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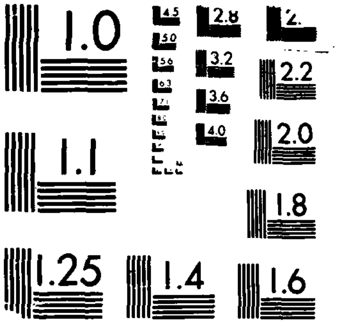

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Superconducting Quantum Interference Device

Capabilities for biomagnetic measurements have been advanced by the successful development of a (SQUID)-based magnetic sensor that does not rely on liquid helium for cooling. This system, known as "CryoSQUID", achieves a sensor noise level that is appropriate for high-sensitivity measurements of the magnetic field of the human brain. It employs an external compressor and a two-stage refrigerator within the sensor's dewar to cool a dc-SQUID and associated detection coil. The sensor can be operated in any orientation, including horizontally and up-side down. [illegible] (E), Magnetoencephalography; Cardiography

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METHODS AND INSTRUMENTATION FOR BIOMAGNETISM

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INTRODUCTION

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Biomagnetism is the study of biological activity through analysis of the magnetic fields such activity produces. This paper is a brief explanation of the principles of biomagnetism, focussing on the instrumentation that make such studies possible and how these measurements are used to learn about the underlying biological structures and events that can be deduced from them. This is not meant to be a comprehensive review, and some important areas of study will not even be mentioned. Readers who wish a more complete coverage may consult a textbook which provides an extensive introduction to this broad topic (Williamson et al., 1983), the proceedings of the last international conference on biomagnetism (Weinberg et al., 1984), and a general review (Williamson and Kaufman, 1981).

BIOMAGNETIC FIELDS

Many organs of the human body produce magnetic fields, as depicted in Fig. 1. There are three classes of sources: magnetic materials, the magnetic susceptibility of tissue, and ionic electrical currents. The first biomagnetic field to be observed from magnetic materials was associated with particles lodged in the lungs, as well as other organs in the thorax (Cohen, 1975). More difficult to observe is the effect of tissue susceptibility, because its value is close to that of water, the body's major constituent, and its value is quite low (Farrell et al., 1978). Nevertheless for patients with substantial iron overloads in the liver, measurements of that organ's susceptibility *in vivo* provide a clinically important measure of the concentration of iron (Brittenham et al., 1982). The class of fields that has attracted the most interest are those arising from electrical currents in the body. The strongest field is associated with the strongest current, that of the heart muscle (Cohen, 1970). The earliest biomagnetic studies focused on mapping at various places across the chest the time-course of cardiac activity, called the *magnetocardiogram* (MCG). A related subject of prime interest is the conduction system of the heart, including the His bundle and Purkinje system that carry excitations from the pacemaker to the ventricles. While these rapidly-moving signals are difficult to observe, the clinical importance of developing a *noninvasive* technique to monitor the conduction system has encouraged intensive research (Erné, 1985). The greatest emphasis has been concentrated on much weaker signals from neural activity within the brain, or *magnetoencephalogram* (MEG). Studies of spontaneous and sensory-related brain activity have demonstrated

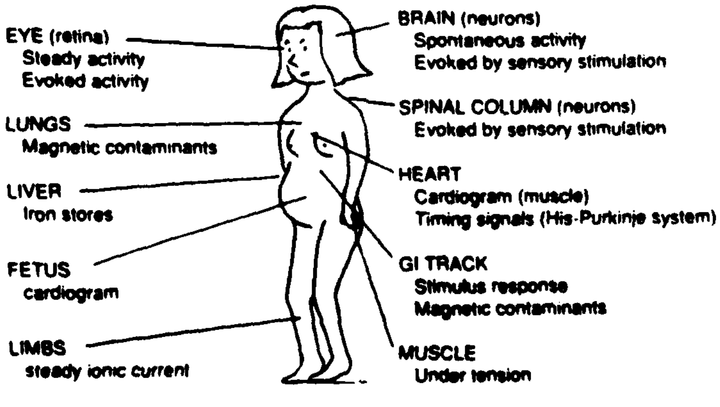

Fig. 1. Representative magnetic fields of the human body.

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their importance for both basic and clinical research (For reviews see: Hari and Ilmoniemi, 1986; Romani and Narici, 1986; Williamson and Kaufman, 1987). Even the very weak fields associated with brainstem activity have been detected (Erné et al., 1987). Recently, magnetic fields have also been observed in the vicinity of the spinal cord in humans (Mizutani and Kuriki, 1986).

These kinds of studies have stimulated interest in better understanding the underlying physiology that gives rise to the fields. Thus Wikswo et al. (1980) studied the field associated with the action potential of an isolated nerve axon *in vitro* and demonstrated that the observed field is due to intracellular currents. Simultaneous measurements of both transmembrane potential and the magnetic field near a nerve have validated the underlying theory and provide accurate measurements for the conductivity of the intracellular medium (Roth and Wikswo, 1985). In a similar spirit, research has begun on isolated brain tissue to gain understanding of the underlying mechanisms when populations of neurons are active (Okada and Nicholson, 1987; Tesche et al., 1987).

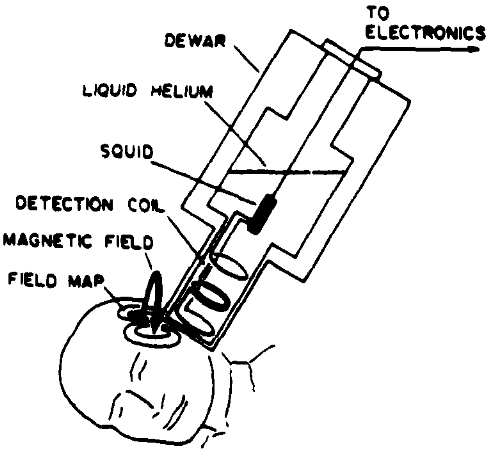
INSTRUMENTATION

While studies of these types have secured for the biomagnetic approach an accepted place in a variety of specialized disciplines, work continues toward developing improved measuring techniques. All biomagnetic fields are extremely weak, the strongest being about 10^{-6} of the earth's steady field of 70×10^{-6} tesla (or 70 μT). Thus the QRS peak of the cardiac field is typically 25×10^{-12} T (or 25 pT), the much weaker alpha rhythm of the brain is about 1×10^{-12} T (or 1 pT) and sensory-evoked fields are about 100×10^{-15} T (or 100 fT). In virtually all cases the investigator must cope with two problems: the weakness of the signal and the strength of competing magnetic noise in the environment. Here we discuss only the basic concepts of how to deal with these problems, for details can be found in a recent review (Romani et al., 1982a).

SQUID Sensors

A cryogenic instrument known as a *superconducting quantum interference device* (SQUID) is used for the most sensitive biomagnetic studies. It is conventionally maintained in a bath of liquid helium at a temperature of 4.2 K (or -269 C), isolated from the outside by a vacuum-insulated contained known as a *dewar* whose external surfaces are at room temperature (Fig. 2). Two components of this system merit special attention: one is the *SQUID* itself and the other is a *detection coil* that is placed as close as possible to the field source. The detection coil is part of a closed-loop superconducting circuit, called a *flux transformer*, with the leads of the coil passing upward to enter the SQUID enclosure where they form a *signal coil*. One property of a closed superconducting loop is that if a magnetic field is applied anywhere within the loop, the superconducting electrons flow through the wire so that their current produces a field that maintains the net magnetic flux in the loop (product of field and area) invarient. Consequently, if a magnetic field passes through loops of the detection coil, current passes around the entire circuit, and the portion flowing in the signal coil imposes a field on the SQUID. Room temperature electronics monitor the response of the SQUID and provide a voltage that is proportional to the magnetic flux in the detection coil. The principal advantage of this arrangement is that the detection coil can be wound with a geometry best meeting the measurement

Fig. 2. Elements of a *SQUID* system for monitoring the magnetic field of a subject's brain.



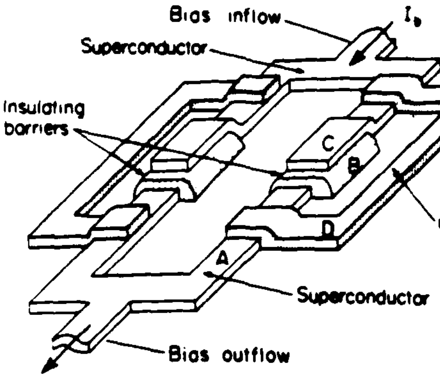


Fig. 3. A thin-film dc SQUID, with A and C being superconducting layers and B a thin insulator. Each junction has a parallel resistive shunt (D) for technical reasons, to avoid a hysteretic response when a magnetic field is applied.

requirements. For instance, Fig. 2 shows a coil having the geometry of a *second-order gradiometer*, namely, three equally-spaced coaxial coils with the center wound in the opposite sense and having twice as many turns as the end coils. This arrangement discriminates against fields from distant noise sources that are uniform in space, yet it retains sensitivity to fields from local sources that are appreciable only in the lowest coil (*pickup coil*). Thus the second-order gradiometer improves the signal-to-noise ratio. In less-noisy environments, such as a rural site or inside a magnetically shielded room, a first-order gradiometer may suffice. This has only two separated coils, wound in the opposite sense. In all gradiometers, the quality of noise rejection depends on how accurately the areas enclosed by each loop are made equal to each other. It is common to attach small pieces of superconducting foil at the appropriate positions to improve the area "balance" to 1 part in 10^4 or even 1 part in 10^5. Detection coils of large diameter enhance sensitivity because they couple more signal energy. Typical diameters are 2 and 4 cm for studies of the brain and heart respectively.

With the advance of technology, thin-film techniques are becoming popular for fabricating SQUIDs. Figure 3 gives a simplified illustration of what is known as a *dc SQUID*. To operate this device a dc current that is fed into the superconducting film (C) at one end, divides and passes through two parallel arms, and recombines in the superconducting film (A) at the other end. Each arm is interrupted by a *Josephson junction*, which is simply a thin insulator (B) that breaks the superconducting circuit. This is named for Brian Josephson who developed the theory for the action of such an insulating juction between two superconductors. At low dc bias current, electrons can "tunnel" through the junctions without exhibiting resistance, but when the current is increased to an appropriate level both junctions exhibit a (common) voltage. This voltage is predicted by Josephson's equations and the electrical behavior of the circuit.

If a signal coil is mounted directly above the area between the two arms applies a magnetic field, the voltage across the junctions varies periodically with increasing field. This feature arises from the fact that the field gives electrons passing along one arm a different momentum than electrons passing along the other, so there is an interference between the two currents where they rejoin that varies with field. The condition for periodicity is fixed by the value of the elementary flux quantum $\phi_o = h/2e = 2 \times 10^{-15}$ tesla-meter^2, which is the smallest non-zero amount of flux that can exist within a closed loop of superconductor. Since the area within the arms of the SQUID is small, and the flux quantum itself is such a small value, counting voltage oscillations provides a senstivity measure of how much the applied field has changed.

This device can be made to respond linearly with applied field, and the sensitivity can be enhanced by a factor of 10^5 or more by adding a feedback loop. With a second coil mounted over the area between the arms and appropriate electronic circuits to monitor the voltage across the junctions, a current can be fed to this coil so that its field just cancels the field of the input coil. With the SQUID serving as a null detector in this way, the voltage provided by the feedback current passing through a resistor is strictly proportional to the current of the signal coil, and hence to the biomagnetic field in the detection coil. The method provides excellent linearity in response, with a wide dynamic range. Other refinements are added to improve sensitivity, such as applying an ac rather than true dc bias, but it is not appropriate to go into such details here. Some commercial SQUID devices with detection coils of 2-cm diameter exhibit a sensitivity of about 20 fT within a 1 Hz bandwidth, and with careful optimization a sensitivity of 5 fT has been achieved. Emphasis has also been placed in developing multiple-sensor systems so that the process of mapping a field pattern over a portion of the body to determine the underlying sources is greatly shortened (Ilmoniemi et al., 1984; Williamson et al., 1984; Romani et al., 1985; Knuutila et al., 1987). Since thin-film fabrication techniques offer many advantages for SQUIDs, there is interest in making detection coils in the same way. Indeed, with sufficient sensitivity, the use of higher-order planar gradiometers (as contrasted with the axial gradiometer shown in Fig. 2) may have advantages in localizing sources of biomagnetic signals.

Magnetic Shielding

SQUID systems using a second-order gradiometer for the detection coil are capable of a wide range of useful measurements in an unshielded setting, including laboratories and clinics. However, ambient noise increases dramatically at low frequencies in noisy locations, and there may be additional noise at discrete frequencies from nearby machinery. High levels of radio frequency noise, as from communication systems, may also interfere with the operation of the SQUID. A room constructed with magnetic and radio-frequency shielding is one effective way to minimize these problems. The first rooms built for biomagnetic applications had four or more widely-spaced, concentric shells of high-permeability material (e.g., Mager, 1981) and are very effective. However, this requires a large space for installation, and the space inside is small, having a characteristic dimension of 2 m. Other magnetically shielded rooms have fewer shells, provide more working space, and yield acceptable shielding for most purposes (Kelhä et al., 1982; Buchanan et al., 1987).

SQUID Refrigeration

Everyone who uses a SQUID system recognizes that liquid helium as a coolant is a nuisance and considerable expense. There would be considerable advantage in using a refrigerator to cool and maintain the low temperature portions of the dewar. A SQUID requires very little refrigeration capacity, and the capacity to cool the electrical leads and insulating vacuum section is modest. The principal challenge is to limit the magnetic noise and vibration that such a system imposes on measurements. This was recognized by Zimmerman and Radebaugh (1978) who developed a successful closed-cycle cryogenic refrigerator, or *cryocooler*, based on a Sterling cycle. This has a long, motor-driven displacer that moves within a close-fitting sleeve to admit helium gas under pressure and subsequently achieve cooling by expansion of the gas as the displacer is withdrawn. It requires only 50 W of input power to produce temperatures of about 7 K, sufficient to operate a niobium rf SQUID that detected the magnetic field of the human heart.

Recently a different type of device has been developed with a noise level that is sufficient for measuring the magnetic field of the brain (Buchanan et al., 1987). It depends on both a commercial Gifford-McMahon refrigerator and a specially designed Joule-Thomson refrigerator, where high-pressure helium gas expands and cools as it passes through a small hole into a low-pressure region. The former cools the dewar from room temperature and maintains a 15 K stage, and the latter is suspended from the cold stage and produces a stable temperature of about 4 K. Figure 4 shows the arrangement of gas lines and thermal links, most of the latter fabricated of fine copper wire. Since there are no mechanical links to the dewar, only fine tubes for conducting helium gas, this device can be easily rotated to operated in nearly any orientation, including horizontally and almost upside down. This makes it especially attractive for measurements about the head. We call this device "CryoSQUID". The movement of the displacer produces magnetic noise, but only at well-defined frequencies. In practice, the noise is so stable that obtaining an average of its time series for 15 seconds or so with a personal computer is sufficient to subsequently allow the computer to subtract this noise in real time from the

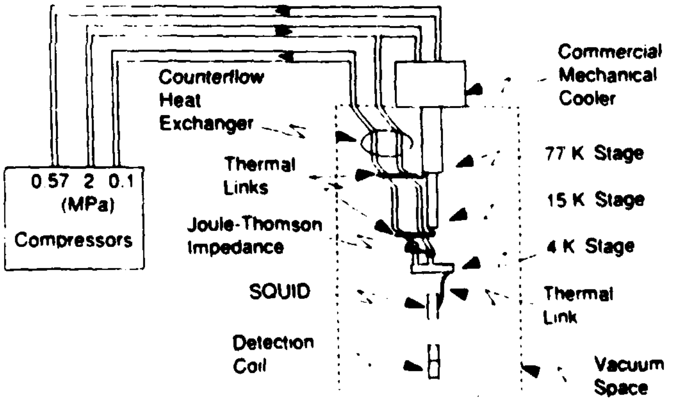


Fig. 4. Schematic for gas flow lines and thermal links in the CryoSQUID system.

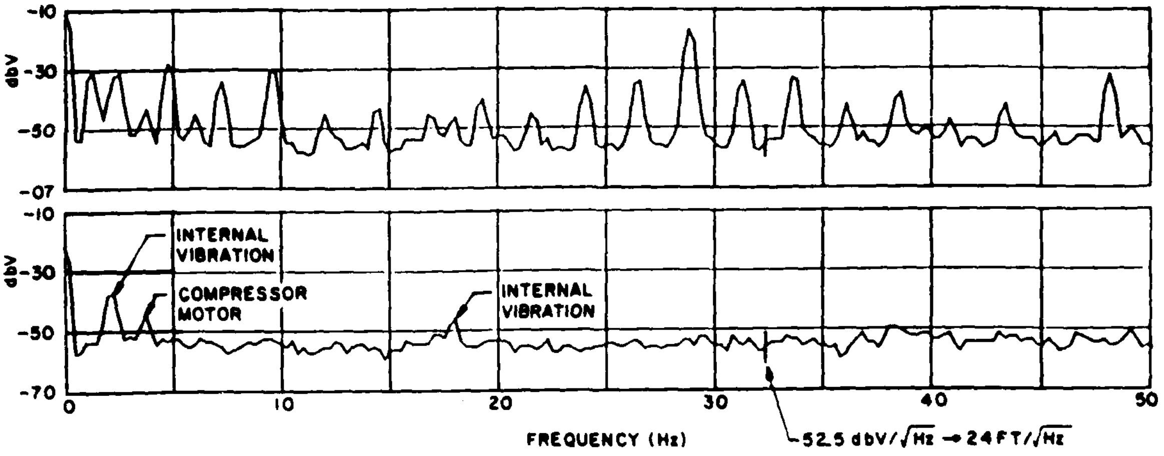


Fig. 5. Noise spectral density of CryoSQUID when the system operates without an adaptive filter (dashed line) and with it (solid line).

incoming data. Figure 5 shows that virtually all of the refrigerator noise is eliminated. With this success it is clear that refrigerator-based SQUID systems are now feasible, elminating the dependence on a steady supply of liquid helium.

PHENOMENA AND METHODS OF STUDY

Magnetic Particles

Magnetic particles exhibit a remanent field once a magnetic field of sufficent strength is applied and then removed. This *remanent field* is generally permanent, and so the presence of small quantities of magnetic materials can be detected with high-sensitivity sensors. In this way changes in the amount or distribution of particles can be inferred (Cohen, 1975). The technique has been applied to assessment of occupational health in environments where magnetic particles are inhaled (Kalliomäki et al., 1976; Freedman et al., 1980). It has also been exploited to provide evidence that smokers clear particles from their lungs more slowly than non-smokers (Cohen et al., 1979). More recently the study of the remanent field from the lungs of small animals where dust had been intentionally introduced into the lungs has revealed that time-dependent phenomena are caused by cellular activity. The steady decline of the remanent field outside the chest after application of a strong magnetizing field can be attributed to rotation of the particles that have been taken up by cells called "macrophages", which are - so to speak - the garbage trucks of the lung (Gehr et al., 1983a). Corresponding behavior has also been discovered within cells of the liver (Gehr et al., 1983b). Thus, studies of this type are revealing aspects of cell physiology that cannot be obtained noninvasively by other techniques (Nemoto, et al. 1985). Measurements of this kind can be carried out by a device called a fluxgate magnetometer, which requires no cooling.

Ionic Currents

Application of biomagnetic techniques to studies of organs such as the heart and brain are motivated by several factors. One is the fact that a magnetic measurement represents a different kind of spatial weighting of the source currents than electrical measurements across the skin, thus suggesting that different kinds of information will be obtained (Wikswo, 1983). Another is the possibility that the nature of intervening tissue may be less important in influencing the field pattern than the potential pattern across the skin. The overriding advantage of magnetic measurements in our opinion is the possibility of determining more accurately the location of confined regions of activity, when the activity can be modeled as a *current dipole*, namely, a small element of current. Localization provides a means of relating observed activity to specific regions of the body, such as in establishing functional maps of the brain. One example is discovery of a tonotopic organization across the auditory cortex of human subjects (Romani et al., 1982b) or in defining the region of an infarct in a diseased heart (Saarinen et al., 1985; Gonnelli et al., 1985).

Locating a Source

If the source is a current dipole, there will be one region where the field is strongest emerging from the body and another region where it is strongest entering the body. For a body with certain types of symmetry, such as one which can be approximated by a flat surface covering a semi-infinite, uniform conducting region (the *half-space model*), the source lies midway between these field extrema and at a depth that is equal to the distance between the extrema divided by $\sqrt{2}$ ($\approx$ 1.4). Similarly, for a current dipole in a sphere, the depth of the source can be deduced from the ratio of the distance between the extrema to the radius of the sphere (Williamson and Kaufman, 1982). Such simple recipes, which are useful for making first estimates, can be refined by more accurate numerical models describing the appropriate region of the body.

There are cases where the field patterns from two or even three simultaneously active sources have been analyzed to reveal the positions of underlying activity; but in general the problem of dealing with multiple sources is just in its infancy. Much more theoretical and experimental work is needed to deal with the more interesting problems of the time sequence of multiply active areas in the brain or the interplay of Purkinje system and myocardium in activating the heart. In all these cases it should be kept in mind that there is no unique solution for the configuration of electrical sources that can be deduced from electrical potential measurements, or magnetic field measurements, or a combination of the two. Electrically and magnetically "silent" sources exist, in the sense that there are source configurations that produce no skin potential distribution or external fields. Rougly speaking, skin potentials and magnetic fields provide complementary information, and there are cases where the two should be used together (Wood et al., 1985).

FUTURE PROSPECTS

Software Reduction of Noise

Biomagnetic measurements continue to face the problem of environmental magnetic noise when applied to the weakest signals. Most magnetically shielded rooms do not completely shield noise at very low frequencies, say below 1 Hz. With growing popularity in the use of systems with multiple SQUID sensors, it becomes feasible to dedicate one or more of the sensors to monitor the ambient noise as a *reference* for purposes of subtracting a portion of it from the noisy signal. Simple fixed electronic balancing techniques have already been applied with success for unshielded measurements (Williamson et al., 1984). We report here a new computer-based approach that in many practical applications markedly reduces excess low frequency noise. The references consist of three SQUID sensors oriented to monitor three mutually perpendicular components of the ambient field. The technique uses computer-controlled attenuators to adjust the amplitude of each reference that is subtracted from each of the signals so as to remove the correlated portion of the noise. Figure 7 gives an example of the kind of improvement that can be obtained within a magnetically shielded room. With such electronic noise cancellation, the noise level is essentially the intrinsic sensor noise from high frequencies down to a frequency below 0.1 Hz. This is sufficient to operate the SQUID sensors in a dc-coupled mode to monitor very low-frequency activity.

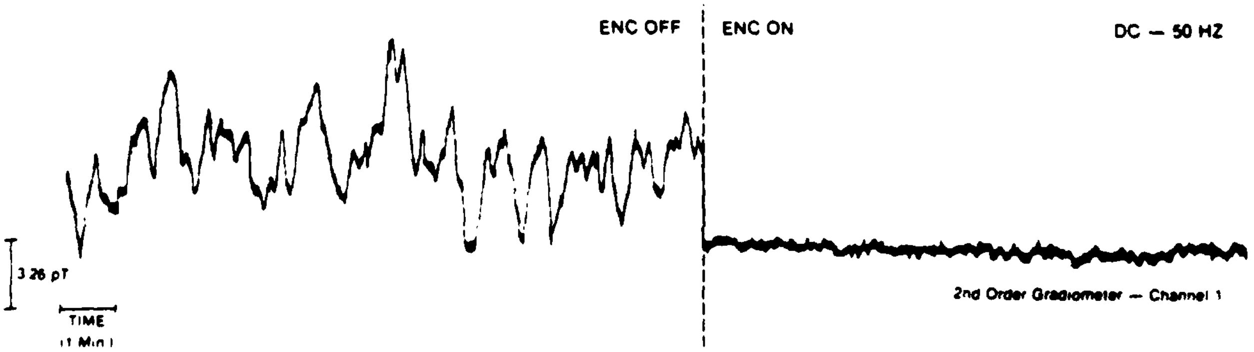


Fig. 7. Time course of the noise in the bandwidth DC-50 Hz observed within the magnetically shielded room at the Center for Neuromagnetism at Bellevue Hospital of the New York University Medical Center, without electronic noise cancellation (left) and with it (right).

High Temperature Superconductors

This past year marked a turning point in the development of superconducting devices with the discovery of superconductivity in the Yttrium-Barium-Copper-Oxygen ceramic system at temperatures as high as 94 K. The race is underway to find ways to make these materials practical for wires, thin films, and SQUIDs. One group recently reported success in making SQUIDs (Zimmerman et al., 1987) that operate up to 80 K. This clearly demonstrates that SQUIDs can be operated at liquid nitrogen temperatures (77 K), but unfortunately the noise levels are several orders of magnitude greater than those of the best SQUIDs operating in liquid helium. Whether high-temperature SQUIDs become useful for biomagnetic applications remains to be seen. Nevertheless, there is reasonable hope that high-temperature detection coils can be fabricated, and this would greatly ease the cryogenic problem. Dewars can be made thinner near the scalp, with a coil operating at 60 or 70 K, and since superconductors are poor conductors of heat the SQUID would not suffer. The prospect for applications of room-temperature superconductors is exciting indeed! When we think of arrays of sensors to measure the field pattern over a large area over the thorax or head, the chief advantage comes from being free from the constraints of a rigid dewar. Then the detection coil positions can be adjusted easily to match the contours of the particular individual. This will enhance signal strengths an permit convenient measurements for children and adults alike.

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