High-resolution imaging of cardiac biomagnetic fields using a low-transition-temperature superconducting quantum interference device microscope

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We have developed a multiloop low-temperature superconducting quantum interference device sensor with a field sensitivity of 450 fT/Hz$^{1/2}$ for imaging biomagnetic fields generated by action currents in cardiac tissue. The sensor has a diameter of 250 μm and can be brought to within 100 μm of a room-temperature sample. Magnetic fields generated by planar excitation waves are associated with a current component parallel to the wave front, in agreement with predictions of the bidomain model. Our findings provide a new basis for interpreting the magnetocardiogram. © 2004 American Institute of Physics. [DOI: 10.1063/1.1704871]

Superconducting quantum interference device (SQUID) magnetometers have been used successfully to study a wide variety of bioelectric phenomena. Of particular interest are diagnostic multichannel systems to detect the magnetic far field outside the body and extrapolate to the source configuration. To address the validity of the source configuration, we must study the magnetic activity at the tissue level with cellular-scale spatial resolution. High resolution imaging of biomagnetic fields will ultimately lead to a better understanding of how the magnetocardiogram (MCG) and the magnetoencephalogram (MEG) are generated and their diagnostic value. To attain high spatial resolution, the sensor must be in close proximity to the room-temperature (RT) sample. Even though high transition temperature SQUID microscopes have achieved a sample to sensor distance of 15 μm, they lack the required field sensitivity to measure the weak magnetic fields due to the distributed sources associated with bioelectric phenomena.

We recently addressed this by using submillimeter superconducting pickup coils supported within the vacuum space of a cryostat and coupled to the flux transformer circuit of a commercial SQUID sensor. Although this configuration achieved a sample-to-sensor spacing of 100 μm with field sensitivities of 330 fT/Hz$^{1/2}$ for a 500 μm diameter pickup coil with 20 turns, it suffers from two major drawbacks. First, the impedance mismatch between the pickup coil and the flux transformer input coil limits the field sensitivity. Second, the cylindrical pickup coil results in a spatial averaging along the coil axis, degenerating the spatial resolution and reducing the flux due to the decay of the magnetic field with distance from the source.

One approach to overcome these drawbacks is to use Nb thin-film monolithic SQUID sensors supported within the vacuum space of a cryostat and coupled to the flux transformer circuit. For the achievable sensitivity of a few pT/Hz$^{1/2}$ is best suited for high-resolution imaging of magnetic dipole sources. In order to increase the field sensitivity further, one has to sacrifice spatial resolution and increase the effective area without increasing the inductance of the SQUID. A design, which achieves large effective areas is a multiloop magnetometer, also known as fractional turn SQUID. This configuration was first introduced by Zimmerman and later adapted by Drung et al. who developed monolithic niobium thin-film sensors with 8 mm pickup coils for biomagnetic multichannel systems to record human MCGs and MEGs and 1.5 mm diameter sensors with integrated flux transformer for nuclear magnetic resonance. We have adapted this design and fabricated Nb thin film monolithic multiloop SQUID sensors with submillimeter resolutions and field sensitivities < 1 pT/Hz$^{1/2}$, which are ideally suited for imaging biological tissue preparations.

In our approach, we use five input coils (spokes) connected in parallel with the Josephson junctions (JJ) located in the center of the device forming the SQUID sensor. An image of our sensor is shown in Fig. 1. A loop around the device is used to feedback magnetic flux for operation in a flux-locked loop (FLL).

The noise performance of a SQUID sensor depends on its total inductance, and is given by the power spectral density of the equivalent flux noise:

$$S_d(f) = \frac{16k_BT L^2}{R_n},$$

where $f$ denotes the frequency, $k_B$ the Boltzmann constant, $T$ the operational temperature, $R_n$ the shunt resistance, and $L$ the inductance of the device. Formula (1) is only approximately valid for $\beta_L = 2LI_c/\phi_0$ close to unity and in the limit of small thermal fluctuations both of which conditions apply to our SQUID sensors. $I_c$ denotes the critical current per junction and $\phi_0$ the flux quantum. A detailed inductance calculation of the multiloop SQUID configuration, $L$ and the geometric effective area, $A_{\text{eff}}$, are given by

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The critical current density of our device are listed in Table I. The noise performance was achieved with five spokes resulting in a total inductance of $L_p$ and a geometric effective area of $A_{eff}$.

$$L = \frac{L_p}{N^2} + L_s + L_j,$$

$$A_{eff} = \frac{A_p}{N} - A_s,$$

where $L_p$ and $A_p$ are the inductance and area of the circular coil without spokes, $L_s$ and $A_s$ are the inductance and area of one spoke, $L_j$ is the small parasitic inductance of the Josephson junction connection lines, and $N$ the number of spokes. Based on the optimization procedure outlined by Drung et al. and calculations by Moya et al., we evaluated the field sensitivity for different numbers of spokes and a fixed sensor diameter of 250 $\mu$m. The best field sensitivity was achieved with five spokes resulting in a total inductance of 24 $\mu$H and a geometric effective area of $7.85 \times 10^{-3}$ mm$^2$.

The Josephson junctions (JJs) were fabricated using a Nb/AlO$_x$/Nb trilayer process with Mo thin film shunt resistors. With our photolithographic process, we achieved a JJ size of $2 \times 2$ $\mu$m$^2$, a JJ self-capacitance $C$ of 0.6 pF/JJ, and a critical current per junction $I_c$ of 15 $\mu$A at a process-specific critical current density of $\sim 100$ A/cm$^2$. The parameters of our device are listed in Table I. The noise performance was measured inside a three layer, $\mu$-metal magnetically shielded room by operating the device in the FLL with a modulated flux of 100 kHz and a dc bias current. By using a pair of Helmholtz coils, we applied a homogeneous field which allowed us to determine the effective area, $A_{eff}$, of $7.86 \times 10^{-3}$ mm$^2$, which is in good agreement with the geometrical area, $A_{eff}$.

Figure 2 shows both the magnetic field and flux noise power spectral density of our multiloop SQUID for frequencies from 0.1 Hz to 1 kHz. The peaks in the spectrum are mainly associated with noise induced through the power supply of the feedback electronics and can be eliminated with tighter specifications. We achieved a magnetic flux noise, $S_{\Phi}^{1/2}$, of 1.7 $\mu$T/Hz$^{1/2}$ and an equivalent magnetic field noise, $S_B^{1/2}$, of 450 fT/Hz$^{1/2}$, both in the white noise region. We found that the 1/f noise, which generally appears for frequencies below 1 Hz, begins around 50 Hz. It has been shown that there are two main sources of 1/f noise in dc SQUIDs, the motion of flux lines trapped in the body of the SQUID and fluctuations in the JJ critical current. At present, it is not clear which type of these most likely sources are responsible for the observed 1/f noise in our devices. However, we expect the component due to $I_c$ fluctuations to be reduced by implementing a bias current reversal scheme.

The multiloop SQUID sensor was incorporated into the vacuum space of our cryostat and brought within 50–100 $\mu$m of a 25 $\mu$m thick RT sapphire window separating the sample and the vacuum space. Details of the chip mounting procedure, the cryogenic design, the magnetic shielding, and the scanning stage are described elsewhere. The imaging properties of the sensor have been evaluated using high resolution scans of a 10 $\mu$m thin film wire with opposite scan directions. We have found no directional dependence of the image, suggesting isotropic flux collection.

To investigate the source of the MCG and validate current cardiac models, we mapped the magnetic field associated with planar excitation wave fronts on the left ventricle (LV) of a reversely perfused isolated rabbit heart pressed lightly against the sapphire window of the SQUID microscope. Using a line of three bipolar stimulation electrodes, we induced a propagating planar wave front onto the LV. The wave front geometry and position was confirmed using an optical imaging system and a voltage–sensitive dye. The location of the imaging area and the electrode configuration are shown in Fig. 3(a).

In order to override the internal pacemaker, we stimulated the heart at frequencies around 3 Hz with current amplitudes of 1–2 mA, which is typically 1.5 times the diastolic stimulation threshold. The stimulation pulse triggers the recording of a MCG. Figure 3(b) shows a typical MCG time trace (z component) of three beats recorded with a bandwidth of 0.1–100 Hz. The largest peaks are due to the stimulation current and precede the actual heartbeats. We estimated a signal-to-noise ratio (SNR) of 10:1 referenced to the amplitude of the heart beats. The SNR can be improved by postprocessing using a comb filter centered on each harmonic.
predictions. The first 50 harmonics are isolated in the frequency domain and used to reconstruct the MCG. Figure 3(c) displays the MCG after signal processing.

We recorded MCGs at 400 locations on a 10 mm × 10 mm grid with a step size of 0.5 mm. Figure 4 shows the magnetic field generated by the excitation wave front 40 ms after the stimulation. The overlaid arrows represent schematically the direction and the amplitude of the action currents generating the magnetic field. The currents were calculated under the assumption of two-dimensional current distribution, as described by Roth et al. The leading edge of the excitation wave front can be identified by a reversal of the sign of the magnetic field amplitude. The main component of the corresponding current is parallel to the depolarization wave front, which was confirmed using membrane bound voltage sensitive fluorescent dyes. This current component can only be explained in the framework of the bidomain model for cardiac tissue. In this model, cardiac tissue is represented by a three-dimensional electrical cable with distinct intracellular and extracellular spaces separated by the cell membrane. The electrical conductivities and their anisotropies in the intra- and extracellular spaces are different. The magnetic field is a superposition from currents in the intra- and extracellular space. Our experiments are the first that demonstrate the importance of the bidomain approach in describing plane wave propagation in cardiac tissue. These observations are a sensitive test of the bidomain model and are in qualitative agreement with theoretical predictions.

In conclusion, we have developed and fabricated monolithic multiloop SQUID sensors with a diameter of 250 μm and a field sensitivity of 450 fT/Hz⁻¹/². The SQUID sensor was incorporated in a SQUID microscope and brought within less than 100 μm of the epicardium of isolated rabbit hearts to image the action current distributions of plane waves. We found a current component parallel to the wave front which is in agreement with predictions of the bidomain model. Consequently, the bidomain model should be the basis for forward calculations of the MCG. We anticipate the use of our system to study a wide variety of biomagnetic phenomena at the tissue level.

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