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(54) Titre : DISPOSITIFS, SYSTEMES, PROCEDES ET OUTILS POUR UNE SURVEILLANCE CONTINUE D'UNE SUBSTANCE A ANALYSER

(54) Title: DEVICES, SYSTEMS, METHODS AND TOOLS FOR CONTINUOUS ANALYTE MONITORING

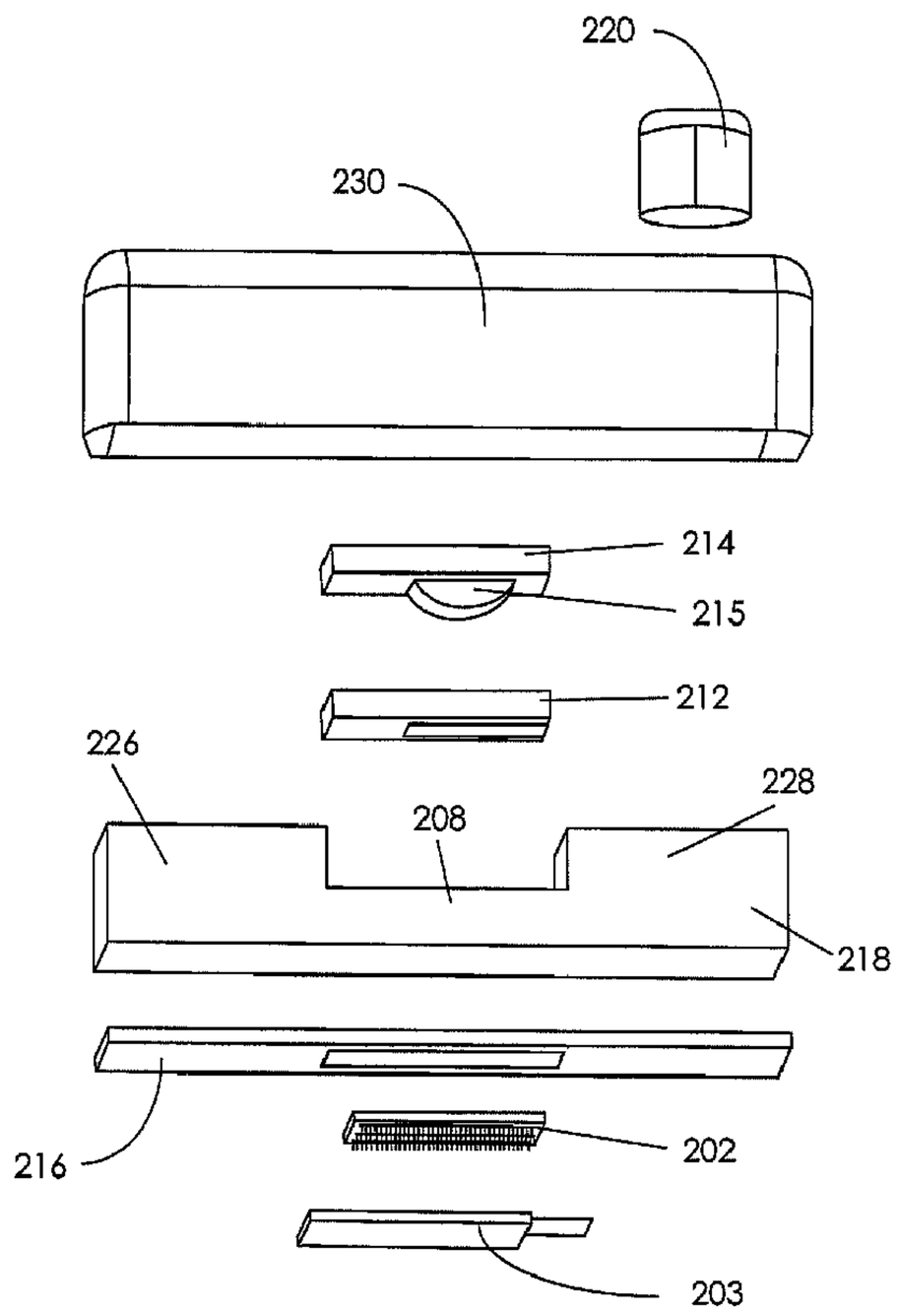

FIG. 2

(57) Abrégé/Abstract:
One aspect of the invention provides an analyte monitor including a sensing volume, an analyte extraction area in contact with the sensing volume adapted to extract an analyte into the sensing volume, and an analyte sensor adapted to detect a concentration of

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(57) Abrégé(suite)/Abstract(continued):
analyte in the sensing volume. The sensing volume is defined by a first face, a second face opposite to the first face, and a thickness equal to the distance between the two faces. The surface area of the first face is about equal to the surface area of the second face and the extraction area is about equal to the surface area of the first and second face of the sensing volume. The analyte sensor includes a working electrode in contact with the sensing volume, the working electrode having a surface area at least as large as the analyte extraction area, and a second electrode in fluid communication with the sensing volume.

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[Continued on next page]

(54) Title: DEVICES, SYSTEMS, METHODS AND TOOLS FOR CONTINUOUS ANALYTE MONITORING

(57) Abstract: One aspect of the invention provides an analyte monitor including a sensing volume, an analyte extraction area in contact with the sensing volume adapted to extract an analyte into the sensing volume, and an analyte sensor adapted to detect a concentration of analyte in the sensing volume. The sensing volume is defined by a first face, a second face opposite to the first face, and a thickness equal to the distance between the two faces. The surface area of the first face is about equal to the surface area of the second face and the extraction area is about equal to the surface area of the first and second face of the sensing volume. The analyte sensor includes a working electrode in contact with the sensing volume, the working electrode having a surface area at least as large as the analyte extraction area, and a second electrode in fluid communication with the sensing volume.

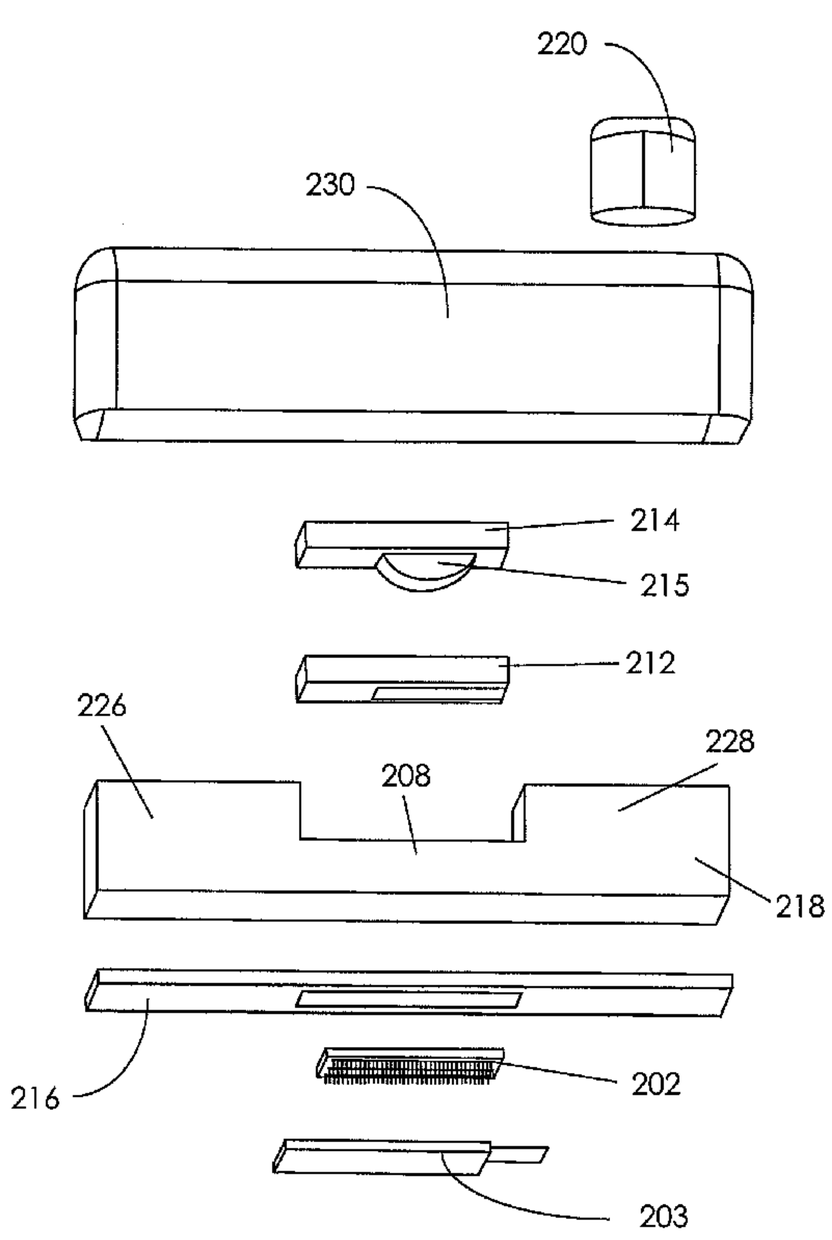

FIG. 2

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DEVICES, SYSTEMS, METHODS AND TOOLS FOR CONTINUOUS ANALYTE MONITORING

CROSS-REFERENCE

[0001] This application is a Continuation-In-Part of U.S. Patent Application No. 12/275,145 filed November 20, 2008 (Publication No. 20090131778), which is a Continuation-In-Part of U.S. Patent Application No. 11/277,731 filed March 28, 2006 (Publication No. 20060219576) and also a Continuation-in-Part of U.S. Patent Application No. 11/642,196 filed December 20, 2006 (Publication No. 20080154107). Each which are herein incorporated by reference in their entirety.

INCORPORATION BY REFERENCE

[0002] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BACKGROUND OF THE INVENTION

[0003] The invention relates to systems, devices, and tools, and the use of such systems, devices and tools for monitoring analytes such as blood glucose levels in a person having diabetes. More specifically, the invention relates to systems, devices, and tools and the use of such systems, devices and tools for monitoring analytes such as blood glucose level continuously, or substantially continuously.

[0004] Diabetes is a chronic, life-threatening disease for which there is no known cure. It is a syndrome characterized by hyperglycemia and relative insulin deficiency. Diabetes affects more than 120 million people world wide, and is projected to affect more than 220 million people by the year 2020. It is estimated that 1 in 3 children today will develop diabetes sometime during their lifetime. Diabetes is usually irreversible, and can lead to a variety of severe health complications, including coronary artery disease, peripheral vascular disease, blindness and stroke. The Center for Disease Control (CDC) has reported that there is a strong association between being overweight, obesity, diabetes, high blood pressure, high cholesterol, asthma and arthritis. Individuals with a body mass index of 40 or higher are more than 7 times more likely to be diagnosed with diabetes.

[0005] There are two main types of diabetes, Type I diabetes (insulin-dependent diabetes mellitus) and Type II diabetes (non-insulin-dependent diabetes mellitus). Varying degrees of insulin secretory failure may be present in both forms of diabetes. In some instances, diabetes is

also characterized by insulin resistance. Insulin is the key hormone used in the storage and release of energy from food.

[0006] As food is digested, carbohydrates are converted to glucose and glucose is absorbed into the blood stream primarily in the intestines. Excess glucose in the blood, *e.g.* following a meal, stimulates insulin secretion, which promotes entry of glucose into the cells, which controls the rate of metabolism of most carbohydrates.

[0007] Insulin secretion functions to control the level of blood glucose both during fasting and after a meal, to keep the glucose levels at an optimum level. In a normal person blood glucose levels are between 80 and 90 mg/dL of blood during fasting and between 120 to 140 mg/dL during the first hour or so following a meal. For a person with diabetes, the insulin response does not function properly (either due to inadequate levels of insulin production or insulin resistance), resulting in blood glucose levels below 80 mg/dL during fasting and well above 140 mg/dL after a meal.

[0008] Currently, persons suffering from diabetes have limited options for treatment, including taking insulin orally or by injection. In some instances, controlling weight and diet can impact the amount of insulin required, particularly for non-insulin dependent diabetics. Monitoring blood glucose levels is an important process that is used to help diabetics maintain blood glucose levels as near as normal as possible throughout the day.

[0009] The blood glucose self-monitoring market is the largest self-test market for medical diagnostic products in the world, with a size of approximately $3 billion in the United States and $5.0 billion worldwide. It is estimated that the worldwide blood glucose self-monitoring market will amount to $8.0 billion by 2006. Failure to manage the disease properly has dire consequences for diabetics. The direct and indirect costs of diabetes exceed $130 billion annually in the United States – about 20% of all healthcare costs.

[0010] There are two main types of blood glucose monitoring systems used by patients: single point or non-continuous and continuous. Non-continuous systems consist of meters and tests strips and require blood samples to be drawn from fingertips or alternate sites, such as forearms and legs (e.g. OneTouch® Ultra by LifeScan, Inc., Milpitas, CA, a Johnson & Johnson company). These systems rely on lancing and manipulation of the fingers or alternate blood draw sites, which can be extremely painful and inconvenient, particularly for children.

[0011] Continuous monitoring sensors are generally implanted subcutaneously and measure glucose levels in the interstitial fluid at various periods throughout the day, providing data that shows trends in glucose measurements over a short period of time. These sensors are painful during insertion and usually require the assistance of a health care professional. Further, these sensors are intended for use during only a short duration (e.g., monitoring for a matter of days to

determine a blood sugar pattern). Subcutaneously implanted sensors also frequently lead to infection and immune response complications. Another major drawback of currently available continuous monitoring devices is that they require frequent, often daily, calibration using blood glucose results that must be obtained from painful finger-sticks using traditional meters and test strips. This calibration, and re-calibration, is required to maintain sensor accuracy and sensitivity, but it can be cumbersome as well as painful.

[0012] At this time, there are four products approved by the FDA for continuous glucose monitoring, none of which are presently approved as substitutes for current glucose self-monitoring devices. All of the approved devices are known to require daily, often frequent, calibrations with blood glucose values which the patient must obtain using conventional finger stick blood glucose monitors. Medtronic (www.medtronic) has two continuous glucose monitoring products approved for sale: Guardian® RT Real-Time Glucose Monitoring System and CGMS® System. Each product includes an implantable sensor that measures and stores glucose values for a period of up to three days. One product is a physician product. The sensor is required to be implanted by a physician, and the results of the data aggregated by the system can only be accessed by the physician, who must extract the sensor and download the results to a personal computer for viewing using customized software. The other product is a consumer product, which permits the user to download results to a personal computer using customized software. The third approved product is a subcutaneously implantable glucose sensor developed by Dexcom, San Diego, CA (www.dexcom.com). A fourth product approved for continuous glucose monitoring is the Glucowatch® developed by Cygnus Inc., which is worn on the wrist like a watch and can take glucose readings every ten to twenty minutes for up to twelve hours at a time. It requires a warm up time of 2 to 3 hours and replacement of the sensor pads every 12 hours. Temperature and perspiration are also known to affect its accuracy.

[0013] Alternative glucose and other analyte monitoring devices have been described in the prior art. Some prior art devices describe possible configurations of glucose monitors. For example, as shown in US Patent No. 6,771,995, the extraction area for an iontophoretic device is restricted by a "mask". This solution however is an inefficient system. As described by the reference, a working electrode and electroosmotic electrodes are coupled to a top surface of a gel, while the mask is coupled to the bottom surface of the gel, blocking a portion of the gel from chemical signal. However, only a small fraction of the gel area can be used for glucose extraction because of the need to accommodate the iontophoresis and other electrodes in contact with the gel.

SUMMARY OF THE INVENTION

[0014] According to some aspects of the invention, a novel analyte monitor with optimized sensitivity and reduced lag times is provided. In some embodiments, the invention comprises an analyte monitor including at least one electrochemical sensor having specific geometry and electrode placement that enables operation of the device with optimized sensitivity and reduced lag times. This geometry and placement of electrodes allows the analyte extracted from the skin by the extraction means to be transported into the chamber through essentially the entire extraction area and essentially the entire sensing volume, which results in minimizing the diffusion path from the extraction means to the sensing electrode through the sensing volume and maximizing the concentration gradient through the sensing volume.

[0015] One aspect of the invention provides an analyte monitor including a sensing volume, an analyte extraction area in contact with the sensing volume adapted to extract an analyte into the sensing volume, and an analyte sensor adapted to detect a concentration of analyte in the sensing volume. The sensing volume is defined by a first face, a second face opposite to the first face, and a thickness equal to the distance between the two faces. The surface area of the first face is about equal to the surface area of the second face and the extraction area is about equal to the surface area of the first and second face of the sensing volume. The analyte sensor includes a working electrode in contact with the sensing volume, the working electrode having a surface area at least as large as the analyte extraction area, and a second electrode in fluid communication with the sensing volume.

[0016] In some embodiments, the extraction area is an area of the analyte monitor that is further adapted to contact skin of a patient. In some embodiments, the ratio of an area of the first face of the sensing volume to the thickness is at least 10 to 1. In some embodiments, the extraction area is in contact with the first face of the sensing volume and the working electrode is in contact with the second face of the sensing volume. In some embodiments, the second electrode is not in contact with the sensing volume. In some embodiments, the second electrode is a reference electrode and the analyte monitor further comprising a counter electrode in fluid communication with the sensing volume.

[0017] In some embodiments, the extraction area comprises a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a proximal opening and an interior space extending between the distal and proximal openings. In some embodiments, the sensing volume comprises a sensing fluid and is in fluid communication with the proximal openings of the tissue piercing elements.

[0018] In some embodiments, the sensing volume comprises a sensing fluid and the analyte sensor is adapted to detect a concentration of analyte in the sensing fluid. In some embodiments, the analyte sensor is an electrochemical sensor.

[0019] In some embodiments, the surface area of the working electrode is in the range of 2 mm^2 to 100 mm^2. While in some embodiments, the surface area of the working electrode is in the range of 10 mm^2 to 50 mm^2.

[0020] In some embodiments, the thickness of the sensing volume is in the range of 50 microns to 3000 microns. In some embodiments, the extraction area is equal to the surface area of the first face of the sensing volume. In some embodiments, the extraction area is the same size and shape as the first face of the sensing volume. In some embodiments, the surface area of the working electrode is equal to the analyte extraction area.

[0021] In some embodiments, the surface area of the working electrode is larger than the analyte extraction area. In some embodiments, the surface area of the working electrode is larger than the analyte extraction area by an amount proportional to an amount that the analyte diffuses laterally away from the extraction area.

[0022] In some embodiments, the analyte monitor further includes a second volume in fluid communication with the sensing volume, and the second electrode is in contact with the second volume. In some embodiments, the second volume is defined by the second electrode, a third face opposite to the second electrode, and a second volume thickness equal to the distance between the second electrode and the third face, the second volume thickness being smaller than the thickness of the sensing volume. In some embodiments, the second electrode is substantially co-planar with the working electrode. In some embodiments, the second volume is in fluid communication with the sensing volume through a fluidic channel. In some embodiments, the fluidic channel has a cross sectional area that is smaller than a cross sectional area of the sensing volume, wherein the cross sectional area of the sensing volume is perpendicular to the first face of the sensing volume.

[0023] In some embodiments, the second electrode is coupled to the working electrode. In some embodiments, the second electrode and the working electrode each have an active surface, wherein the active surfaces of each electrode are facing in opposite directions. In some embodiments, the analyte monitor further includes fluidic connections between the second electrode and the working electrode. In some embodiments, the analyte monitor further includes a substrate having a first face and a second face opposite the first face, and wherein the working electrode is in contact with the first face and the second electrode is in contact with the second face. In some embodiments, the substrate defines a fluidic channel that is adapted to fluidically connect the working electrode and the second electrode.

[0024] In some embodiments, the working electrode and the second electrode are screen printed.

[0025] In some embodiments, the analyte sensor is electrically connected to an external circuit.

[0026] Other embodiments of the invention will be apparent from the specification and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0028] **Figure 1** is a cross-sectional schematic view of an analyte monitoring device according to one embodiment of the invention in place on a user's skin.

[0029] **Figure 2** shows an exploded view of an analyte monitoring device according to another embodiment of the invention.

[0030] **Figures 3(a)** and **(b)** are a schematic representative drawing of a three electrode system for use with the analyte sensor of one embodiment of this invention.

[0031] **Figures 4(a)** and **(b)** are a schematic representative drawing of a two electrode system for use with the analyte sensor of one embodiment of this invention.

[0032] **Figure 5** is a cross-sectional schematic view of a portion of an analyte monitoring device according to yet another embodiment of the invention.

[0033] **Figure 6** shows a remote receiver for use with an analyte monitoring system according to yet another embodiment of the invention.

[0034] **Figure 7** shows an analyte sensor in place on a user's skin and a remote monitor for use with the sensor.

[0035] **Figure 8** is a cross-sectional schematic view of a portion of an analyte monitoring device according to yet another embodiment of the invention.

[0036] **Figure 9(a) and (b)** show a top schematic view and cross-sectional schematic view of a portion of an analyte monitoring device according to yet another embodiment of the invention.

[0037] **Figure 10(a) and (b)** show a top schematic view and cross-sectional schematic view of a portion of an analyte monitoring device according to yet another embodiment of the invention.

[0038] **Figure 11(a) and (b)** show a bottom view and top view of a portion of an analyte monitoring device according to yet another embodiment of the invention.

[0039] **Figure 12** shows an exploded view of an analyte monitoring device according to the embodiment of the invention of Figures 11(a) and (b).

DETAILED DESCRIPTION OF THE INVENTION

[0040] The present invention provides a significant advance in biosensor and glucose monitoring technology: novel analyte monitor geometries and electrode placements that enable operation of the analyte monitor with optimized sensitivity and reduced lag times. The analyte monitor of this invention may be used to measure glucose and other analytes as well, such as electrolytes like sodium or potassium ions. As will be appreciated by persons of skill in the art, the glucose sensor can be any suitable sensor including, for example, an electrochemical sensor or an optical sensor.

[0041] Figure 1 shows a schematic cross-section of one embodiment of the invention in use. The analyte monitor ***100*** has an array of unique hollow microneedles ***102*** or other tissue piercing elements extending through the stratum corneum ***104*** of a user into the interstitial fluid 106 beneath the stratum corneum. Suitable microneedle arrays include those described in Stoeber et al. US Patent **6,406,638**; US Patent Appl. Publ. No. **2005/0171480**; and US Patent Appl. Publ. No. **2006/0025717**. The needles in array ***102*** are hollow and have open distal ends, and their interiors communicate with a sensing area ***110*** within a sensor channel ***108***. Sensing area ***110*** is therefore in fluid communication with interstitial fluid ***106*** through microneedle array ***102***. In this embodiment, sensing area ***110*** and the microneedles ***102*** are pre-filled with sensing fluid prior to the first use of the device. Thus, when the device is applied to the user's skin and the microneedles pierce the stratum corneum of the skin, there is substantially no net fluid transfer from the interstitial fluid into the microneedles. Rather, glucose or other analyte diffuses from the interstitial fluid into the sensing fluid within the needles, as described below.

[0042] Disposed above and in fluid communication with sensor channel ***108*** is an analyte sensor ***112***. In some embodiments, the analyte sensor is an electrochemical glucose sensor that generates an electrical signal (current, voltage or charge) whose value depends on the concentration of glucose in the fluid within sensing area ***110***. Details of the operation of analyte sensor ***112*** are discussed in more detail below.

[0043] Sensor electronics element ***114*** receives the voltage signal from sensor ***112***. In some embodiments, sensor electronics element ***114*** uses the sensed signal to compute a glucose concentration and display it. In other embodiments, sensor electronics element ***114*** transmits the sensed signal, or information derived from the sensed signal, to a remote device, such as through wireless communication. Analyte monitor ***100*** is held in place on the skin ***104*** by one or more adhesive pads ***116***.

[0044] Analyte monitor ***100*** has a novel built-in sensor calibration system. A reservoir ***118*** may contain a sensing fluid having, e.g., a glucose concentration between about 0 and about 400 mg/dl. In some embodiments, the glucose concentration in the sensing fluid is selected to be below the glucose sensing range of the sensor. The sensing fluid may also contain buffers,

preservatives or other components in addition to the glucose. Upon actuation of a pump manually or automatically, plunger or other actuator ***120***, sensing fluid is forced from reservoir ***118*** through a check valve ***122*** (such as a flap valve) into sensing channel ***108***. Any sensing fluid within channel ***108*** is forced through a second check valve ***124*** (e.g., a flap valve) into a waste reservoir ***126***. Check valves or similar gating systems are used to prevent contamination. Because the fresh sensing fluid has a known glucose concentration, sensor ***112*** can be calibrated at this value. After calibration, the sensing fluid in channel ***108*** remains stationary, and glucose from the interstitial fluid ***106*** diffuses through microneedles ***102*** into the sensing area ***110***. Changes in the glucose concentration from over time reflect differences between the calibration glucose concentration of the sensing fluid in the reservoir ***118*** and the glucose concentration of the interstitial fluid which can be correlated with the actual blood glucose concentration of the user using proprietary algorithms. Because of possible degradation of the sensor or loss of sensor sensitivity over time, the device may be periodically recalibrated by operating actuator ***120*** manually or automatically to send fresh sensing fluid from reservoir ***118*** into sensing area ***110***.

[0045] In some embodiments, microneedle array ***102***, reservoirs ***118*** and ***126***, channel ***108***, sensor ***112*** and adhesive pads ***116*** are contained within a support structure (such as a housing ***128***) separate from electronics element ***114*** and actuator ***120***, which are supported within their own housing ***130***. This arrangement permits the sensor, sensing fluid and microneedles to be discarded after a period of use (e.g., when reservoir ***118*** is depleted) while enabling the electronics and actuator to be reused. A flexible covering (made, e.g., of polyester or other plastic-like material) may surround and support the disposable components. In particular, the interface between actuator ***120*** and reservoir ***118*** must permit actuator ***120*** to move sensing fluid out of reservoir ***118***, such as by deforming a wall of the reservoir. In these embodiments, housings ***128*** and ***130*** may have a mechanical connection, such as a snap or interference fit.

[0046] Figure 2 shows an exploded view of another embodiment of the invention. This figure shows a removable seal ***203*** covering the sharp distal ends of microneedles ***202*** and attached, e.g., by adhesive. Seal ***203*** maintains the sensing fluid within the microneedles and sensing area prior to use and is removed prior to placing the analyte monitor ***200*** on the skin using adhesive pressure seal ***216***. In this embodiment, microneedles ***202***, sensing fluid and waste reservoirs ***218*** and ***226***, sensing microchannel ***208*** and electrochemical analyte sensor ***212*** are contained within and/or supported by a housing ***228*** which forms the disposable portion of the device. A second housing ***230*** supports an electronics board ***214*** (containing, e.g., processing circuitry, a power source, transmission circuitry, etc.) and an actuator ***220*** that can be used to move sensing fluid out of reservoir ***218***, through microchannel ***208*** into waste reservoir ***226***. Electrical contacts ***215***

extend from electronics board ***214*** to make contact with corresponding electrodes in analyte sensor ***212*** when the device is assembled.

[0047] The following is a description of glucose sensors that may be used with the analyte monitors of this invention. In 1962 Clark and Lyons proposed the first enzyme electrode (that was implemented later by Updike and Hicks) to determine glucose concentration in a sample by combining the specificity of a biological system with the simplicity and sensitivity of an electrochemical transducer. The most common strategies for glucose detection are based on using either glucose oxidase or glucose dehydrogenase enzyme.

[0048] Electrochemical sensors for glucose, based on the specific glucose oxidizing enzyme glucose oxidase, have generated considerable interest. Several commercial devices based on this principle have been developed and are widely used currently for monitoring of glucose, e.g., self testing by patients at home, as well as testing in physician offices and hospitals. The earliest amperometric glucose biosensors were based on glucose oxidase (GOX) which generates hydrogen peroxide (H_2O_2) in the presence of oxygen and glucose according to the following reaction scheme:

$$\text{Glucose} + \text{GOX-FAD (ox)} \rightarrow \text{Gluconolactone} + \text{GOX-FADH}_2\text{ (red)}$$

$$\text{GOX-FADH}_2\text{ (red)} + O_2 \rightarrow \text{GOX-FAD (ox)} + H_2O_2$$

[0049] Electrochemical biosensors are used for glucose detection because of their high sensitivity, selectivity and low cost. In principal, amperometric detection is based on measuring either the oxidation or reduction of an electroactive compound at a working electrode (sensor). A constant potential is applied to that working electrode with respect to another electrode used as the reference electrode. The glucose oxidase enzyme is first reduced in the process but is reoxidized again to its active form by the presence of any oxygen resulting in the formation of hydrogen peroxide. Glucose sensors generally have been designed by monitoring either the hydrogen peroxide formation or the oxygen consumption. The hydrogen peroxide produced is easily detected at a potential of +0.6 V relative to a reference electrode such as a silver/silver chloride electrode. However, sensors based on hydrogen peroxide detection are subject to electrochemical interference by the presence of other oxidizable species in clinical samples such as blood or serum. On the other hand, biosensors based on oxygen consumption are affected by the variation of oxygen concentration in ambient air. In order to overcome these drawbacks, different strategies have been developed and adopted.

[0050] Selectively permeable membranes or polymer films have been used to suppress or minimize interference from endogenous electroactive species in biological samples. Another strategy to solve these problems is to replace oxygen with electrochemical mediators to reoxidize

the enzyme. Mediators are electrochemically active compounds that can reoxidize the enzyme (glucose oxidase) and then be reoxidized at the working electrode as shown below:

$$GOX\text{-}FADH_2\ (red) + Mediator\ (ox) \rightarrow GOX\text{-}FAD\ (ox) + Mediator\ (red)$$

[0051] Organic conducting salts, ferrocene and ferrocene derivatives, ferricyanide, quinones, and viologens are considered good examples of such mediators. Such electrochemical mediators act as redox couples to shuttle electrons between the enzyme and electrode surface. Because mediators can be detected at lower oxidation potentials than that used for the detection of hydrogen peroxide the interference from electroactive species (e.g., ascorbic and uric acids present) in clinical samples such as blood or serum is greatly reduced. For example ferrocene derivatives have oxidation potentials in the +0.1 to 0.4 V range. Conductive organic salts such as tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) can operate as low as 0.0 Volts relative to a silver/silver cloride reference electrode. Nankai et al, **WO 86/07632**, published Dec. 31, 1986, discloses an amperometric biosensor system in which a fluid containing glucose is contacted with glucose oxidase and potassium ferricyanide. The glucose is oxidized and the ferricyanide is reduced to ferrocyanide. This reaction is catalyzed by glucose oxidase. After two minutes, an electrical potential is applied, and a current caused by the re-oxidation of the ferrocyanide to ferricyanide is obtained. The current value, obtained a few seconds after the potential is applied, correlates to the concentration of glucose in the fluid.

[0052] There are multiple analyte sensors that may be used with this invention. In a three electrode system, shown in **Figure 3(a)**, a working electrode ***302*** is referenced against a reference electrode ***304*** (such as silver/silver chloride) and a counter electrode ***306*** (such as platinum) provides a means for current flow. The three electrodes are mounted on a substrate ***308***, then covered with a reagent ***310***, as shown in **Figure 3(b)**.

[0053] **Figure 4** shows a two electrode system, wherein the working and counter electrodes ***402*** and ***404*** are made of different electrically conducting materials. Like the embodiment of **Figure 3**, the electrodes ***402*** and ***404*** are mounted on a flexible substrate ***408*** as shown in **Figure 4(a)** and covered with a reagent ***410***, as shown in **Figure 4(b)**. In an alternative two electrode system, the working and counter electrodes are made of the same electrically conducting materials, where the reagent exposed surface area of the counter electrode is slightly larger than that of the working electrode or where both the working and counter electrodes are substantially of equal dimensions.

[0054] In amperometric and coulometric biosensors, immobilization of the enzymes is also very important. Conventional methods of enzyme immobilization include covalent binding, physical adsorption or cross-linking to a suitable matrix may be used.

[0055] In some embodiments, the reagent is contained in a reagent well in the biosensor. The reagent includes a redox mediator, an enzyme, and a buffer, and covers substantially equal surface areas of portions of the working and counter electrodes. When a sample containing the analyte to be measured, in this case glucose, comes into contact with the glucose biosensor the analyte is oxidized, and simultaneously the mediator is reduced. After the reaction is complete, an electrical potential difference is applied between the electrodes. In general the amount of oxidized form of the redox mediator at the counter electrode and the applied potential difference must be sufficient to cause diffusion limited electrooxidation of the reduced form of the redox mediator at the surface of the working electrode. After a short time delay, the current produced by the electrooxidation of the reduced form of the redox mediator is measured and correlated to the amount of the analyte concentration in the sample. In some cases, the analyte sought to be measured may be reduced and the redox mediator may be oxidized.

[0056] In some embodiments of the present invention, these requirements are satisfied by employing a readily reversible redox mediator and using a reagent with the oxidized form of the redox mediator in an amount sufficient to insure that the diffusion current produced is limited by the oxidation of the reduced form of the redox mediator at the working electrode surface. For current produced during electrooxidation to be limited by the oxidation of the reduced form of the redox mediator at the working electrode surface, the amount of the oxidized form of the redox mediator at the surface of the counter electrode must always exceed the amount of the reduced form of the redox mediator at the surface of the working electrode. Importantly, when the reagent includes an excess of the oxidized form of the redox mediator, as described below, the working and counter electrodes may be substantially the same size or unequal size as well as made of the same or different electrically conducting material or different conducting materials. From a cost perspective the ability to utilize electrodes that are fabricated from substantially the same material represents an important advantage for inexpensive biosensors.

[0057] As explained above, the redox mediator must be readily reversible, and the oxidized form of the redox mediator must be of sufficient type to receive at least one electron from the reaction involving enzyme, analyte, and oxidized form of the redox mediator. For example, when glucose is the analyte to be measured and glucose oxidase is the enzyme, ferricyanide or quinone may be the oxidized form of the redox mediator. Other examples of enzymes and redox mediators (oxidized form) that may be used in measuring particular analytes by the present invention are ferrocene and or ferrocene derivative, ferricyanide, and viologens. Buffers may be used to provide a preferred pH range from about 4 to 8. The most preferred pH range is from about 6 to 7. The most preferred buffer is phosphate (e.g., potassium phosphate) from about 0.1M to 0.5M and preferably about 0.4M. (These concentration ranges refer to the reagent composition before

it is dried onto the electrode surfaces.) More details regarding glucose sensor chemistry and operation may be found in: Clark LC, and Lyons C, "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," Ann NY Acad Sci, 102:29, 1962; Updike SJ, and Hicks GP, "The Enzyme Electrode," Nature, 214:986, 1967; Cass, A.E. G., G. Davis. G.D. Francis, et. al. 1984. Ferrocene –mediated enzyme electrode for amperometric determination of glucose. Anal.Chem. 56:667-671; and Boutelle, M.G.,C. Stanford. M. Fillenz, et.al. 1986. An amperometric enzyme electrode for monitoring brain glucose in the freely moving rat. Neurosci lett. 72:283-288.

[0058] Another embodiment of the disposable portion of the exemplary analyte monitor is shown in **Figure 5** with a microneedle array ***502*** and a glucose sensor ***512*** in fluid communication with a sensing area in channel ***508***. In this embodiment, actuator ***520*** is on the side of sensing fluid reservoir ***518***, and the waste reservoir ***526*** is expandable. Operation of actuator ***520*** sends sensing fluid from reservoir ***518*** through one way flap valve ***522*** into the sensing area in channel ***508*** and forces sensing fluid within channel ***508*** through flap valve ***524*** into the expandable waste reservoir ***526***.

[0059] In the embodiment of **Figure 5** (and potentially other embodiments), the starting amount of sensing fluid in the calibration reservoir ***518*** is about 1.0 ml or less, and operation of the sensing fluid actuator ***520*** sends a few microliters (e.g., 10 μL) of sensing fluid into channel ***508***. Recalibrating the device three times a day for seven days will use less than 250 μL of sensing fluid.

[0060] Figures 6 and **7** show a remote receiver for use with an analyte monitoring system. The wireless receiver can be configured to be worn by a patient on a belt, or carried in a pocket or purse. In this embodiment, glucose sensor information is transmitted by the glucose sensor ***602*** applied to the user's skin to receiver ***600*** using, e.g., wireless communication such as radio frequency (RF) or Bluetooth wireless. The receiver may maintain a continuous link with the sensor, or it may periodically receive information from the sensor. The sensor and its receiver may be synchronized using RFID technology or other unique identifiers. Receiver ***600*** may be provided with a display ***604*** and user controls ***606***. The display may show, e.g., glucose values, directional glucose trend arrows and rates of change of glucose concentration. The receiver can also be configured with a speaker adapted to deliver an audible alarm, such as high and low glucose alarms. Additionally, the receiver can include a memory device, such as a chip, that is capable of storing glucose data for analysis by the user or by a health care provider.

[0061] In some embodiments, the source reservoir for the calibration and sensing fluid may be in a blister pack which maintains its integrity until punctured or broken. The actuator may be a small syringe or pump. Use of the actuator for recalibration of the sensor may be performed

manually by the user or may be performed automatically by the device if programmed accordingly. There may also be a spring or other loading mechanism within the reusable housing that can be activated to push the disposable portion—and specifically the microneedles—downward into the user's skin.

Sensing Cycle of the Glucose sensor

[0062] The glucose sensor may be operated continuously with respect to the sensing operation of the glucose sensor. In some embodiments, the glucose diffuses through the fluid in the needle lumens of the microneedle array to the electrode surface. The glucose reacts with the chemistry shown above (i.e., paragraphs 0041 and 0042) to produce H_2O_2. The H_2O_2 is then detected in one continuous process. A sensor operating continuously may measure a smaller signal, but likely a more stable signal (which would slowly change as the blood glucose level changes) as compared to a sensor operating periodically/intermittently. When the glucose sensor is operated continuously, the electrodes are likely to be biased and may be kept biased continuously. The glucose sensor may be operated continuously until calibration.

[0063] The glucose sensor may also be operated periodically or intermittently. Periodic operation involves a sensing cycle with regular timing. Periodic operation may occur when the glucose sensor is turned on and off (i.e., when the electrodes are biased and not biased) according to some regular schedule. An example of a regular schedule may be 15 minutes out of every 30 minutes. Periodic sensor operation would allow detection of a larger signal over the shorter times the sensor is activated (and therefore, potentially a better signal to noise ratio).

[0064] Intermittent operation involves a sensing cycle that does not require a regular timing. Intermittent operation may occur when the glucose sensor is turned on and off (i.e., when the electrodes are biased and not biased), but not necessarily in a regular cycle. For example, the user may push a button to initiate an intermittent glucose sensing cycle. Initiation of the glucose sensing cycle may also be prompted by other events (i.e., before or after meals). Intermittent sensor operation may also give discrete readings at some measurement interval (minutes). Intermittent sensor operation may also occur at specific times of the day.

[0065] Any of these types of sensing cycles (i.e., continuous, periodic and intermittent) may involve averaging of signals.

[0066] An example of a sensing cycle is outlined below. Glucose continuously diffuses through the microneedle array into a sensing volume. The glucose sensor may be turned on (or may already be on). As more glucose diffuses in, the H_2O_2 concentration increases. At some point, the electrodes are biased, the entire volume of H_2O_2 is detected coulometrically and its concentration depleted down to substantially zero. Further examples of "sensing to depletion" may be found in U.S. Patent Nos. 6,299,578 and 6,309,351. Equilibrium (i.e., the concentration

of glucose in the chamber is equal to the concentration of glucose in the tissue) does not necessarily need to be achieved. Furthermore, the level of glucose in the chamber does not necessarily need to be at a constant state during the measurement cycle. Additionally, the sensing volume does not necessarily need to be flushed after the glucose is depleted. The timing of when to bias the electrode(s) may be dependent on the type of sensing cycle, and may need to be determined empirically. For example, if a periodic sensing scheme were used, the timing of when to bias the electrodes would be part of the timing of the sensing period. In addition, when the glucose sensor is turned on (or may already be on) and is depleting the H_2O_2, new H_2O_2 is being formed as glucose reacts with the GOx enzyme.

Geometry of the Glucose sensor

[0067] FIG. 8 shows another schematic cross-section of the analyte monitor 100. The analyte monitor 100 includes a microneedle array chip (MAC) 102, working electrode 802 (analyte sensor) based on glucose oxidase (GOX) chemistry 804 and sensing volume 806. FIG. 8 shows an example of desirable geometry 808 of the working electrode 802, sensing volume 806 and microneedle array 102. In this example, the area of the working electrode 802 is similar to or slightly larger than the area of microneedle array 102. The working electrode area should approximate the area (and shape) of the microneedle array 102. In some embodiments, the area of the working electrode may be in the range of 10 mm^2 to 100 mm^2. One example of the working electrode area is 5.5 mm x 5.5 mm, or 30.25 mm^2. An example of the working electrode 802 geometry is a planar electrode that is slightly larger than the microneedle array 102. Another example of the working electrode 802 geometry is a closely spaced electrode strip (as depicted in US 6,139,718). Other examples include electrodes with a similar effective area and which detect a similar sensing volume as sensing volume 806.

[0068] In order to efficiently measure the analyte that is collected through the microneedle array 102, the area of the working electrode 802 should approximate the area of the microneedle array 102 and the working electrode 802 should be located behind the microneedle array 102. As shown in Fig. 8, the working electrode 802 may be located on one side of the sensing volume 806 and on the opposite side of the microneedle array 102. This embodiment may be preferable in some instances because it may minimize the diffusion path from the extraction means to the sensing electrode through the chamber.

[0069] On the other hand, if the working electrode 802 area were much smaller than the area of the microneedle array 102, there would be appreciable analyte collected outside the perimeter of the working electrode 802. The time necessary for this analyte to diffuse to the working electrode 802 may be longer, resulting in a time lag between the interstitial fluid concentration and the measured glucose value. Alternately, if the working electrode 802 were larger than the

extraction area, it would be sufficiently large to measure all the analyte transported into the chamber by the extraction means, however this arrangement would be inefficient because there would be areas on the electrode where no analyte would be detected. In general, the background current of the sensing electrode is proportional to its surface area; therefore a larger working electrode would be non-optimum as it would have a larger background current to analyte signal ratio. In some instances an optimum embodiment includes a working electrode slightly larger than the extraction area. The working electrode may be larger than the extraction area by an amount related to the distance that an analyte may diffuse laterally through the sensing volume (i.e., away from the edges of the extraction area) as it is transported, through the sensing volume, from the extraction area to the working electrode.

[0070] In Figure 8, the thickness of the sensing volume 806 is as small as possible to reduce the distance that analyte must diffuse through the sensing volume 806. Accordingly, the diffusion path from the microneedle array 102 to the working electrode 802 is as short as possible as indicated by the vertical arrows. In some embodiments, the thickness of the sensing volume 806 is in range of about 50 microns to about 3000 microns. In other embodiments, the thickness is between about 50 microns to about 500 microns.

[0071] The thickness of the sensing volume and 806, therefore, its total volume, has effects on the sensing characteristics. As the thickness of the sensing volume is decreased, the diffusion distance and the diffusion time is decreased, thus decreasing the measurement lag time. For the intermittent sensor operation, the smaller volume results in higher analyte concentration in the sensing volume 806. In some embodiments, the ratio of an area of the first face of the sensing volume to the thickness of the sensing volume is at least 10 to 1.

[0072] FIGS. 9(a) and (b) show a schematic cross-section of an exemplary analyte monitor constructed according to aspects of the present invention. In some embodiments, the analyte monitor includes a sensing volume 902, an analyte extraction area 904 in contact with the sensing volume 902 and adapted to extract an analyte into the sensing volume, and an analyte sensor 906 adapted to detect a concentration of analyte in the sensing volume 902. The sensing volume 902 may be defined by a first face 908, a second face 910 opposite to the first face, and a thickness equal to the distance between the two faces. In the embodiment shown, the surface area of the first face is about equal to the surface area of the second face. The extraction area 908 is about equal to the surface areas of the first and second face of the sensing volume. The analyte sensor includes a working electrode 912 in contact with the sensing volume 902 and a second electrode 914 in fluid communication with the sensing volume 902. The working electrode 912 may have a surface area at least as large as the analyte extraction area 904.

[0073] The sensing volume may be a physical chamber containing a liquid (i.e., a container with appropriate fluid connections); a hydrogel layer; a bibulous material such as a paper, polymeric, or fibrous wicking material; and/or any other suitable material or chamber or combination thereof. The analyte extraction area may be defined as the area of contact between the skin and the extraction mechanism. The extraction mechanism may be an array of microneedles, for example, or an area of contact for iontophoresis or passive diffusion. In some embodiments, the extraction area 908 is about equal to the surface areas of the first and second faces of the sensing volume. It may be preferred that at least one of the surface areas of the first and second faces of the sensing volume be of comparable area (i.e., comparable size and shape), or an identical area, as the extraction area. This geometry allows the analyte extracted from the skin by the extraction means to be transported into the chamber through essentially the entire contact area, resulting in minimal concentration gradient across the entire area of the reservoir.

[0074] The analyte sensor may also include a reference electrode (for a two-electrode system) or a combination of reference and counter electrodes (for a three-electrode system) for proper operation of a sensor. As shown in FIGS. 9(a) and (b), the analyte sensor includes a counter electrode 914 and a reference electrode 916. The extraction area 904 is in contact with the first face 908 of the sensing volume 902 and the working electrode 912 is in contact with the second face 910 of the sensing volume 902. The counter electrode 914 and the reference electrode 916 are not in direct contact with the sensing volume.

[0075] The reference and counter electrodes, however, should be placed in fluid communication with the sensing volume 902 and the working electrode 912. For example, the reference electrode 916 and/or counter electrode 914 may be placed in a co-planar manner with the working electrode 912, as shown in FIGS. 9(a) and 9(b), but should be placed outside the desirable geometry (808, as shown in Figure 8) described above. The reference and counter electrodes may be placed in (or placed in contact with) one or two separate volumes which are in fluidic contact with the sensing chamber. As shown in FIGS. 9(a) and (b), these volumes 918 and 920 are fluidically connected to the sensing volume 902. This arrangement will maintain fluidic contact between the sensing volume 902 and the remote electrode volumes 918 and 920.

[0076] In some embodiments, as shown in FIGS. 10(a) and (b), the reference electrode 1016 and/or counter electrode 1014 are again, placed outside the desirable geometry (808, as shown in Figure 8) in a not co-planar manner with the working electrode 1012. The reference and counter electrodes may be placed in (or placed in contact with) one or two separate volumes which are in fluidic contact with the sensing chamber. As shown in FIGS. 10(a) and (b), these volumes 1018 and 1020 are fluidically connected to the sensing volume 1002. This arrangement will maintain

fluidic contact between the sensing volume 1002 and the remote electrode volumes 1018 and 1020.

[0077] As shown in FIGS. 10(a) and (b), these volumes 1018 and 1020 may be connected to the sensing volume 1002 by fluidic channels 1022 and 1024, respectively. In some embodiments, the analyte monitor may further include an electrode substrate 1028 to which the working electrode 1012, counter electrode 1014, and/or reference electrode 1016 are coupled. In some embodiments, the electrode substrate 1028 may define at least one through hole 1026 that couple the fluidic channels 1022 and 1024 to the remote electrode volumes 1018 and 1020, respectively. The fluidic channels 1022 and 1024 and/or through hole 1026 may be narrower than the remote electrode volumes 1018 and 1020 and/or the sensing volume 1002. For example, the fluidic channels 1022 and 1024 may have a cross sectional area that is smaller than a cross sectional area of the sensing volume 1002. The cross sectional area of the sensing volume may be taken perpendicularly to the first face of the sensing volume.

[0078] The cross sectional area of the fluidic channels may be limited by the electrical resistance of the channel. For example, in some embodiments, the supporting electrolyte for the sensor is ionically conductive. The length and width of the fluidic channel(s) will be limited by the increasing electrical resistance of a longer and narrower channel. Higher electrical resistance between the working electrode and the counter and reference electrodes may degrade performance of an analyte monitor by increasing the magnitude of environmental electrical noise induced in the circuit, as well as by increasing the iR drop between the electrodes.

[0079] In some embodiments, as shown in FIGS. 11(a) and (b), analyte monitor 1100 includes reference electrode 1116 and/or counter electrode 1114 that are again placed outside the desirable geometry (808, as shown in Figure 8) in a not co-planar manner with the working electrode 1112. The reference and counter electrodes may be placed in (or placed in contact with) one or two separate volumes which are in fluidic contact with the sensing chamber. As shown in FIGS. 11(a) and (b), these volumes 1118 and 1120 are fluidically connected to the sensing volume (not shown). This arrangement will maintain fluidic contact between the sensing volume and the remote electrode volumes 1118 and 1120.

[0080] As shown in FIGS. 11(a) and (b), these volumes 1118 and 1120 may be connected to the sensing volume 1102 by fluidic through holes 1126 and 1130, respectively. In some embodiments, the analyte monitor may further include an electrode substrate 1128 to which the working electrode 1112, counter electrode 1114, and/or reference electrode 1116 are coupled. In some embodiments, the electrode substrate 1128 may be a ceramic substrate.

[0081] In some embodiments, as shown in FIGS. 11(a) and (b), the reference and/or counter electrode may be coupled to the working electrode. In some embodiments, this may be

accomplished, for example, by laminating a substrate carrying the working electrode 1112, and a substrate carrying the counter and reference electrode 1114 and 1116, back-to-back, so that the electrodes are facing away from each other, i.e. the active surface of the reference and/or counter electrode and the active surface of the working electrode are facing in opposite directions. By making the fluidic connections 1126 and 1130 through the substrates, and fabricating fluidic chambers and channels, these electrodes can be positioned in the same xy-area, but facing in opposite z-directions. Alternately, this embodiment could be fabricated by printing electrodes on both sides of a substrate, which also contains through-substrate fluidic connection holes.

[0082] In some embodiments, these electrodes are fabricated by screen printing technology. Screen printing of the electrodes allows for choice of electrode material, size, and shape. Alternately, the electrodes could be formed by lamination of metal foils, or other printing methods, such as gravure printing, pad printing, or stencil printing. In some embodiments, as shown in FIG. 12, electrical connections 1232 may be made from the electrodes of analyte monitor 1100 to an external circuit. Electrical connections 1232 may be coupled to electrical contact pads 1134 (in FIG. 11(a)). The analyte monitor may include through-substrate conductive vias to provide contact pads 1134 for all the electrodes on one surface of the substrate 1128 (in FIG. 11(a)), thus facilitating connections to, for example, a spring connector. Alternately, the connections could be made by soldering leads to the connection pads. The electrical connections may be kept apart from the fluidic pathways to prevent electrical faults.

Continuous Analyte Monitoring

[0083] As noted earlier, direct fluid communication occurs between the interstitial fluid, the microneedle lumens, and the sensing volume 806. A constant concentration gradient from the interstitial fluid to the analyte sensor causes diffusion of analyte to occur continuously from the interstitial fluid to the electrode surface. The diffusion may occur continuously without interruption. Accordingly, continuous analyte monitoring occurs over time. While this application refers to continuous analyte monitoring, actual analyte sensing may be continuous, periodic or intermittent, or a combination thereof.

Calibration of the Analyte Monitor

[0084] As noted earlier, calibration may also be performed by the analyte monitor 100 automatically without any input from the user. In some embodiments, the sensing (calibration) fluid containing a known concentration of analyte is delivered into the sensing volume 806 and sensed by the analyte sensor. This calibration corrects for any drift in the intrinsic sensor sensitivity over time and may be performed automatically by the device. This intrinsic sensor sensitivity is the amount of sensor signal generated for a given analyte concentration in the sensing volume 806. The overall sensitivity of the analyte monitor device is the amount of

sensor signal generated for a given blood analyte concentration. The overall sensitivity of the system may be a function of both how much analyte is collected through the microneedles and the sensitivity of the sensor.

[0085] The calibration scheme calibrates the intrinsic sensor sensitivity as the microneedle array 102 is bypassed by delivering the calibration fluid directly into the sensing volume 806. The intrinsic sensor sensitivity of the sensor may drift over time because of changes in the electrode surface, poisoning of the platinum catalyst on the surface, or adsorption of other chemical species (e.g., proteins) collected through the needles. The intrinsic sensor sensitivity of the sensor may drift for other reasons as well.

[0086] In some embodiments of the invention, the rate of transport of the analyte from the interstitial fluid to the sensor is constant each time the analyte monitor 100 is used and thus, does not have to be calibrated.

[0087] In addition, multiple calibration fluids may be utilized. These multiple calibration fluids may or may not have different amounts of buffers, preservatives or other components in addition to analyte.

[0088] Using one calibration fluid, a one-point calibration is performed. The one-point calibration may assume an intercept of the calibration curve is zero (or assume some other empirically determined value). The one-point calibration may also adjust the slope of the calibration curve. If two calibration fluids with different analyte concentrations are utilized, an intercept value may not need to be assumed. The best-fit calibration curve may be determined from the sensor signals generated by two different analyte concentrations.

[0089] Calibration may occur in a variety of ways. Calibration may occur with respect to time such as at a predetermined time (or predetermined times) or at a predetermined time interval. Calibration may also occur when the analyte monitor 100 detects drifts in the sensor signal. Drifts in the sensor signal may be determined by monitoring the sensor signal and looking for any excursions that could not be caused by normal analyte level movement or diffusion. Examples of such drifts may be discontinuities in the sensor signal, sharp sensor changes, high noise levels, etc. In addition, calibration may also occur in response to an event or occur at any predetermined points that may or may not be time associated.

[0090] The steps that occur during the calibration process of one exemplary embodiment are detailed below. The sensing (calibration) fluid flows into the sensing volume 806. The sensor is activated or the sensor may already be activated. A sensor signal is acquired that indicates the concentration of analyte in the sensing fluid. The sensing operation may continue for a length of time to acquire the sensor signal. However, the sensing operation should not continue for a length of time such that an appreciable amount of analyte diffuses into the sensing volume 806

from the microneedle array 102. The sensing operation may also continue for a length of time sufficient to deplete the concentration of analyte in the sensing fluid down to the amount of the analyte in the sensing fluid that had originally flowed into the sensing volume 806. The sensing fluid remains in the sensing volume 806 and analyte diffuses from the microneedle array 102 into the sensing fluid.

[0091] The analyte monitor 102 may use an algorithm that uses a measure of the intrinsic sensor sensitivity or the overall sensitivity of the system from the calibration process to make adjustments on the measured analyte concentration diffusing into the sensing volume 806 through the microneedle array 102. As an example, a known analyte concentration may flow into the sensing volume 806 and a sensor signal may be acquired. Accordingly, the sensor signal may be used to make adjustments on the measurement (i.e., continuous measurement) of analyte diffusing into the sensing volume 806. For example, if the previous calibration had generated a sensitivity of "100", and the most recent calibration generates a sensitivity of "95", then it would indicate a loss of sensitivity of the system. The values displayed to the user for analyte collected through the microneedle array 102 would be reading lower than the true value, and would have to be adjusted upwards an amount related to the change in the calibration values to correct for this.

[0092] As noted earlier, the concentration of analyte in the sensing (calibration) fluid is described in the range from 0 to 400 mg/dL. This concentration range is the possible analyte concentrations that could be measured by the device. The concentration of analyte in the sensing volume 806 (when analyte measurements are taken) may be lower than the interstitial analyte concentration because the microneedle array 102 has such a small cross-sectional diffusion area and because the sensor may be continuously operating and depleting the analyte while sensing it. Therefore, the concentration of the analyte in the sensing (calibration) fluid is likely to be on the order of magnitude of the concentration of analyte that is in the sensing volume 806 while the device is operating in a non-calibration mode (i.e., measuring the analyte diffusing through the microneedles). This concentration may then be on the order of micromolar to millimolar (i.e., when the analyte is glucose, 1-3 orders of magnitude lower than the average 100 mg/dL (5.5 mM) blood glucose concentration).

Empty Needles

[0093] One embodiment of the analyte monitor 100 includes microneedle array 102 having microneedles that are pre-filled with sensing fluid prior to the use of the device. Another embodiment of the analyte monitor 100 includes microneedles that are not pre-filled prior to the use of the device. In this embodiment, the microneedle lumens may be filled with the interstitial

fluid once the array 102 is applied to the skin. Analyte may then diffuse from the body's interstitial fluid through the microneedle lumens and into the sensing volume 806.

[0094] The interstitial fluid may flow immediately into the lumens of the microneedles upon insertion of unfilled needles. Capillary action may fill the lumens with interstitial fluid.

[0095] While exemplary embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. For example, the devices, systems and methods described above may be used to monitor analytes other than glucose. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. An analyte monitor comprising:

a sensing volume defined by a first face, a second face opposite to the first face, and a thickness equal to the distance between the two faces, wherein the surface area of the first face is about equal to the surface area of the second face;

an analyte extraction area in contact with the sensing volume and adapted to extract an analyte into the sensing volume, wherein the extraction area is about equal to the surface area of the first and second face of the sensing volume;

an analyte sensor adapted to detect a concentration of analyte in the sensing volume, the analyte sensor comprising:

a working electrode in contact with the sensing volume, the working electrode having a surface area at least as large as the analyte extraction area, and

a second electrode in fluid communication with the sensing volume.

2. The analyte monitor of claim 1, wherein the extraction area is an area of the analyte monitor that is further adapted to contact skin of a patient.

3. The analyte monitor of claim 1, wherein the ratio of an area of the first face of the sensing volume to the thickness is at least 10 to 1.

4. The analyte monitor of claim 1, wherein the extraction area is in contact with the first face of the sensing volume and the working electrode is in contact with the second face of the sensing volume.

5. The analyte monitor of claim 1, wherein the second electrode is not in contact with the sensing volume.

6. The analyte monitor of claim 1, wherein the second electrode is a reference electrode and the analyte monitor further comprising a counter electrode in fluid communication with the sensing volume.

7. The analyte monitor of claim 1, wherein the extraction area comprises a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a proximal opening and an interior space extending between the distal and proximal openings.

8. The analyte monitor of claim 7, wherein the sensing volume comprises a sensing fluid and is in fluid communication with the proximal openings of the tissue piercing elements.

9. The analyte monitor of claim 1, wherein the sensing volume comprises a sensing fluid and the analyte sensor is adapted to detect a concentration of analyte in the sensing fluid.

10. The analyte monitor of claim 1, wherein the analyte sensor is an electrochemical sensor.

11. The analyte monitor of claim 1, wherein the surface area of the working electrode is in the range of 2 mm^2 to 100 mm^2.

12. The analyte monitor of claim 11, wherein the surface area of the working electrode is in the range of 10 mm^2 to 50 mm^2.

13. The analyte monitor of claim 1, wherein the thickness of the sensing volume is in the range of 50 microns to 3000 microns.

14. The analyte monitor of claim 1, wherein the extraction area is equal to the surface area of the first face of the sensing volume.

15. The analyte monitor of claim 1, wherein the extraction area is the same size and shape as the first face of the sensing volume.

16. The analyte monitor of claim 1, wherein the surface area of the working electrode is equal to the analyte extraction area.

17. The analyte monitor of claim 1, wherein the surface area of the working electrode is larger than the analyte extraction area.

18. The analyte monitor of claim 17, wherein the surface area of the working electrode is larger than the analyte extraction area by an amount proportional to an amount that the analyte diffuses laterally away from the extraction area.

19. The analyte monitor of claim 1, further comprising a second volume in fluid communication with the sensing volume, wherein the second electrode is in contact with the second volume.

20. The analyte monitor of claim 19, wherein the second electrode is substantially co-planar with the working electrode.

21. The analyte monitor of claim 20, wherein the second volume is in fluid communication with the sensing volume through a fluidic channel.

22. The analyte monitor of claim 21, wherein the fluidic channel has a cross sectional area that is smaller than a cross sectional area of the sensing volume, wherein the cross sectional area of the sensing volume is perpendicular to the first face of the sensing volume.

23. The analyte monitor of claim 19, wherein the second volume is defined by the second electrode, a third face opposite to the second electrode, and a second volume thickness equal to the distance between the second electrode and the third face, the second volume thickness being smaller than the thickness of the sensing volume.

24. The analyte monitor of claim 1, wherein the second electrode is coupled to the working electrode.

25. The analyte monitor of claim 24, wherein the second electrode and the working electrode each have an active surface, wherein the active surfaces of each electrode are facing in opposite directions.

26. The analyte monitor of claim 24, further comprising fluidic connections between the second electrode and the working electrode.

27. The analyte monitor of claim 24, further comprising a substrate having a first face and a second face opposite the first face, and wherein the working electrode is in contact with the first face and the second electrode is in contact with the second face.

28. The analyte monitor of claim 27, wherein the second electrode is a reference electrode and the analyte monitor further comprises a counter electrode in fluid communication with the sensing volume.

29. The analyte monitor of claim 28, wherein the counter electrode is in contact with the second face of the substrate.

30. The analyte monitor of claim 27, wherein the substrate defines a fluidic channel that is adapted to fluidically connect the working electrode and the second electrode.

31. The analyte monitor of claim 1, wherein the working electrode and the second electrode are screen printed.

32. The analyte monitor of claim 1, wherein the analyte sensor is electrically connected to an external circuit.

33. A glucose monitor comprising:

a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a proximal opening and an interior space extending between the distal and proximal openings;

a sensing volume in fluid communication with the proximal openings of the tissue piercing elements;

sensing fluid extending into the sensing volume; and

a glucose sensor adapted to detect a concentration of glucose in the sensing fluid within the sensing volume.

34. The glucose monitor of claim 33 wherein the glucose sensor is an electrochemical sensor.

35. The glucose monitor of claim 33 wherein an area of a surface that faces the tissue piercing elements of the glucose sensor is substantially similar to an area covering the tissue piercing elements.

36. The glucose monitor of claim 33 wherein an area of a surface that faces the tissue piercing elements of the glucose sensor is larger than the area covering the tissue piercing elements.

37. The glucose monitor of claim 33 wherein an area of a surface that faces the tissue piercing elements of the glucose sensor is in the range of 10 mm2 to 100 mm2.

38. The glucose monitor of claim 33 wherein a thickness of the sensing volume is in the range of 50 microns to 3000 microns.

39. The glucose monitor of claim 33 wherein the glucose sensor is adapted to detect a concentration of glucose in the sensing fluid within the sensing volume without extracting interstitial fluid.

40. The glucose monitor of claim 33 wherein the sensing fluid comprises multiple calibration fluids.

41. The glucose monitor of claim 33 wherein the glucose sensor is configured to operate continuously.

42. The glucose monitor of claim 33 wherein the glucose sensor is configured to operate periodically.

43. The glucose monitor of claim 33 wherein the glucose sensor is configured to operate intermittently.

44. A method of in vivo monitoring of an individual's interstitial fluid glucose concentration comprising:

inserting distal ends of a plurality of tissue piercing elements through a stratum corneum area of the individual's skin, the tissue piercing elements each comprising a distal opening, a proximal opening, an interior space extending between the distal and proximal openings, and a sensing fluid filling substantially the entire interior space;

allowing glucose to diffuse into a sensing volume without extracting interstitial fluid; and

sensing a glucose concentration of the sensing fluid within the sensing volume.

45. The method of claim 44 wherein sensing the glucose concentration further comprises continuing to monitor the glucose concentration over time.

46. The method of claim 44 wherein sensing the glucose concentration comprises continuously sensing the glucose concentration over time.

47. The method of claim 46 wherein continuous sensing of the glucose concentration proceeds until calibration.

48. The method of claim 45 wherein sensing the glucose concentration comprises periodically sensing the glucose concentration.

49. The method of claim 48 wherein periodically sensing the glucose concentration comprises having a sensing cycle with regular timing.

50. The method of claim 45 wherein sensing the glucose concentration comprises intermittently sensing the glucose concentration.

51. The method of claim 50 wherein intermittently sensing the glucose concentration comprises a sensing cycle having irregular timing.

52. The method of claim 44 wherein a glucose sensor senses the glucose concentration, the method further comprising calibrating the glucose sensor prior to the sensing step.

53. The method of claim 52 wherein the calibrating step occurs at a predetermined time point.

54. The method of claim 52 wherein the calibrating step occurs at a predetermined time interval.

55. The method of claim 52 wherein the calibrating step occurs when the glucose sensor detects a drift in the glucose concentration measurement.

56. The method of claim 55 wherein the drift is determined by monitoring a sensor signal from the glucose sensor.

57. The method of claim 52 wherein the calibrating step comprises moving the sensing fluid into the sensing volume.

58. The method of claim 57 wherein the calibrating step further comprises acquiring a sensor signal indicating the concentration of glucose in the sensing fluid.

59. The method of claim 58 further comprising moving sensing fluid out of the sensing area as sensing fluid is moved into the sensing volume.

60. The method of claim 59 wherein the sensing fluid remains in the glucose sensor after the calibrating step.

61. The method of claim 59 wherein the step of moving sensing fluid comprises moving sensing fluid having a glucose concentration of between about 0 mg/dl and about 400 mg/dl.

62. The method of claim 44 wherein sensing a glucose concentration comprises:
diffusing glucose through the tissue piercing elements; and
detecting hydrogen peroxide formation.

63. The method of claim 62 further comprising detecting hydrogen peroxide formation coulometrically.

64. The method of claim 62 wherein the hydrogen peroxide formation is reduced to substantially zero.

65. The method of claim 44 wherein sensing a glucose concentration comprises:
diffusing glucose through the tissue piercing elements; and
detecting oxygen consumption.

66. A method of in vivo monitoring of an individual's interstitial fluid glucose concentration comprising:

inserting distal ends of a plurality of tissue piercing elements through a stratum corneum area of the individual's skin, the tissue piercing elements each comprising a distal opening, a proximal opening, and an interior space extending between the distal and proximal opening;

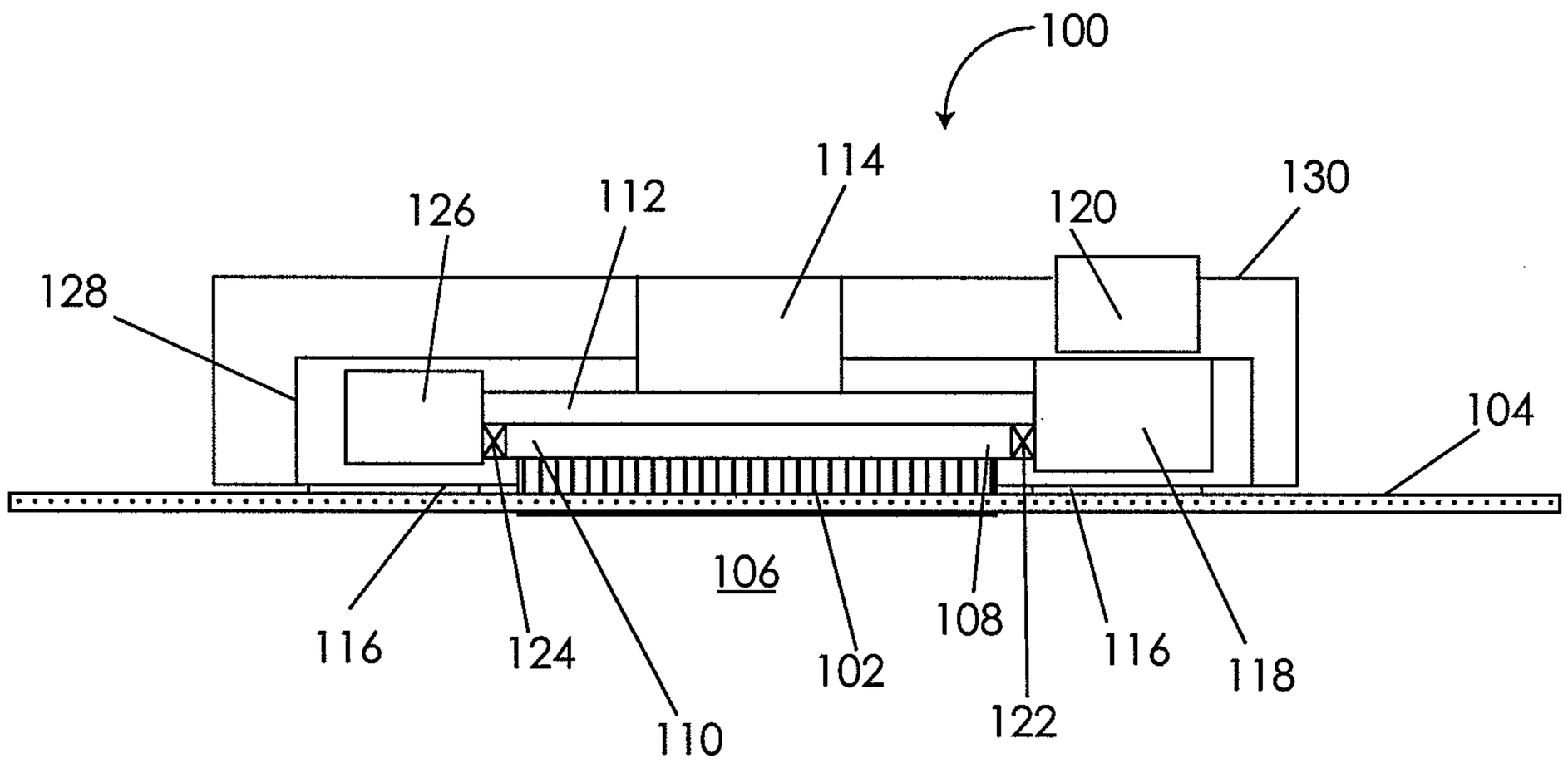
allowing interstitial fluid to flow into the interior space of the tissue piercing elements to substantially fill the interior space;

filling substantially the entire interior space of the sensing area with sensing fluid; and

sensing a glucose concentration of the sensing fluid.

67. The method of claim 66 wherein the interstitial fluid does not flow past the proximal opening.

68. The method of claim 66 wherein the interstitial fluid flows immediately into the interior space of the tissue piercing elements.


100
114
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116
118

FIG. 1

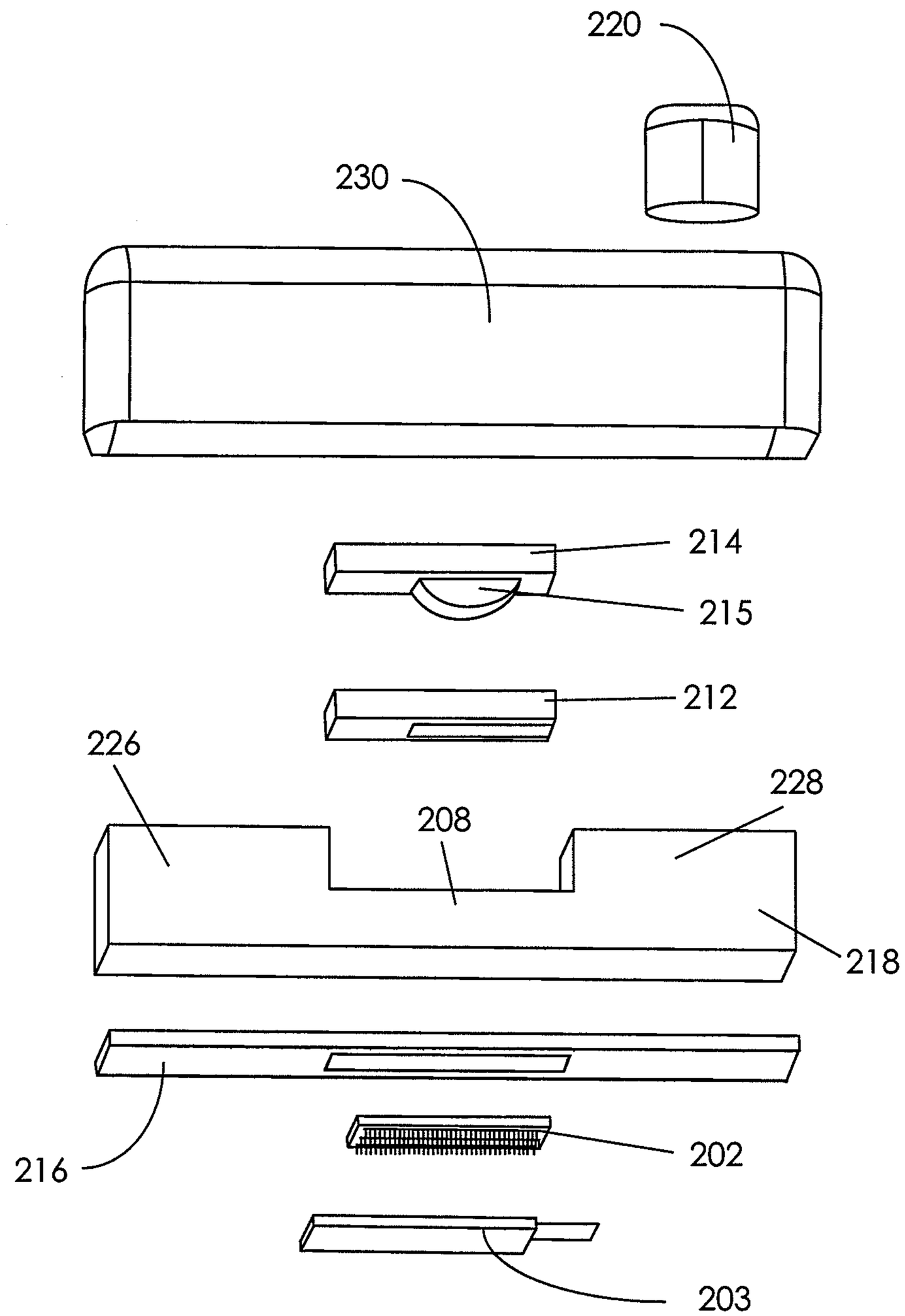

FIG. 2

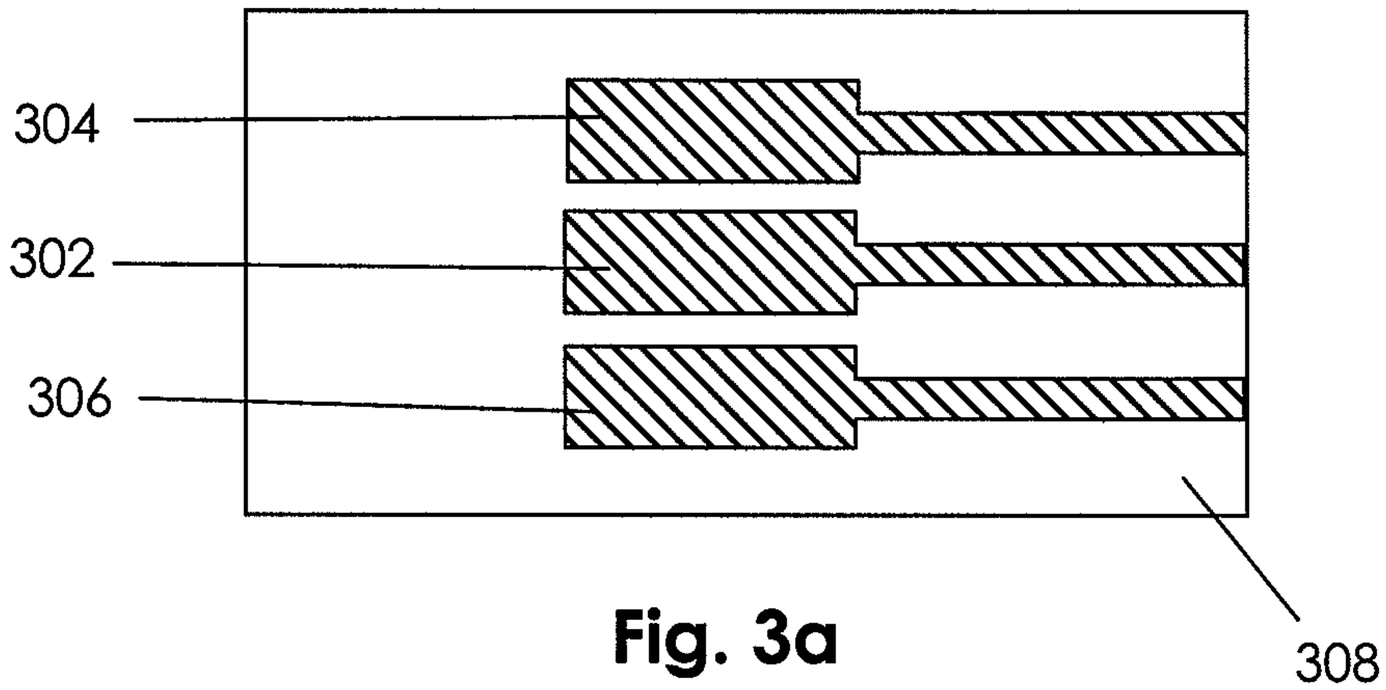

Fig. 3a

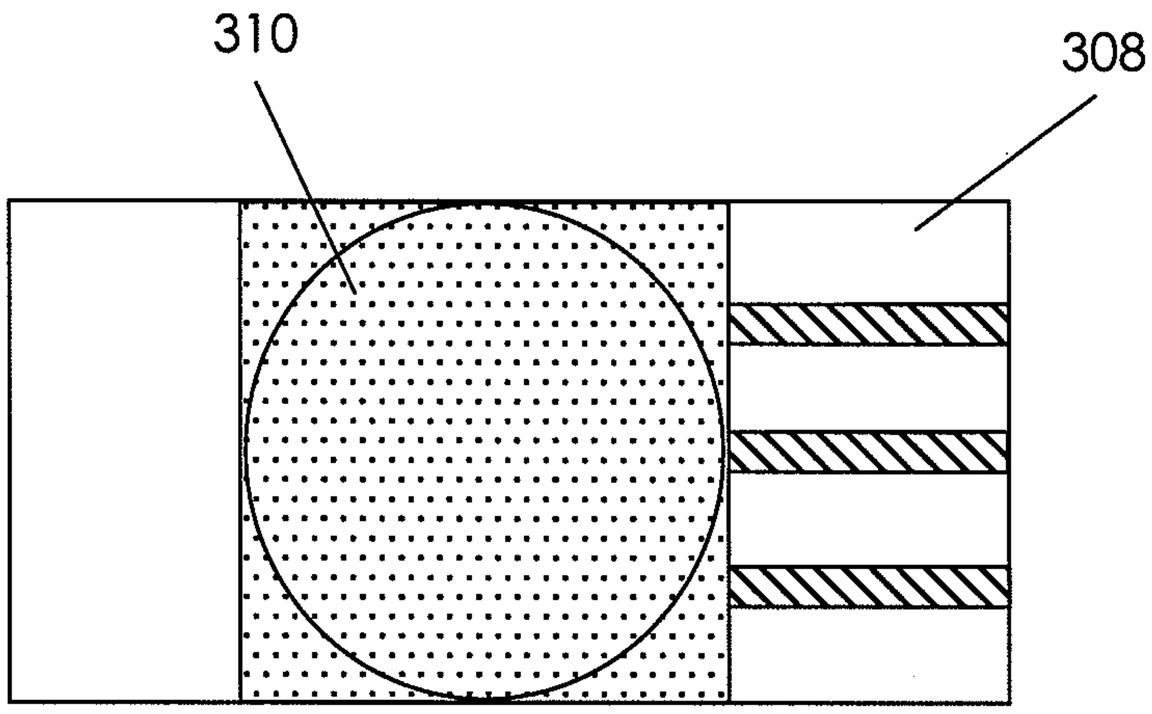

Fig. 3b

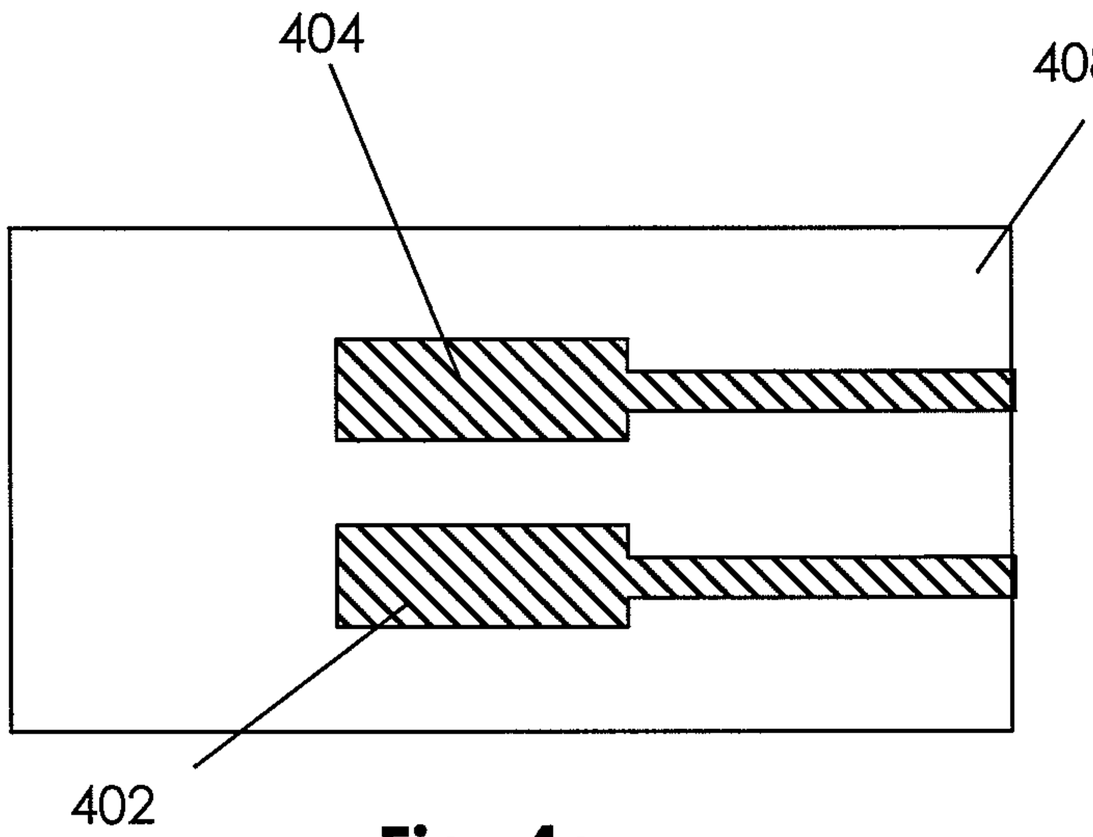

Fig. 4a

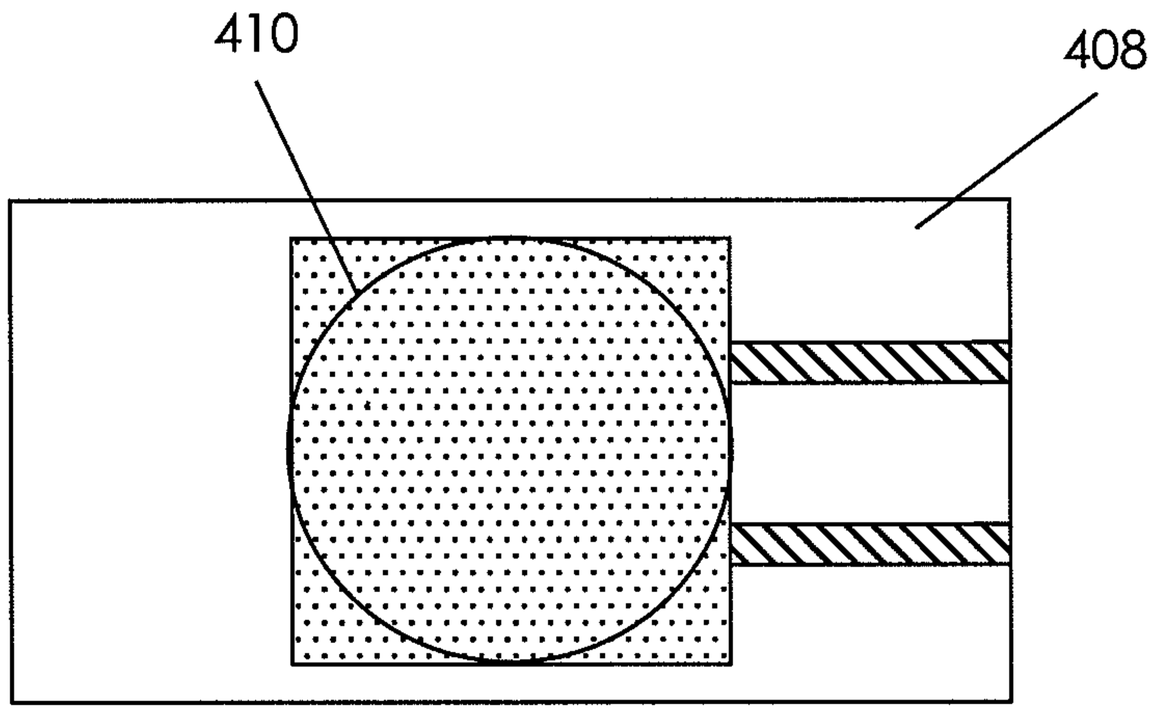

Fig. 4b

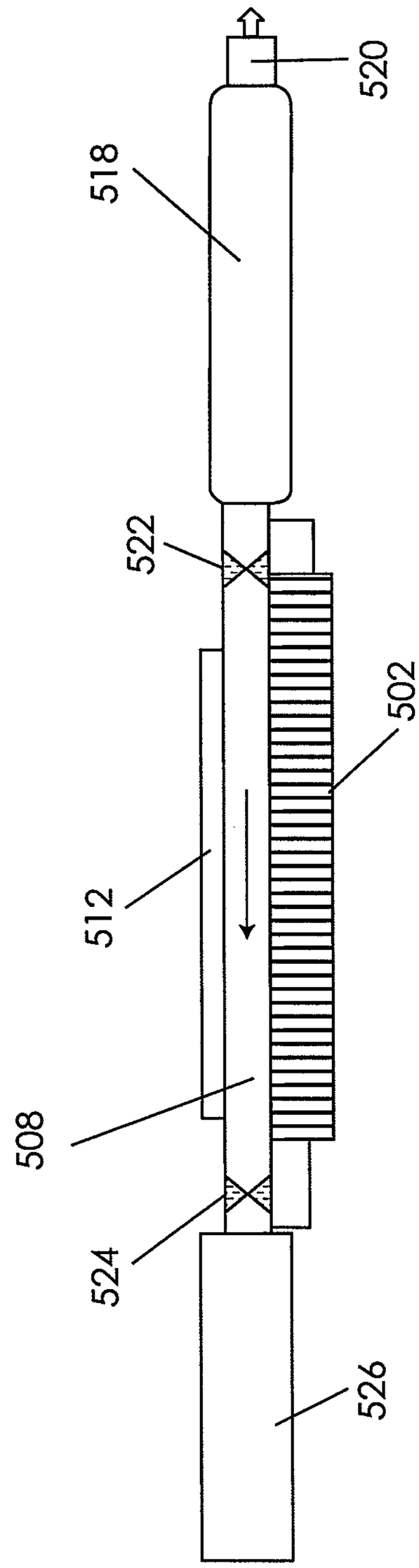

FIG. 5

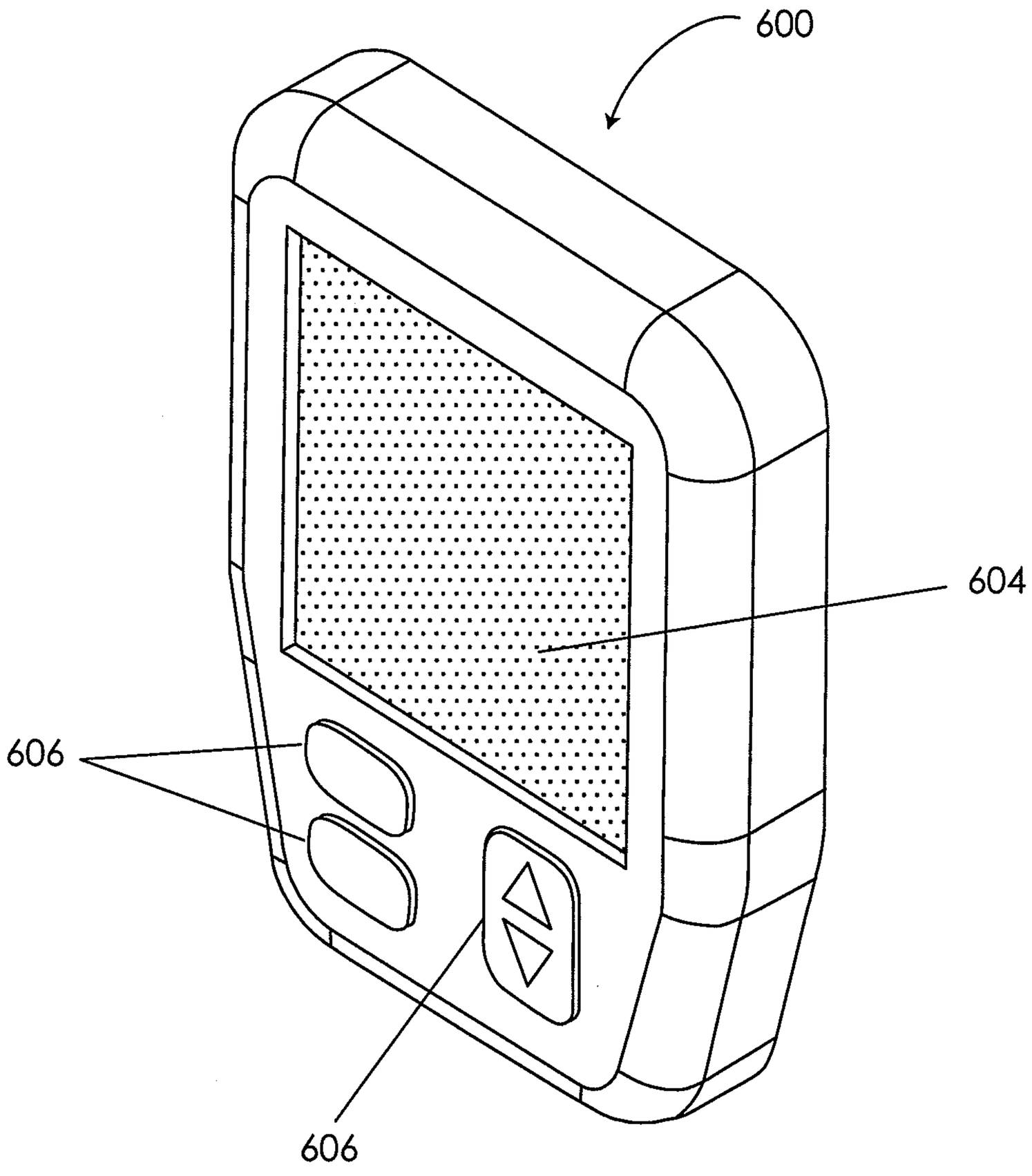

FIG. 6

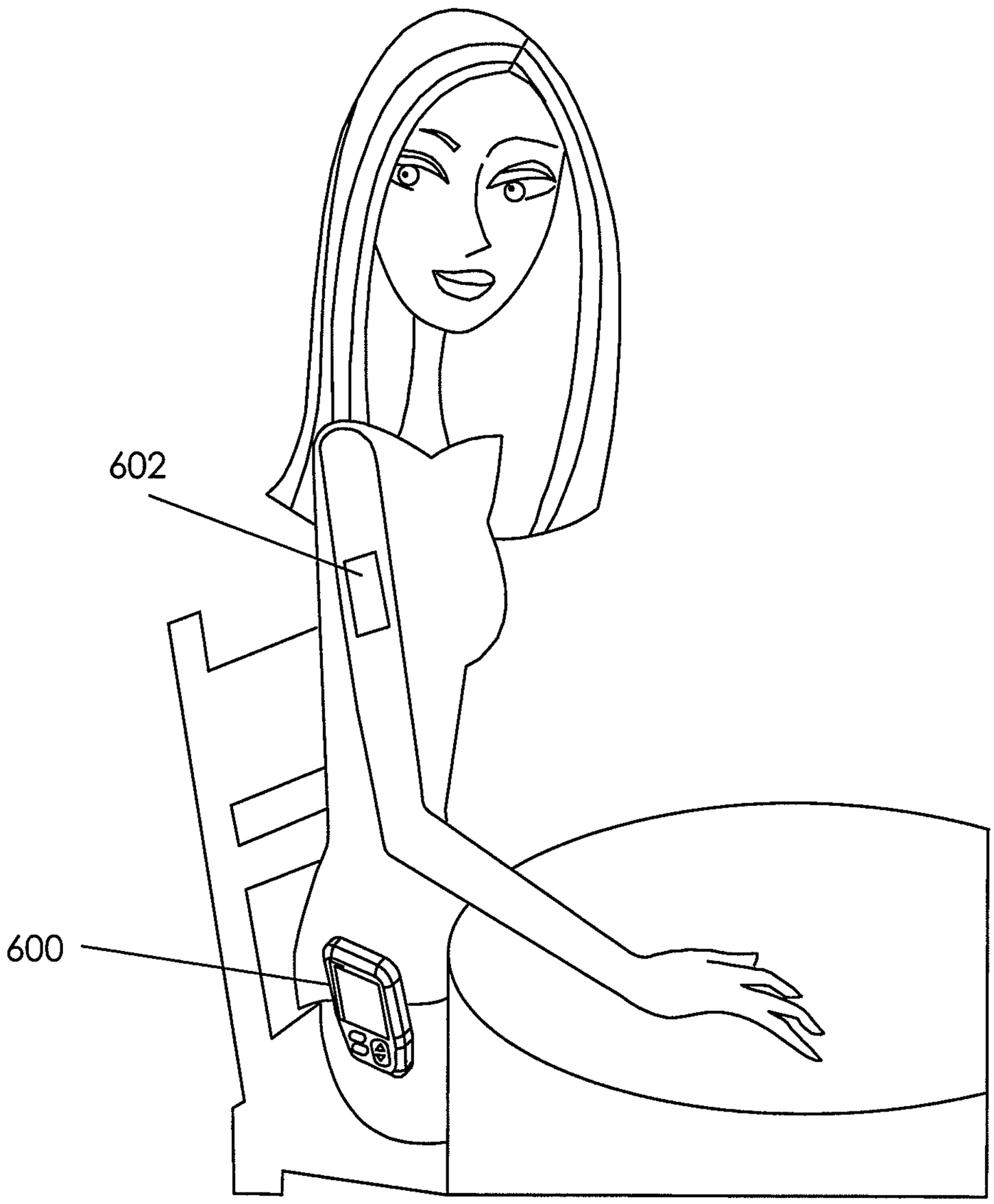

FIG. 7

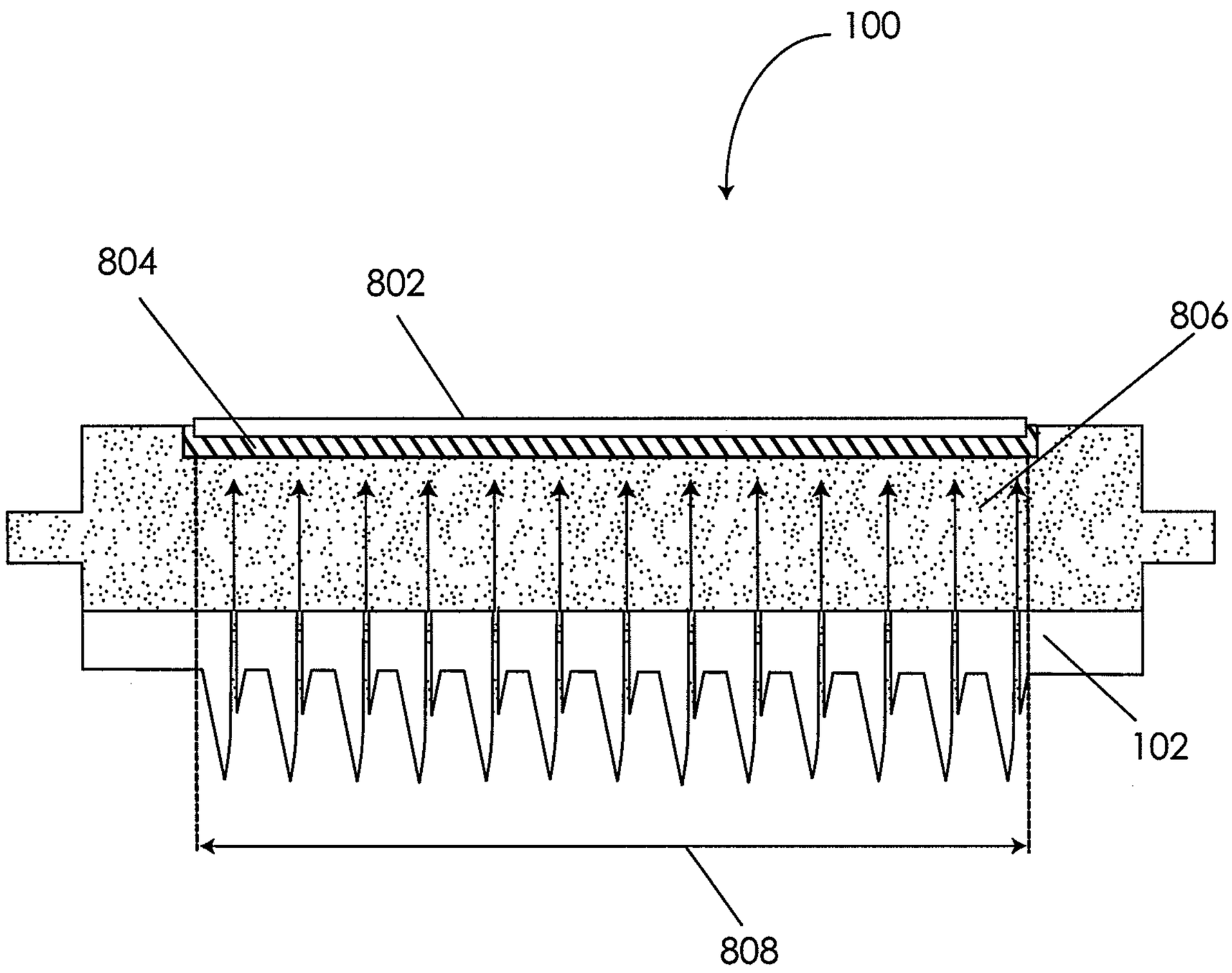

FIG. 8

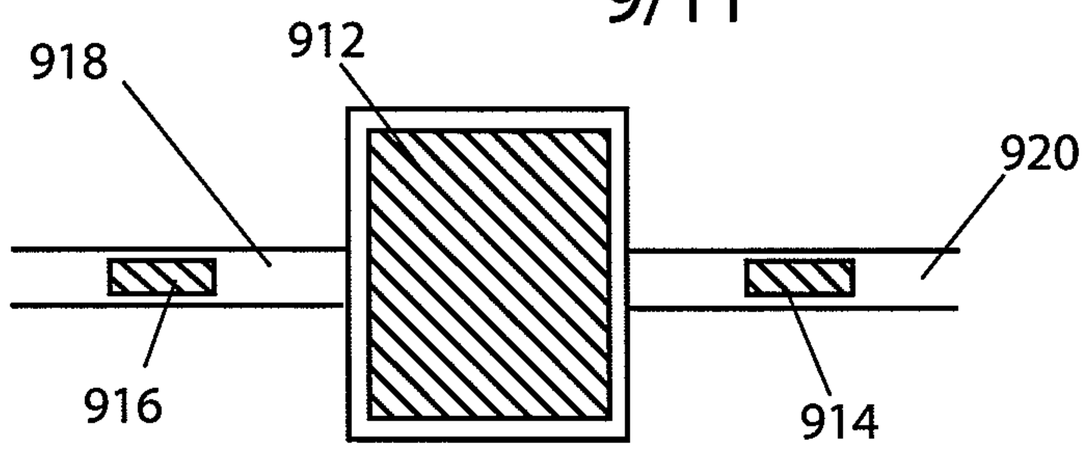

FIG. 9A

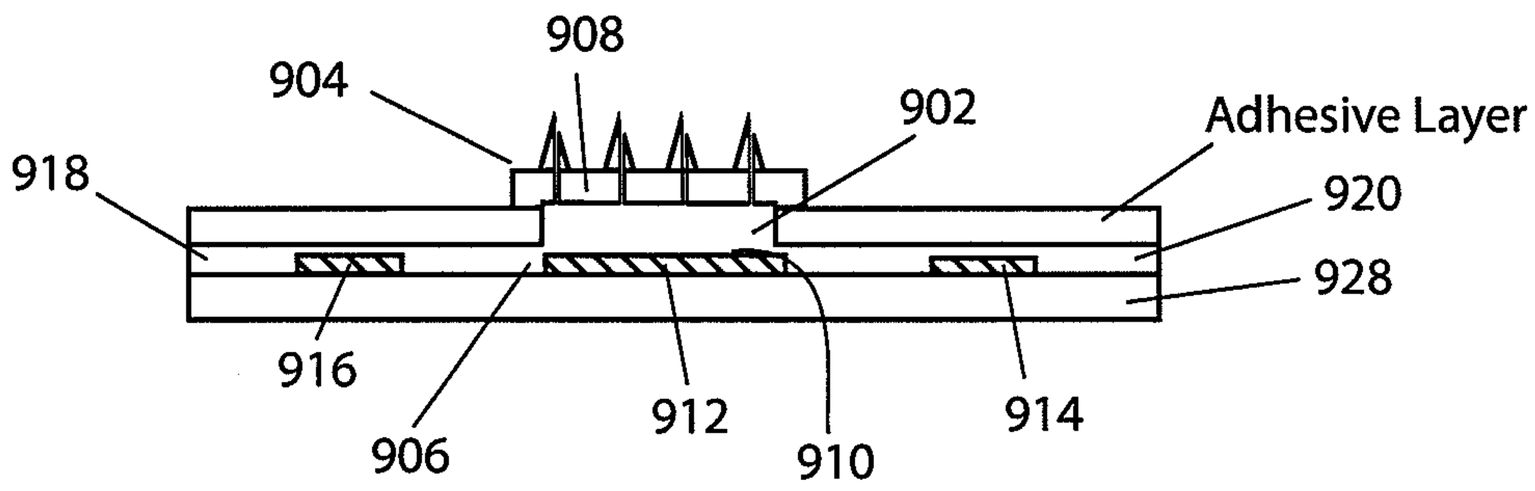

FIG. 9B

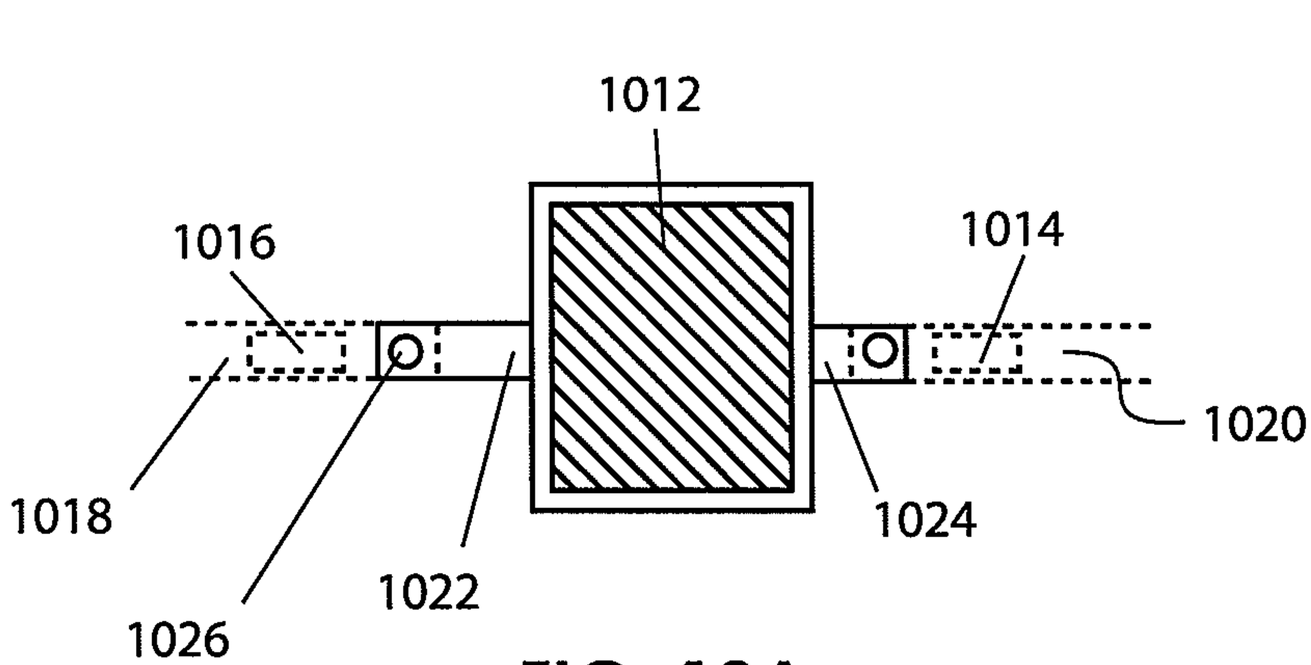

FIG. 10A

FIG. 10B

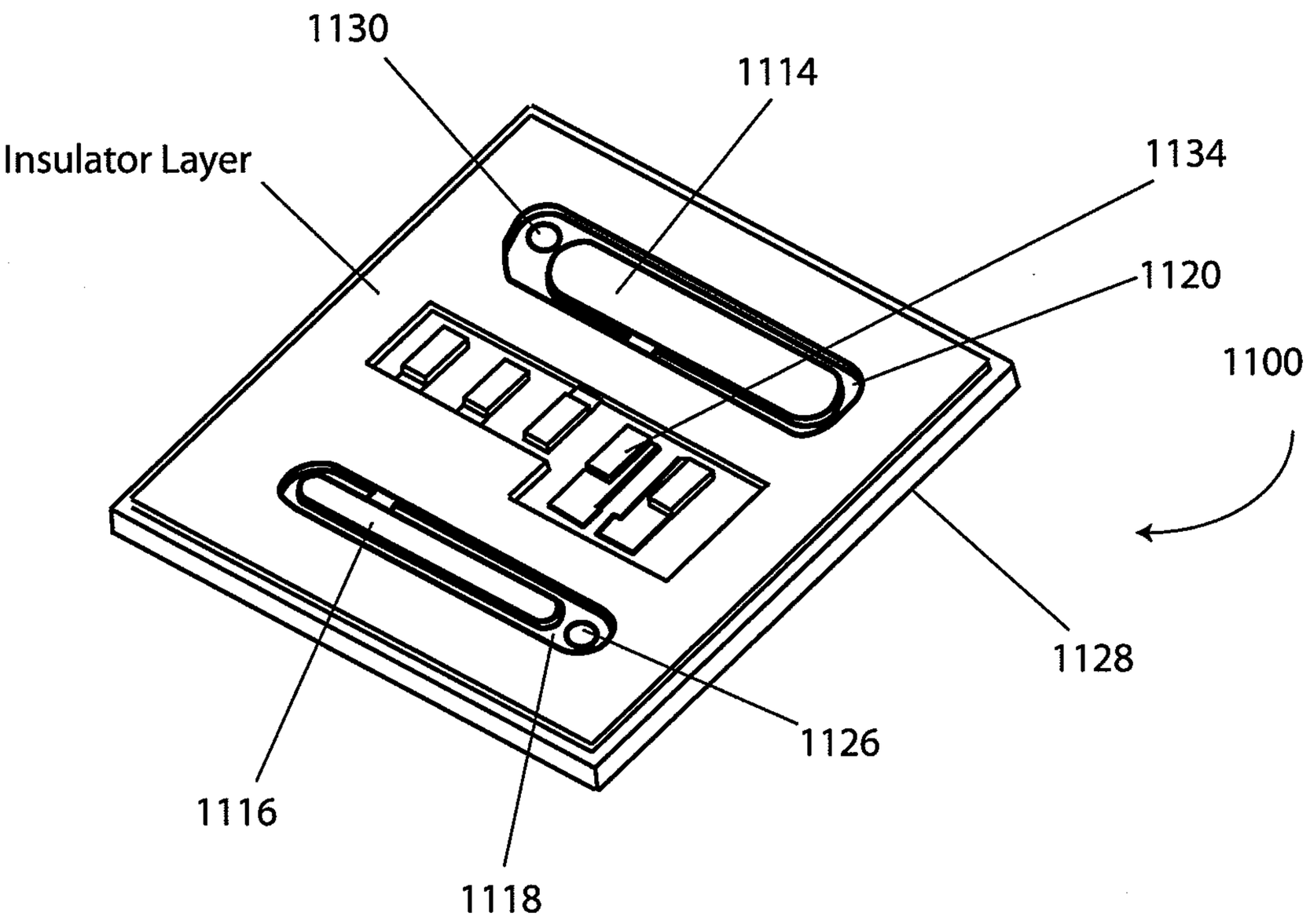

FIG. 11A

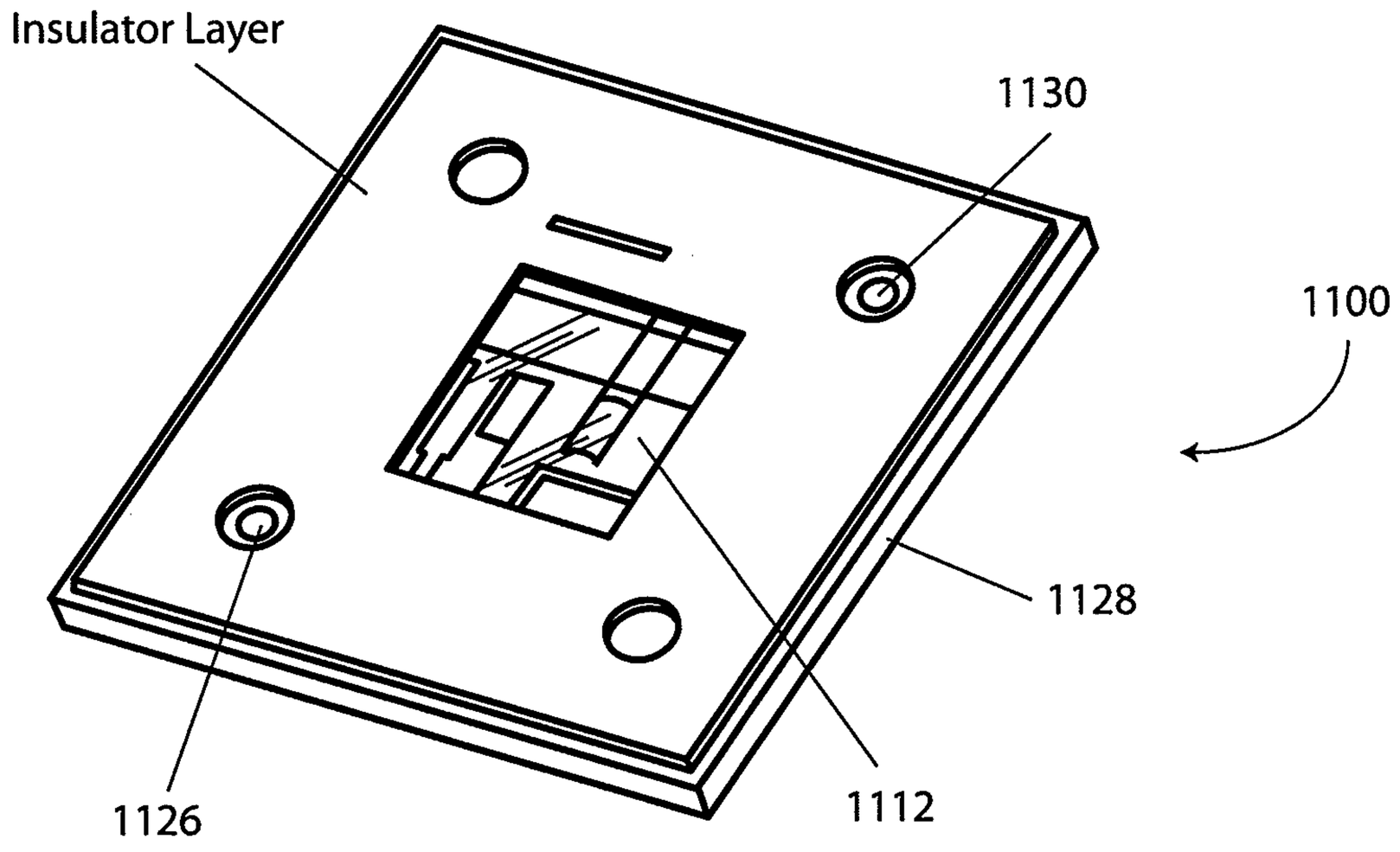

FIG. 11B

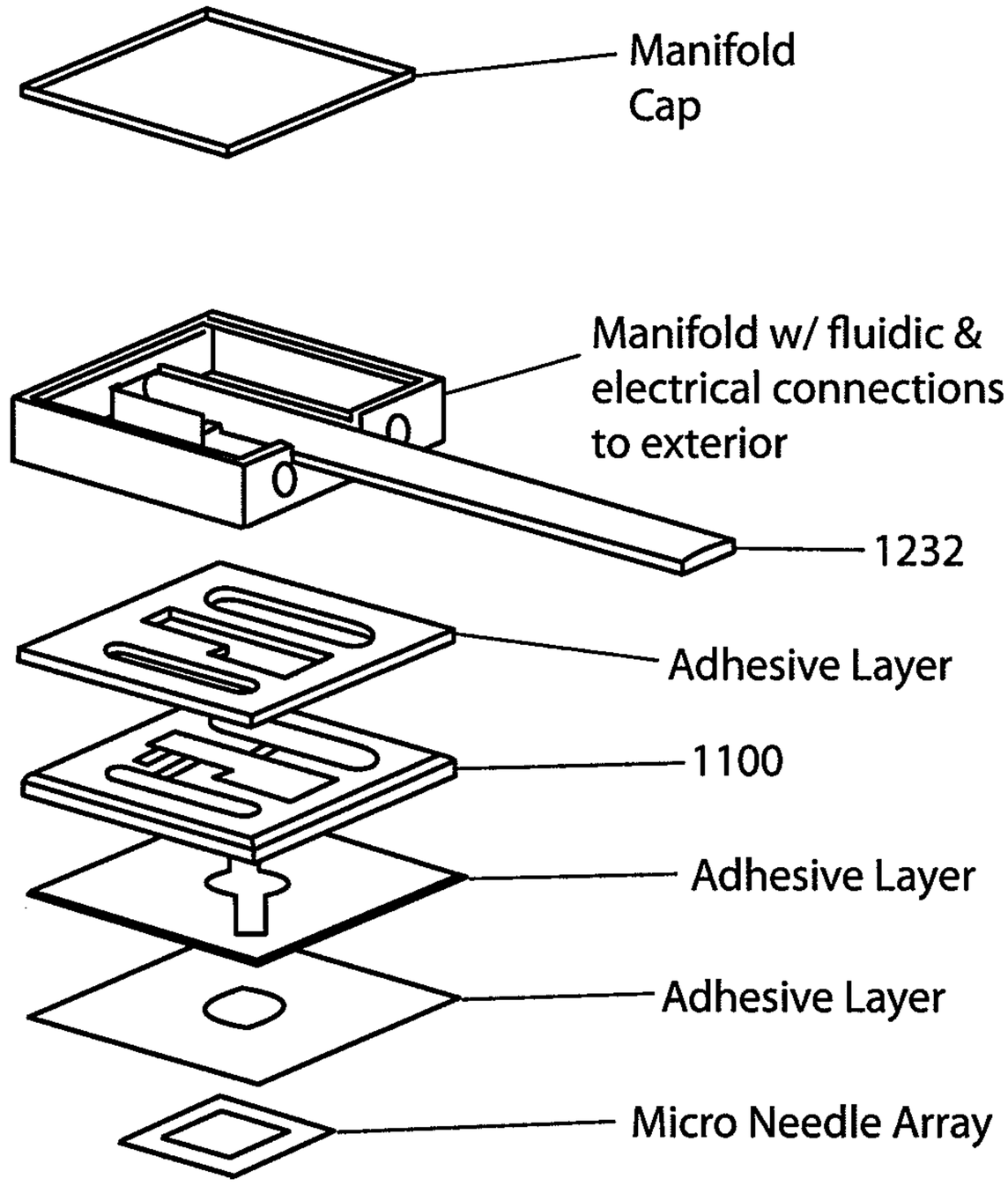
Manifold
Cap
Manifold w/ fluidic &
electrical connections
to exterior
1232
Adhesive Layer
1100
Adhesive Layer
Adhesive Layer
Micro Needle Array

FIG. 12

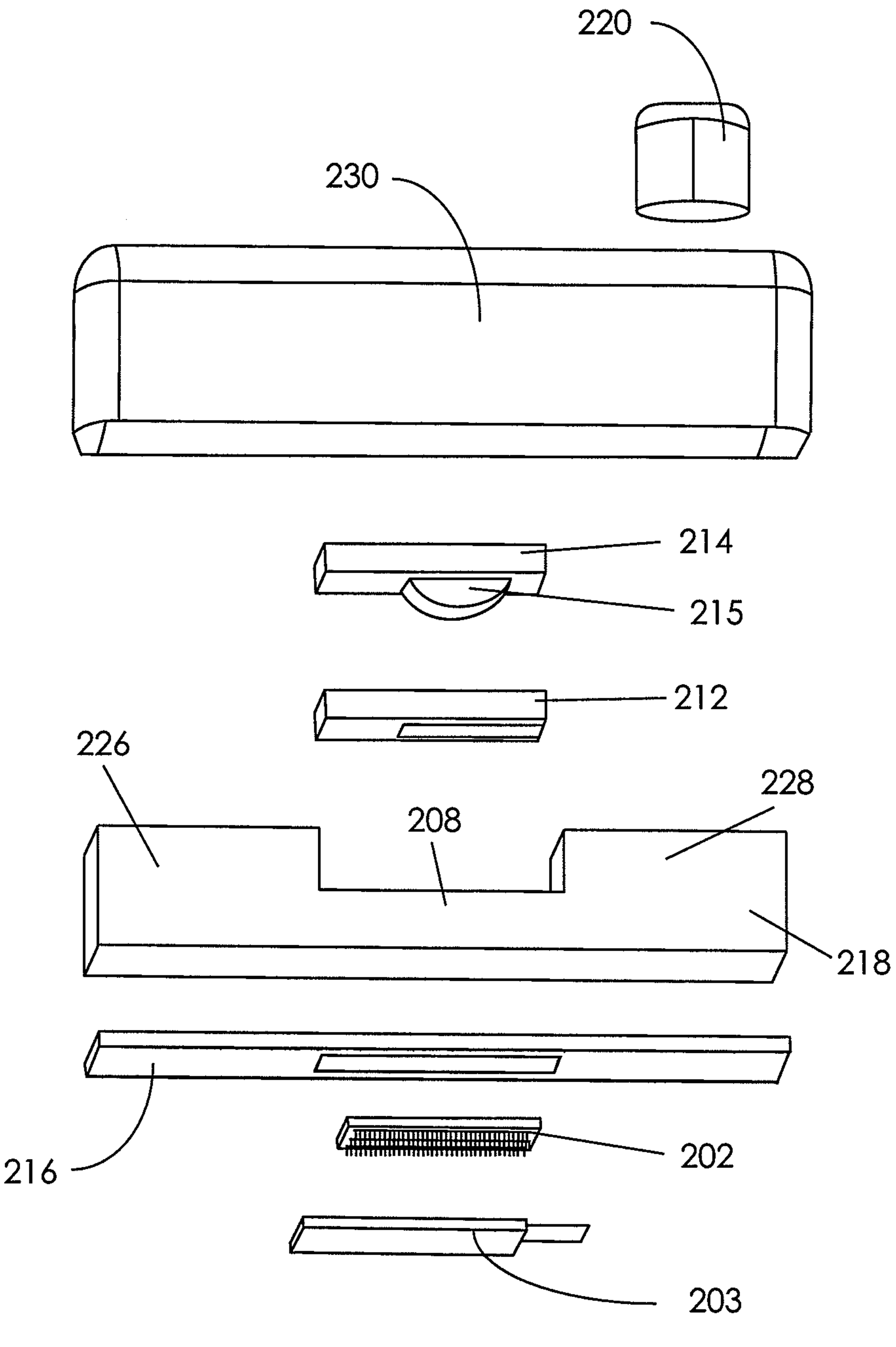

FIG. 2