REIVEW ARTICLE

Magnetic Particle Imaging and Its Application

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Received: 10 October 2020 / Accepted: 01 November 2020

Abstract

Magnetic particle imaging was introduced in 2005 as a new tomographic medical imaging modality and is still under development. Magnetic particle imaging determines the spatial distribution of magnetic nanoparticles by their interaction with an external excitation magnetic field. Therefore, there is no ionizing radiation dose in this trace-based modality. Magnetic nanoparticle imaging provides characteristics, including high spatial and temporal resolution, high sensitivity, expected from an ideal imaging method, and it is also an inherently quantitative method.

In this paper, the properties of magnetic fields and particles used in Magnetic particle imaging, as well as its applications are discussed.

Keywords: Magnetic Particle Imaging; Magnetic Nanoparticles; Superparamagnetic Iron Oxide Nanoparticles; Functional Imaging; Tomography.

DOI: https://doi.org/10.18502/fbt.v8i2.6518

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Tomography imaging has been an essential component of the diagnosis process of many diseases. Computer Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single-Photon Emission Tomography (SPECT) are the most common modalities in tomography imaging [1].

Tomography imaging can be categorized into two methods: feature-based and trace-based. In the first method, one feature of the tissue of interest is directly measured based on a given parameter. The feature determines the image contrast such as proton density in MRI or linear attenuation coefficient in CT. In the trace-based method, images are generated using distributions and/or concentrations of tracers in vivo. Recently, the trace-based method has been considered important in molecular and functional imaging and employed for cancer cell diagnosis [2–4].

In 2005, a completely new quantitative and trace-based molecular imaging modality called Magnetic Particle Imaging (MPI) was introduced [2]. MPI uses the nonlinear re-magnetization behavior of Magnetic Nano Particles (MNPs) as tracers to determine their local concentration. MPI relies on the response of MNPs to an alternating magnetic field [4, 5].

In MPI, the distribution of the MNPs is imaged. It means that selection of proper MNPs is crucial for generating an image [2, 4].

MPI has unique characteristics, including high spatial and temporal resolutions and high sensitivity. For instance, Arami *et al.* imaged a concentration of ~ 550 pgFe/μL (Signal Noise Ratio (SNR) = 4.9) and showed a high spatial resolution of less than 600μm [5]. More interestingly, the biological tissues are not able to generate or attenuate the low-frequency magnetic fields used in MPI, resulting in an ideal contract independent of the source depth [1, 6]. Furthermore, there is a linear correlation between signal intensity and nanoparticles' concentration [7, 8]. These characteristics along with the lack of using ionizing radiation make MPI suitable and safe even for long-term studies [9]. Nonetheless, morphologic data are not available in this modality [1, 4].

To compare MPI with other current modalities, Table 1 is provided. All tomographic imaging modalities have their own advantages and disadvantages. As an example, although CT and MRI have the best spatial resolution and contrast-resolution for soft tissue among the modalities, respectively, they have low sensitivity for molecular imaging and need a high dose of contrast media. In contrast, PET and SPECT have high sensitivity but limited spatial resolution. It is suggested to use two or more imaging modalities for better diagnosis [1, 2, 4]. Considering the above, MPI will be a promising modality for several clinical applications. In this article, the physics behind MPI and some of its applications have been reviewed.

1.1. Nanoparticle Tracers

MNPs used in MPI as tracers are Superparamagnetic Iron Oxide Nanoparticles (SPIONs) [5, 10]. In the presence of a stimulating magnetic field whose strength is increasing, SPIONs' magnetizations increase linearly and then non-linearly until they saturate in a magnetic field (H) with a given strength (Figure 1) [2]. By removing the stimulating magnetic field, the MNPs return to their relaxed state. Since there are no SPIONs in the living tissues, MPI scanners receive only signals from MNPs and the iron available in bodies does not interfere with the resulting signals [11].

Table 1. Comparison of the current imaging modalities

Characteristics	CT	MRI	PET	SPECT	MPI
Spatial Resolution	0.5 mm	1 mm	4 mm	10 mm	200 μm
Temporal Resolution	1 s	1 s - 1 h	1 min	1 min	46 frame/s
Sensitivity	Low	Low	High	High	High
Quantifiability	Yes	No	Yes	Yes	Yes
Harmfulness	X-ray	Heating	β/γ radiation	γ radiation	Heating

Due to the small size of SPIONs, a spatial map of their concentration is produced rather than the determination of their exact locations. Magnetic moment, m, is proportional to 3rd power of SPIONs' diameters. Hence, nanoparticles with smaller size need to be located in H with higher strength for saturation (Figure 1).

More interestingly, the SPIONs with larger size provide better spatial resolution, which is appropriate for MPI [12, 13]. However, there are some limitations. First, larger SPIONs have bigger relaxation time (Temperature and viscosity have also an impact on the relaxation time). In the presence of time-varying magnetic fields, their magnetizations align along the direction of the field with time lag. This time lag determined by the relaxation time results in residual effect for SPOINs [2]. It should be worth mentioning that the impact of the relaxation time is more significant when signal frequency of magnetic fields increases. Second, in some medical applications such as the study of lymph nodes, MNPs need to be small for penetration in them [6].

Long term tracking of the tracers in living organs such as mice is possible in MPI due to its quantitativity [7, 8]; however, the used nanoprobes should have high blood circulation half time [2, 5]. This capability is not available for PET and SPECT because of the short half-life of radionuclides. It is worth mentioning that in preclinical and clinical studies, the used nanoprobes need to have high blood circulation time as well as high uptake in the tissue of interest. In addition, for long-term tracking, the core size of the tracer should be appropriate. The best diameter for the core is suggested to be 30nm [10]. Yet, the selection of the size of nanoparticle for MPI, in addition to considering the spatial resolution it provides, also depends on the intended application.

1.2. Signal Generation and Acquisition

For image generation in MPI, there are two essential requirements: recording of signals generated by SPIONs and allocation of spatial dimension to each signal. For SPIONs' excitation, receiving the signal and spatial encoding, static and time-varying magnetic fields are employed. Each signal includes information about the presence and concentration value of the SPIONs in a tissue of interest. In the end, a spatial map of SPIONs' concentration is produced. Three magnetic fields are needed to meet the requirements: H^E, H^S, and H^D [14, 15].

Excitation magnetic field, H^E, is a time-varying field used to excite the MNPs. By exerting H^E, SPIONs' magnetic moments start to line up towards H^E. Hence, their magnetizations (M) are being changed with time until all Ms are lined up with H^E, which is called total saturation magnetization. A region in which the tracers' magnetization increases is called the dynamic region. After saturation, the region is called the saturation region (Figure 1) [14, 15].

H^E and tracers' magnetization generate an induced signal because of a magnetic flux density, B, in receiving coils. By measuring B, SPIONs' magnetization and, subsequently their concentration can be obtained. To distinguish between SPIONs' and H^E's signals in the Fourier space, it is suggested that H^E had better be sinus shaped with high amplitude. This selection also removes the need for high homogeneity of the magnetic field seen in MRI [2].

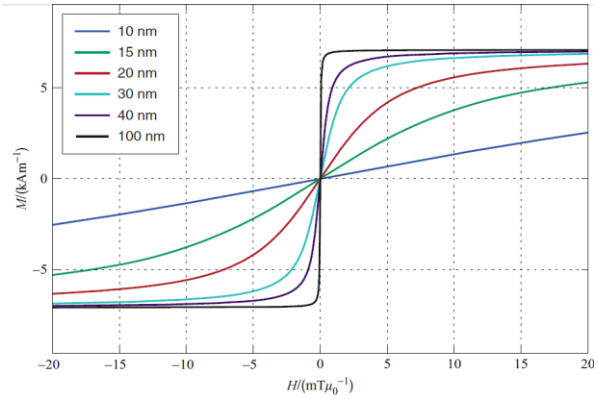

Figure 1. The SPIONs'magnetization as a function of magnetic field (H) and different diameters (D) in a given iron concentration [4]

It should be noted that with the increase of the tracers' diameter, the slope of the M curve increases. As a result, the M curve over time resembles a step function. In this situation, the Full Width at Half Maximum (FWHM)s of the tracers' signal decreases, and consequently, the spatial resolution increases. The amplitude of each harmonic is proportional to the tracers' concentration. Appropriate amplitude of H^E is about $20mT/\mu_0$.

Figure 2 depicts the generation of an induced signal and its Fourier transform.

It should be mentioned that due to SPIONs' interactions with H^E, the tracers are directly detected in contrast to the indirect detection of SPIONs as contrast agents in MRI because of the relaxation time of T2.

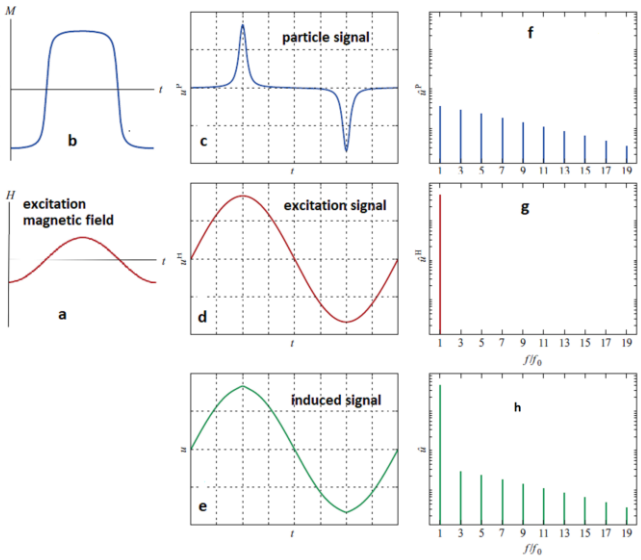

Figure 2. Signal generation in MPI. a) the magnetic nanoparticles are excited by the sinusoidal excitation field (H^E) b) the magnetization curve of the magnetic nanoparticles resembles rectangular over time in the presence of H^E c) the tracer's signal has two sharp peaks after excitation in the receive coil d) the excitation signal in the receive coil, which is distinguishable from the tracer's signal e) the induced signal received by receive coils, which is the combination of the tracer's signal and the excitation signal f) the Fourier transform of the tracer's signal in logarithmic scale g) the Fourier transform of H^E in logarithmic scale h) the Fourier transform of the induced signal in logarithmic scale, indicating the better separation of the two signals [4]

As a result, SPIONs have a positive contrast in MPI. Besides, the tracers' generated signal is several million-fold more than water's generated signal in MRI, which can be concluded that MPI has high sensitivity (ng/ µl of Fe) and [9] quantitativity [7].

A selection magnetic field, H^S, is used for spatial encoding of the induced signal. Two strong magnets produce a magnetic field with the strength of zero called a Field-Free Region (FFR) at the center and strong field elsewhere. Given a scanner type, FFR may be a Field-Free Point (FFP) or Field-Free Line (FFL) (Figure 3). FFP is generated by an HS gradient with a strength of approximately between 3-7 $Tm^{-1}\mu_0^{-1}$ [4, 16].

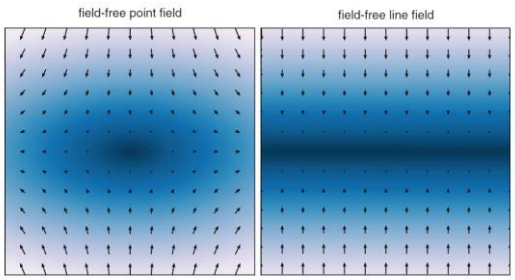

Figure 3. Schematic diagram of the selection gradient field for an MPI scanner based on a) FFP b) FFL. The dark blue and white colors represent the gradient field with zero strength and the maximum strength, respectively [4]

Due to H^S, the tracers' magnetization outside FFP is saturated. The SPIONs can be affected by HE exactly in or in the close vicinity of FFP. Their magnetization changes and signals are produced. Therefore, there is a direct association between the location of FFP and the received signal, which makes the spatial encoding of the tracers possible [2, 4, 14].

Drive magnetic field, H^D, is employed to move FFP over the whole Field Of View (FOV). H^D is a time-varying magnetic field, which could be either a separate magnetic field or the same H^E with high enough amplitude. However, a limitation of moving FFP by H^D is that an FOV of around 1cm could be covered. To eliminate this, a focus magnetic field with a strength of 300 $mT\mu_0^{-1}$ for covering large volumes is introduced so that the whole volume is imaged in a reasonable time [2, 4, 14].

1.3. MPI Applications

MPI offers great potential in a wide range of clinical applications either diagnosis or image-guided therapy, including cancer diagnosis, cardiovascular imaging, sentinel lymph node imaging, gastrointestinal imaging, lung perfusion imaging, infection disease, nanomedicine, stem cell therapy, cell implantation, theranostics, brain injury detection, inflammation, and hyperthermia. Furthermore,

specific ligands can be labeled with SPIONs for targeted imaging as well as chemotherapeutic drugs for targeted therapy [1, 11].

MPI is a very promising method for brain imaging. Graeser *et al.* presented an MPI system with a bore size of 19cm to 25cm fitting an adult's head. The system has a high temporal resolution of 2 frames/s and provided a spatial resolution in the order of 6 mm within the xy-plane as well as and 28 mm in z direction, at high iron concentrations (4.2 mgFe total) and below 1cm spatial resolution at an iron dose of 125µgFe, which would be sufficient for the detection of stroke and cerebral hemorrhage. It was possible to detect the sample without artifacts starting from 512µgFe down to 8µgFe. For 2µgFe (14.7 ng of Fe/ml) several artifacts appeared, but the movement of the tracer was still visible [9].

The other application is the monitoring of bleeding in Traumatic Brain Injury (TBI), which is a common incident in humans and various animals. Orendorff *et al.* investigated the animal model of TBI using MPI. MPI images indicated the infiltration of SPIONs from blood pools to the interstitial space. Moreover, the clearance through lymphatic nodes was evident, which gives hope for using MPI to determine site severity and bleeding depth from a closed skull without considering targeted brain regions and behavioral manifestation of injury [17].

The image-guided treatment causes a precise remedy in the region of interest with minimal side effects on the surrounding tissues [11]. MPI can be used with Magnetic Hyperthermia as a new theranostic method. The conventional magnetic hyperthermia SPIONs, even the targeted SPIONs, may accumulate in off-target organs such as the liver and spleen, subsequently the generated heat in these tissues may sometimes be more than the targeted tissue. Hence, the off-target organs were damaged due to the challenge of localizing hyperthermia [18, 19].

This challenge has been resolved in MPI-hyperthermia using FFR. The SPIONs are saturated by strong magnetic gradients except those within the FFR. The rotation of the magnetic moment generates heating. The heating spot size is linearly correlated with the gradient strength [19].

Tay *et al.* achieved a 7mm spatio-thermal resolution with a 2.35 T/m MPI gradient. They used different frequencies, 20 kHz for imaging-MPI and 354 kHz for hyperthermia-MPI. The higher frequency caused faster rotation of magnetic moments of SPIONs; therefore, the transition of the energy to surroundings would increase. Notably, the same SPIONs could be used for imaging or hyperthermia. When the MPI gradients were turned off and the entire volume was excited at 354 kHz, indiscriminate heating occurred at all locations with SPIONs [18]. The heating mode of the MPI-magnetic hyperthermia system generated heat with temperature > 10°C over the same time of the MPI scan. The tumor and liver reached 43°C in temperature in only 12 minutes. They used a dual tumor mouse to demonstrate arbitrary control of the heating location. With guidance from the initial MPI image, the treatment planning could design a "heating trajectory" for the FFL or FFP and therefore, spared healthy organs such as the liver from collateral damage.

Cell tracking is an integral part of cell transplantation and stem cell therapy efficacy. However, common methods such as histology take months to evaluate the efficacy. There are several preclinical and clinical imaging modalities which have been applied to track cells in vivo [16].

Bioluminescence and fluorescence imaging is the most common preclinical imaging for cell tracking but suffers from limited penetration depth due to its optical inherent. The other modality is radionuclide imaging such as SPECT and PET. Although it enjoys excellent sensitivity and depth penetration, it suffers from the short half-life of radionuclides and radiation dose [16].

MRI is clinically employed for cell tracking using SPIONs as tracers. In contrast to its excellent depth penetration and resolution, MRI is not able to distinguish between low-intensity signals from tissues such as bone or lung and those of the tracer caused by void [12].

To evaluate MPI for cell tracking in cell implantation, Zheng *et al.* built two animal FFL MPI scanners and then implanted SPIO-tagged human Embryonic Stem Cell (hESC)-derived Neural Progenitor Cells (NPCs) in rats which have been tracked over three months [16]. The results showed that the tagged cells have approximately constant signal in the mentioned period. Besides, the tracers which have not been tagged had rapid clearance. The

findings were in vitro confirmed by histology and MRI, proposing that MPI is a reliable modality for long term tracking in cell implantation.

Stem cell therapy, in particular Mesenchymal Stem Cell (MSC) based therapy, is a potential treatment for diseases such as myocardial infarction, traumatic brain injury, and cancer. Yet, tracking the fate of these injected cells is still an open issue [7].

Zheng *et al.* used MPI for tracking and quantifying the administrations of Human Mesenchymal Stem Cell (hMSC) and SPION tracers in animal models. They stated that MPI-CT imaging managed to show the in vivo biodistribution of the SPION with high contrast, quantitative accuracy, and sensitivity. The half-life of the SPIONs' clearance was reported to be 4.6 days after injection. They concluded that MPI was a potential modality for monitoring stem cell delivery and localization longitudinally [7].

Despite the advantages of cell tracking techniques, there are challenges for using these techniques including MPI. The first challenge is the quantification of highly proliferative or apoptotic cells losing their tracer. Applying differentiated cell models for clinical cell tracking is suggested to solve the problem. The other challenge is the determination of the cell viability in vivo. The tracer in dead cells may create false positives in image contrast. The use of relaxation and aggregation-based SPION contrast mechanisms in color-contrast MPI was proposed for the solution.

Finally, the MPI intensity signal decreased over time in vivo due to biological iron clearance. Therefore, there should be adopted strategies to design magnetic nanoparticles with long biological clearance time since the available SPIONs such as Vivotrax and Resovist are essentially designed for MRI.

In this regard, Song *et al.* synthesized Janus nanoparticle Fe_3O_4@PFODBT-COOH for long term cell tracking in MPI and fluorescence imaging [12]. In this study, HeLa cells were labeled with Janus nanoparticles. Then, they were implanted into mice. Their findings indicated that MPI signals were highly correlated with the particles' crystalline structure as well as sizes. The signal of the synthesized nanoparticles was 3 and 7 fold greater than that of Vivotrax and Feraheme at the same concentration of Fe, respectively. Furthermore, the Jonus particles had a sensitivity as low as 250 cells in vivo without depth limitation. Figure 4 demonstrated the linearity of the MPI signal to Fe concentration, which makes the MPI an accurate quantifiable modality for cell tracking.

Wang *et al.* also created new nanoparticles called Cubic Iron Oxide Nanoparticles (CIONs) for long term cell tracking [13]. CIONs had smaller surface anisotropies and less disordered magnetization, resulting in monodisperse CIONs with large magnetization and high magnetic susceptibility. The CIONs were synthesized in three sizes, i.e., 17, 22, and 26 nm in diameter. Different tests on CIONs showed that CIONs had a better performance compared to the other probes either in vivo or in vitro. It was biocompatible without any evidence of cytotoxicity even at high concentrations.

The use of drug-loaded MNPs along with MPI would enable tracking the biodistribution of the drug. Similar to the problems described for other imaging modality in cell tracking, it seems the imaging modality, including optical imaging, photoacoustic imaging, and MRI are not proper modalities for monitoring. Also, MRI is not linearly quantitative and intrinsic/background signals can convolute drug distribution signals, making it generally unsuitable for quantitative clinical measures of drug release. MPI is likely an ideal imaging modality to monitor drug release due to its explained features.

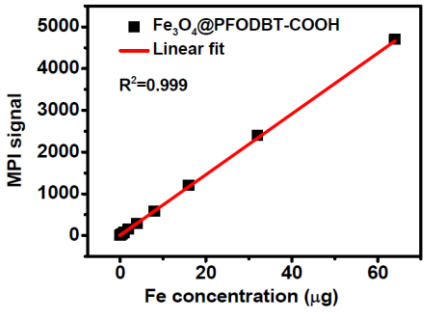

Figure 4. Linear correlation between MPI signal and Fe concentration (R^2=0.999). This correlation offers the exact quantification of the tracer [12]

2. Conclusion

MPI is a great promise for medical applications. MPI has an ideal contrast, zero tissue depth signal attenuation, real-time imaging capability, linearly quantifiable signal, high sensitivity, and high spatial and temporal resolutions. It has great successes in preclinical applications and provides a lot of hope for its use in clinics.

To facilitate the application of MPI in clinical settings, technical developments, and synthesis of highly biocompatible SPIONs should be well considered. By overcoming these, it is possible to monitor tracers' biodistribution and uptake in different parts of the body, which gives us an indication of the functional performance of the body with high temporal and spatial resolutions and without harmful radiation for long-term periods. For instance, the dynamic experiments in Graeser *et al.* study show that it is possible to derive brain perfusion parameters like Time To Peak (TTP), Mean Transit Time (MTT), relative Cerebral Blood Volume (rCBV), and regional Cerebral Blood Flow (rCBF), which are all very useful for the diagnosis of different brain diseases [9].

In MPI, the signals generated by different MNPs in different environments could be separated into different colored images, generating multi-color MPI. Distinguishing targeted MNPs bound to a lesion from those suspended in the blood is one of the numerous applications of multi-color MPI [20]. Furthermore, MPI provides detailed information of the body in combination with other modalities.

So far, MPI has emerged as a powerful imaging modality in preclinical studies. Due to its trace-based method, several investigators have been studying this modality for either synthesis of SPIONs for different applications or the development of scanners and access to clinical scanners through magnetic fields or image reconstruction methods.

Acknowledgements

This article was orally presented in the third TPCF preclinical imaging symposium.

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