



Editorial

Focus on SQUIDs in Biomagnetism

Guest Editors

John Clarke¹,
Yong-Ho Lee² and
Justin Schneiderman³

¹ Department of Physics,
University of California,
Berkeley, CA, United States of
America

² Korea Research Institute of
Standards and Science, Republic
of Korea

³ MedTech West and the Institute
of Neuroscience and Physiology,
University of Gothenburg,
Sweden

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Since the first detection of magnetic signals from the heart by Cohen *et al* [1] in 1970 using the superconducting quantum interference device (SQUID) developed by J Zimmermann, SQUIDs have been used to measure various magnetic fields from the human body. In the early years, biomagnetic measurements involved just a few SQUIDs. Thanks to the development of thin film technology for reproducibly fabricating SQUIDs in the 1970s and 1980s, multichannel SQUID systems for wider coverage areas followed [2, 3]. The two main applications of SQUIDs were initially magnetocardiography (MCG) [4] and magnetoencephalography (MEG) [5]. Since then, the areas of study have been diversified into, for example, lung [6], intestine [7], fetus [8], and spine [9]. Today, SQUID-based non-invasive imaging tools for functional diagnosis of the brain and heart are commercially-available with high temporal resolution and moderate spatial resolution. In addition to *in vivo* measurement capabilities, several diagnostic tools have been developed for *in vitro* diagnosis. For example, SQUID-based readout of bio-functional magnetic nanoparticles (MNPs) [10] is used for detecting cancer [11].

Traditionally, most biomagnetic measurements utilize low-temperature SQUIDs operating at liquid helium temperature. To reduce running costs, two approaches have been pursued. One is the use of high-transition temperature (high- T_c) SQUIDs, cooled with inexpensive liquid nitrogen, and the other involves helium liquefaction systems for recovering the evaporated helium gas and returning the liquid to the SQUID cryostat. Although high- T_c SQUIDs have higher intrinsic noise than their low- T_c counterparts, the reduced distance between SQUID and room temperature provides larger signal strengths. However, poor fabrication yield is currently the main barrier to high- T_c SQUID-based multi-channel systems.

The publications in this focus issue are selected papers presented at Biomagnetism 2016; the 'BIOMAG' conferences are the largest on the subject of biomagnetism.

1. MNP-based diagnostic systems

1.1. MNP-based molecular diagnostics

In magnetic biomolecular sensing techniques, MNPs are coated with a material such as starch or a polymer and tailored antibodies are conjugated on this surface. When such biofunctionalized magnetic markers interact with disease-related antigens, the antigen–antibody binding reaction is detected with a SQUID. Compared with conventional biomolecular assays, an important advantage of this method is that liquid-phase detection is possible, that is, washing processes are not needed [10]. The fluid-suspended MNPs furthermore provide a high surface area to volume ratio compared to conventional well-based assays. As the biochemical detection reactions are surface-based, this improves yield and enables system miniaturization. SQUIDs are advantageous for this application because of their



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high sensitivity and wide bandwidth compared with giant magnetoresistive sensors, induction-coil magnetometers, and optically pumped magnetometers.

Enpuku *et al* [12] review the recent progress in SQUID-based magnetic biomolecular sensing techniques. Depending on the detection method, that is, ac susceptibility, relaxation, and/or remanence-based measurement, one uses magnetic markers with different properties. This discussion focuses on the optimization of the size of the magnetic markers and the corresponding detection method. *In vitro* and *in vivo* measurement examples are given.

1.2. AC susceptometer for human liver diagnostics

When MNPs are injected into the human body for *in vivo* bioassays, one needs to determine the detection limit in terms of the number of MNP tags that must bind to their target tissue (that is, specific disease markers) [13]. Hincapie Ladino *et al* [14] describe phantom experiments used to estimate the detection limit of their ac biosusceptometer. The manganese ferrite MNPs, with their surfaces coated with citric acid, were dissolved in water at various concentrations. The MNPs were magnetized with an applied magnetic field of 145 μT . The induced magnetization signal was measured with a low- T_c RF SQUID coupled to a second-order axial gradiometer (20 mm diameter and 40 mm baseline). The detection limit was estimated to be 9.5×10^9 MNPs ml^{-1} with a sensor-to-phantom distance of 15 mm (from the top of the sample vial to the closest coil of the gradiometer). The authors provide an outline for improved sensitivity, for example, by using more sensitive SQUID sensors and less noisy cryostats.

2. Biomagnetic sensor systems for human imaging

2.1. SQUID magnetospinogram (MSG) system

MSG is a method of recording the weak magnetic fields generated by neural activity in the spinal cord [9]. MSG is a relatively new technique among biomagnetic technologies, but it is a promising tool for the functional diagnosis of spinal cord degenerative diseases such as myelopathy or disc hernia, where there is currently no other suitable electrophysiological diagnostic tool. Since the neural activity area in the spine is narrow, Adachi *et al* [15] developed a three-dimensional pickup coil or vector gradiometer array to provide better spatial resolution. In this way, temporal propagation of the neural current distribution is reconstructed and can be mapped onto morphological images, for example, from magnetic resonance imaging (MRI) or x-rays. Based on the functional image, the propagation delay or decay of the spinal cord signal is measured non-invasively for functional diagnosis of the spinal cord disease. Currently, MSG is installed in only one hospital, and further clinical verification of the technique will be required to broaden the scope of clinical applications.

2.2. Clinical application of SQUID MCG

Inaba *et al* [16] describe the clinical utilization of a commercial 64-channel SQUID MCG system that has been successfully utilized for over 1000 patients per year. More than 10 000 patient data sets have been collected and used to develop a method of translating raw MCG signals to relevant diagnostic parameters that are specific to heart disease, poorly detected with conventional methods (for example, the ‘gold standard’ electrocardiography), and easily interpreted by medical practitioners. Such achievements provide a clear roadmap for how early adoption, regulatory approval (Japan was the first country to provide insurance reimbursement for SQUID-based MCG technology as early as 2003), and continued

medical–technical collaboration can lead to the realization of the potential SQUIDs have for contributing to modern healthcare challenges.

3. System/technical developments

3.1. High- T_c SQUID biomagnetometers

Although high- T_c SQUIDs generally exhibit higher field noise than low- T_c SQUIDs, the shorter distance between high- T_c SQUIDs and the room-temperature environment of biomagnetic sources implies that signals can be larger, and the resulting signal-to-noise ratios can be comparable to those of low- T_c systems [17]. One barrier to overcome for multichannel systems is the relatively lower yield of high- T_c SQUID production compared with low- T_c devices. Faley *et al* [18] review details of their fabrication process of high-quality SQUID magnetometers and place into context proof-of-principle demonstrations of MCG, MEG, and magnetic immunoassays. The two main high- T_c fabrication methods involve bicrystal [19] and step-edge technologies [20]. Bicrystal SQUIDs are simple to fabricate because they are often based on a single-layer of superconducting film. However, yield depends strongly on the quality of commercially-available bicrystal substrates: the present-day low demand for bicrystals is therefore a limiting factor, especially for multichannel systems. Low demand also means that sensor design is restricted to the ‘standard’ bicrystal layout. High- T_c SQUIDs based on step-edge junctions are promising because yield is limited by film growth—a process which is optimized in-house. Furthermore, design is flexible and the integration of multi-layer technology has led to sensitivities approaching those of low- T_c SQUIDs [21]. Combined with the higher signal levels available at close proximity to biological activity (at room temperature), biomagnetism with such low-noise high- T_c SQUIDs may meet—or exceed—the signal-to-noise ratios currently available with state-of-the-art low- T_c systems.

3.2. Crosstalk in high- T_c SQUIDs for MEG

Ruffieux *et al* [22] present a solution to the issue of crosstalk between densely packed high- T_c SQUIDs. Crosstalk is important in terms of the spatial resolution available to multichannel magnetic imaging systems, for example, MEG and MCG. Ideally, sensors should be packed more densely than the highest spatial frequency contained in the biomagnetic field of interest. However, as sensor density increases, crosstalk in the form of inductive coupling between feedback signals applied to adjacent sensors increases. It then becomes difficult to understand what part of a given sensor’s signal is generated by the sources of interest or by its neighboring sensors. Conventional crosstalk reduction methods, for example, nulling the current in an inductively-coupled pickup coil, are not directly applicable to single-layer bicrystal SQUIDs because they consist of a pickup coil and SQUID that are a part of the same superconducting film. A traditional ($\sim 1\text{ mm}^2$ coil-based) high- T_c SQUID feedback approach was compared with a method of applying feedback directly to the SQUID loop (direct injection). For SQUIDs packed edge-to-edge (for maximal practical packing density), the direct injection method demonstrated crosstalk of less than 0.5%. This was more than 10-times lower than the coil-based solution while leaving the noise level of the sensor unchanged. Such low crosstalk is promising, particularly in the field of on-scalp MEG, where the main competition for high- T_c SQUIDs is optically pumped magnetometry (OPM) [23]. To date, OPM-based MEG sensors require coils that produce a homogenous field over an area of several hundred mm^2 ; crosstalk of more than 3% has been measured in a semi-dense array and is understood to become worse when density is increased [24].

3.3. Low-noise SQUID system for sensitive ultra-low magnetic field (ULF)-NMR and MEG

As a component of a low-noise and versatile multichannel system, Storm *et al* [25] describe a modular SQUID magnetometer array consisting of 18 magnetometers with different pickup coil orientations and sizes. Depending on the design, a multi-modular arrangement can be implemented with up to seven modules or 126 channels. The magnetometer module is designed to be used for MEG, magnetorelaxometry, and ultra-low-field nuclear magnetic resonance (NMR), where the latter two applications require pulsed magnetic fields of up to 100 mT.

All the pickup coils are wound from Nb-wire, with each SQUID shielded in a Nb tube. Since the pickup coil is in a magnetometer configuration, it must be operated inside a heavily magnetically shielded room. The magnetometers are distributed in two planes, a sensing and a reference plane, for implementation of software gradiometry. The modular system shows impressively low field noise, between 0.6 and 1.5 fT Hz^{-1/2}, and well below 1 fT Hz^{-1/2} for 17.1 and 74.5 mm diameter pickup coils, respectively.

3.4. Continuous cooling of MEG system with low-noise reliquefier

MEG is the most successful application of SQUID-based biomagnetic technologies. Although MEG systems based on low- T_c SQUIDs are sensitive for accurate diagnosis of brain function, the requirement for periodic refill of liquid helium is a hindrance for the penetration of the technology into the market. Lee *et al* [26] demonstrate a low-noise MEG system that operates continuously without refill of liquid helium. Several groups are also pushing this helium recycling scheme into real applications, but the results shown here are very promising. Installation of SQUID gradiometers in vacuum is the key achievement to minimize vibration from the boiling liquid helium and from the reliquefier system. A minor vibration peak at 1.4 Hz and its harmonics seems acceptable, compared with brain spontaneous noise. Further reduction of noise seems possible if the MEG system were to be operated in a thicker standard shielded room with the addition of reference channels in combination with software gradiometers.

4. Ultra-low field NMR

4.1. SQUID-based NMR in ULFs

NMR and MRI in ULF—typically $\sim 100 \mu\text{T}$ —have the advantage of higher T_1 -contrast between different chemical species or tissues than in the more conventional high field—typically $\sim 1 \text{ T}$. Here, T_1 is the spin-lattice relaxation time. On the other hand, ULFNMR and MRI require an additional prepolarizing magnetic field before the pulse sequence is initiated to produce an acceptable signal-to noise ratio. Liao *et al* [27] report NMR measurements of relaxivity T_1^{-1} at ULF in glucose, fructose, sucrose and cherries using a high- T_c SQUID to determine the signal. For glucose, fructose, and sucrose they show that T_1^{-1} increases linearly with concentration; in addition, for a given concentration, T_1^{-1} in sucrose is approximately three times higher than in glucose and fructose. Furthermore, the authors plot T_1^{-1} versus degrees Brix ($^\circ\text{Bx}$)—a measure of sweetness—for different concentrations of the three sugars. They measure the values of $^\circ\text{Bx}$ using a Brix refractometer. Finally, they plot T_1^{-1} versus $^\circ\text{Bx}$ for 30 cherries with varying values of $^\circ\text{Bx}$, and show that T_1^{-1} increases linearly with $^\circ\text{Bx}$. This novel technique enables them to determine the value of $^\circ\text{Bx}$ in fruit, which normally involves removing the juice, using non-invasive ULFNMR, which preserves the integrity of

the fruit. This method would be invaluable in evaluating the sweetness of very valuable fruits.

5. Summary and future work

MNPs will continue to improve the sensitivity of both *in vivo* and *in vitro* assays using a variety of magnetic markers and detection schemes. As with all SQUID-based biomagnetic measurements, reduced SQUID noise and lower noise cryostats will lead to better resolution. Optimization of the size of the magnetic markers—which determines the magnetic relaxation time—for a given detection scheme will also result in improved performance. There is likely to be an ongoing debate over the relative advantages of high- T_c and low- T_c SQUIDs.

The recent development of MSG to record weak magnetic fields from neural activity in the spinal cord is a promising new tool for the non-invasive functional diagnosis of certain spinal cord degenerative diseases. The time dependence of the neural currents is superimposed on static MRI or x-ray images. Since MSG is currently available in only a single hospital, the most important single advance would be to install it in other hospitals to investigate its reproducibility and broaden its clinical applicability. The completion of a 10 000 patient study of magnetocardiograms with a 64-channel system represents a landmark in the field. This system demonstrably has adequate sensitivity, and the next challenge is to install similar systems in other hospitals to explore the clinical value and uniqueness of this methodology while increasing utilization for the benefit of society.

SQUIDs and their associated hardware continue their inexorable progress. Significant increases in the signal-to-noise ratio achievable with high- T_c SQUIDs and their input circuitry have been achieved via the implementation of cryogenics in which the input circuit is closer to the signal source than is possible with low- T_c devices. The biggest challenge with high- T_c SQUIDs remains their low fabrication yield. The most productive way forward may be the continued development of step-edge junctions, which are likely to offer progressively higher yield together with lower noise. Solutions to practical issues of relevance to high- T_c SQUID-based MCG and MEG, for example, crosstalk inherent to single-layer devices, pave the way for continued development and exploration of the specific benefits gained from reduced source-to-sensor spacing. In the meantime, the performance of low- T_c SQUID magnetometers has been improved via meticulous implementation of long-established design principles. First-order gradiometers are implemented with software subtraction of magnetometers in different planes. The ultimate goal of a magnetic field white noise of $0.1 \text{ fT Hz}^{-1/2}$, the estimated value of thermal noise in the brain, seems attainable by further shrinking the area of the SQUID tunnel junctions. Furthermore, the MEG community is moving steadily away from cryostats that boil off helium gas and need periodic refilling from an external dewar and towards replenishing the liquid with an attached liquefier. This is critically important in making MEG more user friendly, not least because of the substantial increase in the cost of liquid helium in recent times. This transformation will undoubtedly continue in the future.

Generally speaking, ULFNMR has the significant advantage of higher T_1 -contrast than its high field counterpart. A novel experiment using high- T_c SQUID ULFNMR was used to determine the sweetness of very expensive cherries by measuring the concentration of glucose, fructose and sucrose non-invasively. Since other techniques require the removal of the juice, and thus the destruction of the fruit, this new approach is likely to become important in evaluating the

ripeness of very costly fruit. The next step is to explore the accuracy of ULFNMR with other fruit.

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ORCID iDs

John Clarke  <https://orcid.org/0000-0001-6402-7841>

Justin Schneiderman  <https://orcid.org/0000-0002-4441-2360>

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