(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 241 985 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
08.10.2008 Bulletin 2008/41

(21) Application number: **00989577.2**

(22) Date of filing: **28.12.2000**

(51) Int Cl.:
A61B 5/05 *(2006.01)* ***A61B 17/52*** *(2006.01)*
H01F 7/02 *(2006.01)* ***A61B 5/055*** *(2006.01)*
A61B 5/00 *(2006.01)* ***G01R 33/341*** *(2006.01)*

(86) International application number:
PCT/US2000/035554

(87) International publication number:
WO 2001/047415 (05.07.2001 Gazette 2001/27)

(54) METHOD AND APPARATUS FOR NON-INVASIVE ANALYSIS OF BLOOD GLUCOSE

VERFAHREN UND GERÄT ZUR NICHTINVASIVEN ANALYSE VON BLUTGLUCOSE

METHODE ET APPAREIL DESTINES A L'ANALYSE NON INVASIVE DE LA GLYCEMIE

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **28.12.1999 US 173240 P**
20.09.2000 US 234002 P

(43) Date of publication of application:
25.09.2002 Bulletin 2002/39

(73) Proprietor: **Pindi Products, Inc.**
Reno, NV 89506 (US)

(72) Inventor: **FULLER, Milton, E.**
Reno, NV 89506 (US)

(74) Representative: **Howick, Nicholas Keith et al**
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA (GB)

(56) References cited:
EP-A- 0 350 546
US-A- 5 050 607
US-A- 5 626 137
WO-A-99/32897
US-A- 5 411 023
US-B1- 6 184 684

EP 1 241 985 B1

Printed by Jouve, 75001 PARIS (FR)

Description

PRIORITY CLAIM

[0001] This application claims priority to co-pending U.S. provisional patent application serial number 60/173,240, filed on December 28, 1999, and co-pending U.S. provisional patent application serial number 60/234,002, filed on September 20, 2000.

FIELD OF THE INVENTION

[0002] The present invention relates to an apparatus for noninvasive testing and monitoring of biological molecules such as glucose.

BACKGROUND OF THE INVENTION

[0003] Diabetes mellitus is a medical condition in which the body does not adequately produce the quantity or quality of insulin needed to maintain normal levels of glucose in the circulating blood. The two most common types of diabetes are type I, also known as Insulin Dependent Diabetes Mellitus (IDDM), which accounts for 5-10% of all cases, and type II or Non-Insulin Dependent Diabetes Mellitus (NIDDM), which accounts for 90-95% of all cases. IDDM occurs in childhood, and those suffering from the disease require insulin doses throughout their lives. NIDDM generally occurs in adults and, although insulin may be required, the disease may be controllable with oral medication, weight loss, a nutritious diet and a regular exercise program.

[0004] Diabetes affects about 16 million people in the U.S. and over 100 million people worldwide. Diabetes can lead to severe health complications associated with the accumulated affects of poor blood glucose control, including blindness, kidney failure, heart failure, and peripheral neuropathy associated with limb pain, poor circulation, gangrene and subsequent amputation (Davidson, Diabetes Mellitus - Diagnosis and Treatment, 3rd Edition, Churchill Livingstone, New York, 1991). As a result, frequent self-monitoring of blood glucose is crucial for effective treatment and for reducing diabetes-associated morbidity and mortality.

[0005] Currently glucose measurements are done by pricking a finger and extracting a drop of blood, which is applied to a test strip, causing a color reaction between blood glucose and chemicals on the test strip that can be analyzed by an optical meter (glucometer) to give a numerical glucose reading. However, the current glucose tests are painful, disrupt daily life, and may be difficult to perform in long term diabetic patients due to calluses on the fingers and poor circulation. As a result, the average diabetic patient tests his/her blood glucose levels less than twice a day, far fewer than the recommended 4-7 times a day, leading to poor blood glucose control.

[0006] A non-invasive glucose monitoring method that is fast, painless and convenient could provide adequate control and greatly reduce the complications commonly seen in diabetes patients and consequently reduce health care costs.

[0007] Several types of non-invasive glucose monitoring techniques have been proposed. These techniques measure glucose levels in blood, interstitial fluid, ocular fluids and sweat and include microdialysis, wick extraction, implanted electrochemical or competitive fluorescence sensors, extraction fluid technqiues (iontophoresis, skin suction and suction effusion techniques) and optical techniques, such as near-infrared spectroscopy, infrared spectroscopy, Raman spectroscopy, photoacoustic spectroscopy, scatter and polarization changes.

[0008] Currently, the most actively studied non-invasive methods for blood glucose measurement are optical techniques. All are limited by low signal-to-noise ratios and poor reproducibility. Current instrumentation lacks specificity due to substantial chemical and physical interference.

[0009] Several patents have discussed the use of magnetic fields for the non-invasive detection of certain substances in the human body systems. In nuclear magnetic resonance (NMR), for example, permanent magnets have been used to create a first, or biasing magnetic field to align initially randomly oriented hydrogen protons present in the nuclei of a substance in the sample being tested. A second energy field is applied to increase the energy level of the nuclei. When the second energy field is allowed to collapse, the nuclei return to their original, unaligned state, releasing energy that is detected and analyzed in the form of an image or spectrum. Such spectra are characteristic of individual substances. As a result, NMR may be used to establish the presence and identity of such substances and the concentrations in which such substances are present.

[0010] French Patent No. 2,562,785 (Jeandey et al.) discusses a permanent magnet system for NMR imaging medical diagnostics using pole pieces separated by and bridging stacked permanent magnets to form an open examination area and electromagnetic coils to adjust the resulting magnetic field.

[0011] Japanese Patent No. 56-14145 (Nippon Denshi K.K.) discusses an arrangement of permanent magnets held within a cylinder. A spacer is placed within the cylinder and sandwiched about the spacer are a pair of cylindrical pole pieces having raised central portions that extend into the air gap between the pole pieces and from which the operative

flux emanates.

[0012] European patent application EP 0 350 546 and U.S. Patents No. 4,875,486 and 5,072,732 (Rappaport et al.) describe nuclear magnetic resonance apparatus for non-invasive blood glucose testing that includes a pair of opposed biasing permanent magnets, a surface coil apparatus mounted adjacent the biasing magnets, and an electronic circuit controlled by a microprocessor. The microprocessor activates an RF generator and a cyclically-operated gate, which excites the surface coil. The surface coil applies a second magnetic field, raising the energy state of glucose molecules in a patients finger and aligning their nuclei. The microprocessor then deactivates the RF generator, permitting the nuclei (dipoles) to relax and return to their original alignment, releasing energy that is detected by the surface coil and analyzed by the microprocessor. The process is repeated with a standard sample and the test results with the patient's finger are compared with the results obtained with the standard sample to determine the glucose concentration in the patient.

SUMMARY OF THE INVENTION

[0013] I have discovered a novel amplifier for substantially noise-free transmission of an Rf signal. Such an amplifier has many applications, including its use in apparatus for detection or quantitation of an analyte in a sample, such as a non-invasive glucose test apparatus for diabetic patients.

[0014] According to the invention, an apparatus is provided as claimed in claim 1 hereinafter.

[0015] The magnets are preferably high-gauss magnets of grade 26 to grade 60, including but not limited to NdFeB magnets. As described below, permanent magnets of grade 36 to 41 have been used in apparatus for detection of glucose in a biological sample. For use in such apparatus, the transmission node and reflection node are preferably each in close proximity to one of the magnets to improve the Rf signal received by the reflection mode. A magnetically permeable and electrically insulating barrier is optionally disposed between each node and said magnet in close proximity thereto to prevent contact between the nodes and magnets. An Rf source producing an Rf signal having a frequency of about 2 GHz to about 3 GHz has been successfully used in apparatus for detection of glucose, although other frequencies, or a broad spectrum of frequencies, may be used for other purposes. In order to analyze the Rf signal received by the reflection node, such an apparatus may further include an analyzer connected to the transmission node and the reflection node.

[0016] One embodiment of the apparatus is employed as an apparatus for detection or quantitation of an analyte in a sample, such as, for example, a biological sample such as a bodily fluid, tissue, or body part (e.g., a finger). For such purposes, the apparatus described above includes an analyzer.

[0017] Such an apparatus may be used, for example, for detection of a biological molecule, such as glucose, proteinaceous molecules and macromolecules (e.g., hemoglobins, virus particles, etc.), in a sample.

[0018] According to another embodiment of the invention, methods are provided for detecting an analyte in a sample as claimed in claim 15 hereinafter.

[0019] In order to quantitate the concentration of the analyte in the sample, the method may further comprise (d) determining the reduction of the amplitude of the Rf signal at the frequency that is characteristic of the presence of the analyte, and (e) determining the concentration of the analyte on the basis of said reduction of the amplitude.

[0020] The foregoing and other features and advantages of the invention will become more apparent from the following detailed description and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021]

FIG. 1 is a schematic drawing of an amplifier according to the invention, with the north and south poles of the magnets oriented as shown.

FIG. 2 is a schematic drawing of an embodiment of a non-invasive apparatus for detecting and/or quantitating an analyte in a sample according to the invention, with the north and south poles of the magnets oriented as shown.

FIG. 3 is a top view of a glucose testing apparatus.

FIG. 4 is a side view of a glucose testing apparatus.

FIG. 5 is perspective view of a glucose testing apparatus.

FIG. 6 is a top view of an alternative embodiment of the glucose testing apparatus, with the north and south poles of the magnets oriented as shown.

DETAILED DESCRIPTION OF THE INVENTION

Amplifier

[0022] I have discovered a novel amplifier design that employs an arrangement of two or more spaced apart high gauss permanent magnets oriented and aligned so as to create a single magnetic field. In FIG. 1, two spaced-apart high gauss permanent magnets 12, 14 are shown, although more than two permanent magnets may be used. Spaced-apart nodes or nodes 20, 22 comprising an electrically conductive material are positioned within the magnetic field created by the permanent magnets 12, 14, preferably between the magnets with each node 20, 22 in close proximity to a respective magnet 12, 14. In FIG. 1, two nodes are shown, a transmission node 20 and a reflection node 22, although multiple transmission nodes and/or reflection nodes may be used. As shown, the magnets are aligned such that poles of the magnets are at orthogonal to the alignment of the nodes 20, 22, with the north pole 16 of one magnet facing the south pole 18 of the other magnet. Barriers 24, 26 that are permeable to magnetic fields but that are electrically insulating are optionally positioned between the magnets and probes to permit a node to be in close proximity to a respective magnet while preventing direct contact. A source of an Rf signal 28 is connected to the nodes 20, 22.

[0023] High-gauss permanent magnets for use in connection with the amplifiers and apparatus of the present invention include magnets that are preferably about 26 grade to about 60 grade. The shape of the magnet is not critical. Bar magnets having a round or rectangular cross-section have been used successfully, for example, and magnets having other shapes, such as disc, cylindrical, torus, etc., may also be used. In the glucose test apparatus described below, neodymium-iron-boron grade 39H/38H bar magnets are used that have a rectangular cross-section. Alternate embodiments employ a magnet of similar composition and strength having a round cross-section with a diameter of at least 0.4 inches and a length of at least 1.125 inches.

[0024] In operation, the magnetic field permits a detectable, substantially noise-free Rf signal to be received by the reflection node 22 that can be analyzed by an analyzer connected to the transmission mode 20 and reflection mode 22 (not shown). Apparatus for Non-Invasive Detection and/or Quantitation of an Analyte

[0025] According to another embodiment of the invention, an apparatus for non-invasive detection and/or quantitation of an analyte in a sample is provided that employs an amplifier as described above. Such an apparatus 100 is shown in schematic form in FIG. 2. Spaced apart high gauss permanent magnets 102, 104 are oriented so as to create a single magnetic field. Spaced-apart transmission and reflection nodes 106 and 108, respectively, are positioned in close proximity to, but not in contact with, the permanent magnets 102, 104 and within the magnetic field. Multiple transmission nodes and/or reflection nodes may be used. A non-electrically-conductive but magnetically permeable barrier 110, 112 separates each node from the closest magnet. The space or gap 114 defined between the nodes receives a sample 116 that comprises an analyte. As shown in FIG. 2, the sample 116 may consist of a cuvette, test tube or other vessel for holding an aqueous or non-aqueous fluid, gel, or solid sample, such as, for example, a body part (e.g., finger) or tissue of a patient, a body fluid such as blood, saliva, mucous, tears, intercellular fluid, etc., for analysis of analytes such as, for example, glucose, cholesterol, proteins such as hemoglobin Alc or hormones, viruses, and other target analytes.

[0026] An analyzer 118 and an Rf source 120 are connected to the nodes 106, 108. The Rf source 120 may produce a narrow frequency spectrum centered on a particular frequency that is selected to be appropriate for detection of a particular analyte. Such a frequency may readily be determined by experimentation. Alternatively, the Rf source may produce a wider frequency spectrum in order to permit the detection of multiple analytes in a single sample.

[0027] In operation, the sample 116 is placed or inserted between the transmission node 106 and reflection node 108 so as to be positioned between and in contact with or in close proximity to the nodes 106, 108. The magnetic field permits an Rf signal to be received by the reflection node 108. No Rf signal is detectable by the analyzer 118 in the absence of the magnetic field, as can be demonstrated by simply removing the magnets 102, 104 from the apparatus 100. The strength of the magnets 102, 104 (as measured in gauss units) must be sufficient to penetrate the sample 116 and to permit transmission of an Rf signal that is detectable by the analyzer 118. The analyzer 118 serves as a spectrum analyzer and measures the strength of the Rf signal (decibels, dB) as a function of frequency. The presence of the analyte in the tested sample 116 causes the amplitude of the Rf signal at the resonance frequency of the analyte to be reduced, and the magnitude of the reduction correlates with the concentration of the analyte in the sample. The orientation of the sample 116, e.g., a patient's finger, in the magnetic field is not critical.

Non-Invasive Blood Glucose Testing Apparatus

[0028] One embodiment of an apparatus 200 for non-invasive glucose testing for diagnosis and monitoring of diabetes patients is shown in FIGS. 3, 4 and 5. This apparatus can also be used for detection and quantitation of other molecules, such as proteins and lipids, including, for example, hemoglobin A1c (HbA1c). Such an apparatus can be small, lightweight, and portable, making is suitable for use in a doctor's office or at home. The non-invasive glucose test apparatus 200 shown in FIGS. 3-5 includes a body 202 made of a non-electically-conductive material such as plastic (e.g., plexiglass)

that includes a left edge 204, right edge 206, top surface 208 and bottom surface 210. The top surface 208 is shaped to define magnet inserts 212, 214 along the left edge 204 and right edge 206 and a raised central region 216 with a generally hemicylindrical finger insert 218 centrally located in the top surface of the central region 216 to receive a patient's finger. First and second spaced-apart neodymium-iron-boron grade 39h/38h anisotropic permanent magnets 220, 222 having a maximum energy product [BH]max[MGOe] = 36.0 - 41.0 (N38H, Shin-Etsu Magnetics Inc., San Jose, CA, USA) are situated in the magnet inserts 212, 214. As shown, the magnets 220, 222 are so oriented and aligned that the north pole 224 of first magnet 220 faces the south pole 226 of the second magnet 222 on either side of the central region 216. Opposed spaced-apart gold-plated copper transmission and reflection nodes 228, 230 extend into and along the surface of the insert 218 and are separated by an air space, such that a patient's finger (not shown) placed in the finger insert 218 contacts the nodes 228, 230. The nodes 228, 230 are connected to coaxial connectors 232, 234 that extend through the body 202 to extend away from the bottom surface of the body 210. A network analyzer (HP8722D, Hewlett-Packard Company, Palo Alto, CA) (not shown) that includes an Rf source, is connected to the connectors 232, 234.

[0029] In order to analyze a patient's glucose levels for diagnosing or monitoring diabetes, for example, the patient rests her finger in the finger insert 218 in contact with the transmission node 228 and reflection node 230 and within the magnetic field generated by the magnets 220, 222. The Rf output from the network analyzer 236 is a signal (sine wave) having a frequency spectrum ranging from approximately 2 gigaherz (GHz) to approximately 3 GHz. The network analyzer 236 records the magnitude of the resulting Rf signal (measured in decibels, dB) as a function of frequency, which is then analyzed to determine the patient's blood glucose concentration. The change in the magnitude of the Rf signal at about 2.48 GHz correlates well with the concentration of glucose in the sample. Generally, about one second is required for a glucose reading using the apparatus 200.

[0030] FIG. 6 shows a schematic top view of an alternate embodiment of the apparatus 300, which is generally similar to that shown in FIGS. 3-5. Permanent bar magnets 302, 304 having a circular cross-section are disposed in magnet inserts 306, 308 in the body 310 of the apparatus 300. The bottom edge 312, 314 of each of the magnets is aligned with the bottom edge 316, 318 of the transmission node 320 and the reflection node 322. The north-south axes of the magnets 302, 304 are aligned orthogonally to the alignment of the nodes 306, 308, which are spaced apart on opposite sides of the finger insert 324. This arrangement of the magnets with respect to the nodes stabilizes the magnetic field and improve signal transmission.

Data Analysis

[0031] The resulting data may be analyzed by any known method to determine blood glucose levels. In simplest terms, the glucose testing apparatus is used to test a group of non-diabetics who have fasted for an appropriate period, thereby generating a range of standardized wave pattern signals to determine the normal blood level in a standardized population. A patient is then tested after the same fasting period and the patient's wave pattern signals are compared to those of the standardized patterns. The comparison may be accomplished by visual comparison, although it is preferable for speed and reliability to employ computer analysis.

[0032] One method for analyzing such a signal is by fuzzy clustering, which can be summarized as follows. The preprocessed data for each spectrum obtained by testing a patient (sample spectrum) is transformed into a feature vector of 100 dimensions and written to a file. The feature vectors are then input to the fuzzy clustering program that partitions the vectors into groups, or clusters, that are similar. For a sufficiently large sample of spectral patterns (transformed into feature vectors), the range of glucose levels will be well represented, and each cluster will represent a portion of that range. Each cluster is represented by a prototypical feature vector that is determined by the clustering algorithm. After clustering a sufficiently large sample, K prototypes, or representative feature vectors, are used as standards that must be calibrated by the accompanying tests for actual blood glucose level as described below. After calibration, when a patient is observed with the glucose testing apparatus according to the present invention in order to obtain a spectrum, the spectrum is processed the same way as the sample spectra and a feature vector is obtained for that patient. This feature vector is then used to derive the blood sugar level of the patient.

[0033] First, to calibrate the prototypical feature vectors for each group or cluster of samples, it is necessary to know the actual blood glucose level of the patients from which the samples are obtained. The sample spectra and sample blood glucose levels must be taken very close together in time so as to minimize changes in the blood glucose levels. The set of all feature vectors obtained is clustered by means of a fuzzy clustering algorithm. A number K of clusters is obtained. For each cluster, the modified weighted fuzzy average (MWFEV) is taken of that cluster componentwise to obtain a prototype, or typical feature vector, for that cluster. The actual blood glucose levels for each patient whose feature vector falls into that cluster are averaged in the same manner to obtain the MWFEV of the blood glucose level. This MWFEV blood glucose level is, then, the blood glucose level for any patient with that particular feature vector as derived from that patient's spectrum. For each cluster there is a prototypical feature vector and a blood glucose level that represents it and thus calibrates it. The set of all feature vectors and their associated blood glucose levels are used

to determine the blood glucose level of any patient who is later tested.

[0034] For a given patient, a spectrum is obtained using the glucose testing apparatus. The spectrum is then transformed into a feature vector that is compared to the prototypes. The two or three nearest prototypes are found and their blood glucose levels are read from a data table stored on a computer. Suppose that the three prototypes that are the closest to the feature vector of the patient are associated with the blood glucose levels of g_1, g_2, and g_3. Suppose further that the distances (Euclidian, mean-square, Mahalanobis, or other) of the patient's feature vector from the three prototypical feature vectors are d_1, d_2, and d_3. The blood glucose level of the patient is determined by taking a convex combination to interpolate from the three glucose levels via

$$g = \alpha g_1 + \beta g_2 + \gamma g_3 \qquad (1)$$

where

$$\alpha = d_1/(d_1 + d_2 + d_3), \quad \beta = d_2/(d_1 + d_2 + d_3), \quad \gamma = d_3/(d_1 + d_2 + d_3) \qquad (2)$$

[0035] If, for example, the feature vector of the patient is closest to the first prototype, then α is larger than β or y, so the blood glucose for the first prototype has greater influence. This type of interpolation is very accurate if the prototypes are calibrated accurately. Two prototypes are required.

[0036] Next, a particular spectrum is converted into a feature vector. The spectrum file for a patient consists of a header, followed by 800 pairs of values (f, x) where f is a frequency and x is a magnitude value in decibels (positive and negative). The first 200 points and the last 200 points are not critical to the pattern, which depends essentially on the central 400 points. We read these central 400 points and record the second value (x) of each. Then we take the first four recorded decibel values, strip off the maximum value and the minimum value, and average the two remaining values to obtain an accurate representation of the 4-tuple of values. This α-trimmed signal processing is well known. Because this process is symmetrical for positive and negative values, the process is valid over all points processed. Next, we take the following four values and do the same process on them. This continues until the 400 central decibel values have been exhausted. The resulting 100 representative values have the same shape as the central part of the original spectrum. This reduction of the dimension for the feature vectors provides compressed spectra and increases the speed of the process.

[0037] The 100 representative values for each sample spectrum are saved as a 100-dimensional vector to a file of feature vectors, if there are Q samples, then the completed file will contain Q such feature vectors. Once this file is complete, we process it with our fuzzy clustering algorithm to cluster the feature vectors into a number K of groups that is natural (the feature vectors in eRfh group are most alike in that their distance apart is relatively small compared to feature vectors in other groups).

[0038] A simple version of this method is to use each feature vector and actual blood glucose level as a singleton cluster. Thus, we record the feature vectors for a substantial number of patients along with their actual blood sugar levels determined from blood tests. When a patient is tested with a glucose test apparatus according to the present invention, the resulting spectrum is converted to a feature vector. The most similar feature vectors from the stored database of case feature vectors are retrieved along with their actual blood glucose levels. If there are k similar case feature vectors, the distances between the feature vector of the patient and the feature vectors are represented by d_k, and the weights α_k are computed as described in equation (2). The blood glucose level for the patient is determined by the fuzzy weighting of equation (1). The larger the case base of stored feature vectors, the greater is the accuracy in the interpolation. In this simplest approach, we circumvent the need to calibrate the fuzzy prototypes for each cluster of feature vectors.

[0039] Having illustrated and described the principles of the present invention, it will be apparent to persons skilled in the art that the invention can be modified in arrangement and detail without departing from such principles. I claim all such modifications that are within the scope of the appended claims.

Claims

1. An apparatus (100) for detecting or quantifying an analyte in a sample (116), comprising:

(a) a plurality of spaced-apart permanent magnets (102, 104) that generate a magnetic field that improves an Rf signal passing through the sample;

(b) at least one transmission node (106), and at least one reflection node (108) spaced apart from the transmission node with a gap (114) therebetween in which the sample is positioned, that are disposed within the magnetic field, the transmission and reflection nodes comprised of an electrically-conductive material;
(c) a source (120) that generates the Rf signal having a selected frequency spectrum that is connected to the transmission node and reflection node, the Rf signal being transmittable by the transmission node through the sample for detection by the reflection node; and
(d) an analyzer (118) connected to the transmission node and reflection node for analyzing the Rf signal transmitted through the sample, improved by the magnetic field, and detected by the reflection node to detect a quantity the analyte in the sample.

2. The apparatus (100) of claim 1 wherein the permanent magnets (102, 104) are each grade 26 to grade 60 magnets.

3. The apparatus (100) of claim 2 wherein the permanent magnets (102, 104) are each grade 36 to 41.

4. The apparatus (100) of claim 2 wherein the permanent magnets (102, 104) are each NdFeB magnets.

5. The apparatus (100) of claim 1 wherein the transmission node (106) and reflection node (108) are each in close proximity to one of the magnets (102, 104).

6. The apparatus (100) of claim 5 comprising a magnetically permeable and electrically insulating barrier (110, 112) disposed between each node (106, 108) and said magnet (102, 104) in close proximity thereto to prevent contact therebetween.

7. The apparatus (100) of claim 1 wherein the source (120) produces an Rf signal having a frequency of about 2 GHz to about 3 GHz.

8. The apparatus (100) of claim 1 wherein the analyzed (118) detects a change in a magnitude of at least one characteristic frequency within the selected frequency spectrum to detect or quantity the analyte in the sample.

9. The apparatus (100) of claim 1 wherein the sample (116) is a biological sample.

10. The apparatus (100) of claim 9 wherein the sample (116) is a bodily fluid, tissue, or body part.

11. The apparatus (100) of claim 10 wherein the sample (116) is a finger.

12. The apparatus (100) of claim 1 wherein the analyte is a biological molecule.

13. The apparatus (100) of claim 12 wherein the analyte is a concentration level of glucose.

14. A method for detecting an analyte in a sample (116) comprising:

(a) providing an apparatus (100) comprismg (i) a plurality of spaced-apart permanent magnets (102, 104) that generate a magnetic field that improves an Rf signal passing through the sample; (ii) at least one transmission node (106), and at least one reflection node (108) spaced apart from the transmission node with a gap (114) therebetween, that are disposed within the magnetic field, the transmission and reflection nodes comprised of an electrically-conductive material (110, 112); (iii) a source (120) that generates an Rf signal having an amplitude at a characteristic frequency within a selected frequency spectrum that is connected to the transmission node and reflection node; and (iv) an analyzer (118) connected to the transmission node and reflection node;
(b) disposing a sample comprising the analyte in the gap between the transmission node and reflection node; and
(c) detecting a change in the amplitude of the Rf signal at a characteristic frequency at the reflection node with the analyzer, the change in the amplitude being characteristic of the analyte.

15. The method of claim 14 wherein the change in amplitude is a reduction, and further comprising (i) determining the reduction of the amplitude of the Rf signal at the characteristic frequency that is characteristic of the analyte, and (ii) determining a concentration of the analyte on the basis of the reduction of the amplitude of the Rf signal at the characteristic frequency.

16. The method of claim 14 or claim 15, wherein the step of providing the apparatus includes providing an apparatus

in which the gap (114) is configured such that the Rf signal is detectable by the analyzer when the sample is placed in the gap.

Patentansprüche

1. Vorrichtung bzw. Gerät (100) zum Erfassen oder quantitativen Bestimmen eines Analyten in einer Probe (116), das umfasst:

   (a) eine Vielzahl beabstandeter Permanentmagnete (102, 104), die ein Magnetfeld erzeugen, das ein die Probe durchlaufendes RF-Signal verbessert;
   (b) wenigstens einen Sendeknoten (106) und wenigstens einen Reflexions- bzw. Betrachtungsknoten (108), der von dem Sendeknoten mit einem Spalt (114) dazwischen beabstandet ist, in welchem die Probe angeordnet ist, die in dem Magnetfeld angeordnet sind, wobei die Sende- und. Reflexionsknoten aus einem elektrisch leitenden Material bestehen;
   (c) eine Quelle (120), die das RF-Signal mit einem ausgewählten Frequenzspektrum erzeugt, die mit dem Sendeknoten und dem Reflexionsknoten verbunden ist, wobei das RF-Signal von dem Sendeknoten durch die Probe für die Erfassung durch den Reflexionsknoten übertragbar ist; und
   (d) einen Analysator (118), der mit dem Sendeknoten und dem Reflexionsknoten verbunden ist, um das durch die Probe übertragene RF-Signal, das durch das Magnetfeld verbessert wurde und von dem Reflexionsknoten erfasst wurde, zu analysieren, um den Analyten in der Probe zu erfassen oder quantitativ zu bestimmen.

2. Gerät (100) nach Anspruch 1, wobei die Permanentmagneten (102, 104) jeweils Magnete der Güte bzw. Klasse 26 bis 60 sind.

3. Gerät (100) nach Anspruch 2, wobei die Permanentmagneten (102, 104) jeweils Magnete der Güte bzw. Klasse 36 bis 41 sind.

4. Gerät (100) nach Anspruch 2, wobei die Permanentmagneten (102, 104) jeweils NdFeB-Magnete sind.

5. Gerät (100) nach Anspruch 1, wobei der Sendeknoten (106) und der Reflexionsknoten (108) jeweils in nächster Nähe zu einem der Magneten (102, 104) sind.

6. Gerät (100) nach Anspruch 5, das eine magnetisch durchlässige und elektrisch isolierende Sperre (110, 112) umfasst, die zwischen jedem Knoten (106, 108) und dem Magneten (102, 104) in nächster Nähe dazu angeordnet ist, um den Kontakt dazwischen zu verhindern.

7. Gerät (100) nach Anspruch 1, wobei die Quelle (120) ein RF-Signal mit einer Frequenz von etwa 2 GHz bis etwa 3 GHz erzeugt.

8. Gerät (100) nach Anspruch 1, wobei der Analysator (118) eine Änderung in einer Größe von wenigstens einer charakteristischen Frequenz innerhalb des ausgewählten Frequenzspektrums erfasst, um die Menge des Analyten in der Probe zu erfassen oder quantitativ zu bestimmen.

9. Gerät (100) nach Anspruch 1, wobei die Probe (116) eine biologische Probe ist.

10. Gerät (100) nach Anspruch 9, wobei die Probe (116) ein Körperfluid, Gewebe oder Körperteil ist.

11. Gerät (100) nach Anspruch 1, wobei die Probe (116) ein Finger ist.

12. Gerät (100) nach Anspruch 10, wobei der Analyt ein biologisches Molekül ist.

13. Gerät (100) nach Anspruch 12, wobei der Analyt ein Konzentrationsspiegel von Glucose ist.

14. Verfahren zum Erfassen eines Analyten in einer Probe (116), das umfasst:

   (a) Bereitstellen eines Geräts (100), das umfasst; (i) eine Vielzahl beabstandeter Permanentmagnete (102, 104), die ein Magnetfeld erzeugen, das ein die Probe durchlaufendes RF-Signal verbessert; (ii) wenigstens

einen Sendeknoten (106) und wenigstens einen Reflexionsknoten (108), der von dem Sendeknoten mit einem Spalt (114) dazwischen beabstandet ist, die in dem Magnetfeld angeordnet sind, wobei die Sende- und Reflexionsknoten aus einem elektrisch leitenden Material (110, 112) bestehen; (ii) eine Quelle (120), die ein RF-Signal mit einer Amplitude bei einer charakteristischen Frequenz innerhalb eines ausgewählten Frequenzspektrums erzeugt, die mit dem Sendeknoten und dem Reflexionsknoten verbunden ist; und (iv) einen Analysator (118), der mit dem Sendeknoten und dem Reflexionsknoten verbunden ist;
(b) Anordnen einer Probe, die den Analyten umfasst, in dem Spalt zwischen den Sendeknoten und dem Reflexionsknoten; und
(c) Erfassen einer Änderung in der Amplitude des RF-Signals bei einer charakteristischen Frequenz an die Reflexionsknoten mit dem Analysator, wobei die Änderung der Amplitude für den Analyten charakteristisch ist.

15. Verfahren nach Anspruch 14, wobei die Änderung der Amplitude eine Verringerung ist und das ferner umfasst: (i) Bestimmen der Verringerung der Amplitude des RF-Signals bei der charakteristischen Frequenz, die für den analysen charakteristisch ist, und (ii) Bestimmen einer Konzentration des Analyten auf der Basis der Verringerung der Amplitude des RF-Signals bei der charakteristischen Frequenz.

16. Verfahren nach Anspruch 14 oder 15, wobei der Schritt der Bereitstellung des Geräts die Bereitstellung eines Geräts umfasst, in welchem der Spalt (114) derart aufgebaut ist, dass das RF-Signal von dem Analysator detektierbar bzw. erfassbar ist, wenn die Probe in dem Spalt angeordnet ist.

Revendications

1. Appareil (100) pour détecter ou quantifier un analyte dans un échantillon (116), comprenant :

(a) une pluralité d'aimants permanents espacés (102, 104) qui génèrent un champ magnétique qui améliore un signal RF passant à travers l'échantillon ;
(b) au moins un noeud de transmission (106) et au moins un noeud de réflexion (108) espacé du noeud de transmission par un intervalle (114) situé entre eux dans lequel est placé l'échantillon, qui sont disposés à l'intérieur du champ magnétique, les noeuds de transmission et de réflexion comprenant un matériau conducteur électriquement ;
(c) une source (120) qui génère le signal RF ayant un spectre de fréquence sélectionné, qui est connecté au noeud de transmission et au noeud de réflexion, le signal RF pouvant être transmis par le noeud de transmission à travers l'échantillon pour une détection par le noeud de réflexion ; et
(d) un analyseur (118) connecté au noeud de transmission et au noeud de réflexion pour analyser le signal RF transmis à travers l'échantillon, amélioré par le champ magnétique, et détecté par le noeud de réflexion pour détecter ou quantifier l'analyte dans l'échantillon.

2. Appareil (100) selon la revendication 1, dans lequel les aimants permanents (102, 104) sont chacun des aimants de grade 26 à grade 60.

3. Appareil (100) selon la revendication 2, dans lequel les aimants permanents (102, 104) sont chacun des aimants de grade 36 à grade 41.

4. Appareil (100) selon la revendication 2, dans lequel les aimants permanents (102, 104) sont chacun des aimants NdFeB.

5. Appareil (100) de la revendication 1, dans lequel le noeud de transmission (106) et le noeud de réflexion (108) sont chacun à proximité immédiate de l'un des aimants (102, 104).

6. Appareil (100) selon la revendication 5, comprenant une barrière (110, 112) perméable magnétiquement et isolante électriquement, disposée entre chaque noeud (106, 108) et ledit aimant (102, 104) à proximité immédiate de manière à empêcher un contact entre eux.

7. Appareil (100) selon la revendication 1, dans lequel la source (120) produit un signal RF ayant une fréquence d'environ 2 GHz à environ 3 GHz.

8. Appareil (100) selon la revendication 1, dans lequel l'analyseur (118) détecte un changement d'amplitude d'au

moins une fréquence caractéristique à l'intérieur du spectre de fréquence sélectionné pour détecter ou à quantifier l'analyte dans l'échantillon.

9. Appareil (100) selon la revendication 1, dans lequel l'échantillon (116) est un échantillon biologique.

10. Appareil (100) selon la revendication 9, dans lequel l'échantillon (116) est un fluide corporel, un tissu ou une partie du corps.

11. Appareil (100) selon la revendication 10, dans lequel l'échantillon (116) est un doigt.

12. Appareil (100) selon la revendication 1, dans lequel l'analyte est une molécule biologique.

13. Appareil (100) selon la revendication 12, dans lequel l'analyte est un niveau de concentration de glucose.

14. Méthode de détection d'un analyte dans un échantillon (116) comprenant les étapes consistant à :

(a) fournir un appareil (100) comprenant (i) une pluralité d'aimants permanents espacés (102, 104) qui génèrent un champ magnétique qui améliore un signal RF passant à travers l'échantillon ; (ii) au moins un noeud de transmission (106) et au moins un noeud de réflexion (108) espacé du noeud de transmission par un intervalle (114) situé entre eux, qui sont disposés à l'intérieur du champ magnétique, les noeuds de transmission et de réflexion comprenant un matériau conducteur électriquement (110, 112) ; (iii) une source (120) qui génère un signal RF ayant une amplitude à une fréquence caractéristique dans un spectre de fréquence sélectionné, qui est connecté au noeud de transmission et au noeud de réflexion ; et (iv) un analyseur (118) connecté au noeud de transmission et au noeud de réflexion ;
(b) disposer un échantillon comprenant l'analyte dans l'intervalle entre le noeud de transmission et le noeud de réflexion ; et
(c) détecter un changement de l'amplitude du signal RF à une fréquence caractéristique au niveau du noeud de réflexion avec l'analyseur, le changement de l'amplitude étant caractéristique de l'analyte.

15. Méthode selon la revendication 14, dans laquelle le changement d'amplitude est une diminution, et comprenant en outre les étapes consistant à (i) déterminer la diminution de l'amplitude du signal RF à la fréquence caractéristique qui est caractéristique de l'analyte, et (ii) déterminer une concentration de l'analyte sur la base de la diminution de l'amplitude du signal RF à la fréquence caractéristique.

16. Méthode selon la revendication 14 ou la revendication 15, dans laquelle l'étape consistant à fournir l'appareil inclut la fourniture d'un appareil dans lequel l'intervalle (114) est configuré de telle sorte que le signal RF puisse être détecté par l'analyseur lorsque l'échantillon est placé dans l'intervalle.

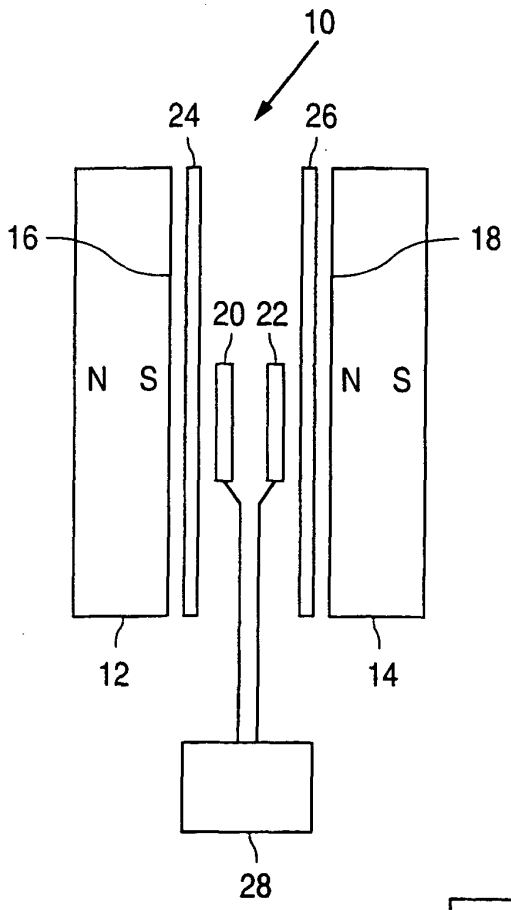
10
24
26
16
18
20
22
N
S
N
S
12
14
28

FIG. 1

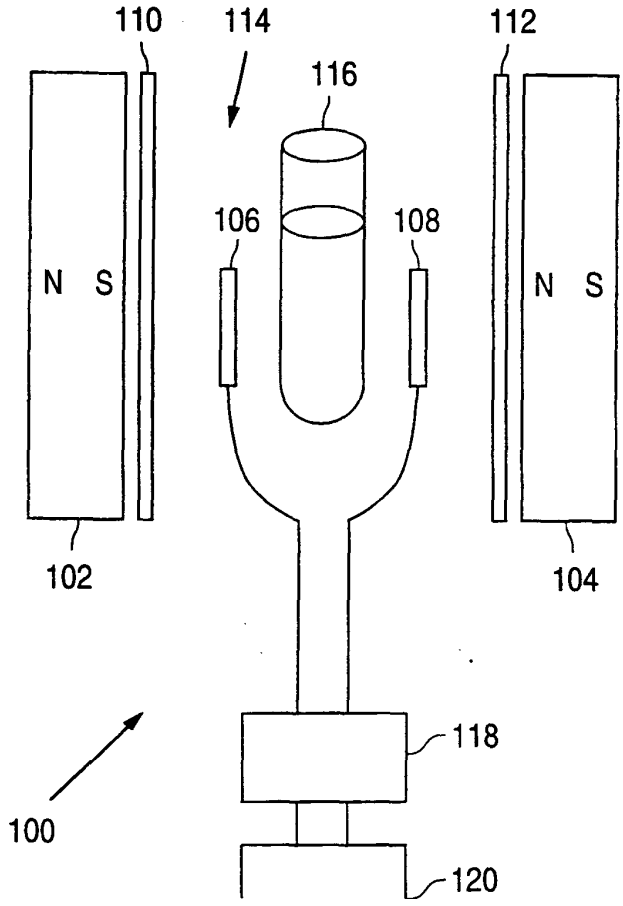
110
114
112
116
106
108
N
S
N
S
102
104
118
100
120

FIG. 2

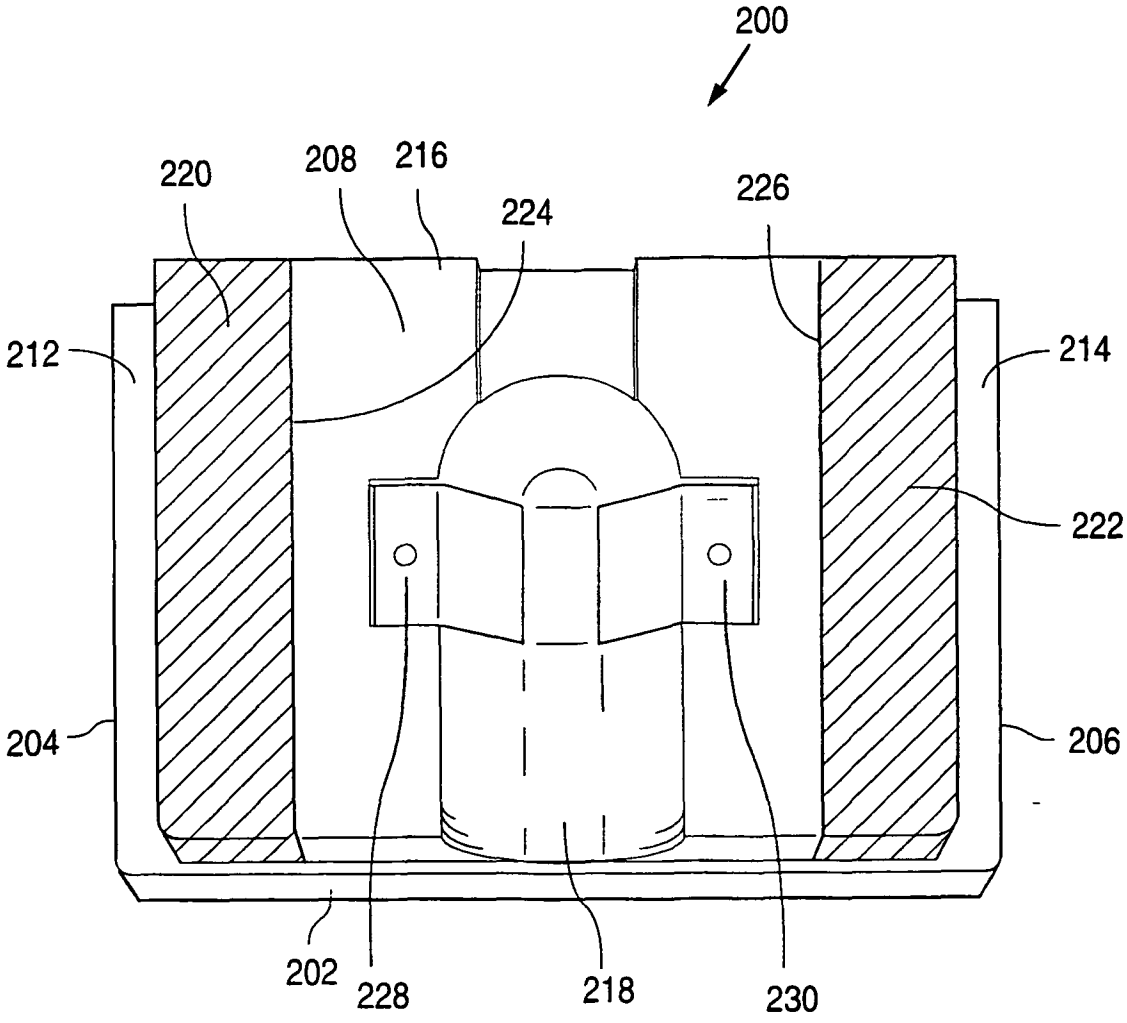

FIG. 3

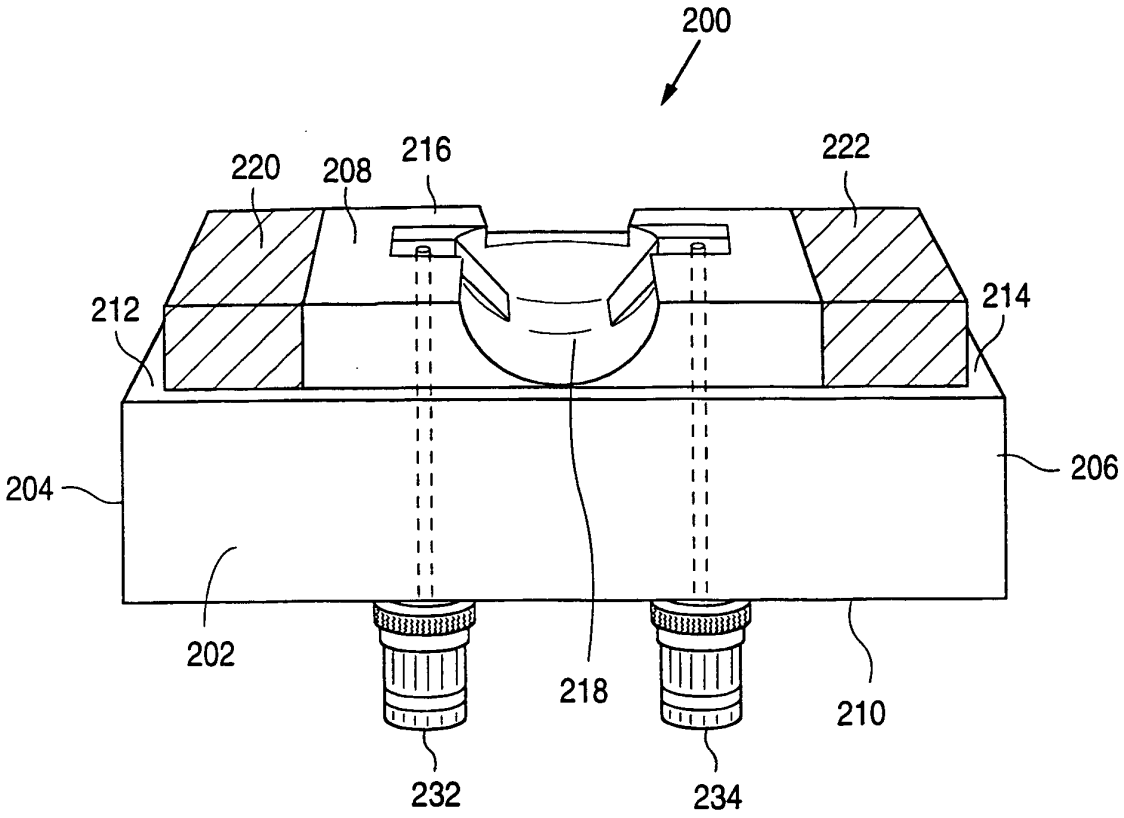
200
220
208
216
222
212
214
204
206
202
218
210
232
234

FIG. 4

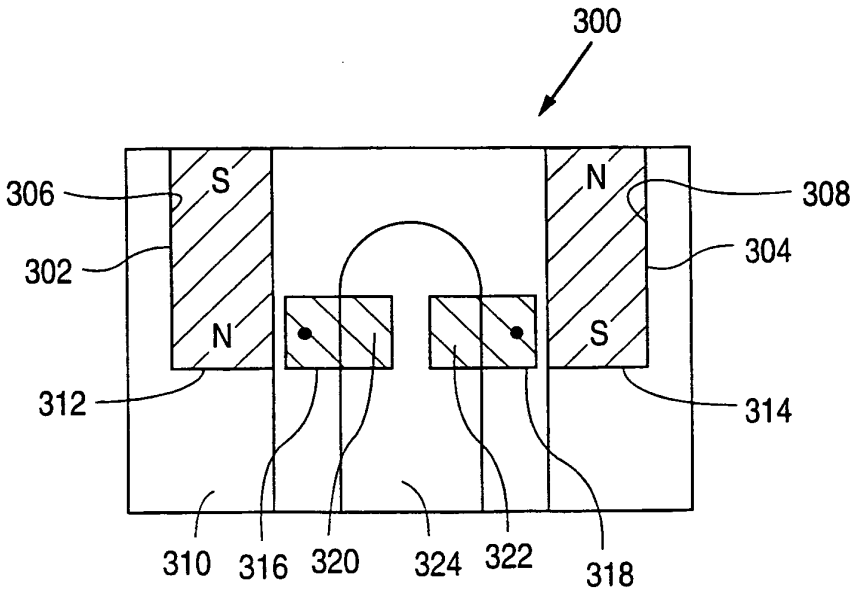
300
306
S
N
308
302
304
N
S
312
314
310
316
320
324
322
318

FIG. 6

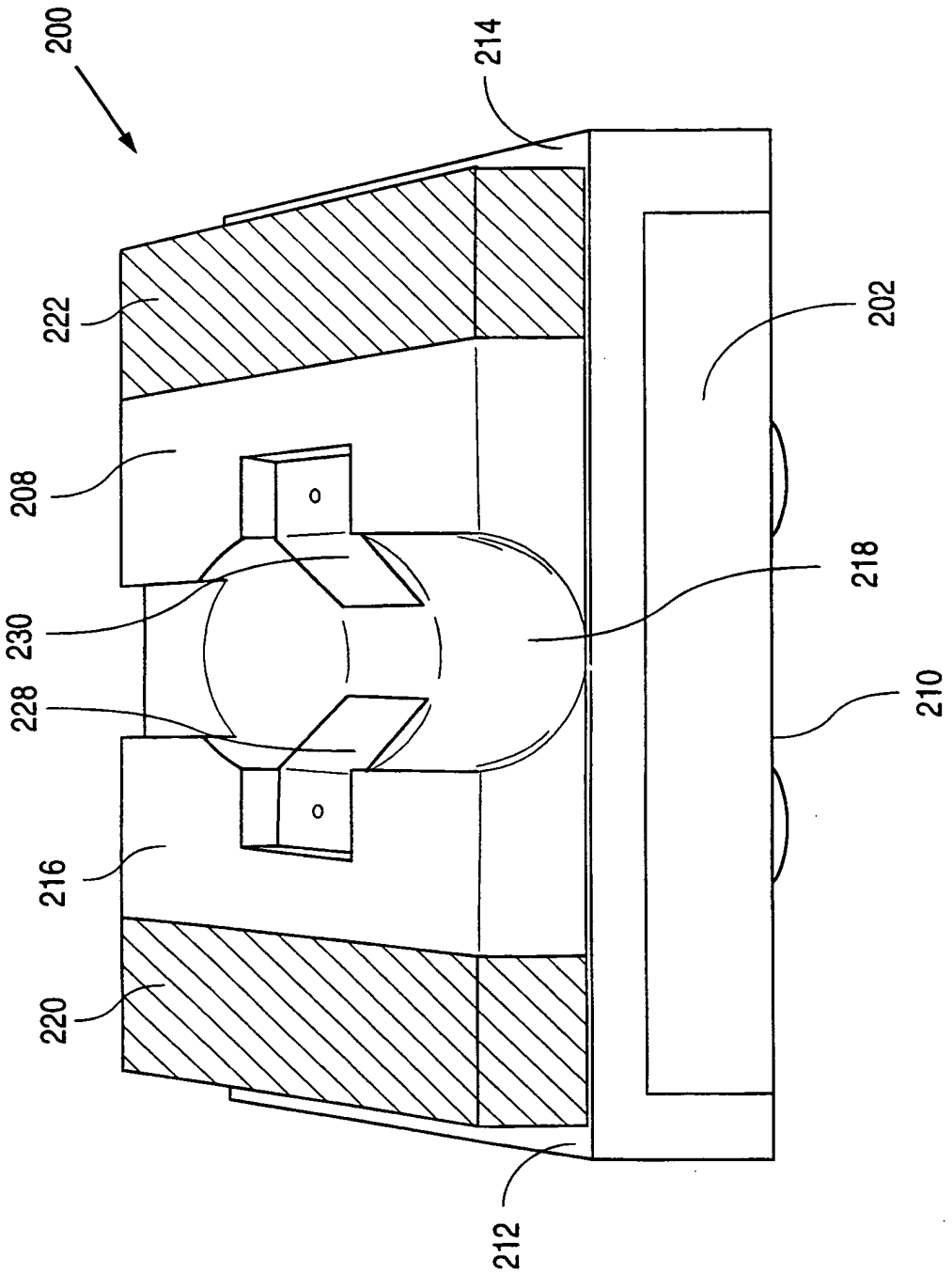

FIG. 5

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 17324099 P **[0001]**
- US 23400200 P **[0001]**
- FR 2562785, Jeandey **[0010]**
- JP 56014145 A, Nippon Denshi K.K. **[0011]**
- EP 0350546 A **[0012]**
- US 4875486 A **[0012]**
- US 5072732 A, Rappaport **[0012]**

Non-patent literature cited in the description

- **DAVIDSON.** Diabetes Mellitus - Diagnosis and Treatment. 1991 **[0004]**

专利名称(译)	用于血糖的非侵入性分析的方法和设备		
公开(公告)号	EP1241985B1	公开(公告)日	2008-10-08
申请号	EP2000989577	申请日	2000-12-28
[标]申请(专利权)人(译)	平迪产品公司		
申请(专利权)人(译)	PINDI PRODUCTS，INC.		
当前申请(专利权)人(译)	PINDI PRODUCTS，INC.		
[标]发明人	FULLER MILTON E		
发明人	FULLER, MILTON, E.		
IPC分类号	A61B5/05 A61B17/52 H01F7/02 A61B5/055 A61B5/00 G01R33/341		
CPC分类号	A61B5/6826 A61B5/05 A61B5/055 A61B5/14532 A61B5/6838 H01F7/0273		
优先权	60/173240 1999-12-28 US 60/234002 2000-09-20 US		
其他公开文献	EP1241985A1 EP1241985A4		
外部链接	Espacenet		

摘要(译)

本发明提供了用于非侵入性检测和定量样品中分析物（例如血糖）的装置。该装置采用一种新型放大器，该放大器使用高斯高斯永磁体（12,14）以允许Rf信号通过样品（116）传输。分析物的浓度可以由特征频率下Rf信号幅度减小的幅度确定。