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Magnetic Particle Imaging

An Introduction to Imaging Principles and Scanner Instrumentation

With the Collaboration of
Jörn Borgert and Bernhard Gleich

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Preface

This volume gives an introduction into the novel imaging technique *magnetic particle imaging* (MPI), which was invented by Bernhard Gleich in 2001 at Philips Research, Hamburg. MPI allows to determine the spatial distribution of magnetic nanoparticles, which can be used as tracers for medical imaging. The method provides a unique combination of features, which makes it a promising method for several clinical applications. It provides high spatial and temporal resolution, high sensitivity and is inherently quantitative. In contrast to several clinically used imaging methods, MPI is free of ionizing radiation and is thus considered to be safe even under long-term considerations.

Since MPI was made public in 2005, several groups started research on MPI. As MPI is inherently a tracer-based method, since the beginning, the research foci lay on both the tracer material and the scanner instrumentation. Research groups in Dartmouth, Washington, Eindhoven, and Lübeck started to develop optimized nanoparticles for MPI and investigated particle physics. In the field of scanner instrumentation, the researchers at Philips continuously improved their scanner hardware and up-scaled the first small animal scanner with a bore diameter of 32 mm to a pre-clinical scanner with a bore diameter of 12 cm. Alternative MPI scanners targeting special applications, for instance, cell tracking and interventional MPI, were developed in Berkeley and Lübeck.

This book originates from a close collaboration between the MPI groups at Philips Research, Hamburg, and the University of Lübeck, which started in 2007 and resulted in several publications and patents. The book covers the most important developments of MPI from 2001 until 2010 and summarizes them in a unified notation. Recent developments initiated in 2011 are also sketched. The book is written for students and researchers with a background in biomedical engineering, medical engineering science, medical physics, medicine (radiology), mathematics, physics, and electrical engineering.

Acknowledgements

We thank several people who have contributed directly or indirectly to this book. First of all we thank Jörn Borgert, Bernhard Gleich, and Jürgen Weizenecker for introducing us into the fascinating MPI technique and sharing their visions with us.

They developed the first MPI scanners, and measured the first in vivo images, and we are glad that we had the opportunity to collaborate with them at these early steps. Several parts of this book are inspired by insights that have been obtained during our collaboration. Additionally, Jörn Borgert and Bernhard Gleich also contributed directly to this book. They contributed substantial parts of the sections about the focus field and hybrid MPI/MRI systems and to the chapter on medical applications of MPI.

From Philips Research we further thank Jürgen Rahmer for fruitful discussions about reconstruction algorithms and MPI in general. Last but not least, among the colleagues from Philips we thank our friend Michael Kuhn for continuously supporting the MPI activities at the University of Lübeck.

We thank our colleagues from the University of Lübeck Timo F. Sattel, Marlitt Erbe, Sven Biederer, Maren Bobek, and Kerstin Lüdtke-Buzug, who made our research group what it is today. This book could not have been written without the uncountable enlightening discussions we had since the group was initiated in 2007. All shown MPI simulation and reconstruction results have been computed with a software framework that was developed by Timo F. Sattel, Sven Biederer, and Tobias Knopp. The book section on single-sided MPI is based on publications, which were written under the auspices of Timo F. Sattel. Marlitt Erbe contributed several ideas to the section about field-free line imaging. We thank Henrik Rogge for the insights he gave us into the field of particle physics, which have influenced the section about relaxation effects. Furthermore, we thank our colleague Andreas Mang for various discussions about MPI and medical imaging in general, which often opened new perspectives for our research.

We thank Gunnar Schütz from Bayer Pharma for providing us TEM images of Resovist®.

For most illustrations we used the open source software tools Inkscape (www.inkscape.org) and matplotlib (www.matplotlib.sf.net). We thank all developers contributing to these great pieces of software.

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Lübeck,
June 2012

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Contents

Introduction 1

Contents

1.1 MPI in the Context of Medical Imaging

Tomographic imaging has revolutionized medical diagnosis over the last decades and has become an indispensable tool for diagnosis of several diseases. By tomographic imaging one usually refers to methods that allow to show slice (Greek *tomos*) images of the inner human body. In the last century, various such methods have been developed. The most prominent and relevant are computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). Each of these methods is based on a different physical effect, which is directly or indirectly exploited for imaging. In general, the methods can be categorized into two groups. The first measure a parameter, which is directly coupled to the property of the tissue under examination. One may call this native imaging. The second apply a tracer to the human body and then image the spatial distribution of the tracer concentration within the body. From the named modalities, CT and MRI fall into the first category and measure the X-ray attenuation and the proton density, respectively, while PET and SPECT fall into the second category and image the distribution of a radioactive tracer. However, tracer material is used in CT and MRI as well, though mainly for contrast enhancement and only rarely for direct tracer imaging.

Each of the named imaging modalities has its pros and cons and is used for medical diagnosis today. The tracer-based methods play an important role in functional imaging and are further used for the detection of cancer cells. Here, the tracers take part in the metabolism and can reveal pathologies before these are manifested in a change of morphology. However, one challenging aspect of tracer-based modalities is that the obtained images do not provide morphological

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Table 1.1 Quantitative comparison of different imaging modalities

	CT	MRI	PET	SPECT	**MPI**
Spatial resolution	0.5 mm	1 mm	4 mm	10 mm	<1 mm
Acquisition time	1 s	1 s–1 h	1 min	1 min	<0.1 s
Sensitivity	Low	Low	High	High	High
Quantifiability	Yes	No	Yes	Yes	Yes
Harmfulness	X-ray	Heating	β/γ radiation	γ radiation	Heating

information. Therefore, one usually uses an overlay with a CT or MR image, which may be obtained in a separate scan or simultaneously in a combined scanner setup, such as the recently appearing PET/CTs and PET/MRIs.

Important characteristics or properties of any imaging modality are:

- Spatial resolution
- Temporal resolution
- Sensitivity
- Quantifiability

Furthermore, the exposure dose is a crucial factor, which can hinder the acceptance of an imaging method. Table 1.1 compares the imaging performance of the named modalities.

In 2005, a completely new quantitative imaging method called magnetic particle imaging (MPI) was introduced, which uses the nonlinear re-magnetization behavior of magnetic nanoparticles to determine their local concentration. Superparamagnetic iron oxide (SPIO) particles represent such suitable nanoparticles, which are readily available as clinically approved contrast agents for liver examinations in magnetic resonance imaging (MRI), and usually administered into the bloodstream via intravenous injection. MPI was invented by Bernhard Gleich in 2001 at Philips Research in Hamburg.

As MPI measures the distribution of the magnetic nanoparticles only, it is a tracer-based method. This means that no image can be taken when no tracer is injected into the patient. Furthermore, it means that MPI does not provide morphological information. Nevertheless, MPI provides a unique combination of features, which make it a suitable method for clinical imaging.

- The MPI measurement is inherently quantitative; its signal, therefore, is a direct measure of how much material is present at a certain location. The correlation of the image signal with material concentration is known from methods in nuclear medicine, like PET and SPECT. This similarity is the reason why contrast agents are called tracer materials in the MPI context.
- Furthermore, MPI promises to deliver high spatial and temporal resolution. This advantage can be exploited to perform true real-time imaging.
- MPI realizes direct imaging of the particles by measuring their magnetic properties. In this way, the sensitivity of MPI in detecting iron oxide can exceed that of MRI by several orders of magnitude, since only indirect particle imaging is realized in MRI, i.e., particles are detected by measuring their influence on the relaxation behavior of protons.

- The method is very flexible and allows for adjusting the imaging performance by appropriate selection of the acquisition parameters. For instance, the sensitivity can be improved by decreasing the temporal resolution.
- Since MPI uses various static and oscillating magnetic fields to perform its measurement, it is completely free of ionizing radiation, as used, for instance, in CT, PET, and SPECT. As far as known today, no adverse or long-term effects on patients are expected from magnetic fields like those applied in MRI or MPI.

In general, MPI aims at applications requiring fast, dynamic imaging, such as blood flow visualization in the case of coronary artery diseases. Further future applications may be in cancer detection, for instance, for sentinel lymph node biopsy [VPV+03, RBK+09], or any application, where tracers are used for diagnosis today (MRI, PET, SPECT). As it is possible to functionalize the nanoparticles for the diagnosis of several diseases, MPI potentially has a wide area of applications.

1.2 Historical Perspective

MPI has experienced a rapid development in the last decade. A summary of the major milestones of MPI is given in Table 1.2.

In its original form, MPI was invented in 2001 at the Philips Research Laboratories in Hamburg. The idea was developed by Bernhard Gleich and published as a patent in 2001 [Gle01]. Together with his colleague Jürgen Weizenecker, Gleich manufactured a first prototype of an MPI scanning device, which has a bore diameter of about 32 mm. First phantom results providing the proof of principle of the method have been published in *Nature* in 2005 [GW05]. Using a phantom consisting of 12 bores filled with undiluted Resovist® representing the letter "P", the scanner was shown to be able to resolve structures in the submillimeter range, as is shown in Fig. 1.1. The acquisition time of the scanner was, at that time, about 1 h. Thus, the scanner was only capable of static imaging. The slow data acquisition was due to mechanical movements, which were necessary to form a 2D image. Furthermore, the trace concentration of the phantom was several orders of magnitude higher than clinically approved.

By extending the scanner setup to be capable of solely electromagnetic 2D spatial encoding, the acquisition time was significantly shortened. This allowed to scan a dynamic sequence of a rotating "P" phantom at a frame rate of 25 frames per second demonstrating the real-time capabilities of MPI [GWB08]. The resulting images are shown in Fig. 1.2. However, the tracer concentration of the phantom was still too high for clinical applications.

In 2009, the first 3D *in vivo* data were published, which revealed the beating heart of a mouse at a temporal resolution of 46 frames per second [WGR+09]. The tracer concentration was considerably lower than for the phantom images and within the clinically approved range. This major improvement in the sensitivity of the scanner was based on a specially developed wide-band, low-noise amplifier, which is necessary to transform the low-voltage measurement signal into the input range of the analog-digital converter. In Fig. 1.3, a picture of the MPI mice scanner is

Table 1.2 Summary of the historical MPI milestones

Year	Milestone
2001	Gleich invented MPI
2005	Gleich and Weizenecker developed the first MPI scanner capable of static imaging
2007	Weizenecker et al. published a simulation study on the sensitivity and spatial resolution of MPI and developed several scaling laws
2008	Gleich et al. extended the scanner and showed first dynamic 2D images
2008	Weizenecker et al. proposed a new encoding scheme, which uses a field-free line and has the potential to increase the sensitivity of MPI. Their setup used currents magnitudes higher than feasible in practice
2008	Weaver et al. showed first spectroscopic MPI results
2009	Sattel et al. developed an alternative single-sided coil topology and showed dynamic 1D phantom images
2009	Weizenecker et al. developed a 3D real-time MPI scanner and showed first in vivo MPI data revealing the beating heart of a mouse at clinically approved tracer concentrations
2009	Goodwill et al. introduced a method to encode the measurement signal in a narrow frequency band and manufactured a 3D scanner capable of static imaging
2010	Knopp et al. introduced model-based reconstruction
2010	Knopp et al. laid down the theoretical foundations for a feasible coil topology for field-free line imaging
2010	Gleich et al. developed a 3D MPI scanner with a focus field to sample a large FOV
2010	Schomberg et al. showed that the MPI imaging equation can be formulated as a 3D convolution. Goodwill et al. derived a similar result with a more sophisticated integral kernel
2011	Knopp et al. analyzed the spatial resolution of MPI and derived a simple but accurate resolution expression

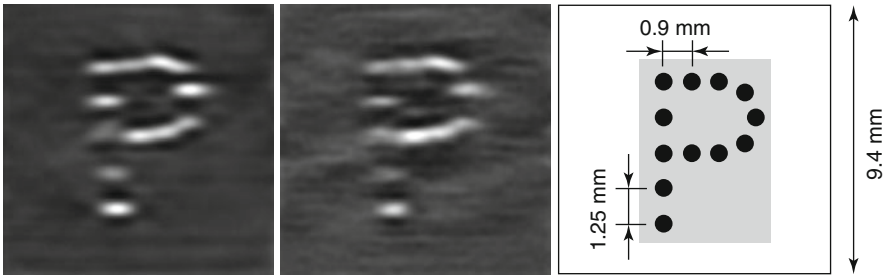

Fig. 1.1 Pictures of the first published MPI data using two different methods for spatial encoding [GW05]. On the *left*, the image obtained by mechanical object movements is shown. The image in the *middle* was determined by a combination of mechanical and electromagnetic spatial encoding. On the *right*, the used "P" phantom is sketched

shown. The magnetic fields in [WGR+09] were generated using permanent magnets and electromagnetic coils. The change of the particle magnetization was detected using receive coils. The imaging volume located at the center of the tube was a cuboid of size $20.4 \times 12 \times 16.8\,\text{mm}^3$ sampled at a grid of size $34 \times 20 \times 28$.

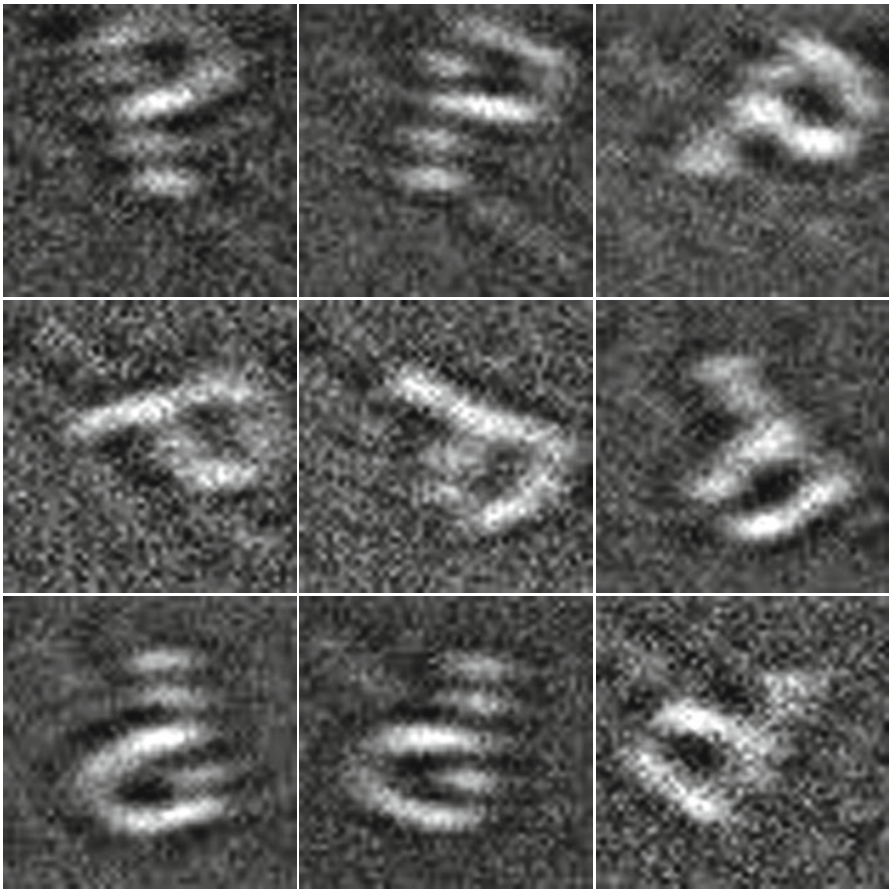

Fig. 1.2 Pictures of the first published dynamic MPI data [GWB08]. The "P" phantom is rotated counterclockwise with 20 rotations per minute. The temporal resolution of the data is 25 frames per second. Shown is every ninth image of the video sequence

Also in 2009, Goodwill et al. demonstrated an alternative approach, using so-called narrowband magnetic particle imaging [GSSC09], which bears potential for more sensitive imaging, while the former efforts by Gleich and Weizenecker et al. aimed at demonstrating MPI's capabilities in real-time image acquisition.

Exploiting the flexibility of magnetic particle imaging in terms of unconventional system geometries, Sattel et al. published first results on the deployment of a single-sided MPI scanner design in [SKB+09]. The coil topology aims at special applications where an open access to the patient is desired, for instance, for interventional imaging. Further applications are low-cost scanners, which are tailored for special applications and for which the scanner is tuned to the needs of the application. One example is the sentinel lymph node biopsy (SLNB) scenario [RBK+09].

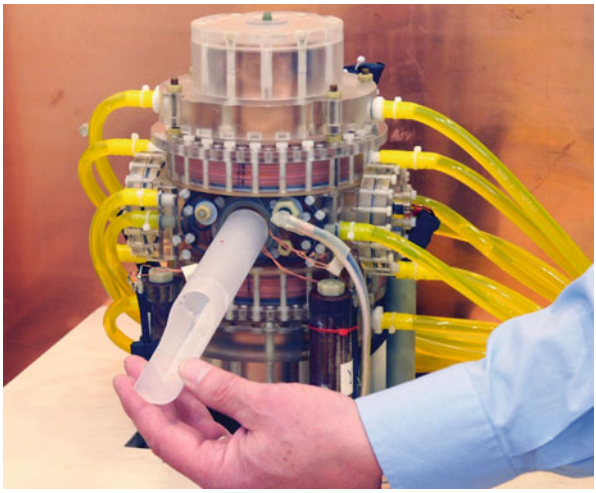

Fig. 1.3 Picture of the MPI mice scanner developed at Philips Research [WGR+09]

One important step toward scaling small animal scanners up to whole-body human scanners was made in 2010 by Gleich et al. [GWT+10]. They developed a 3D MPI scanner with a bore diameter of 12 cm. To sample the increased field-of-view they introduced the so-called focus field concept [SRG+11], which is necessary as the drive field can only scan small volumes for high gradient strengths without the risk of peripheral nerve stimulation (PNS).

Parallel to experimental work, important theoretical achievements have been published to determine the potential of MPI. Starting in 2007, Weizenecker et al. published a simulation study that allowed for the assessment of the image quality of a virtual MPI scanner by taking into account different particle characteristics and concentrations [WBG07]. Several scaling laws have been derived, which expressed the spatial resolution and sensitivity of MPI in terms of the particle, scanner, and acquisition properties. In 2009, Knopp et al. extended this assessment to different trajectories of the field-free point and their influence on the image [KBS+09]. The theory behind signal encoding in MPI was investigated by Rahmer et al. in 2009 [RWGB09]. In this work, it was found that the system function, which describes the relation between the measured MPI signal and the particle distribution can be formulated using Chebyshev polynomials of second kind for a 1D data imaging sequence. Furthermore, the 2D system function was analyzed. Schomberg et al. analyzed the MPI signal in time space and showed that the 3D imaging equation can be formulated as a 3D convolution, if the measurement signal is integrated over time and ideal magnetic fields as well as if sufficiently fast particle relaxation times are assumed [Sch10]. Goodwill et al. introduced the x-space theory in [GC10, GC11], which is similar to the findings of Schomberg et al. but needs no integration of the measurement signal over time but also assumes ideal magnetic fields as well as sufficiently fast particle relaxation times.

To demonstrate that other system topologies can increase the performance of the method, Weizenecker et al. presented an approach using a field-free line instead of a field-free point in [WGB08]. However, the authors conjectured that a realization of a field-free line will not be possible due to an enormous power loss. Later, Knopp et al. provided a proof that a realization of a field-free line is actually feasible in [KSBB10]. The coil topology was further improved in [KEB+10]. Erbe et al. manufactured a field demonstrator to show the feasibility of the coil topology experimentally in [EKS+11]. In [KES+10], an alternative method for field-free line imaging was proposed, which proposes a rotating gantry similar to a CT gantry. Finally, in [KES+11], it was shown by Knopp et al. that the field-free line measurement signal can be transformed into Radon space, enabling efficient reconstruction for this special coil topology.

A method closely related to MPI was introduced in 2007 by Weaver et al. [WRSB08]. The so-called magnetic particle spectroscopy (MPS) is basically zero-dimensional MPI, i.e., MPI without spatial encoding. MPS is a powerful tool for the characterization of magnetic nanoparticles and can be used to determine the mean particle concentration as well as the particle size distribution. In 2008, an MPS was presented, which had the capability of detecting up to 100 harmonics simultaneously [BKS+09].

As an example for other applications of magnetic particle imaging, the group of Weaver et al. used an MPS for temperature measurements [WRH09]. The method was improved in [RW09] by using a static bias field. In [RW10a], it was shown that molecular bindings have an influence on the MPI signal. In [RW10b], MPS was used to determine the viscosity of the particle suspension. To this end, a lower excitation frequency was used and the viscosity was calculated from the Brownian relaxation time. Moreland et al. presented an approach based on a cantilever torque magnetometer to realize a selection field gradient strength of more than $100\,\mathrm{Tm}^{-1}\mu_0^{-1}$ for ultrahigh-resolution MPI for very small samples in [MEL+07].

In 2008, Bohnert et al. started reporting on physiological compatibility of MPI [BGW+08a, BGW+09]. In the important area of research on particle optimization for MPI, first efforts have been reported by Lüdtke-Buzug et al. [LBBS+09a, LBBS+09b], Ferguson et al. [FMK09], and Markov et al. [MHvZ+08]. Ferguson further investigated the optimum particle core size using a particle model, which accounts for the signal loss for particles with high magnetic anisotropy [FMK09, FKMK11]. In 2011, Eberbeck et al. investigated how the size distribution of magnetic nanoparticles effects the particles' MPI performance [EWWT11].

First dedicated results on the use of MPI for medical applications have been published by Bulte et al. in [BGW+08b]. They assessed the use of MPI for stem cell tracking. Ruhland et al. investigated the use of MPI for sentinel lymph node biopsy [RBK+09]. The potential of red blood cells loaded with iron oxide nanoparticles as a tracer material for MPI has been investigated by Markov et al. [MBG+10].

In the area of reconstruction, Knopp et al. introduced a model-based method in 2010 [KSB+10, KBS+10]. It is based on the idea of using a model of the signal chain to rapidly compute the system matrix, which has to be known for reconstruction. Until that time, all MPI groups used a tedious calibration scan to

measure the system function, which is only feasible for small FOVs. Furthermore, Knopp et al. investigated different reconstruction algorithms and showed that iterative methods can significantly shorten the reconstruction time [KRS+10].

In 2011, the spatial resolution of MPI was investigated by Knopp et al. using the modulation transfer function [KBS+11]. It was shown that the resolution depends not only on the particle size and the gradient strength of the applied field but also on the signal-to-noise ratio of the measurement signal in a logarithmic fashion. The simple resolution expression was validated using experimental MPI data and shown to be more accurate than the full width at half maximum (FWHM) resolution measure considered in MPI before.

Also in 2011, the inventors of MPI introduced acoustic MPI, which detects acoustic emissions caused by magnetization changes of magnetic nanoparticles [GWB11]. The aim was to extend MPI to the detection of soft tissue properties, e.g., the velocity of sound and the attenuation caused by the tissue.

1.3 Structure of the Book

This book is structured as follows: In Chap. 2, the basic principles of MPI are introduced. It is discussed how the magnetic nanoparticles can be excited using electromagnetic fields such that they respond with a change of their magnetization. To pick up this characteristic signal, the particle magnetization can be detected using receive coils exploiting the induction principle. A crucial concept of MPI is the strategy of spatial encoding, which uses a magnetic gradient field featuring a field-free point leading to a spatially varying particle response. Beside these basic principles, limitations of MPI regarding spatial and temporal resolution as well as sensitivity are discussed.

The subject of Chap. 3 is how to actually build an MPI scanner. The MPI hardware consists of field generating units, which can be realized either by electromagnetic coils or permanent magnets. Detecting the change of the particle magnetization vector requires several receive coils which are tailored to pick up the broadband MPI signal with high sensitivity. After signal detection, analog filters are applied to extract the nanoparticle signal from the induced voltage, which also consists of the excitation signal directly coupling into the receive coils. The filtered signal is low-noise amplified, digitized and stored in permanent memory either for online or offline reconstruction.

The subject of Chap. 4 is the MPI imaging equation, which is shown to be linear if particle–particle interactions are neglected, which is reasonable for clinical tracer concentrations. The integral kernel of the linear equation is called the system function in MPI. The structure of 1D, 2D, and 3D system functions is investigated, which gives important information for optimal reconstruction of MPI data. Also in Chap. 4, different methods for determining the MPI system function in practice are discussed.

In Chap. 5, the reconstruction of the particle distribution given the measured MPI data is investigated. Reconstruction involves the solution of a large linear system of equations with a dense, ill-conditioned system matrix. Regularization techniques are introduced to cope with the ill-conditioning of the system matrix. To optimize the image quality, a special row-weighting strategy is discussed, which involves a normalization of the system matrix rows. For time- and memory-efficient reconstruction, iterative algorithms for solving linear systems of equations can be used, which converge rapidly if row normalization weights are applied.

In Chap. 6, alternative MPI coil topologies are discussed that differ significantly from the original setup proposed by Gleich and Weizenecker in [GW05]. Besides a single-sided coil topology, which enables an open patient access, a coil topology is presented, which uses a completely different spatial encoding scheme utilizing a field-free line instead of the usually applied field-free point. Furthermore, possibilities are sketched on how one could use an MPI scanner to perform MRI experiments in order to gain morphological information.

In Chap. 7, a brief introduction into potential medical applications is given. Besides applications in diagnostics, MPI can also offer advantages in image-guided treatment and in the field of hyperthermia.

In the appendix, fundamentals of electromagnetism are reviewed. Starting from Maxwell's equations, approximations usually applied in MPI are discussed. One of these is the quasi-static approximation, which is valid in the frequency range considered in MPI. Using these approximations, efficient computation of the magnetic field by means of the Biot-Savart law is discussed. Finally, electromagnetic induction is reviewed including the law of reciprocity, from which the MPI signal equation can be derived.

How Magnetic Particle Imaging Works

2

Contents

2.1 Introduction

In this chapter, the basic concepts of MPI are introduced. In order to get MPI to work, two basic ingredients are needed: First, one has to find a way to get the particles to emit some kind of characteristic signal that reveals their existence. To end up at a quantitative method, this signal should also carry information about the amount of magnetic material, i.e., the *particle concentration*. How this *signal encoding* is done in MPI is explained in Sect. 2.3. As a second component, one needs a way to determine where the signal comes from in relation to the object under examination. This usually is called *spatial encoding* and is achieved by making the emitted characteristic particle signal spatially dependent. In Sect. 2.4, the basic principle of spatial encoding is introduced. As it turns out, the simplest method for spatial encoding is rather slow and cannot fulfill the real-time requirements that potential applications have. Therefore, the subject of Sect. 2.5 is a way to improve the MPI performance with respect to acquisition time. Still, this performance upgrade is only capable of imaging small volumes of few centimeters in length. To circumvent this size limitation, in Sect. 2.6 a way to handle large imaging volumes is introduced. Finally in Sect. 2.7, limitations of MPI in spatial resolution and sensitivity are discussed.

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2.2 Magnetic Particles

The aim of the MPI method is to determine the spatial distribution of magnetic material, injected into the human body. One suitable magnetic material for MPI is iron oxide, which usually is available in the form of iron oxide–based nanoparticles. Such particles consist of a core, which is responsible for its magnetic behavior, and a magnetically neutral coating, which prevents agglomeration of the particles. In Fig. 2.1, a schematic drawing of a spherical magnetic nanoparticle is shown. Typically, the diameter of the particle core is in the range of 1–100 nm. In Fig. 2.2, a picture of magnetic nanoparticles developed at the University of Lübeck is shown (see [LBBS+09a]). One way to visualize the shape of the particle core is transmission electron microscopy (TEM). In Fig. 2.3, a TEM picture of a fraction of the commercial tracer Resovist® (Bayer Schering Pharma) is shown (see [LBM08]).

If the particle coating is sufficiently thick, the nanoparticles show a *superparamagnetic* behavior. This means that the particle–particle interactions are negligibly small such that each particle has its own magnetic domain – the particles are said to be single domain. The prefix "super" essentially means that each particle behaves like a paramagnet with a large magnetic moment, which is significantly higher than the atomic moment [BL59].

2.2.1 Particle Concentration

Due to the small particle size in the nanometer range, it is not possible to determine the precise position of a particular particle using the MPI method. Instead, one images a map of the spatial particle concentration, which is usually displayed as

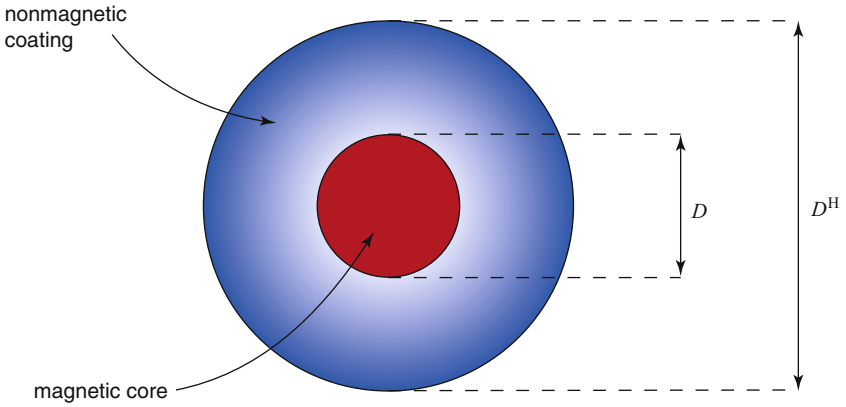

Fig. 2.1 Schematic drawing of a spherical magnetic nanoparticle consisting of a magnetic core (usually magnetite) and a magnetically neutral coating necessary to prevent agglomeration