On the Nature of Phase Contrast in Gradient Echo MRI:A Generalized Lorentzian Approach

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Introduction: A new wave of interest to study brain tissue phase contrast in conventional gradient recalled echo (GRE) MRI has arose due to the recent impressive results obtained at high field (1). Possible origins of this shift, such as susceptibility effects due to lipids, iron, deoxyhemoglobin (1) as well as chemical exchange with the proteins (2) have been suggested, but were not able to fully account for the observed frequency shift, especially the lack of phase contrast between WM and CSF in motor cortex area(1). Herein we propose a theoretical framework based on the concept of generalized Lorentzian field approximation that allows quantitative evaluation of tissue frequency shifts due to the tissue structure at the sub-cellular level, as well as the global tissue organization and orientation with respect to the external magnetic field.

Theory: At the sub-cellular level, protein-rich cytoskeleton fibers, lipid-rich endoplasmic reticulum and cell membranes, as well as iron-rich oligodendrocytes related to myelin, are primarily arranged in a highly anisotropic manner - mainly longitudinally along the axonal direction. To estimate the susceptibility driven local frequency shift of water in axonal cytosol, we adopt a concept of Lorentzian cylinder (or more generally – ellipsoid) rather than the Lorentzian sphere. An imaginary cylinder or very long ellipsoid of rotation (along axonal direction) can be drawn around each water molecule so that no linear structures are included. Anything outside the cylinder can then be treated as macroscopic uniform continuum. Hence, internal, *cell-structure specific* frequency shifts Δf in a single axon due to the magnetic susceptibility effects can be approximated as follows: $\Delta f_{axon} / f_0 = 2 \cdot \pi \cdot (\chi_{axon} - \chi_{cytosol}) \cdot \sin^2 \vartheta + 4/3 \cdot \pi \cdot \chi_{cytosol}$ (Eq. [1]), where cytosol is cytoplasm void of above-mentioned inclusions, f_0 is the base Larmor resonance frequency; ϑ is the angle between axonal direction and external B_0 field. In addition to these cell-structure specific frequency shifts, the MR frequency also depends on the tissue global geometrical orientation and shape as well as inter-tissue and tissue/air interfaces.

Experimental Methods: The study was approved by IRB. A total of three *in vivo* studies were conducted on normal healthy volunteers. Two *ex vivo* studies were conducted on formaldehyde fixed coronal-cut human brain frontal lobe specimens. All images were acquired on a Siemens 3T Trio scanner using multi-gradient echo sequence with spatial resolution 1×1×3 mm^3 for *in vivo* and 0.5×0.5×1 mm^3 for *ex vivo* studies.

Results & Discussion: In human motor cortex area, the global geometrical orientation of tissue boundaries and interfaces can be approximated as parallel structures along superior-inferior axis (direction of B_0 field). Since WM fibers in motor cortex area also run primarily along superior-inferior axis, the frequency shift of the WM can be calculated directly from Eq. [1] with $\theta = 0$. Assuming mostly random orientation of axons in GM, the frequency shift can be calculated by averaging Eq. [1]. Based on the data in Table 1, including the contribution from deoxyhemoglobin in the blood vessel network which can be estimated from its blood volume and oxygenation level (3), the results of tissue frequency shifts are listed in Table 2 (second line). They agree very well with the data of Duyn *et al* (1). At the same time, results estimated under the Lorentzian sphere approach (Table 2, line 3) are inconsistent with the experimental observation.

Figure 1 shows axial frequency shift (in Hz) images from our *in vivo* studies in the motor cortex area. The observed frequency shifts between GM, WM and CSF agree well with theoretical predicted values in Table 2.

Figure 2 displays *ex vivo* T1 weighted images (a, c) and the corresponding frequency images (b, d, in Hz) acquired at two B_0 orientations. Profound changes on the GM/WM phase contrast can be seen. For example, in the area outlined by the black box, the GM/WM frequency shift is –0.7 Hz (-5.7×10^{-3} ppm) when B_0 is parallel to the GM/WM interface. The frequency shift changes to +1.8 Hz (14.6×10^{-3} ppm) when the B_0 becomes perpendicular to the GM/WM interface. These results are consistent with the fiber and tissue orientation in the cortical area of the brain frontal lobe (12). The sensitivity of the phase contrast to the relative orientation between B_0 field and tissue interface clearly demonstrated that the magnetic susceptibility effect is one of the dominant factors in the tissue phase contrast.

Table 1. Cellular content of essential susceptibility inclusions in "normal" human brain. Magnetic volume susceptibility of non heme iron is given in ppm per mg of iron per gram of tissue at body temperature. The data on tissue composition are from (4). [(a)]assumed to be the same as other fat-acid containing lipids [(5)].

	χ (ppm)	GM (%,w.w)	WM (%,w.w)	CSF (%, w.w)	specific density
water	-0.719[(11)]	84	74	~100	1.00
proteins	-0.774[(7)]	9.95	10.90	4.0E-3[(6)]	1.335[(7)]
cholesterol	-0.735[(11)]	1.28	4.24	0	1.07[(11)]
glycolipids	-0.670 [a]	0.13	4.06	0	0.90
phospholipids	-0.670 [a]	4.48	7.06	0	0.90
nonheme iron	0.11[(8)]	4.0E-3[(10)]	4.0E-3[(9)]	3.0E-4[(13)]	--

Table 2. The measured and predicted frequency shifts, Δf ($\times10^{-3}$ ppm), between tissue types in motor cortex area.

	Δf GM-WM	Δf GM-CSF	Δf WM-CSF
Measured (Duyn *et al*)	15.7	14.7	-1.0
Generalized Lorentzian	14.1	12.7	-1.3
Lorentzian Sphere	-9.4	12.7	22.1

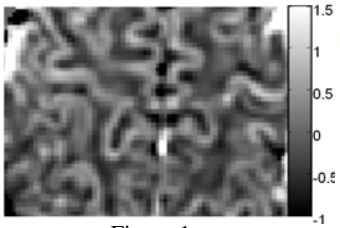

Figure 1

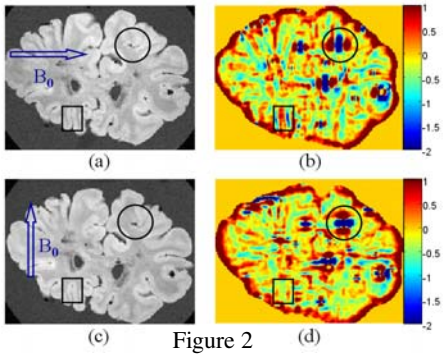

Figure 2

Conclusion: In this study, we have proposed a theoretical framework based on the concept of generalized Lorentzian field approximation that allows quantitative evaluation of tissue frequency shifts due to the internal tissue-specific magnetic susceptibility effects. Our approach takes into account the specific geometric properties of the magnetic susceptibility inclusions (mostly proteins, lipids, deoxyhemoglobin and non-heme iron) in the brain tissue. We demonstrated that not just the amount, but, more importantly, *spatial distribution* of the susceptibility inclusions at the sub-cellular level, as well as global cellular organization and its relative orientation with respect to the external B_0 field are the dominant factors in the observed phase contrast.

Reference: **1.** Duyn, *et al.*, *PNAS* 2007; 104:11796; **2.** Zhong, *et al.*, *Neuroimage* 2008; 40:1561; **3.** He, Yablonskiy, *MRM* 2007; 57:115; **4**. van der Knaap, Valk, *Magnetic Resonance of Myelination and Myelin Disorders*, Springer; 2005; **5.** Szczepaniak, *et al.*, *MRM* 2002; 47:607; **6.** Seyfert, *et al.*, *J Neurol* 2002; 249:1021; **7.** Savicki, *PNAS* 1984; 81:5417; **8.** Schenck, *Ann N Y Acad Sci* 1992; 649:285; **9.** Chen, *et al.*, *Radiology* 1989; 173:521; **10.** Griffiths, Crossman, *Dmentia* 1993; 4:61; **11.** Weast, Astle, *CRC Handbook of Chemistry and physics*, CRC press; 1981-1982; **12.** Wakana, *et al., Radiology* 2004;230:77. **13.** Clardy, *et al., Lab Clin Med* 2006; 147:67;