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(54) **Title:** ATOMIC MAGNETOMETER SENSOR ARRAY MAGNETOENCEPHALOGRAM SYSTEMS AND METHODS

(57) **Abstract:** Devices disclosed according to various embodiments use one or more arrays of atomic magnetometers to detect biologically derived magnetic fields. The disclosed devices and methods relate to application of utilization of a magnetic sensor with unique properties requiring changes in design, allowing new functions, and requiring alternative analysis methodologies. Various embodiments are also directed to methods for obtaining and processing biological magnetic signals. These methods may take advantage of the unique spatial arrangement of the atomic magnetometers and the capacity sensors to be used in either a scalar or a vector mode. Various embodiments have advantages over current magnetometer arrays for the purpose of detecting biological magnetic fields. Such advantages may include, for example: smaller size, lower power consumption, no necessity for cryogenic cooling, potential wafer-level fabrication, and/or the potential of better localization biological signals. In addition, various embodiments may allow increased target or subject mobility.

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ATOMIC MAGNETOMETER SENSOR ARRAY MAGNETOENCEPHALOGRAM SYSTEMS AND METHODS

FIELD

The field of various embodiments is the detection of biomagnetic fields, and more specifically the detection of magnetic fields of the brain and other aspects of the nervous system.

BACKGROUND

Many biological tissues, such as the human brain, produce both magnetic and electrical waves that can be detected using appropriate analysis techniques. Currently, electroencephalograms (EEGs) are used in clinical practice to analyze brain wave patterns, whereas nerve conduction studies (NCS) electromyograms (EMGs), and electrocardiograms are used in clinical practice to analyze peripheral nerve and muscle transmission. The analysis of electrical patterns derived from biological tissue has a number of applications, including detection and localization of seizures, detection and categorization of deficits of other neurological syndromes such as encephalopathies, encephalitidies, and some neurodegenerative disorders, detection and categorization of sleep states and sleep disorders such as obstructive sleep apnea, narcolepsy, REM behavior disorders, other disorders of arousal, identification of lesions in spinal cord, peripheral nerve disease, and characterization of dysfunction of muscle tissues.

With EEGs, the strength of a particular EEG signal is proportional to the proximity of the sensor to the signal. Signals that are closer to the scalp may therefore overwhelm deeper signals. In epilepsy, this has practical applications, as in many cases, including in most cases of temporal lobe epilepsy (the most common indication for epilepsy surgery) where the focus of the seizure activity is deep and difficult to detect with scalp electrodes. It is therefore common practice in epilepsy surgery centers to perform invasive surgery to place deep electrodes to obtain localization information. Additionally, the EEG detects transmitted electrical currents. Therefore, locations on the scalp may not directly overlie the source of the signal. Further, subject movement can affect and obscure the EEG signal.

In the case of nerve conduction studies, only some areas are accessible using current techniques, and the activity of nerve roots and nerves that are deep to the external surfaces of the body, such as autonomic nerves, the phrenic nerve (a nerve important for respiration), and areas where nerve roots interact (called nerve plexuses) are difficult to discern using commonly available techniques.

Unlike EEG, MEG detects current induced magnetic fields (flux through a sensing coil) rather than transmitted current. Compared to EEG, the MEG signal is less distorted by passage through the brain and scalp. The signal is therefore a direct measure of signal strength and direction, and the MEG can directly localize and measure sources of brain activity. Access to an MEG can therefore allow, for example, localization of a seizure focus without the morbidity of an invasive procedure, or monitoring of a deep nerve root that is otherwise not accessible using surface electrodes.

EEG, EMG and nerve conduction studies are volume-conducted. In the case of EEGs, this can make source localization difficult, while in the case of nerve conduction studies, certain potential sources of magnetic fields are not even detectable using surface electrodes. In contrast, magnetic fields are not distorted when traveling through tissue. Thus, MEG typically provides better spatial resolution than the EEG, particularly for deeper structures such as the hippocampus. This property makes the MEG an ideal noninvasive method for localizing epileptogenic foci and for functional brain mapping prior to neurosurgical procedures.

The lack of signal distortion by intervening tissue, as well as the lack of necessity of using a current reference (which is required with EEG) allows the MEG to pick up both high and low frequency signals that are increasingly being shown to be important in understanding the pathophysiology of autism, Alzheimer's disease, Parkinson's disease, and other brain diseases. With better understanding, evidence is also developing regarding a potential role of MEG in monitoring and early diagnosis of many brain conditions.

The MEG however is available at a relative paucity of medical centers, and clinical utilization is currently limited, due primarily to the expense of this technology. In many centers, despite a clinical utilization for detection of epilepsy focus, the major utilization of the MEG is in clinical research. There are a number

of factors that are responsible for the relative limited scope of the MEG in current clinical practice.

One concern with current MEG's is that they are expensive. A typical MEG uses 60 or more magnetic detecting coils in a dewar (an insulated vacuum chamber). Each coil is a Superconducting Quantum Interference Device (SQUID). SQUIDs require cryogenic cooling with liquid helium, which must be delivered by a pump or other means. An MEG typically requires a magnetically shielded room using specially designed Mu metals that can absorb and deflect magnetic fields. The plurality of SQUIDs are typically contained in a large, heavy, non-portable device that fits over the subject's head. SQUIDs measure magnetic flux, which is used to estimate field strength. The energy requirements, cooling requirements, and shielding requirements of the typical MEG result in a technology that is large, bulky, non-portable and expensive (often requiring an investment of 2-3 million dollars per MEG system). The cost of an MEG is markedly greater than that of an EEG.

Below, we describe new atomic-magnetometer based biomagnetic field detection systems which, in various embodiments, address sensor cross talk, shielding, mobility, and necessary algorithms for sensor calibration and data interpretation to allow development of a working MEG using a new sensor type that reduces size and expense and increases portability.

For example, we now disclose, first that atomic magnetometers have several characteristics that require new methodologies to deal with the issue of sensor cross-talk. Atomic magnetometers generate a magnetic field in the course of operation. This particular characteristic of these sensors requires special methodologies of operation and signal processing in order to produce a system that can actually measure biologically relevant magnetic fields in the brain or elsewhere.

Secondly, many atomic magnetometers may detect magnetic fields along only very specific vectors. While potentially advantageous for source localization, this added directional capability requires specific data processing and design elements to allow development of a useful array for measuring biological signals.

Third, the compact size of some atomic magnetometers, and the lack of necessity of supercooled Helium (as is required with SQUIDs), allows the development of an entirely new type of device and method. Specifically a mobile device and method allows the subject to freely move the head, neck, and in some cases ambulation while being continuously monitored.

Fourth, most sensitive atomic magnetometers, such as SERF magnetometers, require provisions for magnetic shielding or field cancellation to be clinically useful. We enumerate a variety of methods for these purposes.

Fifth, the possibility of utilizing large numbers of sensors allows the development of active sensor selection methods, which can in real time detect the optimal number and location of active sensors for a given clinical session or application.

Sixth, the atomic magnetometers operate at elevated temperature and thus may require some level of thermal isolation from the patient. This can come in the form of an insulating layer or active cooling.

Three published U.S. patent applications related to atomic magnetometer based magnetoencephalography are discussed below. U.S. Patent Application 11/319,792 to Park (Publication Number 20070167723, which is referred to herein as "Park"), discloses an array of optical magnetometer, not unlike optical magnetometers described by a multiple of inventors and authors, (e.g. see U.S. Patent 3,206,671 to Colegrove, and Fitzgerald, New Atomic Magnetometer Achieves Subfemtotesla Sensitivity, Physics Today 2003 (July), 21-23 for an excellent review of utilization of atomic magnetometers for biomagnetism). Specifically, *Park* describes a substrate and an array of optical magnetometers placed on the substrate. At least one of the magnetometers comprises a container having a chamber filled with an atomic vapor with an optical property capable of being changed by the presence of an external magnetic field across the chamber. The concept of utilizing an array of optical magnetometers to detect biological signals has been described (see Savukov IM, Romalis MV. NMR Detection with an Atomic Magnetometer. Physical Review Letters, 123001, April 2005; also publicly announced Navy STTR application proposal number N045-002-0070 (FY 2004), which discusses development of multi-magnetometer arrays useful for, among other purposes, "the field of biomagnetism", also see: Claire Bowles. Cheap hand-held MRI scanners may one day be a reality, Website

http://www.medicalnewstoday.com/articles/22435.php (e.g. popular science web-based science press), April 2005).

Park fails to address sensor crosstalk, and specific algorithms necessary for sensor calibration and data interpretation related to the specific capabilities of the sensors and fails to adequately address magnetic shielding. Further, Park and the other references noted above do not disclose a device and method that allows for subject mobility. Nor do they discuss advantages of the system related to vectoral sensing capacity, or the possibility of a system to utilize selective sensor activation to improve clinical utility.

Sensor crosstalk is an issue with respect to construction of a functional multi-celled device – specifically the propensity of atomic or "optical" magnetometers to generate magnetic fields in the context of use. In a low noise environment, the presence of an adjacent firing cell creates significant interfering magnetic fields which may prevent detection of brain magnetic waves.

In summary, while *Park* discloses widely reported developments it fails to adequately describe the features necessary to build a device actually capable of effectively measuring brain magnetic waves.

The disclosure of *Park* is preceded by the patents of *Romalis* (U.S. Patents 7,038,450 and 7,145,333). *Romalis*, in 2003, also discusses in the literature the development of an atomic magnetometer with subfemtotesla sensitivity with "the possibility of mapping non-invasively the cortical modules in the brain." (Kominis IK, Kornack TW, Allred JC, Romalis MV. A subfemtotesla multichannel atomic magnetometer. Nature 2003 April 10; 422(6932:596-599). Romalis' U.S. Patent 7,038,450 also describes a large scale multichannel single magnetometer, as is described in Romalis' 2003 paper. Notably, as is described in the article of Fitzgerald et al., (Fitzgerald, New Atomic Magnetometer Achieves Subfemtotesla Sensitivity, Physics Today 2003 (July), 21-23) the primary development described by Romalis in the longstanding field of atomic magnetometry is the development of an atomic magnetometer with excellent sensitivity and high spatial resolution, while others previously had developed high sensitivity only (see E.B. Alexksandrov et. al., Laser Physics 6, 244 (1996)). The device described by Romalis et. al. involves a single magnetometer, and further describes use for biological purposes. Romalis does not describe utilization of multiple magnetometer (e.g. multiple celled) arrays, or the complexities of a closely packed

array and signal processing that having a portable array of magnetometers would require.

In this application, we describe various devices and methods that, in particular embodiments, serve the relevant clinical needs of mobility, ease of use, and lower cost. In various embodiments, atomic magnetometers, arrayed around a patient's head in a mobile helmet, provide the significant advantages of allowing prolonged monitoring (which as noted cannot be easily performed now) as well as more comfortable monitoring which is necessary for example in optimally measuring children and disabled patients. We describe a number of clinical utilizations made possible by a portable array. We also describe the relevant challenges to developing a portable array in relation to signal processing, inter-sensor interference, magnetic shielding, and other significant challenges, as well as describing the solutions to these challenges. We therefore describe in an enabling fashion, for example, various multi-sensor arrays designed to be clinically relevant for medical use.

SUMMARY OF VARIOUS EMBODIMENTS

A biomagnetic field detection system according to various embodiments comprises: (A) a portable support structure; and (B) a plurality of sensors attached adjacent the portable support structure, each of the sensors being adapted for measuring magnetic field changes generated by a target structure within a living subject's body. In particular embodiments, the biomagnetic field detection system is adapted to detect and measure magnetic fields emanating from a target area within the subject's body and each of the plurality of sensors is an atomic magnetometer.

A subject monitoring system according to particular embodiments of the invention comprises: (A) a monitored area, (B) a sensor shielding apparatus for shielding sensors within the monitored area from the effects of magnetic fields external to the monitored area, and (C) a portable biomagnetic field detection system that is adapted to measure magnetic signals from a target area within a living subject while the living subject is within the monitored area.

BRIEF DESCRIPTION OF THE DRAWINGS

Reference will now be made to the accompanying drawings, which are not necessarily drawn to scale, and wherein:

Figure 1A is a cross-sectional schematic diagram of an exemplary MEG according to various embodiments.

Figure 1B is a plan view of two sensors that are paired for scalar detection in a plane.

Figure 1C is a perspective view of three sensors that are clustered and that are adapted to cooperate to act as a single scalar and vector sensor.

Figure 1D is a cross-sectional schematic diagram of a portion of an exemplary MEG according to a particular embodiment.

Figure 1E is a schematic diagram depicting a single mixed layer of sensors that are, respectively, adapted to operate in vector and scalar modes.

Figure 1F is a cross-sectional schematic diagram of a portion of an exemplary MEG according to a particular embodiment that features an additional layer of sensors for noise reduction purposes.

Figure 1G is a schematic diagram depicting a single mixed layer of sensors that are, respectively, adapted to detect field strength and magnetic flux.

Figure 2 is a cross-sectional schematic diagram of a sensor assembly according to a particular embodiment.

Figure 3 includes two cross-sectional, schematic views of a human eye.

Figure 4 depicts the areas of peak flux associated, respectively, with horizontal and vertical eye movements.

Figure 5 depicts a magnetometer or group of magnetometers with sensitivity along a single field direction as compared to one or more magnetometers that have scalar sensitivity.

Figure 6 is a schematic diagram that depicts how mathematical modeling may be used to define distance from current source.

Figure 7 is a schematic diagram of an MEG device according to particular embodiments.

Figure 8 is a schematic diagram of an exemplary atomic magnetometer that is suitable for use in various embodiments.

Figures 9A and 9B are schematic diagrams showing how a single laser generator may be used to simultaneously illuminate multiple sensors.

Figure 10 is a schematic diagram showing how a single heat source may be used to simultaneously heat multiple sensors.

Figure 11 is a schematic diagram showing examples of various types of measurement errors that may develop in the course of developing a large array of magnetic sensors.

Figure 12A depicts a first representative monitored mobile setting, including a confined recumbent setting allowing mobility specifically for repositioning.

Figure 12B depicts a second representative monitored mobile setting in which freer movement is possible (12.2).

Figure 13 is a schematic representation of shielding and positioning that may be utilized to minimize inter-sensor interactions.

Figure 14A is a schematic diagram of a sensor array that is adapted for in-utero measurement.

Figure 14B is a schematic diagram of a sheet of sensors that may be wrapped or draped over a member such as a patient's arm or chest.

Figure 14C is a schematic diagram of a sheet of sensors that may be wrapped or draped over a patient's spinal cord.

Figures 15A-C depicts a multiplexing sensor array. In particular, these figures demonstrate the concept of multiplexing, which involves operating sensors at temporally disparate points.

DESCRIPTION OF VARIOUS EMBODIMENTS

Various embodiments of the present invention will now be described more fully with reference to the accompanying drawings, in which some, but not all embodiments of the invention are shown. Indeed, this invention may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements.

Overview

Various embodiments are directed to magnetoencephalographic systems (MEGs) that use Atomic Magnetometers to provide an MEG with mobility, reduced size and cost. Various issues are addressed, including sensor crosstalk, electromagnetic shielding and cancellation requirements, and data registration and calibration. Since atomic magnetometers typically operate at a high temperature, in particular embodiments, in order to ensure patient comfort, the system comprises an array of atomic magnetometers and an insulating layer between the atomic magnetometers and the subject's head. The system may optionally also include magnetic shielding around at least some of the atomic magnetometers.

In particular embodiments, the atomic magnetometers record the magnetic fields generated by neuronal activity or other sources of magnetic fields and this information is transmitted by the MEG to a computer (which may be internal or external to the MEG). The computer then saves this information to memory. As part of this process, data will be processed by an algorithm that allows for optimal source location. Sensor registration techniques are utilized to optimize array output to maximize the overall accuracy of the array for the purposes of source localization. Optimally, the sensors will be calibrated and registered prior to use to allow sensor output to be accurately interpreted. The sensor registration process involves measuring a known signal at a known position with respect to the sensor or sensor array and obtaining information from each sensor related to its position, direction, and response. Additionally, in various embodiments, the sensor registration process characterizes cross-talk between sensors and unexpected noise in order to allow accurate signal deconvolution from interfering elements. Sensor registration is often important in accurate reading of large sensor arrays due to the many common sources of intra and inter-sensor differences in sensitivity, position, and interferences. Sensor registration, for example, may allow correction for inaccuracies in sensor placement, response, or operation (see Figure 11).

In particular embodiments, the information obtained by, and transmitted from, the MEG is used to estimate the magnitude, direction, and distance of the field generated by the magnetic field source. Due to the vectoral information available in many atomic magnetometers, special algorithms are required to convert the raw data into useful information related to source localization.

More Detailed Discussion of Particular Embodiments

An MEG according to a particular embodiment comprises a helmet, a sensor array (e.g., an array of atomic magnetometers) disposed adjacent an interior surface of the helmet, and a heat insulator (e.g., a molded heat insulator) that is shaped to fit over the subject's scalp. It should be understood that in various embodiments , unlike SQUIDs, the sensors may measure absolute magnetic field rather than magnetic flux. In other embodiments, more traditional devices measuring magnetic flux may also be used. In various embodiments, the sensor array is disposed between the heat insulator and the helmet's interior surface.

The sensor array may, for example, include a plurality of atomic magnetometers that are arrayed adjacent the subject's scalp. Also, in particular embodiments, each sensor within a particular array of sensors may comprise a cluster of individual sensors that are adapted to cooperate to function as either a single scalar or directional magnetometer.

In an embodiment, a stacked array of two or more positioned atomic magnetometers with capacity to sense magnetic field vectors (see Figure 1A) will be arrayed adjacent to a target. Sensors may also be arranged in such a way to allow scalar detection of field strength at a specific point in space. In other embodiments, more complex arrangements may be utilized. It is understood that nearby sensors will generate magnetic fields during operation that will create an unwanted signal that will interfere with the capability of a given sensor to detect the target signal. In the case of an array of sensors, therefore, it is desirable to address inter-sensor cross-talk.

A number of strategies are disclosed to manage sensor cross-talk, including simple multiplexing, which is a strategy that, in various embodiments, involves serially polling individual sensors. During polling of an individual sensor, the sensor is typically operating and both detecting a field and generating a field. However, adjacent sensors are typically not activated and, therefore, are neither generating a field nor detecting a field. Subsequently, activation of the first sensor is discontinued, and a second sensor is activated.

In particular embodiments, this method prevents development of inter-sensor cross-talk. A potential disadvantage of various embodiments of this technique is that, in large arrays, the time to poll all sensors can be prohibitively long. A further refinement of this technique is serial polling of groups of sensors that do not experience cross talk. There are several parameters that are useful for selecting which sensor groups might be simultaneously activated. For example, in some atomic magnetometers, there are certain angles of minimal sensitivity. Therefore, in various embodiments, sensors with this property, when located at the appropriate angle, may be simultaneously activated with acceptably small inter-sensor interference. Once these sensors are activated, and make their measurement of the field, the sensors are de-activated.

Subsequently, another cluster of sensors with the same properties is activated, making their measurement. In this case, each cluster of sensors functions as a unit that can be safely activated with minimal inter-sensor interference, increasing the number of sensors that can be simultaneously activated during multiplexing. In some embodiments, the distance between sensors, as well as relevant in-device shielding, is used to determine which subgroups are selected for simultaneous activation (see Figures 13, 15).

Figure 13 depicts shielding and positioning that may be utilized to minimize inter-sensor interactions. In this figure: reference number "1" refers to insulation/internal structure; reference numbers "2" and "3" refer to alternating sensors; and reference number "4" refers to magnetic shielding.

Depending on the type of sensors utilized, sensors may generate spurious magnetic fields during operation, which may be measured by adjacent sensors. In an array, methods of packing the sensors may be required to mitigate these effects. In Figure 13, the atomic magnetometer is assumed to generate a magnetic field related to the direction of light propagation within the sensor. In this case, alternating the direction of light propagation in the sensors, and/or including placing sensors in a random orientation, may be utilized to minimize the generation of large scale field effects, although in this case local field effects might still apply. In the case of other atomic magnetometers, different angles may be utilized, such as positioning sensors at angles of low sensitivity, to minimize inter-sensor interactions.

As is shown in Figure 15, which is discussed in greater detail below, multiplexing may be utilized to periodically turn on and off sensors to allow temporal dissipation of magnetic field effects. Additionally, shielding may or may not be interposed between specific sensors or sensor pairs to direct magnetic field lines away from adjacent sensors. As a benefit, magnetic shielding (e.g., creating a window of measurability) may augment the direction sensitivity of a given sensor or sensors. Finally, signal processing may be utilized to remove known frequencies related to operation of sensors from measurements (not shown). It should be understood, in light of this disclosure, that many other configurations using these concepts is possible.

In some embodiments, signal processing algorithms are utilized to allow localization and deconvolution of distal signals within a target by subtracting more proximal signals. In other embodiments, signal processing algorithms are used to subtract environmental noise. In some embodiments, one purpose of deconvolution will be the reconstruction of a three-dimensional map of the locations and intensities of the signals generated by the target structure.

Because, in various embodiments, the sensors do not require cryogenic cooling, and because of the relatively small size of the sensors, sensor density within a particular array of sensors may be higher than in a traditional MEG. For example, in particular embodiments, the sensors may be placed less than 3 mm from the subject's scalp in a closely packed array, thus allowing a higher sensor density that is closer to the target than typically utilized within a conventional MEG.

In particular embodiments, a second sensor (comprising a single magnetometer or cluster of magnetometers) may be positioned distal to a first sensor along the same axis (e.g., an axis that is perpendicular to the surface of the patient's head) at a sufficient distance to measure environmental noise. In such embodiments, because the first sensor is located closer to the signal source than the second sensor, subtracting the signals measured by the two devices will yield a difference in measured magnetic field. This information may then be used to determine signal and noise at the first sensor.

Stacking and grouping of arrays of sensors or arrays of sensor clusters may be utilized to progressively screen signal from noise and to account for spatially uniform sources of noise, or other externally induced magnetic fields. Since atomic magnetometers or similar sensors develop magnetic fields in the course of normal operation (typically related to the direction of light propagation along the sensor), the direction of light propagation among sensors may be alternated, or a random pattern of orientation may be utilized (see figure 13) to minimize large scale field effects. In some cases, additional magnetic shielding (such as mu-metal shielding) may be placed around a sensor or a cluster of sensors, for the purpose of further mitigating inter-sensor interference, and/or in order to provide a further screen for environmental noise. Since sensor-related magnetic fields typically have a particular magnitude and occur at a particular frequency, signal analysis techniques may be utilized to remove the influence of inter-sensor interference from the information derived from the sensors.

Standard methods for detection and localization of target magnetic fields may be utilized to define regions of interest for further analysis. In particular embodiments, fiducial markers may be used as necessary to define the relationship of sensors to the target.

In one embodiment, a selective activation of sensors can be utilized to increase the response speed of the system while monitoring between events. In this technique, a limited number of sensors is continuously monitored until specified event is detected. Subsequently, the appropriate local sensors to best characterize the critical event will be activated using multiplexing or other relevant techniques.

In various embodiments, induction of a magnetic field in at least some of the various sensors within the MEG allows these magnetometers to be used as specific, vector magnetometers. In others, magnetic sensitivity may vary along the axis of the sensor, allowing clusters of sensors to mathematically calculate magnetic field direction. A particular embodiment comprises a plurality of groups of single or clustered sensors. These groups are preferably adapted to detect specific direction of magnetic field. With some types of sensors, the combination of two sensors (in which the two sensors are positioned relative to each other to form a predetermined angle) may be needed to create a scalar sensor. An example of such a combination of sensors is shown in Figure 1B. This figure shows a

bimodal array of sensors. In this figure, two sensors are paired to allow for scalar detection in a plane. In this design, some directional information may be available as well, which may be combined with directional information from other sensors. In the case of one exemplary device, three sensors arrayed at a non-zero angle detect both the magnitude and the direction of a magnetic field.

In particular embodiments, three or more individual MEG sensors may be arranged to form angles relative to each other (with each specific angle dependant on individual sensor properties) to allow for estimation of both field direction and gradient with respect to a single point – e.g., within a single cluster of sensors (See Figure 1C). In various embodiments of a cluster array, atomic magnetometers may be arrayed in clusters of one or more sensors at an appropriate angle. Two examples are shown to indicate that a variety of angles dependant on the direction of maximal sensitivity of the sensor may be used. In this setting, mathematical techniques may be used to operate the sensors to determine both the size and vector of the field.

In particular embodiments, the MEG may include two or more layers of sensors (See Figure 1D). These layers of sensors may, in various embodiments, be used to gather field gradient information, which may be used to improve the spatial resolution of the field source. Turning to Figure 1D, clusters of sensors (each cube may represent one or more individual magnetometers that collectively operate as a single sensor) may be arrayed in groupings to maximize scalar, vector, and gradient detection of field, allowing maximization of localization. In this figure, three-sensor clusters (shown as cubes) are arrayed in successive linear arrays. In particular embodiments, levels A through D are arranged as in Figure 1A.

In various embodiments, the MEG's sensors may be alternatingly arranged within the MEG's various rows of sensors (See Figure 1E). As shown in Figure 1E, sensors may also be grouped so that sensors in a vector mode ("V") are located adjacent to sensors operating in a scalar mode ("S"), and/or in overlapping arrays. One layer is shown, for the sake of simplicity, but multiple layers, with columns of vector and scalar sensors or overlapping vector and scalar sensors, may be used. In most cases, the ideal arrangement of sensors is defined by the best mathematical fit for a particular application.

In addition, in particular embodiments, the MEG's sensors may be arranged so that magnetic shielding is positioned between a first array of sensors and another array of sensors (See Figure 1F). In Figure 1F, an additional layer of sensors, with each sensor comprising one or more atomic magnetometers, is grouped outside of a shielded region to allow for noise reduction. In this figure: (1) item "A" is a patient's scalp; (2) item "B" is insulation; (3) item "C" is a three-dimensional vector, scalar, and gradient detection array (see also Figure 2D); (4) item "D" is a layer of Magnetic shielding, such as mu metal shielding; (5) item "E" is a noise reduction array; and (6) item "F" is an outer shell. One or more arrays of sensors in vector, scalar, and/or gradient mode may be utilized, depending on the application.

Accordingly, in various embodiments, the first sensor array may be utilized for signal detection, and the second sensor array may be utilized to assess the level of noise present in the signals measured by the first sensor array. More particularly, in such embodiments, the signals measured by the first sensor array may include both magnetic fields from a target area within the patient's body (e.g., the patient's brain) and noise. However, because the second sensor array may be shielded from magnetic field's emanating from the target area, in various embodiments, the second sensor may measure substantially only the noise adjacent the first magnetometer. Accordingly, the magnetic fields from the target area may be determined by subtracting the noise (as measured by the second array) from the signals measured by the first sensor array.

In addition, in particular embodiments, atomic magnetometers that detect absolute field strength may be alternated with sensors that detect changes in magnetic flux (See Figure 1G). In Figure 1G, one layer of sensors is shown, for the sake of simplicity, but other arrangements are possible and the ideal arrangement is defined by the application.

Figure 1A depicts an MEG according to a particular embodiment, that may allow for vector and gradient detection. In this embodiment, the MEG includes: (1) an internal insulator that is adapted to insulate the subject's scalp from heat; (2) a sensor compartment that may optionally be thermally cooled; and (3) an outer shell that may comprise magnetic shielding (e.g., Mu metal shielding). In particular embodiments, the MEG includes additional layers of sensors. These

additional layer may be used, for example, as described above, for noise reduction purposes.

As an aside, in Figure 1A: (1) item "A" is patient's scalp; (2) item "B" is a heat insulator; (3) item "C" is the interior of a helmet; and (4) item "D" is an external helmet array, which may comprise magnetic shielding such as Mu metal shielding. In a linear array, sensors are typically arrayed in a substantially linear formation substantially parallel to the subject's scalp. Additional sensors (one or more rows) may be located substantially parallel to the row of sensors closest to the scalp for improvement in targeting and noise reduction. Mathematical techniques across multiple sensors in the array may be used to derive directional information and distance.

In an alternative embodiment, an example of which is shown in Figure 2, a plurality of sensor assemblies may be individually placed adjacent to a target. For example, a plurality of sensor assemblies (such as the sensor assemblies shown in Figure 2) may be attached directly to a subject's head using a suitable medical adhesive. Such assemblies may be used within a helmet, as well.

In Figure 2: (1) item "A" is a subject's scalp; (2) item "B" is thermal insulation; and (3) item "C" is a sensor array comprising one or more sensors. Each cube in this figure may represent one or more magnetometers grouped as a single sensor. Furthermore, in this figure: (1) item "D" refers to magnetic shielding, including mu-metal shielding; (2) item "E" refers to an unshielded sensor array; (3) item "F" refers to external thermal shielding and electronics; (4) item "G" refers to the body of the external device, and (5) item "H" refers to a wire for transmitting information.

In this figure, one sensor is shown. However, more than one sensor may be included in the array. The positions of the elements shown in this figure are exemplary. Other positions, based on issues of best evaluating potential sources of noise, may be included. For example, sensors may be placed laterally adjacent the sensor (e.g., at location E1) or at other locations. Other mechanisms of transmitting information to a central processor (e.g. wireless communication) may also be used.

In various embodiments , the MEG is adapted to measure magnetic fields associated with eye movements, and to use these signals in monitoring the subject. For example, these signals may be used to monitor the subject's alertness.

The human eye is polarized (see Figures 3 and 4), and movement of the eye causes a magnetic flux that can be detected with magnetometers. As shown in Figure 3, Ions are pumped across the retinal epithelium leading to the development of a relative charge differential in the eye that is concentrated in the posterior and lateral aspect of the globe. There is minimal charge differential in the anterior aspect of the globe. As the eye turns through space, the motion through space of the relative charge differential associated with the retinal epithelium creates a time dependent magnetic field that can be detected with magnetic field sensors.

Turning to Figure 4, the peak magnetic flux from an individual eye movement depends on the direction of the eye movement. Eye movements can therefore be detected and either screened from the MEG output, or individually evaluated for additional information.

In particular embodiments, a plurality of sensors may be arranged to optimize measuring the magnetic fields associated with the subject's eye movements. For example, in various embodiments, a plurality of sensors may be embedded into a set of eyewear such as goggles or eyeglasses (e.g., with a plurality of sensors mounted adjacent the circumference of one or more of the goggle's lenses) and used to continuously monitor the magnetic fields associated with the eye movements of a subject who is wearing the eyewear. In other embodiments, the target may be the source of much of the polarization of the eye - the neural tissue at the back of the subject's eyes (the retina). In this embodiment, the sensors are used to conduct a magnetoretinogram.

In another embodiment, a plurality of sensors may be embedded into a helmet (e.g., adjacent the portion of the helmet that would be disposed immediately adjacent to the subject's forehead and/or temples when the helmet is worn by the subject). Such sensors may be used, for example, for screening purposes for noise reduction, or conversely to monitor eye movements (as described above) for a specific application.

Various embodiments include other focused groups of sensors that are similar to the focused groups of sensors included in the goggle example above. For example, a compact group of sensors may be imbedded in the posterior interior portion of a helmet and used to monitor the patient's level of arousal. In other examples, focused arrays of sensors may be positioned, for example: (1) along the subject's spinal cord; and/or (2) along other nerve pathways, such as peripheral

nerves. Such focused arrays may be used separately or in conjunction with cerebral sensors to monitor a subject.

As noted above, sensors according to various embodiments may be vector sensitive. In particular embodiments, vector-sensitive sensors that are most closely aligned with a particular focus may obtain a relatively weak signal or no signal if the field vector is aligned along an axis of minimal detection sensitivity. As the vector of the magnetic field aligns with more distant sensors, detection of the field depends on (1) the vector product of the field with respect to the vector of maximal detection of the sensor, and (2) the distance from the field source (Figure 5).

Figure 5 demonstrates the concept of a vectoral and a scalar input. This figure shows a magnetometer or group of magnetometers with sensitivity along a single field line (1a through 1e) and magnetometers that have scalar sensitivity (2a through 2e). In various embodiments, the magnetometers in Figure 5 are adapted for evaluating the location of a current traveling into the page. A schematic representation of magnetic field lines emanate from this current.

Turning further to Figure 5, in 1a through 1e, the sensors are displayed as being sensitive to field strength along the vertical axis. In this mode, even though field strength is high at 1a, effective detected strength in a vertical direction is 0. In arrays where three scalar sensors are arrayed at an angle, addition and subtraction of the relevant current strengths at each sensor can be used to develop information at each sensor in each mode.

In 2a through 2e, the sensors are operating in a scalar mode. As the magnetic field decays by the inverse square of the distance, progressively smaller amounts of flux may be detected with increased distance. A single line of sensors is shown in Figure 6. However, the same or another sensor or group of sensors in a scalar or additive mode may be able to further define the absolute direction and magnitude of the current source.

If a multi-sensor array is utilized, a particular mathematical computation will, in particular embodiments, allow a scalar mapping of field strength (Figure 6, second row). Although not shown, the different angle of detection will also result in a change in shape of the detected signal which can also be used to better characterize the localization of the focus. A second row or more rows of sensors (not shown in Figure 5) can be also used to better characterize distance of the source, using the law of decreasing signal by the square of the distance.

Turning to Figure 6, an exemplary two-dimensional array of magnetometers is shown to illustrate how mathematical modeling might be used to define distance from current source. In this Figure, a strong dipole is located traveling into the page (in this case, we would assume we are visualizing a dipole traveling into a horizontal gyrus). Sensors are arrayed such that the array has vectoral, scalar, and gradient detection capacity. Combining gradient, vectoral, and scalar detection components, size of current source, direction, and distance can be calculated. Temporal relationships of inputs across the array may also be utilized to resolve location.

In a particular embodiment, a row of sensors having vector and scalar detection capabilities are arrayed in layers in order to determine information on the current location, strength, and distance of the various magnetic fields. In a particular embodiment, these layers of sensors are embedded in or adjacent a portable, helmet-shaped device (which is preferably of a weight that is suitable to be carried on the subject's head for an extended period of time while the subject is walking from place to place, or at least mobile). In particular embodiments, the layers of sensors are arrayed within an internal layer of insulation and an external layer of shielding, with or without external noise reduction sensors.

An exemplary embodiment of a portable MEG device is shown in Figure 7. This embodiment includes an array of sensors located within the helmet. As discussed above, other localized arrays of sensors (such as the eyeglasses or paraspinal arrays described above) may be used simultaneously in conjunction with the helmet. In various embodiments, the MEG device (A) may be connected to a data analysis pack via an electrical cable (B) or via another communication device, including, for example, a fiber-optic cable or a wireless communication device. The data analysis pack (C) might contain, for example common analysis tools used in the state of the art, such as a photodiode, A/D Converter, Amplifier, High and Low Pass Filters, and 60 hz filter. A microprocessor with data analysis software and a graphics display station (D) may be included. A portable data analysis unit comprising items B through D above (recording input but with or without a remote graphics display capability) that can be attached to the subject during mobile capable activity may also be utilized. Although exemplary embodiments of a portable MEG device may include a sensing array located in a

helmet (as discussed above), the MEG device may be in forms other than a helmet, such as in the form of eyeglasses or a paraspinal array.

In particular embodiments, the MEG's various sensor arrays are adapted to communicate (in any suitable manner) with a data analysis pack. For example, in particular embodiments, the sensor arrays may be connected to communicate with the data analysis pack via an electrical cable, a fiber-optic cable, or a wireless communication device.

As may be understood from Figure 7, a suitable data analysis pack may include, for example, suitable analysis tools, such as a photodiode, an A/D Converter, an Amplifier, High and Low Pass Filters, and/or a 50 and/or 60 Hz multiple notch filter. The data analysis pack may further include data analysis software and a graphics display station.

In particular mobile embodiments, the MEG includes a plurality of arrayed sensors that are connected to a portable power source and recording system. In this embodiment, the MEG is preferably adapted to transfer (e.g., upload) data to a remote computer where the data may be processed and viewed. In this case, although a rigid helmet may be used, another embodiment might include embedding sensors in a flexible material that can be expanded to fit a larger head or can contract to closely fit smaller heads. Although in the embodiment the device is flexible, it is anticipated that different device sizes may be needed for different populations (e.g. pediatric versus adult).

In the case of a portable device, various embodiments may include introduction of a portable device into a CT, PET, SPECT, or MRI scanner or other imaging scanner, allowing for MEG to be performed in an MRI suite either temporally close to or, in the presence of appropriate time-locked field information, simultaneously with MRI or fMRI, or simultaneously with a PET scan. Additionally, CT, MRI, fMRI, SPECT, PET scanning, or MR Spectroscopy may be performed in temporal proximity to a MEG. In some embodiments of the invention, an ultrasound may assist with targeting a mobile array or be performed simultaneously or in close temporal proximity to add relevant information.

In a further embodiment of this device, EEG analysis techniques (or other suitable analysis techniques, such as MRI imaging techniques) for defining a known lesion or nucleus may also be utilized to provide useful targeting information to allow for more efficient modeling of potential mathematical solutions to the prospective target.

Various embodiments of the systems described allow for the specific evaluation of deeper nuclei in the brain. In one embodiment, a time-locked signal (such as a somatosensory signal or a movement, such as a leg movement or hand movement) may be used as a repeated signal, and repeated averaging of the evoked response may be used to define a specific signal at a specific location in the brain. For example, a sensor array with a specific field bias may be arrayed to triangulate maximal sensitivity in the direction of deep structure such as the locus coeruleus, basal ganglia, the substantia nigra, or other brainstem or deep nuclear structures of interest. Mathematical algorithms may be used to screen out noise (in this case, other brain activity as well as external activity). This can be used for a registration signal that then allows for further refinement of signal localization and isolation of deep brain signals.

In various embodiments made possible by the mobility of this device, these systems described may be utilized for the specific purpose of evaluating the brain during sleep, during coma, during psychiatric disease (including drug or alcohol addiction), or during periods of altered mental status. In various embodiments, the mobility of this device may allow for more effective prolonged monitoring of the brain in order to localize epileptiform foci. Functional mapping includes mapping of the specific anatomical localization of various brain functions such as language or motor functions. Functional mapping in various embodiments may be utilized for localization of cortical function prior to neurosurgical procedures to guide surgical approach. In other embodiments, it may be utilized for intra-operative mapping or monitoring. In still other embodiments, functional mapping may be used to gauge the results of therapy for neurological or psychiatric disease, or for the purposes of research to better understand brain function. It is anticipated that various embodiments may be able to evaluate or diagnose certain conditions, such as evaluating signals emanating from the brain or eyes that may indicate a decreased level of arousal. In the case of monitoring of level of arousal, it is

anticipated that such monitoring may be useful for individuals involved in tasks where a high level of arousal is important.

It should be understood that a number of different embodiments of the sensory array may fall within the scope of the present disclosure, including sensory arrays that are lightweight and potentially utilizable in mobile capable settings. Utilization of arrays that have specific vectoral capacities and that are adapted to be rotated and focused on an area of interest may also be utilized to improve signal detection.

Although this disclosure focuses, to a large extent, on magnetoencephalograms, it should be understood that the apparatuses and techniques described herein may be used in a wide variety of applications. For example, as noted above, the techniques described herein may be used to monitor a subject's eye movements by monitoring changes in magnetic fields caused by the movement of the subject's eyes. Also, as discussed above, because various embodiments of the magnetometers are small, have low power requirements, and are relatively inexpensive, the sensors may be built into portable helmets or eyeglasses that may be used, for example, for continuously monitoring a subject's eye movements or brain electrical patterns (e.g., as the subject conducts their daily activities). Other biomagnetic applications (e.g. detection of signals from peripheral nerves, autonomic nerves, spinal cord, or biomagnetic signals from other non-neural organs) will be apparent to those skilled in the art.

Because cryogenic cooling is not needed for the performance of various atomic magnetometers, no dewar is needed in particular embodiments. A cooling fan may be needed in some configurations, due to the fact that, in some embodiments, each atomic magnetometer incorporates heaters which heat the detection cell. In some embodiments, heating methods that operate over multiple sensors may have a greater total heat load heating and may result in the need for insulation or other cooling methods. For example, cooled water or another cooling substance may be circulated in an insulator between the subject and the heater in order to minimize unwanted heat transfer.

In the case of MEG, the subject's head should be aligned and held steady within a helmet-shaped cavity. The alignment of the subject's head within this cavity may permit a close approximation of the desired location of the magnetic field sensors. For example, the midpoint of the subject's head may be determined by aligning: (1) a fiducial mark placed on the subject's nose one-half of the distance between the inner edges of the subject's eyes, with (2) a fiducial mark on the posterior aspect of the MEG's helmet portion. In the case of portable magnetometer arrays used for the purposes of monitoring other signal sources, fiducial markers may be placed in other appropriate locations.

Other fiducial markers may be used, preferably oriented or even connected with an inner helmet cavity associated with the MEG. Because one purpose of various embodiments of the MEG is be to correlate brain activity with localization, in particular embodiments, non-magnetic but radio-dense fiducial markers may be used to allow subjects to have a head CT performed after the MEG is conducted. The fiducial markers may then be used to merge the results of the CT scan into the results of a previously performed MRI, allowing precise localization of MEG output.

In another embodiment, a mobile array may be combined with stationary fiducials. These may be used to correct for any relative motion between, for example, a mobile helmet and the patient. Additionally a mobile helmet may be combined with stationary sensors located elsewhere in the room or nearby the patient which are used to correct for environmental noise, for example. In these cases, motion tracking technology may be utilized to augment sensor registration.

Mathematical Analysis of Data

Unlike traditional MEGs, in which a relatively small number of sensors (around 300) are typically utilized, MEGs according to various embodiments may include larger numbers or a more dense placement of sensors for primary sensing, and a similar number of sensors may be utilized, for example, external to Mu metal shielding in a helmet for noise reduction purposes. With this large number of data points, specialized signal processing methods are used to sort signal from noise and optimize the detection capacity of the MEG. Therefore, methods of optimization are used to evaluate signals and remove non-random errors and biases.

For example, in particular embodiments, optimization is utilized to manage sensor registration. A significant problem in some sensor arrays is the accurate registration of sensors in the network. A number of sources of error, including sensor calibration offset, platform flexure, sensor perspective offset, sensor internal clock errors, and coordinate transforms can all degrade the accuracy of a network of sensors. Sensor registration can be seen as the process of accounting for (e.g., removing) non-random errors, or biases, in the sensor data. Without properly accounting for the errors, the quality of the composite image can suffer. Recently, Hirsch, Panos, et al. (Hirsch, Panos, 2006) developed a rapid algorithm for solving the sensor registration problem using a novel continuous meta-heuristic. This algorithm assumes that not all data is seen by all sensors, and that the correspondence of data seen by different sensors is not known a-priori. A key process for measurement of systems comprising large numbers of sensors is sensor registration, which broadly applied refers to applying correction factors to sets of data measured by more than one sensor. Examples of how sensor registration may be used in various embodiments is described below:

A magnetic sensor may read a particular field at the location of the sensor. Other sensors sample values over the region. With a measurement system comprising a distributed array of sensors, the magnetic field characteristics (magnitude, direction, and estimated distance) may be mapped. Furthermore, more detailed characterization of the field characteristics may be acquired if multiple sensors overlap. The field characteristics may be averaged over the readings from multiple sensors, for example. The process of aggregating data from multiple sensors is referred to as data fusion. Proper data fusion requires sensor registration. In this example, magnetic field offsets among the various measurements (magnitude, direction, and estimated distance) are determined. Also, the relationship between the coordinates of a point measured relative to a specific sensor and the coordinates of the same point with respect to a different sensor are determined. Furthermore, since the magnetic fields are measured as a function of time, and if times are read from a time stamp relative to an internal clock in each sensor, synchronization of the clocks to a common reference is required. Further, although location of sensors within the array is presumed to be well known in most cases, and the probability of mis-identifying the location or orientation of a sensor is low, the probability is not zero as there may be errors in

the fabrication device. Figure 11 shows some examples of errors that might occur in a fabricated atomic magnetometer array. The figure is meant to be exemplary, and does not display all the types of errors that may occur in an array.

Turning to Figure 11, an offset in sensors from other sensors in the array (see Item "1" in Figure 11) may result in alterations sensor signal measurement. As shown in Item "2" of Figure 11, sensor movement may be another source of errors. This may be caused, for example, when a sensor moves during the course of measurement (for example, due to patient head movement or internal mechanical vibration). In addition, a fixed offset in sensor angle may cause a change in characteristics of a sensor signal measurement (see Item 3 in Figure 11). Furthermore, in some cases, an internal source of magnetic fields may occur and alter sensor signal measurement (see Item 4 in Figure 11).

The chance of errors is likely to increase as the size of the sensor array increases. Thus, in complex systems such as described in some embodiments, multiple sets of data are collected from multiple signal sources by multiple sensors. With this in mind, the sensor registration should be performed in each mode that will be used for data collection. For correct characterization of the signals, correct identification of the signals must therefore by developed with a process to minimize local non-zero sources of noise (such as magnetic interference that might develop from a design flaw in magnetic shielding or insulation, improper sensor location registration, improper sensor orientation registration, or internal variability from sensor to sensor in sensitivity). One approach to sensor registration between two sensors involves minimizing a likelihood function associating the measurement of the signal by two or more sensors. With this approach, sensor registration falls into the category of optimization problems.

In specific embodiments, a method for registering a first magnetic sensor and a second sensor may be used using a two-step process wherein a systematic error function is separated from an assignment function. The systematic error function is based at least in part on a likelihood function associating a data element from the first set of measurements with a data element from a second set of measurements. The minimum of the systematic error function is generated to determine a correction factor for the systematic error. An assignment method is then used to assign a signal from a first plurality of signals to a signal from a second plurality of signals, based at least in part on the minimized systematic error

function. Decomposing the problem into a systematic error problem followed by an assignment problems leads to a less complex, more computationally efficient method for sensor registration. In more specific embodiments, the systematic error function is minimized by applying a global minimization technique. An advantageous global minimization technique is Continuous Greedy Randomized Adaptive Search Procedure, which is computationally efficient and has a high probability of finding global minima, or a least a good estimate of global minima.

In some embodiments, after the registration process (in the cases where it is used), data must be interpreted. The data coming from each sensor is a convolution of signals from throughout a large area and the response function of the sensor. The results from these sensors is unintelligible without an algorithm for deconvolution of all of the responses of the sensors allowing for localization of each individual signal to a specific region of the brain. One example of a simple algorithm was mentioned earlier, in which common signals from adjacent sensors are subtracted to yield (to first order) signals from deep brain. A full algorithm allows for solution in 3 dimensions of the deconvolution of the each sensor response. Without such an algorithm, the array of optical magnetometers does not yield a 3 dimensional image of the magnetic sources.

Other suitable methods of data optimization may also be utilized to optimize data from various embodiments of the MEGs sensor array. In addition, specific analysis techniques that are appropriate to specific sensor configurations may be developed.

Exemplary Suitable Sensors

As noted above, various embodiments use optical atomic magnetometers to evaluate magnetic fields. In the current state of the art, many of these devices: (1) can be made small (e.g., less than 12 mm^3); (2) do not require cryogenic cooling; (3) are adapted to detect magnetic fields in the picoTesla or femtotesla range; (4) can be made to have a low power requirement (< 200 mW and theoretically as low as 25 mW of power); and (5) can be designed to be produced using wafer-level fabrication techniques, potentially significantly lowering the cost of an MEG.

Further improvements in the state of the art are anticipated, and it should be understood that the techniques described herein may yield other designs for sensors with vector and scalar detection capacities on more compact scales or larger scales. The smaller overall potential scale raises the additional possibility that a more compact shielding array will be feasible. Larger scales may offer advantages of higher sensitivity or allow for more reliable operation.

Figure 8 shows an example of a particular style of chip-scale magnetometer that is suitable for use in various embodiments. In this version, described by Moreland & Hollberg et. al. (2003), the VCSEL (laser) is tuned to the D1 line of ^{87}Rb at 795 nm. A local oscillator modulates the current to the VCSEL at 3.4 GHz, half the hyperfine splitting of the Rb ground state, creating two laser sidebands that are resonant with two hyperfine ground states. The magnetic field is measured by probing the hyperfine transitions between two magnetically sensitive hyperfine states at optical frequencies. Another similar device from the same group uses a slightly different method, using a single beam Larmor frequency, which achieves maximal sensitivity to a field oriented at 45 degrees with respect to the sensor's optical axis (the device is not sensitive to magnetic fields perpendicular or parallel to the axis of the optical axis). With either device, arrangement of three sensors at a variety of angles will result in detection of a magnetic field in any direction, as well as determination of the vector and field strength of the field.

Although the sensors of various embodiments are described herein as atomic magnetometers, it should be understood that any suitable sensor may be used in accordance with various alternative embodiments.

Use of a Single Laser Source For Multiple Sensors

While, in particular embodiments, individual magnetometers may be provided with individual laser sources, in other embodiments, a single laser (or multiple lasers) may be used to provide the light for a portion of a particular array of sensors, or even an entire array of sensors (see Figure 9). Figure 9 is a representation of a remote laser generator with fiber optic lines directing lasers to sensors for an atomic magnetometer array. In this Figure, item "A" is a laser generator, item "B" refers to fiber optic cables carrying lasers, and item "C" refers to sensors. For vectoral sensors that utilize lasers, a single laser can be directed to multiple sensors. As can be seen in this representation, absolute orientation of the

sensors is arbitrary, and dependant on application. Although, in this schematic a limited number of sensors are powered, it is conceivable that a single laser might be utilized for a significant portion of the array, or the entire array.

Use of a Single Heating Source For Multiple Sensors

Similarly, instead of using individual heaters to heat the individual sensors (as is done in various embodiments), the MEG may include a uniform heating mechanism. This may be advantageous because individualized heaters often produce a magnetic field with the induction of electrical current that can interfere with the efficiency of the MEG's sensors, or require more complex multiplexing to avoid interference. Additionally, a method for uniformly heating sensors may result in a lower overall power requirement for a closely packed array of sensors. Suitable exemplary uniform heating mechanisms may include, for example, a heated gas or liquid (See Figure 10).

Turning to Figure 10, a method to collectively heat an array of sensors (rather than have individual ITO heaters) may be employed. A number of possibilities exist, including the circulation of uniformly heated gas or transfer of heat along a uniformly heated liquid or solid that is adjacent to the array and that provides even heating throughout.

Multiplexing of Sensors

In the cases of some exemplary sensors, the operation of the sensor may cause magnetic effects that can be measured by other sensors. In this case, sequential temporal multiplexing of sensors may be utilized (Figure 15). In multiplexing, single or multiple sensors at various locations in the array are triggered along a time course. Sensor registration techniques and optimization paradigms as described above are utilized to account for magnetic effects (if multiple sensors are simultaneously triggered at a particular time), and temporal effects, allowing for signal reconstruction.

Exemplary Multiplexing Sensor Array

Figure 15 is a schematic diagram of a Multiplexing Array. In this schematic, sensors are represented to be detecting a brain magnetic wave arising in the right temporal lobe. As shown in Inset A, a selected series of sensors fire (e.g. are in a detecting mode). In various embodiments, during the firing of sensor series A, each firing magnetic sensor both senses adjacent fields and develops a magnetic field that may be detected by adjacent sensors. Turning to insets B and C, additional sensors series are shown in detecting mode. A number of processing issues may arise during multiplexing, including temporal processing issues (each sensor series is detecting at a slightly different point in the time series, see Inset D) and spatial processing issues engendered by signal and noise created by other sensors in the series. In some embodiments of the invention, sensor registration and processing methods, and global optimization paradigms are utilized in order to modify the signal to re-create an accurate spatiotemporal map of the location and strength of the signal. In various embodiments of the invention, series of sensors may be fired in order to take advantage of such sensor characteristics as maximal and minimal detection regions. For example, if sensors are utilized in which an orthogonal direction is not detected at the individual sensor level, then orthogonally arrayed sensor series may be triggered simultaneously.

Magnetic Shielding

Atomic magnetometers typically require some magnetic shielding in order to function at the sensitivity levels required for biologically relevant signals. Most optical magnetometers are not functional in large external fields. Even devices that are designed to function correctly in the relatively large DC offsets and slow drifts present due to the earth's magnetic field or other offsets are adversely affected by AC interference at 60Hz, 120Hz, 180Hz and further multiples of line frequency which are present in the neurologically interesting frequency spectrum of DC-1kHz. In order to have a useful MEG based on optical magnetometers, the device must be shielded from these external sources of noise. This can be accomplished in several ways. In one exemplary embodiment, each individual sensor is shielded by one or more layers of one or more materials such as Mu metal or ferrites or aluminum which are capable of attenuating magnetic fields. In another exemplary embodiment, the entire array of atomic magnetometers is shielded by one or more

layers of one or more materials such as Mu metal or ferrites or aluminum which are capable of attenuating magnetic fields. In another exemplary embodiment, the atomic magnetometers are each surrounded by coils which are actively driven to cancel out external noise fields. In another exemplary embodiment, the entire array of atomic magnetometers is surrounded by a set of coils designed to be actively driven to cancel out external noise magnetic fields. The shielding solutions can also be applied to the room or a sub-space within the room to allow a smaller field free region. This allows the magnetic shielding to be in place without the necessity of the additional weight and bulk attached to a helmet type device. In addition, combinations of all of these can be used to maximize the effectiveness of the shielding for a given size and weight limitation.

Exemplary Sensor Arrays for Measuring Signals Emanating from the Spinal Cord, Peripheral Nerve, Muscle, or a Human Fetus

Figure 14A is an example of a device utilized for in-utero measurement. The device is designed to be inserted intra-vaginally. In this figure, item "1" is the cervix, item "2" is a support device, which may include a gynecologic speculum; item "3" is insulation; and Item "4" is a sensor array; item "5" is magnetic shielding and item "6" is a set of electronics associated with the device.

Figure 14B demonstrates that sensors may be embedded in a form-fitting structure or embedded into a flexible structure which may be draped or wrapped around a location of interest such as the uterus, a particular nerve or nerve plexus, or muscle. Shielding, insulation, and signal processing/electronics would be included but is not shown in this figure.

As shown in Figure 14C, a sheet of sensors may be created to lie along the spinal column. In this figure, the sensors are shown without shielding, insulation, or signal processing/electronics for purposes of clarity.

Examples of Monitored Mobile Settings

Figures 12A and 12B depict some examples of monitored mobile settings made possible by various embodiments of the invention. In the example shown in Figure 12A, an individual is freely able to move his head and neck as well as other portions of his body while continuing to be monitored. In various embodiments, the subject is confined to a relatively small space (e.g. a confined shielded area) in

which ambulation may not be possible. In other settings, the individual may not be confined to a recumbent posture, but may ambulate, and/or lie in a recumbent posture (see, for example, Figure 12B above). In some settings, the individual may be able to eat, and/or sleep while wearing a device according to various embodiments of the invention. In other settings, the patient may be free to move about without being confined to a specific area or may enter or exit a specific monitored space such as an airplane cockpit or a truck cab. The environments described above may be made possible by embodiments of the invention that are in the form of portable helmets or form fitting arrays, as described above. Other aspects, including the size of the environment (e.g. a small area where the subject may move the head, neck, and limbs within a confined shielded area, or a larger room allowing ambulation and larger scale positional changes), as well as furniture and other amenities may depend on the specific setting.

Conclusion

Many modifications and other embodiments of the invention will come to mind to one skilled in the art to which this invention pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. For example, as will be understood by one skilled in the relevant field in light of this disclosure, the invention may take form in a variety of different mechanical and/or operational configurations. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended exemplary inventive concepts. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for the purposes of limitation.

Claims

We claim:

1. A biomagnetic field detection system comprising:

a portable support structure; and

a plurality of sensors attached adjacent said portable support structure, each of said sensors being adapted for measuring magnetic field changes generated by a target structure within a subject's body; wherein:

said biomagnetic field detection system is adapted to detect and measure magnetic fields emanating from a target area within said subject's body; and

each of said plurality of sensors is an atomic magnetometer.

2. The biomagnetic field detection system of Claim 1, wherein said system is adapted to continuously monitor brain activity within said subject while said subject moves one or more of said subject's body parts that are selected from a group consisting of: said subject's head, and said subject's neck.

3. The biomagnetic field detection system of Claim 1, wherein said support structure is adapted to conform to said target area.

4. The biomagnetic field detection system of Claim 3, wherein said support structure is a portable helmet or hat-shaped structure

5. The biomagnetic field detection system of Claim 3, wherein said support structure comprises a flexible, form-fitting structure.

6. The biomagnetic field detection system of Claim 1, wherein said system is adapted for reducing interference between at least two of said sensors to an extent that is sufficient to allow said system to detect low-magnitude physiologic fields within said subject.

7. The biomagnetic field detection system of Claim 1, wherein said system comprises shielding that is sufficient to reduce interference between at least two of said sensors to an extent that is sufficient to allow said system to detect low-magnitude physiologic fields within said subject.

8. The biomagnetic field detection system of Claim 1, wherein said system is adapted to employ sensor multiplexing to reduce interference between at least two of said sensors to an extent that is sufficient to allow said system to detect low-magnitude physiologic fields within said subject.

9. The biomagnetic field detection system of Claim 1, wherein said sensors are oriented to reduce interference between at least two of said sensors to an extent that is sufficient to allow said system to detect low-magnitude physiologic fields within said subject.

10. The biomagnetic field detection system of Claim 1, wherein said system is adapted to employ data optimization and sensor registration techniques to reduce interference between at least two of said sensors to an extent that is sufficient to allow said system to detect low-magnitude physiologic fields within said subject.

11. The biomagnetic field detection system of Claim 1, wherein said system is adapted to reduce magnetic noise within said system to a sufficient extent that is sufficient to allow said system to detect low magnitude physiologic fields.

12. The biomagnetic field detection system of Claim 1, wherein said system further includes at least one fiber-optic device that is adapted to illuminate one or more of said sensors and to thereby diminish magnetic interference adjacent said one or more sensors.

13. The biomagnetic field detection system of Claim 1, wherein said system comprises a non-electric heating system for diminishing signals from sources of magnetic noise within said system.

14. The biomagnetic field detection system of Claim 13, wherein said non-electric heating system comprises a fluid or gas system that is adapted for heating one or more of said plurality of sensors and to thereby diminish signals from sources of magnetic noise within said system.

15. The biomagnetic field detection system of Claim 1, wherein said system is adapted for using information from said plurality of sensors to:

register signals from a proximal biomagnetic source, and

distinguish biomagnetic signals more distal than said proximal signals.

16. The system of Claim 15, wherein said system is adapted to use one or more mathematical algorithms to distinguish said more distal biomagnetic signals from more proximal biomagnetic signals.

17. The biomagnetic field detection system of Claim 1, wherein said neuro-magnetographic system is adapted for registering both: (1) a first sensor sensing a first set of measurements from a first plurality of signals; and (2) a second sensor sensing a second set of measurements from a second plurality of signals, said step of registering comprising the steps of:

generating a likelihood function associating a data element from said first set of measurements with a data element from a second set of measurements;

generating a systematic error function based at least in part on said likelihood function;

minimizing said systematic error function; and

assigning a signal from said first plurality of signals to the second plurality of signals, based at least in part on said minimized systematic error function.

18. The biomagnetic field detection system of Claim 17, wherein said system is adapted to use a linear assignment method in executing said step of assigning.

19. The biomagnetic field detection system of Claim 17, wherein said step of minimizing said systematic error function comprises generating a global minimum of said systematic error function.

20. The biomagnetic field detection system of Claim 17, wherein said step of minimizing said systematic error function comprises using a Continuous Greedy Randomized Adaptive Search Procedure to minimize said systematic error function.

21. The biomagnetic field detection system of Claim 1, wherein said system is adapted for executing a sensor registration method, said method comprising the steps of:

generating a known magnetic field at one or more locations in proximity to said biomagnetic field detection system;

measuring a response of each sensor within said biomagnetic field detection system to said known magnetic field; and

utilizing information generated from each sensor for the purposes of sensor registration.

22. The biomagnetic field detection system of Claim 1, wherein said system is adapted to use fiducial markers to assess the location or motion of target structures or anatomical features relative to the system or other instrumentation.

23. The system of Claim 1, wherein said system comprises one or more lasers for generating fiducial information to assess the location of motion of target structures or anatomical features relative to the system or other instrumentation.

24. The biomagnetic field detection system of Claim 1, wherein said system is adapted to improve source localization or diminish magnetic noise by using one or more types of information selected from a group consisting of: vector information, scalar information, gradient information, and temporal information.

25. The biomagnetic field detection system of Claim 1, wherein said biomagnetic field detection system is adapted to detect one or more biological signals.

26. The biomagnetic field detection system of Claim 25, wherein said biomagnetic field detection system is adapted to use anatomical imaging techniques to detect said one or more biological signals.

27. The biomagnetic field detection system of Claim 25, wherein said system is adapted to evaluate one or more of said biological signals in response to said subject being exposed to at least one stimulus.

28. The biomagnetic field detection system of Claim 25, wherein said system is adapted to localize physiologic wave forms emanating from said target structure.

29. The biomagnetic field detection system of Claim 25, wherein:

said target area is a first target area within said subject's body; and

said system is adapted to utilize signal processing to evaluate a functional interaction between said first target area and a second target area within said subject's body.

30. The biomagnetic field detection system of Claim 25, wherein said target area is selected from a group consisting of: said subject's brain, said subject's peripheral nerves, said subject's muscle tissue, said subject's eyes, and said subject's spinal cord.

31. The biomagnetic field detection system of Claim 25, wherein said system is adapted to execute functional mapping of one or more biological systems.

32. The biomagnetic field detection system of Claim 25, wherein said system is adapted to monitor said subject's state of arousal.

33. The biomagnetic field detection system of Claim 25, wherein said system is configured to detect biological signals from a fetus.

34. The biomagnetic field detection system of Claim 1, wherein said system is adapted to use one or more of types of information to determine which of said sensors should be activated at a particular time, said one or more types of information being selected from a group consisting of: vector information, gradient information, scalar information, and temporal information.

35. The biomagnetic field detection system of Claim 1, wherein:

said system is adapted for simultaneously triggering a subset of said plurality of sensors, and

said system is adapted for determining which of said plurality of sensors to simultaneously trigger by:

determining, for each of said plurality of sensors, angles of maximal and minimal detectability; and

using information regarding said angles to identify one or more of said plurality of sensors that are located in an area of relatively low.

36. The biomagnetic field detection system of Claim 1, wherein said system provides sensor shielding adjacent one or more of said plurality of sensors.

37. The biomagnetic field detection system of Claim 36, wherein said sensor shielding comprises active field cancellation.

38. The biomagnetic field detection system of Claim 36, wherein said sensor shielding comprises a physical shielding mechanism that is disposed distal to an array of said plurality of sensors.

39. The biomagnetic field detection system of Claim 36, wherein:

a first plurality of said sensors is oriented to detect magnetic fields;

a second plurality of sensors is oriented to detect magnetic fields; and

magnetic shielding is interposed between said first plurality of sensors and the second plurality of sensors

40. The biomagnetic field detection system of Claim 1, wherein said system comprises magnetic shielding that is disposed around one or more of said sensors.

41. The biomagnetic field detection system of Claim 1, wherein said system is adapted to use one or more data processing algorithms in the deconvolution of overlapping sensor signals or noise to generate spatial, temporal, or magnitude information.

42. The biomagnetic field detection system of Claim 1, wherein a first plurality of sensors is oriented as an array to detect a target signal, and a second plurality of sensors is oriented as an array to detect environmental magnetic noise.

43. The biomagnetic field detection system of Claim 1, wherein said system comprises thermal insulation adjacent one or more sensors.

44. A subject monitoring system comprising:

a monitored area, and

a sensor shielding apparatus for shielding sensors within the monitored area from the effects of magnetic fields external to the monitored area, and

a portable biomagnetic field detection system that is adapted to measure magnetic signals from a target area within a living subject while said living subject is within said monitored area.

45. The subject monitoring system of Claim 44, wherein said monitored area is a monitored area that is sufficiently large to allow a human subject to walk within said monitored area.

46. The subject monitoring system of Claim 44, wherein said portable biomagnetic field detection system comprises:

a portable support structure; and

a plurality of sensors attached adjacent said portable support structure, each of said sensors being adapted for measuring magnetic field changes generated by a target structure within a subject's body; wherein:

said biomagnetic field detection system is adapted to detect and measure magnetic fields emanating from a target area within said subject's body; and

each of said plurality of sensors is an atomic magnetometer.

47. The subject monitoring system of Claim 46, wherein:

said plurality of sensors is a first plurality of sensors;

said subject monitoring system comprises a second plurality of sensors that are disposed within said monitored area, said second plurality of sensors being adapted for monitoring environmental noise within said monitored area.

48. The subject monitoring system of Claim 47, wherein said subject monitoring system is adapted to use sensor registration and data optimization techniques to integrate information from said first and second pluralities of sensors.

5

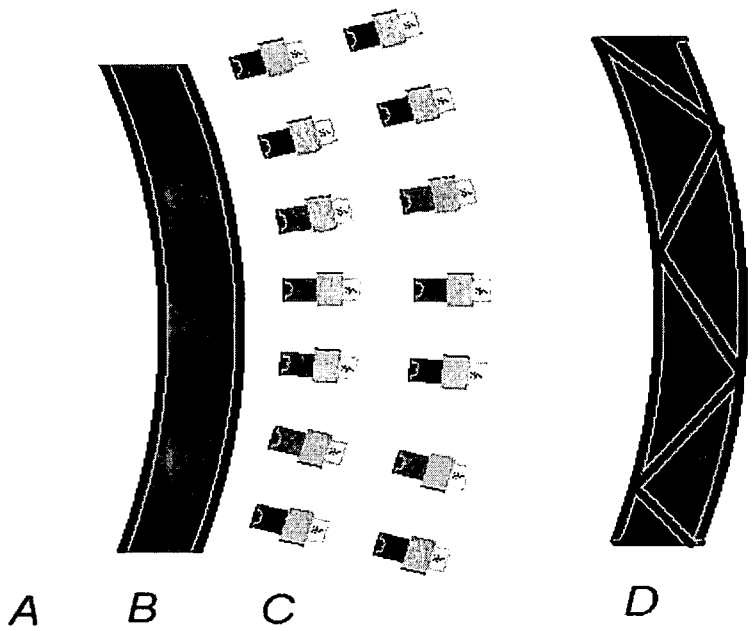


FIG. 1A

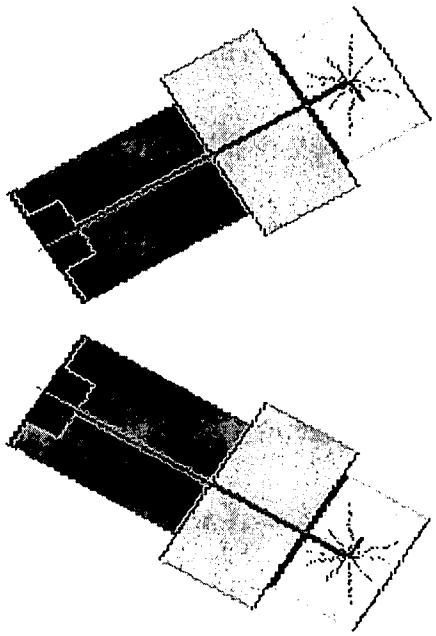


FIG. 1B

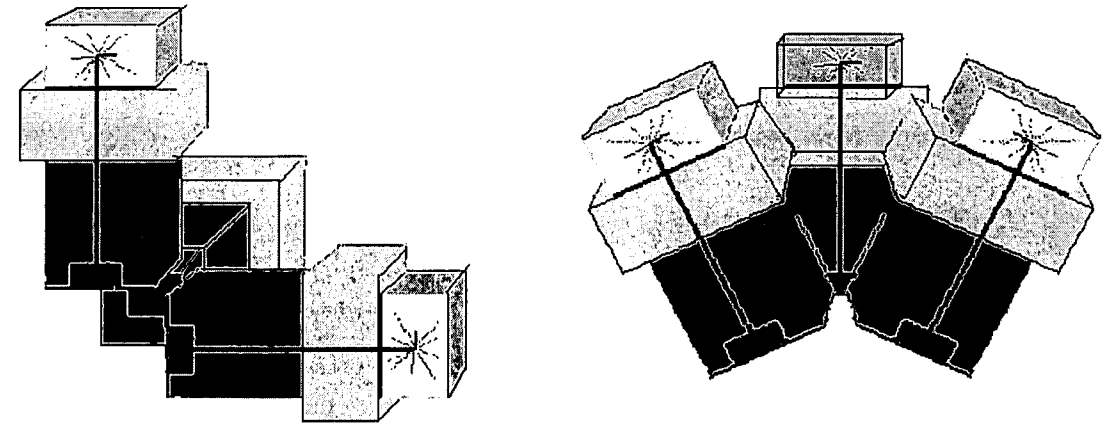


FIG. 1C

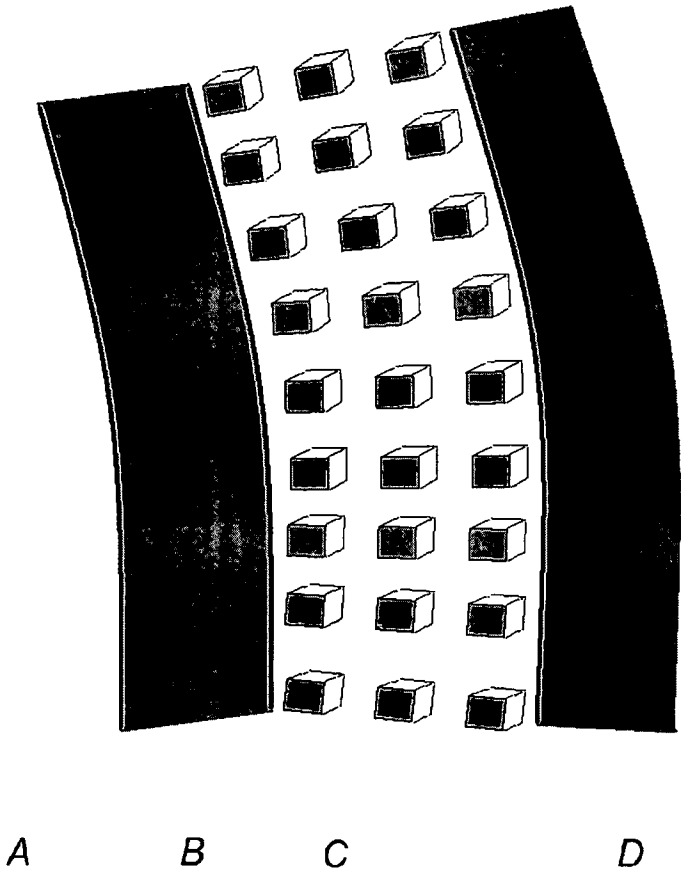


FIG. 1D

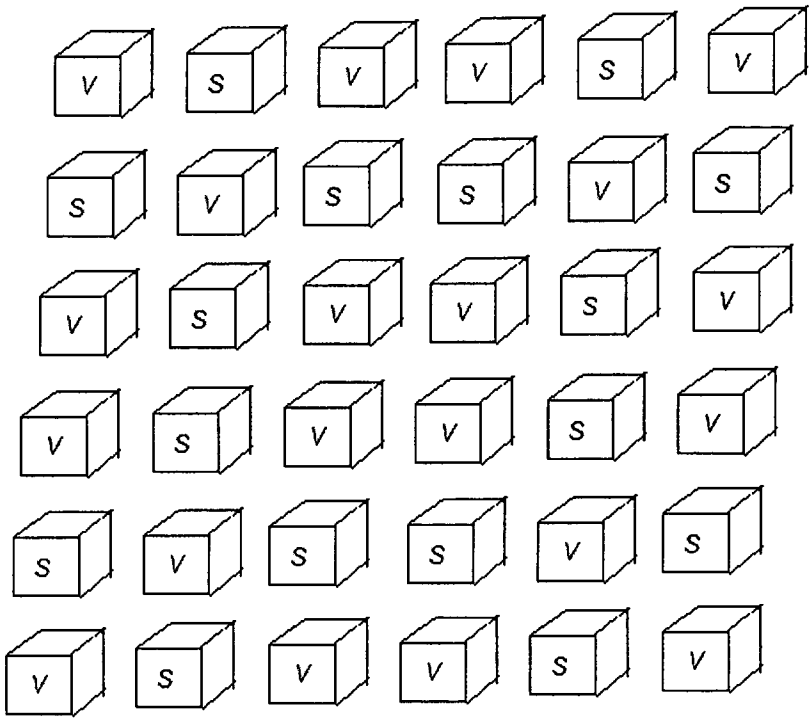


FIG. 1E

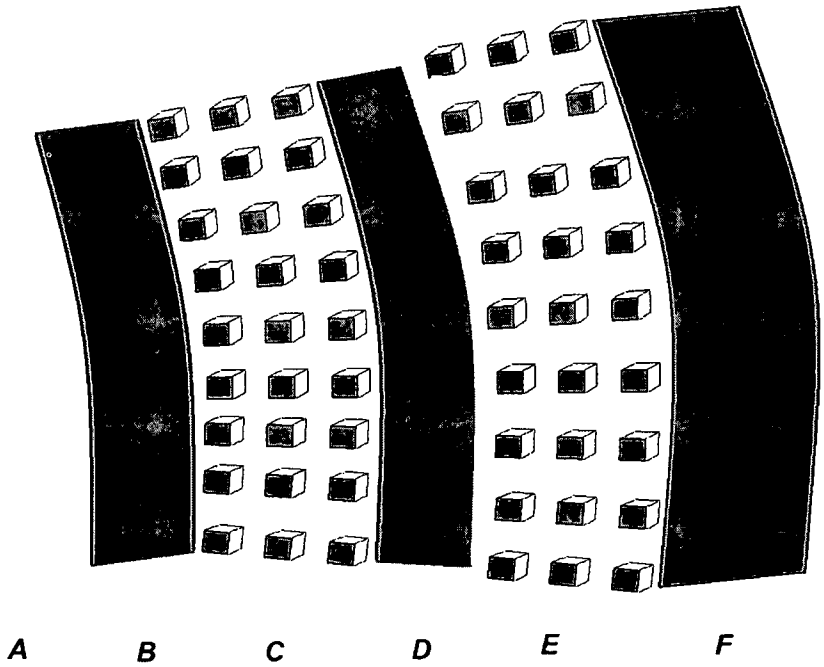


FIG. 1F

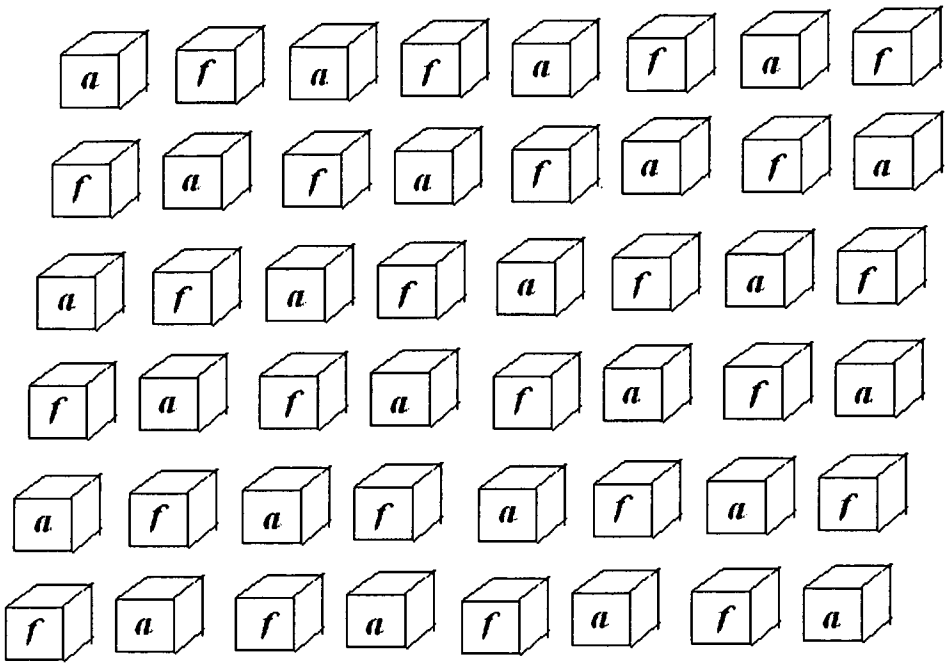
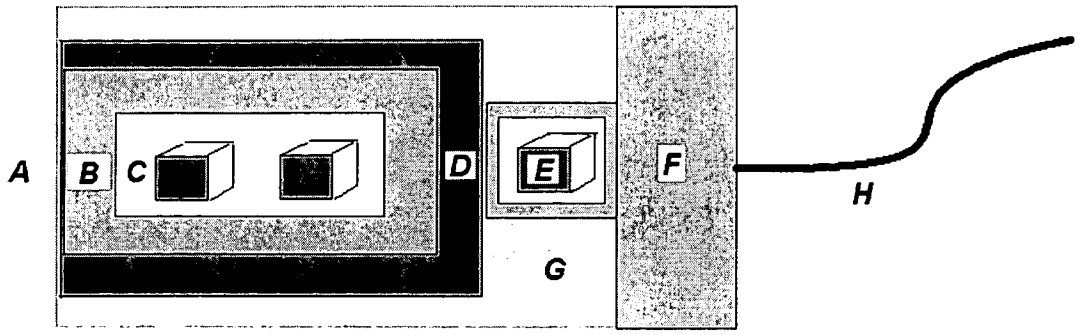


FIG. 1G


A
B
C
D
E
F
G
H

E1

FIG. 2

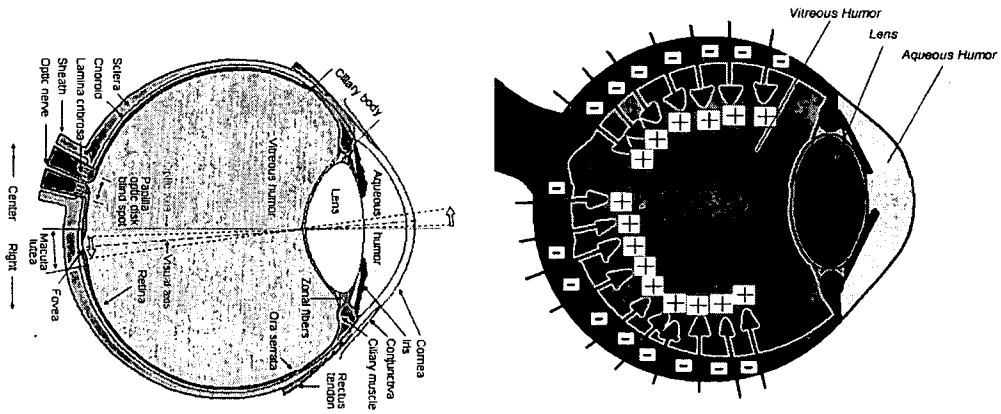
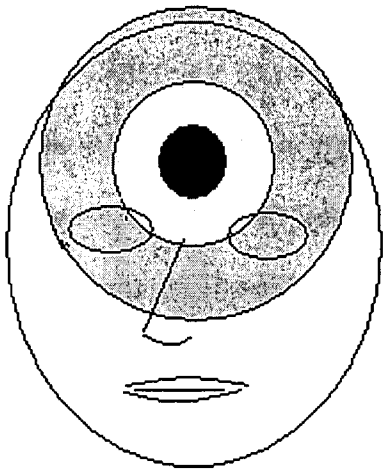
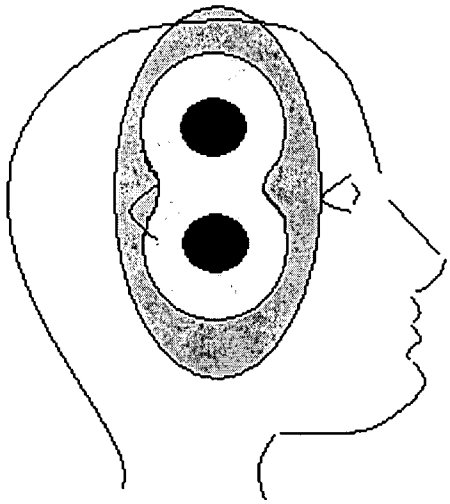

Optic nerve
Sheath
Lamina cribrosa
Choroid
Sclera
Ciliary body
Vitreous humor
Aqueous humor
Lens
Center
Right
Macula lutea
Fovea
Retina
Visual axis
Ora serrata
Zonal fibers
Ciliary muscle
Conjunctiva
Iris
Cornea
Rectus tendon
Vitreous Humor
Lens
Aqueous Humor

FIG. 3





Area of Peak Flux, Horizontal Eye Movements	Area of Peak Flux, Vertical Eye Movements

FIG. 4

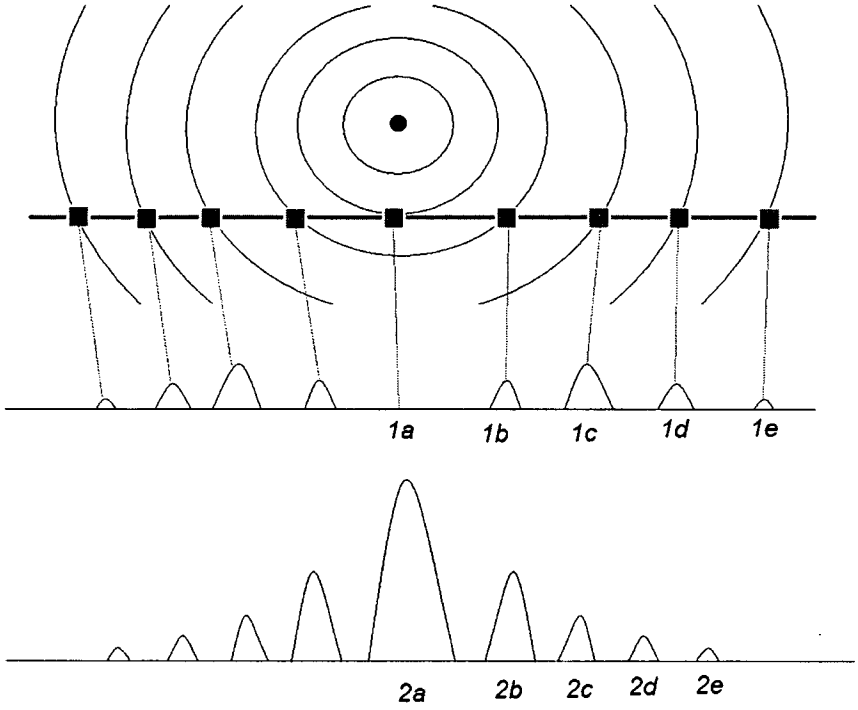


FIG. 5

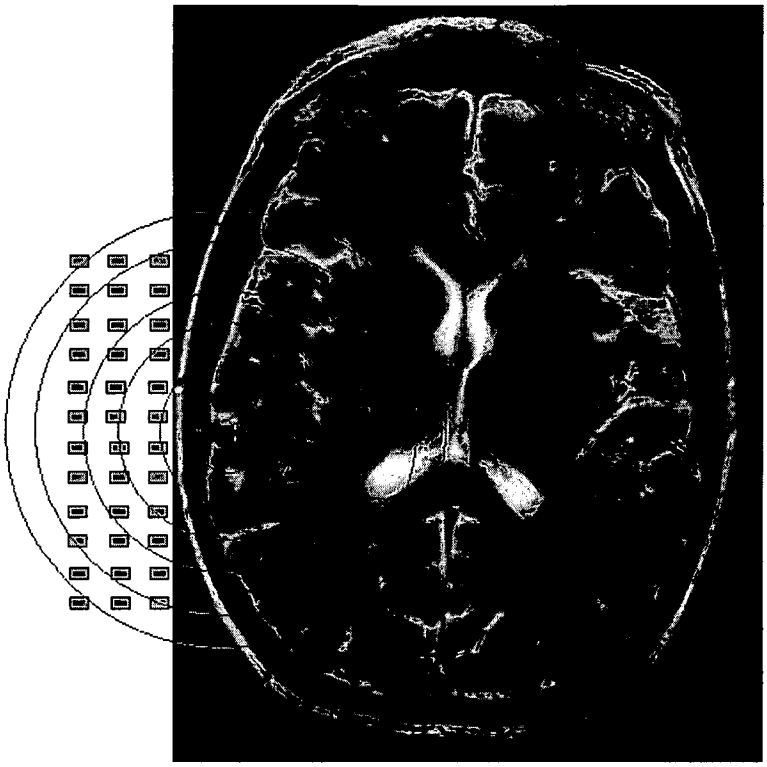


FIG. 6

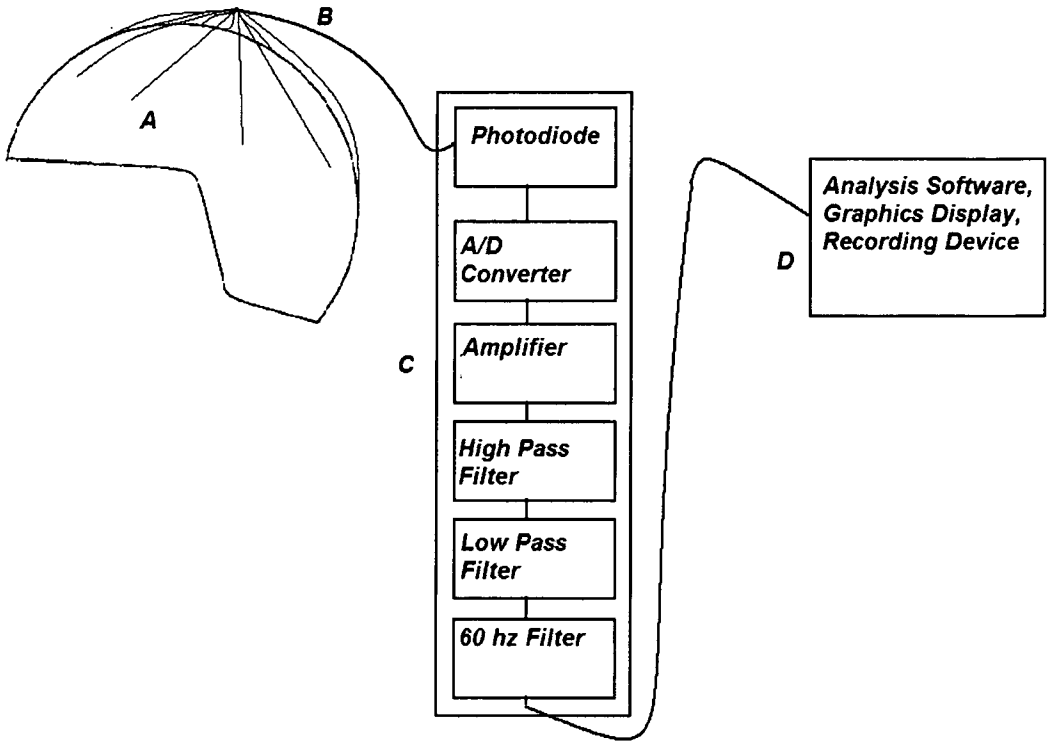
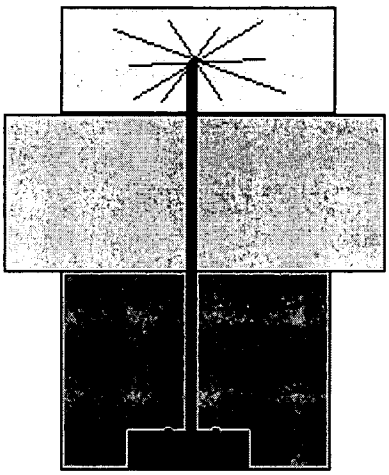

A
B
C
D
Photodiode
A/D Converter
Amplifier
High Pass Filter
Low Pass Filter
60 hz Filter
Analysis Software, Graphics Display, Recording Device

FIG. 7



Photodiode (Detector)

Rb vapor cell with transparent ITO heaters

Optics (Glass Spacer, Neutral Density Filter, Refractive Microlens with a spacer, quartz waveplate, and neutral density filter)

Vertical Cavity Surface Emitting Laser (VCSEL)

FIG. 8

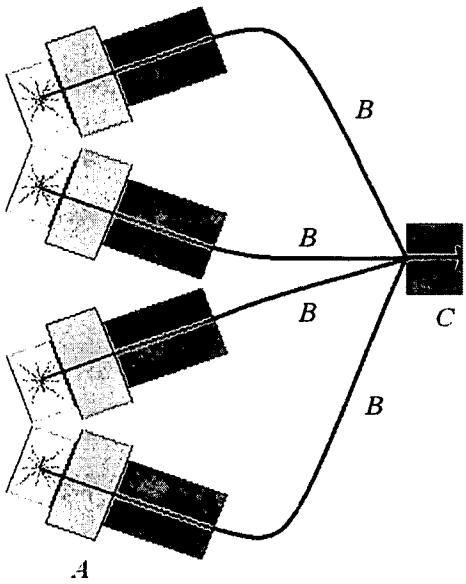


FIG. 9A

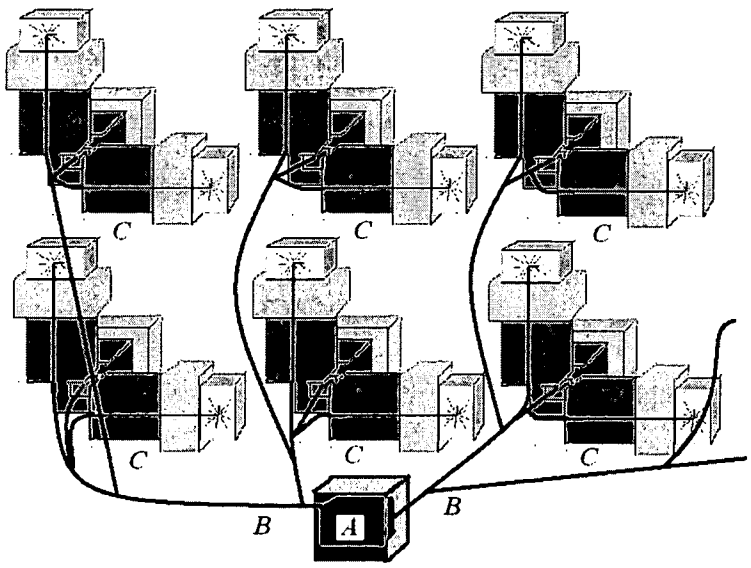


FIG. 9B

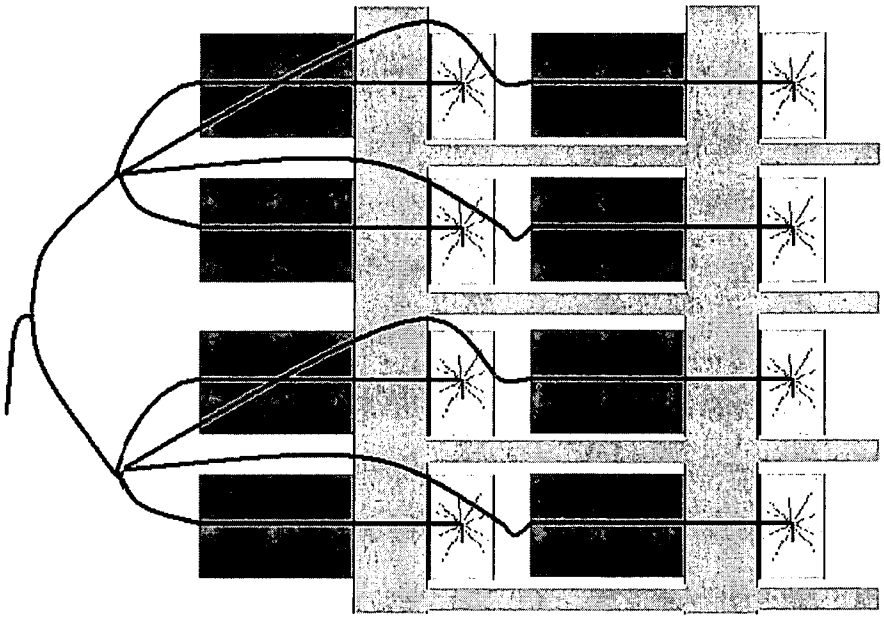


FIG. 10

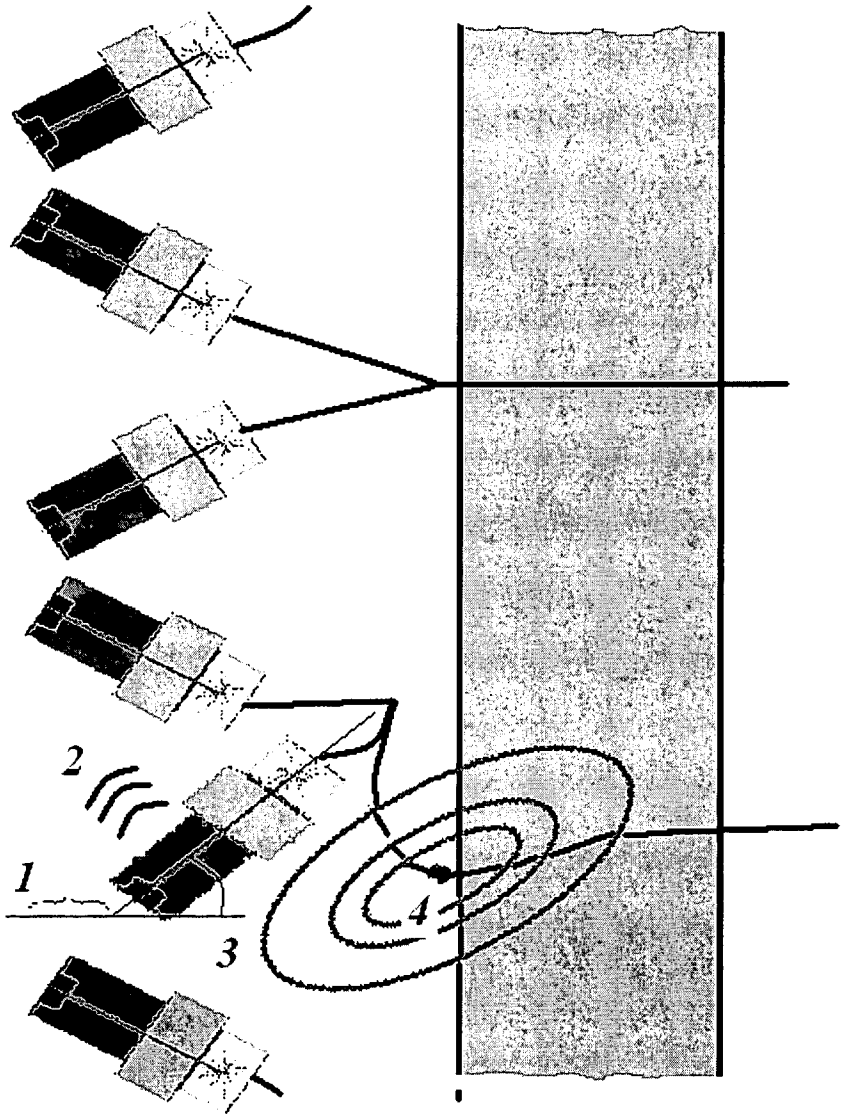


FIG. 11

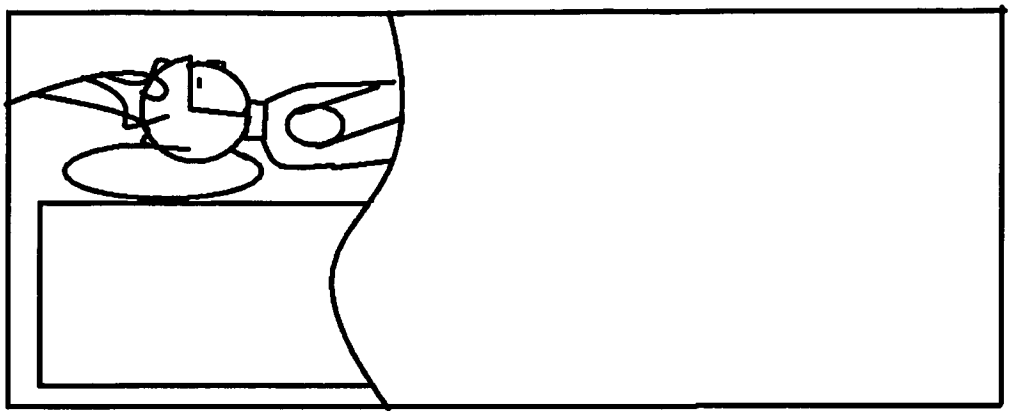


FIG. 12A

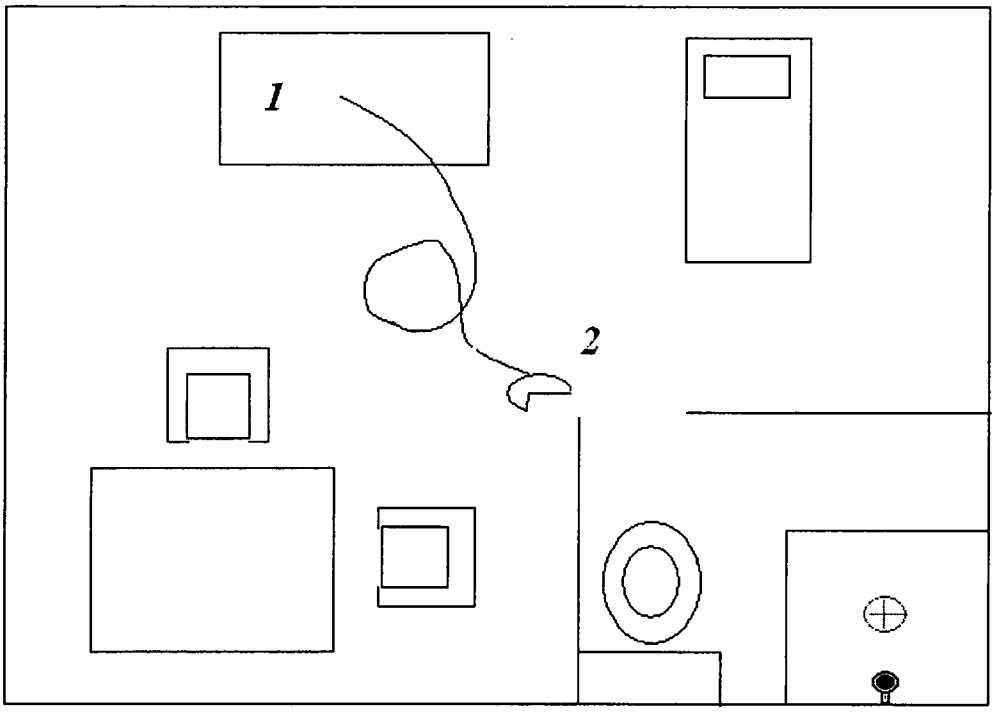


FIG. 12B

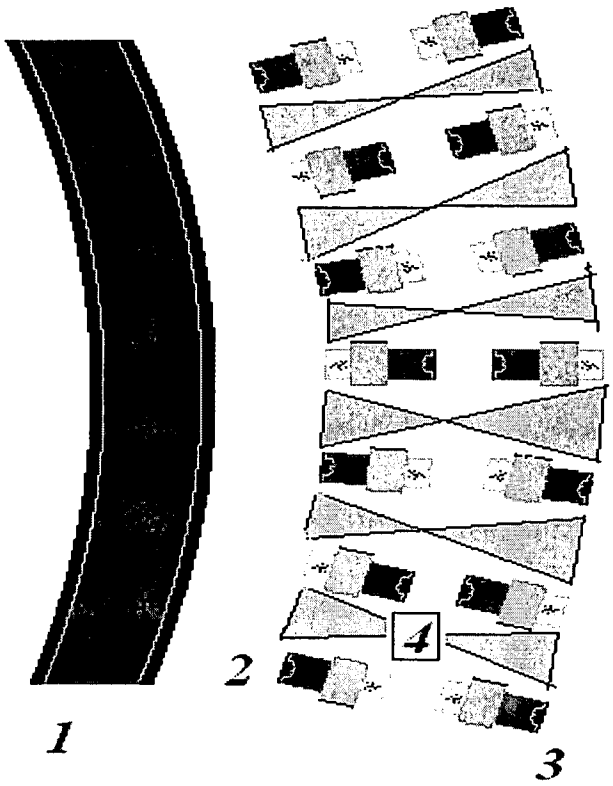


FIG. 13

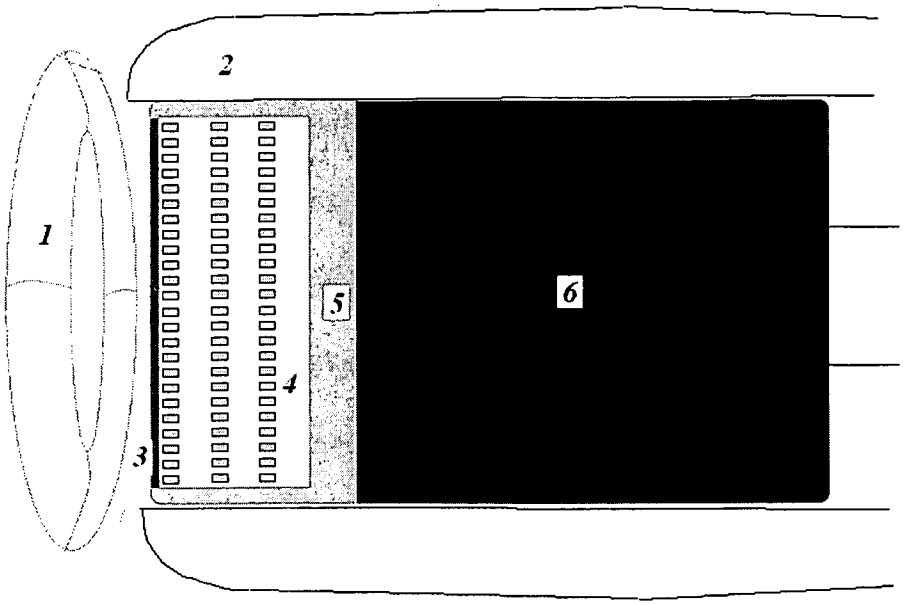


FIG. 14A

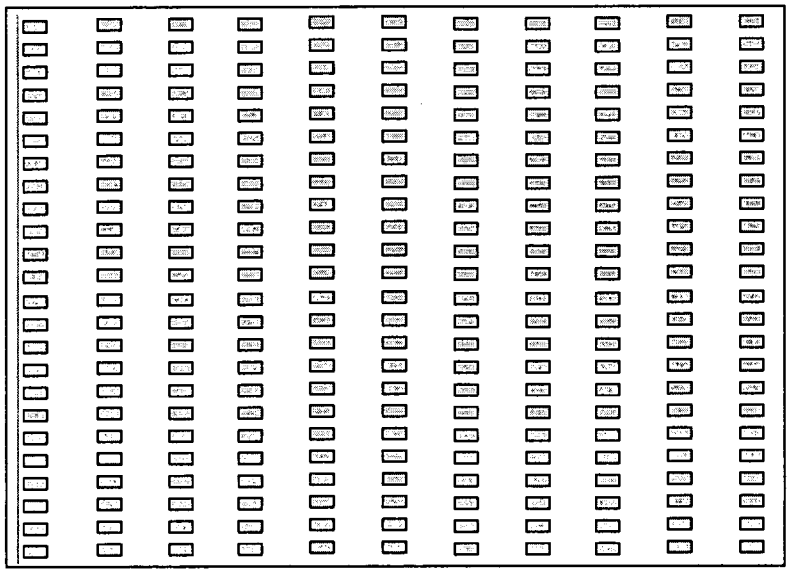


FIG. 14B

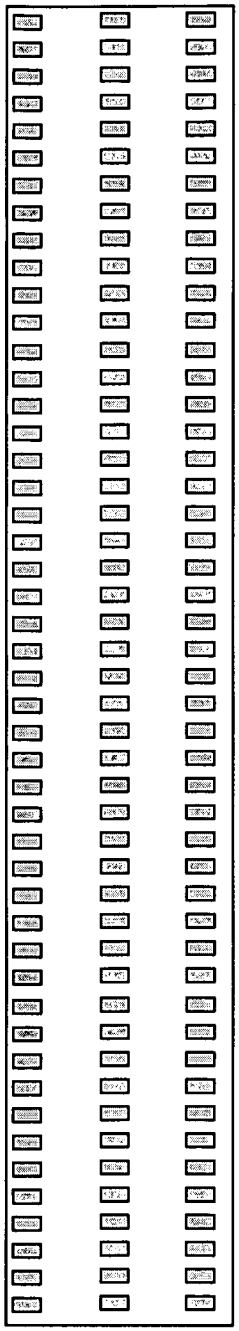
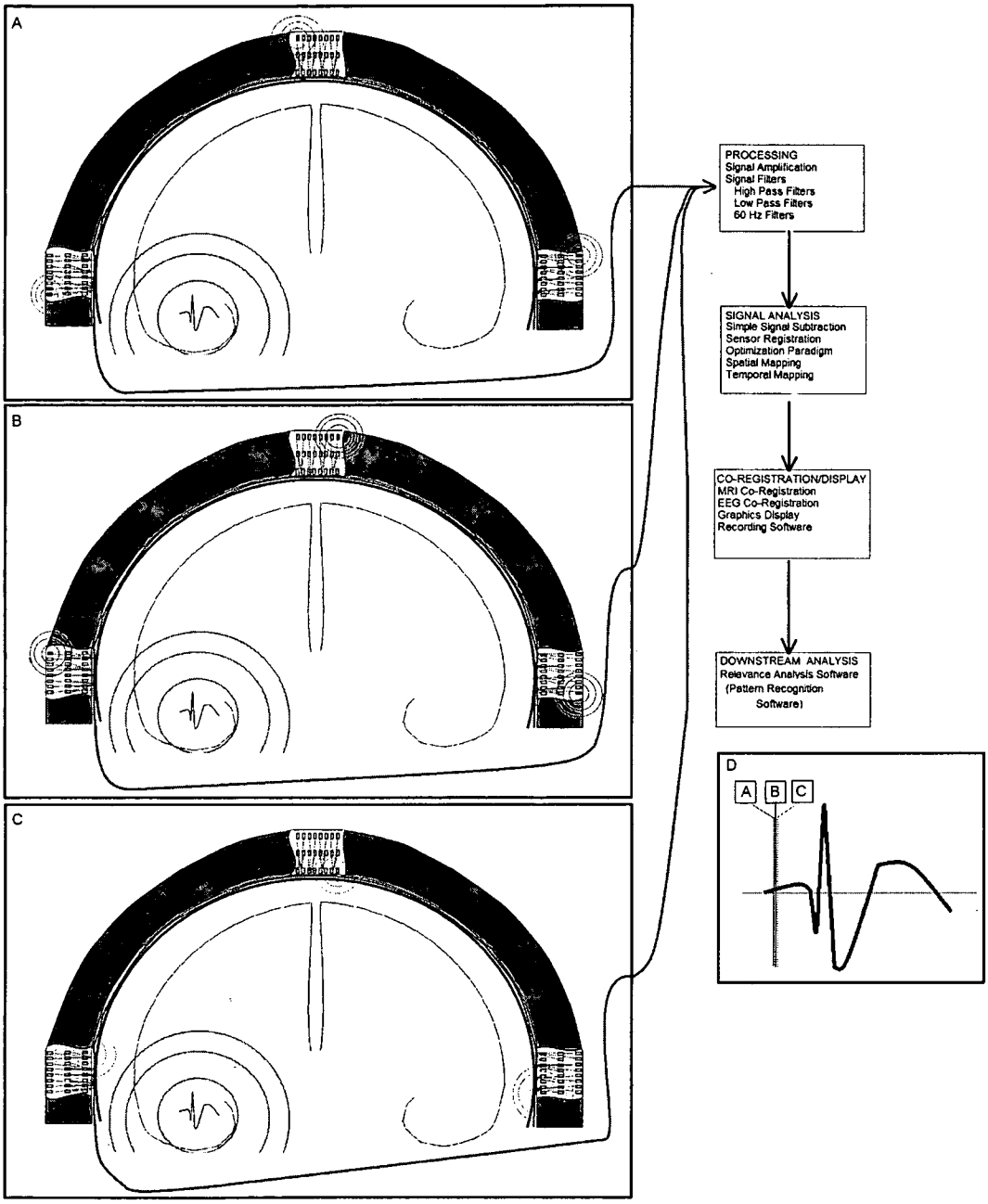


FIG. 14C


A
B
C
PROCESSING
Signal Amplification
Signal Filters
High Pass Filters
Low Pass Filters
60 Hz Filters
SIGNAL ANALYSIS
Simple Signal Subtraction
Sensor Registration
Optimization Paradigm
Spatial Mapping
Temporal Mapping
CO-REGISTRATION/DISPLAY
MRI Co-Registration
EEG Co-Registration
Graphics Display
Recording Software
DOWNSTREAM ANALYSIS
Relevance Analysis Software
(Pattern Recognition
Software)
D
A
B
C

FIGS. 15A - 15C