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High-T_c SQUID Array for Detection of Moving Magnetic Particles in Magnetic Drug Delivery System

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Abstract. Magnetic particles have high reaction rate due to the large surface area per volume, and can give materials, which are combined with the magnetic particles, the abilities to separate, transport, and concentrate through magnetism. Magnetic drug delivery system (MDDS) is one of the applications of the magnetic particles, in which drug combined with magnetic particles is injected in blood vessel and the drug is delivered to affected area by means of magnetic induction effectively. In this study, we developed a sensitive high-T_c (HTS-) SQUID array system to measure the distribution of the magnetic field from moving magnetic particles to localize and quantify the magnetic particles noninvasively for practical use of MDDS. Using this system, we measured the magnetic field distribution from magnetic particles flowing in a silicon tube, which imitated blood vessel, and showed that the information of three-dimensional position and quantity of the moving particles could be estimated. We demonstrated the visualization of the trace of magnetic particles flowing in a branch silicon tube by making iso-field contour maps of the magnetic field from the moving magnetic particles.

Keywords: High-T_c SQUID Array; Magnetic Particle; Magnetic Drug Delivery System; Visualization

1. Introduction

Magnetic nanoparticles (MNPs) attract attention recently, since MNPs have high reaction rate due to the large surface area per volume, and can give materials combined with MNPs the abilities to separate, transport, and concentrate through magnetism [Hafeli et al., 1997, Pankhurst et al., 2003]. As one of the medical applications of such MNPs, magnetic drug delivery system (MDDS) has been investigated, in which drug combined with MNPs is injected in blood vessel and the drug in the blood flow is delivered to affected area by means of magnetic induction effectively using magnets outside of body [Mishima et al., 2006]. At present, arrival of drug with MNPs to affected area is confirmed in animal experiment by dissection of the test animal and observation of the MNPs in organs or extracted blood. However, to establish MDDS technology, the position and quantity of drug with MNPs in body must be detected non-invasively from the outside. So far, it is difficult to detect the drug or the MNPs, which flow in blood vessel at high speed (up to 500 mm/s in main artery), by the conventional technologies such as ultrasonic testing and magnetic resonance imaging (MRI) due to the lack of sensitivity and time resolution. Thus, in this research, we propose a new method to detect moving MNPs in blood vessel magnetically using high-T_c superconducting (HTS-) SQUIDs with high magnetic sensitivity and time resolution. We constructed a MNP detection system using 3-channel HTS-SQUID array to measure the distribution of the magnetic field from moving MNP in a silicon tube, and demonstrated that the three-dimensional (3D) position and the quantity of the MNP can be estimated from the distribution. We also demonstrated the visualization of the trace of MNPs flowing in a branch silicon tube by making iso-field contour maps of the magnetic field from the moving magnetic particles.

2. Three-channel HTS-SQUID Array System

This section describes the constructed MNP detection system using 3-channel HTS-SQUID array.

2.1. Three-channel HTS-SQUID array

A three-channel HTS-SQUID array was designed as shown in Fig. 1 (a), and fabricated in our laboratory [Hatsukade et al., 2009]. A bicrystal $SrTiO_3$ substrate with the size of 10 mm x 10 mm and mis-orientation angle of 30 degrees was used. A 200-nm-thick $YBa_2Cu_3O_{7-x}$ thin film was deposited on the substrate using sputtering technology and patterned using photolithography and ion-milling. The SQUID array consists of three directly-coupled HTS-dc-SQUID magnetometers, whose outer dimension is 1.5 mm x 1.5 mm. These magnetometers align on the bicrystal line with the separation distance of 2.5 mm between device centers. We mounted it on the top of a sapphire rod in a FRP cryostat constructed for multi-channel HTS-SQUID measurement, in which a liquid nitrogen was stored in a copper tank, where the sapphire rod was installed, to cool the SQUID array by means of heat conduction at about 77 K [Tanaka et al., 2007]. The characteristics and the noise levels of the SQUID array were measured in our magnetically shielded room (MSR) using flux locked loop operation. The SQUIDs have approximately identical characteristics. The averaged V_{pp}, flux and field sensitivities of the SQUID magnetometers in the white-noise region was about 15.5 μV, 15 $\mu\phi_0/Hz^{1/2}$ and 650 $fT/Hz^{1/2}$, respectively. The field sensitivities of the 3-channnel SQUID array are shown in Fig. 1 (b). Using 500-μm-thick sapphire window, the minimum distance between the SQUID array and room temperature is about 1 mm. In this study, the SQUIDs were set to measure the vertical component B_z.

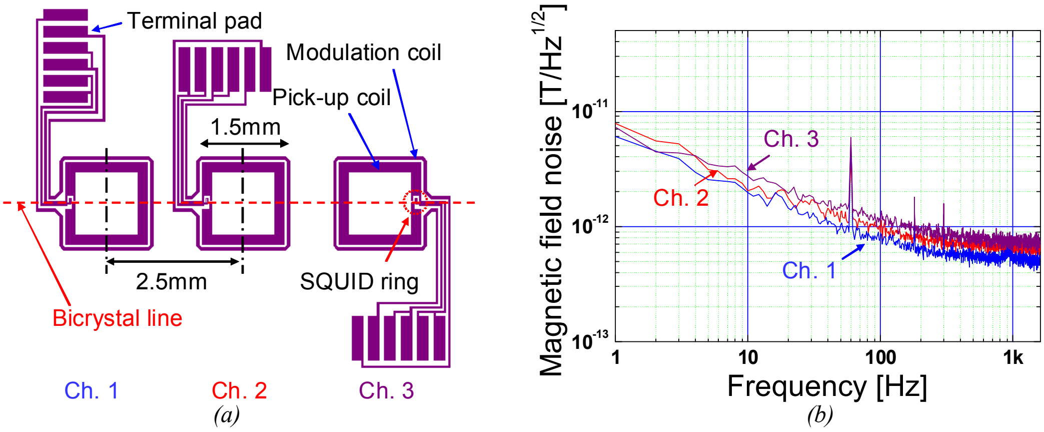

Figure 1. *Three-channel directly-coupled HTS-dc-SQUID array. (a) Design. (b)Field noise spectra of the array.*

2.2. Measurement System

The three-channel HTS-SQUID system for detection of moving MNPs is schematically shown in Fig. 2. The system consists of the 3-channel HTS-SQUID array in the cryostat, a multi-channel SQUID electronics, rectangular Helmholtz-type excitation coil, a silicon tube, a motor, a function generator, a multi-channel data logger and a note personal computer (PC). The cryostat was set in the MSR. MNP sample in solution was put in the silicon tube, and moved by means of the electric motor or syringe at velocity of 5 - 10 mm/s. The rectangular Helmholtz-type excitation coil, which was set around the SQUID array, was used to apply a uniform field to MNP sample moving above the SQUID array to magnetize them in the *x*-direction (See the inset of Fig. 2). The center axis of the excitation coil was set to be perpendicular to the line of the SQUID array. The position of the excitation coil was carefully adjusted so that the leakage of the excitation flux that coupled to each SQUID became the minimum. The function generator supplies a DC current to the coil to generate an excitation field. The SQUID output data are stored in the PC through the data logger.

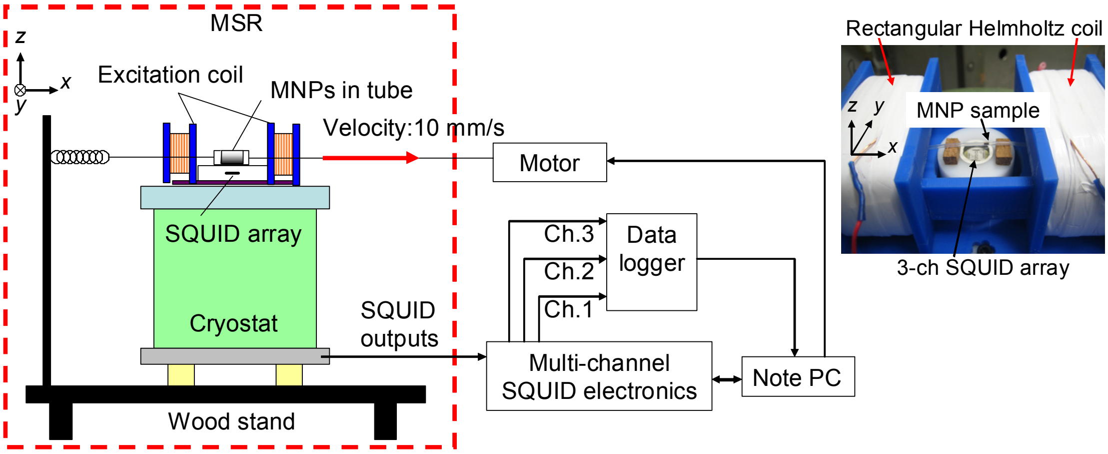

Figure 2. *MNP detection system using 3-channel HTS SQUID array in MSR..The inset in the right-hand shows a bird's-eye view of the cryostat that includes the SQUID array, excitation coil, and MNP sample in tube.*

3. Experiments and Results

In this study, we used commercial MNPs, which were composed of superparamagnetic Fe_3O_4 cores with averaged diameter of 15 nm and dextran coating with total averaged diameter of 45 nm. These particles were brought in a solution. This section describes three different detections of the MNP solution using the 3-channel HTS-SQUID array system.

3.1. Detection of 2D Position of MNPs Moving in XY-plane

In the first experiment, the MNPs of 1 μg in solution of 3 μl was pulled in a silicon tube with inner diameter of 1mm, and then moved in the *x*-direction at 10 mm/s above the SQUID array, which aligned in the *y*-direction, while applying a DC magnetic field of 0.3 mT in the *x*-direction. The lift-off distance between the array and the MNP solution was about 2.5mm. The magnetic field above the SQUID array was measured while moving the solution just above the 1st channel of the SQUID array (Ch.1) as shown in Fig. 3. The inset shows the path of the solution. As shown in the figure, each SQUID detected a pair of magnetic signal peaks from the MNPs. Since the distance between the solution and 1st channel SQUID was the nearest, the signal detected by the 1st channel was the largest. We found that signal amplitude at each channel was inverse-proportional not to the cubic, but to the square of the distance between each SQUID and the MNP solution. Signal amplitude from a magnetic dipole is inverse-proportional to the cubic of the distance r between a point and the dipole, i.e. the amplitude is proportional to $1/r^3$. In the experiment, the solution had a length of about 5 mm, which is larger than the lift-off. Therefore, the solution should be approximated not to a magnetic dipole, but to a set of dipoles. This is because the signal amplitude was inverse-proportional to the square of the distance r.

On the other hand, when the same solution was moved in the minus *y*-direction above the SQUID array in the same magnetic field, each SQUID detected the magnetic signal peaks in turn, starting from the 1st channel to the 3rd channel, with a time interval of 0.25 ms. The interval corresponds to the distance 2.5 mm between each SQUID. These results imply that the SQUID array can detect the 2D position and the moving speed of the MNP solution in the *x*-*y* plane.

3.2. Detection of Distance between SQUID Array and MNPs

In the next experiment, the same MNP solution was moved in the *x*-direction and measured in the same way as the first experiment, while changing the lift-off distance between the SQUID array and the solution from 2.5 mm to 9 mm. In this experiment, the distance between the positive and negative peaks such as the peaks shown in Fig. 3 changed with the lift-off distance. The relation between the distance D and the lift-off L, which was measured using the 1st channel SQUID, while moving the MNP solution just above the 1st channel SQUID, is shown in Fig. 4. As shown in the figure, the distance increased proportionally with the lift-off. The relation can be described as D = L + 3.5 mm. From this equation, it can be said that the distance between the SQUID array and the MNP solution, i.e. the *z* position of the solution can be estimated from the peak-to-peak distance of the magnetic signal from the MNP solution. In addition to the results of subsection 3.1., the information of the 3D position of the MNP solution can be estimated by measuring 2D distribution of magnetic field from MNPs.

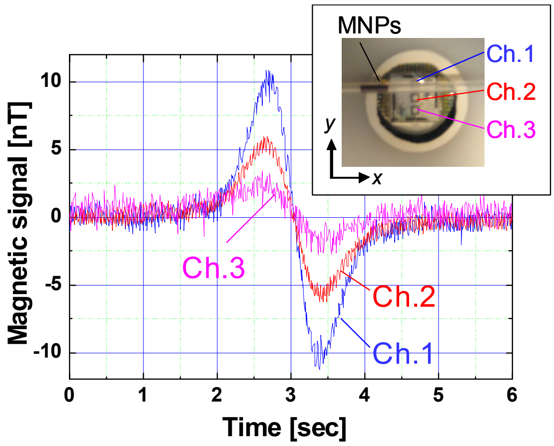

Figure 3. Magnetic signals detected by the 3-channel SQUID array, Ch.1, Ch.2, and Ch.3. The right-upper inset shows the experimental setup.

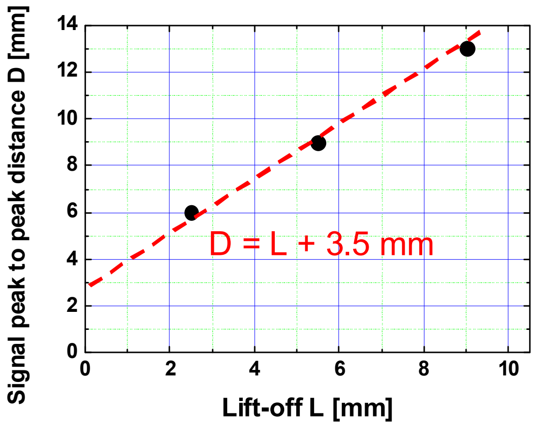

Figure 4. The relationship of the lift-off L between the SQUID array and the MNPs solution, and distance D

3.3. Estimation of Quantity of MNPs

In the third experiment, we measured the magnetic signals from various quantities of MNPs in the same amount of solution 5 μl, ranging from 0.5 to 3 μg. The moving speed, the direction and the path of the solution, the lift-off distance and the applied magnetic field were 10 mm/s, in the *x*-direction, above the 1st channel SQUID, 2.5 mm and 0.3 mT in the *x*-direction, respectively. The peak-to-peak amplitude of magnetic signal measured by the 1st channel SQUID was proportional to the quantity of the MNPs as shown in Fig. 5. Thus, it can be said that after you measure the 2D distribution of the magnetic field from the moving MNPs and estimate the 3D position of them, then you can estimate the quantity of them from such the relationship at a constant lift-off as the graph in Fig. 5.

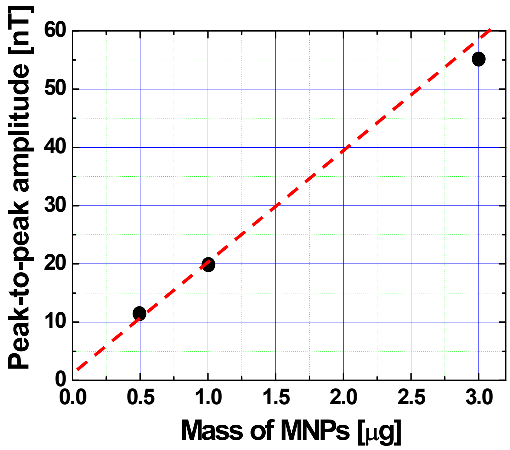

Figure 5. The relationship between peak-to-peak amplitude and mass of MNPs in solution with a lift-off distance2.5 mm.

4. Visualization of Trace of MNPs Moving in Branch Tube

Finally, we demonstrated the visualization of the trace of MNP solution flowing in a branch silicon tube. As shown in Fig. 6 (a), we made a two-way branch silicon tube with inner diameter of 2 mm. One end of the branch was closed while the other was open, in order to pull the MNP solution into the lower path by means of the syringe. The quantity of the MNPs was 1.25 μg, and the minimum lift-off distance between the SQUID array and the path of the solution in the *x*-*y* plane was set to be about 5 mm. A magnetic field of 0.3 mT was applied in the *x*-direction. In this experiment, since we intended to imitate the 2 D measurement of the field distribution using 2D SQUID array, that we have not yet, we changed the position of the SQUID array and the excitation coil with an interval of 5 mm in the *x*-direction, while fixing the branch tube. We assumed that the solution was moved at 5 mm/s and measured the magnetic field distribution at each position of the SQUID array. The branch tube, the path of the solution, the position of the virtual 2D SQUID array and the iso-field contour maps of the magnetic field from the moving solution at times are shown in Fig. 6 (b) - (g). We superposed all measured results and calculated the amplitude above each SQUID as the absolute value between such the positive and negative peaks as shown in Fig. 3. One can see that the MNP solution moved into the lower pass in the branch from the time trace of the 2D magnetic field distribution.

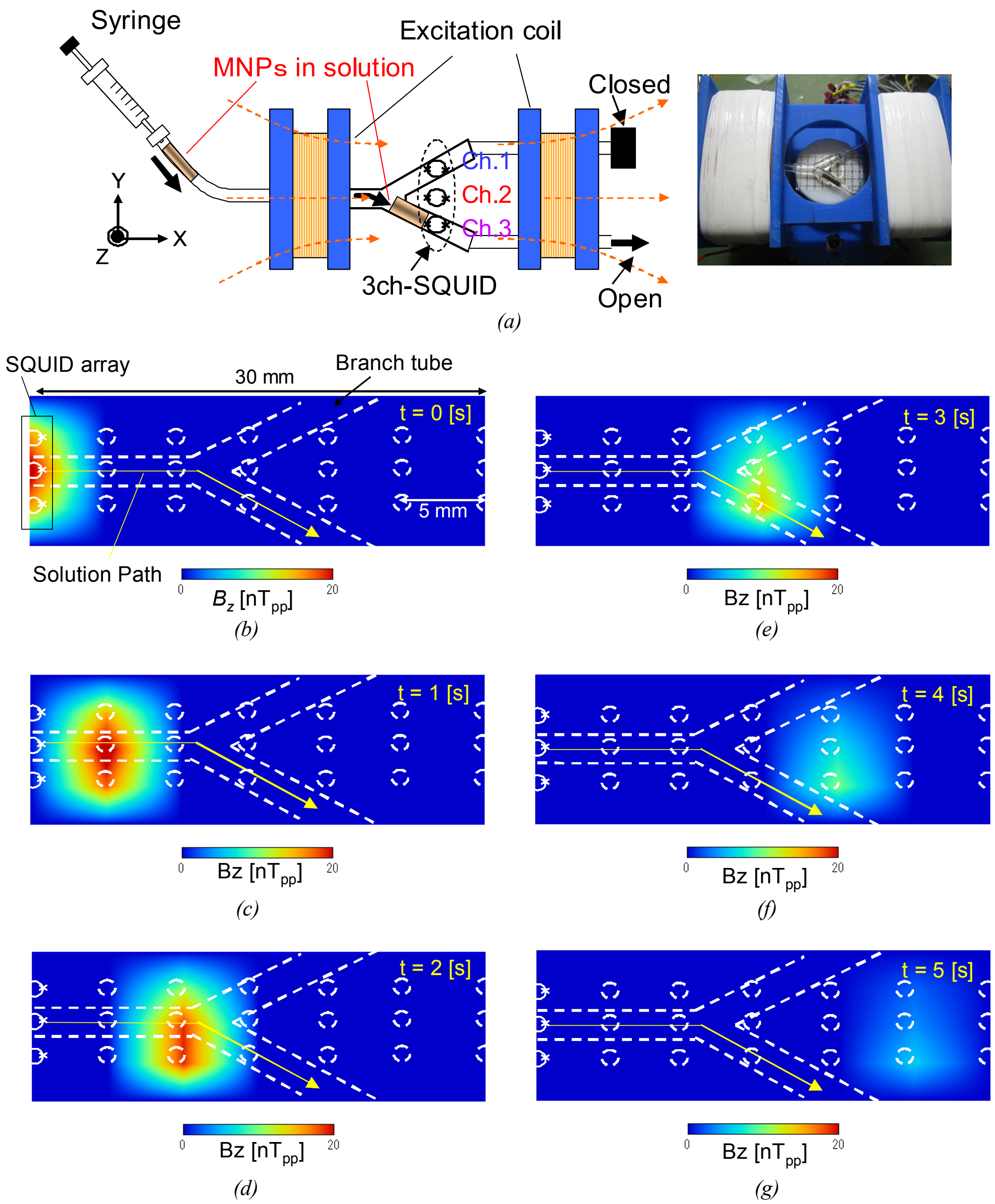

Figure 6. Demonstration of visualization of the trace of the moving MNP solution using a virtual 2D SQUID array. (a) Experimental setting.The SQUID arrray and the excitatoin coil were moved and rearranged with an interval of 5 mm in the x-direction and measured the magnetic field distribution while fixing the branch tube. The inset shows the bird's-eye view of the exitation coil, branch tube and SQUID array. (b) – (g) The iso-field contour maps of the magnetic field above the SQUID array from 0 sec to 5 sec.The positions of the branch tube and virtual 2D SQUID array are depicted in the same figures.

5. Conclusion

In this study, we constructed a three-channel HTS-SQUID array system to measure the magnetic field distribution from moving MNP solution to localize and quantify the MNPs for practical use of MDDS. Using this system, we measured the magnetic field distributions from MNP solutions flowing in a silicon tube with various conditions, and showed that the information of three-dimensional positions and quantity of the moving particles could be estimated. We demonstrated the visualization of the time trace of the MNP solution flowing in a branch silicon tube by making iso-field contour maps of the magnetic field from the moving magnetic particles. 2D HTS-SQUID array is under development. We expect that this kind of measurement technique will be a useful tool for realization of the MDDS technology in the near future.

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