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Publications and Reviews

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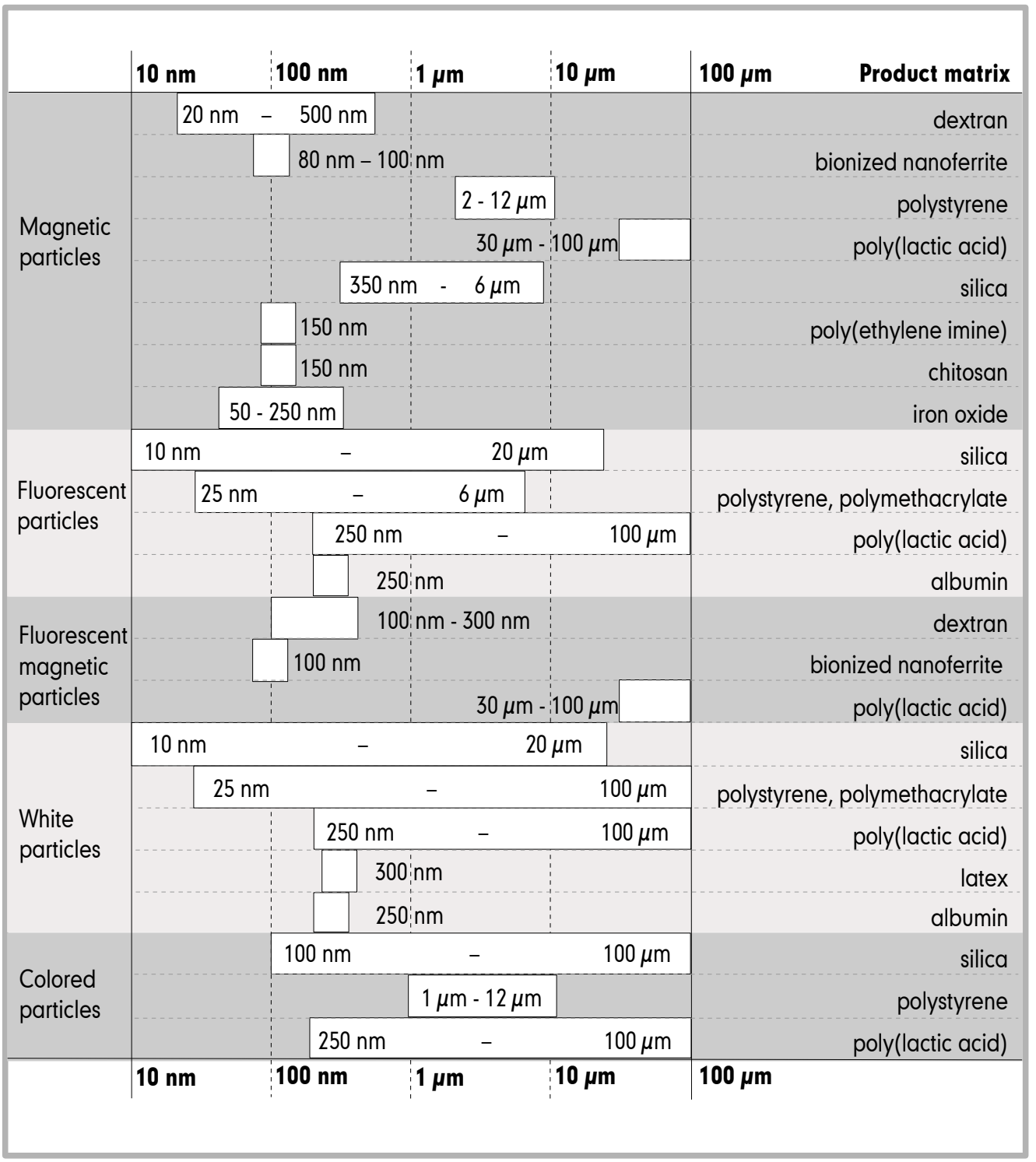

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7 Magnetic nanoparticles as tracers for Magnetic Particle Imaging (MPI)

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7.1 Introduction

Magnetic particle imaging (MPI) is a new imaging technique, providing three-dimensional imaging of magnetic nanoparticle (MNP) tracers with high spatial and temporal resolution [1]. In MPI, only the MNPs generate the signal, in contrast to hydrogen being the signal origins of Magnetic Resonance Imaging (MRI). The MPI signal is generated by the nonlinear magnetic response of the tracers to a sinusoidal magnetic field, which produces higher order harmonics in the signal that can be analysed by Fourier transformation as illustrated in Fig. 1. Further on, the higher harmonics can be filtered out. When the particles are additionally exposed to a superpositioning magnetic field of certain amplitude the generation of higher harmonics can be suppressed. A spatial encoding is possible [1] by generating a single point in the sample, a so called field free point (FFP), where the superpositioning field is zero. This can be obtained using a Maxwell coil pair which consists of two opposing coils driven by current flowing in opposite directions. A scanning movement of the FFP over the sampling volume can be used for a spatial image reconstruction of MNP positions.

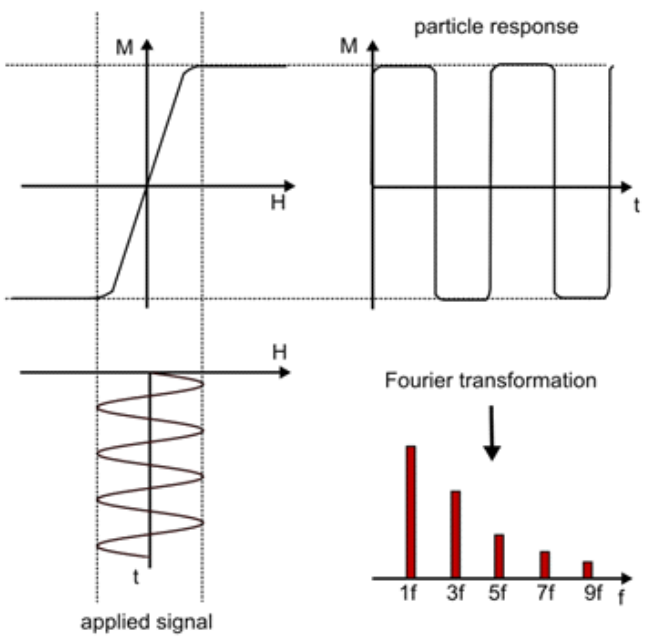

Fig. 1: Schematics of the MPI working principle.

The sensitivity of MPI depends critically on the magnetic moment of the tracers. Acceptable performance is expected for magnetite MNP with a core size of 30 nm and larger [2]. To date, Resovist® as approved contrast agent for MRI has been used in most MPI studies because of its comparatively large signal strength. This high MPI performance was not well understood since the size of the magnetite/maghemite cores is only about 5 nm [3]. However, there are clusters of primary 5 nm cores present in Resovist®, which have been identified as the most relevant MPS-active tracers [4]. Micromod's perimag® nanoparticles (former name: nanomag®-MIP or M4E) also have clusters and show promising tracer signals in MPI. The amplitude A3 of the 3rd harmonic in the MPS spectrum of perimag® is twice as high as that of Resovist® (Figure 2). Here

we provide a summary on the application of perimag® and nanomag®-D-spio particles as model contrast agents to demonstrate various new strategies for the enhancement of the MPI technique. Furthermore initial approaches to improve the evidence of imaging results in comparison to established imaging techniques (e.g. MRI or SPECT) will be addressed.

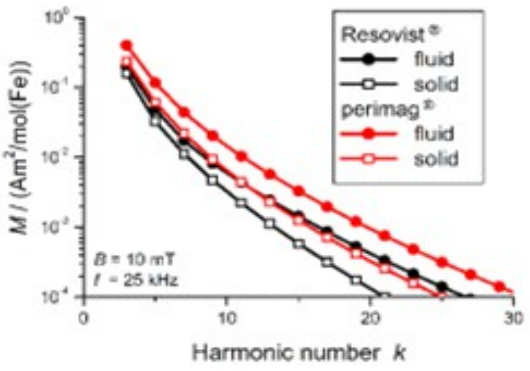

Figure 2. MPS-data obtained for suspended and immobilised (by freeze drying) MNPs of Resovist® and perimag [2].

7.2 Enhancement of the MPI technique to improve the imaging quality

Alternatively to image reconstruction by Fourier transformation the x-space approach raised increasing attention [5]. The x-space analysis commonly utilizes the FFP magnetic field gradient to localize magnetic nanoparticles. With the benefits of two orders of magnitude reduced acquisition time or one order of magnitude signal-to-noise ratio (SNR) improvement, a gradient called a Field Free Line (FFL) has been theoretically developed, and experimentally demonstrated. The FFL localizes particles to a line instead of a point. Konkle et al. have used a FFL with sample rotation and projection reconstruction to demonstrate experimental images with a 20 fold improvement in acquisition time compared to the first projection reconstruction (PR) MPI results. To gain this 20 fold speed up, a z-direction focus field coil configuration was implemented instead of the previously utilized translation stage [6]. Nanomag®-D-spio particles were used as tracers to prove this approach. The x-space approach overcomes time restrictions from overlap of FFP movement and harmonic analysis of a volume element by assuming an instant MNP response to traversing FFP, leading to the detection of a Point Spread Function (PSF). Mathematical analyses of the PSF by direct currency (DC) recovery methods are often more robust against variations in MNP characteristic spectroscopic signal response. Quantitative MPI across rat sized fields of view was demonstrated with x-space reconstruction methods. Critical to any medical imaging technology is the reliability and accuracy of image reconstruction. Furthermore, Konkle et al. have formulated x-space reconstruction as a 3d convex optimization problem and applied robust *a priori* knowledge of image smoothness and non-negativity to reduce non-physical banding and haze artifacts. Figure 3 demonstrates the improved imaging quality with the newly developed method [7]. Croft et al. have explored how nanoparticle relaxation affects image resolution. The influence of the time constant of nanoparticle rotation on the final image resolution was studied to reveal nonobvious conclusions for tailoring MPI imaging

parameters for optimal spatial resolution and explain how a drive field sequence optimization can improve the MPI spatial resolution of multicore particles like perimag® (formerly known as nanomag®-MIP) [8].

Recently, there is a growing interest in the functional imaging capabilities of MPI. "Color MPI" techniques show the possibility of separating different nanoparticles, which could potentially be used to distinguish nanoparticles in different states or environments. Viscosity mapping is a promising functional imaging application for MPI, as increased viscosity levels *in vivo* have been associated with numerous diseases such as hypertension, atherosclerosis, and cancer. Utkur et al. proposed a viscosity mapping technique for MPI through the estimation of the relaxation time constant of the nanoparticles. Importantly, the proposed time constant estimation scheme does not require any prior information regarding the nanoparticles. The method was validated with extensive experiments in an in-house magnetic particle spectroscopy (MPS) setup at four different frequencies (between 250 Hz and 10.8 kHz) and at three different field strengths (between 5 mT and 15 mT) for viscosities ranging between 0.89 mPa·s to 15.33 mPa·s. For these experiments perimag® suspensions were diluted with different mixtures of water and glycerol. The results demonstrate that the viscosity mapping ability of MPI is in the biologically relevant viscosity regime [9].

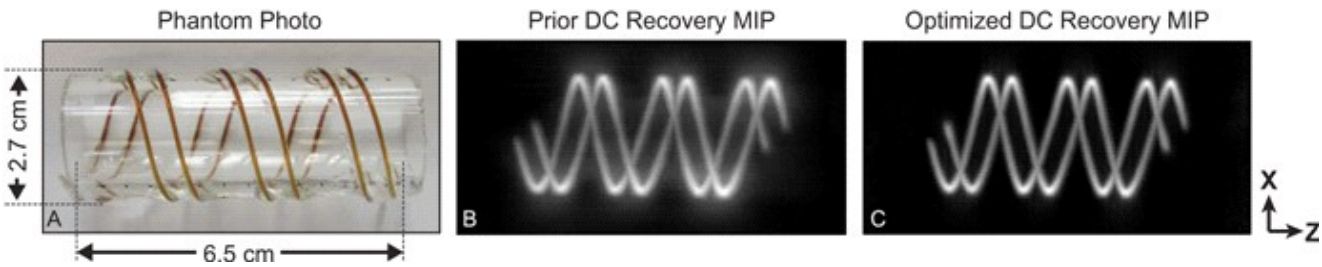

Figure 3. Experimental data from a double helix phantom filled with perimag® particles. The 3D dataset was reconstructed using the previous DC recovery method (middle) and the newly developed method (right) [7]

7.3 Biomedical imaging applications

MPI has a high potential for angiographic and cell tracking applications. MPI exhibits near perfect contrast with no background signal, as well as quantitative imaging capabilities [10]. Especially stem cell therapies have enormous potential for treating many debilitating diseases, including heart failure, stroke and traumatic brain injury. For maximal efficacy, these therapies require targeted cell delivery to specific tissues followed by successful cell engraftment. But commonly intravenous deliveries of mesenchymal stem cells (MSCs) become entrapped in lung microvasculature instead of the target tissues. Zheng et al. demonstrated that MPI can directly image MNP-tagged cells *in vivo*. Therefore MPI, fluorescence, and MRI tracer imaging techniques were compared by injection of perimag® particles together with Angiosense 680 EX fluorescent tracer into post-mortem mouse to demonstrate the advantages of the MPI technique [11]. The dynamic trafficking of intravenous MSC administrations using MPI indicates that injections of MNP-labelled MSCs are immediately entrapped in lung tissue and then cleared to the liver within

one day, whereas standard iron oxide particle (e.g. Resovist®) injections are immediately taken up by liver and spleen [12]. Drews et al. have selectively targeted and delivered a contrast agent to atherosclerotic plaques through the use of peptides that bind to unique markers of plaque development with the goal to use Magnetic Particle Imaging (MPI) to diagnose atherosclerotic plaques. Therefore aminated perimag® particles were conjugated to RGD peptide for injection into carotid ligation mice, and to CREKA peptide for injection in ApoE knockout mice. ApoE knockout mice develop atherosclerotic plaques in the aorta, which provides a greater surface area for contrast agent to bind. The selective binding of CREKA conjugated perimag® particles resulted in a low signal in the brachiocephalic artery present in MRI and MPI images. This effect was not visible for RGD conjugated perimag® in the carotid ligation mice model [13].

Aminated perimag® particles with a medium positive zeta potential (M4E) show direct uptake in human mesenchymal stem cells (hMSCs) without use of transfection agents. Kilian et al. analyzed the suitability of positively charged perimag® for safe human stem cell (hMSC) labelling and determined cell labelling maintenance in 2D and 3D culture for cell tracking by MRI and MPI (Fig. 4). The experiments demonstrated that the particles have whether toxic effects nor alter the function of the stem cells [14].

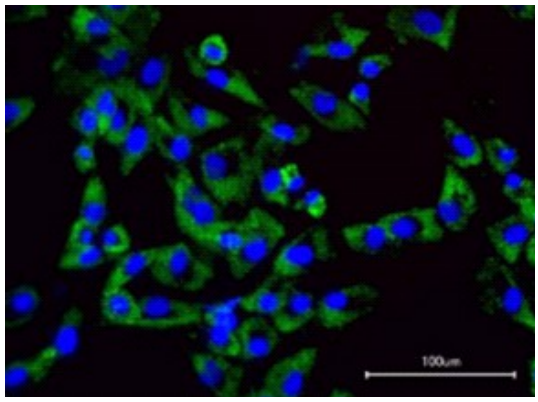

Figure 4. Labeling of hMSC with fluorescent perimag® (nucleus: blue; perimag®: in cytoplasm: green) [14].

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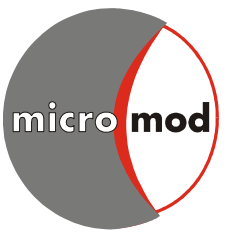

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