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Magnetic signal evaluation and imaging of magnetic nanoparticles in and ex vivo mouse brain specimen

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Abstract

Magnetic Particle Imaging (MPI) is an imaging modality that directly detects the nonlinear response of magnetic nanoparticles (MNPs). Spatial encoding is realized by saturating the magnetic moment of MNPs most everywhere except in the special point called the field free reagion in which magnetic field vanishes. Recently, it has been shown that the sensitivity of MPI can be improved by using a field free line (FFL) in which the field free region formed as a line. We developed a MPI equipmemt with FFL using a neodymium magnet and an iron yoke, and magnetic particle imaging of a *ex vivo* mouse brain specimen was successfully performed. In addition, we studied the magnetization response of MNPs in the brain and found that the magnetic response of magnetic moment to external magnetic field in the brain is different from that in buffer solution.

I. Introduction

Magnetic particle imaging (MPI) is an attractive imaging modality to detect disease by injecting magnetic nanoparticles (MNPs) with superparamagnetism into the body as tracers and acquiring AC magnetization signals of MNPs[1]. MPI would be one of future alternatives to Positron Emission Tomography (PET) because MPI can provide a non-invasive functional diagnostic imaging which does not need radioactive tracers. Functional imaging is expected to be used not only for the diagnosis, but also for the study on drug dynamics in biological systems. There would be a lot of opportunities for MPI. In recent years, in order to launch commercial MPI product as a functional image diagnostic, dynamic characteristics of MNPs in biological system has been intensively studied, such as AC magnetization characteristics of MNPs in biological solution[2].

We have been working both on developing MPI equipment and on functional MNPs which are specifically attached to pathological target. The functional imaging on neurological disease such as Alzheimer's disease are currently demanded, and thus MNPs as amyloid-beta tracer are our current development target. It is well known that the blood-brain barrier (BBB) makes it difficult for MNPs to go into the brain via intravenous injection. We thus plan to apply a transnasal administration method instead of an intravenous injection. However, a transnasal administraion is also difficult to realize a high transfer

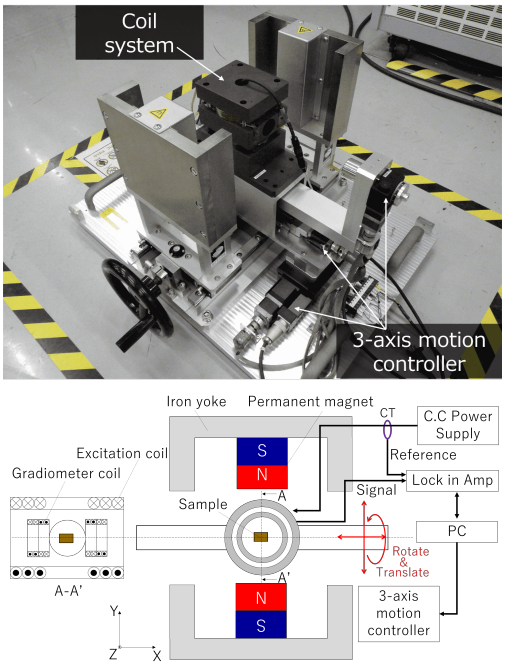

Figure 1: Overview (top) and system diagram of the MPI and equipment (bottom)

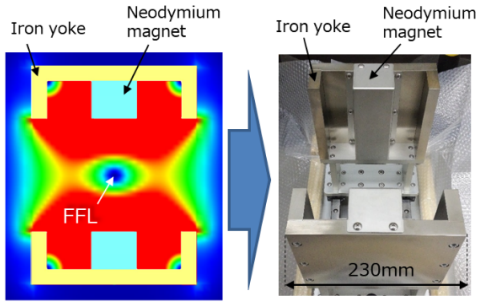

Figure 2: Magnetic field analysis for FFL.

rate of MNPs into the brain, and the detection of magnetic signal from a small amount of MNPs is necessary. In this paper, we overview of the MPI equipment and compare the magnetization response of MNPs in brain phantom and that in buffer solution using the developed MPI equipment. Details on imaging methods for mouse brain are also discussed.

II. Material and methods

The MPI equipment consists of a gradient magnetic field source (permanent magnet system) that generates a static magnetic field region with Field Free Line (FFL), and an excitation coil that applies AC magnetic fields. When MNPs exist on FFL, the magnetization of the MNPs fluctuates due to the applied AC magnetic field. As a result, the receiving coil can detect the magnetic signal as a voltage. When MNPs exist in a none-zero statical magnetic field, the magnetization of the MNPs can be saturated, and the magnetic signal can not be detected. Using this scheme, a static magnetic field region with a zero magnetic field can be scanned, and the three-dimensional distribution as an imaging of MNPs can be acquired [1]. The signal from the MNPs is not only the fundamental wave of the applied alternating magnetic field, but also a harmonic signal of odd order with the nonlinearity of the magnetic susceptibility curve [3]. The magnitude of the applied AC magnetic field is several tens of mT, while the detected magnetization signal is the magnetic field strength at the pT level. In order to separate the magnetic signals from MNPs and those from the excitation AC magnetic field, synchronous detection using a lock-in amplifier is utilized [4].

Fig. 1 shows an overview and a system diagram of the MPI equipment used in this study. Generally, FFL method has a wider signal acquisition area and then higher detected signal than the field-free point (FFP) method which forms a point-like zero magnetic field region. On the other hand, we aim at the imaging of objects with small amount of MNPs because it is usually difficult to inject MNPs into brain as mentioned above. Therefore, the FFL method is appropriate to our objectives. In this system, a field-free line (FFL) is formed by a pair of neodymium magnets and U-shaped iron yokes (Fig. 2). A coil system consists of an excitation coil and a receiving coil, and a target sample is simultaneously translated and rotated. Accordingly, we scan a target sample to obtain projection data and reconstruct a cross-sectional image. The gradient of magnetic field is able to be continuously controlled from 1 T/m to 4 T/m by changing the distance between a pair of opposing neodymium magnets. A lock-in amplifier is used to calculate the phase difference of the measured magnetic signal by referring to the background signal applied by the excitation coil. Since the information on phase difference is determined by the time constant of the measurement instrument and the relaxation time of MNPs, the phase difference can be utilized for discriminating noise and evaluation on relaxation time change of MNPs.

The magnetic signal in MPI generally increases as the frequency of the AC magnetic field increases. Switched-mode power supply would be needed to realize high-frequency excitation, but noise due to the switching of the semiconductor devices occurs. Noise in the high frequency band lowers the signal-noise ratio (SNR) when it superimposed on the harmonic signal of the MPI system. Therefore, the excitation frequency of our MPI equipment is designed to below 1 kHz to realize low noise and then high SNR.

In order to study the imaging performance at a low frequency, we performed imaging at an low excitation frequency of 500 Hz (AC magnetic field strength: 30 mTp-

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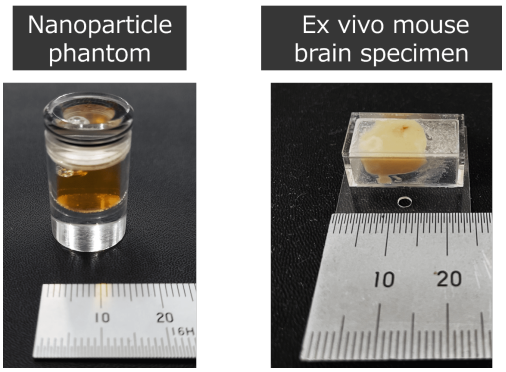

Figure 3: Photographs of phantoms: nanoparticle phantom (left), *ex vivo* mouse brain specimen (right)

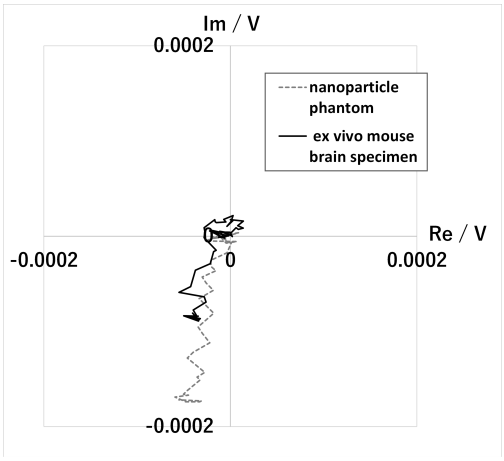

Figure 4: Lissajous curves using absolute value of 3rd harmonic signal.

p). MNPs which we prepare for this evaluation would have highly sensitive response to magnetic field because they were magnetically collected from Ferucarbotoran (Meito Sangyo Co., Ltd.) by simple magnetic separation method using permanent magnets, which is called as Ferucarbotran_Magnetic (FcM). Note here that when MNPs exist in environments with different salt concentrations, the aggregation level of the MNPs changes, and then the signal intensity and relaxation time in the magnetization response changes [5]. We prepared a biological phantom – *ex vivo* mouse brain specimen in which FcM was directly administered to one location in the fresh mouse brain (approximately 400 µL). The total amount of iron content of this phantom was set to be 55.6 µg. For comparison, a nanoparticle phantom was also prepared by dilution of FcM with pure water so that 400 µL solution contained 77 µg of MNPs whose iron content is similar to *ex vivo* mouse brain specimen. The phantoms used for the evaluation are shown in Fig. 3.

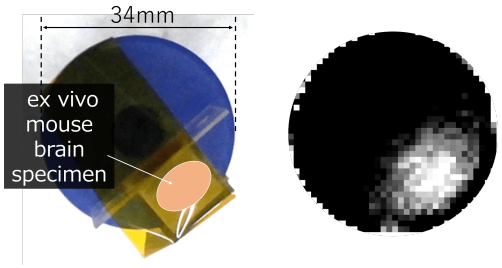

Figure 5: Imaging result using absolute value of 3rd harmonic signal: sample of *ex vivo* mouse brain specimen (left), reconstructed image of *ex vivo* mouse brain specimen (right)

Table 1: Result of 3rd harmonic signal amplitude and phase.

	Amplitude (V)	Phase (degree)
Nanoparticle phantom	0.00017	259
Ex vivo mouse brain specimen	0.00009	249

III. Results and discussion

The result of 3rd harmonic signal amplitude and phase from MPI obtained by scanning the *ex vivo* mouse brain specimen and nanoparticle phantom in the X-axis direction are presented in Table 1.The Lissajous curves using absolute value of 3rd harmonic signal are shown in Fig. 4. The phase of the magnetic signals from the *ex vivo* mouse brain specimen and the nanoparticle phantom is different. This would mean that the magnetic response (like relaxation time) is changed when it administered to brain even in the low frequency below 1kHz. It would be a consequence from the change in the aggregation level of MNPs caused by salt concentration. Accordingly, we assume that when MNPs were administered to brain *in vivo*, there is a possibility that the magnetic response of MNPs is totally different from that in vitro, and it would affect the imaging quality. Fig. 5 shows the results of image reconstruction of the *ex vivo* mouse brain specimen. The entire *ex vivo* mouse brain specimen was imaged in white because the magnetic nanoparticles spread throughout the brain after administration. We successfully performed the *ex vivo* mouse brain specimen imaging with a small amount of MNPs injection even at a low excitation frequency of 500 Hz.

IV. Conclusions

In this study, we demonstrate the magnetic particle imaging with developed MPI equipment at low excitation frequency of 1 kHz or less in order to avoid the superposition of noise in the high-frequency band generated by power supply. We compare the phase of magnetic signal

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for two types phantoms. One is the *ex vivo* mouse brain specimen, in which FcM was directly administered to the mouse brain. The other is a nanoparticle phantom, in which FcM was just diluted with pure water. Magnetic signals of MNPs were evaluated at an low excitation frequency of 500 Hz. We found the difference in the magnetic response of MNPs to AC magnetic field between the *ex vivo* mouse brain specimen and the the nanoparticle phantom even in the low frequency. We thus assume that the aggregation level of MNPs would be different between *ex vivo* mouse brain specimen and nanoparticle phantom, which would be a consequence of the difference in salt conentration.

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Author's statement

Conflict of interest: Authors state no conflict of interest. Informed content: Informed content has been observed from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors ' institutional review board or equivalent committee.

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