian Tensor Approach (GLTA)) including multi-compartment tissue structure. We demonstrate here that, by accounting for both the tissue symmetry and multi-compartment structure, the GLTA leads to the following general equation for magnetic susceptibility-induced MRI signal frequency shift:

$$\delta f = f_0 \cdot \text{IFT} \left\{ \left[\mathbf{n} \cdot \hat{\mathbf{L}}_{\mathbf{k}} \cdot \mathbf{n} - \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n})}{k^2} \right] \right\}, \hat{\mathbf{L}}_{\mathbf{k}} = \text{FT} \{ \hat{\mathbf{L}}(\mathbf{R}) \} \quad [9]$$

For the important case of two types of the susceptibility inclusions in WM (isotropic and longitudinal), the tensors $\hat{\chi}$ and $\hat{\mathbf{L}}$ for a single compartment model are:

$$\hat{\chi} = \begin{pmatrix} \chi_{iso} & 0 & 0 \\ 0 & \chi_{iso} & 0 \\ 0 & 0 & \chi_{iso} \end{pmatrix} + \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & \chi_a \end{pmatrix} \quad [10]$$

$$\hat{\mathbf{L}} = \frac{1}{3} \cdot \begin{pmatrix} \chi_{iso} & 0 & 0 \\ 0 & \chi_{iso} & 0 \\ 0 & 0 & \chi_{iso} \end{pmatrix} + \frac{1}{2} \cdot \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad [11]$$

For a multi-compartment model, the expression for the tensor $\hat{\chi}$ remains the same, while the expression for the tensor $\hat{\mathbf{L}}$ becomes:

$$\hat{\mathbf{L}} = \frac{1}{3} \cdot \begin{pmatrix} \chi_{iso}^{(app)} & 0 & 0 \\ 0 & \chi_{iso}^{(app)} & 0 \\ 0 & 0 & \chi_{iso}^{(app)} \end{pmatrix} + \frac{1}{2} \cdot \begin{pmatrix} \chi_r^{(app)} & 0 & 0 \\ 0 & \chi_r^{(app)} & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad [12]$$

where $\chi_{iso}^{(app)}$ and $\chi_r^{(app)}$ are *apparent* magnetic susceptibilities (see below).

The tensor $\hat{\mathbf{L}}$ (which we term the *Lorentzian* tensor) is substantially different from the susceptibility tensor $\hat{\chi}$ in several ways. First, contributions from isotropic and longitudinal structures are “weighted” in $\hat{\mathbf{L}}$ by different numerical coefficients (1/3 and 1/2, correspondingly). Second, the axial component χ_a does not contribute to $\hat{\mathbf{L}}$ at all. Third, in the case when water also resides inside the inclusions (e.g., in axons), the cylindrical symmetry of the Lorentzian term is preserved, Eq. [12], but the components of $\hat{\mathbf{L}}$ should be considered as apparent because they depend not only on the original components of $\hat{\chi}$ but also on details of the multi-compartment tissue relaxation properties and pulse sequence parameters. Specific relationships can be deduced from a theoretical multi-compartment approach for describing the tissue signal. Below we provide such relationships, Eqs. [48]–[49], derived based on our modeling results (13,14).

It is important to note that Eq. [9] substantially differs from Eq. [7] proposed in (7). In Eq. [7], both the terms in the brackets contain the same tensor $\hat{\chi}_k$. In Eq. [9], the second term is the same as in Eq. [7], however, the first (Lorentzian) term is defined by Eqs. [11]–[12] and depends on the components of magnetic susceptibility tensor in a quite different way – compare Eqs. [10] and [11]–[12].

In our previous papers (8–10,21,22), the theoretical consideration was based on the concept of a Lorentzian cavity (22), which is a convenient mathematical tool for calculating the effective magnetic field created by local environment. A detail discussion of the Lorentzian cavity approach is provided in (10). Here we only note that Lorentz himself discussed a problem of a local field affecting a point dipole and induced by other point dipoles. In biological system, it is an analog of a local field at a water molecule, induced by other water molecules playing a role of susceptibility inclusions. In our approach, when susceptibility effects are referenced to water, the effect of water-on-water is implicitly included in the reference frequency.

In the current paper we employ another method that is based on a general consideration of Maxwell’s equations and a statistical approach without enlisting the concept of Lorentzian cavity. Our approach accounts for both types of anisotropy: the anisotropy of magnetic

susceptibility and the structural anisotropy. We also provide equations bridging the phenomenological and microscopic considerations.

METHODS

Consider an imaging voxel comprising water molecules and susceptibility inclusions. An MR signal at time t after RF pulse is

$$S(t) = S_0 \cdot \langle \exp[-i\varphi(t)] \rangle \quad [13]$$

where S_0 is the signal amplitude and $\varphi(t)$ is a phase accumulated by a single water molecule diffusing along a given trajectory $\mathbf{r} = \mathbf{r}(t)$:

$$\varphi(t) = 2\pi \cdot \int_0^t dt' f[\mathbf{r}(t')] \quad [14]$$

The angular brackets in Eq. [13] mean averaging over all possible initial positions and trajectories of the diffusing molecules. Besides, if magnetic susceptibility inclusions are randomly distributed, $\langle \dots \rangle$ also includes averaging over possible positions of the inclusions. In what follows, we assume that the signal from a single-compartment system can be described as

$$S(t) = S_0 \cdot \exp(-2\pi i \cdot \bar{f} \cdot t) \cdot \exp[-\Gamma(t)] \quad [15]$$

where $\bar{f}$ is a net frequency and $\Gamma(t)$ is the attenuation function. This approximation is valid in the static dephasing regime (23) and in the motional narrowing regime when each molecule samples all possible positions in the voxel. The case of multi-compartment tissue structures will be discussed in the following sections.

Initially we assume that the inclusions do not contain water molecules. In this case, the frequency shift $\delta f = \bar{f} - f_0$ in a given voxel $\mathbf{R}$ is determined by the induced magnetic field averaged over the volume $V_e(\mathbf{R})$ outside the inclusions (in what follows, for brevity, we omit the argument $\mathbf{R}$ labeling the voxels):

$$\delta f = \frac{\gamma}{2\pi} \cdot \langle \mathbf{H}_e \cdot \mathbf{n} \rangle, \mathbf{H}_e = \langle \mathbf{h}(\mathbf{r}) \rangle_{outside} = \frac{1}{V_e} \cdot \int_{V_e} d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad [16]$$

The field $\mathbf{H}_e$ should be distinguished from the macroscopic magnetic field

$$\mathbf{H} = \frac{1}{V} \cdot \int_V d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad [17]$$

obtained by averaging the local field over the *total* voxel volume V . It is important to emphasize that just the magnetic field $\mathbf{H}$ (not $\mathbf{H}_e$!) satisfies the macroscopic magnetostatic Maxwell equations

$$\nabla \mathbf{H} = -\nabla \mathbf{M}, \nabla \times \mathbf{H} = 0 \quad [18]$$

where

$$\mathbf{M} = \frac{1}{V} \cdot \int_V d\mathbf{r} \mathbf{m}(\mathbf{r}) \quad [19]$$

is the average magnetization in the voxel, and $\mathbf{m}(\mathbf{r})$ is given by Eq. [1]. Equations [18] can be solved similar to Eq. [5].

Obviously, the quantities $\mathbf{H}$ and $\mathbf{H}_e$ are related:

$$\mathbf{H} = (1 - \zeta) \cdot \mathbf{H}_e + \zeta \cdot \mathbf{H}_i \quad [20]$$

where

$$\mathbf{H}_i = \left\langle \mathbf{h}(\mathbf{r}) \right\rangle_{inside} = \frac{1}{V_i} \cdot \int_{V_i} d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad [21]$$

is the local magnetic field averaged over the volume V_i inside the inclusions and ζ is the volume fraction occupied by the inclusions in the voxel.

Consider first the case when in a given voxel there is a single type of identical susceptibility inclusions of the same shape and orientation, occupying the volume fraction ζ and described by the volume magnetic susceptibility tensor $\hat{\chi}^{(0)}$. In this case, the magnetization is also the same within all the inclusions, $\mathbf{m} = \mathbf{m}_0 = \hat{\chi}^{(0)} \cdot \mathbf{B}_0$, and $\mathbf{M} = \zeta \mathbf{m}_0$. In addition to $\mathbf{B}_0$, each inclusion “feels” the position-dependent induced magnetic field $\mathbf{h}_e(\mathbf{r})$ created by all other inclusions and the field induced by the inclusion itself. In what follows, we assume that the shape of the inclusions can be approximated by an ellipsoid (spheres, long cylinders, in particular). In this case, the induced magnetic field within a given inclusion, $\mathbf{h}_i(\mathbf{r})$, is related to $\mathbf{h}_e(\mathbf{r})$ by a well-known expression for a shift of the magnetic field within a homogeneously magnetized ellipsoid: $\mathbf{h}_i(\mathbf{r}) = \mathbf{h}_e(\mathbf{r}) - \hat{\mathbf{N}} \mathbf{m}_0$, where $\hat{\mathbf{N}}$ is the so called demagnetization tensor determined by the inclusion’s shape (analytical expressions and tables for this tensor can be found, e.g., in (24,25)). By averaging this equation over all the positions (but not orientations) of the inclusions (similar to the statistical approach used in (23)), we find that the average fields $\mathbf{H}_i$ and $\mathbf{H}_e$ are related as follows:

$$\mathbf{H}_i = \mathbf{H}_e - \hat{\mathbf{N}} \mathbf{m}_0 \quad [22]$$

Combining Eqs. [20] and [22], we get

$$\mathbf{H}_e = \mathbf{H} + \mathbf{H}_L; \mathbf{H}_L = \hat{\mathbf{N}} \hat{\chi} \mathbf{B}_0 \quad [23]$$

where $\hat{\chi} = \zeta \cdot \hat{\chi}^{(0)}$ is the average volume magnetic susceptibility, often called bulk volume magnetic susceptibility. As already mentioned in the Introduction, the average volume

susceptibility is designated $\hat{\chi}$ (no superscript⁽⁰⁾) to distinguish it from $\hat{\chi}^{(0)}$ (with the superscript⁽⁰⁾) - intrinsic volume magnetic susceptibility of inclusions themselves.

Thus, the magnetic field $\mathbf{H}_e$ determining the frequency shift δf in Eq. [16] comprises two parts: the field $\mathbf{H}$ satisfying Maxwell Eqs. [18], and the field $\mathbf{H}_L$. The latter can be called the *Lorentzian* field:

$$\mathbf{H}_L = \hat{\mathbf{L}}\mathbf{B}_0, \hat{\mathbf{L}} = \hat{\mathbf{N}}\hat{\chi} \quad [24]$$

Correspondingly, the frequency shift can be represented as

$$\delta f = \delta f_H + \delta f_L, \delta f_H = \frac{\gamma}{2\pi} \cdot (\mathbf{H} \cdot \mathbf{n}), \delta f_L = f_0 \cdot (\mathbf{n} \cdot \hat{\mathbf{L}} \cdot \mathbf{n}) \quad [25]$$

Thus, the frequency shift δf_L (defined by the *Lorentzian* tensor $\hat{\mathbf{L}}$ in Eq. [24]) is determined by the two types of anisotropy: the structural anisotropy of inclusions (spheres, cylinders, etc.), described by the demagnetization tensor $\hat{\mathbf{N}}$, and the anisotropy of susceptibility, described by the susceptibility tensor $\hat{\chi}$.

Equations [24]–[25] can be readily generalized for the case when the voxel contains the susceptibility inclusions of several types, each of them characterized by its own volume fraction ζ_j , demagnetization tensor $\hat{\mathbf{N}}_j$, and intrinsic susceptibility tensor $\hat{\chi}_j^{(0)}$. In this case, the volume susceptibility tensor $\hat{\chi}$ and the Lorentzian tensor $\hat{\mathbf{L}}$ are simply the sums of the contributions of all types of the susceptibility inclusions:

$$\hat{\chi} = \sum_j \zeta_j \hat{\chi}_j, \hat{\mathbf{L}} = \sum_n \hat{\mathbf{N}}_j \hat{\chi}_j, \hat{\chi}_j = \zeta_j \cdot \hat{\chi}_j^{(0)} \quad [26]$$

The frequency shift δf , Eq. [25], can also be presented in the form similar to Eq. [9]:

$$\delta f = f_0 \cdot \text{IFT} \left\{ \left[\mathbf{n} \cdot \hat{\mathbf{L}}_{\mathbf{k}} \cdot \mathbf{n} - \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n})}{\mathbf{k}^2} \right] \right\} \quad [27]$$

RESULTS

Single Compartment Model

When considering biological tissue, two types of the susceptibility inclusions are of main importance:

- A. Randomly distributed spherical-like inclusion (e.g., small sub-cellular structures, iron stores) with isotropic susceptibility described by a single scalar χ_{iso} ; in this case, the tensors $\hat{\chi}$, $\hat{\mathbf{N}}$ and $\hat{\mathbf{L}}$ are simply proportional to the unit tensor $\hat{\mathbf{I}}$:

$$\hat{\mathbf{N}}_{iso} = \frac{1}{3} \cdot \hat{\mathbf{I}}, \hat{\chi}_{iso} = \chi_{iso} \cdot \hat{\mathbf{I}}, \hat{\mathbf{L}}_{iso} = \frac{\chi_{iso}}{3} \cdot \hat{\mathbf{I}} \quad [28]$$

It can be easily demonstrated that, due to the orientation averaging, the same result takes place when the inclusions with isotropic susceptibility χ_{iso} are not spheres but their orientations are random. Indeed, the orientation averaging of the quantity δf_L , Eq. [25], leads to $\delta f_L = f_0 \cdot \chi_{iso} \cdot \langle n_\alpha n_\beta \rangle_{orient} = f_0 \cdot \chi_{iso} / 3$ (because $\langle n_\alpha n_\beta \rangle_{orient} = \delta_{\alpha\beta} / 3$, $\delta_{\alpha\beta}$ is the Kronecker delta, and $\text{Tr}(\hat{\mathbf{N}}) = 1$).

- B.** Longitudinally arranged inclusions (neurons) which can be considered as long parallel cylinders with the anisotropic susceptibility described by two different components: axial χ_a and radial χ_r . In this case the tensors $\hat{\chi}$, $\hat{\mathbf{N}}$ and $\hat{\mathbf{L}}$ (with the Z-axis oriented along the inclusions) are:

$$\hat{\mathbf{N}}_{cyl} = \frac{1}{2} \cdot \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \hat{\chi}_{cyl} = \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & \chi_a \end{pmatrix}, \hat{\mathbf{L}}_{cyl} = \frac{1}{2} \cdot \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad [29]$$

Importantly, the axial component of susceptibility tensor is not present in the Lorentzian tensor $\hat{\mathbf{L}}_{cyl}$ and, consequently, in the Lorentzian part of the frequency shift δf_L . Note that if the longitudinal inclusions are not parallel to each other (as in WM) but uniformly oriented (as in GM), the averaged Lorentzian tensor takes the form as in Eq. [28] with the substitution $\chi_{iso} \rightarrow \chi_r$. It should be emphasized, however, that despite this resemblance, the result is still different from that obtained by using the Lorentzian spherical cavity approach and from Eq. 7: the axial component χ_a does not contribute to the averaged Lorentzian tensor.

If both the types (A) and (B) are present in a voxel, the average magnetic field $\mathbf{H}_e$ defining the resonance frequency (similar to Eq. [23]) is

$$\mathbf{H}_e = \mathbf{H} + (\hat{\mathbf{N}}_{cyl} \cdot \hat{\chi}_{cyl} + \hat{\mathbf{N}}_{iso} \cdot \hat{\chi}_{iso}) \cdot \mathbf{B}_0 \quad [30]$$

The tensors $\hat{\chi}$ and $\hat{\mathbf{L}}$ in Eq. [27] in this case are:

$$\hat{\chi} = \hat{\chi}_{iso} + \hat{\chi}_{cyl} = \begin{pmatrix} \chi_{iso} & 0 & 0 \\ 0 & \chi_{iso} & 0 \\ 0 & 0 & \chi_{iso} \end{pmatrix} + \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & \chi_a \end{pmatrix} \quad [31]$$

$$\hat{\mathbf{L}} = \hat{\mathbf{L}}_{iso} + \hat{\mathbf{L}}_{cyl} = \frac{1}{3} \cdot \begin{pmatrix} \chi_{iso} & 0 & 0 \\ 0 & \chi_{iso} & 0 \\ 0 & 0 & \chi_{iso} \end{pmatrix} + \frac{1}{2} \cdot \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad [32]$$

and the frequency shift is given by Eq. [25] and [27]. In this case, the Lorentzian part of the frequency shift, δf_L , can be presented as in Eq. [8], which is exactly the same as obtained in (8) using the GLA with accounting for the structural anisotropy and in (10) using the GLA with accounting for both the structural and susceptibility anisotropy.

Effects of multi-compartment tissue structure

In the previous section, we provided the phenomenological expressions for the frequency shift assuming that the MR signal from water molecules originates only from the space *outside* the susceptibility inclusions. Due to multi-compartment brain tissue structures, in which the frequency shifts are different in different compartments (26), the above-derived expressions should be modified. This effect is especially important in WM where water in the axons surrounded by the myelin sheath and water within the myelin sheath itself contribute to the GRE MR signal (11–14). As was experimentally demonstrated in (11,12), this leads to a substantial non-linear dependence of the GRE signal phase from WM.

Here we use the model of neuronal fiber developed in (13,14) and presented in Fig. 1. The axon contains two types of magnetic susceptibility inclusions: randomly distributed and oriented inclusions with the isotropic susceptibility $\chi_{iso}^{(A)}$ and longitudinally arranged inclusions (neurofilaments) with anisotropic susceptibility characterized by the susceptibility tensor $\hat{\chi}^{(A)}$ of cylindrical symmetry (as in Eq. [29]). The magnetic susceptibility of the lipoprotein layers is characterized by the parameters $\chi_{\parallel}^{(ml)}$ and $\chi_{\perp}^{(ml)}$, which are the susceptibilities parallel and perpendicular to the local radial direction in the myelin rings. For generality, we assume that the aqueous layers in myelin and extracellular space also contain randomly distributed and randomly oriented inclusions with isotropic susceptibilities $\chi_{iso}^{(mw)}$ and $\chi_{iso}^{(e)}$, respectively. All these susceptibilities represent contributions of corresponding inclusions to the bulk volume magnetic susceptibilities of a given compartment of a neuronal fiber (as there is no water in lipoprotein layers, the bulk susceptibilities $\chi_{\parallel}^{(ml)}$ and $\chi_{\perp}^{(ml)}$ coincide with their intrinsic values).

The volume fractions ε_n ($n = A, ml, mw, e$) of the four compartments in Fig.1: axon (A), myelin lipoprotein layers (ml), myelin aqueous layers (mw), and extracellular space (e) are:

$$\varepsilon_A = \zeta \cdot g^2, \varepsilon_{ml} = \zeta \cdot (1 - g^2) \cdot \frac{d}{d + d_w}, \varepsilon_{mw} = \zeta \cdot (1 - g^2) \cdot \frac{d_w}{d + d_w}, \varepsilon_e = 1 - \zeta \quad [33]$$

where ζ is the volume fraction of the neurons (axons + myelin sheaths); $g = R_A/R_e$ is the so called g-ratio. The components of the net (bulk) volume magnetic susceptibility of the object (neurons + extracellular space), determining the macroscopic magnetic field $\mathbf{H}$, can be presented in the form of Eq. [31] with

$$\chi_{iso} = \varepsilon_A \cdot \chi_{iso}^{(A)} + \varepsilon_{mw} \cdot \chi_{iso}^{(mw)} + \varepsilon_e \cdot \chi_{iso}^{(e)} \quad [34]$$

$$\chi_r = \varepsilon_A \cdot \chi_r^{(A)} + \varepsilon_{ml} \cdot \bar{\chi}^{(ml)}, \bar{\chi}^{(ml)} = \frac{1}{2}(\chi_{\parallel}^{(ml)} + \chi_{\perp}^{(ml)}) \quad [35]$$

$$\chi_a = \varepsilon_A \cdot \chi_a^{(A)} + \varepsilon_{ml} \cdot \chi_{\perp}^{(ml)} \quad [36]$$

(the structure of $\chi^{(ml)}$ is due to angular averaging of angle-dependent local susceptibility of the lipoprotein layers (13,14)).

In contrast to the susceptibility tensor $\hat{\chi}$ depending mainly on the tissue electron structure, the Lorentzian tensor $\hat{\mathbf{L}}$ for a multi-compartment structure is substantially affected by the details of MRI experiment. While the symmetry and the structure of $\hat{\mathbf{L}}$ remains the same as in Eq. [32], the components of $\hat{\mathbf{L}}$ in Eq. [32] become “apparent”.

In the model proposed in (13,14), the signal is a sum of signals from three compartments (myelin lipid compartment does not directly contribute to the MR signal) and is as follows:

$$S(TE) = \sum_n \varepsilon_n \cdot S_n(TE) \cdot \exp(-i2\pi \cdot \delta f_n \cdot TE) \quad [37]$$

Here $S_n(TE) = S_n(0) \cdot \exp(-\Gamma_n(TE))$ are the signal amplitudes at echo time TE , $\Gamma_n(TE)$ are the attenuation functions describing the signal decay, and δf_n are the average frequency shifts in three compartments ($n = A, mw, e$):

$$\frac{\delta f_A}{f_0} = \frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d+d_w} \Delta \chi^{(ml)} \cdot \ln \left(\frac{1}{g} \right) + \left(-\frac{1}{2} \sin^2 \alpha + \frac{1}{3} \right) \cdot \chi_{iso}^{(A)} \quad [38]$$

$$\frac{\delta f_{mw}}{f_0} = \frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d+d_w} \left\{ \Delta \chi^{(ml)} \cdot \left[\frac{1}{2} + \frac{g^2 \ln g}{(1-g^2)} \right] - \lambda \cdot \chi_{\parallel}^{(ml)} \right\} + \left(-\frac{1}{2} \sin^2 \alpha + \frac{1}{3} \right) \cdot \chi_{iso}^{(mw)} \quad [39]$$

$$\frac{\Delta f_e}{f_0} = \left(-\frac{1}{2} \sin^2 \alpha + \frac{1}{3} \right) \cdot \chi_{iso}^{(e)} \quad [40]$$

where $\Delta \chi^{(ml)} = \chi_{\parallel}^{(ml)} - \chi_{\perp}^{(ml)}$, α is the angle between the axonal and external magnetic field $\mathbf{B}_0$ directions (as in Eq. [8]); the term $(-\lambda \cdot \chi_{\parallel}^{(ml)})$ corresponds to the “hop-in hop-out” mechanism proposed in (14), in which the parameter λ defines the apparent fraction of time that a water molecule resides in the lipid layer (in (14) this parameter was denoted as ζ). The hop-in hop-out mechanism describes an origin of the additional phase shift for water molecules associated with the aqueous layers but not with the lipoprotein layers. Equation [40] and the last terms in Eqs. [38]–[39] are due to the presence of randomly distributed and randomly oriented structures forming cellular matrix (neurofilaments, etc.). These terms are obtained in the framework of the GLA, for a circular cylindrical shape of a neuronal fiber (and pure water outside the fiber). Importantly, the longitudinally oriented part of these structures is “invisible” in local frequency shifts, though it contributes to the frequency shifts outside these structures (8). The first term in Eq. [38] is similar to that first derived by Wharton and Bowtell in the framework of the “hollow cylinder” model (11). Whereas Eq. [39] for the myelin water signal is different from the corresponding expression in (11) (see detail discussion in (14)).

It is convenient to re-write Eq. [37] in the form

$$S = \bar{S}_0(TE) \cdot \exp(-2\pi i \cdot \bar{\delta f} \cdot TE) \cdot \sum_n \varepsilon_n \cdot c_n(TE) \cdot \exp(-i2\pi \cdot \Delta f_n \cdot TE) \quad [41]$$

where

$$\bar{S}_0(TE) = \sum_n \varepsilon_n \cdot S_n(TE), c_n(TE) = \frac{S_n(TE)}{S_0(TE)} \quad [42]$$

$$\bar{\delta f} = \sum_n \varepsilon_n \cdot c_n(TE) \cdot \delta f_n, \Delta f_n = \delta f_n - \bar{\delta f} \quad [43]$$

The total signal phase, in general, substantially depends on gradient echo time TE in a nonlinear way due to (i) exponential factors with different f_n in the sum in Eq. [41], and (ii) since the “weighting factors” c_n depend on MRI pulse sequence parameters, compartments’ relaxation properties and TE . At any TE , the *instant* frequency shift of the signal can be obtained by differentiating the signal phase. In what follows, we consider the case of sufficiently short times, when for all the compartments $2\pi \cdot f_n \cdot TE < 1$. In this case, the sum in Eq. [41] is close to 1 and can be omitted. As a result, the signal phase can be characterized by a single (though TE -dependent) average frequency $\bar{\delta f}$, Eq. [43]. This approximation is also valid in the regime when the signal contribution from one of the compartments becomes negligible (e.g. $\Gamma_n(TE) > 1$), even if the condition $2\pi \cdot f_n \cdot TE < 1$ for this compartment fails. An example of such a compartment is myelin water that has a large frequency shift and a very short $T2^*$ (11,12).

Hence, the total frequency shift $\bar{\delta f}$ is given by Eq. [43] with ε_n and δf_n defined by Eqs. [33] and [38]–[40]:

$$\bar{\delta f} = \varepsilon_A \cdot c_A(TE) \cdot \delta f_A + \varepsilon_{mw} \cdot c_{mw}(TE) \cdot \delta f_{mw} + \varepsilon_e \cdot c_e(TE) \cdot \delta f_e \quad [44]$$

The expression for $\bar{\delta f}$ in Eq. [44] should satisfy the general Eq. [25]: $\bar{\delta f} = \delta f_H + \delta f_L$. For the circular cylindrical axonal fiber considered above, δf_H is the same as for a homogeneously magnetized circular cylinder forming an angle α with $\mathbf{B}_0$. Using the demagnetization tensor for a long cylinder, as in Eq. [29], we obtain:

$$\delta f_H = -f_0 \cdot \frac{1}{2} \cdot (\chi_{iso} \cdot \chi_r) \cdot \sin^2 \alpha \quad [45]$$

where χ_{iso} and χ_r are given in Eqs. [34]–[35]. Due to the cylindrical symmetry of the system, we can present the frequency shift δf_L similar to Eq. [8] with the susceptibilities considered as *apparent* and denoted as $\chi_{iso}^{(app)}$ and $\chi_r^{(app)}$:

$$\delta f_L = f_0 \cdot \left(\frac{1}{3} \cdot \chi_{iso}^{(app)} + \frac{1}{2} \cdot \chi_r^{(app)} \cdot \sin^2 \alpha \right) \quad [46]$$

Indeed, in this case, the total frequency shift is

$$\delta f = \delta f_H + \delta f_L = f_0 \cdot \left[\frac{1}{3} \cdot \chi_{iso}^{(app)} + \frac{1}{2} \cdot \left(\chi_r^{(app)} - \chi_r - \chi_{iso} \right) \cdot \sin^2 \alpha \right] \quad [47]$$

Comparing this expression with $\overline{\delta f}$ in Eq. [44], we obtain the relationships between the “true” and apparent susceptibilities:

$$\chi_{iso}^{(app)} = \varepsilon_A \cdot c_A(T E) \cdot \chi_{iso}^{(A)} + \varepsilon_{mw} \cdot c_{mw}(T E) \cdot \chi_{iso}^{(mw)} + \varepsilon_e \cdot c_e(T E) \cdot \chi_{iso}^{(e)} \quad [49]$$

$$\begin{aligned} \chi_r^{(app)} = & \chi_r + \chi_{iso} - \chi_{iso}^{(app)} \\ & + \frac{d}{(d+d_w)} \left\{ \varepsilon_A \cdot c_A(T E) \cdot \Delta \chi^{(ml)} \ln \left(\frac{1}{g} \right) + \varepsilon_{mw} \cdot c_{mw}(T E) \cdot \left[\Delta \chi^{(ml)} \cdot \left(\frac{1}{2} + \frac{g^2 \ln g}{(1-g^2)} \right) - \lambda \cdot \chi_{\parallel}^{(ml)} \right] \right\} \quad [49] \end{aligned}$$

It is important to emphasize that Eqs. [46, 48, 49] describe the Lorentzian contribution to the frequency shift and are valid not only for a single neuronal fiber but for an arbitrary shaped neuronal bundle of parallel fibers (the shape of the bundle and surrounding medium affect only the term δf_H). These expressions (derived in the framework of our model of neuronal fiber (13,14)) along with Eqs. [9]–[12] provide the basis for analyzing the phase images obtained by means of gradient echo MRI.

DISCUSSION

QSM is a potentially powerful technique for providing quantitative information on tissue magnetic susceptibility. However, to achieve this goal, equations connecting measured signal phase with underlying tissue microstructure should take into account a number of important effects described in this paper.

We would like to emphasize once again that the Lorentzian sphere approximation often used in QSM literature is not valid in the presence of long cells (e.g. axons). The structure of the Lorentzian tensor $\hat{\mathbf{L}}$, Eq. [12], is substantially different from the structure of the susceptibility tensor $\hat{\chi}$, Eq. [10], in several ways: magnetic susceptibility contributions from isotropic and longitudinal structures are “weighted” in $\hat{\mathbf{L}}$ by different numerical coefficients; the axial component χ_a of the magnetic susceptibility tensor $\hat{\chi}$ does not contribute to $\hat{\mathbf{L}}$; if water resides also inside the inclusions (e.g., in axons) and contributes to the MR signal, the cylindrical symmetry of the Lorentzian term $\hat{\mathbf{L}}$ is preserved but the components of $\hat{\mathbf{L}}$ become dependent not only on the original components of $\hat{\chi}$ but also on tissue relaxation properties (e.g. T_1 , T_2^*) and pulse sequence parameters (e.g. TE , TR , flip angle θ). Equations [48]–[49] provide specific relationships for the parameters of $\hat{\mathbf{L}}$ derived using our previous modeling results (13,14). The dependence of these parameters on the pulse sequence can be established for each particular case. For a standard GRE sequence we have:

$$S_n(0) \sim \frac{1 - \exp(-TR/T_{1n})}{1 - \exp(-TR/T_{1n}) \cdot \cos \theta} \cdot \sin \theta \quad [50]$$

Using Eqs. [48]–[50], one can obtain a set of data with different sequence parameters, which makes it possible to determine “true” magnetic susceptibilities. Also, different techniques can be used to selectively suppress or enhance specific compartments. One should keep in mind the conditions under which Eqs. [48, 49] were derived.

The anisotropic behavior of GRE signal phase predicted in (8) was confirmed in a number of publications, e.g. (27–31). A rather strong similarity between signal phase anisotropy and diffusion anisotropy determined by DTI (7,32) suggests that some features of DTI and GRE phase signals are defined by common mechanisms. Equations [48]–[49] can provide further insights into this interesting phenomenon and obtain complementary information on the effects of tissue microstructure that are common and/or different for DTI and GRE.

Equations [48]–[49] can also provide explanation of the tissue-dependent frequency differences between NAA, Cho, Cr and water signals reported in (33). Indeed, due to a different localization of metabolites and water, their contributions to these equations are quite different. In the spectroscopy experiment (33), the water signal is generated mostly by intra-cellular and extra-cellular compartments (contribution of myelin water signal is negligible because very long echo times, 144 ms, was used), while NAA is known to be located mostly intracellular.

Some of the components of susceptibility and Lorentzian tensors can be found by comparing with published data. Unfortunately, in most papers only results obtained by analysis using Lorentzian sphere approximation are reported and these data cannot be used for this purpose. In Table 1 we provide results obtained by re-analyzing raw data published by Luo et al (30). It is important to note that the value for $\chi_r + \chi_{iso}$ represents true volume susceptibility difference between the optic nerve and water, while the value of $\chi_r^{(app)}$ depends on pulse sequence parameters and tissue relaxation properties. The value for $\chi_r + \chi_{iso} = -0.1$ ppm is similar to value of -0.085 ppm found in (31), though no information on the reference solution was provided there.

CONCLUSION

In this paper we introduce the Generalized Lorentzian Tensor Approach (GLTA) – a phenomenological method describing magnetic-susceptibility-induced gradient echo MRI signal frequency shift in the presence of longitudinal structures such as axons in WM. The GLTA is essential tool to decipher information on tissue structural and magnetic anisotropy. We also provide equations bridging the phenomenological and microscopic considerations.

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Figure 1. (modified from (13)). A schematic structure of an axon (A) with radius R_A surrounded by a myelin sheath with external radius R_e consisting of interleaved lipoprotein layers (ml) of thickness d marked in grey, separated by aqueous layers (mw) of thickness d_w . Each lipoprotein layer is formed by highly organized radially-oriented long molecules (shown as ellipsoids in inset) with presumed anisotropic magnetic susceptibility.

Table 1

True and apparent parameters obtained by re-analyzing the data for optic nerve (30). The values in the first row are obtained by analyzing the signal phase outside the nerve and, therefore, are determined by the net nerve transverse susceptibility which, in the notation of Eqs. [34]–[35], is $\chi_r + \chi_{iso}$.

(ppm)	(fresh nerve)	fixed nerve
$\chi_r + \chi_{iso}$	-0.100 ± 0.010	-0.106 ± 0.028
$\chi_r^{(app)} - \chi_r - \chi_{iso}$	0.044 ± 0.004	0.090 ± 0.018
$\chi_r^{(app)}$	-0.056 ± 0.011	-0.016 ± 0.033

The values for both, fresh nerve (suspended in 1% PBS solution) and fixed nerves (suspended in formalin) are listed with respect to water using magnetic susceptibilities of the solutions that were measured in (30) independently. The values in the second row are calculated from the slope of the $\sin^2\alpha$ -dependence of the frequency shift within the nerve. The third row is a linear combination of the first two. The difference between the “apparent” parameters for fresh and fixed nerves can be explained by their different relaxation properties. Whereas the combination of the “true” susceptibilities $\chi_r + \chi_{iso}$ does not depend on the pulse sequence and therefore is the same for the fresh and fixed nerves.