In vivo quantification of SPIO nanoparticles with phase gradient mapping

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INTRODUCTION

The susceptibility gradients generated by super-paramagnetic iron oxide (SPIO) nanoparticles make them an ideal contrast agent in magnetic resonance imaging (MRI). Contrast agents based on SPIO nanoparticles are ideally suited for a wide range of applications in MRI, including liver imaging, MR angiography, and tracking of labeled cells *in vivo*. Traditional quantification methods for SPIO nanoparticle based-contrast agent rely on either T_2* relaxometry method (1-3) or by modeling the magnetic field inhomogeneities generated by the contrast agent (4). In this abstract, we propose to use a positive contrast method, known as phase gradient mapping (PGM) (5), to quantify the concentration of SPIO nanoparticles *in vivo*. Previous work on SPIO quantification using a PGM-based method has utilized a cylindrical model to quantify different concentrations of SPIO nanoparticles embedded within cylindrical vials in a phantom (6). However, no *in vivo* measurements were attempted in (6). Here, we propose a modified PGM-based SPIO quantification method to include objects with arbitrary shapes by modeling each voxel within the object as a homogeneous sphere. The proposed method is then tested on SPIO-labeled tumors that were implanted in the flank of nude mice.

THEORY

The field map of a given image displays the z-component of the magnetic field inhomogeneities and is experimentally constructed from two phase maps taken at different echo times. The x component of the gradient of the field map is $\nabla_x f(x,y) = (\nabla_x \varphi_1(x,y) - \nabla_x \varphi_2(x,y))/ (\gamma \Delta TE)$ where $\varphi_1(x,y)$ denotes the phase map taken at the first echo time, $\varphi_2(x,y)$ denotes the phase map taken at the second echo time, γ denotes the gyromagnetic ratio of hydrogen, and ΔTE denotes the difference between the echo times. Theoretically, a magnetic field will be induced when a sphere with susceptibility is placed in a homogeneous magnetic field. The strength of the induced magnetic field and the x component of the gradient of the induced magnetic field are

$$B(x,y) = \frac{\mu_0 m R^3}{3}\left(\frac{2z^2 - x^2 - y^2}{(x^2+y^2+z^2)^{5/2}}\right) \quad \text{and} \quad \nabla_x B(x,y) = -\mu_0 m R^3 x\left(\frac{4z^2 - x^2 - y^2}{(x^2+y^2+z^2)^{7/2}}\right)$$

where m denotes the magnetic moment per unit volume of the induced magnetic field and R denotes the radius of the sphere. Similar expressions can be found for the y and z components of $\nabla f(x,y)$ and $\nabla B(x,y)$. In principle, the SPIO concentration can be estimated by fitting the components of theoretical field,$\nabla B(x,y)$, to the components of experimental field, $\nabla f(x,y)$.

MATERIALS AND METHODS

Three mouse data sets were acquired using a 3T clinical scanner (Achieva, Phillips Healthcare, the Netherlands) with a 4 cm receive-only RF coil (Phillips Research Europe, Hamburg, Germany). Each mouse was subcutaneously implanted in the flanks with 1×10^5 labeled and 1×10^6 Unlabeled C6 glioma cells (ATCC, Manassas, VA), and both groups of cells were suspended in 100 μl of PBS. Feurmoxides (Berlex Laboratories, Wayne, NJ) were used to label the C6 glioma cells. The Fe content in the injected cells was approximately 19.4 pg/cell in labeled cells and 1.2 pg/cell in unlabeled cells. The estimated concentration of Feurmoxides was approximately 7 μg/ml, estimated by total amount of Fe over total injection volume. The contrast agent generates 1 emu per gram of Fe and has a relaxivity of 160 s^{-1} at 0.47 T. MR images were acquired with 3D FFE sequence with FOV = 40 mm x 40 mm, slice thickness = 0.5 mm, matrix size = 256 x 256, TR = 12.6 ms, and TE = 4.6, 6.9ms, respectively.

Each voxel within the tumor was modeled as a homogeneous sphere with magnetization m. The magnetic field gradient from each voxel was then superimposed to form the theoretical magnetic field gradient of the tumor, which was then fitted to the gradient of the experimental field map, measured by the acquired phase maps. A Hamming window was applied to phase gradient calculated presented in (7) and the modified phase gradient calculation method used to calculate the phase gradient maps from the two phase maps. All data analysis was performed using MATLAB (the MathWorks, Natick, Massachusetts).

RESULTS AND DISCUSSION

The implanted tumor, the phase gradient map, and its x-components for subject 2 are shown in Fig. 1. It is observed that the concentrations of 7 μg/ml within implanted areas do not give a large phase gradient. The estimations of concentration in the implanted area from the proposed quantification procedure are displayed in Table 1.

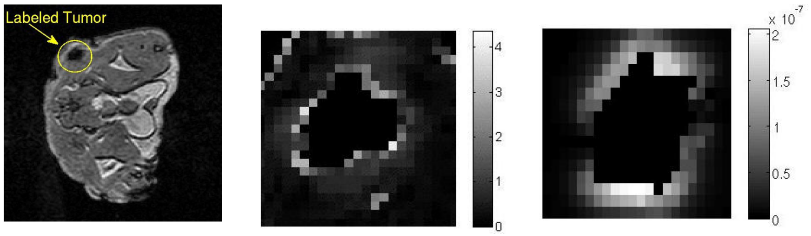

Figure 1. A: An axial view of subject 2. The arrow points to the implanted area. B: The phase gradient map surrounding the implanted area in subject 2. C: An axial view the x-component of $\nabla B(x,y)$ that is generated by the implanted area in subject 2. D: An axial view the x-component of $\nabla_x f(x,y)$ that is generated by the implanted area in subject 2.

Unlike in the phantom case that was considered in (6), where larger concentrations of contrast agent provided steeper phase gradients and consequently this resulted in more accurate estimations of the concentration of contrast agent within the SPIO doped vials. In the present study, the background for the *in vivo* data sets is not homogeneous. The inhomogeneities are primarily caused by susceptibility gradients, generated by tissue-tissue interfaces, air-tissue interfaces, and tissue-fluid interfaces. The susceptibility gradients add uncertainty to the estimation of concentration of the contrast agent. Another potential drawback of the proposed method is that the PGM method is unable to determine whether the phase gradients are caused by labeled cells or by the different interfaces.

Subject	Estimated Concentration from $\nabla_x f(x,y)$ [μg/ml]	Estimated Concentration from $\nabla_x f(x,y)$ [μg/ml]
1	8.27	8.52
2	7.60	0.05
3	12.68	0.01

Table 1. The results from the quantification process applied to the three data sets considered in this abstract.

In summary, the proposed quantification method gives estimates of the contrast agent concentration that are on the order of the known concentration in the implanted area. Future work will be focused on improving the estimate of the theoretical field gradient, $\nabla B(x,y)$, of arbitrary shapes. It is also expected that the proposed method will give more accurate estimates when higher concentrations of contrast agent are used in the implanted area.

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