MICROENGINEERED MULTISPECTRAL CONTRAST AGENTS FOR MAGNETIC RESONANCE IMAGING

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ABSTRACT
This paper introduces a novel type of contrast agent for multispectral magnetic resonance imaging (MRI) applications which could enable multiplexing functionalities for MRI, similar to those which labeling technology has brought to optical imaging. The advantages of this agent include signal amplification and differentiability of particles with different geometry or composition based on characteristic MRI signatures, as well as future potential in functionalization given the open geometric configuration. Proof-of-concept experiment was done with millimeter scale particles and arrays of the double-disk structured particles at micron scale, with ferromagnetic iron disks and polyimide spacers, were fabricated pending further testing.

KEYWORDS: Magnetic resonance imaging, Contrast agents, Multispectral, Biocompatible

INTRODUCTION
MRI is a non-invasive imaging technique which does not require ionizing radiation and has wide applications both in research and clinical settings. However, the capability of performing multiplexing functionalities with MRI, such as simultaneous in vivo tracking/imaging of complex biological systems is still largely lacking. Compared to the existing chemically synthesized contrast agents, including gadolinium-based agents [1] and superparamagnetic iron oxides [2], the contrast agent particles introduced in this paper are precisely engineered to yield a local magnetic field alteration, resulting in distinct spectral resonance properties. This fact affords the differentiation of particles with varying geometry using MRI. Compared to previous works [3, 4], biocompatibility issues were heavily considered for future clinical potentials, therefore iron and polyimide was chosen to construct the particles, for use as the magnetic disk and non-magnetic spacer materials respectively.

THEORY
This particular geometry (as shown conceptually in Figure 1-left) generates a homogeneous, distinct local magnetic field (simulation results shown in Figure 1-right) when placed in an external field, yielding resolvable spectral signatures. The precession frequency of any hydrogen proton that diffuses through the disks will be altered based on the exact geometry and magnetic material property, according to equation (thin disk approximation, h ≪ 2S ≈ R)

\[ \Delta \omega \approx -\gamma J_s \left( \frac{hR^2}{2\left( R^2 + S^2 \right)^{3/2}} \right) \]

where \( \Delta \omega \) is the frequency shift, \( \gamma \) is the gyromagnetic ratio, \( J_s \) is the saturation magnetic polarization and \( h, R, \) and \( 2S \) define the geometry: disk thickness, radius, and disk-to-disk center separation, respectively [3]. Therefore, two particles of differing sizes result in clearly distinguishable MRI characteristics with resultant multiplexing capabilities.

The open design of this particle, as well as engineering flexibilities, make it possible to functionalize the particles with environmentally responsive fillings or coatings, such as temperature, pH, or even enzyme responsive hydrogels [5, 6, 7], yielding more accurate diagnosis and characterization of myriad pathologies, including cancer or inflammatory states such as atherosclerosis given their distinct local biological environments.
EXPERIMENTAL

The fabrication process (shown in Figure 2) employed a standard lift-off technique to pattern the bottom iron disks, after electron beam evaporated iron thin film deposition. Polyimide was spin-coated and cured, and followed by a second lift-off process to pattern the top iron disk. Using both anisotropic and isotropic reactive ion etching (RIE), we were able to get arrays of particles with disk diameter ranging from 5µm to 10µm, disk thickness approximately 200nm, separated by a 2µm polyimide column spacer (SEM photos in Figure 3).

![Process flow chart](image)

**Figure 2:** Process flow chart. a. Lift-off pattern first magnetic layer; b. Spin coat polyimide and lift-off pattern second magnetic layer; c. anisotropic RIE etching polyimide; d. isotropic RIE etching polyimide.

![SEM photos](image)

**Figure 3:** SEM photos of the arrays of 9µm diameter fabricated particles after isotropic RIE etching. “Hairy” material were etching residue from polyimide.

RESULTS AND DISCUSSION

![Fourier-transformed free induction decay signal](image)

**Figure 4:** (Left) Fourier-transformed free induction decay signal of a two-particle system showed the unshifted central peak of hydrogen proton signal, and two distinct peaks from those corresponding two particles with different geometry. (Right) Two-dimensional chemical shift imaging. Frequency spectrum related to the particle precession frequency has been assigned a color scale, clearly demonstrating the homogeneity of the internal field within the particle as well as its abrupt transition surrounding the particle.
Proof-of-concept MRI spectroscopy and chemical shift imaging (CSI) experiments were done, so far, at the millimeter scale to demonstrate the MRI capabilities of such double-disk configuration. Iron foils with a thickness of 0.001 inch (=250μm) were cut into disks of varying diameter, and then suspended in agarose gel and placed into an 11.7 Tesla MRI for imaging experiments. Free induction decay (FID) signals were captured (Figure 4-left), sweeping through the theorized shifting frequencies of the particles. Different separations (2S) and diameters (2R) were examined, and results showed clear shifted peaks of hydrogen proton precession frequency with respect to different particle geometries. Two dimensional chemical shift images (CSI) were also acquired (Figure 4-right). Frequency spectrum related to the particle’s precession frequency has been assigned a color scale, clearly demonstrating the homogeneity of the internal field within the particle as well as its abrupt transition surrounding the particle.

CONCLUSION

The contrast agent particles we presented here, to our best knowledge, were the first biocompatible multispectral MRI contrast agents. Not only do these agents have the potential to introduce colors to the current grey-scale image reconstruction process via their distinct spectral features, engineering flexibility also affords the future possibility of functional MRI applications, incorporating environmentally responsive material for in vivo sensing capability.

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REFERENCES


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