

# Designing Micro-fabricated fiducials for cellular tracking with MRI

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**Abstract**—A Magnetic Resonance Imaging (MRI) scanner typically has a minimum resolution of  $0.2 \times 0.2 \text{ mm}^2$  with a high-field 7T scanner and  $0.5 \times 0.5 \text{ mm}^2$  with a clinical 3T scanner[1].

Cells are generally much smaller than this resolution:<sup>1</sup> red blood cells are  $6\text{--}8 \mu\text{m}$ , human muscle cells are  $1\text{--}40 \text{ mm}$  in length and  $10\text{--}50 \mu\text{m}$  in width [2] squamous Epithelial Cells are  $30\text{--}60 \mu\text{m}$ , irregular thin flat flagstone shape with distinct edges [3], an *E. coli* bacterium is rod-shaped and approximately  $0.7\text{--}1.4 \mu\text{m}$  in diameter by  $2\text{--}4 \mu\text{m}$  in length [4].

Small particles of magnetic material are used as contrast agents in MRI. These particles can be smaller than the resolution of the scanner because the particles produce dark spots in the image that are larger than the particles. Individual particles as small as  $1.68 \mu\text{m}$  can be detected using 7T MRI scanners, and as small as  $15 \mu\text{m}$  using clinical 3T scanners. Particles produced by micro-fabrication processes can be more uniform and be easier to detect than those produced by chemical synthesis.

## I. OVERVIEW

MRI scanners offer a safe technique for imaging tissue deep within a living body. However, it is often difficult to differentiate a tissue of interest from its surroundings using only magnetic resonance. Additionally, the tissue of interest may be too small to detect. To solve these problems, MRI markers (also called tags or fiducials) are used, along with contrast agents. This literature review compares MRI marking methods.

MRI markers include nano-scale MRI-contrast agents [5], micro-scale particles, micro-fabricated MRI labels, and centimeter-scale fiducials.

MRI contrast agents and micro-particles usually require large concentrations of the material because

individual particles are difficult to resolve with MRI.

Many groups are designing MRI labels for single-cell tracking. These usually require either *ultra-high field MRI*, defined as scanners with field strengths  $\geq 7\text{T}$ , specialized coil systems, or large particles.

Zabow et al. designed  $\approx 2\mu$  micro-fabricated markers for MRI with a key property that by varying lengths of the design, a scanning sequence could be designed to detect only one variety of the markers at a time. They designed a stacked disc structure and a cylindrical shell[6]. Each designed owed its high signal to noise ratio on the fact that water would flow through the shape.

Later the same team designed special micro-fabricated cuboids composed of iron or nickel covered in gold. These are more effective than chemically produced spheres because they contain a.) purer magnetic material and b.) more magnetic material than similarly sized spheres [7].

## II. ENGINEERED PARTICLES THAT CAN BE INDIVIDUALLY DETECTED

### A. Micro-engineered particles for multi-spectral MRI

Zabow et al. [6] designed labels that frequency shift water by discrete amounts. The phase shift can be designed to make multiple distinguishable markers. The markers must be aligned with the MRI  $B_0$  field, but were designed anisotropically so they passively align. They presented a design using two nickel disks of radius  $R$  separated by distance  $S$ .

Their Figure 3 showed  $1.24\text{mm}$  discs designed for three different frequencies. Each was distinguishable, Resolution was  $500 \times 750 \mu\text{meter}$ . Fig-

<sup>1</sup>For a catalog of useful biological numbers, see [bioNumbers.org](http://bioNumbers.org)

ure 5 resolution was 100 x 100  $\mu\text{m}$  with much smaller particles 5  $\mu\text{m}$  disks separated by 2  $\mu\text{m}$ . Each voxel contained 10 to 20 particles.

They claim that their design with an open interior have a  $10^4$  greater signal-to-noise ratio than enclosed designs.

Competing methods: labeling cells with superparamagnetic iron oxide (SPIO) nanoparticles or dendrimers[8], or micrometer-sized particles of iron oxide (MPIOs). These methods magnetically dephase the signal from water surrounding these particles.

Specially engineered micro coils can be used for high resolution MRI imaging, but this requires the coils to be placed close to the target [9]. This paper referred to tests with 5 nano-liter samples for NMR spectroscopy. The coils used surrounded the capillary containing the liquid under interrogation. The coils were 1mm long, with an OD of 0.5mm. Since these are not for imaging, they could instead be used to indicate whether a compound was present or not.

#### B. Magnetodendrimers

*Magnetodendrimers* are magnetic tags used to efficiently label mammalian cells. These tags are diffused into the cell culture, and brought into the cells through a membrane adsorption process with subsequent localization in endosomes. They are visible in MR with doses as low as 1  $\mu\text{g}$  iron/ml culture medium. Labelled cells were detected with 9-14 pg/cell for up to 6 weeks after transplant [8].

#### C. Stainless steel microparticles in capillaries

This work by Olamaeni et al. [1] is inspired by therapeutic magnetic micro carriers –  $\approx 50\mu\text{m}$  diameter drug capsules that can be steered and tracked by an MRI scanner.

Magnetic bodies create susceptibility artifacts in the MRI image. The paper[1] includes equations describing how the particle distorts the MRI image. Testing used 0.4mm diameter chrome steel spheres with Gradient-Echo imaging. Pairs of particles are distinguishable when their distance is  $\approx 40$  diameters apart. The imaging used 0.5 mm pixels on a 1.5 T Magnetom Siemens scanner. The

authors demonstrate a 15  $\mu\text{m}$  sphere is detectable in a clinical scanner [10]. Such a particle can navigate in large capillaries, which are 20  $\mu\text{m}$  in diameter, but cannot reach small capillaries, which are 4-5  $\mu\text{m}$  in diameter.

Later they demonstrated tracking 50  $\mu\text{m}$  diameter droplets of ferrofluid using a 1.5T scanner [11]. The droplets moved along a 50  $\mu\text{m}$  capillary and were tracked with Gradient-Echo imaging with 0.6mm voxels. The droplets contained 10% MNP ( $\text{Fe}_3\text{O}_4$ ).

### III. CONTRAST AGENTS AND MRI FIDUCIALS

#### A. nano-particle MRI contrast agents

These typically use iron-oxide nanoparticles as MRI contrast agents. Often the particles are collected by cells in the body, e.g. macrophages, and show as dark pixels in an MRI image [?].

#### B. Commercial MRI fiducial Markers

There are many products available today for MRI fiducials, used for image registration to link current scanned data with previous scans and targets. MRI fiducials used in routine care range from large 20 mm markers designed to be stuck on the skin, or  $\approx 20\text{mm}$  gold markers inserted via needle into the skin. These have a variety of forms, but are centimeter-scale large objects.

MRI fiducials inserted by a 17-Gauge needle, made of 99.95% gold construction with a snake-like design. , 1.15mm x 1 cm, to 0.85mm x 3cm<sup>2</sup>

Skin markers: <sup>3</sup>, 1.75 cm Radiance<sup>TM</sup> filled flexible packets, 1.5cm Radiance<sup>TM</sup> filled tubes, to 3cm Radiance<sup>TM</sup>-filled tubes.

Multi-modality Center-hole markers: <sup>4</sup>, a flat disc with 2mm center hole, 15 mm outer diameter, 3.5mm thick, bright in MRI image.

<sup>2</sup><http://www.mriequip.com/store/pc/viewPrd.asp?idproduct=929>

<sup>3</sup><http://www.beekley.com/MRI/MRSPOTS.asp>

<sup>4</sup><http://www.universalmedicalinc.com/Center-Hole-Mammography-Skin-Marker-p/mm3002.htm>

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