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Lorentzian Effects in Magnetic Susceptibility Mapping of Anisotropic Biological Tissues

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Abstract

The ultimate goal of MRI is to provide information on biological tissue microstructure and function. Quantitative Susceptibility Mapping (QSM) is one of the newer approaches for studying tissue microstructure by means of measuring phase of Gradient Recalled Echo (GRE) MRI signal. The fundamental question in the heart of this approach is: what is the relationship between the net phase/frequency of the GRE signal from an imaging voxel and the underlying tissue microstructure at the cellular and sub-cellular levels?

In the presence of external magnetic field, biological media (e.g. cells, cellular components, blood) become magnetized leading to the MR signal frequency shift that is affected not only by bulk magnetic susceptibility but by the local cellular environment as well. The latter effect is often termed the Lorentzian contribution to the frequency shift. Evaluating the Lorentzian contribution - one of the most intriguing and challenging problems in this field - is the main focus of this review.

While the traditional approach to this problem is based on introduction of an imaginary Lorentzian cavity, a more rigorous treatment was proposed recently based on a statistical approach and a direct solution of the Maxwell equations. This approach, termed the Generalized Lorentzian Tensor Approach (GLTA), is especially fruitful for describing anisotropic biological media. The GLTA adequately accounts for two types of anisotropy: anisotropy of magnetic susceptibility and tissue structural anisotropy (e.g., cylindrical axonal bundles in white matter). In the framework of the GLTA the frequency shift due to the local environment is described in terms of the Lorentzian tensor $\hat{\mathbf{L}}$ which can have a substantially different structure than the susceptibility tensor $\hat{\chi}$. While the components of $\hat{\chi}$ are compartmental susceptibilities “weighted” by their volume fractions, the components of $\hat{\mathbf{L}}$ are additionally weighted by specific numerical factors depending on cellular geometrical symmetry.

In addition to describing the GLTA that is a phenomenological approach largely based on considering the system symmetry, we also briefly discuss microscopic approaches to the problem that are based on modeling of the MR signal in different regimes (i.e. static dephasing vs. motion narrowing) and in different cellular environments (e.g., accounting for WM microstructure).

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Graphical Abstract

Keywords

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

1. Introduction

In the presence of the external magnetic field B_0 , all atoms and molecules forming biological tissue become magnetized and create a secondary magnetic field B_0 that is sensed by water protons (the source of MRI signal), thus modifying protons' Larmor frequencies. This creates a tissue-specific contrast in the phase of Gradient Recalled Echo (GRE) MRI and potentially opens a new window to study biological tissue microstructure. To explore this opportunity, we need to understand how the GRE signal phase measured from large (usually millimeter-size) voxels related to tissue microstructure at the cellular and sub-cellular (micron-size) levels.

In most papers, the effect of the local environment on the MR resonance frequency shift is described by introducing the so called the "Lorentzian frequency shift" δf_L (in *SI* units):

$$\frac{\delta f_L}{f_0} = \frac{1}{3} \chi \quad (1)$$

where $f_0 = \gamma B_0 / 2\pi$ is the reference frequency, γ is the gyromagnetic ratio, χ is bulk magnetic susceptibility (microscopic magnetic susceptibility averaged across the voxel).

Equation (1) is based on the Lorentzian Sphere approximation which, according to Lorentz [1], can only be applied to certain symmetrical cases (see detail discussion in [2]). Indeed, Eq. (1) does not allow to explain one very curious phenomena usually seen in phase images of adult human brain – a very small contrast between WM and cerebrospinal fluid (CSF) [3, 4] in the brain regions where WM bundles are nearly parallel to B_0 (motor cortex and other areas at the top of the brain) – the WM darkness effect [5]. This effect is highly counterintuitive because WM structure is very different from CSF. WM is a cellular structure containing a high concentration of cell-building materials – proteins, lipids, etc. As a result, a very strong contrast between WM and CSF is usually seen on practically all

standard MRI images based on T1, T2, magnetization transfer (MT), and diffusion mechanisms.

To explain the WM darkness effect, He and Yablonskiy [3] (see also [2, 6, 7]) introduced a new theoretical concept called the Generalized Lorentzian Approach (GLA). An important insight from this conceptual framework is that the contribution from the local environment in the neighborhood of a hydrogen nucleus to the MRI signal phase depends not on the bulk magnetic susceptibility of the tissue, but on the “magnetic micro-architecture” of the tissue – i.e., the geometrical distribution of magnetic susceptibility inclusions (lipids, proteins, iron, etc. that become magnetized in the external magnetic field $\mathbf{B}_0$) at the cellular and sub-cellular levels. This theory provided an explanation why the *structural anisotropy* of WM (comprised mostly of longitudinally arranged cylindrical myelinated fibers) leads to a very low WM/CSF phase contrast independent of the sign and value of the WM magnetic susceptibility. The theory also provided a conceptual platform for the quantitative interpretation of data from MR phase imaging of white matter diseases [5].

The theoretical analysis in [3] was based on generalization of a broadly used concept of a Lorentzian cavity – an imaginary surface surrounding a point of interest where a local Larmor frequency of water proton is calculated. The next theoretical step has been made in [8], where expressions for the frequency shift was derived directly from the Maxwell equations for magnetostatic fields without incorporating such an imaginary surface. In the framework of this approach, the concept of the *structural anisotropy* in forming phase contrast was combined with the concept of the *magnetic susceptibility anisotropy* of WM [9]–[10]. This resulted in a development of the Generalized Lorentzian Tensor Approach (GLTA) [8] – the mathematical background for describing the relationship between the GRE signal phase/frequency and underlying tissue microstructure in biological tissues with anisotropic arrangements of cellular components, e.g. white matter fibers.

In this review we recast the main biophysical ideas behind the anisotropic behavior of GRE signal phase and provide major equations describing the relationships between the underlying biological tissue microstructure and GRE MRI signal phase.

2. Is Eq. (1) general and valid in any case? No!

Consider a system comprised of water molecules and magnetized particles (lipids, proteins, iron, etc.) that will be termed hereafter as the susceptibility inclusions. If magnetic susceptibility of the inclusions χ is different from magnetic susceptibility of water, χ_{water} , these particles induce the secondary magnetic field, shifting the local field in the point $\mathbf{r}$ as follows:

$$\Delta H_{res}(\mathbf{r}) = \sum h_n(\mathbf{r} - \mathbf{r}_n) \quad (2)$$

where h_n is a contribution of the n th susceptibility inclusion located at a point $\mathbf{r}_n$. The local frequency shift is

$$\delta f(\mathbf{r}) = \gamma \cdot \mu_0 \cdot \Delta H_{res}(\mathbf{r})/2\pi \quad (3)$$

(μ_0 is the permeability of free space).

To obtain an MRI-measurable frequency shift, the local frequency shift $\delta f(\mathbf{r})$ should be averaged across an imaging voxel (see the additional discussion in the Chapter 5). In the next section we will provide a regular mathematical procedure allowing calculating $\delta f(\mathbf{r})$ for arbitrary distributions of magnetic susceptibility inclusions. In this section, we consider several instructive examples. First, we consider an example depicted in Figure 1: two long cylinders (with height much bigger than their diameter) placed parallel to the external magnetic field B_0 and filled with pure water (A) or with water and long impermeable susceptibility inclusions (rods with volume fraction ζ) with arbitrary susceptibility χ_{rod} inserted parallel to the cylinder's axis (B). Bulk susceptibilities of these two cylinders are, obviously, different: $\chi_A = \chi_{water}$ $\chi_B = (1-\zeta) \chi_{water} + \zeta \cdot \chi_{rod}$. However, the Larmor frequencies in both the cases are the same, $\delta f_A = \delta f_B$, because, as well known, longitudinal structures parallel to the external magnetic field create very small magnetic field around themselves as long as their length is much bigger than their transverse sizes [11] (analog of fast decreasing magnetic field around MR scanner as we departure from the magnet edges). This result obviously contradicts Eq. (1): the latter predicts that the frequency shift completely determined by a bulk magnetic susceptibility, hence would be different for the cases A and B.

Figure 2 provides another example when Eq. (1) fails and demonstrates how “randomization” of ideal cylindrical structure (with a preservation of the total volume of magnetic susceptibility inclusions, hence the bulk volume magnetic susceptibility χ) affects the frequency shift. The structure changes from a magnetic susceptibility inclusion in the shape of an ideal long cylinder (solid bold line in the center of the outer cylinder in Figure 2a) to a random distribution of the cylinder's fragments. (Figure 2c). The magnetic field was numerically calculated based on the solution of Maxwell equations for a given geometry of particles and their distribution in space. The signal frequency $\delta f_L = \langle \delta f \rangle$ was calculated by averaging local frequencies over space occupied by water molecules outside the susceptibility inclusions.

The simulations reveal that for all “disorder levels”, the frequency shift can be presented as a product of the bulk volume magnetic susceptibility of the susceptibility inclusions χ and a coefficient LF (“Lorentzian factor”) depending on the disorder level:

$$\frac{\delta f_L}{f_0} = LF \cdot \chi \quad (4)$$

An increase in the “disorder” parameter R (horizontal axis) from zero (intact longitudinally organized structure) to one (fully disordered structure) changes the LF from zero to the “spherical” value of $1/3$, as in Eq. (1). Hence, Eq. (1) represents a reasonable approximation

for the case when magnetic susceptibility inclusions are randomly distributed (as in Figure 2c), but in the presence of the longitudinally ordered (as Figure 2a) or slightly disordered (as Figure 2b) structures, Eq. (1) is no longer valid. Note that, according to Eq. (4), measuring the frequency shift within the cylinder makes it possible to obtain only the product of the parameters LF and χ . To obtain these parameters separately, one needs to get susceptibility χ from an independent experiment, e.g. by measuring the field distribution *outside* the cylinder.

To calculate the Lorentzian frequency shift in the case when magnetic susceptibility inclusions form longitudinally oriented structures, another method – the Generalized Lorentzian Approach (GLA) was proposed [3]. This approach allows to correctly calculate the Lorentzian frequency shift in the case of longitudinally oriented structures. In contrast to Eq. (1), in this case, the Lorentzian contribution to the frequency shift depends on an angle α between the external magnetic field and the cylinder's axis [3]:

$$\frac{\delta f_L}{f_0} = \frac{1}{2} \cdot \chi \cdot \sin^2 \alpha \quad (5)$$

Figure 3 illustrates the results of numerical calculations of the frequency shift for a simple model analogous to that described in Figure 2, but with an arbitrary angle α between the external magnetic field $\mathbf{B}_0$ and the cylinder's axis. In both the cases, the total frequency shift is a sum of the Lorentzian frequency shift (Eq. (1) for the fully disordered structure and Eq. (5) for the ideal cylindrical inclusion) and the frequency shift caused by the magnetic field induced by the external surface of the cylinder:

$$\frac{\delta f_{surface}}{f_0} = -\frac{1}{2} \cdot \chi \cdot \sin^2 \alpha \quad (6)$$

The surface contribution and the Lorentzian term compensate each other in the case of ideal cylindrical inclusion, leading to the zero frequency shift for all angles α (green dots).

This important result means that for a circular cylindrical myelinated axonal bundle (tract), the frequency shift with respect to the surrounding isotropic medium (like CSF or GM) is not contributed by the longitudinal structures. Therefore, in the regions of the brain, such as the cortex, where gyri and sulci abut one another, the intact cylindrical axons in gyri should have very small frequency shifts relative to CSF in the sulci. This effect, first predicted by He and Yablonskiy [3], is counterintuitive, because there is a substantial difference between the content of cell-building materials in WM and CSF, presumably leading to a substantial difference between their magnetic susceptibilities - χ_{WM} and χ_{CSF} . One could, therefore, expect a substantial phase contrast between WM and CSF. However, the susceptibility of longitudinal structures, being one of the major component of χ_{WM} , does not contribute to the frequency shift, leading to a very little contrast between WM and CSF [3]. Importantly, this result does not depend on the value and the sign of the WM susceptibility χ_{WM} .

It is also important to note that, if WM contained only such longitudinal structures, there would be no angle dependence of the frequency shift in WM. However, a real situation is more complicated due to several reasons: (a) WM has anisotropic magnetic susceptibility not accounted for in Figure 3, and (b) WM is a multi-compartment tissue and it comprises not only the longitudinal structures but isotropic susceptibility inclusions as well. Other discussion of this subject can be found in [2, 12]. A more adequate description of the frequency shift in WM is given by the GLTA (see below), which predicts the $\sin^2 \alpha$ - dependence of the frequency shift. Such a dependence was experimentally observed in rat [7] and pig [13] optic nerves. An angular dependence of the phase/frequency shift in WM was also reported in several experimental studies (e.g., [14, 15] – marmoset brain, [13, 16, 17] – human brain, [18] – rat brain).

As already mentioned above, the WM darkness effect takes place in the brain regions where WM bundles are nearly parallel to $\mathbf{B}_0$ (motor cortex and other areas at the top of the brain), whereas in other brain areas, a WM/CSF phase contrast can be observed, e.g. [19–21].

In previous examples we considered only the Larmor frequency shifts of water protons due to the presence of magnetic susceptibility inclusions. However, water molecules themselves also have magnetic susceptibility leading to the Lorentzian contribution to their Larmor frequency. Due to the liquid nature of water and the corresponding symmetric distribution of water molecules, their Lorentzian factor in Eq. (4) is equal to 1/3 and corresponding frequency shift can be adequately described as:

$$\frac{\Delta f_{\text{water-water}}}{f_0} = \frac{1}{3} \cdot \chi_{\text{water}} \quad (7)$$

with magnetic susceptibility $\chi_{\text{water}} = -9$ ppm. Here we use a subscript “water-water” to underline that a source and “recipient” of the induced magnetic field are water molecules. As $f_{\text{water-water}}$ frequency shift is present in any MRI experiments based on water protons, it is convenient to add this shift to the reference frequency f_0 and to reference susceptibilities of all other sources (lipids, proteins, iron, etc.) to susceptibility of water. In all further consideration we will follow this approach and will no longer discuss “water-water” contributions.

3. Generalized Lorentzian Tensor Approach (GLTA)

While the GLA has already predicted anisotropic behavior of GRE signal phase resulted from the structural anisotropy of WM [3], it was suggested later [9, 10] that the magnetic susceptibility of WM comprising myelinated axons, could be anisotropic. In [8] (see also [22]), the GLA was generalized to account for both, *structural anisotropy* and *magnetic susceptibility anisotropy* of biological tissue (hence the term Generalized Lorentzian Tensor Approach - GLTA) including multi-compartment tissue structure. This approach is based on a general consideration of Maxwell’s equations and a statistical approach without enlisting the concept of the Lorentzian cavity. The main ideas and results and of the GLTA are presented below.

Initially we assume that the inclusions do not contain water molecules. In this case, the frequency shift δf 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):

$$\delta f = \frac{\gamma \mu_0}{2\pi} \cdot (\mathbf{H}_e \cdot \mathbf{n}), \quad \mathbf{H}_e = \langle \mathbf{h}(\mathbf{r}) \rangle_{outside} = \frac{1}{V_e} \cdot \int_{V_e} d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad (8)$$

Here $\mathbf{n}$ is the unit vector along the external field $\mathbf{B}_0$, $\mathbf{h}(\mathbf{r})$ is the secondary magnetic field induced by the magnetization $\mathbf{m}(\mathbf{r}) = \hat{\chi}_u^{(0)}(\mathbf{r}) \cdot \mathbf{H}_0$, $\mathbf{H}_0 = \mathbf{B}_0 / \mu_0$, $\hat{\chi}_u^{(0)}(\mathbf{r})$ is the position-dependent intrinsic volume magnetic susceptibility tensor, referenced to water:

$$\hat{\chi}_u^{(0)}(\mathbf{r}) = \hat{\chi}^{(0)} \cdot u(\mathbf{r}), \quad \hat{\chi}^{(0)} = (\hat{\chi}_{inclusions}^{(0)} - \hat{\mathbf{I}} \cdot \chi_{water}^{(0)}) \quad (9)$$

where $\hat{\mathbf{I}}$ is the 3×3 unit matrix, 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 :

$$\hat{\chi} = \zeta \cdot \hat{\chi}^{(0)} \quad (10)$$

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

$$\mathbf{H} = \frac{1}{V} \cdot \int_V d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad (11)$$

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

$$\text{div } \mathbf{H} = -\text{div } \mathbf{M}, \quad \text{curl } \mathbf{H} = 0 \quad (12)$$

where

$$\mathbf{M} = \frac{1}{V} \cdot \int_V d\mathbf{r} \mathbf{m}(\mathbf{r}) \quad (13)$$

is the average magnetization in the voxel.

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

$$\mathbf{H} = (1 - \zeta) \cdot \mathbf{H}_e + \zeta \cdot \mathbf{H}_i \quad (14)$$

where

$$\mathbf{H}_i = \langle \mathbf{h}(\mathbf{r}) \rangle_{inside} = \frac{1}{V_i} \cdot \int_{V_i} d\mathbf{r} \mathbf{h}(\mathbf{r}) \quad (15)$$

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, $\mathbf{m} = \mathbf{m}_0 = \hat{\chi}^{(0)} \cdot \mathbf{H}_0$, 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 [23, 24]). By averaging this equation over all the positions (but not orientations) of the inclusions (similar to the statistical approach used in [25]), we find that the average fields $\mathbf{H}_i$ and $\mathbf{H}_e$ are related as follows:

$$\mathbf{H}_i = \mathbf{H}_e - \hat{\mathbf{N}} \mathbf{m}_0 \quad (16)$$

Combining Eqs. (14) and (16), we get

$$\mathbf{H}_e = \mathbf{H} + \mathbf{H}_L; \quad \mathbf{H}_L = \hat{\mathbf{N}} \hat{\chi} \mathbf{H}_0 \quad (17)$$

where $\hat{\chi} = \zeta \cdot \hat{\chi}^{(0)}$ is the contribution of magnetic susceptibility inclusions to the bulk volume magnetic susceptibility (Eq. (10)). As already mentioned, 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. (8) comprises two parts: the field $\mathbf{H}$ satisfying Maxwell equations, Eqs. (12), and the Lorentzian field $\mathbf{H}_L$:

$$\mathbf{H}_L = \hat{\mathbf{L}} \mathbf{H}_0, \quad \hat{\mathbf{L}} = \hat{\mathbf{N}} \hat{\chi} \quad (18)$$

Correspondingly, the frequency shift can be represented as

$$\delta f = \delta f_H + \delta f_L \quad (19)$$

$$\delta f_H = \frac{\gamma \mu_0}{2\pi} \cdot (\mathbf{H} \cdot \mathbf{n}), \quad \delta f_L = f_0 \cdot (\mathbf{n} \cdot \hat{\mathbf{L}} \cdot \mathbf{n})$$

The first (Maxwell) term δf_H in Eq. (19) depends on the *macroscopic* $\mathbf{H}$ field determined by the Maxwell equations (12)–(13). The second (Lorentzian) term δf_L in Eq. (19) depends on the local *microscopic* environment of water molecules.

For the case when the voxel contains the susceptibility inclusions of several types, each of them characterized by its own demagnetization tensor $\hat{\mathbf{N}}_j$ and volume magnetic susceptibility tensor $\hat{\chi}_j$, the Lorentzian tensor $\hat{\mathbf{L}}$ is simply the sum of the contributions of all types of the susceptibility inclusions:

$$\hat{\chi} = \sum_j \hat{\chi}_j \quad \hat{\mathbf{L}} = \sum_n \hat{\mathbf{N}}_j \hat{\chi}_j \quad (20)$$

Two types of susceptibility inclusions are of the main importance in biological tissue:

(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 $\hat{\mathbf{I}}$:

$$\hat{\mathbf{N}}_{iso} = \frac{1}{3} \cdot \hat{\mathbf{I}}, \quad \hat{\chi}_{iso} = \chi_{iso} \cdot \hat{\mathbf{I}}, \quad \hat{\mathbf{L}}_{iso} = \frac{\chi_{iso}}{3} \cdot \hat{\mathbf{I}} \quad (21)$$

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, using the identity $\langle n_\alpha n_\beta \rangle_{orient} = \delta_{\alpha\beta}/3$ ($\delta_{\alpha\beta}$ is the Kronecker delta), and $\text{Tr}(\hat{\mathbf{N}}) = 1$, the orientation averaging of the quantity δf_L , Eq. (19), leads to

$$\frac{\delta f_L}{f_0} = \chi_{iso} \cdot \langle n_\alpha N_{\alpha\beta} n_\beta \rangle_{orient} = \frac{1}{3} \cdot \chi_{iso} \quad (22)$$

(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:

$$\hat{\mathbf{N}}_{cyl} = \frac{1}{2} \cdot \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \hat{\chi}_{cyl} = \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & \chi_a \end{pmatrix}, \quad \hat{\mathbf{L}}_{cyl} = \frac{1}{2} \cdot \begin{pmatrix} \chi_r & 0 & 0 \\ 0 & \chi_r & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad (23)$$

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 :

$$\frac{\delta f_L}{f_0} = \frac{1}{2} \chi_r \cdot \sin^2 \alpha \quad (24)$$

where α is an angle between the external magnetic field and the cylinder's axis.

If both the types (A) and (B) are present in a voxel, the Lorentzian tensor is $\hat{\mathbf{L}} = \hat{\mathbf{L}}_{iso} + \hat{\mathbf{L}}_{cyl}$ and the Lorentzian frequency shift in this case is equal to

$$\frac{\delta f_L}{f_0} = \frac{1}{3} \chi_{iso} + \frac{1}{2} \chi_r \cdot \sin^2 \alpha \quad (25)$$

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. (22) 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: *the axial component χ_a does not contribute to the averaged Lorentzian tensor* and, consequently, to the Lorentzian frequency shift:

$$\frac{\delta f_L}{f_0} = \frac{1}{3} \chi_r \quad (26)$$

All the above consideration is based on a phenomenological approach that largely relies on considering system symmetry and ignoring actual tissue cellular microstructure. From this perspective, all the magnetic susceptibilities entering above equations should be treated as

“apparent”, i.e. representing average values of microscopic parameters “weighted” by their volume fractions and affected by MRI pulse sequence parameters [8]. More detail description of the GRE signal phase can be obtained by modeling tissue microstructure which is briefly discussed in the next section.

4. Does the averaged microscopic frequency completely describe the net MR signal frequency shift?

Above we calculated the magnetic-susceptibility-induced MR signal frequency shift by averaging the local (microscopic) frequency shift across a large (macroscopic) volume containing numerous magnetic susceptibility inclusions. Such an approach is, of course, an approximation because the MR signal from a macroscopic volume should be calculated by averaging individual (microscopic) signals from all water molecules diffusing between magnetic susceptibility inclusions in this macroscopic volume. Generally, the MR signal at time t after RF pulse can be presented as

$$S(t) = S_0 \cdot \langle \exp [-i \varphi(t)] \rangle \quad (27)$$

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

$$\varphi(t) = 2\pi\gamma \cdot \mu_0 \cdot \int_0^t dt' \mathbf{h}[\mathbf{r}(t')] \cdot \mathbf{n} \quad (28)$$

Here $\mathbf{h}(\cdot)$ is the secondary magnetic field induced by the magnetized susceptibility inclusions (as in the Section 3). The angular brackets in Eq. (27) 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 the case of sufficiently fast diffusion, each water molecule samples all possible values of the microscopic magnetic fields $\mathbf{h}(\mathbf{r})$ around the susceptibility inclusions. Hence, the phases of all molecules in Eq. (28) become the same and proportional to the average magnetic field $\mathbf{H}_e$. As a result, the net phase of the signal in Eq. (27) can be characterized by a single frequency

$$\delta f = \gamma \cdot \mu_0 \cdot (\mathbf{H}_e \cdot \mathbf{n}) / 2\pi \quad (29)$$

Hence, in this case the problem is reduced to calculating the average frequency described by Eqs. (19) (see the Section 3).

It should be noted that the similar result can be obtained for short times t or for small characteristic microscopic frequency shifts when $\varphi(t) = 2 \cdot \pi \cdot \delta f \cdot t \ll 1$. This, however, can restricts our consideration to rather short gradient echo times. Indeed, even for a small characteristic frequency shift of 10 Hz, the gradient echo time TE should be much shorter than 15 ms.

For longer times, the case of slow diffusion and in its limiting case of static dephasing regime require more careful analysis. In the static dephasing regime, the solution was found in [26] for some simple geometries of susceptibility inclusions (spheres and long cylinders). It was shown that for randomly distributed spheres with intrinsic magnetic susceptibility $\chi^{(0)}$ and volume fraction ζ , for sufficiently long time, $\delta\omega_s \cdot t > 1.5$ ($\delta\omega_s = \gamma / 3 \cdot \chi^{(0)} H_0$) an additional frequency shift $\delta f'$ appears:

$$\frac{\delta f'}{f_0} = \frac{1}{3} \cdot \chi \cdot C, \quad C = \frac{2}{3} \cdot \left[\frac{1}{\sqrt{3}} \cdot \ln \frac{\sqrt{3} + 1}{\sqrt{3} - 1} - 1 \right] \approx -0.16 \quad (30)$$

where $\chi = \chi^{(0)} \zeta$ is the bulk magnetic susceptibility of the inclusions. Interestingly, parallel oriented long cylinders do not create an additional frequency shift at any time: $\delta f' = 0$.

5. The role of the multi-compartment tissue structure

The above consideration provides theoretical background for understanding GRE signal phase for the systems when there is no water molecules *inside* the susceptibility inclusions and the MRI signal originates only from the space *outside* the inclusions. However, actual structure of biological tissues is more complicated as water molecules residing in multiple intra-and extra-cellular spaces. Herein we will discuss WM where long neuronal fibers comprise the axons surrounded by the myelin sheath which, in its turn, is surrounded by the extracellular space. These compartments (axon, myelin sheath, extracellular space) contain water molecules contributing to the GRE MR signal.

A multi-compartment-based theory of the influence of the anisotropic structure of myelin layers on signal frequency was proposed by Wharton and Bowtell by introducing a hollow cylinder model [16] and predicting a very interesting effect of MR signal frequency shift in the hollow (intracellular axonal) space due to the radial distribution of long lipoprotein chains in the body of the cylinder (myelin layer). A similar model was also explored by Sati et al [15] by means of numerical computer simulations. While these papers considered myelin structure as a homogeneous media, Sukstanskii and Yablonskiy [27] developed the theory that took into consideration the layer structure of myelin sheath (Fig. 4). This resulted in the following expressions for the myelin-induced frequency shifts of the MR signal from the water in the axon and myelin sheath with respect to the extracellular space:

$$\frac{\Delta f_a}{f_0} = \frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d + d_w} \cdot \Delta \chi \cdot q_a(g), \quad q_a(g) = \ln \left(\frac{1}{g} \right) \quad (31)$$

$$\frac{\Delta f_m}{f_0} = \frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d + d_w} \cdot \Delta \chi \cdot q_m(g), \quad q_m(g) = \frac{1}{2} + \frac{g^2 \ln g}{(1 - g^2)} \quad (32)$$

Here $\Delta \chi = \chi_{\parallel}^{(ml)} - \chi_{\perp}^{(ml)}$ is the difference between longitudinal (radial) and transverse (tangential) components of magnetic susceptibility of lipoprotein chains in myelin sheath, $g = R_{axon}/R_{ext}$ and α is the angle between the axonal axis and the external magnetic field $\mathbf{B}_0$ direction.

While the first term in Eq. (31) describing the axonal frequency shift is similar to the result of [16], the second term describing myelin water frequency shift is different from that in [16]. The matter is that in [16] (as well as in [15]) myelin water was assumed to be homogeneously distributed within the entire myelin sheath and the signal frequency shift was described in the framework of the Lorentzian sphere approximation. Whereas in [27], the myelin sheath was considered in a more realistic model consisting of lipid layers separated by aqueous layers, e.g. [28–30], as illustrated in Figure 4. However, as was pointed out by Duyn [31], Eq. (32) predicts the negative frequency shift for $\alpha = 90^\circ$ (assuming $\chi < 0$), while experimental data [15, 16] suggest a positive shift. To resolve this discrepancy between experimental data and Eq. (32), we proposed a modification of theory, based on a simple and realistic “Hop-in hopout” mechanism [6].

In the presence of a magnetic field, the lipid layers become magnetized and create an additional magnetic field. This field can be described as a result of magnetostatic charges $\rho = -\text{div}\mathbf{M}$ formed on the layers’ surfaces (surface charges) and inside the lipid layers (volume charges). The volume charges are solely due to the anisotropy of magnetic susceptibility [27] leading to frequency shifts described by Eqs. (31)–(32), whereas the surface charges exist even in the case of isotropic susceptibility. Only the surface charges (see Figure 4) are of interest for the proposed hop-in-out mechanism. The magnetic field induced by these charges is similar to the electric field of a capacitor. To experience this induced magnetic field, the water molecules do not need to get deep in the lipid layer because magnetostatic charges are located right on the layer’s surface, they (water molecules) just need to “Hokey Pokey dance” from aqueous phase to just beyond the lipid surface. A typical width of the aqueous phase between lipid layers is about 2.5 nm [30]. Given that the water diffusion coefficient in the tissue is about $1 \mu\text{m}^2/\text{ms}$, it takes only about 3 ns to diffuse across this width. Hence, it is reasonable to assume that all water molecules in the aqueous space can rapidly hop in and out the superficial areas of the lipid layers. Such rapid exchange would lead to an additional term in the myelin-associated water frequency shift:

$$\left. \frac{\Delta f_m}{f_0} \right|_{\text{hop-in-out}} = -\frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d + d_w} \cdot \zeta \cdot \chi_{\parallel} \quad (33)$$

where parameter ζ defines the apparent fraction of time that a water molecule resides in the lipid layer. The coefficient $1/2$ appears due to averaging over the azimuthal angle. By

combining Eqs. (32) and (33), the total frequency shift of myelin water due to the presence of lipid layers can now be presented as:

$$\frac{\Delta f_m}{f_0} = \frac{1}{2} \sin^2 \alpha \cdot \frac{d}{d + d_w} \cdot (\Delta \chi \cdot q_m(g) - \zeta \cdot \chi_{\parallel}) \quad (34)$$

This equation explains both major features of myelin signal frequency shift – the absence of the shift for the fibers parallel to $\mathbf{B}_0$ and the positive shift in the perpendicular case. Importantly, it explains these features without requirement $\chi_{\perp} = 0$ or additional exchange terms as in [16]. Even more importantly, Eq. (34) is consistent with the axial symmetry of the axonal structure.

In addition to the myelin-induced frequency shifts, all the compartments (axon, myelin and extracellular) have frequency shifts due to the presence of “other” structures forming cellular matrix (neurofilaments, etc)

$$\frac{\Delta f_{a,m,e}}{f_0} = \left(-\frac{1}{2} \sin^2 \alpha + \frac{1}{3} \right) \cdot \chi_{iso}^{(a,m,e)} \quad (35)$$

where $\chi_{iso}^{(a,m,e)}$ describes magnetic susceptibility of isotropically distributed structures within the axon (a), myelin (m), and extracellular space (e), respectively. Importantly, the cylinder-type structures (filaments, etc.) do not contribute to Eq. (35), i.e. they are “invisible” in local frequency shifts. Though they affect the frequency shifts outside these structures as they disturb the Maxwell field $\mathbf{H}$. This effect, predicted in [3] and proved by computer simulations in [5], was experimentally demonstrated in a carefully designed experiment in an optic nerve [32].

As was demonstrated in [8], this complex multi-compartment behavior of MRI signal can still be approximated by equation

$$\delta f_L = f_0 \cdot \left(\frac{1}{3} \cdot \chi_{iso}^{(app)} + \frac{1}{2} \cdot \chi_r^{(app)} \cdot \sin^2 \alpha \right) \quad (36)$$

which is similar to Eq. (25) with *apparent* magnetic susceptibilities $\chi_{iso}^{(app)}$ and $\chi_r^{(app)}$. Details of this consideration can be found in [8]. Here we only notice that the *apparent* magnetic susceptibilities in Eq. (36) are determined by magnetic susceptibilities of different compartments with different relaxation properties. Therefore, they depend 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). The identical symmetry of Eqs. (25) and (36) suggests that the frequency shift in a multi-compartment structure can also be described in

terms of the Lorentzian tensor with the same symmetry as in Eqs. (21) and (23) but with apparent components.

6. Conclusion

In this paper we did not discuss QSM applications that can be found elsewhere (e.g. recent review [33]). Instead, we focused on biophysical mechanisms responsible for formation GRE signal phase. Most of the QSM studies aiming at estimating magnetic susceptibility χ rely on Eq. (1) and the following (comparably simple) expression for the frequency shift of the GRE signal:

$$\delta f = f_0 \cdot \text{IFT} \left\{ \left[\frac{1}{3} - \frac{(\mathbf{k} \cdot \mathbf{n})^2}{\mathbf{k}^2} \right] \cdot \chi_{\mathbf{k}} \right\}, \quad \chi_{\mathbf{k}} = \text{FT} \{ \chi(\mathbf{R}) \} \quad (37)$$

where FT denotes a standard 3D Fourier transform, and IFT is an inverse FT ($\mathbf{k}$ is a vector in the Fourier domain). The first term in Eq. (37) is a Lorentzian factor for *isotropic media* and the second term is a Maxwell factor obtained by means of Fourier transform of the Maxwell equations (e.g., [34–36]).

In the presence of longitudinal structures, the frequency shift is determined by two different tensors, the susceptibility tensor $\hat{\chi}$ and the Lorentzian tensor $\hat{\mathbf{L}}$ [8]:

$$\delta f = f_0 \cdot \text{IFT} \left\{ \left[\mathbf{n} \cdot \hat{\mathbf{L}}_{\mathbf{k}} \cdot \mathbf{n} - \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n})}{\mathbf{k}^2} \right] \right\}, \quad \hat{\mathbf{L}}_{\mathbf{k}} = \text{FT} \{ \hat{\mathbf{L}}(\mathbf{R}) \} \quad (38)$$

The structure of the Lorentzian tensor $\hat{\mathbf{L}}$ (especially, in multi-compartment tissues), is substantially different from the structure of the susceptibility tensor $\hat{\chi}$ in several ways:

- a. Magnetic susceptibility contributions from isotropic and longitudinal structures are “weighted” in $\hat{\mathbf{L}}$ by different numerical coefficients;
- b. The axial component χ_a of the magnetic susceptibility tensor does not contribute to $\hat{\mathbf{L}}$;
- c. If water resides also inside the susceptibility 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. $T1$, $T2^*$) and pulse sequence parameters (e.g. TE , TR , flip angle).

It is important to note that an additional contribution to the magnetic susceptibility-induced frequency shift of the MR signal may appear in the static dephasing regime (slow diffusion) and the following equation should be used instead of Eq. (38):

$$\delta f = f_0 \cdot \text{IFT} \left\{ \left[\mathbf{n} \cdot \hat{\mathbf{L}}_{\mathbf{k}} \cdot \mathbf{n} - \frac{(\mathbf{k} \cdot \mathbf{n}) \cdot (\mathbf{k} \cdot \hat{\chi}_{\mathbf{k}} \cdot \mathbf{n})}{\mathbf{k}^2} \right] \right\} + \delta f' \quad (39)$$

where $\delta f'$ for random sphere-like inclusions is given by Eq. (30).

It is quite understandable that implementation of Eq. (38) instead of much more simple Eq. (37) for analyzing experimental data is an extremely challenging task. However, ignoring structural anisotropy in WM containing longitudinal structures leads to incorrect interpretation of experimental data, and the results cannot be considered as quantitative.

In this review, we provide the theoretical background of the anisotropic (structural and magnetic susceptibility) phenomena affecting QSM, discuss the “standard” Lorentzian surface approach as well as the advanced Generalized Lorentzian Tensor approach (GLTA) - a phenomenological method describing magnetic-susceptibility-induced gradient echo MRI signal frequency shifts in the presence of magnetic susceptibility inclusions of arbitrary shape and characterized by an arbitrary magnetic susceptibility tensor. The latter is based on direct solution of the Maxwell equations and does not require introducing an imaginary Lorentzian surface. The GLTA is essential tool to decipher information on tissue structural and magnetic anisotropy in WM comprising longitudinal structures (axons).

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References

1. Lorentz, HA. The Theory of Electrons. Leipzig, New York: B.G. Teubners; 1909.
2. Yablonskiy DA, He X, Luo J, Sukstanskii AL. Lorentz sphere versus generalized Lorentzian approach: What would Lorentz say about it? *Magn Reson Med*. 2014; 72:4–7. [PubMed: 24771317]
3. He X, Yablonskiy DA. Biophysical mechanisms of phase contrast in gradient echo MRI. *Proc Natl Acad Sci U S A*. 2009; 106:13558–13563. [PubMed: 19628691]
4. Duyn JH, van Gelderen P, Li TQ, de Zwart JA, Koretsky AP, Fukunaga M. High-field MRI of brain cortical substructure based on signal phase. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:11796–11801. [PubMed: 17586684]
5. Yablonskiy DA, Luo J, Sukstanskii AL, Iyer A, Cross AH. Biophysical mechanisms of MRI signal frequency contrast in multiple sclerosis. *Proc Natl Acad Sci U S A*. 2012; 109:14212–14217. [PubMed: 22891307]
6. Yablonskiy DA, Sukstanskii AL. Biophysical mechanisms of myelin-induced water frequency shifts. *Magn Reson Med*. 2014; 71:1956–1958. [PubMed: 24700617]
7. Luo J, He X, Yablonskiy DA. Magnetic susceptibility induced white matter MR signal frequency shifts--experimental comparison between Lorentzian sphere and generalized Lorentzian approaches. *Magn Reson Med*. 2014; 71:1251–1263. [PubMed: 23637001]
8. Yablonskiy DA, Sukstanskii AL. Generalized Lorentzian Tensor Approach (GLTA) as a biophysical background for quantitative susceptibility mapping. *Magn Reson Med*. 2015; 73:757–764. [PubMed: 25426775]
9. Liu CL. Susceptibility Tensor Imaging. *Magnetic Resonance in Medicine*. 2010; 63:1471–1477. [PubMed: 20512849]

10. Lee J, Shmueli K, Fukunaga M, et al. Sensitivity of MRI resonance frequency to the orientation of brain tissue microstructure. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:5130–5135. [PubMed: 20202922]
11. Jackson, JD. *Classical Electrodynamics*. New York: J Wiley & Sons, Inc; 1998.
12. Duyn JH, Barbara TM. Sphere of Lorentz and demagnetization factors in white matter. *Magn Reson Med*. 2014; 72:1–3. [PubMed: 24764306]
13. Wharton S, Bowtell R. Effects of white matter microstructure on phase and susceptibility maps. *Magn Reson Med*. 2015; 73:1258–1269. [PubMed: 24619643]
14. Shmueli K, De Zwart JA, Van Gelderen P, Li TQ, Dodd SJ, Duyn JH. Magnetic susceptibility mapping of brain tissue in vivo using MRI phase data. *Magn Reson Med*. 2009; 62:1510–1522. [PubMed: 19859937]
15. Sati P, van Gelderen P, Silva AC, et al. Micro-compartment specific T2* relaxation in the brain. *Neuroimage*. 2013; 77:268–278. [PubMed: 23528924]
16. Wharton S, Bowtell R. Fiber orientation-dependent white matter contrast in gradient echo MRI. *Proc Natl Acad Sci U S A*. 2012; 109:18559–18564. [PubMed: 23091011]
17. Denk C, Hernandez Torres E, MacKay A, Rauscher A. The influence of white matter fibre orientation on MR signal phase and decay. *NMR Biomed*. 2011; 24:246–252. [PubMed: 21404336]
18. Rudko DA, Klassen LM, de Chickera SN, Gati JS, Dekaban GA, Menon RS. Origins of R2* orientation dependence in gray and white matter. *Proc Natl Acad Sci U S A*. 2014; 111:E159–167. [PubMed: 24374633]
19. Lee J, Shmueli K, Kang BT, et al. The contribution of myelin to magnetic susceptibility-weighted contrasts in high-field MRI of the brain. *Neuroimage*. 2012; 59:3967–3975. [PubMed: 22056461]
20. Klohs J, Politano IW, Deistung A, et al. Longitudinal Assessment of Amyloid Pathology in Transgenic ArcAbeta Mice Using Multi-Parametric Magnetic Resonance Imaging. *PLoS One*. 2013; 8:e66097. [PubMed: 23840405]
21. Wei H, Dibb R, Zhou Y, et al. Streaking artifact reduction for quantitative susceptibility mapping of sources with large dynamic range. *NMR Biomed*. 2015; 28:1294–1303. [PubMed: 26313885]
22. Yablonskiy DA, Sukstanskii AL. Effects of biological tissue structural anisotropy and anisotropy of magnetic susceptibility on the gradient echo MRI signal phase: theoretical background. *NMR Biomed*. 2017:30.
23. Stoner EC. Demagnetising Factor for Ellipsoids. *Phil Mag*. 1945; 36:803–821.
24. Osborn JA. Demagnetising Factor for the General Ellipsoid. *Phys Rev*. 1945; 67:351–356.
25. Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues: the static dephasing regime. *Magn Reson Med*. 1994; 32:749–763. [PubMed: 7869897]
26. Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues: the static dephasing regime. *Magn Reson Med*. 1994; 32:749–763. [PubMed: 7869897]
27. Sukstanskii AL, Yablonskiy DA. On the role of neuronal magnetic susceptibility and structure symmetry on gradient echo MR signal formation. *Magn Reson Med*. 2014; 71:345–353. [PubMed: 23382087]
28. Raine, CS. *Myelin*. Morell, P., editor. New York: Plenum; 1984. p. 1-41.
29. Inouye H, Kirschner DA. Membrane interactions in nerve myelin. I. Determination of surface charge from effects of pH and ionic strength on period. *Biophys J*. 1988; 53:235–245. [PubMed: 3345332]
30. Min Y, Kristiansen K, Boggs JM, Husted C, Zasadzinski JA, Israelachvili J. Interaction forces and adhesion of supported myelin lipid bilayers modulated by myelin basic protein. *Proc Natl Acad Sci U S A*. 2009; 106:3154–3159. [PubMed: 19218452]
31. Duyn JH. Frequency shifts in the myelin water compartment. *Magn Reson Med*. 2014; 71:1953–1955. [PubMed: 24700549]
32. Luo J, He X, Yablonskiy DA. Magnetic susceptibility induced white matter MR signal frequency shifts-experimental comparison between Lorentzian sphere and generalized Lorentzian approaches. *Magn Reson Med*. 2013

33. Wang Y, Liu T. Quantitative susceptibility mapping (QSM): Decoding MRI data for a tissue magnetic biomarker. *Magnetic Resonance in Medicine*. 2015; 73:82–101. [PubMed: 25044035]
34. Sukstanskii AL, Yablonskiy DA. Gaussian approximation in the theory of MR signal formation in the presence of structure-specific magnetic field inhomogeneities. *J Magn Reson*. 2003; 163:236–247. [PubMed: 12914839]
35. Salomir R, de Senneville BD, Moonen CT. A Fast Calculation Method for Magnetic Field Inhomogeneity due to an Arbitrary Distribution of Bulk Susceptibility. *Concept Magn Reson*. 2003; 19B:26–34.
36. Marques JP, Bowtell R. Application of a fourier-based method for rapid calculation of field inhomogeneity due to spatial variation of magnetic susceptibility. *Concepts in Magnetic Resonance Part B-Magnetic Resonance Engineering*. 2005; 25B:65–78.

- Cellular environment in biological tissues affects MR signal frequency
- Generalized Lorentzian Tensor Approach (GLTA) accounts for tissue anisotropy
- GLTA describes Lorentzian frequency shift in terms of Lorentzian tensor
- Lorentzian tensor depends on both structural and magnetic susceptibility anisotropies

Figure 1.

Two cylinders in the external magnetic field $\mathbf{B}_0$ parallel to their axes. (A) cylinder filled with water; (B) cylinder filled with water and inserted long magnetized rods. This example clearly demonstrates inability of Eq. 1 to correctly predict the frequency shift.

Figure 2.

a) An “ideal” cylindrical magnetic susceptibility inclusion (black cylinder); b) “mildly” randomized structure – fragments of the cylinder are slightly scattered; c) “severely” randomized structure - fragments of the cylinder are scattered randomly. Lower panel – the dependence of the Lorentzian Factor (LF) in Eq. (4) on the “level of disorder” $\Delta R / R_0$ (ΔR – an average fragments’ displacement, R_0 – the outer cylinder radius).

Figure 3.

The relative frequency shift as a function of the angle α between the external magnetic field B_0 and the cylinder's axis. Green dots – “ideal” structure (black cylinder) shows zero frequency shift for all angles α ; red dots – fully disordered structure.

Figure 4.

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 the right inset) with anisotropic magnetic susceptibility. In the presence of magnetic field $\mathbf{B}_0$ the lipid layers become magnetized and create an additional magnetic field which can be described as a result of magnetostatic charges $\rho = -\text{div}\mathbf{M}$ formed on the layers' surfaces (surface charges) and inside the lipid layers (volume charges). The volume magnetostatic charges generate the magnetic field that leads to the frequency shift described by Eqs. (32). The surface magnetostatic charges which are of interest for the hop-in hop-out mechanism are shown as + and - signs in the left insert. The signs of the surface charges and the direction of $\mathbf{B}_0$ within the lipid layers correspond to $\chi_{\parallel} < 0$. Blue dots represent water molecules performing "Hokey-Pokey dance" from aqueous to lipid layers. When a water molecule jumps from water layer to lipid layer, it experiences an additional field (shown as arrows) induced by the surface charges.