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Magnetic Source MRI: A New Quantitative Imaging of Magnetic Biomarkers

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***Abstract*—A new approach to generating MRI contrast by solving the magnetic field to susceptibility source inverse problem is presented to address the quantification difficulties associated with traditional T1/T2 relaxation and susceptibility weighted T2* methods. The forward problem from source to field is reviewed. Its inverse field to source problem is ill posed. Accurate solutions are found by conditioning the data acquisition or regularizing the solution. Preclinical and clinical applications using this magnetic source MRI are discussed for quantitative mapping magnetic biomarkers such as contrast agents in molecular MRI and iron deposits in diseases.**

I. Introduction

Quantification is essential in experimental methods used to study biochemical reactions, biomolecular pathways and biological processes in health and disease. The importance of quantifying molecular/cellular events cannot be overemphasized for molecular imaging [1]. For example, the use of nanoparticles as delivery vehicles for diagnostic and therapeutic agents requires accurate counts of nanoparticles accumulated at the diseased tissue to make diagnostic decisions and gauge therapeutic dose. The measurement of drug dose at targeted sites is essential for monitoring therapy. The count of stem cells homing at diseased tissue would be essential in optimizing cell therapy protocols. The goal of in vivo study of biochemistry through imaging necessitates a means to quantify molecular events. Quantitative accuracy and reproducibility have to be established to standardize and cross-validate molecular MRI methods. So far there is no effective tool to quantify molecular/cellular events. Molecular MRI investigations have been only qualitative or semi-quantitative. Estimation of signal changes currently used in MRI, such as hypointensity in detecting SPIO labeled or targeted cells [2, 3] does not provide absolute quantification and may be highly dependent on imaging parameters, pulse sequences and field strengths. Absolute quantification of magnetic biomarkers will enable longitudinal investigations and inter- and intra-scanner evaluations that are essential to molecular imaging based diagnostics and therapeutics.

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II. Difficulties of Quantification in Molecular MRI using Traditional Relaxation Susceptibility Contrast Mechanisms

A. Difficulty with quantifying contrast agent (CA) through relaxation contrast

The mechanism for T1/T2 relaxation enhancement consists of 1) metallic electronic spins interacting with bounded water spins and 2) bounded water exchanging with surrounding bulk water (metal↔bound H_2O↔bulk H_2O) [4]. Because MR signal magnitude depends on T1/T2 relaxation enhancement in a complicated manner, determination of absolute contrast agent concentration [CA] requires calibration and is very susceptible to flip angle errors [5]. This [CA] quantification relies on the assumption that the change in T1/T2 relaxation rate (R1/R2) is linearly proportional to [CA]. However, the linearity coefficient (relaxivity) depends on the bulk water availability. When tissue and CA distributions are uniform, this relaxivity is a constant over space [6]. For CA targeting specific biomolecules and cells, bulk water surrounding CA will become limited and varying in space. Consequently, [CA] becomes indeterminable from relaxation enhancement effects, and assumption of constant relaxivity leads to erroneous results [7]. Experimental results with contrast agents that are localized in cells with reduced exchange with bulk water confirm this variation in relaxivity [8, 9], showing the well known T1 relaxation quench . Therefore, T1/T2 relaxation measurement does not provide reliable [CA] quantification.

B. Difficulty with quantifying contrast agent (CA) through susceptibility contrast

The susceptibility-relaxation contrast (T2* weighted imaging) is the intravoxel dephasing effect due to the iron dipole field dispersion in a voxel, in addition to the T2 transverse relaxation signal decay [10]. While T2* weighted imaging offers a negative contrast very sensitive to the presence of metal in CA, [CA] may not be quantified from this hypointensity contrast. Geometric factors including voxel size, voxel location and CA spatial distribution affect susceptibility contrast (sometimes defined as R2' = 1/T2* - 1/T2) [7]. Imaging parameters including echo time and field strength also affect the susceptibility contrast. Phases of spins in a dipole field are dispersed and the phase dispersion increases with echo time. When a very small voxel is used for imaging, the signal loss of intravoxel dephasing can be small where the field has less variation, or large where the

field has large variation. When a large voxel is used in imaging, there is inevitably substantial dephasing. It has also been noted that the T2* exponential decay model may be inadequate for an accurate description of intravoxel dephasing loss; a Gaussian for a short echo time or a Lorentzian for a large echo time may be applicable [7, 10]. Recognizing the difficulty of the T2* concept, other attempts including anisotropy [11] and mean field correlation [12] ideas have been introduced to achieve a more accurate description of susceptibility inhomogeneity effects on MR signal. Susceptibility quantification and mapping methods remain to be developed.

III. Field Source Inverse Solution to Quantify Contrast Agents in MRI

We propose a novel approach to quantify magnetic biomarkers or contrast agents by mapping their magnetization using both magnitude and phase information in T2* imaging. In MRI, magnetization is the magnetic susceptibility times B0 (we will interchangeably use the terms magnetization and susceptibility). Magnetic susceptibility is a fundamental property of a material, characterizing its response to an applied magnetic field. The volume susceptibility mapped in MRI in this research is the concentration times a constant specific to a contrast agent (molar susceptibility/molar mass). To explore biomedical applications, magnetic susceptibility measurements of biomaterials have been investigated using a superconducting quantum interference device (SQUID) [13] and MRI signal phase [14, 15]. The basic approach for estimating an object's susceptibility is to polarize the object with a known primary magnetic field and measure the field associated with the magnetization of the polarized object. The Maxwell equations determine the relation between the measured field and object magnetization [16]. The fields of several objects are added together linearly according to the superposition principle [16]. The volumetric magnetic susceptibilities for biomaterials and contrast agents at practical concentrations are much smaller than one (<<100ppm), and accordingly their mutual polarization effects may be ignored.

A. The forward problem from magnetization to MRI measured field.

We formulate here the exact relation between tissue magnetization and magnetic field directly from the fundamental Maxwell equation. For a given magnetization distribution $\mathbf{m}(\mathbf{r})$ of tissue in an MR scanner, the corresponding macroscopic magnetic field $\mathbf{b}(\mathbf{r})$ can be derived from the Maxwell Equations of static magnetism,

$$\nabla\cdot\mathbf{b} = 0,\ \nabla\times\mathbf{b} = \mu_0\nabla\times\mathbf{m}. \quad (1)$$

It should be noted that MRI phase measures the local field $\mathbf{b}_{local}$ experienced by water spins, which is different from the macroscopic field $\mathbf{b}$ because of the susceptible materials surrounding the water spin. The Lorentz sphere correction model may be used that gives [16], $\mathbf{b}_{local} = \mathbf{b} - (2/3)\mathbf{m}$. We will solve Eq.1 first and then apply the Lorentz correction. The two first order differential equations in Eq.1 can be combined into a single second order differential equation,

$$\nabla^2\mathbf{b} = \mu_0[\nabla(\nabla\cdot\mathbf{m}) - \nabla^2\mathbf{m}]. \quad (2)$$

The solution to Eq.2 can be easily derived in Fourier domain $\mathbf{b}(\mathbf{r}) = \int d^3k\mathbf{B}(\mathbf{k})e^{i\mathbf{kr}} = FT^{-1}[B(\mathbf{k})]$, where differentiation becomes multiplication by $\mathbf{k}$, the k-space position vector:

$$\mathbf{k}^2\mathbf{B}(\mathbf{k}) = \mu_0[\mathbf{k}^2\mathbf{M}(\mathbf{k}) - (\mathbf{k}\cdot\mathbf{M}(\mathbf{k}))\mathbf{k}]. \quad (3)$$

Therefore, after applying the Lorentz correction,

$$\mathbf{B}_{local}(\mathbf{k}) = \mathbf{B}_0\delta(\mathbf{k}) + \mu_0[\mathbf{M}(\mathbf{k})/3 - (\mathbf{k}\cdot\mathbf{M}(\mathbf{k}))\mathbf{k}/k^2], \quad (4)$$

where the first term is the magnet B0 field at k=0 where Eq.B4 is problematic. The magnetization is related to susceptibility defined as $\chi(\mathbf{r}) \equiv \mu_0\,\mathbf{m}(\mathbf{r})/B_0$ (for all tissues, << 1). The equilibrium directions of magnetization and magnetic fields are along z. Let $\delta_b(\mathbf{r}) \equiv (b_{local}(\mathbf{r}) - B_0)/B_0$ be the relative difference field, whose Fourier transform $\Delta_b(\mathbf{k})$ can be simply expressed as

$$\Delta_b(\mathbf{k}) = (1/3 - k_z^2/k^2)X(\mathbf{k}), \quad (5)$$

where $X(\mathbf{k}) = FT[\chi(\mathbf{r})]$, the Fourier domain susceptibility. Using direct Fourier transformation, the corresponding formulation in image space is

$$\delta_b(\mathbf{r}) = (1/4\pi)\int d^3r'\ (3\cos^2\theta_{\mathbf{rr}'} - 1)/|\mathbf{r}-\mathbf{r}'|^3\chi(\mathbf{r}') = d(\mathbf{r}) \otimes \chi(\mathbf{r}), \quad (6)$$

where $d(\mathbf{r}) = (1/4\pi)(3\cos^2\theta - 1)/r^3 = FT^{-1}[(1/3 - k_z^2/k^2)]$. Eq.6 can be derived directly from the Maxwell equation in image space using the integration form [16].

Another image space derivation for Eq.6 is to use the magnetic field formula for a single dipole [16]. The superposition principle gives the field of an arbitrary distribution $\mathbf{m}(\mathbf{r})$ as summation over all dipole contributions. The z-component along B0 direction for the macroscopic magnetic field is, $b(\mathbf{r}) - B_0 = \int d^3r'm(\mathbf{r}')(\mu_0/4\pi)\,[(3\cos^2\theta_{\mathbf{rr}'} - 1)/|\mathbf{r}-\mathbf{r}'|^3 + 8\pi/3\ \delta(\mathbf{r}-\mathbf{r}')]$, which leads to Eq.6 as its second term is canceled by the Lorentz correction.

B. Difficulty with the inverse problem from measured field to magnetization source.

A direct point-wise division of the field map in k-space,

$$X(\mathbf{k}) = \Delta_b(\mathbf{k})/(1/3 - k_z^2/k^2), \quad (7)$$

would not generate a meaningful susceptibility map because of the zeroes at $k_z^2 = k^2/3$ [7]. These zeroes form two opposing cone surfaces at the magic angle ($\sim 54.7^0$ from the main magnetic field). The susceptibility at these cone surface cannot be determined, i.e., any $X(\mathbf{k})$ will give zero magnetic field at these cone surfaces. This causes the ill-posedness of the inverse problem.

It was suggested that these cone surfaces may be avoided in discretized k-space data acquisition using carefully chosen sampling grids [7]. However, the discrete problem remains ill-conditioned, because k-space points sampled close to the zero cone surfaces will cause severe noise amplifications. The condition number of the system Eq.B6, which characterizes the upper bound of noise propagation, is [17],

$$\kappa = \max_k[(1/3 - k_z^2/k^2)]/\min_k[(1/3 - k_z^2/k^2)] = k_m/(2\varepsilon), \quad (8)$$

where k_m is the maximal value of sampled k_z and ε is the closest distance the sampled point to the zero cone surface at

maximal k_z. Therefore, this condition number is large, resulting in large noise propagation.

C. *Condition the inverse problem through multiple orientation sampling – COSMOS.*

The zero cone surfaces in Eq.6 are the origin of ill-posedness, are fixed with respect to the B0 field. By rotating the object relative to the B0 field, the zero cone surfaces can be rotated to a different angle, and data sampling at the new angle allows magnetization determinable at the old cone locations. Therefore data sampling at multiple orientations improves the conditioning of the inverse problem as in computed tomography [18]. We term this method as Calculation Of Susceptibility using Multiple Orientation Sampling (COSMOS) [19]. In molecular MRI, it is easy to rotate a mouse object in an magnet with respect to B0. Let $\delta_{bp}(\mathbf{r})$ be the field map measured at object orientation angle p, and k_{zp} the k_z value at angle p, and N the total number of orientations, then the forward problem Eq.B1 becomes

$$(1/3\text{-}k_{zp}^2/k^2)X(\mathbf{k})= FT[\delta_{bp}(\mathbf{r})], \text{ for } p=1,\ldots,N \quad (9)$$

This problem can be solved for susceptibility at any **k** location, as long as one of the coefficients $(1/3\text{-}k_{zp}^2/k^2)$ is sufficiently larger than zero. For most susceptibility values $X(\mathbf{k})$ is over-determined and can be solved using a weighted least squares solver.

$$X(\mathbf{k})=\text{argmin}_{X(\mathbf{k})}\sum_p\sum_{\mathbf{r}}|w_p(\mathbf{r})[\delta_{bp}(\mathbf{r})\text{-}FT^{-1}[(1/3\text{-}k_{zp}^2/k^2)X(\mathbf{k})]]|^2. \quad (10)$$

Here the weighting factor $w_p(\mathbf{r})$ is the signal magnitude at the p^{th} orientation ($\propto$ phase SNR) thresholded at 10% of its maximum intensity, to account for noise effects in measurement. An algorithm for sparse linear equations and sparse least squares (LSQR) can be used to solve Eq.10 iteratively. This iteration converges rapidly (30 iterations in a few minutes in our preliminary 3D data on a Pentium 4 PC using Matlab), because the problem in Eq.9 is well conditioned. Our preliminary data demonstrate that this COSMOS method is very robust and accurate in quantitatively mapping susceptibility [19]. While a patient may be rotated in an open magnet, the difficulty to rotate a human in a closed magnet warrants methods without rotation.

D. *Regularize the inverse problem for a priori solutions.*

A powerful general approach to the ill-posed inverse problem is regularization using a priori knowledge of the solution[20], and this regularization approach does not require reorienting the object in the magnet. Magnetic markers in molecular MRI may be sparsely distributed in mice. In this situation, a reasonable sparse solution can be identified from the infinite possible solutions to the ill-posed inverse problem by penalizing the solution towards sparsity. For example, the L1 norm can be used to promote sparsity[21], and the sparse susceptibility image can be constructed from the following minimization using convex optimization solvers [22]:

$$\chi(\mathbf{r})=\text{argmin}_{\chi(\mathbf{r})}[\sum_{\mathbf{r}}|w(\mathbf{r})(\delta_b(\mathbf{r})\text{-}d(\mathbf{r})\otimes\chi(\mathbf{r}))|^2+\alpha R(\chi(\mathbf{r}))], \quad (11)$$

where $R[\chi(\mathbf{r})]$ is the regularization term expressed as the L1 norm of intensity or gradient of image $\chi(\mathbf{r})$, $w(\mathbf{r})$ is as in Eq.10, and the regularization parameter α may be determined according to errors in the sparsity model and data noise. Our preliminary studies using the L1 norm and other norms to regularize sparsity have shown that this regularization method is very promising for generating acceptable susceptibility images [23]. The convex optimization search for solution in Eq.11 using L1 norm is much more time consuming than that for Eq.10. This search time for solution may be reduced to a few minutes by introducing differentiability in Eq.11 and by using dedicated graphics cards.

The magnitude image information can be used to constrain the susceptibility image reconstruction, improving reconstruction accuracy and convergence speed, as demonstrated in PET and EEG/MEG. For example, it may be reasonable to assume that the susceptibility is constant over a small local region of uniform signal intensity. This assumption vastly reduces the number of unknowns, rendering the original inverse problem an over-determined problem for susceptibility in each region. The magnitude image allows segmentation of the object into a set of these local regions. Let χ_p be the susceptibility of region p and d_p the dipole kernel convoluted with region p, $d_p(\mathbf{r}) = (1/4\pi)\int_p d\mathbf{r'}(3\cos^2\theta_{\mathbf{rr'}}\text{-}1)/|\mathbf{r}\text{-}\mathbf{r'}|^3$ (geometric factor), then the convolution integral in Eq.6 is reduced to a summation,

$$\sum_p \chi_p d_p(\mathbf{r}) = \delta_b(\mathbf{r}). \quad (12)$$

Because there are so many voxels with spins to detect the magnetic field, Eq.12 is an over-determined problem, which can be rapidly solved using the weighted least squares method [24]:

$$\boldsymbol{\chi} = (D^TWD)^{-1}D^TW \quad (13)$$

where the vector $\boldsymbol{\chi}$ has elements χ_p, the matrix D has elements $D_{pr} = d_p(\mathbf{r})$, the matrix W has only nonzero diagonal elements $w(\mathbf{r})$, and the vector $\boldsymbol{\delta}$ has elements $\delta_b(\mathbf{r})$. This method is shown to be very useful for estimating [Gd] in contrast enhanced MRA [25]. The constraint imposed in Eq.13 may be too strong and may be relaxed into a prior that edge information in the susceptibility image is similar to edge information in the magnitude T2* weighted image. The edge similarity may be measured using an L1 norm, and the reconstruction of susceptibility image may be formulated as a minimization problem consisting of a data term enforcing consistency with the phase image and a prior term derived from the magnitude image. The solution can be obtained using convex optimization solver [26]:

$$\chi(\mathbf{r}) = \text{argmin}_{\chi(\mathbf{r})}[\sum_{\mathbf{r}}|w(\mathbf{r})(\delta_b(\mathbf{r})\text{-}d(\mathbf{r})\otimes\chi(\mathbf{r}))|^2 + \alpha R_1(\chi(\mathbf{r}),I(\mathbf{r})) + \beta\, R_2(G[\chi(\mathbf{r})],G[I(\mathbf{r})]), \quad (14)$$

where $G[I(\mathbf{r})]$ is the magnitude of the gradient vector of the magnitude image I at location **r**; R1 is the regularization term based on image intensities and R2 is the regularization term based on image gradients. This kind of minimization formulation would provide a powerful way to combine MRI phase and magnitude information for quantitative susceptibility imaging.

IV. Preclinical and clinical applications

The field source inverse solution enables quantitative mapping of susceptibility. Similar to MEG, it is static magnetic source MRI (msMRI), providing direct measure of contrast agents. This will be an important tool for molecular MRI. For example, iron oxide nanoparticles have been used as MRI markers in tracking cell migration, gene expression, angiogenesis, apoptosis and cancer detection. msMRI can be used to map and measure local drug dose delivered by magnetic nanovehicles targeting diseased tissue cells . msMRI can be used to map and measure the initial migration and homing density of stem cells labeled magnetically . These msMRI measurements will be very valuable for optimizing protocols for drug development and delivery and cell therapy. As a specific outcome of this research, msMRI will be developed as a non-invasive and non-radioactive estimation of biodistribution of nanoparticles in time following injection of targeted contrast agents, a very important goal of molecular MRI.

msMRI techniques have important medical applications. For example, it is difficult to have a definitive diagnosis of iron overloading diseases such as hemochromatosis and thalassemia major cardiomyopathy, and generally invasive tissue biopsy is required. msMRI techniques developed in this research can be extended to human heart and liver imaging to quantify iron deposition in tissue, providing accurate evaluation of iron overloading diseases. Local iron overloads are also found in neurodegenerative diseases including Parkinson and Alzheimer diseases. Absolute iron mass mapping may allow a definitive assessment of neurodegeneration. msMRI would be a very useful tool for early evaluation of patients at risk for neurodegenerative diseases and for helping to develop an effective therapy to preserve the patient's neuronal function. Another example of potential msMRI application may be in diagnosing bone disease. MRI has been used to assess bone density to avoid the invasive biopsy procedures and exposure to radiation and to assess structure and function of trabecular bone. Bone susceptibility imaging would provide insightful measure of bone mineralization and density.

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