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Imaging neural architecture of the brain based on its multipole magnetic response

Chunlei Liu [a,b,*], Wei Li [a]

[a] Brain Imaging and Analysis Center, School of Medicine, Duke University, Durham, NC, USA
[b] Department of Radiology, School of Medicine, Duke University, Durham, NC, USA

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ABSTRACT

Although magnetic fields interact weakly with biological tissues, at high fields, this interaction is sufficiently strong to cause measurable shifts in the Larmor frequency among various tissue types. While measuring frequency shift and its anisotropy has enabled NMR spectroscopy to determine structures of large molecules, MRI has not been able to fully utilize the vast information existing in the frequency to elucidate tissue microstructure. Using a multipole analysis of the complex MRI signal in the Fourier spectral space, we developed a fast and high-resolution method that enables the quantification of tissue's magnetic response with a set of magnetic susceptibility tensors of various ranks. The Fourier spectral space, termed **p**-space, can be generated by applying field gradients or equivalently by shifting the **k**-space data in various directions. Measuring these tensors allows the visualization and quantification of tissue architecture. We performed 3D whole-brain multipole susceptibility tensor imaging in simulation, on intact mouse brains *ex vivo* and on human brains *in vivo*. We showed that these multipole susceptibility tensors can be used to image orientations of ordered white matter fibers. These experiments demonstrate that multipole tensor analysis may enable practical mapping of tissue microstructure *in vivo* without rotating subject or magnetic field.

Introduction

Magnetic fields can penetrate deep into the body since they interact with biological molecules weakly as evidenced by the routine application of MRI in human bodies. Because of this weak interaction, MRI has traditionally relied on the amplitude of the nuclear magnetization from the very beginning to generate tissue contrast (Lauterbur, 1973). However, at high fields, interaction between magnetic field and the orbital electrons of biomolecules may introduce a measurable perturbation on the resonance frequency of surrounding water protons. This perturbation in turn reflects the molecular content and microstructure of the tissue. A notable example is the relative frequency shift between gray and white matter and between layers of the cortex which is thought to originate from variations of magnetic susceptibility (Duyn et al., 2007; Rauscher et al., 2005). Although frequency shift has provided a new image contrast for MRI, utilizing this contrast to infer neural architecture and brain structural connectivity remain challenging.

One potential way to fully utilize this frequency is to borrow techniques from NMR spectroscopy. Indeed, measuring frequency shift has been instrumental in NMR spectroscopy for probing molecular structure. While high-resolution NMR techniques provide a wealth of information (de Beer et al., 1994; Otting et al., 1990; Tolman et al., 1995; van Zijl et al., 1984), adapting those techniques to high-resolution imaging is not yet possible. The difficulty is partially due to low sensitivity, limited scan time and vastly more complex physiological conditions encountered in volumetric brain imaging. Because of these difficulties, frequency shift measured by MRI has been limited to the zero-*th* order information, i.e. the mean frequency of a whole voxel (Dixon, 1984; Glover and Schneider, 1991; Haacke et al., 1995; Rauscher et al., 2005; Weisskoff and Kiihne, 1992). Higher-order information such as susceptibility anisotropy of dipoles and quadrupoles, if resolved, would provide important information of sub-voxel tissue and cellular architecture. Similar to the important role that NMR has played in untangling molecular structure (Cavalli et al., 2007; Otting et al., 1990; Wishart et al., 1992), imaging higher-order frequency variation could provide a powerful tool for probing tissue microstructure such as brain connectivity noninvasively.

The backbone of brain connectivity is composed of bundled long projecting axons. Structurally, this connectivity backbone may be compared to the backbones of macromolecules. Ordered arrangement of atoms along the chain axis of macromolecules gives rise to an NMR measurable anisotropic susceptibility tensor. Similarly, on the tissue scale, the ordered arrangement of axon bundles also produces anisotropic frequency (He and Yablonskiy, 2009) and susceptibility (Lee et al., 2010; Li et al., 2012b; Liu, 2010). Although the mean susceptibility of a voxel can be measured with a gradient echo (de Rochefort et al., 2008; Li, 2001; Salomir et al., 2003), it does not measure the orientation dependence of the susceptibility (Li et al., 2011). To measure the anisotropy of magnetic susceptibility, the method of susceptibility tensor

* Corresponding author at: Brain Imaging and Analysis Center, 2424 Erwin Road, Suite 501, Campus Box 2737, Durham, NC 27705, USA. Fax: +1 919 681 7033.
E-mail address: chunlei.liu@duke.edu (C. Liu).

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imaging (STI) has been used (Liu, 2010). A recent study also explored the capability of STI for tracking neuronal fibers in 3D in the mouse brain *ex vivo* (Liu et al., 2012). In large fiber bundles, the orientation determined by STI was found to be comparable to that by diffusion tensor imaging (DTI) of diffusion anisotropy (Basser et al., 1994, 2000; Moseley et al., 1990). However, this experimental procedure of STI requires rotating the object or the magnetic field. The requirement is clearly not convenient or even impractical for routine brain imaging on standard MRI scanners *in vivo*.

Here, we developed a method to measure higher-order frequency variations based on a single image acquisition without rotating the object or the magnet. This method utilized a multipole analysis of the MRI signal in a sub-voxel Fourier spectral space termed "**p**-space" for short. By sampling the **p**-space with pulsed field gradients or by shifted image reconstruction, we were able to measure a set of dipole and quadrupole susceptibility tensors. We illustrated the methodology in a simulation of aligned axons and demonstrated its use for 3D high-resolution imaging of mouse brains *ex vivo* at 9.4 Tesla and human brains *in vivo* at 3.0 Tesla. We anticipate that the **p**-space approach may provide a powerful method for studying tissue microstructure and brain connectivity *in vivo* and non-invasively.

Methods

The spectral space (p-space) of microscopic magnetic field

For a given imaging voxel containing heterogeneous structures, magnetic field within the voxel is also heterogeneous due to the interaction between tissue and external field. The total magnetization of the voxel is an integral of all spins within the voxel, each experiencing a slightly different local magnetic field. The phase angle of the resulting integral represents the amplitude of the mean field. The spatial heterogeneity, however, is lost during the ensemble averaging. If the field distribution within the voxel can be recovered, it will allow us to infer the underlying tissue microstructure.

One way to recover the field distribution is to apply an external magnetic field gradient which will modulate the resonance frequency of the spins within the voxel. Specifically, given a voxel of width [v_1, v_2, v_3] centered at location **r** in the laboratory's frame of reference, the field distribution within the voxel can be denoted as $\mathbf{B}(\mathbf{r}+\mathbf{x})$. Here, **x** is the coordinate of a spin in the voxel's frame of reference whose origin is at the center of the voxel. Both **r** and **x** are normalized by the width of the voxel, thus dimensionless. In the presence of a pulsed field-gradient **G**, the voxel-averaged MRI signal $s(\mathbf{r})$ at time t, ignoring T_2-relaxation, is given by

$$s(\mathbf{r}) = \int_{\mathbf{x}} \rho(\mathbf{r}+\mathbf{x}) e^{-i\gamma\left(B_3(\mathbf{r}+\mathbf{x}) + \sum_{j=1}^{3} G_j \cdot \left(r_j + x_j\right) v_j\right) t} \mathrm{d}\mathbf{x} \quad (1)$$

Here, i is the imaginary number and the index j represents the three axes of a Cartesian coordinate system with (1, 2, 3) corresponding to (x, y, z) respectively. $B_3(\mathbf{r}+\mathbf{x})$ is the z-component of $\mathbf{B}(\mathbf{r}+\mathbf{x})$ which is along the direction of the $\mathbf{B}_0$ field; $\rho(\mathbf{r})$ is the spin density at position **r** and γ is the gyromagnetic ratio. Eq. (1) can be rewritten as

$$s(\mathbf{r}) = e^{-i2\pi\mathbf{p}\cdot\mathbf{r}} \int_{\mathbf{x}} \rho(\mathbf{x}) e^{-i\gamma B_3(\mathbf{x})t} e^{-i2\pi\mathbf{p}\cdot\mathbf{x}} \mathrm{d}\mathbf{x} \quad (2)$$

where **p** is a dimensionless spatial frequency vector with $p_j = \gamma G_j v_j t / 2\pi$. The symbol **r** has been dropped from the integral with the understanding that both ρ and B_3 are expressed in the voxel's coordinate system. In other words, the magnetization is proportional to the Fourier spectrum of the complex magnetization distribution function. Herein, this spectral space will be referred to as the **p**-space to differentiate it from the **k**-space that is commonly used in image acquisition. The Fourier integral in Eq. (2) can be separated into magnitude $m(\mathbf{r},\mathbf{p})$ and phase $\Phi(\mathbf{r},\mathbf{p})$ as

$$s(\mathbf{r}) = e^{-i2\pi\mathbf{p}\cdot\mathbf{r}} m(\mathbf{r},\mathbf{p}) e^{-i\Phi(\mathbf{r},\mathbf{p})} \quad (3)$$

Both the magnitude and the phase are expected to depend on the applied field gradient. Notice that if the voxel is an ideal delta function, i.e. $\rho(\mathbf{x})e^{-i\gamma B_3(\mathbf{x})t} = \delta(\mathbf{x})$, then the integral in Eq. (2) will be always equal to 1 regardless of the **p**-vector. In this extreme case, no additional information can be gained by applying field gradients. In reality, however, all imaging voxels have a finite dimension with a distributed magnetization. Sampling the **p**-space will thus allow us to probe sub-voxel magnetization and magnetic field distribution.

Multipole susceptibility tensors in the **p***-space*

In a second-order multipole expansion (Jackson, 1975) (or Taylor's expansion in Cartesian coordinates) (Appendix A), $\Phi(\mathbf{r},\mathbf{p})$ can be written as

$$\Phi(\mathbf{p}) = \Phi_0 + \gamma B_0 t\, \hat{\mathbf{p}}^{\mathbf{T}} \boldsymbol{\chi}_d \hat{\mathbf{p}}\, p + \gamma B_0 t\, \hat{\mathbf{p}}^{\mathbf{T}} \boldsymbol{\chi}_q \hat{\mathbf{p}}\, p^2 \quad (4)$$

In Eq. (4), the first term is the mean phase. The second term is a dipole moment in which $\boldsymbol{\chi}_d$ is a rank-2 dipole susceptibility tensor and $\hat{\mathbf{p}}$ is the unit directional vector. The third term is a quadrupole moment expressed in terms of a rank-2 quadrupole susceptibility tensor $\boldsymbol{\chi}_q$. More specifically, Φ_0 is the phase when no gradient is applied and it is related to the image-space dipole susceptibility tensor (rank 2) $\boldsymbol{\chi}(\mathbf{r})$ following (Liu, 2010)

$$\Phi_0 = \gamma t\, FT^{-1}\left\{\frac{1}{3}\hat{\mathbf{B}}_0 FT\{\boldsymbol{\chi}\}\mathbf{B}_0 - k_3 \frac{\mathbf{k}^{\mathbf{T}} FT\{\boldsymbol{\chi}\}\mathbf{B}_0}{k^2}\right\} \quad (5)$$

Here, $\hat{\mathbf{B}}_0$ is a unit directional vector (dimensionless). The quadrupole tensor $\boldsymbol{\chi}_q$, in its complete form, is a rank-3 tensor (Jackson, 1975). However, since $\mathbf{B}_0$ is in the z-direction, the third dimension of $\boldsymbol{\chi}_q$ is locked to the z-direction, thus reducing it to a rank-2 tensor.

Similarly, the magnitude can be expanded as

$$m(\mathbf{p}) = m_0\left(1 + \gamma B_0 t\, \hat{\mathbf{p}}^{\mathbf{T}} \boldsymbol{\eta}_d \hat{\mathbf{p}}\, p + \gamma B_0 t\, \hat{\mathbf{p}}^{\mathbf{T}} \boldsymbol{\eta}_q \hat{\mathbf{p}}\, p^2\right) \quad (6)$$

where both $\boldsymbol{\eta}_d$ and $\boldsymbol{\eta}_q$ are dimensionless rank-2 tensors. Given a set of **p**-vectors, Eqs. (4) and (6) can be used to determine the multipole tensors.

Measuring p-space susceptibility tensors

To measure **p**-space multipole tensors, a standard gradient-echo sequence could be used with an added spectral sensitizing gradient (Fig. 1a). The spectrum-sensitizing gradient induces a shift in the **k**-space. Utilizing this shifting effect, we achieved spectral weighting during image reconstruction by simply shifting the **k**-space data with the desired **p**-vector. This strategy allowed the sampling of the **p**-space without applying physical gradients. By shifting the reconstruction window in various directions and with various distances, a series of images can be reconstructed (Fig. 1b). For each shift in the **p**-space, a linear phase term is also added to the image as described in Eq. (2). This linear phase must be removed before calculating the phase spectrum (Fig. 1b).

The **p**-space can be sampled in many different ways. If it is sampled on a spherical surface with a constant radius of p, the susceptibility tensors can be calculated by inverting the resulting system of linear equations defined by Eqs. (4) and (6). Alternatively, the **p**-space can be sampled continuously along a given direction, thus allowing the