Development of an MCG/MEG system for small animals and its noise reduction method

Masakazu Miyamoto¹, Jun Kawai¹, Yoshiaki Adachi¹, Yasuhiro Haruta², Kazuo Komamura³ and Gen Uehara¹
¹ Applied Electronics Laboratory, Kanazawa Institute of Technology, 3 Amaike, Kanazawa, Ishikawa, Japan
² MEG Center, Yokogawa Electric Co., 2-3 Hokuyo-dai, Kanazawa, Ishikawa, Japan
³ Department of Cardiovascular Dynamics, Research Institute, National Cardiovascular Dynamics, 5-7-1 Fujishiro-dai, Suita, Osaka, Japan

E-mail: hndkmq@gmail.com

Abstract. Accurate capture of the biomagnetic signals from a rat or a mouse greatly benefits the development of new medicine and pathology. In order to improve the efficiency and accuracy of biomagnetic measurement of small animals, we developed a biomagnetic measurement system specific to small animal measurement. A superconducting quantum interference device (SQUID) sensor array and a table for the system were newly developed and were integrated into a transportable chassis having dimensions of 1.3 m width \times 0.7 m depth \times 1.8 m height and housing all principal components for the system. The integrated 9ch low-Tc SQUIDs magnetometer array designed to improve spatial resolution covers 8 mm \times 8 mm measurement area. We have also developed a real-time noise canceling method suitable for this system. The advantage of this method is that the noise reduction process is carried out in real time. We have confirmed the efficacy of this method using the measurement system which was installed in typical laboratory environment. The noise reduction effect was measured to be roughly 16 dB at power line frequency and its harmonics. We measured a magnetocardiogram (MCG) of a mouse using the system with the real-time noise canceling method, and the feasibility of small animal MCG measurement was ensured.

1. Introduction

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use demands safety tests for newly approved drugs with respect to their pro-arrhythmic potential. The enactment of these guidelines by regulatory organizations will lead pharmaceutical companies to employ extra safety test process with small animals in drug development.

However, obtaining biosignals such as electrocardiograms from a small animal is an inefficient process because several preparatory steps, such as shaving body hair and attaching electrodes on a subject, are necessary in prior to the measurement for the object. In an experiment, it is sometimes the case that the measured data are affected by electrode placement errors and changing electrode-skin contacts, which results in reducing data reliability and reproducibility of measurement. There is a potential demand in drug-development process for an alternative biosignal measurement system which has more productivity and reliability compared to conventional measurement system. A biomagnetic measurement system, as a contact-free
measurement method, has sufficient capability to improve measurement efficiency and are being studied [1, 2].

To measure up to this expectation, we have developed a small-sized biomagnetic measurement system aimed at practical use in the field of drug development. The newly developed system has a compact outline which is mostly the same size as a general office desk so that the system has flexibility for installation site. Additionally, to keep robustness against environmental noise disturbance, we have developed a noise canceling method suitable for this objective and implemented this method in analogue electronics within the flux locked loop (FLL) circuit of this system. The noise canceling method works in real time to acquire biomagnetic signal which has good signal-to-noise ratio suitable for analyzing.

In this paper, we describe the system in detail, show the effectivity of the noise canceling method, and show results for MCG measurement of a mouse using this system.

2. Instrument description

Figure 1 shows the appearance of the measurement system. The system consists of two parts: the measurement unit and the data acquisition (DAQ) unit. The measurement unit which houses all components for driving the superconducting quantum interference device (SQUID) sensors is shown in the right part of Figure 1 (a)(b). The dimension of the measurement unit is 1.4 m in width, 0.7 m in depth, 1.8 m in height, and 300 kg in weight.

The right side of the measurement unit (a) houses the principal components for the system: a magnetically shielded box, a cryostat with sensors, FLL circuits, and a table for subject. As an electromagnetic shield, copper plate (t=2 mm) covers the FLL circuits. To the left side of the measurement unit (b), we have placed a vacuum pump and a vacuum gauge for maintenance of the cryostat. The vacuum pump is connected with the cryostat by a vacuum pipe to facilitate maintenance. The DAQ unit (c) houses peripheral equipment to support the measurement unit and a PC for controlling the system and analyzing the acquired data. The DAQ system has the dimension of 0.6 m in width, 0.7 m in depth and 1.2 m in height.

2.1. Magnetically shielded box and cryostat

We designed the inside dimension of the shielded box to be suitable for handling typical body sized rat, about 300 mm in length, inside the shielded box. We determined the inside dimension of the shielded box as 500 mm in width, 300 mm in depth, 400 mm in height, and the shielding structure in two-layers with 1 mm thickness mu-metal. For the administration of medicine, plastic tubes must be placed through the shielded box during an experiment. We designed the
door of the shielded box as hinged double doors with a small slit at the center of where the the
doors meet to ensure the flexibility of handling the tubes.

![Diagram of cryostat and magnetically shielded box](image)

**Figure 2.** Cross-section of the cryostat and the magnetically shielded box.

We designed a cryostat which fits the integrated 9ch SQUID sensor and a reference sensor and having capability of more than 12 hours operating-time. As a result of the design, cryostat has approximately 6 liters capacity of liquid helium reservoir tank with fiber reinforced plastic (FRP) tube of 35 mm in diameter. Figure 2 shows cross-section of the cryostat and magnetically shielded box and show the position of the integrated 9ch SQUID sensor and the reference sensor. The distance between the 9ch SQUID sensor and the reference sensor is 150mm. We placed the cryostat on the top of the magnetically shielded box, and the FRP tube which houses the sensors is placed inside of the box through a hole on the box. We have confirmed that the shielding factor of the magnetically shielded box is more than 60 dB at 10 Hz.

### 2.2. SQUID sensors

The integrated sensor has nine SQUIDs of 2.5 mm in diameter, and are arranged in a $3 \times 3$ square matrix with 2.75-mm distance between each coil [3]. In each SQUID, 6 sectoral pick-up loops are directly connected in parallel to the Josephson junctions to achieve good coupling factor between the Josephson junction and the pick-up loops. The effective pick-up area is equal to that of one sectoral loop.

Figure 3 shows the appearance of the sensor. The sensor is fabricated on a silicon substrate and mounted on a printed circuit board to be wired with FLL circuit by flip-chip interconnection technology [4]. The flip-chip interconnection technology provides the connection of the SQUID sensor and the printed circuit board without wire, so that the space for the connection is minimal. With this technology, the distance between the SQUID sensor and the subject was minimized to 2 mm.

![Images of SQUID sensors](image)

**Figure 3.** Integrated 9ch SQUID sensor.
(a) A bare SQUID sensor. (b) Assembled SQUID sensor with a printed circuit board of 19 mm in diameter.

The SQUID sensor is covered with synthetic resin to protect from contraction stress by temperature difference between liquid helium temperature and room temperature. The sensor covers an area of 8 mm $\times$ 8 mm which is adequate for MCG and magnetoencephalogram (MEG) measurement of small animals. We have confirmed that the noise of a sensor is less than 10 fT/$\sqrt{Hz}$ at white noise region.
2.3. Table for subject
We designed a new nonmagnetic linear 3-axis stage to ensure the reproducibility and reliability of the measurement system. The 3-axis stage employs a detachable plate to fix a subject and equips temperature controlling capability to stabilize the physical condition of the subject. The 3-axis stage accurately controls the distance and position between the sensor and the subject to maximize signal level and ensure the reproducibility of measurement.

The detachable plate on the stage is temperature-controlled with hot water flowing into the plate. During measurement, the subject’s temperature is stabilized by controlling the temperature of water flow into the plate in order to minimize the disturbances caused by alternation in body temperature.

3. Noise canceling method
For its intended purpose, this biomagnetic signal measurement system should have the following features: the capability of capturing sporadical signals, and the capability of real-time monitoring for response of subject. To achieve the features in our biomagnetic measurement system, we have developed noise canceling method works at low frequency disturbances such as power-line noise, which is dominant at every system-installed site.

Many of the noise canceling methods which were developed as post processing methods at data analyzing stage are used in MCG/MEG systems [5], but it is more convenient if the canceling is done in real-time manner. A SQUID sensor design which has a capability of real-time noise canceling was proposed [6], but well-balanced sensitivity of the two sensors, a reference sensor and a SQUID sensor for biosignal detection, was required to achieve good noise canceling effect.

So, we have applied an attenuator in the noise canceling method to adjust the sensitivity difference of the two sensors in order to optimize the noise canceling effect. Thereby, this noise canceling method performs well by adjusting the attenuator, without considering the balance of the two sensors. It is notable that the reference sensor does not need to be a SQUID based sensor because the sensitivity of the reference sensor is adjustable with the attenuator. For example, flux gate sensors can be utilized as a reference sensor.

3.1. Algorithm
Figure 4 shows the block diagram of the noise canceling method. The environmental noise signal captured with the reference sensor is subtracted from the feedback signal from the FLL circuit for biomagnetic signal detection SQUID sensor. The environmental noise signal is transformed into a magnetic signal at a feedback coil and cancels environmental magnetic noise. An attenuator adjusts the environmental noise signal level to optimize the canceling effect.

![Figure 4. Block diagram of the noise canceling method.](image)

Since the environmental magnetic field noise is canceled at the feed-back coil on the SQUID sensors, readout signal of the sensors have low environmental noise disturbances. It means that
the output signal of the FLL circuit have an improved signal-to-noise ratio signal compared to a signal without the noise canceling.

3.2. Evaluation of the method

We have implemented this method in analogue electronics within the FLL circuit of this system. All the necessary controls and adjustments for the noise canceling is manipulated by the PC of the DAQ unit. We measured the effectiveness of the noise canceling method with the system installed in a typical biological science laboratory provided by our collaborator of this research. In addition, we measured a magnetocardiograph of a mouse using the system to demonstrate performance of the real-time noise canceling. The system houses the integrated 9ch SQUID sensor as a detector for biomagnetic signal and a multi-loop SQUID as a reference sensor. The reference sensor has a 2.2 mm-square pick-up loop and the signal resolution of 40 fT/√Hz. All of the sensors have the effective frequency range of DC to 5 kHz achieved by adjusting FLL circuits.

After installation of the system, we have adjusted the attenuator in the noise canceling circuit with the parameter which was derived from the acquired environmental magnetic noise data from the reference sensor and the 9ch SQUID sensor.

![Figure 5](image1.png)

**Figure 5.** Effect of the noise canceling method: time domain comparison.
(a) Without noise canceling. (b) With noise canceling.

![Figure 6](image2.png)

**Figure 6.** Effect of the noise canceling method: frequency domain comparison.
(a) Without noise canceling. (b) With noise canceling.

Figure 5 shows the comparison between with and without noise canceling in time domain data. Figure 6 shows the comparison of effectiveness in frequency domain data. We have confirmed that the effect of this noise canceling method was measured to be 6 dB in time domain data and was around 16 dB and 10 dB at the power-line frequency and its 5th harmonics, respectively. On the other hand, the noise floor of the result of noise canceling method is increased by around 10dB compared to the data without noise canceling. The increase of the noise floor is attributed to the white noise of the reference sensor, which we plan to improve in the near future. We have confirmed that the root-mean-square (RMS) value of the noise signal before and after the noise canceling is 8.4 pTrms and 2.5 pTrms, respectively.
After the evaluation of the effectiveness of the noise canceling method, we measured a magnetocardiograph of a mouse to confirm measurement performance of the system. The preparation procedure for the subject of this measurements were in two steps. First, to administer an anesthetic to the subject, then to fix the subject on the plate. The preparation and fixation took only 5 or 6 minute to complete because the detachable plate makes it easier to handle the subjects.

Figure 7 shows a waveform of the biomagnetic signals from a mouse acquired with the developed system. The trace shows a clear QRS complex whose amplitude is approximately 70 pTp-p. In actual measurement of small animals, the signal-to-noise ratio of biomagnetic signals are affected by several factors. In a typical laboratory space which houses many measuring instruments, it is often the case that the major factor is the magnetic field generated by the power-line which supplies electrical power to these instruments. In this experiment, we have achieved good signal-to-noise ratio biomagnetic signals which have adequate quality to analyze cardiograph parameters, even in a typical laboratory space in a magnetically noisy environment.

4. Conclusion
We developed a biomagnetism measurement system suitable for small animal biomagnetic signal measurement. The system incorporates a newly developed low noise integrated 9ch low-Tc SQUIDs magnetometer array. The small chassis of the system contains all the essential components so that the system can be maintained with minimum work.

We have developed real-time noise canceling method suitable for this measurement system, and have confirmed that the effectiveness of the method was in the 10 dB to 15 dB range on peaks in frequency domain data, and was 6 dB in time domain data.

The feasibility of the small animal MCG measurement using the system was ensured.

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