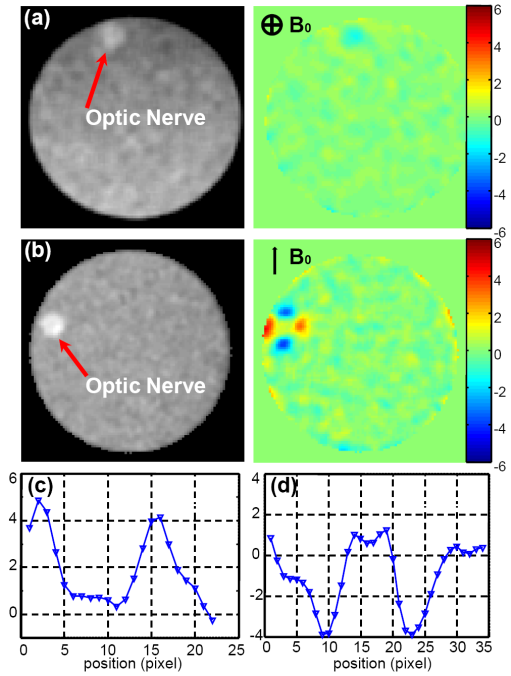
Non-Lorentzian Sphere Behavior of Magnetic Susceptibility Induced MR Signal Frequency Shift in White Matter: Validation Study

X. He[1], J. Luo[2], and D. A. Yablonskiy[1]

[1]Mallinckrodt Institute of Radiology, Washington University in St Louis, School of Medicine, St. Louis, Missouri, United States, [2]Department of Chemistry, Washington University in St Louis, St Louis, Missouri, United States

Introduction: Recently reported contrast in MR gradient echo phase images between brain gray matter (GM) and white matter (WM) holds a great promise for *in vivo* study of biological tissue structure with substantially improved resolution, which is profoundly enhanced at high field [1]. Possible origins of this contrast have been debated but mostly attributed to magnetic susceptibility effects. It is usually assumed that a relationship between local tissue magnetic susceptibility χ and corresponding MR frequency shift can be calculated using Lorentzian sphere approximation: $\Delta f / f_0 = (4/3) \cdot \pi \cdot \chi$. While this approximation is adequate for isotropic structures [2, 3], it fails taking into account anisotropic microstructure of WM where magnetic susceptibility has contribution from longitudinal structures like protein-rich cytoskeleton fibers, myelin sheath, etc. Recently a theory of phase contrast has been proposed based on a newly introduced concept of generalized Lorentzian approach that takes into account anisotropic microstructure of axons and dendrites [4]. The theory quantitatively explained the frequency contrast between GM, WM, and CSF previously reported in brain motor cortex area [1]. In this study, the concept of generalized Lorentzian approximation is validated using *ex vivo* fresh rat optic nerve model. The ex vivo isolation of optic nerve ensures a well-defined environment to eliminate any field contamination from neighboring tissues during phase measurement.

Methods: Optic nerve was selected because it has all typical structures characteristic to WM. All experiments were performed on Varian 4.7 T scanner with surface transmit/receive RF coil. All surgical procedures were conducted under the guidance of the Washington University Animal Care and Use Committee. The optic nerves of male Sprague-Dawley rats weighting 200-400 g were removed and bathed longitudinally in a cylindrical NMR tube filled with phosphate buffer solution (PBS) for immediate MRI study. The length of nerve was about 8 mm, while the diameter was about 0.5 mm. 2D gradient echo images were acquired perpendicular to the optic nerve with the following parameters: TR 85 *ms*, TE 9 *ms* and 19 *ms*, FOV 12.8x12.8 mm^2, slice thickness 1 *mm*. In plane resolution was 50x50 μm^2. Phase difference between two echo times was used to estimate the frequency shift, while the macroscopic field inhomogeneities in the phase image were removed.



Results: Figures (a) and (b) show the T1 weighted images (first column) and the corresponding frequency maps (second column) of the fresh prepared optic nerve and surrounding PBS media obtained at two nerve orientations: parallel and perpendicular to the external B_0 field. As expected, frequency distribution outside of the nerve is uniform in parallel orientation and has a dipolar pattern in perpendicular case. For the latter case, the frequency profiles (in Hz) along the equatorial (horizontal) and polar (vertical) directions are illustrated in Figures (c) and (d), respectively.

Frequency difference in the surrounding media between positions on the pole and equator, about -8 Hz, allows direct calculation of magnetic susceptibility difference between optic nerve and PBS media ($\Delta\chi$): $\Delta f / f_0 = 4 \cdot \pi \cdot \Delta\chi$. If Lorentzian sphere approach would be valid, the predicted frequency shift between optic nerve and PBS would be -2.6 Hz ($\Delta f_{\square} / f_0 = 4/3 \cdot \pi \cdot \Delta\chi$) when positioned parallel to B0. This is significantly bigger than the observed value of -1.0±0.2 Hz. Such a discrepancy can only be explained by the generalized Lorentzian theory [4] which predicts frequency shift $\Delta f_{\square} / f_0 = 4/3 \cdot \pi \cdot \Delta\chi_{cytosol}$ that does not depend on the longitudinal magnetic susceptibility inclusions such as myelin and neurofilaments, and only depends on the susceptibility difference between the isotropic cytosol component and PBS, $\Delta\chi_{cytosol}$, which is very small, as observed from this study.

Generalized Lorentzian approximation also predicts that the shift of perpendicular positioned nerve is $\Delta f_{\perp} / f_0 = -2/3 \cdot \pi \cdot \Delta\chi_{cytosol}$, which is half of the shift when positioned parallel to the field, but with the opposite sign. However, our measurement shows this value is +0.84±0.24 Hz. The discrepancy can be attributed to the effect of water-macromolecule exchange [5], which is independent of tissue orientation and can be estimated from our data as +0.23 Hz. This would correspond to a 0.7% (v.v) free protein solution [6], which is much smaller than total WM protein concentration of approximate 10%.

Conclusions: In this study we investigated the frequency shift of brain WM using rat optic nerve. Our results demonstrate that generalized Lorentzian approach provides satisfactory explanation of experimental data while Lorentzian sphere approximation fails to describe the local magnetic field sensed by water molecules within WM.

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References: **1.** Duyn, J.H., et al., PNAS, 2007. 104: p11796-801; **2.** Chu, S.C., et al., MRM 1990. 13: p239-62; **3.** Lorentz, H.A., *the Theory of Electrons*, 1909, p. 133; **4.** He, X. and D.A. Yablonskiy, PNAS 2009. 106: p13558-63; **5.** Zhong, K., et al., Neuroimage 2008. 40: p1561-6. **6.** Luo, J., et al., JMR 2009.