Journal of Magnetic Resonance xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

Lorentzian effects in magnetic susceptibility mapping of anisotropic biological tissues

Dmitriy A. Yablonskiy *, Alexander L. Sukstanskii

Department of Radiology, Washington University, St. Louis, MO 63130, USA

ARTICLE INFO

Article history:
Received 28 December 2017
Revised 23 April 2018
Accepted 24 April 2018
Available online xxxx

Keywords:
Phase contrast
Generalized Lorentzian Tensor Approach
White matter
Magnetic susceptibility
Quantitative susceptibility mapping

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 a 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).

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 ΔB_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):

$$\frac{\delta f_L}{f_0} = \frac{1}{3}\chi \tag{1}$$

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).

Eq. (1) is based on the Lorentzian Sphere approximation which, according to Lorentz [1], can only be applied to certain

* Corresponding author at: Mallinckrodt Institute of Radiology, Washington University, 4525 Scott Ave., Room 3216, St. Louis, MO 63110, USA.
E-mail address: yablonskiyd@mir.wustl.edu (D.A. Yablonskiy).

https://doi.org/10.1016/j.jmr.2018.04.014
1090-7807/

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 $\mathbf{B}_0$ (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, $\chi \neq \chi_{water}$, these particles induce the secondary magnetic field, shifting the local field in the point $\mathbf{r}$ as follows:

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

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

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

(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 Fig. 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: $\chi_A = \chi_{water}$, $\chi_B = (1-\zeta)\cdot\chi_{water} + \zeta\cdot\chi_{rod}$. 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.

Fig. 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 Fig. 2a) to a random distribution of the cylinder's fragments. (Fig. 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:

$$\frac{\delta f_L}{f_0} = LF \cdot \chi \tag{4}$$

An increase in the "disorder" parameter ΔR (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 Fig. 2c), but in the presence

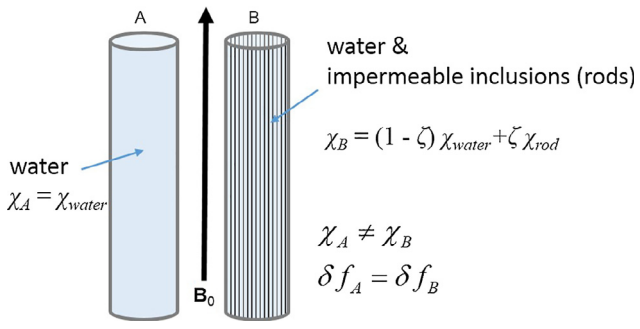

Fig. 1. Two cylinders in the external magnetic field $\mathbf{B}_0$ parallel to their axes. (A) cylinder filled with water; (B) cylinder filled with water and inserted long magnetized rods. This example clearly demonstrates inability of Eq. (1) to correctly predict the frequency shift.

Please cite this article in press as: D.A. Yablonskiy, A.L. Sukstanskii, Lorentzian effects in magnetic susceptibility mapping of anisotropic biological tissues, J. Magn. Reson. (2018), https://doi.org/10.1016/j.jmr.2018.04.014