Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2306530 A1 2001/10/25

(21) 2 306 530

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(22) Date de dépôt/Filing Date: 2000/04/25

(41) Mise à la disp. pub./Open to Public Insp.: 2001/10/25

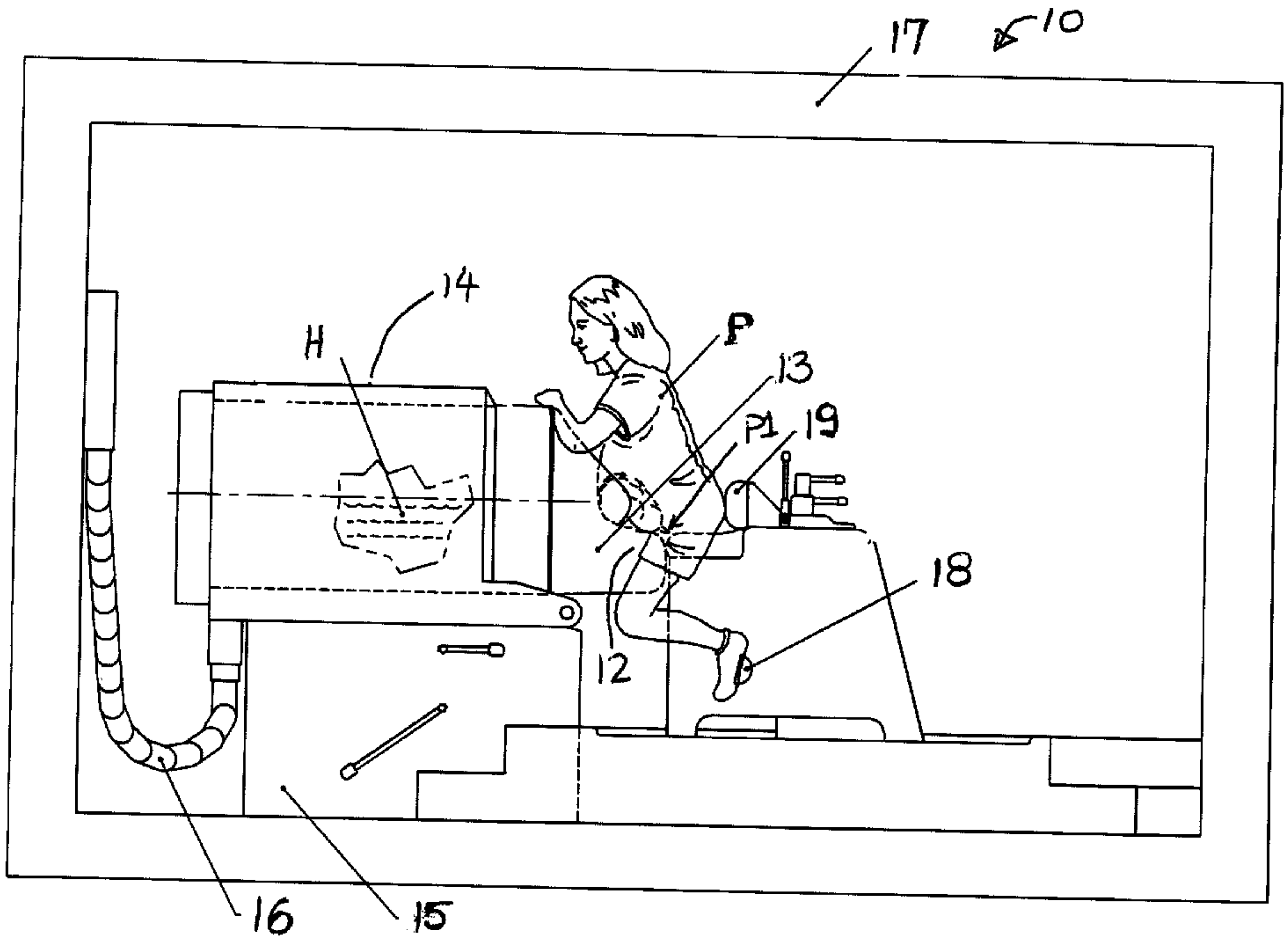
(51) Cl.Int.^{7}/Int.Cl.^{7} A61B 5/00

(71) Demandeur/Applicant:
CTF SYSTEMS INC., CA

(72) Inventeurs/Inventors:
VRBA, JIRI, CA;
TILLOTSON, MARK ALAN, CA;
ROBINSON, STEPHEN ELLIS, CA;
FIFE, ALISTAIR ANGUS, CA

(74) Agent: OYEN WIGGS GREEN & MUTALA

(54) Titre : APPAREIL ET METHODES POUR LA MAGNETOMETRIE FOETALE
(54) Title: APPARATUS AND METHODS FOR FETAL MAGNETOMETRY



(57) Abrégé/Abstract:
A magnetometry system adapted for fetal magnetometry has an array of sensors against which a pregnant mother can press her abdomen. The array of sensors extends into a support which the mother can sit astride. A vibration cancellation system reduces vibration-induced noise.

Abstract of the Disclosure

A magnetometry system adapted for fetal magnetometry has an array of sensors against which a pregnant mother can press her abdomen. The array of sensors extends into a support which the mother can sit astride. A vibration cancellation system reduces vibration-induced noise.

APPARATUS AND METHODS FOR FETAL MAGNETOMETRY

Technical Field

This invention relates to medical imaging and diagnostic apparatus and methods. In particular, the invention relates to medical magnetometry. Specific embodiments of the invention are useful for measurement of signals from the fetal brain (fetal magnetoencephalography – fMEG), and fetal heart (fetal magnetocardiogram – fMCG).

Background

There are, at present, no instruments for non-invasive diagnosis of fetal neurological status. The fetal electroencephalogram (EEG) cannot be detected without placement of electrodes directly on the fetal scalp; this cannot be done, prior to delivery, without surgically exposing the fetal head. Alternative functional imaging diagnostics such as PET or functional MRI are potentially risky to the fetus and mother. PET requires the introduction of radioisotopes into the fetal blood stream, and fMRI exposes the fetus to heating by radio-frequency energy. The risk-benefit ratio of these technologies for assessing fetal brain activity is generally considered to be unacceptable.

Magnetometry has some desirable attributes for medical imaging and diagnostics. It is non-invasive and passive. The idea of medical magnetometry is quite simple. Electrically active organs such as brain, nerves, heart, and muscle can generate magnetic fields that extend beyond the surface of the body. One or more magnetic field sensors are provided adjacent a subject. The sensors detect magnetic signals that provide information about magnetic fields associated with the electrophysiological activity of the subject. The signals are amplified and processed to yield images of the organ activity or other medically useful information.

Notwithstanding the simplicity of this concept there are formidable technical obstacles to making a practical medical magnetometry system. Not the least of these problems is that the world is magnetically noisy. For example, the earth's own magnetic field is typically on the order of 10^9 times stronger than biomagnetic signals of interest. Motors and other electrical devices generate electromagnetic fields that can interfere with magnetometry. Other problems are introduced because the best magnetic sensors are superconducting quantum interference devices (SQUIDs). SQUIDs must be operated at cryogenic temperatures. Another problem is that the strength of many magnetic signals of interest falls rapidly with distance from the signal source. Therefore sensors must be located as closely as possible to the signal sources in medical magnetometry. Advances in the field have overcome these problems to some degree.

Some reported experiments have attempted to measure magnetic fields associated with fetuses. Magnetic signals from the fetal heart have been reliably recorded. However, it is not clear whether or not these experiments were successful at detecting the much weaker fetal brain magnetic fields.

The sensors used to measure magnetic fields in a number of these cases have been contained within a dewar suspended from a gantry above a patient. It can be physically uncomfortable for a pregnant woman to lie flat on her back for significant periods. Further some pregnant women do not like having large heavy objects suspended over their abdomens.

In other cases systems having only a single channel or a few channels have been reported for monitoring discrete areas of a mother's abdomen. Such systems have all demonstrated significant artefact due to problems relating to excessive vibrational noise and long collection times.

In 1986, Blum, et al published a paper claiming to have recorded an auditory evoked magnetic field from a human fetus, *in utero*. In that study, a 7-channel SQUID sensor array was placed over the mother's abdomen, in the general vicinity of the fetal head. Sound, in the form of periodic tone bursts, was coupled to the mother's abdomen. The magnetic field measured above the abdomen was then recorded and signal averaged synchronously with the tone bursts. The averaged magnetic signals, although very noisy, revealed a peak at about one tenth of a second after the tone burst start. This peak was alleged to correspond to activation of the auditory cortex in the fetal brain.

There is a need for methods and systems for medical magnetometry that can be used to detect magnetic fields associated with the lower abdomen of a person. There is a particular need for medical magnetometry systems capable of measuring magnetic fields associated with a fetus *in utero*.

Summary of the Invention

This invention provides a magnetometry system comprising a support on which a human subject can sit astride and an array of magnetic sensors. The array extends into the support so that sensors in the array are adjacent a perineal region of a human sitting astride the support. A noise cancellation system reduces the effects of vibration induced noise on the signal. In preferred embodiments the noise cancellation system includes a number of reference sensors which are mounted rigidly to the sensors in the array.

Further features and advantages of the invention are described below.

Brief Description of Drawings

In figures which illustrate non-limiting embodiments of the invention:

Figure 1 is a side elevational view of apparatus according to the invention;

Figure 2 is a perspective schematic view of a sensor array located to detect magnetic signals from a fetus;

Figure 3 is a longitudinal section through the apparatus of claim 1; and,

Figure 4 is a block diagram illustrating the signal processing components for generating images from the apparatus of Figure 1.

Description

This invention provides apparatus for magnetometry of a patient's abdomen. The apparatus has particular application to fetal magnetometry. In this disclosure the apparatus is described as being applied to magnetometry of fetal brain signals ("fMEG"). However it is to be understood that the apparatus may also be applied to other magnetic studies such as magnetometry of the fetal heart (fMCG), uterine smooth muscle, and other nerve or muscle of the fetus or mother.

Figure 1 shows apparatus **10** according to the invention. Apparatus **10** does not include a heavy dewar that must be suspended over a prone pregnant woman. As shown in Figure 1, woman **P** leans forward against a dewar **14** containing a magnetic sensor array **11**. The woman **P** sits astride a support **12** with her abdomen resting comfortably against the contoured end **13** of a dewar **14** which contains the sensor array **11**. As shown in Figure 2, sensor array **11** extends into support **12**. Preferably sensor array **11** extends over an area covering the abdomen of woman **P**, roughly from her sternum to pubic bone and continuing to the perineum (crotch).

In the version illustrated in Figure 1, the surface **14A** of dewar **14** facing woman **P** is contoured so that it conforms to her body when she leans against it. The orientation of surface **14A** is not particularly important. However, in order to minimize noise generated by skeletal muscle activity, the mother should preferably be laying passively across surface **14A**. Most preferably, the portion of surface **14A** which contacts the woman's lower abdomen is inclined at an angle in the range of about 15 degrees to about 60 degrees to the vertical. A backstop **19** prevents woman **P** from sliding rearwardly on support **12** away from dewar **14**. Adjustable footrests **18** provide a comfortable position while straddling support **12**. It can be appreciated that woman **P** is in control of her positioning at all times during measurement, and can comfortably adjust her position on dewar **14** without stress.

Dewar **14** and the weight of woman **P** are supported by gantry **15**. Gantry **15** is also constructed of non-magnetic materials, and preferably allows dewar **14** to be oriented with its longitudinal axis at any angle between a few degrees from vertical and horizontal. This permits the woman **P** to be seated upright or draped comfortably over surface **14A** while reclining forward, a position that is observed to reduce stress and improve blood flow.

Array **11** is preferably located inside a magnetically shielded enclosure **17**. The magnetic shielding of enclosure **17** reduces magnetic interference. Enclosure **17** is not essential to the operation of array **11**. Most preferably support **12** is mounted on a raised floor so that array **11** can be positioned near the centre of magnetically shielded enclosure **17**.

Electrical signals from the sensors in dewar **14** are carried via transmission lines **16** to control and processing electronics. The control and processing electronics are preferably located outside of enclosure **17**. Example control and processing electronics are illustrated in Figure 4 and described below.

Figure 2 illustrates a possible arrangement of the sensors **11A** in array **11**. The array **11** of sensors **11A** covers most of the abdomen of woman **P** and stretches down into the perineal area **P1** thus covering most possible locations of the fetus **F** relative to the mother's abdomen and assuring that at least some sensors will be close to the fetal brain. This allows optimal response for mid-term to late-term pregnancies. In Figure 2, a fetus **F** positioned head-downward in the mother's abdomen is shown. It can be seen that, despite the low position of the fetal head, a number of sensors **11** are close to the head of fetus **F**. Sensors **11A** may detect magnetic fields associated with the fetal brain, heart, and other electrically active internal organs of the fetus. Sensors **11A** will also detect magnetic fields associated with the woman **P**.

Array **11** may contain various numbers of sensors **11A**. Preferably there are more than about 50 sensors **11A**. Most preferably there are more than 110 sensors **11A** in array **11**. In the current embodiment of the invention 151 sensors are employed. The number of sensors can, of course, be varied without departing from the invention. An array **11** having a large number of sensors **11A** permits meaningful data to be collected with short measurement times (for example, of the order of a few minutes), and facilitates separation of fetal magnetic brain signals from that of other organs in the fetus and mother's abdomen.

Sensors **11A** preferably comprise SQUIDs. As is known in the art, each SQUID has a small superconducting loop (or thin film washer) interrupted by one or two Josephson junctions. At the present time, the dc-SQUID (having two Josephson junctions) is the most sensitive detector of magnetic fields. The SQUID device, alone, yields a voltage that is periodic, rather than linear, with respect to changing magnetic flux. Supplementary electronics, termed a flux-locked loop (FLL) are used to provide an output that varies linearly with respect to magnetic flux. The FLL circuitry may be analogue or digital. In the preferred embodiment of the invention the FLL electronics close the flux-locked loop digitally and provide a wide dynamic range.

Since typical SQUIDs have dimensions too small to couple effectively to fields of biological origin, the SQUIDs are preferably coupled to the measurement region by means of flux transformers. A flux transformer is a superconducting circuit having a collection of coils exposed to the measured fields, leads, and a coupling coil to the SQUID. The frequency response of a superconducting flux transformer is flat from DC to the maximum operating frequency of the SQUID electronics. Furthermore, the superconductive circuits provide noiseless gain. Flux transformer coils may be constructed in various configurations to measure either magnetic fields or spatial magnetic field gradients.

Numerous configurations for flux transformer coils are known in the field of SQUID magnetometry. Those skilled in the art will understand that many such configurations could be used in this application. For example, well known flux transformer configurations include radial magnetometers, vector magnetometers, 1st-order radial gradiometers, 1st-order planar gradiometers, 2nd-order gradiometers, 3rd-order gradiometers, and so on. Array **11** preferably comprises flux transformer coils configured as first-order radial gradiometers. Radial gradiometers provide better signal to noise ratios than magnetometers, because they reject environmental noise more effectively and are more immune to vibrations. The preferred configuration for the primary fetal field sensors **11A** in array **11** are radial gradiometers which have two superconducting coils wound in opposition from a single wire, and separated along their common axis. The separation distance between the two coils is called the gradiometer baseline.

In the embodiment of Figure 2, cylinders **11A** each represent a flux transformer of a 1st-order radial gradiometer sensor. The distribution of the sensors **11A** over surface **14A** may be uniform with equal spacing between sensors **11A**, or non-uniform with e.g. sensors **11A** more densely concentrated in areas likely to be of particular interest.

Sensors **11A** are exposed not only to the desired magnetic fields associated with the fetus, but also to the ambient magnetic noise. The magnetic flux measured by sensors **11A** may also vary as a result of motion and vibrations. If sensors **11A** of array **11** move relative to the environmental magnetic fields and gradients, then this motion induces changes of fields and gradients at the sensors and consequently the sensors **11A** generate signals proportional to the magnitude of the motion. The woman **P** is seated on support **12** that is attached to sensor array **11**. The woman's body constantly moves (for example by breathing, heartbeats and blood pulsations, various shifting of body weight, etc.). All these motions will be transmitted to some degree to array **11** and will cause vibrationally-induced magnetic noise in the outputs from sensors **11A**.

Apparatus **10** therefore has a magnetic noise cancellation system. A suitable magnetic noise cancellation system is described, for example, in Vrba et al. U.S. patent No. 5,657,756 entitled "Method and Systems for Obtaining Higher Order Gradiometer Measurements with Lower Order Gradiometers" which is incorporated herein by reference. The noise cancellation system may comprise additional magnetic sensors **11B**, which are positioned at a distance from the fetal sources. Sensors **11B** may be called "reference sensors" or "references". Sensors **11B** are far enough away from the woman's abdomen that they are primarily sensitive to environmental noise and vibrations. Bio-magnetic fields associated with woman **P**, or her fetus, make a negligible contribution to the magnetic fields detected by reference sensors **11B**.

Signals from reference sensors **11B** can then be used to synthetically reduce the noise in the main or "primary" sensors **11A**. In the preferred embodiment, reference sensors **11B** include multiple vector magnetometers and tensor gradiometers. In combination with 1st-order gradient primary sensors **11A**, these reference sensors are sufficient to synthesise up to 3rd-order gradiometer response. This provides best signal-to-noise ratio (S/N). Gradiometers behave as spatial high-pass filters and remove low spatial frequencies of the noise and signal. The signal sources of interest are usually in the near field and therefore they contain mostly high spatial frequencies that are detected without significant attenuation by gradiometer sensors **11A**. On the other hand, noise sources are usually distant, and their contributions correspond mostly to lower spatial frequencies and are strongly attenuated by spatial gradiometers. The gradiometer order determines the "sharpness" of the filter that attenuates the distant (noise) sources. Adaptive magnetic noise cancellation systems could also be used.

Sensors **11A** and **11B** should be highly sensitive and exhibit low intrinsic noise (instrumental or SQUID noise) because the fetal signal amplitudes are very low. Sensors **11A** and **11B** should also be highly linear since successful noise cancellation requires accurate subtraction of large amplitude signals.

Sensor array **11** should be mounted on a mechanically rigid support so that vibrations induced in sensor array **11** by movement of the woman **P** in while in contact with surface **14A** are minimized. Both primary sensors **11A** and reference sensors **11B** are rigidly mounted to a non-magnetic, monolithic shell **13** and plate structure **14** also of high rigidity. For best noise cancellation the relative vibrational movements between primary sensors **11A** and reference sensors **11B** must be minimized. That is, the primary sensors **11A** and reference sensors **11B** must move essentially as one unit. Only then can the reference sensors **11B** generate signals that can be used to attenuate noise caused by mechanical vibrations of apparatus **10**. If the reference sensors **11B** moved independently of sensors **11A**, then the gradiometer synthesis would be highly inaccurate and the environmental noise would not be rejected.

The preferred embodiment of the invention achieves the required internal rigidity of array **11** by mounting both primary sensors **11A** and reference sensors **11B** to a monolithic composite capsule, comprising a moulded shell **13** which follows the contours of surface **14A** and a bonded "end-piece" **13A** to which reference sensors **11A** are mounted.

As current SQUID sensors operate at cryogenic temperatures, system **10** must include a suitable cryogenic cooling system. In the illustrated embodiment sensors **11A** and **11B** are cooled by liquid helium **H** contained in insulated dewar **14**. A unique feature of dewar **14** is the shape of its outer surface which includes surface **14A**. The envelope of dewar **14** extends into support **12** and may include a moulded shape **20** to provide shorter distances between array **11** and the head of a fetus **F** during measurement. Primary sensors **11A** are located very close to surface **14A** to provide the best S/N for the fMEG signals.

The outer hull **14B** of dewar **14** may comprise a single strong FRP (fiber reinforced plastic) shell rigidly mounted to gantry **15**. Surface **14A** is an integral part of the dewar outer hull. Hull **14B** is constructed so that breaches to the integrity of hull **14B** are unlikely to occur in the vicinity of surface **14A**. Dewar **14** is safely attached to a massive, rigid gantry **15**. Any cryogenic problems occurring during measurement (for example, vacuum loss, cold helium vapour escape etc.) will be directed away from the woman **P**.

Dewar **14** is insulated by vacuum and radiation shields **17** and is constructed of non-magnetic materials. The main volume of dewar **14** may be filled with liquid helium **H** which maintains sensors **11A** and **11B** in isothermal equilibrium. Preferably insulating support pegs bridge the vacuum gap of dewar **14** at spaced apart locations to prevent the inner vessel of dewar **14** from vibrating significantly relative to the outer vessel of dewar **14**.

In the currently preferred embodiment dewar **14** is cylindrical and is mounted horizontally with the sensors and SQUIDs sealed into the liquid helium reservoir. Other dewar geometries could also be used. For example, dewar **14** could be elbow or arc-shaped with dewar access necks large enough to accommodate the array insertion.

Preferably system **10** includes a stimulator **30** which, when actuated, generates a stimulus for the fetus, or other tissues being studied. The stimulus may be, for example, acoustic, tactile and/or photic. It is known that a fetus will respond to sound touch and light.

Figure 4 illustrates a signal processing system that may be used with apparatus **10** of the invention. The "SQUID Control Electronics" element converts signals from primary sensors **11A** and reference sensors **11B** into a linear digital representation of the magnetic field or gradient at each sensor.

The "Signal Conditioning" element provides for user-specified frequency-domain filtering (high and lowpass filtering), and offset (baseline removal), for all sensors. Signal conditioning may be performed either in special-purpose hardware prior to data acquisition or in software after data has been acquired and stored.

The "Noise & Vibration Cancellation" element receives signals from both primary sensors **11A** and reference sensors **11B**. The noise and vibration cancellation element computes linear combinations of reference signals with the signal from each primary sensor. This effectively attenuates signals that result from noise and vibration and increases the S/N for the system. The outputs from the noise and vibration cancellation element are noise-reduced signals for each primary sensor **11A**. As with the signal conditioning element, noise and vibration cancellation algorithms may be performed either in special-purpose hardware prior to data acquisition or in software after data has been acquired and stored.

The data acquisition element receives the noise-reduced signals and stores a digitised representation of each signal in a data storage device. The "Data Acquisition" element optionally receives synchronising signals from the "Stimulus" element. As described below, stimulus element controls the actuation of stimulator **30**. The synchronising signals, denote the timing of each stimulus. The synchronising signals may either be recorded along with SQUID sensor data, or used to synchronously trigger data acquisition. This, in turn, permits computation of the averaged evoked response (of the brain) in subsequent analytic steps. Data may be recorded with or without stimulus.

The "Stimulus" element controls the operation of stimulator **30**. The Stimulus element causes stimulator **30** to generate selected stimuli at selected times. The stimuli are applied transabdominally, to evoke a response from the brain of the fetus. Repetitive stimuli are commonly used in MEG and EEG studies (of adults and children) to permit computation of an averaged evoked response. Stimuli are optional.

The "Signal Processing & Analysis" element provides for reduction of the magnetic signals to some meaningful form. There are many ways in which useful information may be derived from the signals recorded by the data acquisition element. For example:

- Signal averaging: The averaged evoked response to repetitions of a stimulus can be used to enhance the signal-to-noise ratio for the parts of the brain responding to the stimulus. Random unrelated brain activity and residual magnetic noise sum destructively, whereas signals that are synchronised with the stimulus add constructively.
- Inverse solution: The sources of the magnetic field may be determined by fitting a model to the observed fields. For example a compact current source can be modelled as an equivalent current dipole (ECD). More complex sources may be

modelled as multiple ECDs. Inverse solutions include linear methods such as the minimum-norm solution, and non-linear methods such as the equivalent current dipole fit.

- Spatial filtering: Spatial filtering (e.g., by synthetic aperture magnetometry, SAM) provides for a method of separating the desired signal (from the fetal brain) from the nearby clutter (fetal heart, uterine muscle, maternal heart, etc.). The spatial sensitivity pattern of each individual primary sensor is typically insufficient to distinguish among sources of magnetic signal in the abdomen. The fetal brain is only a few centimetres from the fetal heart. The fetal heart can generate magnetic signals over one hundred times larger than that of the fetal brain. Signal averaging, alone, is not adequate for separating this "clutter." The spatial filtering methods involve computation of linear combinations of primary sensors (and, possibly, reference sensors) so as to attenuate or null unwanted signal components while adding constructively for signals emanating from a specified target location or signal vector direction. Further, the SAM method provides for evaluating sources at intervals throughout the abdomen. In this way, a three-dimensional image of activity can be generated. Synthetic aperture magnetometry methods that may be applied in the context of this invention are described, for example, in Robinson, S.E. and Vrba, J. (1999) *"Functional Neuroimaging by Synthetic Aperture Magnetometry (SAM),"* in T. Yoshimoto, et al (eds), *Recent Advances in Biomagnetism*, Tohoku University Press, pp. 302-305, which is hereby incorporated by reference in this disclosure.

The "Diagnostic Data Display" element provides means for displaying or printing averaged signals, source localisations, or source images (from SAM). When this information is combined with anatomic data, such as a diagnostic ultrasound image of the abdomen, the signals can be related to specific anatomic structures (for example, anatomical structures within the fetal brain). The "Anatomic Image" information is fused with the SAM image (or inverse solution) data by aligning the two to a common size scale and reference frame. The SQUID sensors can, optionally, localise the magnetic fields generated by three small coils ("localisation coils") that may be placed at fiduciary points on the mother's body. If these fiduciary points can be identified in the corresponding anatomic image, then the magnetic and anatomic data can be fused.

It can be appreciated that the approach to fetal magnetometry described herein has several advantages over the prior art. With an array of sensors that extends over a wide area of the mother's abdomen there is no need to hunt for the ideal locations where fetal brain signals are at a maximum. There will be at least some sensors detecting fetal brain signals. The remaining sensors are useful in that they characterise the magnetic signal "clutter" generated by organs other than fetal brain. The mother is safely and comfortably seated, and is able to relax during measurement. If she becomes uncomfortable, she can stand up and walk away, with little assistance. This approach is in sharp contrast with prior art for which a small array of sensors is positioned using a movable gantry. With the mother draped over the sensor array the fetus is likely to be closer to the sensors than would be the case if the mother were lying on her back. With the sensor array extending into a support which the mother sits astride sensors can be located in the mother's perineal region in a manner which is not threatening to the mother.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof.

WHAT IS CLAIMED IS:

1. A magnetometry system comprising a support on which a human subject can sit astride, and an array of magnetic sensors, the array extending into the support so that sensors in the array are adjacent a perineal region of a human sitting astride the support.

2. Apparatus and methods for magnetometry substantially as described herein.

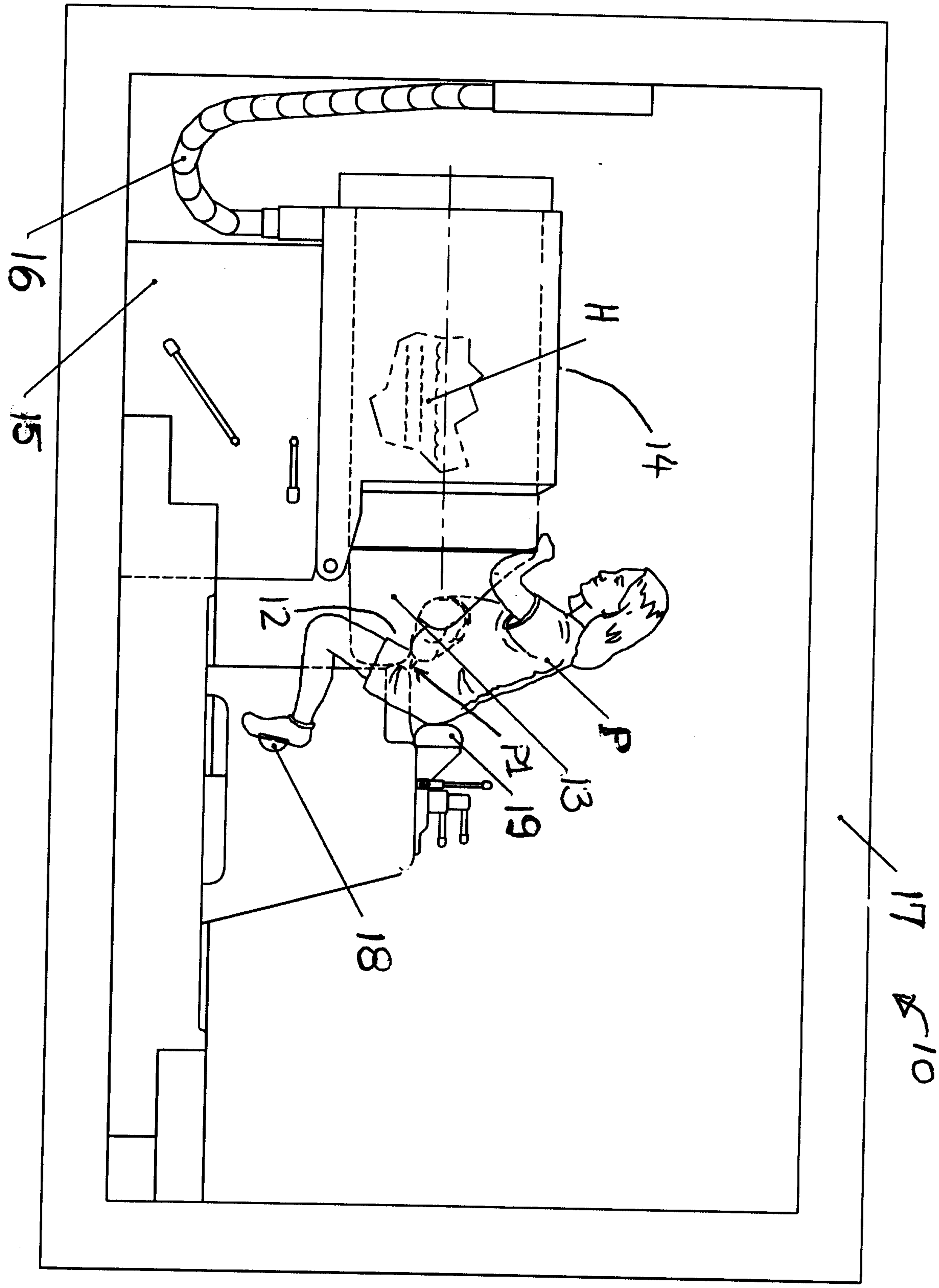


Figure 1

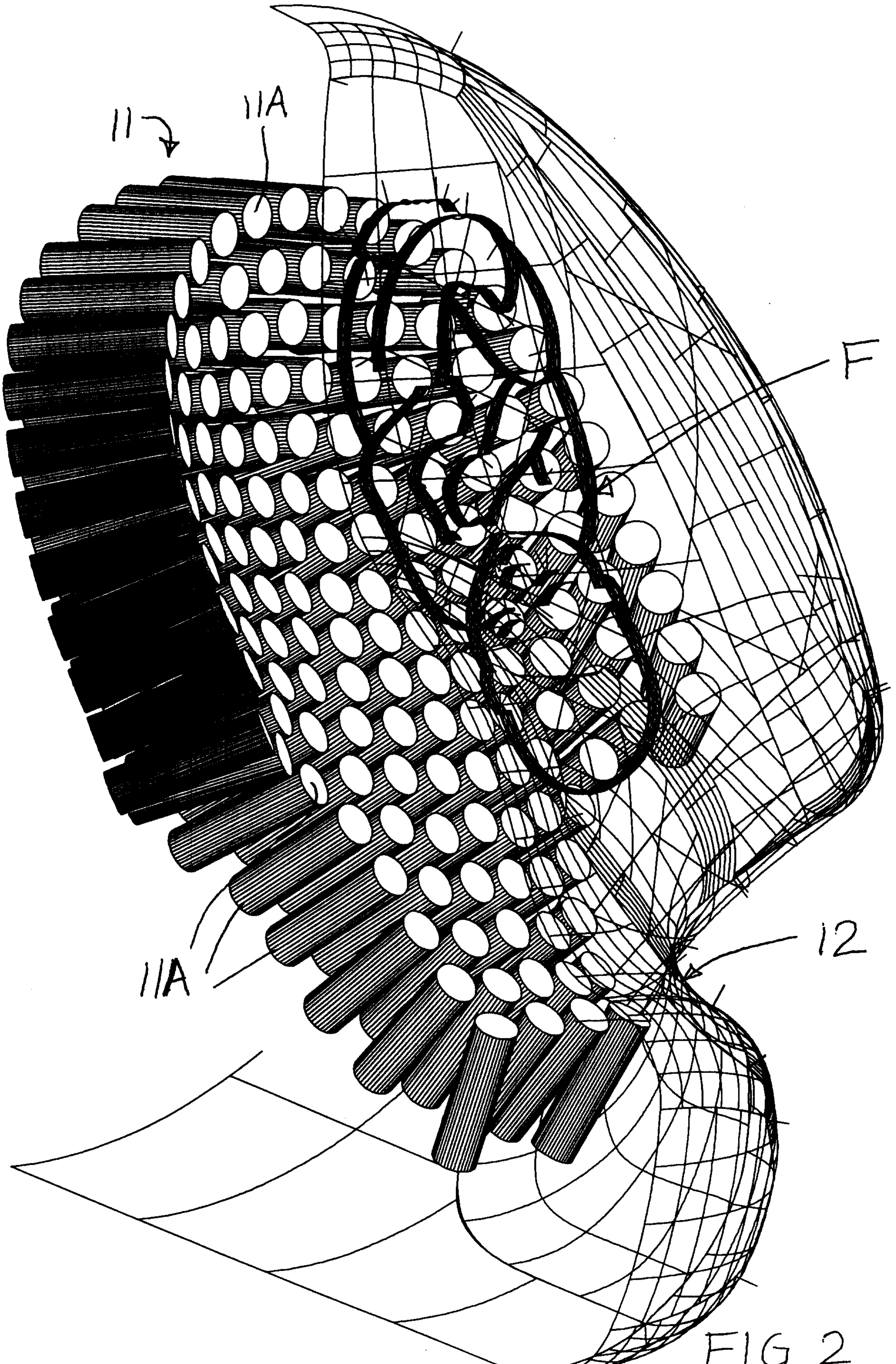


FIG 2

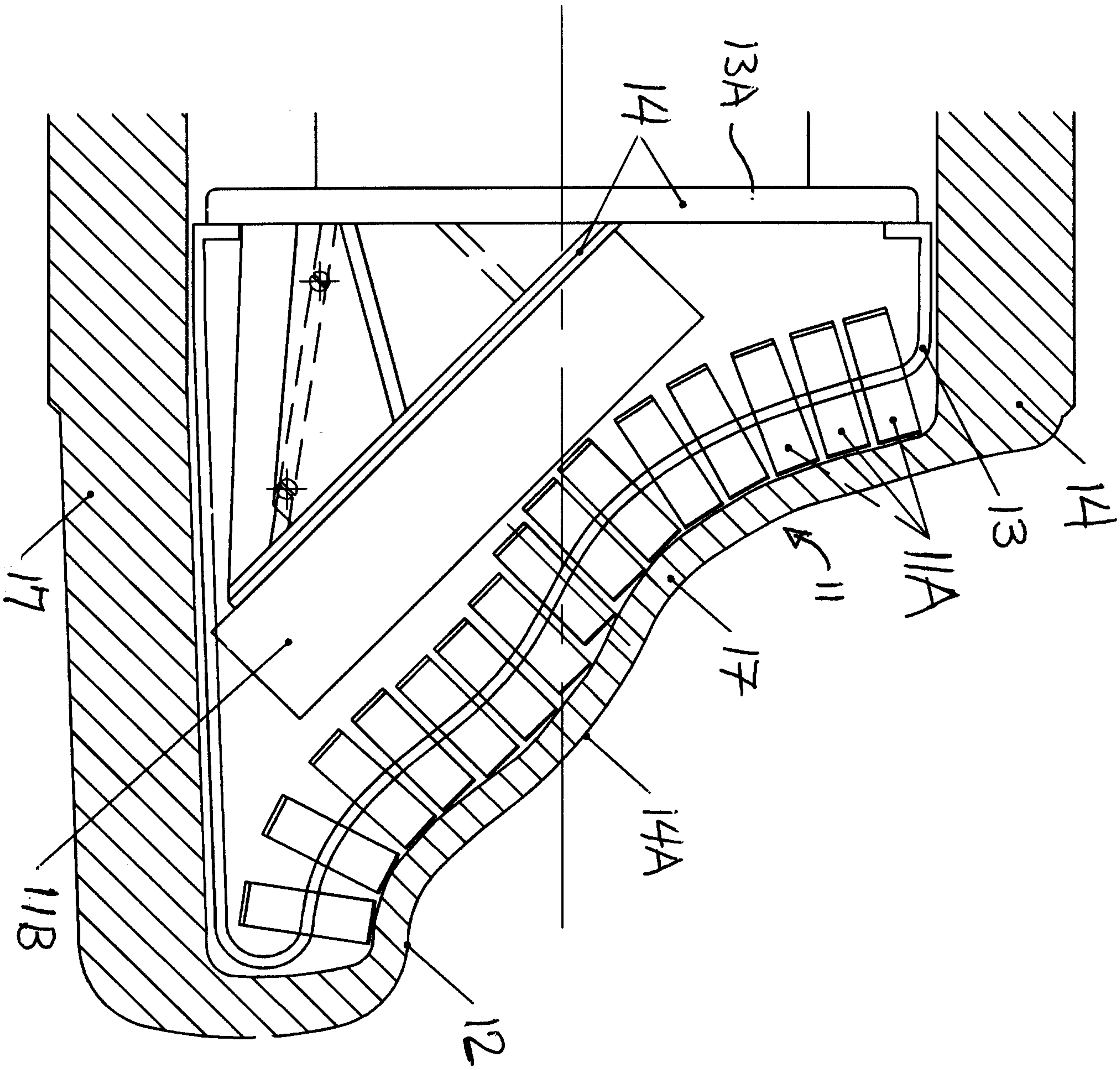


Figure 3

Fetal Biomagnetometer Signal & Information Flow

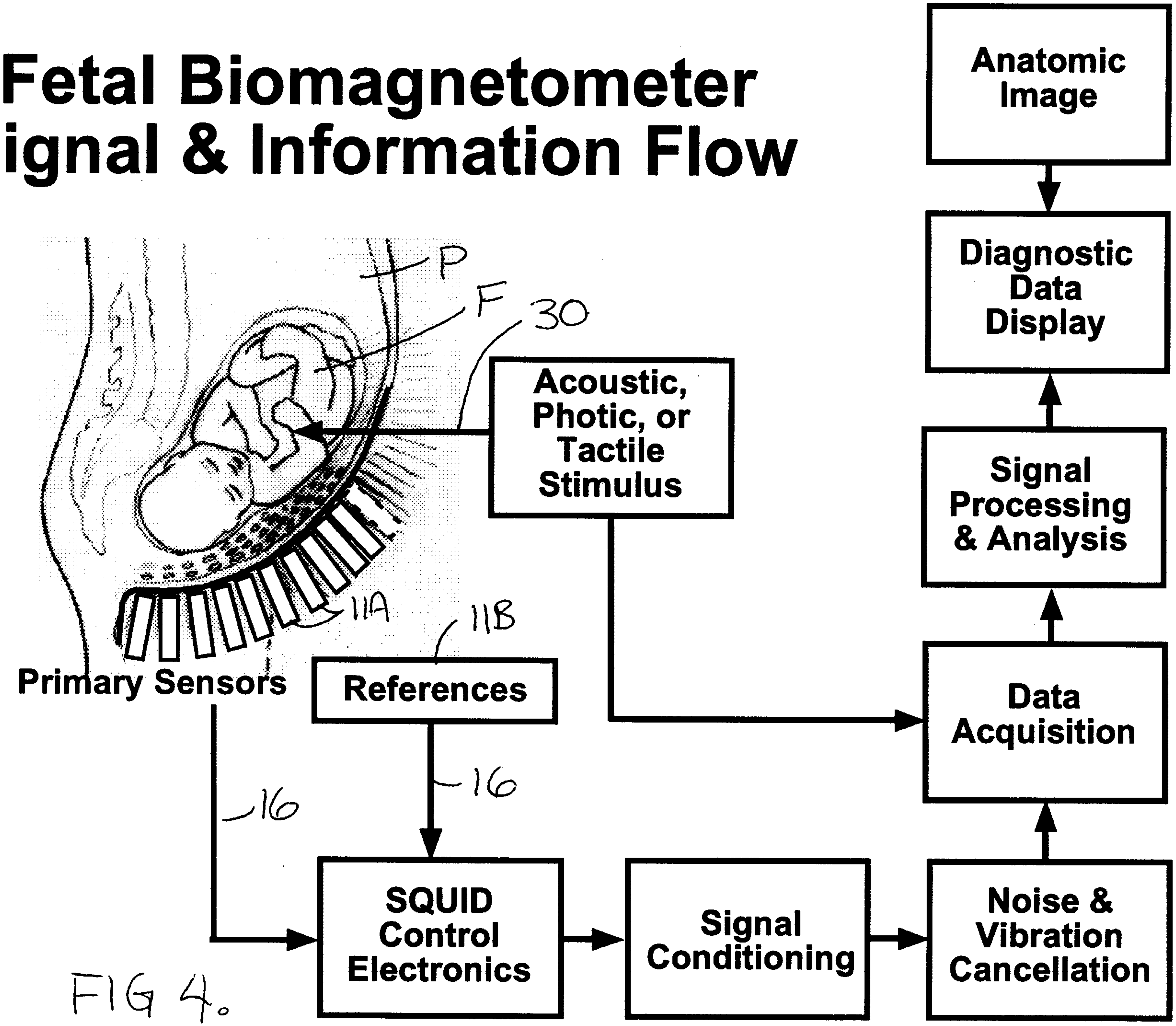
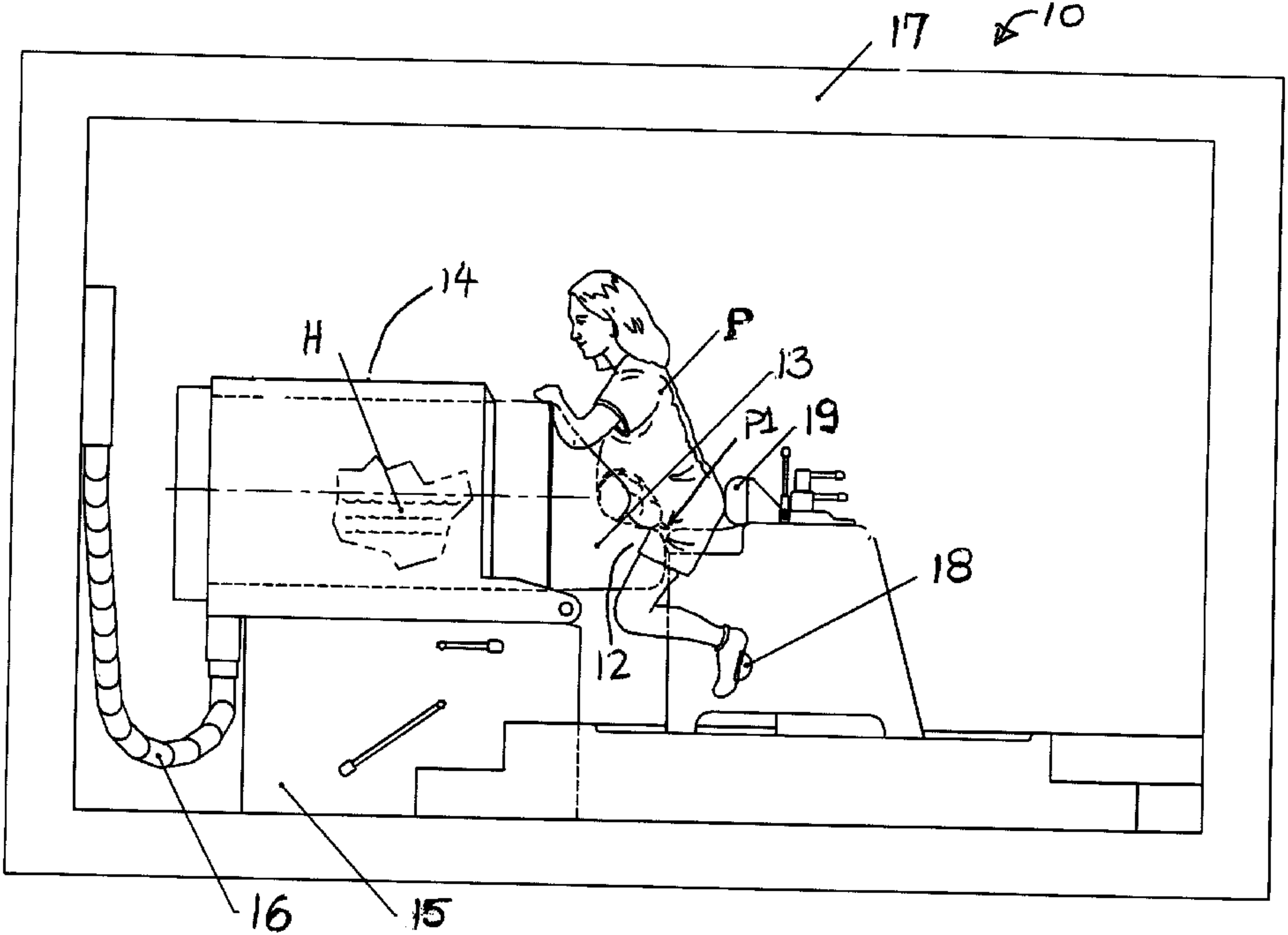


FIG 4.


17
10
14
H
P
13
P1
19
18
12
16
15