immunoassay prepared inside the wells. The SQUID sensor consists of a direct-coupled magnetometer with a small 1.6 mm pickup coil and a magnetic field sensitivity of 200 fT per root Hz at 1 Hz. We have demonstrated a detection limit of <4 attomoles on IL-6 for a sandwich immunoassay. With this system, we have performed over a thousand measurements using magnetic labels ranging from 50-150 nm in diameter. We have also performed experiments in a serum matrix to examine non-specific binding. Significantly, the unbound labels do not need to be separated from the bound labels and kinetics measurements can be performed with our system.
Supported by NIH.

1EL02 High T_c SQUID System and Magnetic Marker for Biological Immunoassays
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High T_c SQUID system is developed for the detection of the biological binding-reaction between antigen and its antibody. In this measurement, antibody is labeled with magnetic nanoparticles, and the reaction is detected by measuring the magnetic field from the nanoparticles. When we use conventional magnetic nanoparticles, external field of a few mT is applied in parallel to the SQUID in order to magnetize the nanoparticles. In this case, vertical component of the external field couples to the SQUID due to mechanical misalignment, and causes the degradation of the SQUID performance. In order to solve this problem, we develop a switch made of bicrystal junctions instead of the conventional flux dam. The switch can electrically control the opening and closing of the pickup coil. Since the switch can decrease the circulating current with a short time, the so-called long waiting time in the case of the flux dam can be solved. We also develop a new magnetic marker that has remanence, where a few magnetic nanoparticles (25 nm in diameter) are embedded in the polymer (180 nm in diameter), and COOH is attached around the surface of the polymer. Using the remanence, we can detect the marker as small as 10 pg.

1EL03 Detection of Magnetically-tagged Microorganisms with a SQUID-based Gradiometer
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We use a SQUID-based gradiometer to increase the sensitivity of a magnetic immunoassay that detects small quantities of specific microorgansims or molecules. We bind the target analytes to a substrate placed in the sample cell of a high- T_c SQUID microscope and add a solution containing magnetite nanoparticles coated with antibodies specific to the target. The particles are superparamagnetic with a Neel relaxation time of ~1s. A pulsed magnetic field aligns the dipole moments, and the SQUID measures the magnetic relaxation signal when the field is turned off. Unbound magnetic particles relax in ~15 microseconds by Brownian rotation and are not detected. However, particles bound to targets cannot rotate and instead relax slowly via the Neel mechanism. Thus, only bound particles contribute to the signal. The sensitivity of our previous experiments, which used a magnetometer, was limited by the background magnetic field originating from metal parts of the microscope. Employing the gradiometer reduces this background to the level of the SQUID noise and allows us to detect 4000 particles reproducibly, an order of magnitude higher sensitivity.
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1EL04 Detection of Magnetic Nanoparticles in Lymph Nodes of Rat by High T_c SQUID
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The performance of a lymph node detection system used with an ultra-small superparamagnetic iron oxide and a high- T_c SQUID was investigated. This system is applicable for sentinel lymph node biopsy which is a newly developed surgical technology. The sentinel node biopsy is a kind of examination 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, you can leave the rest of the lymph-nodes because of no concern for progression. Conventionally, a radio isotope was used to identify the sentinel lymph node. We propose the use of radio exposure-safe ultra small ion oxide particles such as a magnetic resonance imaging (MRI) contrast agent.

After giving a shot of a MRI contrast agent to an arm of an anesthetic rat, a sentinel lymph node was extracted from the rat. Then the lymph node was measured by the SQUID system. We could successfully measure the magnetic signal from the lymph node. Although the real detection of the location of the lymph node in vivo was not performed yet, this result was good enough to apply the technology for the real detection.
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1EL05 SQUID-detected Nuclear Magnetic Resonance in Microtesla Magnetic Fields
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We have constructed a spectrometer based on a low- T_c SQUID to detect nuclear magnetic resonance (NMR) signals from room temperature samples in microtesla magnetic fields. In such low fields, one can achieve very narrow NMR linewidths even in the presence of gross field inhomogeneities, since the variation in the field across the sample remains very small. The sensitivity of the SQUID magnetometer, which involves an untuned, superconducting flux transformer, is independent of frequency. It is therefore possible to enhance both signal-to-noise ratio and spectral resolution by detecting the NMR signal in magnetic fields of a few microtesla. NMR frequencies as low as 25 Hz have been detected from samples with a volume of a few milliliters, with a signal-to-noise ratio on the order of tens for a single acquisition. Resolution of scalar couplings has been achieved in ^{1}H-^{31P} and ^{1}H-^{13C} systems. The technique of bandwidth narrowing through measurement in microtesla fields can also be applied to magnetic resonance imaging (MRI). We describe a SQUID-based system for in vivo MRI in fields on the order of a few microtesla.
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1EL06 Biomagnetic Measurement with HTS SQUID Electronic Gradiometer
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The biomagnetic measurement with a HTS SQUID electronic gradiometer was implemented in the moderately shielded environment. The system consisting of two HTS dc SQUID magnetometers arranged axially to form the electronic gradiometer. The noise of the component SQUID magnetometers shielded with a tri-layer magnetic shielding chamber were 50 fT/Hz1/2 above 10 Hz and 100 fT/Hz1/2 at 0.1 Hz. The magnetocardiogram of the small animal was measured with the SQUID system in the moderately shielded environment. The magnitude of the QRS complex measured with the first order electronic gradiometer was found to be around 10 to 100 pT with the signal-to-noise ratio better than 10. The accuracy of the source localization is investigated by solving the inverse problem with an equivalent current-source model.
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