Medical Application of Small Magnetic Particles and SQUID Magnetic Sensor

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Abstract

We have proposed two medical applications using ultra-small magnetic particles. One is a Lymph-node detection system and the other is a DNA probing system. In both cases, magnetic particles are detected by a sensitive high Tc SQUID magnetic sensor. We demonstrate that lymph nodes containing particles extracted from the rat were successfully measured by a SQUID system. In the application of DNA detection system, a preliminary experiment has been done. These results are described in this paper.

Detection of lymph node of rat

We have proposed the application of a high-T_c superconducting quantum interference device (SQUID) for sentinel node biopsy, which is a newly developed surgical technology. Sentinel node biopsy is used to investigate whether the sentinel node, which initially receives malignant cells from a breast carcinoma, is disease-free or not. If the sentinel node is free of disease, it is unnecessary to remove the rest of the lymph-nodes because of no concern for the progression. An infected area (primary tumor) is connected with axillary lymph nodes. This biopsy is based on the hypothesis that if the first lymph node is free of disease, the second and the rest of the nodes must be also negative. In case of positive, all of the lymph nodes should be dissected because of the possibility of the progression in the future. In case of negative, you can preserve the rest of the lymph nodes. We propose a localization system combined with a high sensitivity superconducting quantum interference device (SQUID) gradiometer and ultra-small iron oxide particles. The particles are injected into the breast; and the high-T_c SQUID is used as a sensing detector for the particles. Male Wister Shionogi rats were used in the following experiments. The core of the particle is iron oxide Fe_3O_4 (magnetite) which is coated with an alkali-treated dextran. The average core diameter was 11nm. The particles had superparamagnetic properties. The particles were supplied in the form of an aqueous magnetic fluid. As shown in Fig. 1, a rat lymph node sample on a polyethylene sheet was drawn by an induction motor installed outside the MSR. The signal was measured by a SQUID gradiometer. The iron content of the lymph node sample can be calculated as 10 μg, which value correspond to 0.2% of the injected iron. Although it is difficult to estimate the accumulated weight of iron particles for the human case, we think it must be more than 10μg because the volume of the injection must be 20 times larger than that of the rat. This performance is good enough to apply this system to the real sentinel lymph node biopsy.

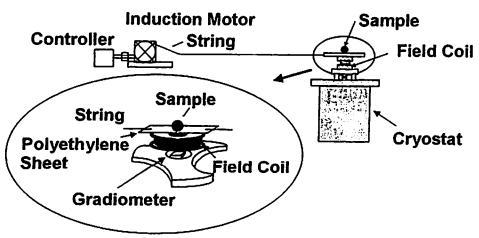

Fig.1. Schematic diagram of the measurement system.

DNA Detection system

We have developed a detection system for DNA using a high Tc SQUID. A hybridization of DNA with relatively short length (30 bp) was investigated. One strand (Sample DNA) was labeled with Fe_3O_4 ultra-small magnetic particles and the other (probe DNA) was anchored on a glass slide. They were hybridized each other on the slide. Then the hybridized DNA was evaluated in the presence of ac excitation field by high Tc SQUID. The particles had superparamagnetic properties. The COOH group is attached around the surface of the dextran. The DNA will be connected to the COOH group via a proper linker. We took 4μl of each liquid sample with desired concentration and put it on the glass sample holder. The holder was covered with an adhesive tape and then moved above the SQUID. The recorded typical signal trace is shown in Fig.2. This sample contains 0.73 pmol of nanoparticles. The peak to peak value shows magnetic field of 100 $m\phi_o$. Then we tried to make hybridaization on the substrate. After applying 20 pmol of the probe DNA, unbound DNA was washed. The particles with sample DNA were applied to the substrate. After wash the excess DNA, which was not hybridized with probe DNA, the sample was measured. Several sample DNA with different concentration were applied to the probe DNA. The concentration of the probe DNA was constant and 20 pmol. Fig.3 shows the relation between the magnetic signal and the mol of sample DNA. Signal shows a tendency of slow increment more than at about 5 pmol of the DNA, which corresponds to 0.07 to 0.2 pmol of the nanoparticles. Since the one particle has about three ssDNA, the number of DNA devoted the hybridization can be calculated and becomes 0.2 to 0.6 pmol. This number is almost consistent with the number of probe DNA on the substrate after wash. Thus the properties implies that the signal increases along with the number of the sample DNA and then shows the tendency of saturation at the number of the probe DNA on the substrate. Therefore it is found that the signal does not increase even if the number of the applied sample DNA was increased at more than 0.2-0.6 pmol, because the reaction is determined by the number of probe DNA on the substrate. This result indicates that the hybridization was successfully done.

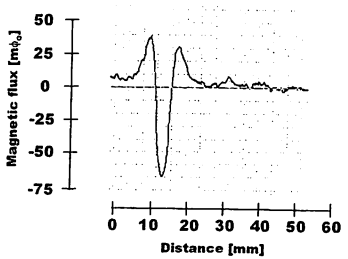

Fig.2. Typical signal of a liquid sample with particles.

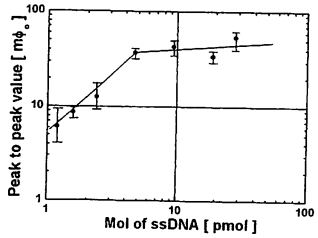

Fig.3. Magnetic signal v.s. mol of sample DNA.

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