Fundamentals and Applications of Magnetic Particle Imaging

J. Borgert1§, J.D. Schmidt1, I. Schmale1, J. Rahmer1, C. Bontus1, B. Gleich1, B. David1, R. Eckart1, O. Woywode2, J. Weizenecker3, J. Schnorr4, M. Taupitz4, J. Haegel5, F.M. Vogt5, J. Barkhausen5

1Tomographic Imaging Group, Philips Technologie GmbH Innovative Technologies, Research Laboratories, Röntgenstraße 24-26, 22335 Hamburg, Germany
2Philips Medical Systems DMC GmbH, Röntgenstraße 24-26, 22335 Hamburg, Germany
3Department of Electrical Engineering, University for Applied Sciences, Moltkestraße 30, 76133 Karlsruhe, Germany
4 Department of Radiology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
5 University Hospital Schleswig-Holstein, Campus Lübeck, Clinic for Radiology and Nuclear Medicine, Ratzeburger Allee 160, 23538 Lübeck, Germany

§Corresponding author; joern.borgert@philips.com

Introduction

Magnetic particle imaging (MPI) is a new medical imaging technique that performs a direct measurement of the magnetization of ferromagnetic nanoparticles to quantify their local concentration. These particles are usually called SPIOs, i.e. superparamagnetic iron oxides. Specific formulations of these nanoparticles have been clinically approved as contrast agents for magnetic resonance imaging (MRI). As MPI does not image anatomical background, it is similar to methods from nuclear medicine, e.g. PET or SPECT, and consequently, the contrast agent is called a tracer in the context of MPI.

The method has been invented in 2001 by Bernhard Gleich and Jürgen Weizenecker, who first reported about it in nature in 2005 [1]. MPI offers a unique combination of capabilities that sets it apart from other established modalities for medical imaging. An MPI measurement is inherently quantitative: the signal strength is proportional to the amount of nanoparticles and thus a direct measure of the tracer concentration at a certain location. MPI is capable of delivering both high spatial and temporal resolution [1]. In comparison to MRI, a technique that also utilizes electromagnetic field for imaging, MPI has the potential to realize higher voxel rates. This can be used to realize true real-time imaging. As MPI performs a direct imaging of the tracers’ nanoparticles, its sensitivity in detecting iron oxide can exceed that of MRI, which only does indirect particle imaging. MPI uses magnetic fields to perform its measurement. As a consequence no ionizing radiation is applied.

The Function Principle of Magnetic Particle Imaging
In order to determine the spatial distribution of the magnetic tracer material with high sensitivity and resolution, MPI measures the magnetization change in the tracer material in a time varying external magnetic field. A suitable theory for describing the magnetization behavior of small mono-domain particles is the Langevin-theory [2], which assumes that the particles are in thermal equilibrium, i.e. the magnetization is always in line with the external field and consequently, no hysteresis effects appear. The relation between the external magnetic field and the magnetization is non-linear, as shown by the green curve in the upper left part of figure 1. This results in the presence of harmonics in the received signal. If the relation were linear, only the fundamental frequency of the MPI excitation field, usually in the range of several tenths of kilohertz, could be detected. The detection of harmonics, i.e. the MPI signal, reveals the presence of magnetic material.

To locate the origin of the detected signal, an additional static gradient field is introduced for spatial encoding. Usually, as depicted in figure 2, two magnets are arranged in a Maxwell configuration, i.e. they oppose each other with identical poles. Within a Maxwell configuration, the gradient field exhibits a symmetric point with zero magnetic field, named the field free point (FFP). At the FFP, the particles’ magnetization is free to follow the excitation field. Outside the FFP, however, the particles become saturated and are unable to follow the excitation field. As a consequence, they do not produce any MPI signal anymore.

In a simple but perfectly working realization of an MPI system [1], this is enough to acquire an image that represents the quantitative distribution of the tracer material throughout an object. To this end, the object under examination is moved in relation to the instrument. At equidistant points, which form a raster in either two or three
dimensions, the signal level of a suitable harmonic is translated into relative gray level values. Together with a calibration measurement, which relates a known quantity of the magnetic tracer material to a signal level, this results in a quantitative image of the iron oxide distribution in two or three dimensions. This would constitute a single voxel imaging method.

The main disadvantage of this approach is its speed. The mechanical movement of the object is slow. However, the whole process can be accelerated by introducing additional time-varying, homogeneous electromagnetic fields, named drive fields, to move the FFP in space. This approach is fast enough to realize real-time imaging as demonstrated in two dimensions in phantoms [3] and in three dimensions in vivo [4].

![Diagram of field generation](https://via.placeholder.com/150)

**Figure 2:** A selection field generated by two magnets in Maxwell configuration, i.e. with opposing poles. In the center of the configuration the field distribution has a point of zero field strength, names the field free point (FFP). In this area, the magnetization of a magnetic nanoparticle can be changed easily by the application of an external field, whereas at some distance to the FFP, the field strength of the selection field has increased and the particles are in saturation. As a consequence, the external field leads to negligible change in magnetization in these areas, c.f. figure 1.

For such a faster realization of an MPI system, the simple relation between the location of a measurement and the gray value in the final image, as with the single voxel approach, is no longer given. The time signal that is being acquired during one repetition of the drive field sequence encodes all the information about the distribution of the magnetic tracer material and can be reconstructed into an image using additional information that is being represented by the system function (SF). The information in the SF, which is usually mapped into a matrix form, is acquired by measuring the systems’ response to very small, δ-like samples of the magnetic...
material, and contains both the dynamics of the tracer and the systems’ properties, e.g. coil sensitivities and transfer functions. For other modalities, e.g. MRI, the information encoded in the SF can be represented by analytical functions, e.g. the Fourier series. To date, analytical representations of the MPI SF have only approximate character [5]. Therefore, attempts to avoid the measurement of the complete SF have to rely on a calculated model. First approaches presented in [6] look promising. After an inversion of the SF matrix, which can be computationally very demanding, the actual reconstruction step is rather simple, as it is given by a mere vector-matrix-multiplication [1].

**An Estimation on Resolution and Detection Limit**

In the simple, single voxel view on MPI, particles can contribute to the acquired signal as long as they are at or near the FFP. At a certain distance to the FFP, the particles are saturated and thus silenced. Consequently, the faster the field strength rises when leaving the FFP, i.e. the higher the gradient $G$ of the selection field, the faster the particles get into saturation and the higher is the resolution. Furthermore, a steeper magnetization curve (cf. figure 1) also improves the resolution. As a good estimate, the width of the area that enables reaction to the external field can be given by the full width at half maximum (FWHM) of the derivative of the magnetization curve. Taking both the gradient strength and the width of the derivative of the magnetization curve into account, the resolution can be estimated by

$$R = 2 \frac{H}{\sqrt{G}}.$$  \hspace{1cm} (1)

The magnetization curve as given by the Langevin theory [2]

$$M = M_0 L \left( \frac{H \cdot V \cdot M_s \cdot \mu_0}{k_B \cdot T} \right) \text{ with } L(\alpha) = \coth(\alpha) - \frac{V}{\alpha}$$  \hspace{1cm} (2)

with $M_0$ being the saturation magnetization of the sample, $H$ being the external field, $V$ being the volume of the particle, $M_s$ being the saturation magnetization of the particles’ material, $\mu_0$ being the magnetic permeability of the vacuum, $k_B$ the Boltzmann constant, and $T$ being the absolute temperature, explains that the resolution of MPI is depending on the volume $V$ of the tracers’ magnetic core. Larger core sizes result in a steeper magnetization curve and, thus, a better the resolution.
Figure 3 visualizes the dependency of the spatial resolution on the gradient field strength and the particle diameter. It shows that particles with a diameter of 30 nm, as proposed in the original literature [1], are sufficient to realize a true, reconstructed resolution, some also called native resolution [7], of 1 mm for a gradient strength of 2.5 T/m/μ₀, which could be achieved in a clinical scanner with reasonable effort. This, of course, corresponds to a minimal linear extension of a voxel of 0.5 mm. In practical imaging setups, the resolution can deviate from these values in both directions, either towards higher or lower spatial resolution, depending on the signal to noise ration.

To determine the signal to noise ratio, the signal and noise voltages from test measurements on sample coils have to be calculated as described in [8]. These signal voltages can be translated into iron amount and concentrations, which show that the theoretical detection limit of MPI for a measurement time of 1 second and a voxel size of 1 mm³ is approximately 300 nmol(Fe)/l. In comparison, the steady state concentration of a clinically approved contrast agent like Resovist®, which is based on superparamagnetic iron oxide and applied to prescription, is approximately 400 times higher. More details on the determination of the detection limit can be found in [9].

**Applications**

Due to the unique characteristics MPI has the potential to play an important role in clinical diagnostic imaging in the next decade. The high temporal and spatial
resolution of MPI perfectly fulfills the requirements of cardio-, neuro- and peripheral vascular applications. Currently available magnetic tracer materials like Resovist® can be administered intravenously and the tracer material is distributed in the vascular system for a limited amount of time, until it accumulates in the reticuloendothelial system (RES). Therefore these agents combined with the ultrafast imaging capabilities of MPI are well suited for first pass measurements, including dynamic angiography of the heart and the great vessels as well as cerebral and myocardial perfusion studies.

Compared to the currently available techniques for the measurement of tissue perfusion, including nuclear techniques, MRI, CT and ultrasound, MPI offers several important advantages. Compared to SPECT, PET and CT the lack if ionizing radiation has to be mentioned, and allows for repetitive and follow-up measurements. Due to the proportional relationship between the tracer concentration and the MPI signal, the technique allows for non-invasive quantitative measurements of tissue perfusion given as ml of blood per gram of tissue. The extremely fast data acquisition capabilities provide coverage of the entire heart or the entire brain with a temporal resolution of more than forty 3D data sets per second. Furthermore, these quantitative functional flow measurements can easily be combined with morphologic information, given by non-invasive angiography with sub millimeter spatial resolution (minimum voxel size < 0.2 mm³). For example, a cardiac MPI measurement lasting less than a minute may provide high resolution non-invasive coronary angiography combined with quantitative perfusion measurements for the assessment of myocardial ischemia. First in vivo studies that underpin the potential of MPI in cardio-vascular application have recently been presented [4].

However, MPI may not only be used as a diagnostic test. The fast 3D imaging capabilities combined with specially coated instruments can be used for image guided interventions. In this setting an intravenous injection of tracer material can be used to visualize the vessels in three dimensions. Together with the visualization and tracking of the instruments, this would allow an MPI-based interventional navigation in a three-dimensional image-guided scenario without ionizing radiation. This application will be beneficial for coronary artery as well as electrophysiological interventions.

Additionally, the high sensitivity and specificity perfectly qualifies MPI for molecular imaging. First studies [10, 11] explored the use of MPI to detect stem cells. These cells can be loaded with up to 10 pg of iron, which should be within the theoretical and technical possible detection limit of MPI. Similarly, red blood cells (RBC) can be loaded with iron oxide based tracer materials, which would result in a blood pool contrast agent with extremely long blood retention times of up to 120 days [12, 13], which would support long procedures like those performed today in the electrophysiology lab or the assessment of therapy response in oncology by revisiting a tumor to monitor its remission.
Conclusions

MPI is a promising new modality that has a lot of potential for diagnostics as well as therapy. It can be utilized to perform a quantitative detection of magnetic tracer materials based on superparamagnetic iron oxide with high temporal resolution. The spatial resolution is comparable with other medical imaging techniques and can be expanded beyond what has been demonstrated to date by improvements in field generation and tracer materials.

This paper presented an introduction to the basic function principle of MPI, together with an estimation of the spatial resolution and the detection limit. Furthermore, several medical applications have been discussed with respect to the potential use of MPI. In diagnostics, immediate and considerable impact can be assumed in the area of cardio-vascular applications, spanning from diagnostics of the large vessels, coronary assessment, and myocardial perfusion to interventional procedures, which would greatly benefit from MPI being radiation free and the use of trackable devices. Other applications in oncology, cell labeling and tracking are investigated and it will be exciting to see which one makes best use of MPI’s unique capabilities.

Acknowledgements

This work was financially supported by the German Federal Ministry of Education and Research (BMBF) under the grant number FKZ 13N9079 and 13N11087 to 13N11093.

References


