Microfabricated magnetic microparticles enable high contrast MRI agents

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Introduction

Chemically synthesized magnetic nanoparticles[1], dendrimers[2], and micrometer-sized particles of iron oxide (MPIOs)[3,4] are becoming increasingly popular as T_2^* MRI contrast agents. Among them, the larger microparticles are proving useful for labeling single cells for *in vivo* imaging[5-7]. In particular, the large magnetic moments of MPIOs means that even individual particles can be detected[8] pointing to the possibility of MRI tracking of cells labeled with single particles. Towards such goals, techniques that can increase the fractional metal content of the particles, or that can use materials of higher magnetization than iron oxide, are desirable for increasing each particle's signal without also increasing its size. Recently it has been demonstrated that top-down microfabrication of MRI contrast agents may enable novel agent properties[9]. Here we show that such top-down microfabrication techniques can also be used to micromachine magnetic microparticles of controlled composition with higher (and more consistent) magnetic moments than their more commonly available chemically synthesized counterparts.

Methods and Results

Gold-coated nickel and gold-coated iron micro-discs were fabricated via a combination of metal evaporations and ion-milling resputterings, using regular lift-off patterning techniques. Figure 1 shows a sample scanning electron micrograph (SEM) of microfabricated 2-micrometer diameter gold-coated nickel discs (about 300 nm thick nickel). Specifically, the SEM shows micro-disc particles that have been released from their fabrication substrate via a selective wet-etch of an underlying sacrificial copper layer, and that have subsequently been washed, pipetted out onto a separate surface, and left to dry. For performing the MR imaging, the particles were resuspended in agarose and scanned in an 11.7 T magnet at 50 and 100 micrometer resolution (isotropic) using 3d gradient echo imaging with T_R = 35 ms and T_E = 12 ms. As seen in Figure 2, the extent of magnetic dephasing around both the gold-coated nickel and gold-coated iron discs yields greater image contrast than do commercial 1.63 micrometer mean diameter Bangs microparticles, chosen as a comparison because they represent commonly used particles[4] of a similar volume. The observed contrast gains are explained simply on the basis of particle magnetic moments: these are larger for the micro-discs, made with solid nickel or solid iron interiors, than they are for iron-oxide particles because of the relative saturation levels of iron, nickel and iron-oxide, and because generally only some fraction of each iron-oxide particle is actually comprised of iron-oxide. In summary, while we have not yet imaged these micro-discs *in vivo*, we believe that their larger saturation magnetic moments and associated larger T_2^*-contrast make them promising candidates for possible future single-particle MRI cell-tracking.

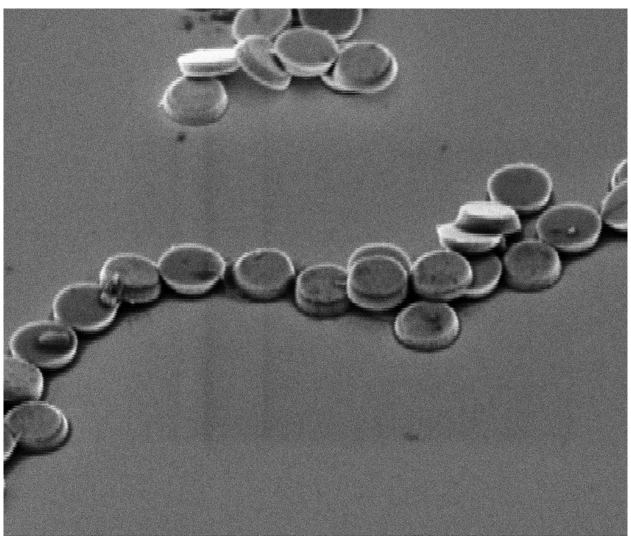

Figure 1. Tilted perspective view scanning electron micrograph (SEM) of photolithographically patterned, surface micromachined 2-micrometer diameter gold-coated nickel micro-discs used as T_2^*-contrast agent

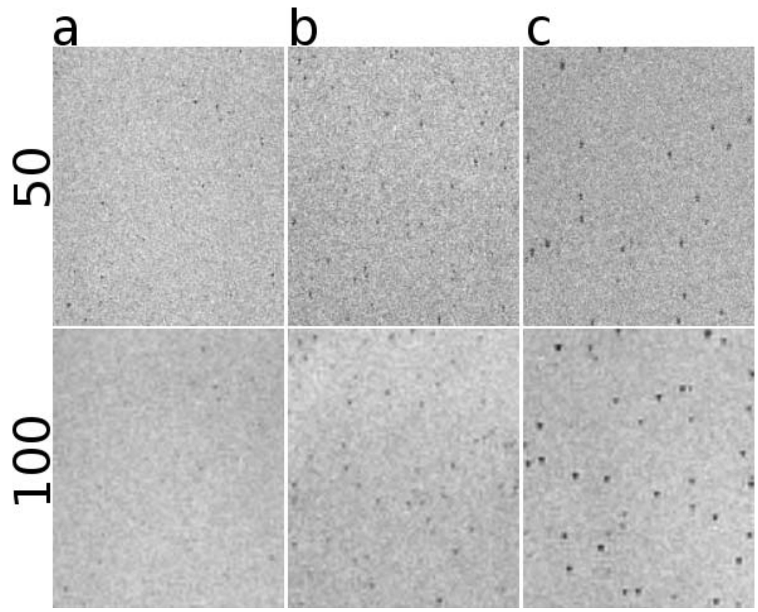

Figure 2. Comparison of contrast produced by (a) individual commercial Bangs 1.63-micrometer iron-oxide beads, (b) individual gold-coated 2-micrometer nickel discs and, (c) individual gold-coated 2-micrometer iron discs, all suspended at similar particle concentration in agarose. All images are taken on 11.7 Tesla scanner. Top and bottom row images are at 50 and 100 micrometer isotropic resolution, respectively.

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