論文の内容の要旨

論文題目　Positive Contrast Magnetic Resonance Imaging for Superparamagnetic Iron Oxide Nanoparticles
（超常磁性酸化鉄ナノ粒子によるポジティブコントラスト磁気共鳴撮像法）

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1. Introduction:

a) Magnetic Resonance Imaging (MRI)

MRI is a non-invasive technique commonly used in radiology to visualize the internal structure and function of the body. MRI uses no ionizing radiation and provides better soft tissue contrast than computer tomography (CT). Besides nuclei density, there are two other major contrast mechanisms based on the difference in spin-lattice relaxation time T_1 and spin-spin relaxation time T_2 respectively. Therefore, MR image reflects more inherent values than CT does.

b) Contrast Agent SPIO

In some situations, it is difficult to generate enough image contrast from inherent characteristics such as nuclei density, T_1 or T_2 to show subtle difference in anatomy and pathology. In this case contrast agent may be administered. Many kinds of contrast agents have been approved in clinical use. Generally, contrast agent can be classified into two groups: positive contrast agent and negative contrast agent. The former one has stronger T_1-shorten effect and the latter one has stronger T_2-shorten effect. The most popular T_1-shorten contrast agent is gadolinium-based chelate whose toxic to patients with kidney malfunction is still a debatable question. Iron compound that has no toxicity is a widely used negative contrast agent due to its strong ability to change the surrounding magnetic field.

Superparamagnetic iron oxide (SPIO) and ultra superparamagnetic iron oxide (USPIO) nanoparticles are the most commonly used iron compound contrast agent. As early as the mid 1980s, studies concluded that this iron based contrast agent causes a dramatic shortening of T_2 relaxation time of normal liver where the particles are taken up by Kupffer cells [1)]. Abnormal liver parts, such as a primary liver tumor or liver metastasis, remain unaltered signal intensity and stand out from the dark surrounding regions of normal tissues. Subsequently, SPIOs that have a longer blood half-life were used in macrophage cell imaging for lymph nodes [2)] and bone marrow [3)]. Normal lymph nodes will appear dark, while tumor metastases remain the same signal as the pre-contrast image. Furthermore, iron oxide particles have been developed to target specific receptors or antigens such as the metabolite of tumor [4)].

c) Positive contrast imaging method for SPIO.

One disadvantage of this negative contrast agent is the similarity between its dark signal and that from other hypointense sources such as voids, fluids and calcification. As a result, it is difficult to identify SPIO targeted region simply by negative contrast imaging. Several methods have been proposed to solve this problem by producing positive contrast signal at

SPIO regions based on different mechanisms. The common objective is to enhance the signal at SPIO and suppress the signal from others.

Some studies use the comparison of images before and after injection to identify the region containing SPIOs. It takes long treating time because two scans are required before and after drug administration. Positive contrast imaging can also be achieved by exciting off-resonance frequency around SPIOs using selective gradient compensation [5)], specially designed RF pulse [6)] or small-flip-angle steady state free precession (SSFP) [7)]. These methods require the knowledge of magnetic field and MRI physics to optimize the scanning parameters such as compensation gradient strength, RF pulse shape or flip angle. Besides these protocol based methods, several post-processing methods are proposed to generate positive contrast without protocol modification. Susceptibility weighted imaging (SWI) and phase image filtering methods produce positive contrast at SPIOs because phase variation is directly related with magnetic field distortion. Some studies utilize the shift of echo position to enhance the regions with magnetic field gradient caused by the susceptibility change of SPIO [8)]. Compared with directly measuring phase change, the echo shift method avoids phase unwrapping procedure which is still a challenging problem.

d) Positive contrast method in this thesis

In this thesis, four positive contrast methods are proposed based on different MRI mechanisms. The first method utilizes the magnetic distortion effect of SPIO on slice-selective gradient. The slice change due to magnetic distortion varies according to the strength and direction of slice-selective gradient. Therefore, images from two gradients can separate the region containing SPIO. The second method is similar to the first one but based on the distortion effect caused by readout gradient. Phase mapping is also a direct way to enhance the distorted magnetic field generated by SPIO because phase change is in direct ratio to the magnetic field variation. This is the idea of the third method. Local magnetic gradient caused by susceptibility change at SPIO leads to position shift of echo time in Fourier domain. The last method produces positive contrast image by analyzing the position shift of maximum point in the Fourier domain.

2. Methods:

a) Two-slice-selective-gradient method

With a slice-selective gradient and a radiofrequency (RF) pulse, the slice that satisfies a certain magnetic field value can be excited. Local field inhomogeneity leads to slice-selective mismatch. Therefore, slice change appears only in the targeted region with distorted magnetic field. If different G_z gradients are used, the difference between two images will show brightness only in the region that contains paramagnetic particles. As a result, the targeted region can be separated from other parts.

b) Two-readout-gradient method

In ordinary Spin-Warp MRI protocols, the coexistence of frequency-encoding gradient and ΔB causes voxel displacement [9)]. The direction and distance of shift vary with readout gradient. If the images with different readout gradients are compared, the region with distorted magnetic field can be separated.

c) Phase imaging method

MRI signal is first acquired as time-domain data that are the summation of signals all over the sample with frequency and phase encoding. Time-domain signal is also named k-space because each acquisition time point corresponds to a single k value. Spatial image is the inverse Fourier transform of k-space image. Spatial image is composed of by complex data. Normally, only the magnitude image is used in clinic. Actually, phase data include the same amount of information. Phase change for gradient echo imaging is proportional to the magnetic field distortion, therefore could be directly used for SPIO detection.

d) Echo shift method

Materials with different magnetic susceptibilities create a local magnetic field that can be treated as a distortion to the uniform external field B_0. In this method, we only consider the linear part (gradient G_{sus}) of magnetic field inhomogeneity caused by susceptibility difference of magnetic materials. The combination of G_{sus} and imaging gradient G_{im} causes an unbalanced timing of the echo at T_E, which change the position of maximal value in the Fourier domain. The echo position is determined by complete cancellation of the phase from imaging gradient and the phase from gradient of SPIO particles. For the region with homogenous magnetic field, the echo position is located in the center of k-space. For the region with susceptibility gradient caused by SPIO particles, the echo position is displaced from k-space center at a certain distance depending on local susceptibility gradient. It provides a criterion to separate the region containing SPIO particles from homogenous background.

3. Results

Not all the results are displayed in this abstract. We only focus on the result of echo shift method. Nude mice bearing human pancreas tumor are scanned using gradient echo pulse sequence. Echo shift positive contrast method is performed to enhance the tumor region containing SPIO. The figure shows the comparison of images before and after enhancement. In the conventional gradient echo images, tumor region containing SPIOs show dark signal. After enhancement, those SPIO accumulated regions are highlighted so that the enhanced image can show the position of tumor.

Figure: Nude mice tumor image with SPIO targeting. (A) Gradient echo axial image; (B) Positive contrast image of axial image; (C) Gradient echo coronal image; (D) Positive contrast image of coronal image.

4. Discussion

In this thesis, four kinds of positive contrast imaging methods are proposed for the detection of magnetic field distortion caused by iron particles. The first and second methods in the thesis utilize the distortion artifact through and along the slice to single out distorted magnetic field around SPIO particles. There are also limitations for the two methods. Obvious geometric distortion along slice-selective direction requires strong magnetic field distortion because the thickness of slice is much larger than the resolution in the two-dimensional image. The limitation of the method using two readout gradients comes from chemical shift effect and motion. Lipid components in the body contribute similar spatial shift effect as magnetic field distortion. The method using phase image only requires one ordinary scan which is an advantage of this method. Magnetic field distribution can be directly revealed by phase map.

The challenge is the necessary phase unwrapping procedure to discriminate the multiplicity of phase. The echo shift positive contrast imaging method also requires only one scan and it can be used to any gradient echo based protocols. Image regions with specific susceptibility gradient are enhanced by choosing corresponding echo shift value. SPIO regions that contain large gradient can be enhanced and other regions with relatively smaller gradient can be suppressed. The echo shift method is verified by simulation, phantom experiment, rat lymph nodes imaging and tumor imaging for nude mice. This method seems a promising positive contrast method that can be applied into several fields, including stem cells tracking, inflammation detection and magnetic material classification.

5. Conclusion

This dissertation investigates some positive contrast methods for SPIO particle enhanced MRI. Positive methods can be used to facilitate the diagnosis of the body parts that can accumulate SPIOs. Advantages and disadvantages are analyzed and compared among these methods. The echo shift method is proven to be effective in lymph node detection, tumor monitoring and magnetic material analysis.

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