# Three-dimensional real-time *in vivo* magnetic particle imaging

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# MPI is a new tomographic imaging technique using iron oxide based nanoparticles.

#### MPI promises to deliver high spatial and temporal resolution.

Magnetic particle imaging (MPI) is a new tomographic imaging method invented in 2001 by Philips Research, first published in Nature in 2005[2] and shortly afterwards in Medicamundi [3]. MPI uses the magnetic properties of iron oxide based nanoparticles, called tracer materials in the context of MPI, to determine the local concentration. The measurement is inherently quantitative in that it shows exactly how much material is present at a certain spot. Furthermore, MPI promises to deliver high spatial and temporal resolution with a sensitivity exceeding that of magnetic resonance imaging (MRI) [4, 5, 6] in the detection of iron oxide.

Although MPI is capable of rapid threedimensional (3D) dynamic imaging of magnetic tracer materials, until now only static [2, 3] and dynamic two-dimensional (2D) phantom [7] experiments with high tracer concentrations have been demonstrated. To pave the way for meaningful clinical applications, the next important step was to demonstrate that 3D imaging would work *in vivo* while limiting the tracer dose to clinically approved concentrations.

MPI can use commercial tracer materials made from iron oxide. These are generally known as superparamagnetic iron oxides (SPIOs). One such material is Resovist<sup>®</sup>, made by Bayer Schering Pharma [8], that is approved for use as an MRI contrast agent in the diagnosis of liver carcinoma.

This report demonstrates that a single bolus injection of from 8 µmol (Fe)/kg up to 45 µmol

(Fe)/kg Resovist<sup>®</sup> is enough to acquire three-dimensional real-time volumetric images of a beating mouse heart. This is with an acquisition time of 21.5ms per volume and a spatial resolution sufficient to resolve all heart chambers. As no breath hold was required during image acquisition, and no retrospective triggering was needed during reconstruction, the above represents the raw performance of the imaging system.

While these abilities are convincing, the ultimate question remains: What are the medical applications that would benefit from MPI? Because the tracer material is formulated for intravenous injection, the obvious applications are those that can capitalize on the material staying in the blood stream for a certain time. One widespread application that meets this criterion is the diagnosis and assessment of cardiovascular disease (CVD).

One of the most important aspects of CVD is coronary artery disease (CAD). It is responsible for the condition known as myocardial infarction, with unstable or stable angina, which is commonly referred to as a "heart attack". All of these conditions are caused by either a partial closure (stenosis), or a complete obstruction (occlusion), of vessels that supply the heart muscle with blood, resulting in necrosis of the heart muscle.

In acute cases, a direct referral to the cath lab for catheterization and angiography, with the option to intervene by angioplasty and stenting, is still the most common course of action. However, in subacute cases, a clear trend to replace this invasive step with noninvasive methods gave rise to the use of contrast enhanced computed tomography (CT) [9, 10] for coronary angiography. Consequently, only those patients that show a stenosis or obstruction in the CT exam will be subject to an intervention.

In most cases, these diagnostic steps are preceded by other examinations to determine the status of the heart, such as electrocardiography (ECG). They can also include a determination of the levels of certain enzymes released following cell death in the heart muscle. These include creatine phosphokinease (CPK) and more recently, troponin [11]. In some countries, the diagnostic process is combined with a cardiac stress/rest test using single photon emission computed tomography (SPECT) [12]. Sometimes positron-emission tomography (PET) [13, 14] is used to determine the myocardial perfusion. Areas of decreased perfusion can indicate the presence of a stenosis or occlusion, increasing the diagnostic evidence and indicating the need for intervention.

All of this information is collected to develop a comprehensive understanding of the state of the patient's heart. MPI can possibly provide an alternative source of information for both the diagnostic and the interventional scenario for cardiovascular disease. To be more specific, most of the information that is now collected by deploying diverse modalities can be acquired by MPI alone.

As shown in the study presented in this article in a pre-clinical setting, the tracer material can be followed through various parts of the heart and the cardiovascular system. After the material has entered the right atrium by way of the vena cava, it is possible to assess wall motion of the right ventricle and the ejection dynamics into the pulmonary vessel system. In a similar manner, left ventricle wall motion and ejection dynamics complete the function information picture.

In a next step, the coronary blood supply can be imaged in a similar manner to an angiography performed in the cath lab. However, the information delivered by MPI is threedimensional and acquired without the use of any harmful radiation. Immediately after imaging the coronary blood supply, the myocardial vitality can be assessed by measuring myocardial perfusion. In a similar way to the cardiac stress/rest test using SPECT or PET, this information will be correlated to the state of the coronaries with respect to stenosis or occlusions. As a result, most of the information used today to form a comprehensive overview of the state of the cardiovascular system, could be acquired with MPI in a single session. However, determination of the levels of the enzymes CPK and troponin in the blood, indicating cell death in the heart-muscle, would still have to be done separately.

MPI could also address future diagnostic options, for example, determination of plaque burden. Using MPI, a quantitative measurement of the accumulated iron, and therefore the plaque burden, is within reach. There is widespread research effort into deciphering the accumulation processes that could be exploited to label vulnerable plaque with iron oxide [15]. The coatings of the tracer materials determine the physiological properties and the pharmacokinetics of the tracer. Therefore, it may be possible that improved tracer materials with custom made coatings to support the accumulation process will lead to vast improvements in efficiency of the method.

For other diseases, determination of the blood supply of certain tissues, such as tumor tissue in the case of cancer, could provide interesting diagnostic information. New studies have investigated the importance of measuring micro-vascularization for tumor staging [16].

Specifically during therapy, monitoring of the blood supply can indicate the success of the therapy by showing a decrease in the blood supply. Similar to the case with plaque, there are ongoing investigations into whether iron oxide based tracer materials have the potential to migrate into tumor tissue or lymph nodes after systemic injection [17].

Focusing on the imaging of the cardiovascular system of a mouse, this article indicates that medical applications of MPI that make use of an injection of tracer materials into the blood stream are indeed feasible. This article goes on to show that it is possible to track a bolus injection through the cardiovascular system of a living mouse using 3D MPI is now possible. Being able to use tracer concentrations between 8 and 45 µmol (Fe)/l, and with 40 µmol (Fe)/l still being considered a safe dosage, the sensitivity is already high enough for imaging clinically approved dosages of commercially available MRI contrast agents.

All studies have been approved and carried out in accordance with the appropriate local guidelines and regulations. MPI could acquire comprehensive information on the cardiovascular system in a single session.

A quantitative assessment of plaque burden is now within reach.

# INTERMEZZO MPI: the basic principles



Figure I. Principle of MPI: a "selection field" is applied that is relatively high at the edges but approaches zero in the center. This central point is referred to as the "field-free point" (FFP). Any magnetic material outside the FFP, i.e. located in the high field, will be saturated and therefore remains unaffected by an applied radio-frequency field, while magnetic material within the closely defined FFP will be free to respond.

If an additional weak radio-frequency field is applied, the magnetization of material at the FFP (A) will start to oscillate, inducing a signal in the detection circuit, while magnetic material in the saturated areas will be unaffected (B). This signal can thus be unambiguously assigned to the narrow field-free region. By systematically varying the position of the field-free area in the object, a map can be created that gives the spatial distribution of the magnetic particles.

Magnetic Particle Imaging (MPI) is a new imaging technique based on the magnetic properties of iron oxide based nanoparticles. The measurement is inherently quantitative, and promises to deliver high spatial and temporal resolution with a sensitivity exceeding that of conventional magnetic resonance imaging (MRI).

In MPI, a "selection field" is applied that is high at the edges but approaches zero in the center. This central point is referred to as the "field-free point" (FFP). Any magnetic material outside the FFP, i.e. located in the high field, will be saturated and therefore unaffected by any applied radio-frequency field, while magnetic material within the closely defined FFP will be free to respond (Figure I).

If an oscillating "modulation field" is applied, the magnetic material in the FFP will respond with oscillations at the same frequency as the applied field, but much weaker. However, the induced oscillations are accompanied by a series of higher harmonic frequencies. These higher frequencies can be separated from the applied signal by appropriate filtering, providing a signal that can be unambiguously assigned to the narrow FFP. The resolution in MPI is determined solely by the size of the area of non-saturated particles around the FFP, independently of the size of the detectors, making it possible to achieve a resolution of 1 mm or less.

Scanning the FFP through the region of interest provides the data for a tomographic image. The FFP can be scanned through the region of interest by applying three additional orthogonal homogeneous magnetic fields, referred to as "drive fields". The drive field in the vertical (z) direction is produced by the selection field coils. The drive fields in the two orthogonal (x, y) directions are produced by dedicated coils, which are driven at the same amplitude. Appropriate adjustment of the drive fields can position the FFP at any desired point within the object.

# **Technical introduction**

The basic principles of MPI are outlined in the Intermezzo accompanying this article. Articles with more detail have been published previously in Nature [2] and Medicamundi [3]. In brief, MPI requires ferromagnetic nanoparticles as a tracer material, a static magnetic field ("selection field"), an oscillating field ("drive field"), and signal receive coils. The basic scanner setup is schematically shown in Figure 1. The selection field provides a single field-free point in space (FFP), while it is non-zero at all other spatial positions. This field topology can be achieved using a Helmholtz-type coil set up supplied with opposing currents.

In close vicinity to the FFP, the orientation of the magnetization of the ferromagnetic nanoparticles will easily align with an applied oscillating drive field. At all other positions, the orientation is forced to align with the local selection field direction. Since the particles have a non-linear magnetization curve, magnetization reorientation occurring around the FFP induces a signal in the receive coils at the drive field frequency  $f_0$  and its higher harmonics.

The signal is proportional to the concentration of particles at this position. If the FFP is moved over the object in a sufficiently dense trajectory, it can be used to image the local particle concentration. For fast spatial encoding, the FFP can be moved using homogeneous oscillating fields. It turns out, that sufficiently large drive field amplitude induces onedimensional motion of the FFP over the object enabling one-dimensional spatial encoding.

To encode three spatial coordinates, two additional orthogonal drive fields are necessary. If the respective drive frequencies differ only slightly, the FFP will follow a threedimensional Lissajous trajectory. Broadband acquisition of the signal generated by the changing particle magnetization under the influence of the FFP motion yields the MPI signal. The image is reconstructed from the information encoded in the higher harmonics and combinations of the three drive frequencies.

To establish the relation between frequency response and spatial position, a calibration scan with a dedicated voxel-sized reference sample has to be performed once for a given combination of scanner set up and tracer material. The "system function" acquired in this calibration scan is necessary for solving the inverse reconstruction problem [18].



The original MPI scanner setup [2, 3] combined one-dimension FFP motion as described above with orthogonal mechanical FFP movement to achieve two-dimensional spatial encoding. However, the mechanical spatial encoding scheme was far too slow to be useful for practical medical applications. A second drive field was introduced to overcome the speed limitations for two-dimensional imaging [7]. Real-time MPI with 25 frames per second was demonstrated in phantom experiments using a two-directional Lissajous FFP trajectory.

While these experiments required tracer concentration orders of magnitude higher than clinically applicable dosages, simulations [18] indicated that imaging with physiologically tolerable tracer dosages could be feasible. Despite these theoretical findings, agglomeration of the nanoparticles due to contact with tissue could not be excluded for *in-vivo* imaging. This would strongly degrade the MPI signal while leaving the MRI performance almost unchanged.

To realize the level of speed and sensitivity required for volumetric *in-vivo* imaging, several innovations and improvements had to be introduced into the scanner concept previously used for dynamic two-directional imaging.

## Methods

Figure 1 schematically shows the basic setup of the 3D scanner. The scanner has an effective bore of 32 mm. A pair of permanent magnets and a pair of coils produces the selection field gradient. The permanent magnets contribute  $3 T\mu_0^{-1}m^{-1}$  and the coils 2.5  $T\mu_0^{-1}m^{-1}$  to the

Figure 1. Schematic scanner setup. The mouse was inserted into the x drive/receive-coil cylinder using an animal support. The bore diameter is 32 mm. The selection field is generated by both the permanent magnets and the coil pair in z direction. The drive field coils can move the FFP in all three spatial coordinates. For signal reception, each spatial component of the magnetization is detected by a corresponding receive coil. In the x direction, the drive field coil is also used for signal reception.



Figure 2. Dynamic MPI images (left) fused with static MRI images (acquisition time 23 min) in orthogonal views at selected points in time. The MPI video acquisition (21.5 ms per volume) was started before injecting the tracer (Resovist<sup>®</sup>) into the tail vein. The colored triangle in the color frame indicates the position of the orthogonal slice in the image framed in the corresponding color. The position of the slices in the MRI volume is also given by the three numbers at the corners of the frames and is not always kept constant between the different images. The time axis on the right side describes the successive phases of the bolus passage. The spatial and temporal resolution enables resolution and identification of all heart chambers as well as parts of the vessel tree.

magnetic field gradient, respectively. This gradient strength is achieved in the vertical direction in the yellow-framed images in Figure 2.

The scanner uses three sets of drive field coils to enable three-dimensional imaging. The drive field  $H_D$  with amplitude 18m  $T\mu_0^{-1}$  in the vertical direction is produced by the selection field coils. The drive fields in the two orthogonal directions are produced by dedicated coils, which are driven at the same amplitude.

The three drive field frequencies are chosen to move the FFP along a three-dimensional Lissajous trajectory. Frequencies for the three directions are

- 2.5 MHz/ 99 ≈ 25.25 kHz,
- 2.5 MHz/ 96  $\approx$  26.04 kHz and

 $2.5 \text{ MHz}/102 \approx 24.51 \text{ kHz}$ , respectively. The Lissajous trajectory has a repetition time of 21.5 ms, corresponding to encoding 46.42 volumes per second, and covers a volume of about 20.4 x 12 x 16.8 mm.

The size of the gaps in the Lissajous pattern was chosen to match the desired resolution of approximately 1 mm. Two saddle-type receive coil pairs are aligned approximately perpendicular to the bore. In the axial direction, the solenoid drive field coil is also used for receiving the signal.

A new receive amplifier concept was implemented to reduce noise by a frequency dependent factor of between 5 and 100. In an ideal scanner, receive-chain noise is only generated by current fluctuations in the patient. In reality, coil noise and receive-amplifier noise contribute to the noise level. MRI achieves patient-dominated noise, because the small signal bandwidth allows mitigation of the amplifier noise contribution by resonant matching.

This strategy fails in MPI, since the receive signal is distributed over a wide frequency range. To provide the essential noise reduction, we designed a liquid cooled J-FET based amplifier reaching an input noise voltage of 80 pV/ $\sqrt{Hz}$  (input capacity 1 nF) over the relevant frequency band from 50 kHz to 1 MHz. In addition, the noise voltage of the receiving coils alone is 50 pV/ $\sqrt{Hz}$ so the total noise is about 100 pV/ $\sqrt{Hz}$ . In the present set up, the noise contribution of the mouse is negligible due to its small size and the associated low coil loading [19].

Before starting the animal experiments, the system was first calibrated to secure a functioning system. It was measured on a grid of  $34 \times 20 \times 28$  with a voxel size of  $(0.6 \text{ mm}^3)$  using a small reference sample of undiluted (500 m mol (Fe)/l) Resovist® (Bayer Schering Pharma, Berlin). To a certain degree, the chosen voxel size is arbitrary, however, it should be smaller than the true resolution. That is determined by particle properties, selection field gradient strength, and the level of regularization used in image reconstruction [18].

In other words, in MPI, voxel size is not equivalent to image resolution. The reference sample was in the form of a cube with the extensions exactly matching the voxel size of the grid. It was positioned and measured at all voxel positions of the grid. Positioning was performed using a robot (Flachbettanlage 1, Iselautomation KG, Eichenzell, Germany). The data acquisition time per grid point was 0.6 seconds. The total measurement time including robot motion and background measurement was about six hours.

# For reconstruction, the functional $\|\mathbf{G}\mathring{\mathbf{C}} - \mathring{\mathbf{U}}\|^2 + \lambda \|\mathring{\mathbf{C}}\|^2$

was minimized using a row relaxation method called algebraic reconstruction technique (ART) [20, 21]. Here, the matrix G represents the system function, U the measured mouse data, C the desired image, and  $\lambda$  a regularization parameter chosen to adjust the balance between signal-tonoise ratio (SNR) and resolution for best visual image impression. True image resolution depends on the regularization parameter and is usually lower than the voxel resolution.

The iterative reconstruction approach does not require the inversion or factorization of the huge 3D system function matrix and furthermore, allows for easy integration of reconstruction constraints into the iteration to account for *a priori* knowledge. This feature has been used to improve image quality by the exclusion of non-physical negative tracer concentrations in the image.

Image resolution and SNR are not completely homogeneous over the entire field of view (FOV) because of the physical constraint of having a different selection field gradient strength in at least one direction. In our case, the gradient in anterior-posterior (AP) direction (vertical direction in the yellow and green framed images in Figure 2) had twice the strength of the orthogonal gradients. In addition, the speed of the FFP motion is lower at the edges of the FOV, thereby stimulating only a weaker particle response. That leads to lower SNR and resolution in these regions, and a signal fade-out right at the rim.

The series of *in vivo* experiments comprised scans on 18 mice using different concentrations of Resovist<sup>®</sup> [8]. Ten of the experiments were conducted with dosages low enough for human usage. The approximate range being between the standard dosage of 8  $\mu$ mol (Fe)/kg Resovist used in MRI scans, and a dosage of 45  $\mu$ mol (Fe)/kg, which is slightly above the safe dosage of 40  $\mu$ mol (Fe)/kg for human applications [22].

Each mouse (female NMRI out bred mice, Charles River Laboratories, Sulzfeld, Germany) was anesthetized with 120 mg/kg ketamine and 16 mg/kg xylazine. An insulin syringe (BD Micro-Fine +, 0.5 ml) filled with 20  $\mu$ l diluted Resovist was introduced to the tail vein and attached to the tail. Resovist was diluted in physiological saline solution. To achieve a dosage of 45  $\mu$ mol (Fe)/kg, a 10% dilution was prepared for a 22.4 g mouse and to achieve a dosage of 10  $\mu$ mol (Fe)/kg, a 2.5% dilution was prepared for a 24.5 g mouse.

The mouse was then placed in supine position on a cylindrical animal support with an inner diameter of 29 mm so that the heart was within the FOV after insertion into the scanner bore. The raw data acquired after bolus injection were reconstructed to 1800 three-dimensional volumes.

To relate the MPI signal to the mouse anatomy, reference MR images of the selected mice were acquired after the MPI scans. The mice were carefully transferred from the MPI system to the dedicated MRI animal support to facilitate later image fusion. The MR scanner was a commercial 3.0T human whole-body scanner (Achieva, Philips Healthcare, the Netherlands) with a dedicated mouse coil insert for high SNR signal reception.

A standard T1-weighted turbo-spin-echo (TSE) sequence was applied to acquire sagittal multi-slice data. A FOV of 48 x 80 x 27 mm was covered with an in-plane resolution of 0.25 mm and a slice thickness of 0.50 mm. Total scan time amounted to 23 minutes.

After interpolating the MPI data to the MRI resolution, image overlays were made by manual rigid-body registration using three-dimensional translations according to different anatomical landmarks such as the vena cava and the heart chambers. In the overlay images, the MPI data are displayed using a color map with a color change from red to yellow to allow easy differentiation from the grayscale MRI data and to visualize a high dynamic range.

#### Results

From the 18 exams, two representative results have been selected for presentation.

In Figure 2, the dynamic MPI data are displayed and compared to the static MRI data obtained with a dosage of 45  $\mu$ mol (Fe)/kg Resovist. Due to the high temporal resolution, no triggering or gating was necessary to compensate for motion. In Figure 2a, the bolus enters the FOV via the vena cava. Due to the anisotropic gradient strength described above, the MPI resolution in AP direction is better than in the orthogonal directions. Ten of the 18 experiments were conducted with contrast dosages low enough for use in humans.

 The MPI scans were superimposed on MRI images.



#### ▲

Figure 3. Temporal dynamics of the tracer concentration at different locations in the vessel system for a dosage of 45 µmol (Fe)/kg Resovist<sup>®</sup>. After injecting into the tail vein, the magnetic particles first arrive in the vena cava, then in the right atrium and then the right ventricle. As expected, the contractions of the atrium and the ventricle are out of phase. The blood needs about 1.4 seconds to pass through the pulmonary circulation before it is observed in the left atrium and the left ventricle. The apparent modulation of the concentration in synchronicity with the heartbeat is a partial volume effect, due to the small size of the mouse heart and the limited resolution of the system. The contractions of the atrium and the ventricle are in phase. A heart rate of

240 beats per minute is derived from the periodicity of the contractions. The small crosses on the curve of the left ventricle illustrate the sampling points. Finally, a second pass and a third pass through the body with a respective delay of about 5.1 seconds produces the shallow concentration peaks as seen in the inset. The spatial distribution of the concentration at times

Thus, in left-right direction, the MPI signal is not completely confined to the vena cava visible in the MR image. In Figure 2b, the tracer just reaches the right atrium. It can be deduced that the vena cava crosses different sagittal slices to end up at the atrium. The right ventricle fills with tracer just after the right atrium. Figure 2c displays the tracer concentration three heartbeats later. The right ventricle is clearly visible from the MPI data and matches the MRI data.

Moreover, the pulmonary arteries can be identified in the transversal slice of the MPI data. The intensity around these arteries increases over time (see Figure 2d), which can be attributed to the filling of the pulmonary veins. The small vessels in the lung contribute to an average signal. After passing the lung cycle, the tracer reaches the left heart chambers. The left ventricle can be identified clearly in Figure 2e.

In the transversal (green) and sagittal (yellow) slice of the MPI data, the left and right ventricle can be distinguished. Selected slices presented in Figure 2 are also available online as a full video sequence at <u>http://stacks.iop.org/0031-9155/54/L1</u> showing the bolus passage.

To exploit the high temporal resolution of magnetic particle imaging, concentration dynamics at selected voxels (vena cava, right and left atrium, right and left ventricle) are presented in Figure 3. The bolus passage through the vena cava and the four heart chambers is reproduced by the time-shifted concentration maxima at the different positions. This supports the mapping of anatomical features presented in Figure 2.

From the time shift between the filling of the right and left heart-chambers, the pulmonary passage circulation time can be estimated to be about 1.4 seconds. An apparent modulation of the concentration can be observed at the heart chamber positions. The temporal onset, the modulation frequency and the opposite phase observed in the atria and the ventricles, show this corresponds to the heartbeat.

This can be attributed to a partial volume effect, due to the small size of the mouse heart and the limited resolution of the system. This creates an apparent concentration modulation, even when the real particle concentration within the heart chambers remains constant. The heart rate of the mouse can be determined from the apparent modulation to be about 240 beats per minute. That is low for a mouse, but can be expected for ketamine/xylazine anesthesia [23]. In addition, the concentration dynamics in the vena cava shows the second and third passage of the bolus, as displayed in the inset graph in Figure 3. The total time, which the tracer takes to pass through the whole circulatory system, is about 5.1 seconds.

The results of an experiment with a dosage of  $10 \mu mol$  (Fe)/kg are presented in Figure 4. All features discussed above can still be identified in these images, however with a higher artifact level than that observed for the 4.5 fold dosage.

#### Discussion

The MPI results presented here do not indicate a drop in tracer performance in the *in-vivo* situation. The data provide a spatial and temporal resolution sufficient for the identification of different structures in the beating mouse heart. For example, the left and right pulmonary arteries with a diameter of about 500 µm [24] can be observed, albeit not fully resolved, and are considerably smaller than the smallest coronary arteries usually treated in humans. While with better contrast agents, high resolution imaging with MPI is potentially feasible [18], it is difficult to assess the resolution achieved with the current agent in the *in-vivo* situation. As described above, resolution also depends on the level of regularization in the reconstructed image. From the comparison of the vena cava crosssection in the MR image and the MPI image, we estimate the achieved MPI resolution to be roughly 1.5 mm in AP direction and 3 mm in the orthogonal directions.

On the other hand, the vena cava is located close to the edge of the FOV, where, as described above, the resolution is reduced. At the center, we therefore expect a higher resolution of about 1 and 2 mm for the respective directions. A resolution on this order is also found in phantom experiments [7].

#### **Clinical potential**

In the following, we try to assess the performance that could be expected of a human whole-body MPI scanner.

Scaling the system for human applications would increase the patient noise contribution. SNR estimations would have to noise contributions from the patient as well as those from the coil and amplifier. We estimate that with single-loop receive coils, due to the different scaling of noise contributions with size [25], amplifier noise would be dominant. With similar technology to that used in this study, SNR in the human-size system would be at around 10% of that reported here.

However, other amplifier designs (parametric amplifier, SQUID-based amplifier), cryogenic cooling of silicon J-FET amplifiers, or modified tuning could lower the amplifier noise contribution to the level of the patient noise contribution.

To compare the mouse scanner with a hypothetical improved human-size system, we have to compare the respective ratio between coil sensitivity and noise voltage at a given bandwidth.

With the current system, noise voltage as stated above is about 100 pV/ $\sqrt{Hz}$ , while receive coil sensitivity at the isocenter is about 150  $\mu$ T/A (24-loop coil, split into two circular coils with mean diameter of 18 mm and coil separation 36 mm). In a patient-noise limited human-size scanner, as described in a previous simulation study [18], patient noise voltage would be 1.8 pV/ $\sqrt{Hz}$  (at 1 MHz) and coil sensitivities would be 1.4  $\mu$ T/A (single-loop rectangular receive coil (10 x 10 cm) at 10 cm depth).



Figure 4. Temporal dynamics of the tracer concentration at different locations in the vessel system for a dosage of 10 µmol (Fe)/kg Resovist®. Following injection into the tail vein, the magnetic particles first arrive in the vena cava, then in the right atrium and the right ventricle. As expected, the contractions of the atrium and the ventricle are out of phase. The blood needs about 1.2 seconds to pass through the pulmonary circulation, after which it is seen in the left atrium and the left ventricle. The contractions of the atrium and the ventricle are again out of phase, whereas the contractions of the left and right ventricle are in phase. A heart rate of 320 beats per minute is derived from the periodicity of the contractions.

If the same particle concentration is imaged at an identical resolution using a comparable scanning sequence, SNR scales proportional to this ratio, that is for the human-size system; the expected SNR would be 52% of the SNR found in the present system. Further room for improvement exists in the tracer material, the encoding sequences, and reconstruction algorithms, potentially summing up to a factor of more than 100 [2, 3, 26].

The selection field strength of 5.5 T $\mu_0^{-1}$ m<sup>-1</sup> can also be achieved over a large FOV. However, without expensive superconductors, only about 3 T $\mu_0^{-1}$ m<sup>-1</sup> might be feasible. Resolution with this selection field strength would probably be slightly too low for direct assessment of the diameters of the relevant human coronary arteries. But by using the ability to quantify particle concentration (and therefore indirectly, blood volume) and the dynamic information, it should be possible to detect stenosis. On the other hand, as described above, technical improvements still offer the potential for substantially higher resolution.

Regarding patient heating, the chosen combination of drive field amplitude and frequency may be feasible. Wust et al. [27] reported that at the fourfold frequency, an amplitude of about 10 mT is applicable to humans, corresponding to fourfold patient heating when compared with our parameters. Heating increases with the square of the frequency and the square of the drive field amplitude [19]. In the cited publication, Wust et al. [27] reported no peripheral nerve stimulation.

However, further research is required to find a drive field frequency, amplitude, and spatial distribution that would minimize the risk of stimulation. Moreover, for coronary imaging, the drive fields need to be applied for only a few seconds, allowing an increase in drive field frequency, improving the already excellent temporal resolution even further.

To cover the whole heart, an additional field similar to the drive field but at a lower frequency (less than 100 Hz) can be applied. This "focus field" can move the volume covered by the drive fields to any volume of interest. This patching method has the additional advantage that the encoding speed of the sub-volumes is unchanged, which minimizes motion artifacts within each sub-volume. From these considerations, we infer that a human scanner can be realized without significant loss in speed and resolution.

An additional potential for improving MPI can result from optimized FFP trajectories, more efficient reconstruction approaches, and improved tracer material. For the sake of technical simplicity, we used a Lissajous trajectory for the FFP motion. However, more sophisticated trajectories may be possible to improve the signal quality as discussed in [26]. Additionally, more *a priori* knowledge about the object can be used in the reconstruction to improve image quality and speed, as it is already done in MRI [5, 6] and CT [28].

The highest potential, however, can be found in the tracer material. As already shown [2, 3], the fraction of the magnetic particles contributing to the MPI signal in Resovist<sup>®</sup> is only a few percent. Thus, the applied concentration might be lowered by at least one order of magnitude, if an adequate separation technique can be found. New approaches for particle synthesis may even improve tracer response determined by the slope of the tracer magnetization curve, allowing for lower selection field strengths and an increased spatial coverage, therefore resulting in a higher imaging speed.

To conclude, this report showed that magnetic particle imaging could image a beating mouse heart with high temporal and spatial resolution, using a commercially available MRI tracer material at clinically tolerable dosages. The results show that as a new imaging modality, MPI is capable of *in-vivo* imaging and therefore has the potential to become a clinically adopted imaging modality.

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