Using ellipsoidal microshells to generate multispectral contrast

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Introduction: In recent years, it has been shown that certain shaped micro- and nanoscale magnetic particles can be used to provide multispectral image contrast. Due to their specific geometry, when magnetized by the B_0 field these particulate agents produce spatially-extended, locally uniformly, shifted magnetic fields that discretely shift the Larmor resonance frequency of water protons in the local uniform field. Differently shaped particles yield different local fields and NMR frequency shifts, thereby providing a set of distinguishable, selectively addressable, contrast agents, or effectively, a set of different "color" agents. Thus far, only two different microparticle shapes have been demonstrated to yield the requisite locally uniform magnetic fields: a spaced, double disk structure[1], and a short, hollow cylindrical structure[2]. Here we introduce a third possibility: an ellipsoidal microshell. Although ellipsoidal shells may initially appear more geometrically complex than disks or cylinders, in magnetic terms they are theoretically simpler structures. Indeed, ellipsoidal shells represent, at least in principle, an optimal geometry for such agents with the potential to yield higher spectral resolution than previously demonstrated structures. In this work the theory behind these new agents is described, consideration of how such ellipsoidal structures can be microfabricated is presented, and preliminary NMR measurements from the first sets of such elliptical agents is demonstrated.

Methods: Because ellipsoidal geometries are ill-suited to traditional microfabrication methods and technologies, a new rotating evaporation process that transforms microspheres into microellipsoids and into the requisite microellipsoidal shell structures has been developed. As a demonstration, 1-μm inner radii ellipsoidal shells of varying aspect ratios and thicknesses were produced from nickel (magnetic polarization saturation density of 0.6 T). Figure 1 shows a scanning electron micrograph of an array of microfabricated ellipsoidal shells together with a schematic cross-section through such an ellipsoidal shell structure. Using home-built RF coils and sample holders, arrays of such structures were submerged under water and scanned in either 11.7 T or 14 T MRI. To detect water inside the ellipse a magnetization transfer experiment is performed taking advantage of exchange with the surrounding water to indirectly detect the resonance frequency of the water inside the ellipse. Figure 2 shows a typical z-spectrum showing, as a function of frequency, the decrease in water magnetization due to off-resonance saturation at each frequency. Data were acquired using preparatory off-resonance irradiation comprising 6 s duration pulse trains of 100 μs, π/2 pulses separated by 250 μs, following by an on-resonance π/2 pulse and fid collection. With two averages and a TR of 12 s, typical z-spectra such as in fig. 2 are acquired in under 10 minutes. The absorption-like dip in the spectrum corresponds to the resonance frequency of the water inside the ellipsoids, confirming that such structures produce a locally uniform, shifted field. The magnitude of this frequency shift can be engineered over a broad spectral range by changing ellipsoidal shell materials, thicknesses, and aspect ratios.

Conclusion: A new ellipsoidal geometry for multispectral MRI contrast agents based on microfabricated magnetic structures has been demonstrated. The linewidths of the frequency shifted water generated by these new structures are currently limited by imperfect agent microfabrication, but improved fabrication should see such linewidths narrow. This would improve detection sensitivity as well as lead to better multiplexing of agents Ultimately, the ellipsoidal geometries can theoretically exceed the spectral resolution of previously demonstrated multispectral agents.

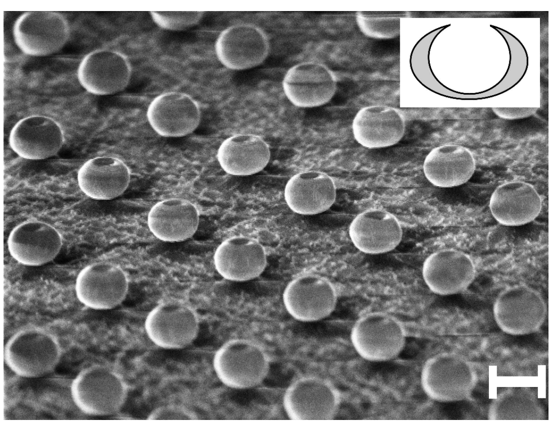

Figure 1. Scanning electron micrograph [SEM] of array of magnetic hollow ellipsoidal shells microfabricated for use as multispectral MRI contrast agents. Scale bar is 2 μm. Inset shows schematic cross-section of ellipsoidal shell.

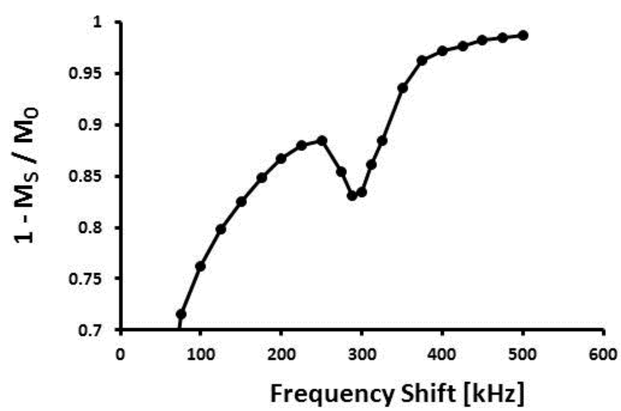

Figure 2. Z-spectrum acquired from water-submerged array of ellipsoidal microshells showing magnetization saturated out, M_S, from bulk water magnetization M_0. Dip around 300 kHz corresponds to ellipsoidal shell shifted water resonance.

References:
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(2) Zabow G., Dodd S.J., Moreland J. & Koretsky A.P. *Nanotechnology* 20, 385301 (2009)

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