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A NEW METHOD FOR MAGNETOENCEPHALOGRAPHY

APL's Bioelectromagnetics Laboratory is testing the feasibility of using multi-axis magnetic gradiometers to localize and track neuronal activity in the brain. This work is directed toward the design and development of a superconducting device for localizing epileptic sources in a clinical setting and for functional brain imaging in psychophysiological experiments.

INTRODUCTION

Magnetoencephalogram (MEG) techniques passively measure the magnetic fields emanating from neuronal sources in the brain. The MEG is the magnetic analogue of the electroencephalogram (EEG), which is a measure of potential differences about the brain caused by the electric fields emanating from neuronal sources within the brain. MEG and EEG signals originate from sources that can be modeled by current dipoles. Figure 1 shows a hypothetical dendrite of dipole moment Q immersed in the electrically conducting brain. The current dipole causes volume currents to flow in the brain and surrounding tissue, resulting in potential differences at the scalp. Those potentials are the signals measured by the EEG. A magnetic field, B, associated with the current dipole also is generated. This neuromagnetic field, which is measured by the MEG, has a field-spatial pattern giving contours of constant field (plus contours for B exiting, minus contours for B entering). The magnitude of the field diminishes as the contour radius increases. Figure 2 illustrates the magnetic field contours from a source in the temporal lobe of the brain.

The MEG has theoretical advantages over the EEG.[1] The vector $\bar{B}$ gives directional information about the source orientation. The neuromagnetic field $\bar{B}$ is not distorted by the brain, because the brain has the same permeability as air. The MEG is an absolute measure of source strength, not measured with respect to a reference, as is the EEG. The MEG is not affected by bad electrode contact or tissue artifacts, as is the EEG. The MEG does not need to touch the head, as does the EEG.

Originally discovered in 1968,[2] the MEG has led to several investigations for locating the neuronal sources of magnetic signals emanating from the brain under normal or pathological conditions. Neuromagnetic signals seen under normal conditions might be evoked responses from visual, auditory, somatic, or other stimuli.[3] Normal brain rhythms (e.g., alpha and beta) are also seen. Neuromagnetic signals observed under pathological conditions might be associated with epilepsy[4] or some other disease. The MEG shows potential for noninvasively localizing some sources of epilepsy located deep in the brain. At present, such sources are often localized by using EEG electrodes penetrating the brain. The MEG also shows potential for straightforward functional imaging of brain activity in mind–brain investigations. For
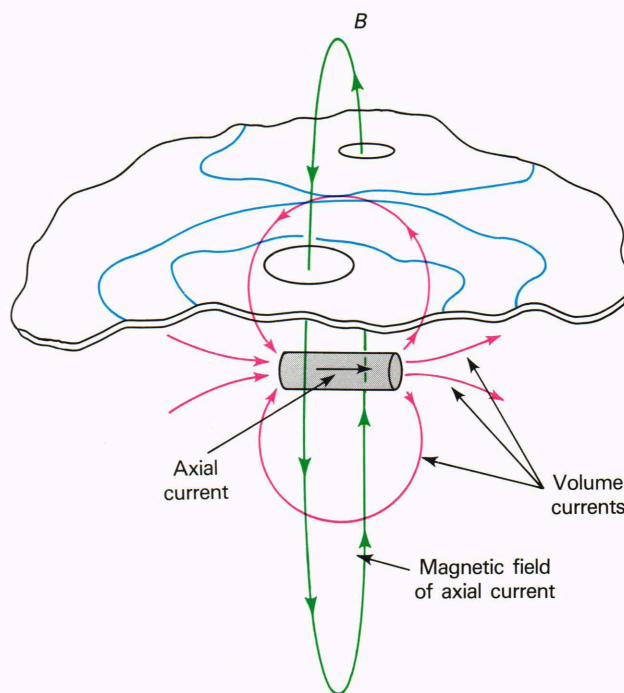

Figure 1—A magnetic field, generated by neuronal axial currents, emanating from the brain. The volume currents are responsible for the scalp potentials of the EEG.

example, psychophysiological tests have shown that the MEG can measure brain activity not only during motor action, but also in anticipation of motor action and in the absence of motor action. Such a dynamic real-time imaging response is not readily attainable by expensive positron emission tomography or magnetic resonance imaging systems.

We review in this article the present method for MEG localization, which moves a single sensor to multiple measurement stations (or a bundle of multiple sensors, each sensor being used independently). We also present a new method, which is less time-consuming and less susceptible to experimental error. This method is the focus of investigation at APL to determine the performance limitations of MEG localization techniques.
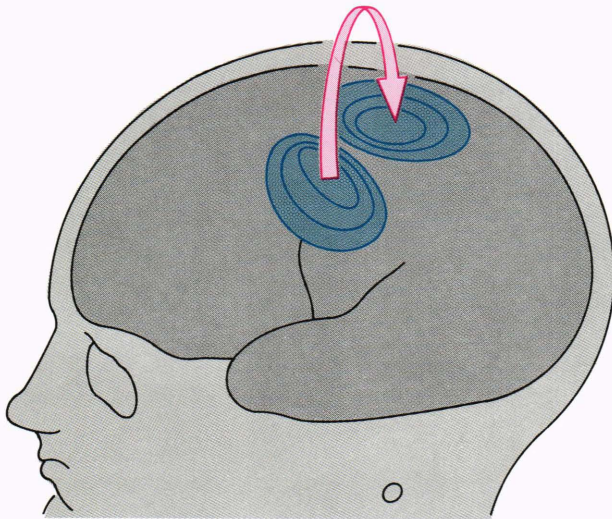
Figure 2—Magnetic field contours encompassing the point of emanation and the point of re-entry of the magnetic field generated by neuronal axial currents.

SUPERCONDUCTING SINGLE-AXIS GRADIOMETERS

Existing MEG devices are based on very sensitive single-axis magnetometers that can measure neuromagnetic signals as small as 10 femtotesla (1 femtotesla = 10^{-15} tesla = 10^{-15} weber/m^2). Neuromagnetic signals may be as large as 1500 femtotesla. Figure 3 shows four single-axis magnetometers. A single pickup coil, shown in Fig. 3a, detects the neuromagnetic signal plus noise. The noise can be a factor of 10,000 times larger than the neuromagnetic signal. Generally, the noise originates from sources distant from the biological signal, and the noise field is spatially uniform. A second pickup coil, usually spaced several centimeters from the signal coil, is used to measure just the noise and not the neuromagnetic biological signal. Figure 3b shows this two-coil arrangement. When the output of each one is subtracted from the other, this first-order difference subtracts out the spatially uniform noise field and reveals the signal. That difference can be accomplished by using one wire and winding the coils in opposing directions, as shown in Fig. 3b. Such a simple, one-difference device is called a single-differencing (or first-order) gradiometer. If the noise field is not spatially uniform, but varies linearly with distance, two additional coils are used, as shown in Fig. 3c, to form a difference of a difference (i.e., double difference) to cancel the noise. Such a device is called a double-differencing (or second-order) gradiometer. If the noise field varies quadratically with distance, then a third-differencing (or third-order) gradiometer, as shown in Fig. 3d, is used.

These gradiometer magnetometers can have multiturn coils immersed in a cryogenic fluid (e.g., liquid helium) to allow the coils to become superconducting. At present, superconducting loops are connected to a superconducting quantum interference device (SQUID), which is usually another wire loop with a Josephson tunneling junction used to detect the current flowing in the pickup loop. A typical MEG device is the single-axis superconducting second-differencing gradiometer (SSDG), as shown in Fig. 4. Here, a single-field point measurement is made with the SSDG at one station. A single SSDG can be moved about the head to as many as 100 measurement stations to map the magnetic field contours. Several commercial MEG systems use an array of five or seven SSDG devices in a single dewar to reduce the number of measurement stations.

The MEG measurement is difficult. Table 1 presents the origins of background magnetic noise sources competing with the neuromagnetic signals. Although gradiometry can reduce the effects of some noise sources, the best MEG measurements also require the use of a mag-
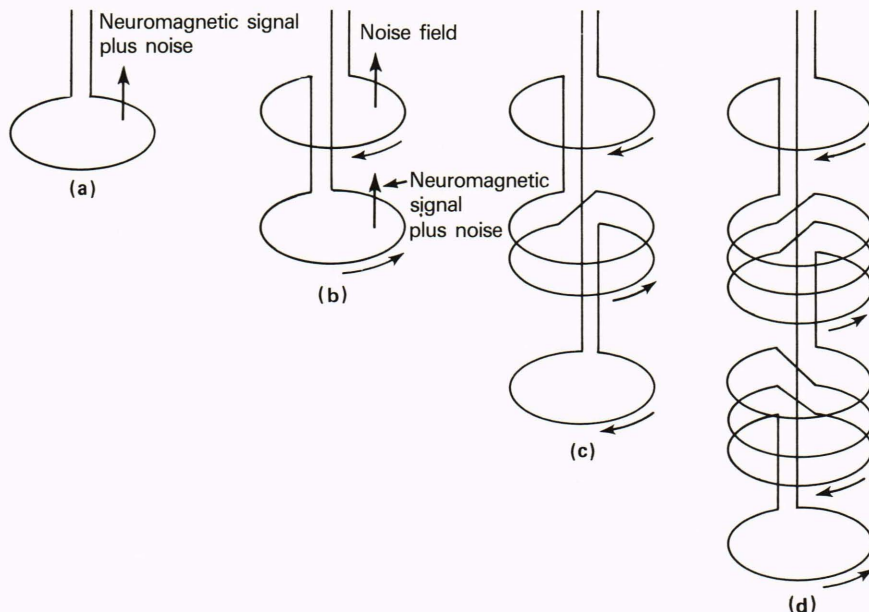

Figure 3—Receiver coil configurations for different order gradiometers used to help reduce the effects of ambient magnetic field noise: (a) single-coil magnetometer, (b) first-order gradiometer, (c) second-order gradiometer, and (d) third-order gradiometer.
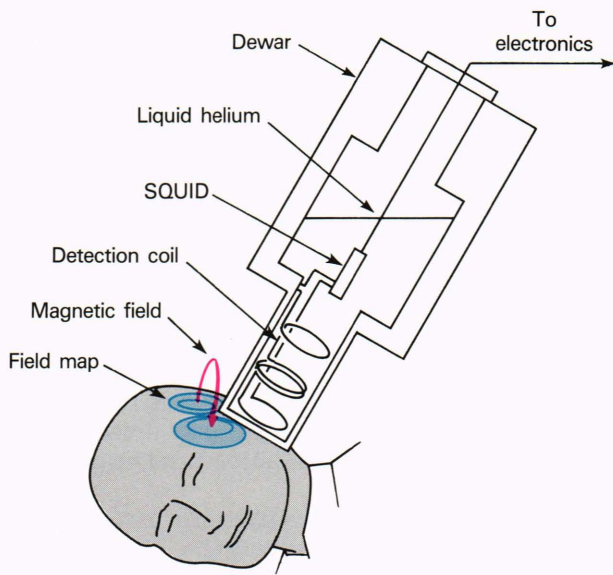
Figure 4—Double-differencing single-axis gradiometer receiving coils are used with a SQUID to detect magnetic fields from the brain. The coils and SQUID are supercooled by liquid helium in a cryostatic dewar.

Table 1—The origins of six types of magnetic noise and approaches used to reduce their effects.

Noise Type	Origin	Reduction Approach
Geomagnetic	Ionosphere, storm activity	Sensor design, shielding
Geologic	Earth's geology	Location, stationary
Urban	Power lines, cars, motors, radio stations	Auxiliary sensors, signal processing, shielding
Seismic	Natural seismic activity, traffic	Auxiliary sensors, signal processing
Biological	Neuroactivity, blood flow	Auxiliary sensors, signal processing
Sensor	Intrinsic property of sensor or electronics	Sensor design, materials

netically shielded room, seismic isolation, and auxiliary sensors, along with adaptive signal processing[5,6] to further reduce noise.

DIFFICULTIES WITH MEG LOCALIZATION METHODS

Figure 5 illustrates a typical measurement position matrix, giving points over which an SSDG MEG device is stationed. A contour map is drawn from the data, and the dipole location is found along a line drawn to connect the positive peak contour with the negative peak contour. Source depth is derived using algebraic theory for the magnetic field from a dipole in a sphere. Several problems occur in this localization method. First, it takes hours to accomplish the measurements, and the neuronal source is assumed to be temporally and spatially constant. Second, the mathematical model used to attain source depth is valid only for a sphere, which the head is not. Third, the accuracy of localization depends on the signal-to-noise ratio (S/N), the number of measurement points, and dipole orientation relative to the SSDG axis. Fourth, the algorithms used to fit theory to contour maps are computationally burdensome.

In Fig. 6a, we show the results of *in vitro* measurements performed at APL's Bioelectromagnetics Laboratory.[7] The SSDG measures the magnetic field at different angular positions around oscillating current dipoles located 0.5, 1.5, 2.5, and 3.5 cm away from the center of a sphere filled with saline solution. The measurements show well-defined peaks that fit well with theory, provided the S/N is large enough.[8] In Fig. 6b, we show the empirical results of similar *in vitro* measurements on oscillating current dipoles located 0.5, 1.0, 1.5, 2.5, and 3.5 cm away from the center of a nonspherical, teardrop-shaped reservoir filled with saline solution. There is virtually no peak in the magnetic field pattern for in-depth sources, and localization using the spherical theory is impossible.

Many investigators fail to quantify the S/N, laboratory noise, and the dependence of their localization on the number of measurement points and the choice of localization algorithm. Figure 7 shows the result of a Monte Carlo simulation of 10,000 trials of the localiza-

Figure 5—An illustration of the information gained from the magnetic field contours obtain with an SSDG: (a) field map measurement positions over which the gradiometer is placed, (b) magnetic field data taken sequentially for 1 s at each position. Up to 4 h is required to complete the measurement sequence. Two subtle signals shown as (1) and (2) in (b) lead to subtle changes in contour map (c) for event (1) and (d) for event (2).
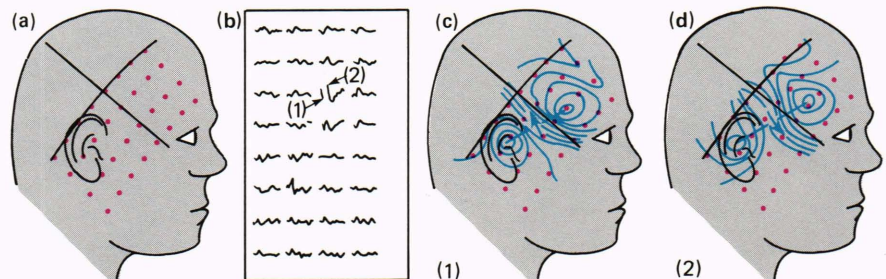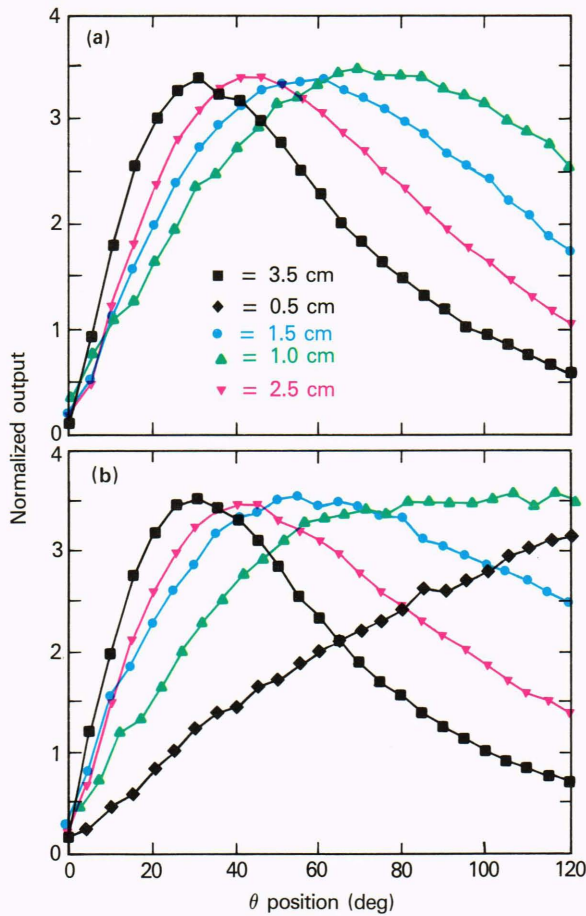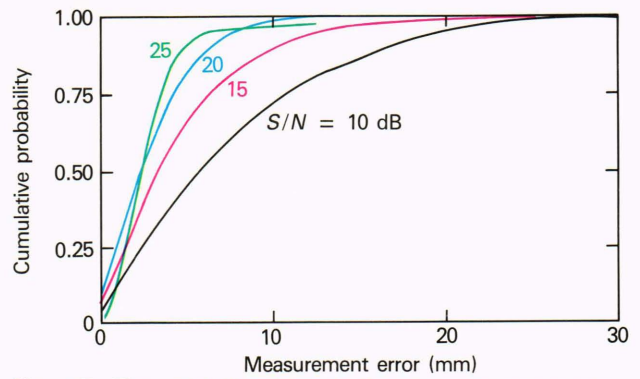
Figure 7—The probability of localization measurement error for a dipole in a sphere (radius = 10 cm) is described in terms of the S/N of the measurement. Here, the dipole is held 4 cm from the sphere center. The probability for error increases as the dipole is positioned closer to the sphere center.

Figure 6—Data obtained *in vitro* using (a) a 500-ml spherical flask and (b) a 500-ml teardrop-shaped flask, each enclosing an electric dipole in saline solution (SSDG location = 6.8 cm). The dipole distance relative to the center of the flask is changed, and localization peaks are found in each flask for near-surface dipoles, but peaks are not found in the teardrop-shaped flask for in-depth dipoles.

tion performance amidst laboratory Gaussian noise. Clearly the probability of reduced localization error is highly dependent on the S/N.

Moving SSDG MEG devices from station to station causes three major problems. First, because of their extreme sensitivity and vector measurement potential, they can vibrate and give false signals resulting from their motion in the earth's static magnetic field. At each measurement station, the experimental vibration spectrum is different. Second, MEG devices are cryogenically cooled with liquid helium (i.e., they are superconducting magnetometers). Movement of those sensors from station to station around the head to generate contour maps causes inaccuracies in calibration because of tilt and changes in helium levels. Third, at each new station or measurement point, the balance between the static magnetic field and internal magnetic trim tabs changes, creating another calibration error.

MULTI-AXIS LOCALIZATION

Wynn et al.[9] showed that a five-axis gradiometer magnetometer (Fig. 8a) could yield a three-dimensional
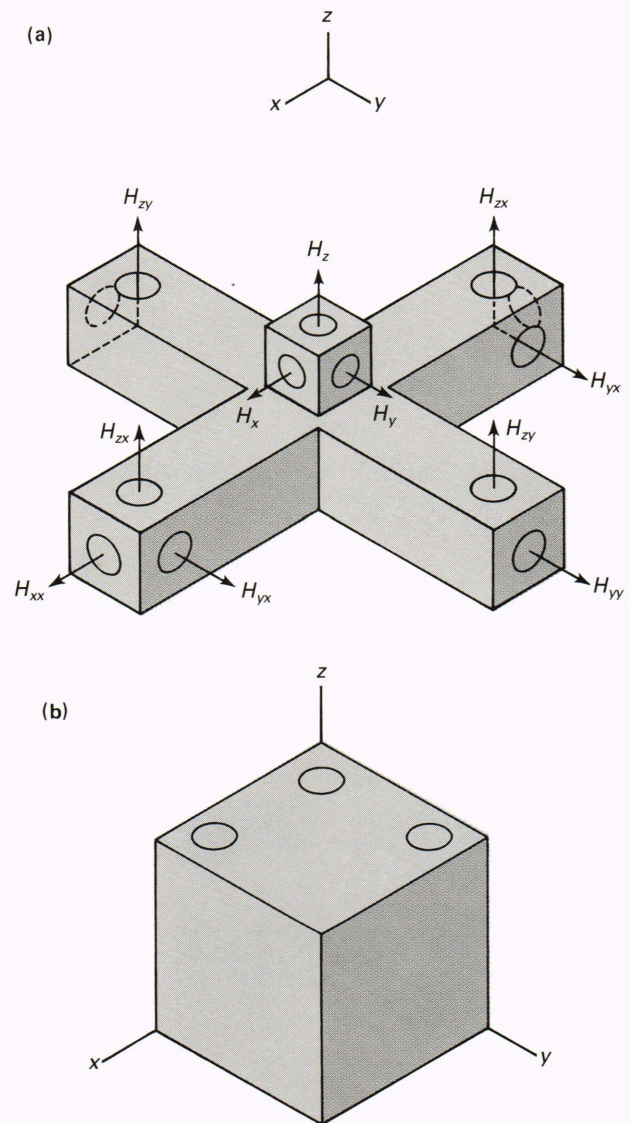
Figure 8—The concept for sensor loop orientation in a multi-axis gradiometer is given by (a) the complete gradient tensor for three-dimensional tracking and (b) a reduced three-gradient version for x–y tracking.

localization. It could also track a static, ferromagnetic dipole at ranges from tens to thousands of meters, depending on the dipole source strength and magnetometer sensitivity. Their device, which was not intended or designed for neuromagnetic measurements, used magnetic sensors spaced many centimeters apart. They also showed that a simpler three-axis device (Fig. 8b) could provide two-dimensional localization and tracking. Here, three magnetic sensors are oriented to measure the z component of the magnetic field. These sensors are positioned laterally along the x and y directions. Taking the difference between sensors 1 and 2 gives the gradient

$$\frac{H_1 - H_2}{\Delta x} = \frac{\Delta H_z}{\Delta x} = H_{zx} . \tag{1}$$

Taking the difference between sensors 2 and 3 gives the gradient

$$\frac{H_2 - H_3}{\Delta y} = \frac{\Delta H_z}{\Delta y} = H_{zy} . \tag{2}$$

The x and y locations of the dipole are given by

$$x = \frac{-3 H_z H_{zx}}{H_{zx}^2 + H_{zy}^2} \tag{3}$$

$$y = \frac{-3 H_z H_{zy}}{H_{zx}^2 + H_{zy}^2} , \tag{4}$$

and the vertical magnetic-moment source strength, M_z, of the dipole is given by

$$M_z = -H_z (x^2 + y^2)^{1/2} . \tag{5}$$

In the APL Bioelectromagnetics Laboratory, a reduced-size, three-axis coil gradiometer configured as shown in Fig. 8b was tested, with the coils separated by about 2.5 cm. The x and y locations were determined from this prototype device using the analog electronic circuit shown in Fig. 9. A small oscillating dipole was detected, localized, and tracked as it moved several millimeters in an x–y plane about 2.5 cm from the plane of the sensor loops. An example of this observation is given in Fig. 10. This demonstration showed the feasibility of using a three-axis gradiometer to localize and track small dipoles, within the dimensions of a head, using a device small enough to place beside the head.

Conceptually, a device such as that shown in Fig. 11 may be made to achieve three-axis localization in near real time from only one or two measurement stations. Localization may be done through empirical, stereotaxically implanted calibration dipoles, obviating the need for intensive model-dependent calculations. Features of this new device are as follows:

1. Each sensor can be any of the single-axis-type magnetometers shown in Fig. 3. The choice depends on the noise environment and whether magnetic-shielded enclosures are used. For example, Fig. 11 shows the use of an SSDG for each sensor in the device.
2. Simple superconducting coils connected to SQUIDs may be used, but any sensor will do if it provides sensitivities from 5 to 500 femtotesla.
3. Cryogenic cooling liquids may be used if required to attain sensitivity.
4. Three-dimensional localization may be attained with either two three-axis gradiometers oriented orthogonally or a single three-axis gradiometer moved to a second measurement position orthogonal to the first measurement position.
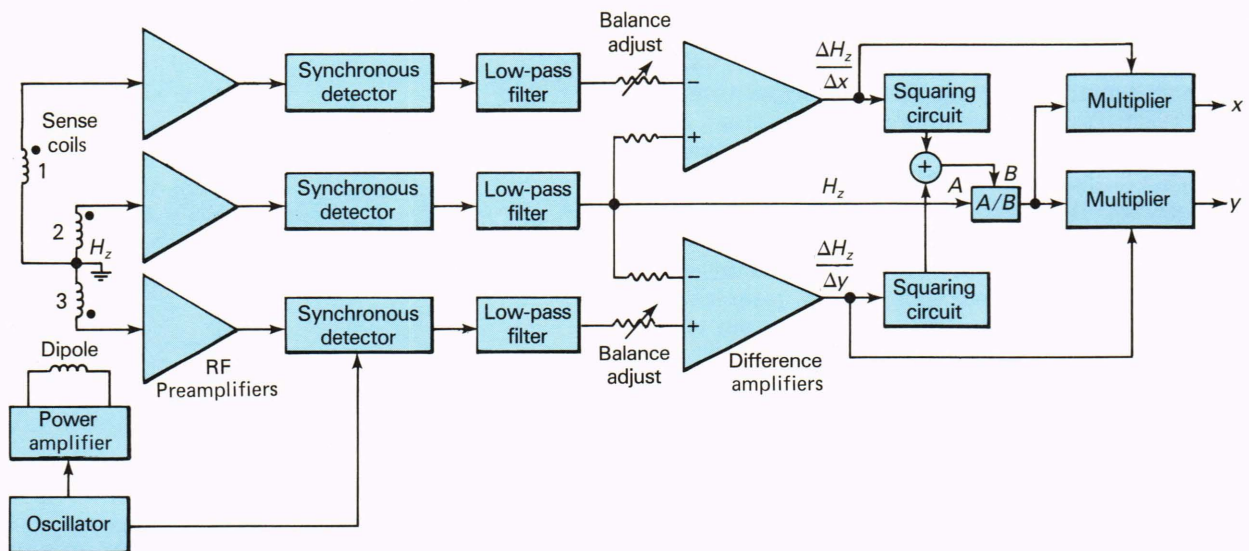5. The analog electronics used to attain the two-di-

Figure 9—Processing for the three-gradient x–y tracking gradiometer is straightforward and can be achieved with standard analog electronics.
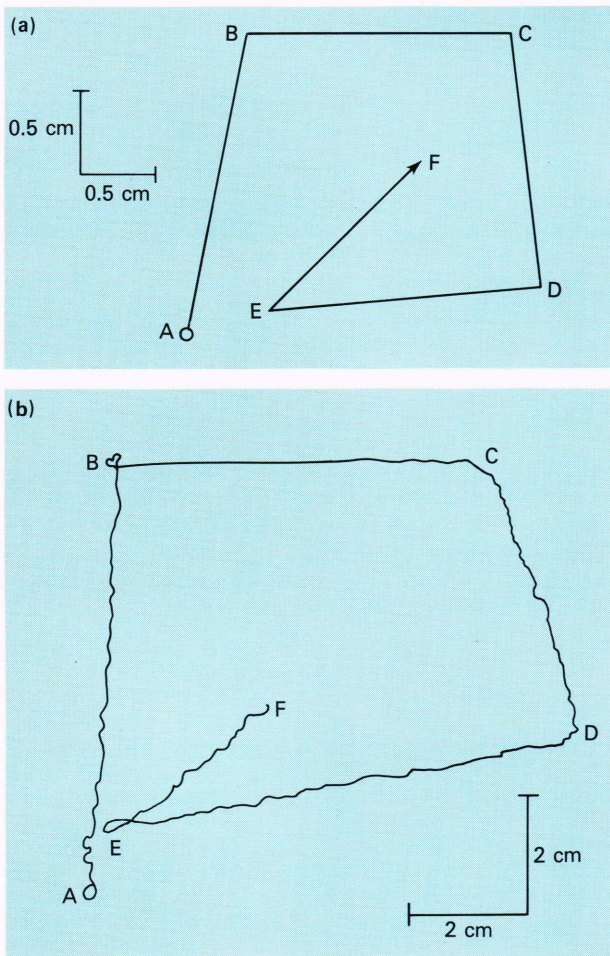
Figure 10—A demonstration of the two-dimensional tracking of a magnetic dipole with the three-gradient technique. The localization result can be displayed on either an x–y plotter or an oscilloscope (gradiometer position is 3 cm from source): (a) source-dipole motion and (b) localization display.

Figure 11—The concept of three individual second-differencing single-axis gradiometers used to reduce background noise and provide signals for two-dimensional tracking.

mensional localization (Fig. 10) can be replaced by a computer calculation of Eqs. 1 to 5 using the sensor output voltages.

Figure 12 is a systems diagram for a localization measurement using the MEG three-axis gradiometer, with auxiliary sensors to reduce noise contamination from sources such as sensor vibration; external, intermittent magnetic anomalies; and unwanted biomagnetic signals from the subject. Also shown in Fig. 12 is the use of a synchronization signal (e.g., one or two EEG channels) to help start or trigger the localization process.

SUMMARY

Ongoing research at APL's Bioelectromagnetics Laboratory is directed toward improving our new MEG device before it is fabricated and tested for clinical use. The localization performance of such a new device must be examined as a function of sensor loop size, sensor axis spacing and alignment, and source–sensor separation. We also must develop phenomenological descriptions for the neuronal sources to determine whether the
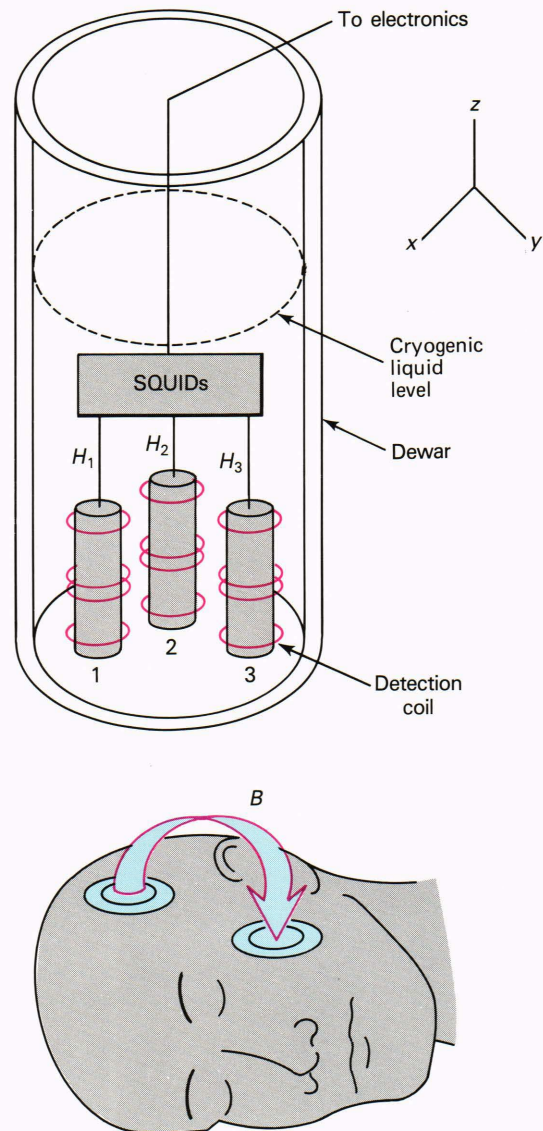
simple magnetic dipole assumption is reasonable. If these and other issues are addressed successfully, this new MEG approach will open exciting avenues for clinical use and functional brain research.

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Figure 12—A system-level description for the use of a three-axis gradiometer for tracking neuronal sources. Auxiliary magnetometers and accelerometers are used with adaptive filter signal processing to reduce background noise effects. A synchronous sensor, such as the EEG, is used to help trigger the gradiometer measurement.
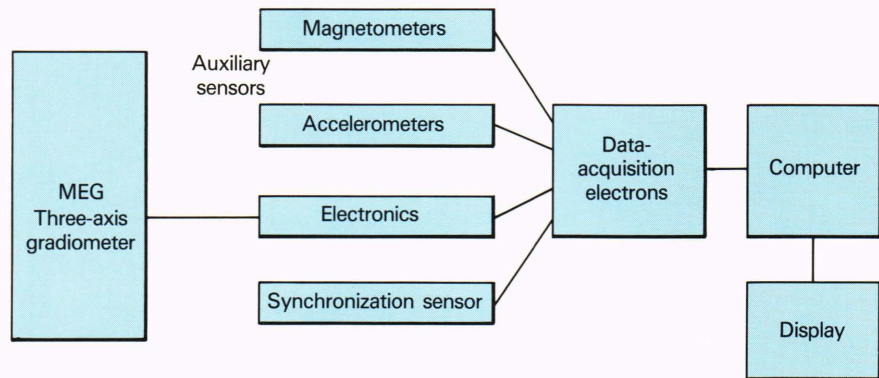
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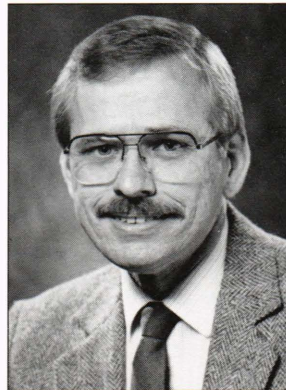
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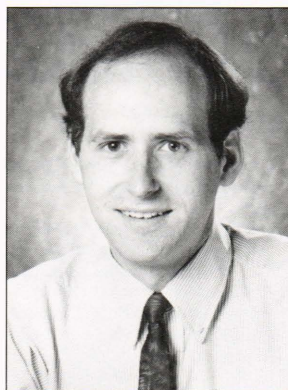
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