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(54) **ANALYTE MONITOR**

ANALYTÜBERWACHUNGSGERÄT

DISPOSITIF DE SURVEILLANCE D'ANALYTE

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Description

[0001] While efforts have been undertaken to increase the ease with which analytes from body fluids, such as glucose, can be periodically monitored, no proposed solution has proved entirely satisfactory. The present invention provides a new monitoring device which allows convenient such monitoring with reduced pain.

[0002] Diabetes mellitus, a disease in which the pancreas fails to produce insulin or cells fail to respond to insulin for cellular metabolism of glucose, is a world-wide public health problem in terms of loss of quality of life and corresponding cost of care.

[0003] The World Health Organization estimates, as of 1994, there are 110 million diabetics worldwide with 14-16 million in the USA. This number is increasing and expected to double by 2030. Approximately 12-14 million diabetics are classified as noninsulin dependent, or Type II, diabetics who can control their glucose levels by changes in life style, by the use of medication or by the infrequent use of insulin. For approximately 1-2 million diabetics, classified as Type I diabetics, injections of insulin are needed to maintain glucose levels. Data from the Diabetes Control and Complications Trial (DCCT), reported in 1993, show that the quality of life may significantly be improved for people with diabetes if good control of blood sugar (glucose) levels is maintained. Thus, there is a need for frequent and accurate self-testing of glucose.

[0004] To meet this need, the most widely used, reliable and accurate method is a direct assay for glucose in a small amount of, typically, venous blood. Hand-held instruments, which measure the amount of glucose based on the interaction of glucose with reagents predeposited on test strips, are now widely available. Typically these instruments detect the amount of glucose in blood to plus or minus 4%, based on specific enzymatic reactions using microliter samples of blood.

[0005] While the chemistry for these test are reliable, and the manufacturers of the test strips have demonstrated good quality control, current self-testing remains a conscious process in which the diabetic must elect to take a blood sample and do the assay protocol for the hand-held instrument of choice. The primary failure for diabetics to do frequent self-testing for blood glucose levels, as recommend by the conclusions of the DCCT, is the pain associated with obtaining blood samples on a frequent schedule as well as the inconvenience of this, particularly in public places.

[0006] To reduce pain and inconvenience, blood glucose assays based on interstitial fluid, on transport through the skin (iontophoresis) and by implanted glucose sensors are technologies currently proposed, in development, or FDA approved. Cygnus, Inc. (Redwood, CA) has received FDA approval for the "GlucoWatch" a noninvasive glucose testing device that is based on electrode-driven iontophoresis. MiniMed Inc. (Sylmar, CA) has developed and received FDA approval of an invasive

glucose sensor which may be used to monitor glucose continuously for up to three days.

[0007] US-A-5 971 941 describes a blood sampling apparatus that includes a cartridge and a housing with a driver. A lancet is housed in the cartridge and is urged by the driver in the housing to extend outside the cartridge.

[0008] Provided here is a reliable and reduced pain or essentially pain-free approach to frequent glucose monitoring, or for monitoring of any blood metabolize. The use of very small samples, microliter or less, combined with a sensitive and reliable chemical test for the metabolite in an automated device allows for metabolite monitoring with convenience, comfort and reduced pain. The automation of the glucose testing offers an inherent psychological advantage in that the occurrence of the testing is essentially unknown to the user. Automation offers a further advantage in that a specific program can be applied for frequent testing based on the user's life style. With the present invention, a large number, for example 120, of blood tests can be provided per unit, thus allowing frequent testing for up to a month period. Furthermore, miniaturization allows for the design of a small device that can be in the shape of, e.g., a "watch", allowing for portability and unusual convenience.

Summary of the Invention

[0009] The invention provides an analyte monitoring device as set forth in claim 1.

Brief Description of the Drawings

[0010]

Figure 1 displays an analyte monitoring device of the invention.

Figure 2A-2C schematically shows the operation of one analyte monitoring device of the invention.

Figure 3A-3C shows the operation of another analyte monitoring device of the invention,

Figure 4A-4B shows the operation of an analyte monitoring device of the invention.

Figure 5 shows an additional analyte monitoring device of the invention.

Figure 6 shows an optical analytic device that can be used in the invention.

Figure 7A-7F schematically shows the operation of one analyte monitoring device of the invention.

Figure 8A-8D shows the operation of another analyte monitoring device of the invention.

Detailed Description of the Invention

[0011] Figure 1 shows an interior view of a relatively small analyte monitoring device which can be worn strapped or taped to an appropriate tissue from which a biological fluid can be drawn via relatively short, small

diameter needles for analysis. The device can be, for example, just over 60 mm (two inches) in diameter.

[0012] Monitoring device **60** contains a plurality of needles **53**, in this case sufficient to conduct a number of analyses (e.g., three to twenty-four) on each of a number of days (e.g., twenty, or forty, or more). The needles are associated with chambers **50** in which, in this embodiment, the analyses are conducted. Such chambers are optionally windowed. Axle **63** rotates platform **62** and arm **61** to align the arm with a needle **53** and the detector **64** on the platform with an associated chamber **50**. The detector can contain, for example, a light source and a light detector. The light detected can be used to calculate an absorbance for sample in the chamber **50** (where the light path is reflected back to the detector), or a fluorescence from the sample. A stepper motor, wound spring with appropriate gearing, Geneva mechanism (producing intermittent rotary motion) with a DC motor, or the like can be used to move the platform and arm relative to the respective chamber and needle. A processor **65** accepts data from the detector. In some embodiments, the processor processes the data to derive normalized values, or monitors and controls the positioning of the moving parts of the monitoring device. Where the illustrated ring of chambers is located, for example, 25 mm (one inch) from the center of rotation of the arm, they will be located on a circumference of just under 160 mm.

[0013] The circular format illustrated in **Figure 1** provides a convenient format, but other formats can be used. For example, detectors can be provided with solid state LEDs and charge-coupled devices (CCDs), such that one or more light sources, and one or more pixels of a CCD can be permanently aligned with each operative chamber, so that control of detector operations is electronic. In other words, the light sources can be serially operated as necessary, and the serial draining of the charge collected in the appropriate CCD can be used to isolate the charges collected in currently operative pixels. One of ordinary skill will also note that all (or a significant subset) of the light sources can be operated, with detector site particularity derived from analyzing the appropriate detectors. However, even when using the differential excitation/emission wavelengths used in fluorescence detection, it is preferable to limit possible sources of cross-talk or electronic noise. Needle movement can be accomplished by a robotic device movable from location to location on x-y oriented cables, or by permanently assigned devices such as electromagnetically operated solenoids.

[0014] **Figure 2A-C** illustrates the operation of an embodiment of the monitoring device. Chamber **10** is separated from needle **12** by septum **11**. After the needle pierces skin **5** (**Fig. 2B**), the other end of the needle pierces the septum. Chamber **10** can be packaged in vacuum, such that the vacuum provides a drawing force to quickly fill the chamber with fluid **13** drawn from the subject. The increase in filling speed provided by the vacuum helps further assure that no analytical reagents in the chamber

will migrate to the patient. The fluid is typically blood or interstitial fluid (ISF). As illustrated, both the needle and the chamber move relative to the skin in this embodiment.

[0015] **Figure 3A-C** illustrates the operation of another embodiment of the monitoring device. Chamber **20** is isolated from atmosphere by first septum **21** and second (thick) septum **24**. Needle **22** has a side port **23**. As illustrated, insertion of the needle into skin **5** brings side port **23** into communication with a vacuum in chamber **20**, which vacuum serves to pull fluid **25** into the chamber. The needle is sized, and the side port positioned so that the side port does not open to the chamber until the needle is inserted in the subject. The vacuum used in these embodiments is particularly useful where one seeks to draw blood, as the acceleration in drawing time provided by the vacuum avoids interference from blood coagulation. Nonetheless, vacuum is not required for operation of the invention. Note that the device of **Figure 3** can be used with a second septum, or a thicker first septum **21** to isolate the needle prior to use. After use, the needle is retracted to its original position. In this illustrative embodiment, only the needle moves relative to the skin.

[0016] **Figure 4A-B** illustrates the operation of another embodiment of the monitoring device. The needle **72** is actuated through a hole in platform **70**, on which platform is located a support **74** (which can be a membrane). When the needle is actuated, it pierces protective membrane/septum **75** and then the skin **5** of the subject. When fully actuated, a port **73** of the needle provides contact for primarily capillary flow from the subject to the support **74**. In one embodiment, the support is a membrane on which the reagents needed to drive the analytical reaction have been deposited. Since the reaction volume is typically small, such as 300 nL or less, the reaction can occur primarily within the pores of the membrane. As discussed in US Patent 6,118,126, and in WO 99/23492, appropriate membranes, can be fabricated to provide sufficient amounts of fluorophors in the pores with appropriate proximity to the surface, thereby markedly enhancing fluorescence detected from the fluorophors. The fluorescence enhancement applies where the detector is aligned with backscatter from the excitation light source.

[0017] **Figure 5** illustrates a further embodiment of the monitoring device. The needle **82** is supported by bracket **86**, which guides it toward protective membrane/septum **85** and then the skin **5** of the subject. The needle is actuated by engaging actuating bar **87**, which is illustrated as sitting over reservoir **81**. The reservoir serves in this case as a means of drawing a greater volume of fluid through ports **83**. Note that preferred needles are of narrow inner and outer diameter, which means that the volume drawn by the needles by capillary action will typically be small, such that the illustrated reservoir can serve to increase that volume. In this embodiment, when the needle is actuated, liquid is drawn by capillary action. Upon removal of the actuating force, the needle retracts (see discussion below) and its upper opening contacts porous support **84**, which is supported by platform **80**.

[0018] The chambers in which the analytical reactions occur, or the platforms on which analytical reaction support reside can be translucent to the wavelengths of light used in the analysis. For example, the platform **80** illustrated in **Figure 5** can be translucent. Thus, as illustrated in **Figure 6**, a light source **90** with filter **91** can direct light to support **84** through platform **80**, and reflected or emitted light can be collected along a pathway through the platform leading to filter **93** and detector **92**. Note that even in this embodiment one can take advantage of the surface effects enhancing fluorescence. The depth of porous support **84**, or its porosity distal from the support-platform interface, can be adjusted such that the bulk of the fluorophors will be generated within pores sufficiently adjacent to the interface to provide a useful enhancement in measured fluorescence. For example, the depth at which e.g. $\geq 90\%$ of the fluorophors will reside at the detection stage can be no greater than about 80 microns, or no greater than about 40, 20 or 10 microns.

[0019] Note that in the embodiment of **Figure 5**, used as illustrated in **Figure 6**, the bottom surface of support **84** can be used to isolate cells such as red blood cells away from the portion of the support on which the analytical chemistry and detection shall be conducted. For example, if support **84** is a membrane, the pore size can be selected to exclude the cells. Even with relatively open pores in a porous support, it is anticipated that the cells will not migrate through the support to the support—platform interface that in some embodiments is more important to the analytical determination.

[0020] In another embodiment illustrated in **Figure 7A-F**, the monitoring device has a tray **40** of chambers **30**, such as more specifically identified chambers **30A**, **30B**, etc., separated by spacers, supports **34**. The chambers have associated needles **32**, which are indicated in **Figure 7A** in hashed lines as they are initially aligned before or behind the tray **40**. The chambers are enclosed below by a septum layer **31**. The septum layer can be thick to assure no loss of vacuum in the chambers during needle puncture, as here illustrated by a second septum layer **33A**. **Figure 7B** shows an end view of a cut-out of chamber **30A**, together with associated needle **32A**. A needle actuator **36**, which can be specific to needle **32A**, or which can be robotically or rotatably aligned with the appropriate needle as needed. The needle is pushed by actuator **36** until it locks into place, for example into slots in floating alignment brackets **39**. Needle **32A** can be provided with a bevel **35**. Tray actuator **37** can move in the direction indicated by the arrow to engage the ends of the needle **32A** in second septum **33A** and third septum **33B**. The tray actuator also serves as a vertical needle actuator. Further movement of the tray actuator causes the needle to pierce the skin **5** and the chamber **30A**, while floating brackets **39** compress to allow for movement. In some embodiments, an initial vacuum in chamber **30A** helps fill the chamber with biological fluid **38**. The bevel **35** can act to help bring the needle out of the subject when the actuating force is removed.

[0021] As illustrated, a large number of chambers can be formed in a single piece of material. The portion of the chambers illustrated in **Figure 7A** forming the top wall of the chambers, for example, can be formed of the same single piece that in this embodiment forms the cavities. It can also be formed separately and sealed to the supports **34**. Of course, the septum **31** and second septum **33A** are formed separately. However, as illustrated, septa acting for a number of chambers are preferably formed of one piece of material.

[0022] In another embodiment illustrated in **Figure 8A**, tray **110** has chambers **101**, such as specific chambers **101A**, **101B**, etc., enclosed top and bottom by first septum **104** and second septum **105A**, respectively. Needles **102** have side ports **103**. In **Figure 8B**, needle **102F** is partially actuated so that first septum **104** is breached, but second septum **105A** is not. At this stage, a vacuum in the housing in which the needles are stored equilibrates with the interior of chamber **101F**. A pump can be actuated as needed to create, maintain or supplement the vacuum in the housing. Care is taken to preserve the vacuum while the needle is further actuated by use of a thicker second septum **105A** or the use of a third septum **105B** supplemented by an evacuated space between the second and third septa. Spacers **107** support the third septum. Vacuum is not substantially compromised while the needle tip relatively quickly travels to pierce skin **5**, leading to biological fluid **108** filling chamber **101F**. In one embodiment, fluid **108** can then be transferred to support **111** by capillary action, as illustrated in **Figure 8D**. As previously, optical measurements can be made from either face of the support, with measurement on the reverse face allowing the support to act as a filter removing cells from the area generating the spectroscopic data.

Chambers

[0023] Chambers can be made of a number of materials which have proven stable to, for example, blood analysis samples and reagents, and which preferably are compatible with one or more sterilization processes. Such materials include suitable plastics, glass, silicon, quartz and the like. Suitable plastics include, for example, polycarbonate, polysulfone, acrylic (e.g. polymethyl methacrylate), polystyrene, styrenic copolymers such as NAS copolymer of polystyrene and acrylic, styrene acrylonitrile copolymers (e.g., SAN), polyurethane, polyethylene, polyethylene terephthalate and 4-methyl-1-pentene (e.g., TPX) plastics. See, "Guide to Engineering Thermoplastics," in Medical Devices and Diagnostic Industry, April, 1995; and The Handbook of Plastic Optics, 2nd Ed., U.S. Precision Lens, 1983. Since it is frequently desirable to make the analytical spectroscopic measurements of material in the chamber, a simplified method of providing a suitable optical window is to manufacture the chambers of materials that transmit light of the wavelengths required for the analysis. Since the wavelengths needed for many of the analyses are sufficiently high, a

number of plastics are suitable, including those identified above.

[0024] With plastics, for example, structures can be formed by injection molding, casting, machining, and other methods known in the art. Where particularly fine dimensions are needed, LIGA (a German language acronym for lithography, electroplating, and molding) molding, wherein molds are formed by photolithography from relatively thick photoresist layers, can be used. With glass, silicon, and the like, etching techniques, particularly techniques that generate well defined walls, such as reactive ion etching, can be used.

[0025] The size of the chambers will typically be small, such as sufficient to draw a small volume such as 5,000 nL, 2,000 nL, 1,000 nL, 500 nL, 300 nL, or less. Note that a 0.67 mm (26 mils) by 0.67 mm by .067 mm space provides a volume of about 300 nL. Of course, the size of the space used to draw the desired volume will typically be larger than the volume obtained by the drawing process, as can be established by ordinary experimentation.

[0026] The device has for example 32, 64, 96, 128, 160 or more chambers (and associated needles) to provide 1, 2, 3, 4, 5 or more daily samplings over the course of about a month.

[0027] Note that where optical detection is conducted from substantially the direction of the light source, a reflective surface (if needed) can be incorporated into the monitoring device, such as on an outside surface of the chamber.

Septa

[0028] A septum or protective membrane used in the invention can be made of a polymer, such as a silicone rubber, Teflon (polyperfluoroethylene), polyethylene or an elastomeric film (such as a natural rubber, ABS rubber, or polyurethane elastomer film). In other contexts, greater thicknesses are needed to preserve vacuum in an associated chamber during actuation of the associated needle until the vacuum comes into play in helping draw fluid. A number of factors in selecting the septum will be considered by those of ordinary skill, such as the limitations of the septum-forming method, the flatness of the top surface of a septum as produced by a given method, the hardness of the septum-forming material, the open area to be sealed by the septum, and compatibility with a suitable method of sterilization.

[0029] One method of attaching the septum is screen-printing. The printed septum can be made of silicone or another chemically-resistant, resilient material. Preferably, the septum is made of a mixture of (a) a silicone rubber-forming material such as that available under the Sylgard 184™ brand from Dow Corning, Midland, Michigan or MDX4-4210™ also from Dow Corning and (b) an inert filler, such as the amorphous fumed silicon sold as M-5 grade Cab-o-sil™ (Cabot Corp., Boston, MA). Sylgard 184 and MDX4-4210 are sold in two components. One component is an emulsion containing particles of

silicone rubber and a polymerization catalyst and the second component is a preparation of a bi-valent monomer, which monomer serves to crosslink and thereby cure the silicone rubber. Component one of MDX4-4210, i.e. the "elastomer component," is made up of dimethylsiloxane polymer, reinforcing silica, and a platinum catalyst. Component two of MDX4-4210, the "curing agent," also contains dimethylsiloxane polymer, in addition to a polymerization inhibitor, and a siloxane crosslinker. The components are generally mixed according to the manufacturer's recommendations. For example, for MDX4-4210, ten parts by weight of emulsion, i.e. elastomer, are mixed with one part of monomer solution, i.e. curing agent.

[0030] As examples of the use of inert fillers, about 7.5% by weight of M-5 grade Cab-o-sil can be added to the Sylgard 184, or about 2-3% by weight of M-5 grade Cab-o-sil can be added to the MDX4-4210. Filler can serve to thicken the pre-polymerized composition to improve its screen printing properties. Septum-forming materials can generally be cured at room temperature, or curing, can be accelerated, for example, with heat. Prior to curing, the septum-forming material is capable of flow, though generally viscous flow, which flow is sufficient to facilitate the screen printing process. The septum-forming material is also sufficiently adhesive to adhere either to the plate to which it will be applied or to an underlying first layer of septum-forming material.

[0031] In one version of the screen printing process, a first layer of septum-forming material is printed onto the plate and then cured. After this first printing, a second layer of septum-forming material is overlaid on the first, a smooth platen of appropriate shape (generally very flat) is overlaid upon the printed septum-forming material so that a uniform weight is applied to the printed septum-forming material (while taking precautions to prevent destructive adhesions of septum-forming material to the platen such as described further below), and the septum-forming material is cured. The use of two printings of septum-forming material helps form a foundation of septum-forming material prior to the smoothing process conducted after the second printing. To achieve this smoothness and uniform thickness, it is important to apply a sufficiently uniform pressure to the septum during a final curing process. This pressure should be selected to be, for the particular septum-applying process, sufficiently high to create the needed uniformity during the curing process, but not so high as to overly compress cured portions of septum-forming material such that upon release of the pressure these portions re-expand and create a non-uniform seal thickness. A single print process can also be used, and such a single print process is generally preferred since it is simpler and more readily applied to a production process. In a single print process, which is described further below, a platen is applied directly after the first (and only) printing of septum-forming material, and prevented from settling down too far or too unevenly by mechanical stops.

[0032] Preferably, the width of each print feature on

the screen is uniform, as width nonuniformities increase the probability of a thickness non-uniformity at the end of the process. After printing and processing, the applied septum patterns are broadened. For example, in applications using the two-print process and 6 mil wide pattern on the print screen, an 18 mils wide pattern has been produced.

[0033] Because the septum material is applied over openings forming chambers, the initial formation of the gasket is usefully conducted on a flat surface adapted to not adhere the septum-forming material, such as glass treated with a release agent such as silicone oil or a siliconizing agent. A second layer of septum-forming material can be applied, and the septum transferred to the surface on which the cavities are formed while the septum-forming material of the second layer is still sufficiently tacky to adhere.

Needles

[0034] An important feature of the invention is the provision of small-scaled needles with sufficient rigidity and durability. The small scale is important to provide the number of analyses in one device needed to substantially ease the burden of conducting numerous analyses over the course of, for example, a week. Small size also reduces the pain associated with piercing the subject's skin. The needles are able to sustain a 0.3 mN force to allow insertion through, for example, a subject's skin.

[0035] Preferably, the needles are 8 mils or 200 μm or less in diameter, preferably with an inner diameter of at least about 50% of the outer diameter. Inner diameters of 6 mils (150 μm), 4 mils (100 μm), 2 mils (50 μm) or 1 mil (25 μm) or less are contemplated. The length of the needles is adapted to provide the communication with internal constituents of the monitoring device and sufficient penetration into tissue to obtain the desired biological fluid. Typically, the needles can be 10 mm or less, 4 mm or less, 2 mm or less, or 1 mm or less in length. Where ISF is the targeted biological fluid, the length adapted to penetrate the subject will be sufficiently short to avoid piercing through the dermis, which typically has a depth of 2 to 3 mm.

[0036] The needles can be made by small-scaled molding of suitable plastics. One such small-scaled molding technique uses LIGA (German acronym for lithography, electroplating, and molding) to create small-scaled molds. Suitable plastics include polyetheretherketone (PEEK) and polyethersulfone (PES). The polymer can be filled with a reinforcing substance, such as 10-40% filled with glass or carbon fiber.

[0037] Plastics can be extruded with outer diameters of, for example, 4 mils (100 μm) or less, and inner diameters of 2 mils (50 μm) or less.

[0038] Glass and suitable plastics can be drawn to suitable inner and outer diameters. It should be noted that the inner to outer diameter ratio is maintained during the drawing process. Glass needles can be diamond coated

by vapor deposition.

[0039] Silicon wafers can be used to form needles by reactive ion etching or other high definition etching techniques. For example, 40:1 height:width ratio features can be created. The needles are formed from the wafer leaving a tab connecting the needles formed from the wafer. The needles are, for example, mechanically separated. The wafer can be etched at an angle to create a beveled needle tip. A sharp tip can also be formed with an initial etch using an anisotropic etching method, such as ethylene diamine/pyrocatechol/water (EDP) or KOH etching.

[0040] Alternatively, the needles so formed of silicon can be used as reverse molds to form molds for plastic needles. Or, the wafer can be directly etched to form the molds.

[0041] The needles can also be formed of, for example, sapphire (Al_2O_3) or quartz. For example, edge-defined methods can be used wherein molten material is contacted with an initial mold which draws up a leading edge by capillary action. Subsequently the mold is drawn upwards, and the sapphire or quartz material crystallizes in a geometry matching the leading edge drawn from the molten material.

[0042] Needles can also be of metal. Metallic needles are formed, for example, by drawing needles formed to a larger scale. Electrochemical cutting, for example, can be used to cut the needles while electrochemically removing burrs or other ruff edges. Alternatively, needles can be formed by extrusion and ground to the appropriate shape.

[0043] Bevels can also be created by, for example, laser cutting of the needle ends.

Supports

[0044] In some embodiments, the assay is conducted on a support on which assay reagents have been previously deposited. The support can be calibrated to wet with a desired volume of fluid sample.

[0045] It is believed that an important characteristic for achieving the fluorescence enhancement result described here is the presence of voids on the surface or interior of the material. It is believed that such voids provide "microcavities" or "scatter cells" which contribute to the phenomenon, basically by increasing the pathlength of the excitatory radiate energy, thereby increasing the probability of fluorescence excitation events. It is further believed that the voids should be present in sufficient density to so that the beam of excitatory light sees a uniform density of such microcavities or scatter cells. The material should not absorb light of the excitatory wavelength that is to be used to induce the fluorescence. If broad band light is to be used, then the material should not be absorptive of the portion of the light that is effective to induce the fluorescence. A narrow band of light, or even laser light source, is preferred as the source of excitatory light. It is because of the absorption issue that, when nylon membranes are used, fluorescent reagents

that are excited by, for example, He-Ne lasers are preferred over those excited by argon lasers.

[0046] It is further believed with many textured materials the enhancement effect is most pronounced when the emissions are collected over a relatively narrow collection surface positioned at and around an axis corresponding to the angle of reflectance for the excitatory light. Preferably, the collection surface covers no more than about the area of a 20° cone extending from the textured surface and symmetrically positioned about the above-described axis. More preferably, the collection surface covers no more than about the area of a 10° or 5° cone. Preferably, the angle of incidence of the excitatory light is substantially 90° relative to the textured surface, such that the collection zone is along the same axis, as illustrated in Figure 1. "Substantially" 90° in this context refers to an angle which helps maintain at least about 75%, preferably at least 85%, 90% or 95%, of the fluorescence yield available with a 90° angle.

[0047] Suitable textured materials include, but are not limited to, nylon, poly(carbonate), poly(vinylidene difluoride) ("PVDF"), and nitrocellulose membranes. Preferably, nylon membranes are used, including commercial nylon membranes, such as those from Pall Corp. (East Hills, NY, or particularly, Biosupport Division, Port Washington, NY), Amersham Pharmacia Biotech, Inc. (Piscataway, NJ) and Cuno Inc. (Meriden, CT).

Assay Reagent

[0048] The reagents for use in creating a fluorescent signal in response to the analyte are typically enzymes, enzyme cofactors, buffering agents, salts, and stabilizing reagents. The reagents are selected from reagents that can be stored in dry form and dynamically re-hydrate to active form. One common assay design makes use of one or more steps in a biosynthetic or catabolic pathway that generates a reduced form of NAD⁺ or NADP⁺ or other electron carrier (e.g., FMN, FAD). The assay can make use of a cascade of enzyme-mediated reactions that generate in excess of one equivalent of reduced electron carrier per analyte equivalent. The reduced electron carrier is used to reduce a fluorophor precursor to create the fluorophor, for example, using diaphorase.

[0049] For example, where glucose is the analyte, ATP and glucose kinase can be used to generate glucose-6-phosphate (G6P). An oxidized form of an electron carrier, e.g., NADP⁺ G6P is then acted on by a 6-phosphogluconate dehydrogenase to generate the reduced form of the electron carrier. The reduced form of the electron carrier and a suitable fluorophor precursor are then acted upon to generate the fluorophor. Such methods are described, for example, in US Patent 5,360,595 (colorimetric strip assay), US Patent 5,302,513 (fluorometric assay using diaphorase) and US Patent 5,912,139.

[0050] Buffering agents, if needed, are provided in amounts suitable to stabilize the pH in a range that allows effective action by all the enzymes used in the assay.

Similarly, salts, if needed, are provided in amounts determined to support all of the enzymes used. Stabilizing agents, such as glycerol and inert polymers such as PEG are provided as empirically determined to be useful.

[0051] Dyes which have enhanced fluorescence in a reduced state and which have been shown or are thought to be useful with a diaphorase include salts of 7-hydroxy-3H-phenoxazin-3-one (Resazurin), neutral red, 4',6-diamidino-2-phenylindole (DAPI), bisbensimide (Hoechst 33258), and the-like.

[0052] The assay agents can be provided on a polymer support that dissolves or disperses on hydration. As discussed elsewhere, the assays can be conducted on a more stable support on which the assay agents are deposited. Deposition techniques will be recognized by those of ordinary skill. These include drying from liquid form and the method described in US Patent 6,045,753 (Loewy et al.)

Optical Detection Elements

[0053] Individually addressable LEDs can be constructed by packaging individual LEDs of suitable dimensions on a circuit board allowing the individual illumination either of each LED or a subset of the LEDs. For example, the semiconductor laser diodes (visible and infrared wavelengths) available from Opto Power Corporation (Tucson, AZ) or SDL, Inc. (San Jose, CA) can be so packaged. Alternatively, such LEDs with emitter center-to-center dimensions of 14 micrometers or 100 micrometers are available pre-packaged in multiples of 4 from SDL, Inc. For such relatively closely spaced light emitters, optics are generally used to direct the individual beams towards the more widely spaced-apart detection sites. The closely packed emitters have advantages in cost and simplicity of the housing requirements. Where each emitter will be directly aligned with a detection site, preferably the center-to-center dimension used in the present application ranges from about 1 mm to about 20 mm. In various embodiments, preferred ranges are from about 1 mm to about 20 mm, from about 1 mm to about 10 mm, or from about 1 mm to about 5 mm.

[0054] Detector arrays can be, for example, a charge coupled device (CCD, such as that available from DALSA, Inc. (Easton CT), Sarnoff Corporation (Princeton, NJ) or Princeton Instruments (Trenton, NJ)), all intensified COD array (such as that available from Princeton Instruments, Hamamatsu Corp. (Bridgewater, NJ) or Photometrics Ltd. of Tucson, AR), a focal plane array (such as that available from Scientific Imaging Technologies, Inc. (Beaverton, OR), Eastman Kodak Co., Inc. (Rochester, NY) or Sarnoff Corporation), a photodiode array (such as that available from Reticon Corp. (Sunnyvale, CA), Sensors Unlimited, Inc. (Princeton, NJ) or Hamamatsu) or photodetector array (such as that available from FLIR Systems Inc. (Portland, OR), Loral Corp. (New York, NY), or Hughes Electronic Corp. (Los Angeles, CA)).

Controller

[0055] The monitoring device is operated by an internal controller. The controller keeps count and track of the used needles and chambers, operates the actuating devices, light emitting devices and detectors, and collects the raw output from the light detectors. The controller also calculates an outcome from the raw data sufficient to determine if the value is in some cases too high or too low. The outcome can be reported by a stored value that is later downloaded for consideration, in a visual analog or digital display on a scale, in a visual or sound-mediated signal giving an indication that the result falls in one of two or more categories (e.g., a. satisfactory, b. alarm; a. satisfactory, b. borderline out-of-acceptable range, c. alarm), or the like.

[0056] In one embodiment, the controller has a device for transmitting outcome data or outcome-derived instructions to another device. Such transmission can be for example by wire-mediated electronic communication, Rf signaling, IR signaling, or the like. The other device can comprise a device for delivering therapeutic substances in response to the measured amount of a monitored analyte. The device can also be integrated with, or adapted for coupling with, a personal digital assistant (PDA), such as one of the Palm series of PDAs available from Palm, Inc. (Santa Clara, CA; a subsidiary of 3Com).

[0057] The controller incorporates a timing device. In some embodiments, the monitoring events (needle actuation, etc.) are triggered according to a pre-established timetable. In other embodiments, the user or medical personnel can program the timetable or choose between two or more pre-established timetables.

[0058] Interactions with the controller can be through any number of devices, such as a small-scaled keypad incorporated into the monitoring device, a more limited set of switches such as are used to program a digital watch, by communication with an external device which can have, for example, a more robust input device.

[0059] It will be recognized that the various controller functions described here can be incorporated into, for example, one integrated circuit, or multiple integrated circuits or other electronic devices.

Other Device Features

[0060] Output devices are incorporated into the monitoring device. These can comprise a visual display, such as an LCD or LED-mediated display, a sound generating device that can emit either simple tones or synthesized speech, electronic devices for transmitting data, and the like.

[0061] The energy source for the device can be, for example, a battery, or a small-scaled fuel cell.

[0062] Small-scaled solenoids or like pushing devices are described, for example, in Elan Corporation, WO 99/62576.

[0063] Tissues or body parts to which the monitoring

device can be affixed/secured include wrists, forearms, upper arms, torso, thighs, calves, ankles, and the like. The device is preferably secured with a strap. The device can also be secured with adhesive, which can also be used to supplement the hold gained with a strap. Suitable adhesives, particularly hypoallergenic adhesives, are available for example from the 3M Corporation. The monitoring device can be affixed to a tissue having a low density of pain-sensing nerves, such as the forearm or thigh.

[0064] To retract the needle after use, the distal end of the needle can be affixed to a spring, which includes any of a number of devices known to those of skill in the art that store potential energy derived from a displacement, and tending to provide a force favoring a reversal of the displacement. The actuator can thus, when it applies force to move the needle to the extended position, push against the spring, allowing the spring to provide a force favoring the return of the needle to the retracted position once the force from the actuator is removed.

[0065] In another embodiment, the housing cannot be reversibly opened such that the analyte monitoring device is disposable. For example, the needles, pushing apparatus, energy source and analysis sites can be within the housing, where the housing cannot be reversibly opened such that the device is adapted for disposable use. Or, the device has a housing adapted to not be re-openable such that the energy source is not replaceable or rechargeable.

Cassette

[0066] In one embodiment, the needles, chambers and the lower portion of the monitoring device through which the needles traverse are mounted in a removable cassette. Thus, the more expensive portions of the monitoring device, such as light detection devices and controllers can be reused, while the portions that contact biological fluid are periodically replaced by substituting cassettes. In one embodiment, a power source is mounted in the cassette to assure periodic replacement. In other embodiments, the power source (e.g., battery, fuel cell) is in a separate accessible compartment and is separately periodically replaced.

Calibration Control

[0067] In one aspect, the monitoring device has a slot for receiving a control package having one or more chambers containing a calibration control, such as a fixed concentration of the analyte to be monitored (plus control), or components designed to mirror the material components of a sample less the analyte to be monitored (minus control). The monitoring device either senses the presence of the control package to activate a control algorithm, or its interface allows the user to signal to initiate a control algorithm. In such a control algorithm, at least one chamber and associated needle are engaged with

a control fluid from the control package. The control fluid tested can be the plus control, or, using two chambers, the plus control and the minus control. The algorithm (a) operates to adjust calculation parameters in light of the control result, (b) operates to adjust the calculation parameters only if a sufficient deviation from norms is encountered, (c) operates to confirm that the monitoring device is within norms or notes a deviation indicating a need to change or service the monitoring device, (d) makes its determination to adjust or indicate a deviation only after conducting a further control assay, or the like.

Enhancement of ISF Recovery

[0068] In one embodiment, a near infra-red or visible light emitting device is incorporated into an ISF-drawing device. The emitted light heats the tissue from which ISF will be drawn, resulting in increased ISF recovery. Without limitation to theory, it is believed that one aspect of the increased ISF recovery is increased ISF flow to the heated tissue. Preferably, the light emitting device, such as a diode or solid-state laser, emits light in the 1.3 to 1,6 micron wavelength range.

Definition

[0069] The following terms shall have, for the purposes of this application, the respective meanings set forth below.

- **Diaphorase.** The name "diaphorase" has been applied to several enzymes which catalyze the oxidation of either beta-NADH or beta-NADPH in the presence of an electron acceptor such as methylene blue or 2,6-dichlorophenol-indophenol. Diaphorases are typically specific for either beta-NADH or beta-NADPH. The pig heart enzyme of Straub (Straub, Biochem, J. 3: 787, 1939) has diaphorase (beta-NADH specific) as well as lipoic and lipoamide dehydrogenase activities. The enzyme is reported to be a single protein, but Massey reports that "diaphorase" is may be a denatured lipoamide dehydrogenase. Pre-incubation of the pig heart preparation with Cu⁺⁺ reduces the lipoamide dehydrogenase activity and proportionately increases the beta-NADH diaphorase activity, Massey and Veeger, Blochim, Biophys. Acta 48: 33, 1961. Source examples include *Clostridium kluyveri*, Torula yeast, *Bacillus stercophilus* and other sources apparent to those of ordinary skill. • **Spring.** A spring is any device, including the myriad of such devices known in the art, that mechanically stores kinetic energy as potential energy.

[0070] While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations in the preferred devices and methods may be used and that it

is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the scope of the invention as defined by the claims that follow.

Claims

1. An analyte monitoring device (60) having a housing, the device comprising:
 - a. a plurality of needles (53), each configured to pierce the skin and draw fluid for analysis, having a retracted position and a position wherein it is extended from the housing a distance adapted to pierce skin;
 - b. an electrically or spring powered needle pushing apparatus (87, 37) to move each needle (53) from the retracted position to the extended position;
 - c. an energy source located within the housing;
 - d. a plurality of analysis sites (50) comprising an analysis preparation, each adapted to receive liquid drawn from a respective needle to wet the analysis preparation;
 - e. one or more light sources (64) adapted to direct light at the analysis site;
 - f. one or more light detectors (64) adapted to direct light at from the analysis sites; and
 - g. a processor (65);

wherein elements a and d can be replaceably inserted into the analyte monitoring device as part of a cassette.
2. The analyte monitoring device of claim 1, further comprising:
 - h. a Rf or IR signaling transmitter adapted for communicating with a second, external processor.
3. The analyte monitoring device of claim 1, further comprising:
 - (h) a plurality of evacuated sites, each adapted to engage an associated needle during or following needle movement to apply the vacuum to the needle while it is in an extended position.
4. The analyte monitoring device of claim 3, wherein the device has a housing adapted to not be re-openable such that the energy source is not replaceable or rechargeable.
5. The analyte monitoring device of claim 1, further comprising

(h) a light source fixed to the housing aligned to heat a tissue aligned to intercept the extended positions of the needles.

6. The device of any one of claims 1 to 5, wherein the analyte comprises glucose.
7. The device of any one of claims 1 to 6, wherein the needles (53) have a diameter of 200µm or less.
8. The device of any one of claims 1 to 7, wherein the analysis sites (50) comprise a reagent deposited on a support and adapted to react with the analyte to produce a measurable signal.
9. The device of claim 8, wherein the reagent is capable of producing a fluorescent signal upon reaction with the analyte.

Patentansprüche

1. Analytkontrollvorrichtung (60) mit einem Gehäuse, wobei die Vorrichtung Folgendes umfasst:
 - a. eine Vielzahl an Nadeln (53), die jeweils ausgebildet sind, um die Haut zu durchstechen und Fluid für eine Analyse zu entnehmen und eine zurückgezogene Position und eine Position, in der sie sich aus dem Gehäuse über eine für das Durchstechen der Haut geeignete Distanz erstrecken, aufweisen;
 - b. eine elektrisch oder durch eine Feder betriebene Nadelvorschubvorrichtung (87, 37), um jede Nadel (53) aus der zurückgezogenen Position in die ausgefahrene Position zu bewegen;
 - c. eine Energiequelle, die in dem Gehäuse angeordnet ist;
 - d. eine Vielzahl an Analysestellen (50), die ein Analysepräparat umfassen und jeweils geeignet sind, um aus einer entsprechenden Nadel gezogene Flüssigkeit aufzunehmen, um das Analysepräparat zu befeuchten;
 - e. eine oder mehrere Lichtquellen (64), die geeignet ist/sind, um Licht auf die Analysestellen zu richten;
 - f. einen oder mehrere Lichtdetektoren (64), der/die geeignet ist/sind, um Licht von den Analysestellen zu empfangen, und
 - g. einen Prozessor (65);

wobei die Elemente a und d als Teil einer Kassette austauschbar in die Analytkontrollvorrichtung eingesetzt werden können.

2. Analytkontrollvorrichtung nach Anspruch 1, die ferner Folgendes umfasst:

h. einen HF- oder IR-Signalsender, der geeignet ist, um mit einem zweiten externen Prozessor zu kommunizieren.

3. Analytkontrollvorrichtung nach Anspruch 1, die ferner Folgendes umfasst:

h. eine Vielzahl luftleerer Stellen, die jeweils geeignet sind, um während oder nach der Bewegung einer Nadel mit einer entsprechenden Nadel in Eingriff zu gelangen, um die Nadel unter Vakuum zu setzen, während sich diese in einer ausgefahrenen Position befindet.

4. Analytkontrollvorrichtung nach Anspruch 3, worin die Vorrichtung ein Gehäuse aufweist, das angepasst ist, um nicht wieder geöffnet werden zu können, so dass die Energiequelle nicht austauschbar oder wiederaufladbar ist.

5. Analytkontrollvorrichtung nach Anspruch 1, die ferner Folgendes umfasst:

h. eine an dem Gehäuse befestigte Lichtquelle, die ausgerichtet ist, um ein Gewebe zu erwärmen, das ausgerichtet ist, um die Nadeln in ihrer ausgefahrenen Position zu schneiden.

6. Vorrichtung nach einem der Ansprüche 1 bis 5, worin der Analyt Glukose umfasst.
7. Vorrichtung nach einem der Ansprüche 1 bis 6, worin die Nadeln (53) einen Durchmesser von 200 µm oder weniger aufweisen.
8. Vorrichtung nach einem der Ansprüche 1 bis 7, worin die Analysestellen (50) ein Reagens umfassen, das auf einem Träger abgeschieden ist und geeignet ist, um mit dem Analyt zu reagieren, um ein messbares Signal zu erzeugen.
9. Vorrichtung nach Anspruch 8, worin das Reagens in der Lage ist, bei Reaktion mit dem Analyt ein Fluoreszenzsignal zu erzeugen.

Revendications

1. Dispositif de surveillance d'analyte (60) comportant un boîtier, le dispositif comprenant:

a. une pluralité d'aiguilles (53), chacune configurée pour percer la peau et pour aspirer du fluide pour l'analyse, ayant une position rétractée et une position dans laquelle elle s'étend du boîtier sur une distance apte à percer la peau;

b. un appareil de poussée d'aiguille (87, 37) actionné électriquement ou par ressort pour ame-

- ner chaque aiguille (53) de la position rétractée à la position étendue;
- c. une source d'énergie située dans le boîtier;
- d. une pluralité de sites d'analyse (50) comprenant une préparation d'analyse, chacun apte à recevoir du liquide aspiré par une aiguille respective pour mouiller la préparation d'analyse;
- e. une ou plusieurs sources de lumière (64) aptes à diriger la lumière sur les sites d'analyse;
- f. un ou plusieurs détecteurs de lumière (64) aptes à recevoir la lumière des sites d'analyse; et
- g. un processeur (65);
- où les éléments a et d peuvent être insérés de manière échangeable dans le dispositif de surveillance d'analyte en tant que partie d'une cassette.
2. Dispositif de surveillance d'analyte selon la revendication 1, comprenant en outre:
- h. un transmetteur de signalisation Rf ou IR apte à communiquer avec un deuxième processeur externe.
3. Dispositif de surveillance d'analyte selon la revendication 1, comprenant en outre:
- (h) une pluralité de sites évacués, chacun apte à venir en prise avec une aiguille associée durant ou à la suite du mouvement de l'aiguille pour appliquer le vide à l'aiguille pendant qu'elle se trouve dans une position étendue.
4. Dispositif de surveillance d'analyte selon la revendication 3, où le dispositif comporte un boîtier ne pouvant pas être réouvert de sorte que la source d'énergie n'est pas remplaçable ni rechargeable.
5. Dispositif de surveillance d'analyte selon la revendication 1, comprenant en outre
- (h) une source de lumière fixée au boîtier alignée pour chauffer un tissu aligné pour intercepter les positions étendues des aiguilles.
6. Dispositif selon l'une quelconque des revendications 1 à 5, où l'analyte comprend du glucose.
7. Dispositif selon l'une quelconque des revendications 1 à 6, où les aiguilles (53) ont un diamètre de 200µm ou moins.
8. Dispositif selon l'une quelconque des revendications 1 à 7, où les sites d'analyse (50) comprennent un réactif déposé sur un support et apte à réagir avec l'analyte pour produire un signal mesurable.
9. Dispositif selon la revendication 8, où le réactif est

apte à produire un signal fluorescent lors de la réaction avec l'analyte.

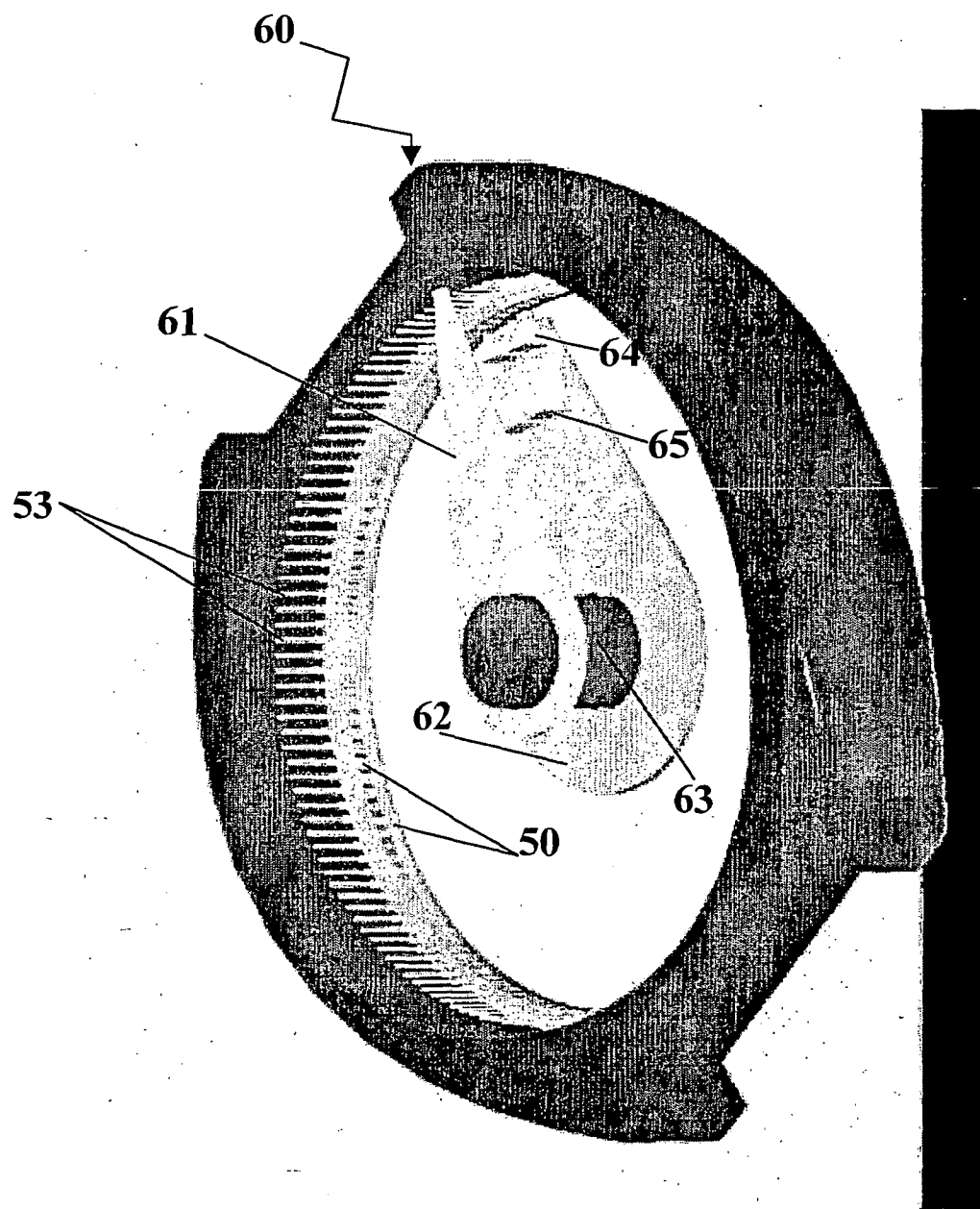


Fig. 1

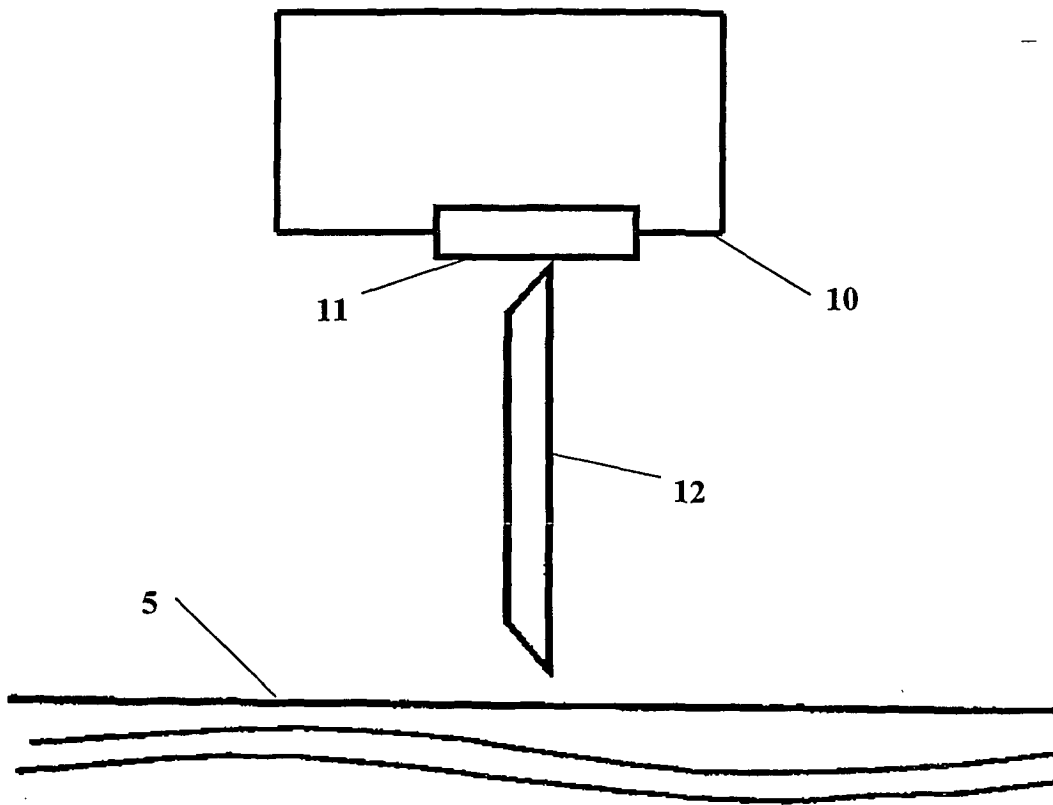


Fig. 2A

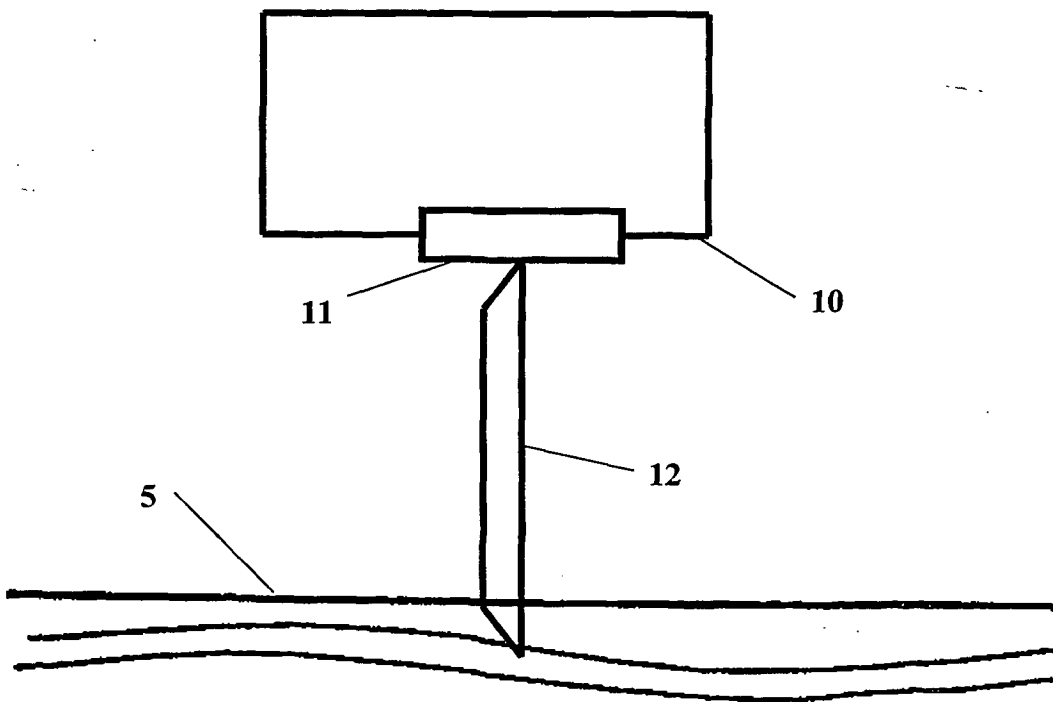


Fig. 2B

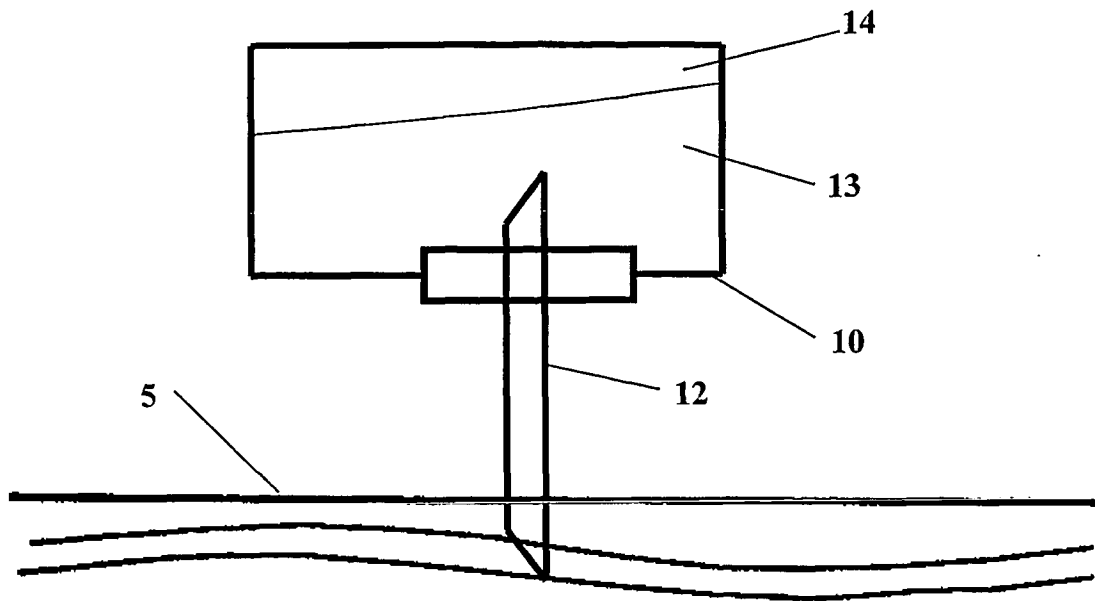


Fig. 2C

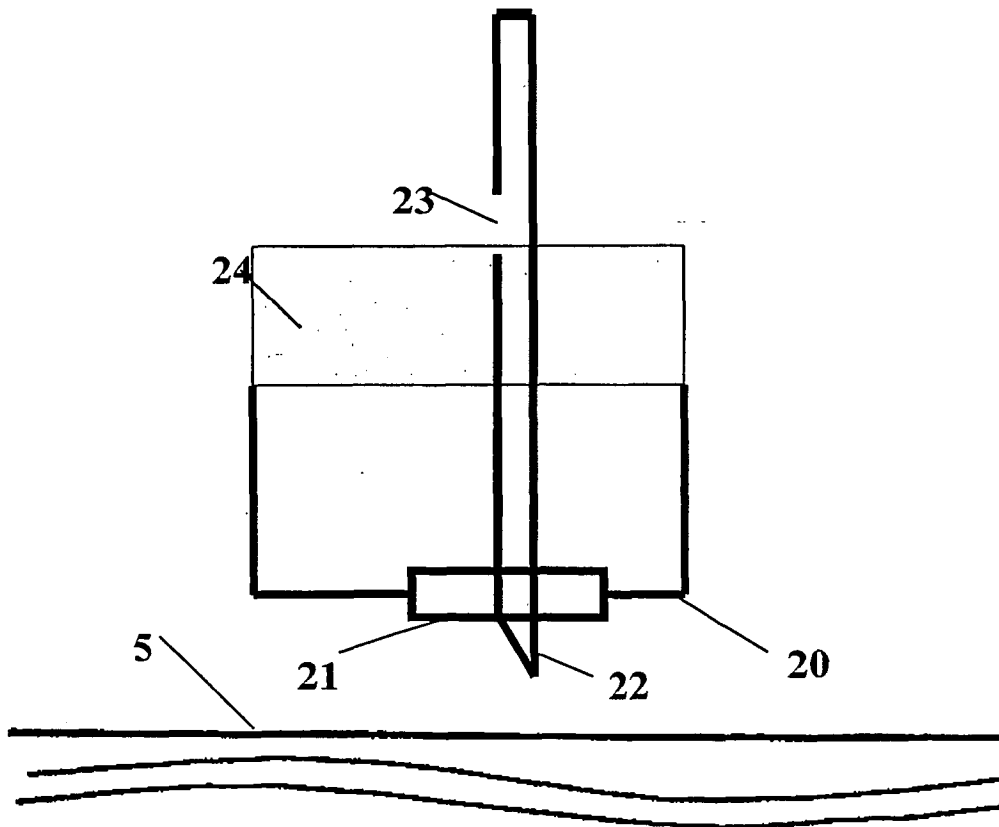


Fig. 3A

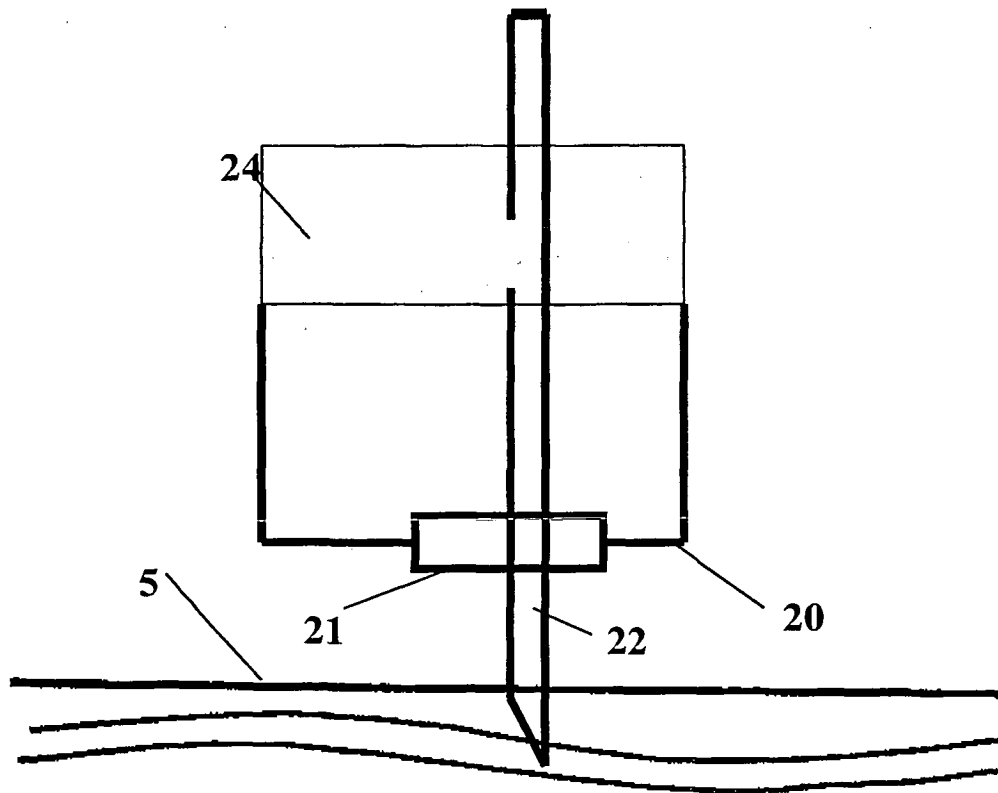


Fig. 3B

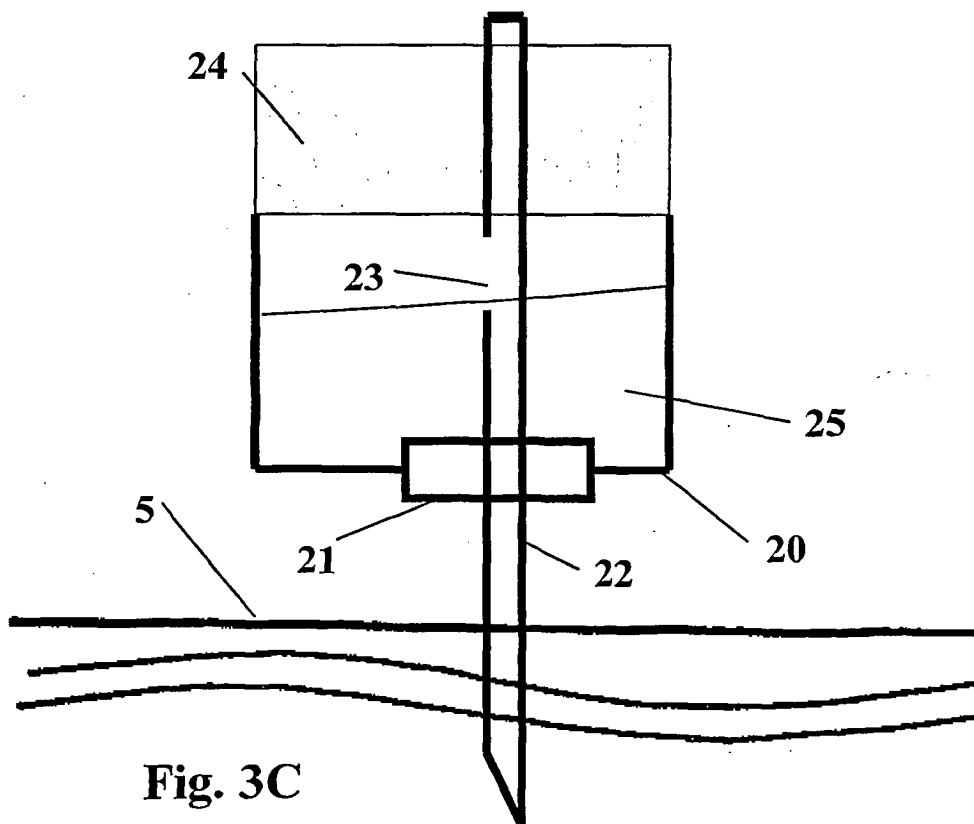


Fig. 3C

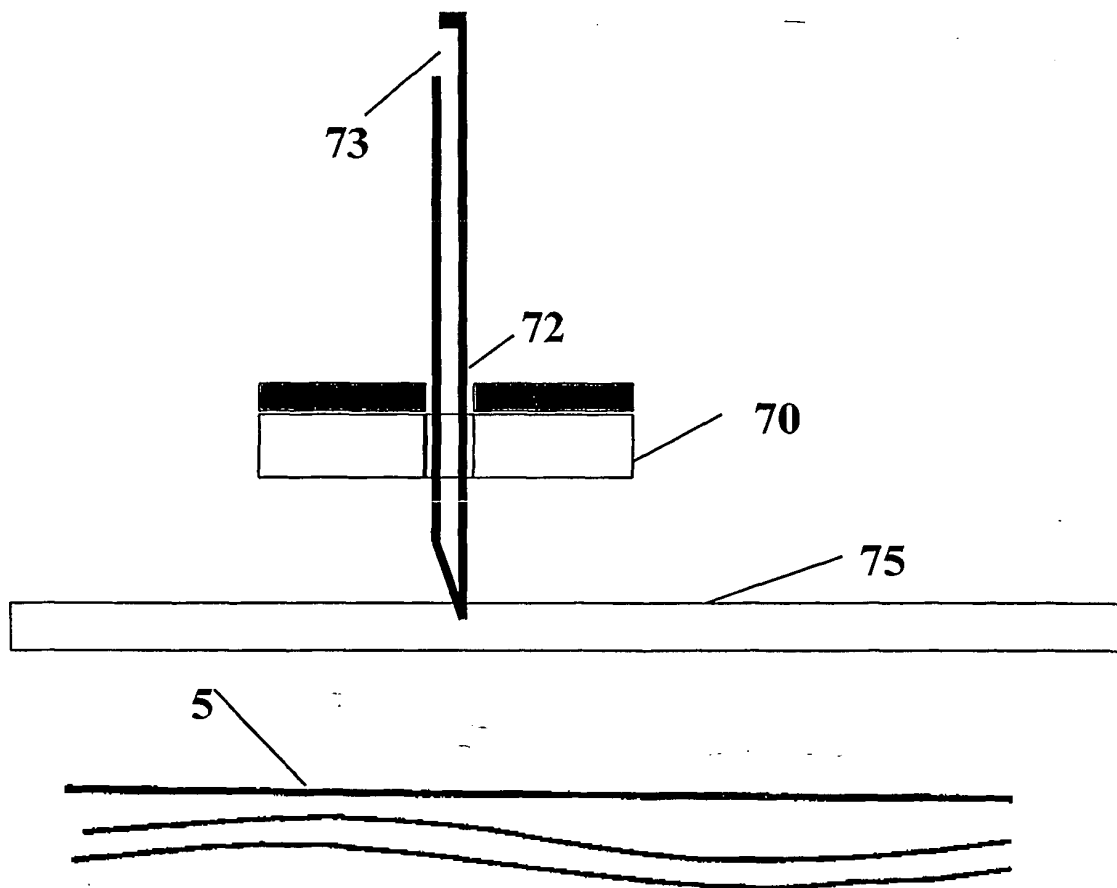


Fig. 4A

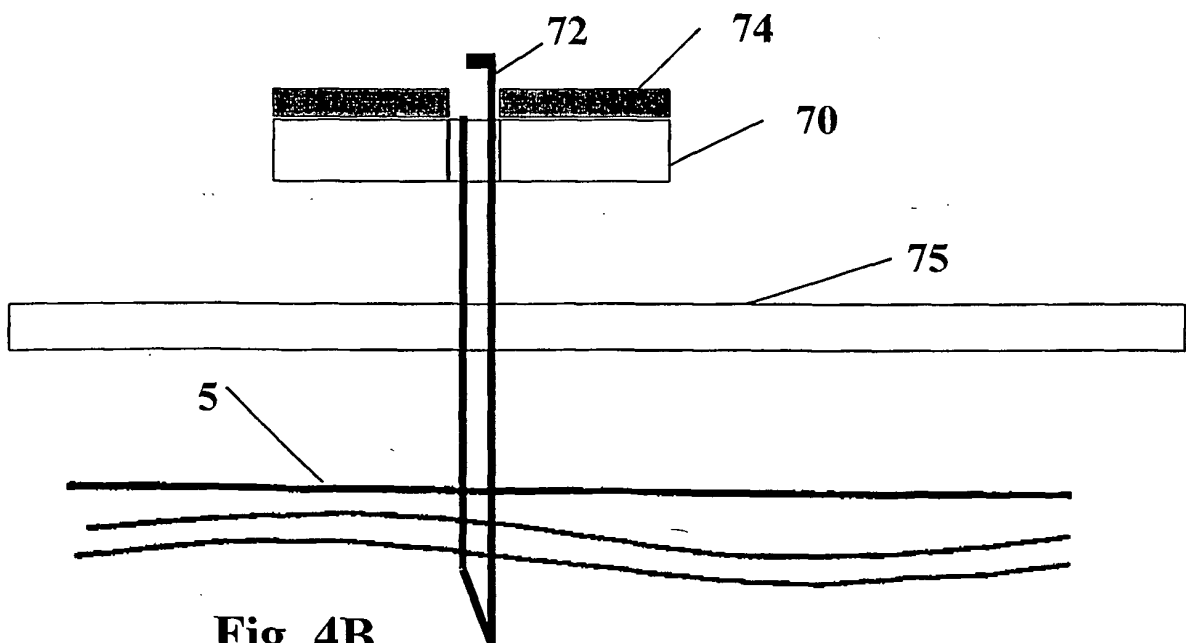


Fig. 4B

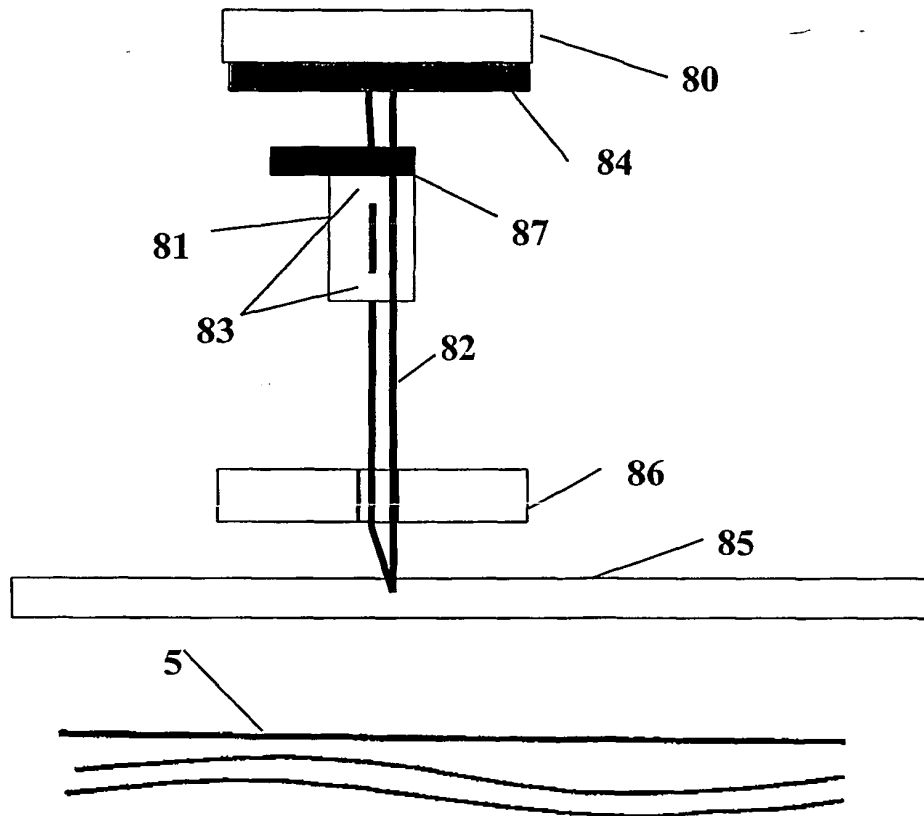


Fig. 5

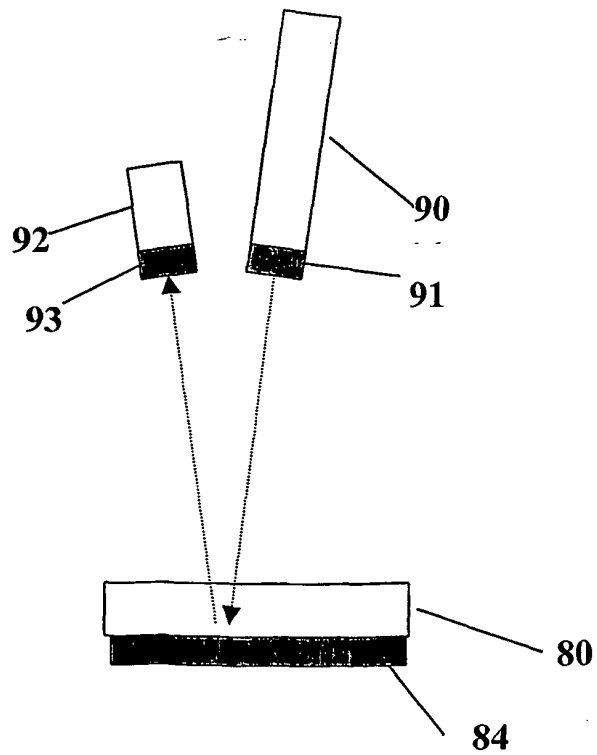


Fig. 6

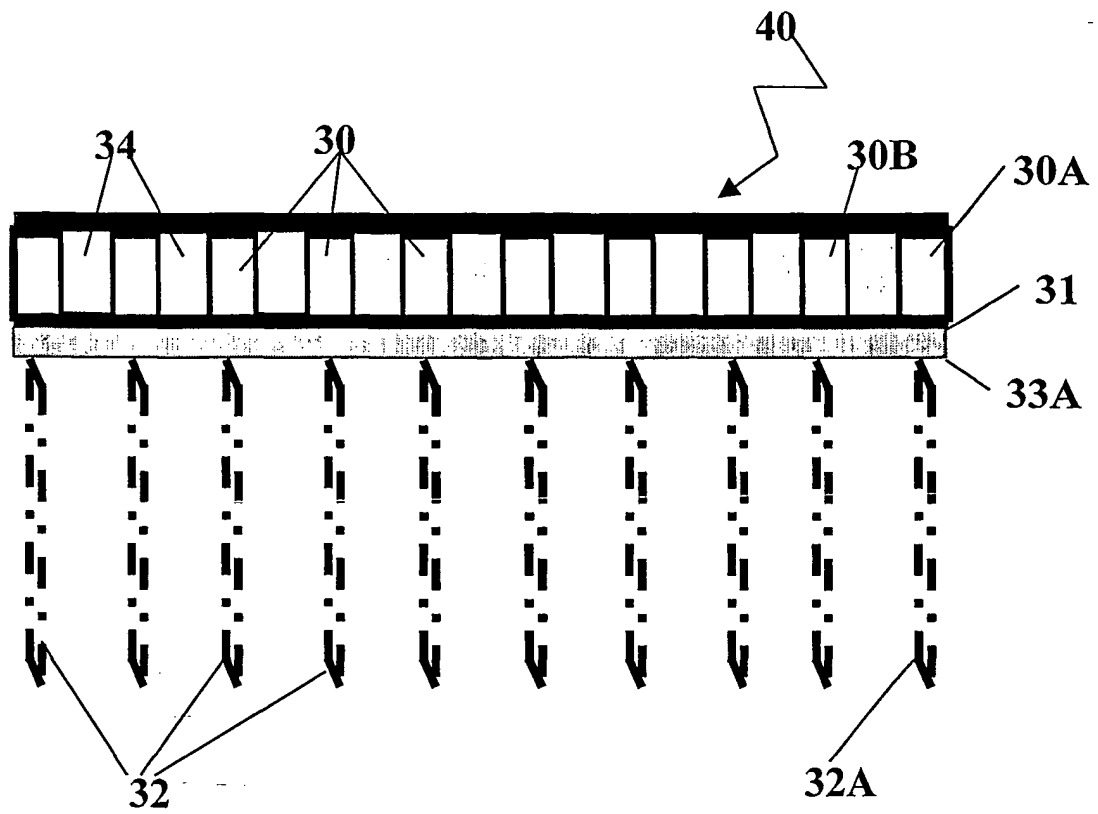


Fig. 7A

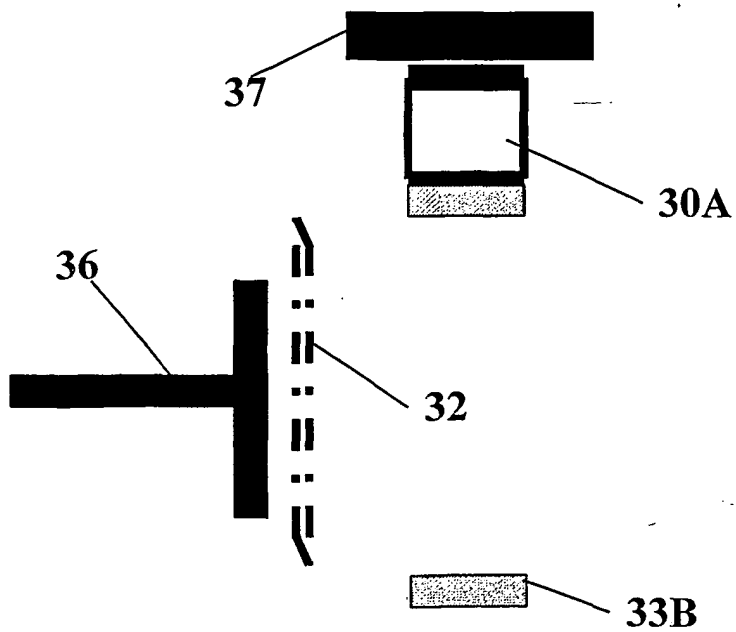


Fig. 7B

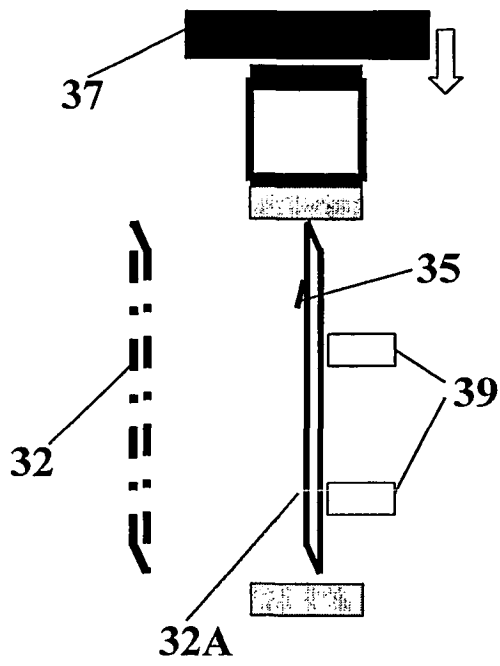


Fig. 7C

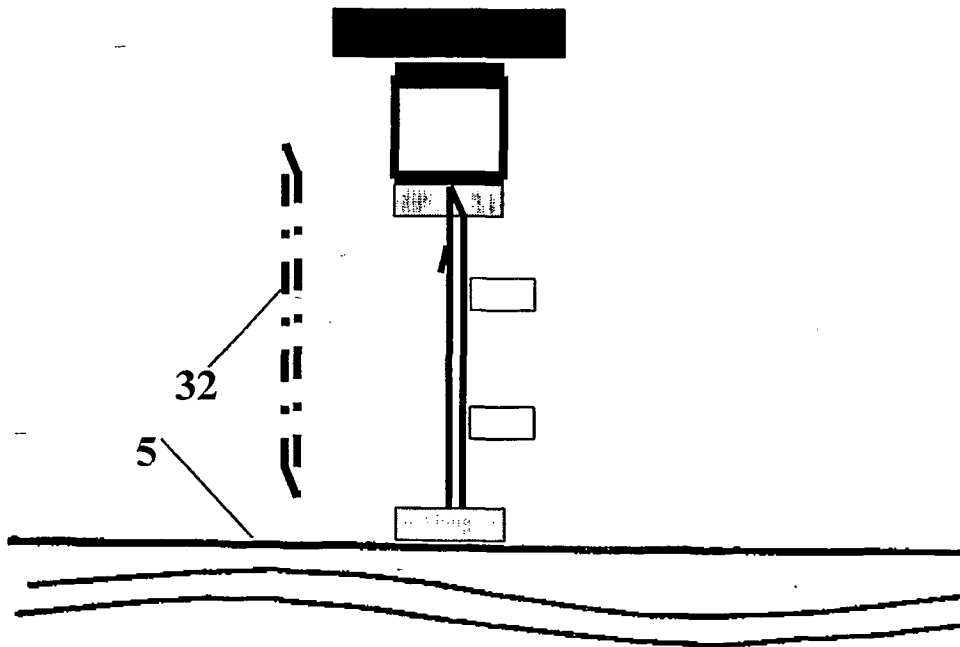


Fig. 7D

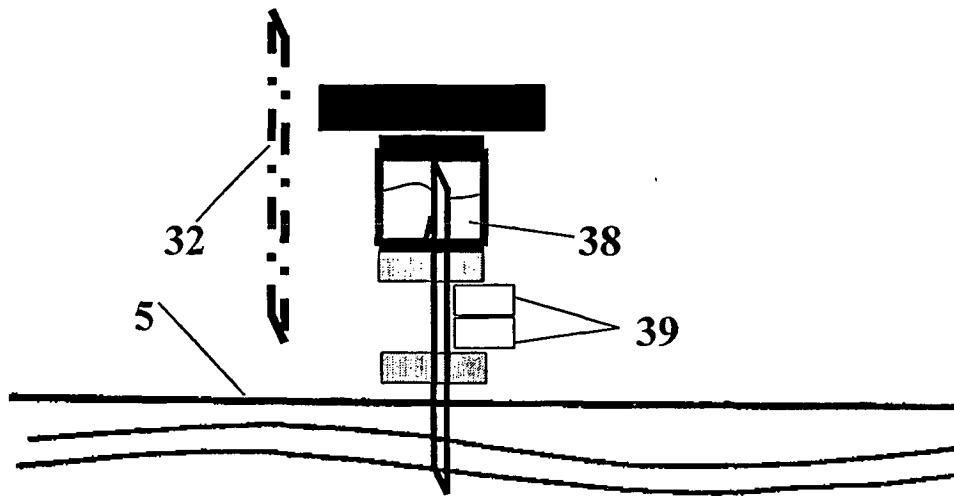


Fig. 7E

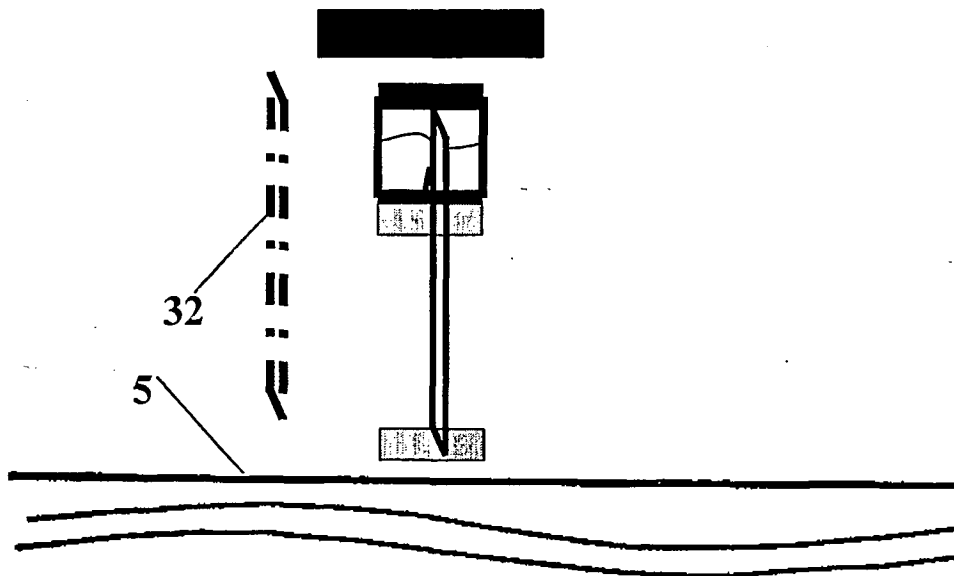
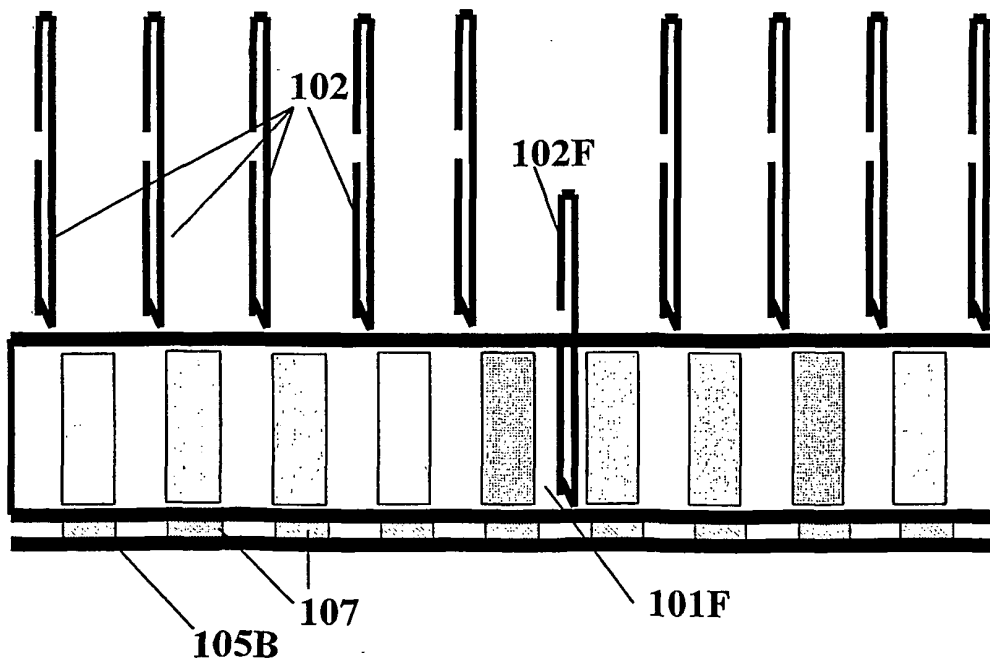
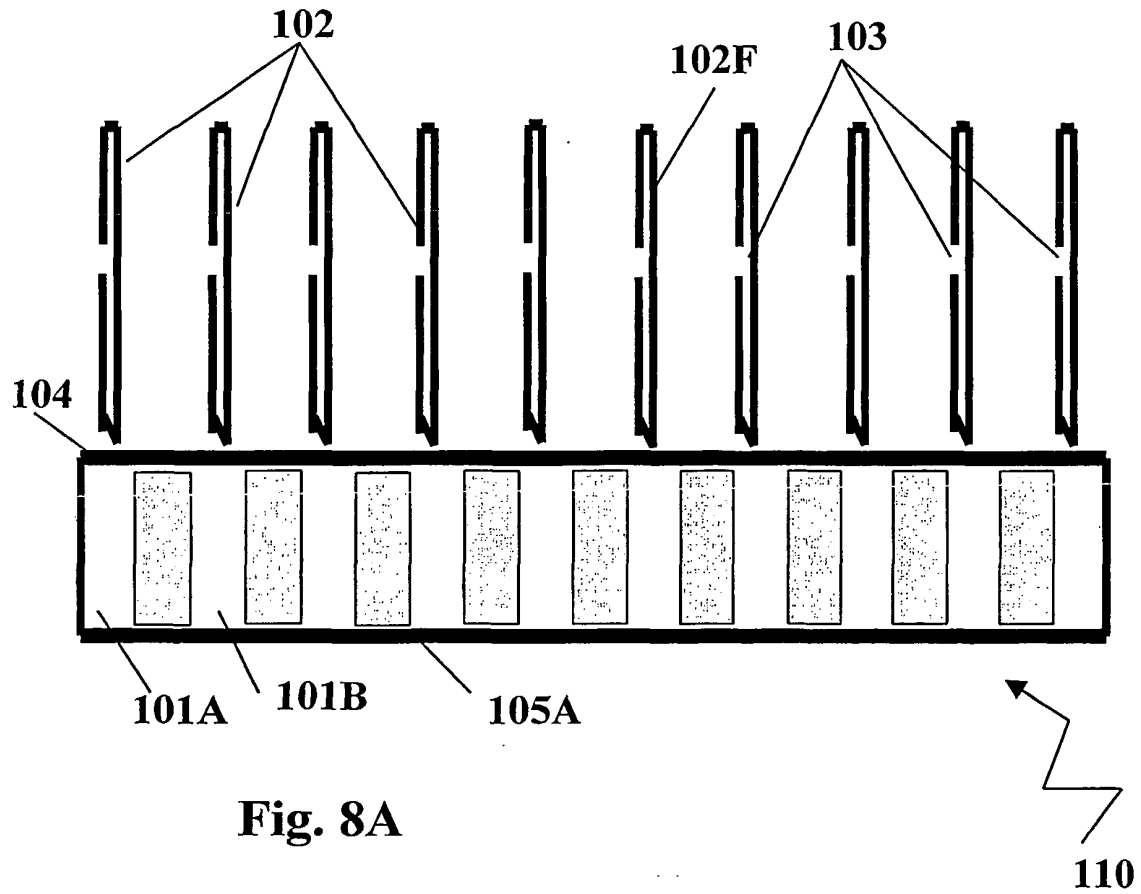


Fig. 7F



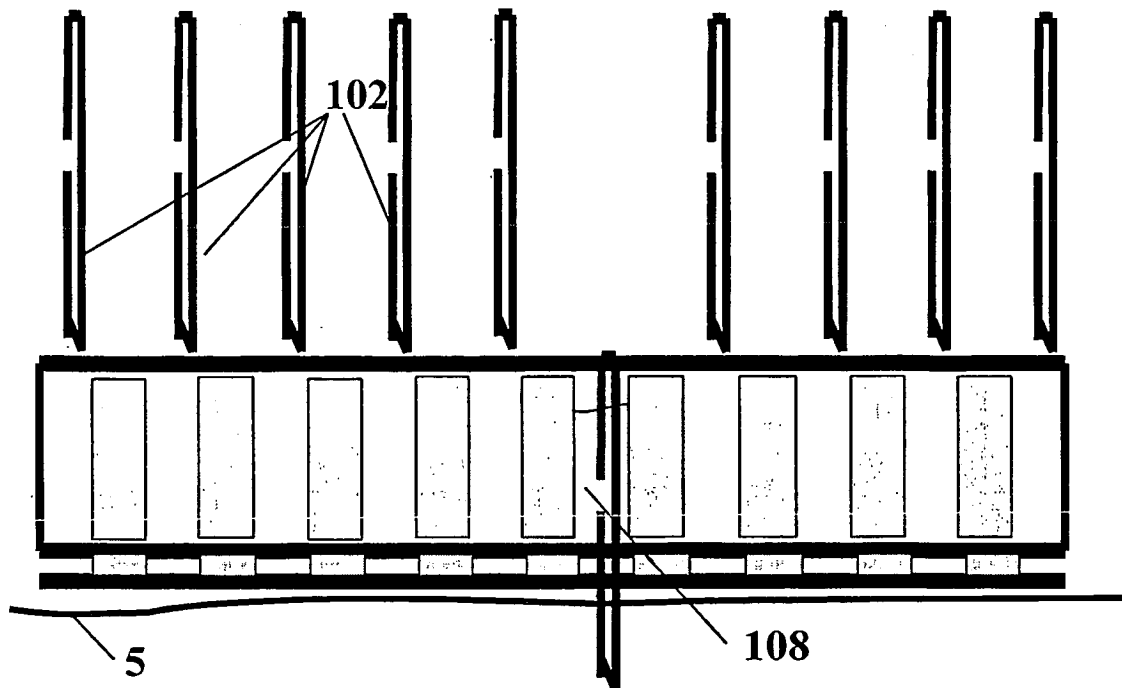


Fig. 8C

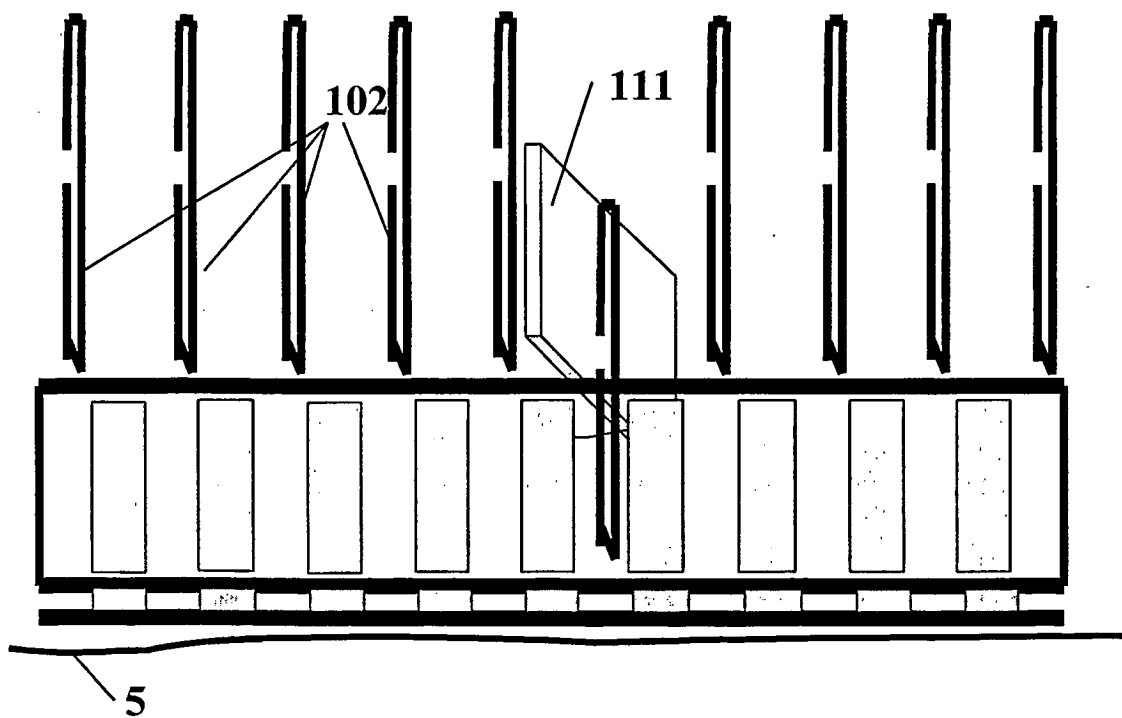


Fig. 8D

REFERENCES CITED IN THE DESCRIPTION

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申请(专利权)人(译)	Sarnoff公司		
当前申请(专利权)人(译)	INTUITY MEDICAL , INC.		
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摘要(译)

提供了一种具有外壳 (60) 的分析物监测装置, 该装置包括多个针 (53), 每个针 (53) 具有尖端, 缩回位置, 尖端从外壳伸出的位置适于刺穿皮肤的距离; 电子或弹簧驱动的针头推动装置, 其可移动以分别接合每个针头以将每个针头从缩回位置移动到伸出位置; 位于外壳内的能源; 包括分析制剂的多个分析位点, 每个适合于从针头接收液体以润湿分析制剂; 一个或多个适于将光引导至分析部位的光源 (64); 一个或多个适于从分析部位接收光的光检测器; 和处理器 (65)。

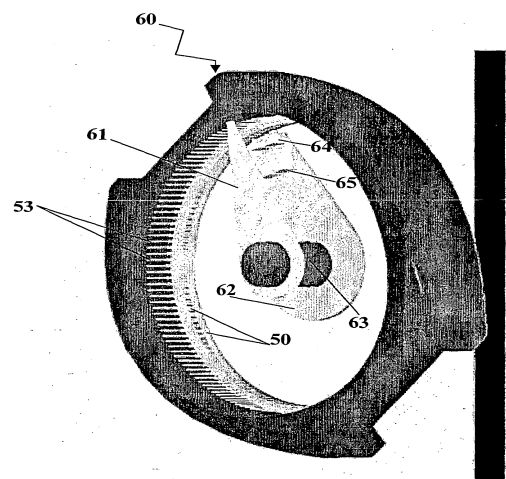


Fig. 1