

CHAPTER 2

Magnetic Particle Imaging

Magnetic particle imaging (MPI) is a young and very promising tomographic modality capable of imaging a distribution of biocompatible superparamagnetic iron oxide (SPIO) nanoparticles within a patient with a sub-millimeter resolution in three dimensions (3D) and real-time without the need of harmful, ionizing radiation [GW05, WGR⁺09]. The potential held by this revolutionary new tomographic method was already demonstrated in the first, impressive *in-vivo* MPI images of a beating mouse heart presented in [WGR⁺09]. No existing modality is capable of providing 3D real-time images of the inside of the human body. To classify MPI within established medical imaging modalities, the crucial properties of computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are compared to those of MPI in Fig. 2.1.

Due to these characteristics, MPI has the potential to revolutionize imaging of fast blood flow phenomena, as needed for example for the visualization of coronary artery diseases as well as interventional imaging in the catheter laboratory [HRG⁺12]. Another promising application is the localization of cancer cells when using MPI in the sentinel lymph node biopsy (SLNB) [RBK⁺09, FRB⁺10]. A closer look at such medical applications will be taken in the subsequent section 2.1.

To spatially and temporally resolve a distribution of SPIO tracer particles within a patient, the interaction between static and dynamic magnetic fields and the characteristic magnetization behavior of the tracer material is exploited. To in-

	CT	MRI	PET	MPI
Resolution	0.5 mm	1 mm	4 mm	< 1 mm
Sensitivity	low	low	high	high
Acquisition Time	1 s	10 s - 1 h	1 min	< 0.1 s
Radiation	yes	no	yes	no

Figure 2.1 Comparison of the performance of MPI with established medical imaging modalities [Kno11].

Introduce the underlying technology, in a first step, the magnetic properties of the SPIO particles will be discussed in section 2.2 on the tracer’s characteristic fingerprint. Subsequently, the methods applied for signal reception (section 2.3), signal encoding (section 2.4) and spatial encoding (section 2.5) will be introduced. Before discussing MPI reconstruction in section 2.7, the role of the MPI system function needs to be described (section 2.6). Since the final goal of this thesis is the implementation of the first dynamic FFL scanner, the signal chain, which is the basis for scanner implementation in MPI, is presented in section 2.8.

2.1 Medical Applications

Regarding medical applications for MPI, several different scenarios arise. Since MPI offers not only one advantage compared to existing medical imaging technologies, the applications vary depending on which of the advantages improves diagnostics or therapy.

The intrinsic property of MPI to provide 3D data might considerably improve cardiovascular interventions. Today, fluoroscopy including intraarterial digital subtraction angiography (DSA) is commonly used in cardiovascular interventional procedures [BBE⁺12]. The drawbacks of DSA of providing only two dimensional (2D) data and exposing the patient as well as the medical doctor to ionizing radiation is compensated for using MPI, where the vasculature including its pathologies can be visualized in 3D and real-time without the need

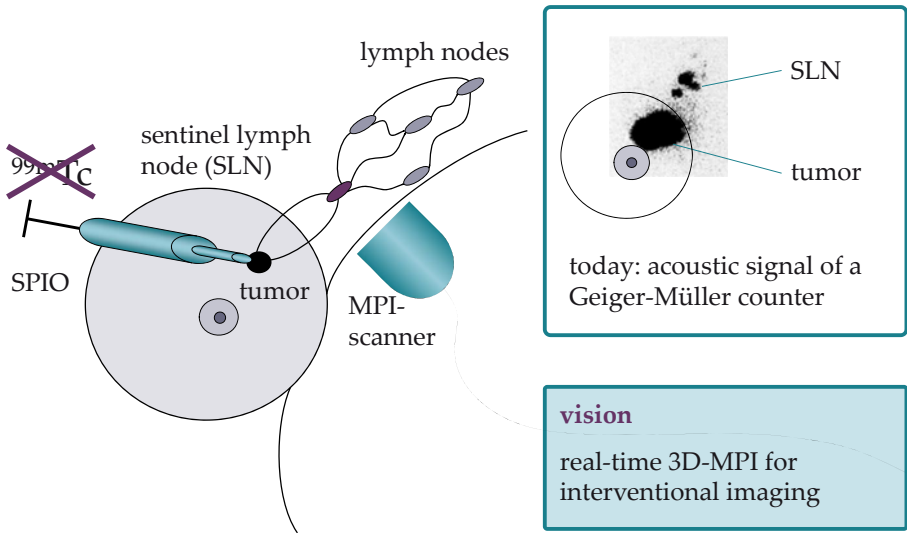


Figure 2.2 A hand-held single-sided MPI scanner will be applied in the SLNB to detect the localization of the sentinel lymph node as well as the lymph nodes connected to it using an SPIO tracer.

of harmful radiation. This way, imaging of stenosis and occlusions using MPI will improve not only diagnostics and therapy planning, but will also offer the possibility of supervision during interventions. Furthermore, the success of the intervention can be verified after the procedure. The navigation of instruments coated with SPIO nanoparticles might also play an important role regarding interventional MPI [HRG⁺12].

Another very promising scenario is the use of a single-sided MPI scanner [SKB⁺09] in the SLNB [RBK⁺09, FRB⁺10, SEB⁺12]. The sentinel lymph node (SLN), which is located closest to the tumor in the case of lymphogenous metastasis, is most likely infiltrated by cancer cells. Today, in the SLNB either dye or a radionuclide tracer is used to detect the SLN as well as lymph nodes connected to it, which are also likely to be tumorous and hence need to be removed. When using dye, the physician needs to perform a surgery to trace the dye within the patient, which is with no doubt an invasive procedure. Using a radionuclide like technetium, which is traced by a Geiger-Müller counter, exposes the patient and the physician to harmful radiation.

MPI might provide a solution to perform an SLNB without the need of surgery or radiation for identifying the critical lymph nodes. In this scenario, a hand-held single-sided MPI scanner is used to trace the SPIO nanoparticles, which are injected into the tumor and will from there proceed to the connected lymph nodes. A single-sided MPI scanner provides all components on only one side of the patient and therefore ensures perfect patient access. In the presented scenario, all single-sided MPI components are integrated in a hand-held scanner comparable to an ultrasound probe. The SPIO tracer particles inside the critical lymph nodes will be located using 3D MPI data. The application of a hand-held single-sided MPI scanner supporting the SLNB is illustrated in Fig. 2.2.

The imaging of fast blood flow phenomena was impressively demonstrated by Weizenecker et al. in [WGR⁺09], where a beating mouse heart was visualized using the first experimental MPI scanner setup. Regarding the progress of MPI in all areas, not only scanner generation, but also concerning reconstruction methods and image processing, the potential held by MPI has only been touched in those experiments. Applications involving fast dynamic blood flow phenomena, as also the catheter laboratory does, will considerably benefit from this new imaging technology especially once MPI has grown to its full potential.

2.2 Fingerprint of the MPI Tracer

MPI is a revolutionary tracer-based medical imaging modality. SPIO nanoparticles are injected into the patients blood circulation, where they can be traced due to their specific magnetization behavior, when exposed to a combination of dynamic and static magnetic fields. When excited, the SPIO nanoparticles exhibit a non-linear change in magnetization, which induces a characteristic voltage signal in receive coils such as a fingerprint.

To understand the origin of the magnetic properties of the nanoparticles enabling their detection and localization, a closer look at their composition as well as at superparamagnetic material in general needs to be taken.

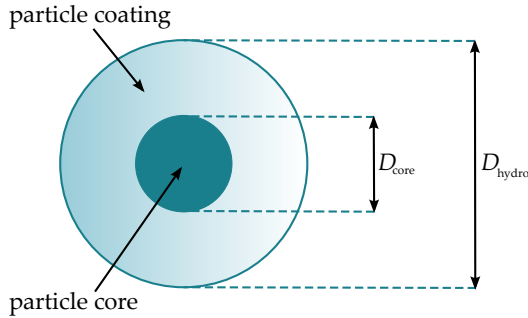


Figure 2.3 Composition of the SPIO tracer particles. The magnetic core is coated with a biocompatible shell.

2.2.1 Composition of SPIO Nanoparticles

The significance of magnetic nanoparticles regarding medical applications considerably increased within the last decade. Such particles are not only used as tracer in MPI or as contrast agent in MRI, where the magnetic properties of these particles are exploited to image their distribution or to increase image contrast, but also as therapeutic appliance for example in hyperthermia, where magnetic nanoparticles are used for cancer therapy.

Since the magnetic nanoparticles are injected into the patient body, biocompatibility will always be an issue. Fortunately, the clinically approved MRI contrast agent Resovist[®] [LBF⁺97] by Bayer Schering Pharma shows significant performance as MPI tracer material. This incident is an important aspect towards clinical acceptability of MPI, since the first *in-vivo* mice images were performed at a clinically approved concentration of Resovist[®] [WBG07].

Regarding the composition of magnetic nanoparticles, two aspects are of importance: the magnetic core and the non-magnetic coating. Relevant for the imaging process are the magnetic properties of the core material of the particle. However, the characteristic magnetization behavior only arises for non-interacting particles. Without an appropriate coating, the particles would cluster due to their magnetic properties and would not exhibit superparamagnetic behavior. The coating also ensures biocompatibility of the particles. The schematic structure of an MPI tracer particle is illustrated in Fig. 2.3. The hydrodynamic di-

ameter D_{hydro} of the particle including its coating is an important property with respect to medical applications, because it determines the overall size of the particle. The overall size gains importance, for example, when considering applications, in which the particles need to cross the blood-brain barrier. The important property concerning the imaging process is the diameter of the magnetic core D_{core} , since the shape of the magnetization curve of the particles strongly depends on this parameter.

2.2.2 Phenomenology of Superparamagnetism

A simple but very common model describing the magnetization behavior of SPIO nanoparticles is Langevin's theory of paramagnetism. However, the magnetic core of the particles consists of a ferromagnetic substance. Why use a theory originally developed to describe paramagnetic material? To answer this question, it is necessary to examine the magnetic properties of ferromagnetic materials.

Ferromagnetic materials are characterized by the formation of magnetic domains, named Weiss domains, in which the atomic magnetic moments μ_a are aligned resulting in a non-zero magnetization. Even in the absence of an external magnetic field, Weiss domains are present. Exposing a ferromagnetic material to an external magnetic field will parallelize the direction of the orientation of the atomic magnetic moments μ_a of all domains. The size of these domains depends on the corresponding material. For spherical particles, the critical diameter D_{cr} , which is identical to the largest diameter being energetically efficient for a particle to consist of one single domain [Kro07], can be calculated by

$$D_{cr} = \frac{72 \sqrt{AK_A}}{\mu_0 M_{\text{sat}}^2}, \quad (2.1)$$

where K_A is the anisotropy constant and A is the exchange stiffness constant. The critical diameter D_{cr} only depends on material constants [Rog11]. In MPI, magnetite Fe_3O_4 is most often used as tracer and the corresponding saturation field strength of magnetite is given by [KB12]

$$M_{\text{sat}} = 0.6 \text{ T} \mu_0^{-1}. \quad (2.2)$$

The critical diameter of magnetite is not consistently specified in literature. Values from 12.4 nm [Kro07] up to a range of 30 - 100 nm [RMC03] are mentioned

[Rog11]. The MPI tracer particles used today range from some nanometers up to not more than 30 nm, where the larger particles are present in a much lower density than the smaller ones. Due to this reason, we will for now assume a one domain structure of the SPIO tracer particles. Hence, all aligned atomic magnetic moments μ_a of each particle add up to one (*super*) large particle magnetic moment μ_p .

Considering a distribution of such one domain nanoparticles, another property is of importance: the non-magnetic coating. As discussed in the previous section, the coating ensures biocompatibility of the tracer. In addition, however, it also prevents agglomeration of the particles. Adequately coated, the SPIO particles may therefore in good approximation be assumed as non-interacting. The behavior of the magnetic moments μ_p of the SPIO particles can hence be compared to the behavior of the non-interacting atomic magnetic moments μ_a of a paramagnetic material. This instance is the historical origin of the name *superparamagnetism*, which describes the paramagnetic behavior of the much larger *super* particle magnetic moments μ_p of the SPIO nanoparticles. And exactly for this reason, a theory describing paramagnetism can be applied for nanoparticles made of a ferromagnetic substance [BL59].

2.2.3 Magnetic Moment

Regarding a distribution of SPIO particles in a stable suspension, i.e. a ferrofluid, the magnetic moment of a single particle depends on the volume of the particle core V_c as well as on the bulk saturation magnetization of the core material M_{sat} (Eq. (2.2)) [Rog11]

$$\mu = V_c M_{\text{sat}} \hat{e}_\mu, \quad (2.3)$$

where $\hat{e}_\mu$ denotes a unit vector in direction of the orientation of the magnetic moment of the SPIO particle.

However, this equation may - as the assumption of considering purely one domain particles - only be regarded as an approximation, since it describes the case of perfectly aligned atomic magnetic moments μ_a in the one magnetic domain of the corresponding nanoparticle. The magnetic moment of an SPIO particle, however, depends on the exact formation of the magnetic domains, which will in reality not always be ideally homogeneous. For different particle sizes, in-

homogeneities in the magnetic alignment may occur. For particle sizes below 3 nm, the intrinsic force of the particle will not suffice to cause ferromagnetic behavior [GSV06]. Furthermore, surface effects and the formation of vortices occurring for particles with a diameter close to D_{cr} will also influence domain formation [Gui09, Rog11].

2.2.4 Magnetization

The significant property of SPIO particles regarding image generation in MPI is their characteristic non-linear magnetization behavior. Magnetization is generally defined as the magnetic moment per volume

$$\mathbf{M} := \frac{d\boldsymbol{\mu}}{dV} \quad (2.4)$$

and is a physical quantity defined for a distribution of magnetic moments. Considering a small finite volume ΔV , which is of the size of an image voxel, and N being the number of SPIO particles in this volume, a discrete version of Eq. (2.4) can be derived

$$\mathbf{M} = \frac{1}{\Delta V} \sum_{j=1}^N \boldsymbol{\mu}_j, \quad (2.5)$$

where $\boldsymbol{\mu}_j$ denotes the magnetic moment of the j th SPIO particle. From now on we will describe the magnetic behavior of SPIO particles including all assumptions introduced in the previous sections. The subscript p has therefore been omitted and $\boldsymbol{\mu}$ will denote the particles magnetic moment in the following.

For a distribution of SPIO particles, it is convenient to introduce a mean magnetic moment

$$\bar{\boldsymbol{\mu}} = \frac{1}{N} \sum_{j=1}^N \boldsymbol{\mu}_j. \quad (2.6)$$

When defining the SPIO particle concentration c as the number of particles N per volume ΔV , the magnetization of the particles in Eq. (2.5) can be reformulated using Eq. (2.6) as

$$\mathbf{M} = \frac{N}{\Delta V} \bar{\boldsymbol{\mu}} = c \cdot \bar{\boldsymbol{\mu}}. \quad (2.7)$$

Hence, a linear connection between the particle magnetization $\mathbf{M}$ and the concentration of SPIO particles c in a considered volume unveils. As will be discussed in section 2.3, the signal measured in MPI receive coils is proportional to the derivative of the particle magnetization with respect to time. Since the derivative is a linear operation, the connection of the MPI receive signal and the particle concentration can also be described in a linear manner.

When applying an external magnetic field $\mathbf{H}$ to a distribution of SPIO particles, the magnetic moments of the particles tend to align within the direction of $\mathbf{H}$ resulting in a non-zero magnetization. At a specific field strength H_{sat} , all magnetic moments are aligned within the direction of $\mathbf{H}$ so that further increasing the field strength will not increase the magnetization. This mechanism is illustrated in Fig. 2.4 and results in a non-linear magnetization behavior. At zero field strength, the magnetic moments of the particles are thermally distributed and the magnetization is equal to zero (petrol region). When increasing the field strength, the particles begin to align within the direction of the field and cause a non-zero magnetization (turquoise region). Increasing the field strength beyond H_{sat} , however, will not lead to a further increase in magnetization. The particle distribution is magnetically saturated (gray region).

Precisely this non-linear magnetization behavior is the fundamental characteristic of a superparamagnetic material enabling their detection using MPI. Neglecting anisotropy of the particles as well as hysteresis effects, the magnetization behavior of a distribution of SPIO particles can be described using Langevin's theory of paramagnetism, which will be derived in the subsequent section.

2.2.5 Langevin Theory of Paramagnetism

Langevin's theory of paramagnetism describes the non-linear magnetization behavior of SPIO tracer particles if anisotropy and hysteresis effects are neglected. The presented derivation is based on [CC64].

If an external magnetic field $\mathbf{H}$ is applied to a distribution of non-interacting magnetic moments $\boldsymbol{\mu}$, a couple of force $-\boldsymbol{\mu}\mathbf{H} \sin \theta$ will act on each of the particle's magnetic moments. The angle between the external magnetic field $\mathbf{H}$ and the direction of the magnetic moment $\boldsymbol{\mu}$ is denoted θ . This force is responsible for the tendency of the particles to align in direction of the external magnetic

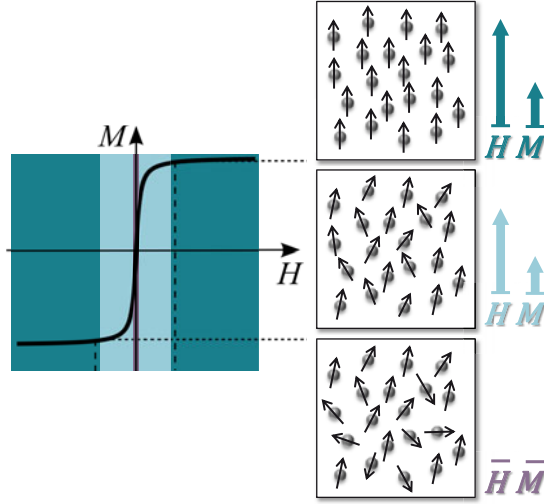


Figure 2.4 The effect of saturation of a distribution of SPIO nanoparticles. At no external magnetic field H , the magnetic moments of the SPIO particles are thermally distributed and no magnetization arises. When applying an external magnetic field H , the particles' magnetic moments start to align within the direction of H . At the saturation field strength, all magnetic moments of the particles are aligned along the direction of the external magnetic field H and an increase in field strength will not result in an additional increase in magnetization. Figure based on [KB12].

field, which does finally lead to the phenomenon of magnetic saturation once all magnetic moments are parallelized.

For a finite temperature, thermal agitation counteracts this tendency and leads to a potential energy

$$E_p = -\mu_0 \mu H \cos \theta \quad (2.8)$$

of each moment μ , when defined according to Eq. (2.3) with the bulk saturation magnetization given by Eq. (2.2).

The total number of magnetic moments in a unit volume, which are rotated by an angle between θ and $\theta + d\theta$ with respect to the orientation of the external magnetic field H needs to be proportional to the solid angle $2\pi \sin \theta d\theta$ as well as to the Boltzmann factor [CC64].

Field Free Line Magnetic Particle Imaging

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