On the role of neuronal magnetic susceptibility and structure symmetry on Gradient Echo MR signal formation

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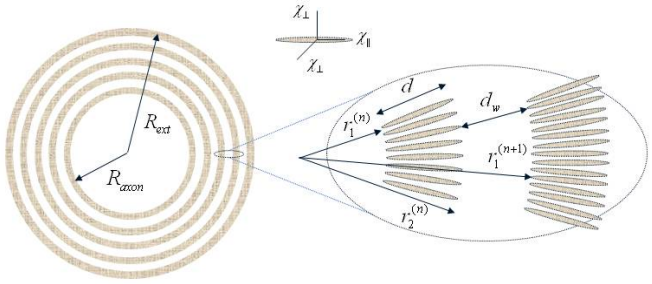
Introduction Phase images obtained with gradient-recalled echo MRI provide new contrast in the brain at high magnetic fields that is distinct from that obtained with conventional T1- and T2-weighted images. However, the biophysical origins of the phase (frequency) contrast are not well understood yet. Myelin was proposed as one of the main contributors to MR signal phase in white matter (1-3). A traditional point of view relates MR signal frequency shift due to the presence of local magnetic susceptibility inclusions (iron, proteins, lipids, etc.) to their bulk magnetic susceptibility χ by means of Lorentzian sphere approximation: $\Delta f / f_0 = 4\pi\chi / 3$ (CGS units), where f_0 is the base Larmor frequency. However, as it was proposed in (4) and confirmed by computer simulations in (5), the local contribution to the MRI signal phase does not directly depend on the bulk magnetic susceptibility of the tissue, but on the "magnetic micro-architecture" of the tissue, i.e., on the distribution of magnetic susceptibility inclusions (lipids, proteins, iron, etc.) at the cellular and sub-cellular levels. This effect is especially important for anisotropically arranged cellular structures such as axons. For such structures, the Lorentzian sphere approximation is not valid and should be substituted by Generalized Lorentzian approach (GLA) (4)

$$\Delta f / f_0 = 4\pi \cdot \chi_{iso} / 3 + 2\pi \cdot \chi_L \cdot \sin^2\alpha \qquad [1]$$

where χ_{iso} is magnetic susceptibility of isotropically distributed components of cellular structure, χ_L is magnetic susceptibility of longitudinally arranged components (neurofilaments, myelin sheath , etc.) and α is the angle between $\mathbf{B_0}$ and orientation of neuronal fibers. One of the important consequences of Eq. [1] is anisotropy of phase contrast in WM – correlation between MR signal phase and orientation of neuronal fibers with respect to $\mathbf{B_0}$. Eq. [1] predicts anisotropic behavior of phase contrast due to cylindrical symmetry in the arrangement of WM fibers. Eq. [1] , however, does not take into account anisotropy of WM magnetic susceptibility (6,7). As shown in (8) for a spherical case and in (9) for a cylindrical case, the presence of a layer formed by highly radially-oriented long-chain lipoprotein molecules, surrounding a central compartment, leads to a non-zero frequency shift in this compartment. The goal of the present communication is to incorporate this effect in the GLA.

Theory We consider WM as a system comprising 3 water-containing compartments: extracellular, intracellular (axons), and myelin sheath. All the frequencies are referenced to the frequency of the extracellular compartment. The myelin sheath is modeled as a set of N ($N >> 1$) concentric lipid layers of thickness d, separated by aqueous layers of thickness d_w (see Figure). In an external magnetic field $\mathbf{B_0}$, the lipid layers are magnetized and induce the secondary inhomogeneous magnetic field. By solving Maxwell equations for this induced field and using results of the GLA (4), we find the following expression for the frequency shift inside the circular cylindrical axon surrounded by myelin sheath:



$$\frac{\Delta f_{axon}}{f_0} = 2\pi\sin^2\alpha \cdot \frac{d}{d+d_w}\Delta\chi \cdot \ln\left(\frac{R_{ext}}{R_{axon}}\right) + \left(-2\pi\sin^2\alpha + \frac{4}{3}\pi\right)\cdot\chi_{iso}^{(axon)} \qquad [2]$$

where $\Delta\chi = \chi_\parallel - \chi_\perp$, $\chi_\parallel$ and $\chi_\perp$ are longitudinal and transverse components of volume magnetic susceptibility of long molecules forming lipid layers of myelin sheath, respectively; $\chi_{iso}^{(axon)}$ describes magnetic susceptibility of isotropically distributed structures within the axon, R_{axon} is the axon radius, R_{ext} is the external radius of the myelin sheath. As in (4), longitudinally distributed structures within the axon (e.g., neurofilaments) do not contribute to this frequency shift. Importantly, the first term in Eq. [2] is solely due to the susceptibility anisotropy $\Delta\chi$ within the myelin sheath.

Our theory also predicts that the time course of the gradient echo (GRE) signal from myelin water cannot be described in terms of a simple T2* decay. It is Gaussian for short gradient echo times *TE*, whereas for long *TE* it might exhibit *sinc*-function-type oscillations. The phase of the MR signal from water inside the myelin sheath depends on *TE* nonlinearly. For short *TE*, it can be approximated as a linear function of *TE* with the frequency shift:

$$\frac{\Delta f_{myelin}}{f_0} = 2\pi\sin^2\alpha\cdot\Delta\chi\cdot\left[\frac{1}{2} + \frac{\rho^2\ln\rho}{(1-\rho^2)}\right], \quad \rho = R_{axon}/R_{ext} \qquad [3]$$

Discussion Our results provide specific dependences of frequency shifts on myelin geometric parameters; hence they might be helpful in deciphering WM tissue microstructure and changes that take place in different diseases. For example, as demonstrated in (5), myelin structural disordering in MS leads to increase in MR signal frequency because of a "redistribution of contributions" to Lorentzian signal frequency shift in Eq. [1] – longitudinally arranged myelin becomes disordered and contributes to isotropic part of magnetic susceptibility. This effect can be enhanced due to an additional frequency shift described by the first term in Eq. [1] because it will also "disappear" if myelin sheath is structurally damaged.

Conclusions Our theoretical results show that both, anisotropy of neuronal tissue "magnetic micro-architecture" and anisotropy of myelin sheath magnetic susceptibility, are important for describing GRE signal phase and magnitude. Our model describes the GRE signal comprising of three compartments – axonal, myelin and extracellular. The myelin-induced frequency shifts reach extrema for axon oriented perpendicular to the magnetic field and are zeros in a parallel case. The myelin water signal is substantially non-T2* type.

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