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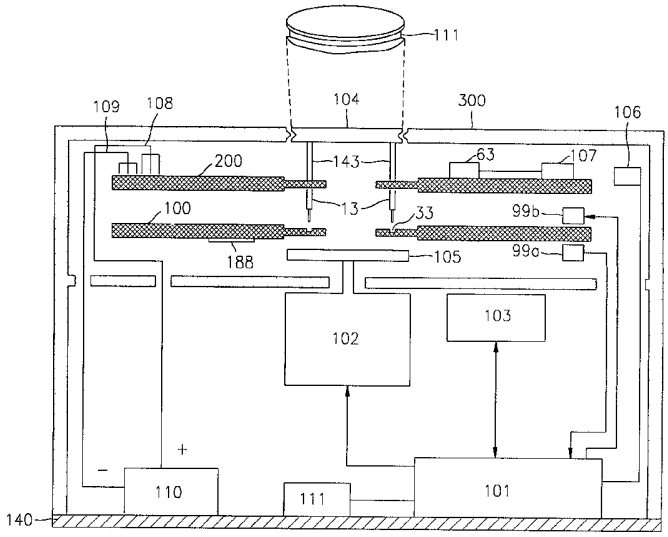


(57) Abstract: A non-optical bio-disc, a bio-disc device including the non-optical bio-disc and/or an optical disc, a bio-driver apparatus in which a controller disc including a controller for the bio-disc is installed, and an assay method using the same, which are suitable for labs-on-a-chips for various diagnostic assays, nucleic acid hybridization assays, and immunoassays, are provided. The bio-driver apparatus is compatible with general optical discs, including audio CDs, CD-Rs, game CDs, DVDs, etc., and the assay method is compatible with general optical disc drivers, including CD-ROMs, DVD players, etc. Thus, the bio-driver apparatus and the assay method offer and economical and convenient alternative to existing products. In addition, the bio-driver apparatus can be readily and easily applied in connection with a computer for remote diagnosis via the Internet.

WO 03/080868 A1

BIO-DISC, BIO-DRIVER APPARATUS, AND ASSAY METHOD USING THE SAME

Technical Field

The present invention relates to a non-optical bio-disc, a bio-disc device including the non-optical bio-disc and/or an optical disc, a bio-driver apparatus, and an assay method using the same. More particularly, the present invention relates to a bio-disc with a lab-on-a-chip for various diagnostic assays, nucleic acid hybridization assays, or immunoassays, a bio-driver apparatus integrated with a controller disc including a controller for the bio-disc, and an assay method using the same.

Background Art

The present invention is a continued application of International Patent Application No. PCT/KR02/00126, which was filed 27 January 2002 and claims the priority of Korean Patent Application No. 10-2001-0003956, filed 27 January 2001, and International Patent Application No. PCT/KR02/01035, which was filed 31 May 2002 and claims the priority of Korean Patent Application No. 10-2001-0031284, filed 31 May 2001. International Patent Application No. PCT/KR02/00126 and its priority Korean application are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or single strand of nucleic acids or oligonucleotides", and International Patent Application No. PCT/KR02/01035 and its priority Korean application are entitled "Micro valve apparatus using microbead and method for controlling the same". The disclosures of the above previous applications are incorporated herein by reference in their entirety.

The nucleic acid hybridization assay method and device using a cleavage technique responsive to a complementary double strand or single strand of nucleic acids are applicable to diverse quantitative or qualitative assay devices. In addition, the micro valve is an essential element to control the flow of fluid in a lab-on-a-chip.

The nucleic acid assay device may comprise a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device to detect uncleaved or cleaved signal elements. The detected results can be digitized as computer executable software and provided through an established communications network, such as the Internet, to a patient or a doctor. In this manner, a remote diagnostic system ensuring convenience to both patient and doctor can be implemented based on the nucleic acid assay device. A capacitance and impedance measurement for the detector may include interdigitated array electrodes with cleavable signal elements, as disclosed in the previous application.

As a continued application from the previous applications, the present invention relates to a non-optical bio-disc, a bio-disc device, a bio-driver apparatus, and an assay method using the same, which are applicable to various kinds of diagnostic assay devices, nucleic acid hybridization assay devices, and immunoassay devices.

Most clinical diagnostic assay devices developed so far for the detection of small quantities of analytes in fluids are used in serial or parallel connection with multiple-sample preparation and automated reagent addition devices for the simultaneous analysis of numerous test samples with higher efficiency. Such automated reagent preparation devices and automated multiplex analyzers are often integrated into a single device.

Clinical laboratory analyzers of this type can accurately perform hundreds of assays using small quantities of samples and reagents in

one hour automatically or semi-automatically. However, these analyzers are expensive and only centralized laboratories and hospitals can afford them. Such centralization necessitates sample transport to the laboratory or hospital and often precludes urgent or emergent analysis of time-critical samples.

Thus, to address these problems, there is an increasing need for clinical analyzers which are cheap and easy-to-handle for everyone, such as clinical analyzers suitable for use at the patient bedside of in the patient's home without dedicated detectors.

< Optical and Non-optical Bio-discs >

The standard compact disk is formed from a 12-cm polycarbonate substrate, a reflective metal layer, and a protective lacquer coating. DVD stands for digital video disk, a type of optical disk of the same size as the compact disk, but with significantly greater recording capacity.

The polycarbonate substrate is optical-quality clear polycarbonate. In a standard pressed CD or DVD, the data layer is part of the polycarbonate substrate, and the data are impressed as a series of pits by a stamper during injection molding. In the injection molding process, melted polycarbonate is injected into a mold under high pressure and cooled in a mirror image of the mold or stamper. As a result, reverse pits of the stamper are formed on the polycarbonate disk surface during mastering as binary data. The stamping master is typically glass.

As is widely known to one of ordinary skilled in the art, information written to general optical discs, such as audio CDs, CD-Rs, game CDs, DVDs, etc., is read from the differential reflectivity of data pits or the refractivity in their dye layer. In a common CD using a differential reflectivity detection method, indentations of pits are formed in the CD to a depth on the order of one-eighth to one-quarter of the wavelength of an incident laser beam. The indentations cause destructive interference in

a reflected beam and correspond to bits having a "0" value. Flat areas of the CD reflect the incident laser beam toward a detector and correspond to bits having a "1" value.

U.S. Patent No. 5,580,696 discloses materials of a dye layer for optical discs using refractivity-based data detection. An optical disk using the dye layer is rotated about a rotary shaft and scanned by laser to read data from the dye layer.

However, a general optical pickup for the above-described optical discs includes both a light emitting unit and a light receiving unit in a single module. In this structure, its optical traveling path is relatively long, and there is a poor sensitivity problem of the light receiving unit. In addition, laser scanning for information reading requires actuating the optical pickup to a predetermined location on an optical disc and rotating the optical disc. Furthermore, when such an optical disc read by laser scanning is applied to a bio-assay device, problems such as physical deformation of probes and inaccurate assay results occur.

Various technologies regarding CD-based assay devices have been disclosed: "Optical confocal compact scanning optical microscope based on compact disc technology" (*Applied Optics*, Vol. 30, No. 10, 1991), "Gradient-index objectives for CD applications" (*Applied Optics*, Vol. 26, Issue 7, 1987), and "Miniature scanning optical microscope based on compact disc technology" (*Proc. Soc. Photo-opt. instrument Eng.* 110, page 1139-1169, 1989).

Patents regarding CD-based assay devices include U.S. Patent No. 4,279,862 entitled "Centrifugal photometric analyzer" (published on 21 July 1981) and U.S Patent No. 4,141,954 entitled "Reaction tube assembly for automatic analyzer" (published on 27 February 1979).

GB 1075800 (published on 12 July 1967), entitled "Disc for centrifuge", discloses a device for flowing a sample fluid supplied via n inject hole of a disc over its surface by centrifugal force. EP 3335946

(published on 12 April 1965), entitled "Separating disks for centrifuge", discloses an apparatus for separating fluid samples injected via an inject hole of a disc by inducing flow of the samples through channels or chambers formed in the disc by centrifugal force.

U.S. Patent No. 4,311,039 (published on 19 January 1982), entitled "Disc centrifuge photosedimentometer", discloses a disc type chemical assay device using centrifugal force and optical detection.

However, the above-listed conventional assay devices failed to ensure perfect automation in assay and diagnosis and are unsuitable for a lab-on-a-chip.

Unlike the conventional optical discs using differential reflection from physical pits or the refractivity in dye layers, a bio-disc according to the present invention reads information using light transmission, capacitance and impedance measurements, or electrochemical detection, wherein the bio-disc includes chambers as fluid reservoirs and channels as flow paths. Such a bio-disc according to the present invention is referred to as a "non-optical bio-disc", in contrast to the conventional "optical" bio-discs using the differential reflection of laser light scanned over the bio-disc. The conventional ones could not detect information using light transmission due to their structure which includes a reflective metal layer and a dye layer.

The term "non-optical bio-disc" throughout the specification refers to a bio-disc which allows for selective detection of analytic sites using light transmission, capacitance and impedance measurements, or electrochemical detection, without need to rotate the bio-disc and scan it with laser light. Therefore, the "non-optical bio-disc" of the present invention could involve optical assay detectors.

The term "optical bio-disc" throughout the specification refers to a bio-disc using a common optical pickup scanning laser light over the bio-disc to read data from its differential reflectance.

Common polycarbonate substrates can be modified to suit to bio-discs, which are thin film type assay devices, for detecting a small quantity of an analyte in a fluid sample for the diagnostic purpose. In this case, instead of pits and a dye layer, channels as fluid flow paths and chambers as buffer reservoirs are formed in a surface of a polycarbonate substrate through injection molding. In addition, micro valves for controlling fluid flow through the channel and flow rate and an electronic controlling method of the micro valves are needed.

In a bio-disc according to the present invention, channels as fluid flow paths and chambers as buffer reservoirs may be formed in a silicon wafer using semiconductor manufacturing processes. Such a bio-disc according to the present invention includes an electronic circuit integrated into the silicon wafer to control fluid flow and flow rate.

Disclosure of the Invention

The present invention provides a non-optical bio-disc, a bio-disc device using the non-optical bio-disc and/or an optical bio-disc, a bio-driver apparatus, and an assay method using the same, which are applicable for remote diagnosis, sample diagnosis, DNA assays, and immunoassays.

A bio-disc according to the present invention is controlled by a controller disc installed in a bio-driver apparatus. The controller disc includes a controller to control the bio-disc with various control signals and is built in the bio-driver apparatus for the convenience of assays. In other words, it is enough to just load only one bio-disc into and eject it from the bio-driver apparatus according to the present invention. Alternatively, the controller disc may be combined with a non-optical bio-disc or with both a non-optical bio-disc and a general optical disc, instead of be built in the bio-driver apparatus.

The controller disc detects whether a currently loaded disc is a

common optical disc, such as an audio CD, a CD-RW, a game CD, or a DVD, or a bio-disc. The controller disc operates in a common mode for optical discs if the currently loaded disc is determined to be a common optical disc and outputs various control signals to control a lab-on-a-chip integrated in a bio-chip if the currently loaded disc is determined to be a bio-disc.

The present invention also provides a controller-disc combined bio-disc device in which a bio-disc and a controller are combined, an optical disc-combined bio-disc device in which a bio-disc and a common optical disc are combined, and an assay method using the bio-disc devices. The common optical disc of the bio-disc device is compatible with a bio-driver apparatus as well as general optical drivers for optical discs, such as CDs. In other words, audio data, such as music, written to the optical disc of the bio-disc device can be read by means of the bio-driver apparatus or any general optical driver, such as a CD driver.

The present invention also provides a bio-disc for polymerase chain reaction (PCR) and a bio-disc for electrophoresis.

In accordance with an aspect of the present invention, there is provided a non-optical bio-disc comprising: a solid substrate in which channels as fluid flow paths, a chamber as a buffer reservoir, a hole connecting the channels, and an assay site with biomolecular arrays immobilized thereon are integrated; and a valve used to open and close the hole connecting the channels, wherein an analyte-specific signal from the assay site is detectable using a detector including a light transmission type device, an electrochemical device, or a capacitance and impedance measurement device.

The term "assay site" used throughout the specification also can be referred to as an "array chamber" because of its structure including biomolecules arranged therein, or a "hybridization chamber" or an "antigen-antibody reaction chamber" because hybridization or

antigen-antibody reaction takes place therein. In addition, the analyte-specific signal includes an uncleaved signal element and a cleaved signal element.

In specific embodiments of the non-optical bio-disc according to the present invention, the biomolecular arrays may be made from at least one selected from the group consisting of DNA, RNA, PNA, and protein probes.

The chamber of the non-optical bio-disc may comprise at least one selected from the group consisting of: a preparation chamber for preparing a DNA sample from blood, cells, or RNA; a PCR chamber for amplifying the DNA sample through polymerase chain reaction (PCR); a hybridization chamber in which assay and diagnostic probes are arrayed for hybridization with the amplified DNA from the PCR; and a trash chamber for collecting wastes generated from washing. The preparation chamber may reserve a lysis buffer solution used to extract a DNA through lysis and ferroelectric beads having affinity to the extracted DNA. The non-optical bio-disc according to the present invention may comprise a plurality of PCR chambers. In this case, each PCR chamber may reserve one type or several types of primer. Alternatively, all of the PCR chambers may reserve the same type of primer.

Alternatively, the chamber of the non-optical bio-disc according to the present invention may comprise at least one chamber selected from the group consisting of: at least one preparation chamber for preparing a serum sample, an antigen, or an antibody from blood or cells; at least one antigen-antibody reaction chamber in which immuno probes are arrayed for antigen-antibody reaction with the prepared antigen or antibody; and a trash chamber for collecting waste generated from washing. In this case, the chamber may further comprise a filter at an outlet of the preparation chamber and a conjugate antibody chamber as a conjugate antibody reservoir. The conjugate antibody chamber

reserves conjugate antibodies labeled with colorimetric moiety selected from gold and latex.

The valve of the non-optical bio-disc according to the present invention may comprise: a microbead which plugs or opens the hole connecting channels; and electromagnets with an air core or a non-magnetic core, which are arranged above and below the microbead. In this case, the microbead may be a film-like cylindrical permanent magnet.

The light transmission type device of the non-optical bio-disc according to the present invention may comprise: a laser device which emits a laser beam onto an uncleaved signal element and a cleaved signal element; and a photodetector which detects a differential light transmission signal between the uncleaved signal element and the cleaved signal element. According to specific embodiments of the present invention, at least one photodetector may be arrayed along an outer perimeter region of the bio-disc to correspond to each assay site. A smaller distance between the photodetector and the corresponding assay site offers higher detection sensitivity. Alternatively, at least one set of a laser device and a photodetector is arrayed along an outer perimeter region of the bio-disc to correspond to each assay site. In this case, the analyte-specific signal can be detected from the assay site in a non-scanning manner without need to rotate the bio-disc.

The electrochemical device or the capacitance and impedance measurement device of the non-optical bio-disc according to the present invention may comprise: interdigitated array electrodes on the substrate of the assay site; and a horse radish peroxidase and/or a metal microsphere attached to the end of cleavable signal elements. In this case, the electrochemical device or the capacitance and impedance measurement device using the interdigitated array electrodes may further comprise a multiplexer and/or a frequency generator.

It is preferable that the non-optical bio-disc according to the present invention further comprises a memory or an integrated circuit card storing a protocol of the bio-disc, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, bio-driver software, educational information for patients on clinical assays, a variety of web sites and links enabling a patient to communicate with a doctor or hospital at a remote location based on his/her diagnosis result, or encrypted personal information.

In accordance with another aspect of the present invention, there is provided a bio-disc device comprising; the above-described non-optical bio-disc according to the present invention or an optical bio-disc; a controller disc including a controller which supplies power or a control signal to the bio-disc; and an interfacing zone for connecting the bio disc and the controller disc.

The term "optical bio-disc" used throughout the specification refers to a bio-disc which can be read from a differential reflectance of laser light scanned over it using a general optical pickup.

In the above bio-disc device, the interfacing zone may comprise: a plurality of control signal nodes via which the control signal is supplied; and/or a power node via which power is supplied. Alternatively, the interfacing zone may comprise: grooves formed in the bio-disc and coated with a conductive material; and conductive arms protruding from the controller disc and engaging the grooves.

In specific embodiments of the bio-disc device according to the present invention, power is supplied to the controller disc via frictional contact between brushes connected to an external power supply and an annular electrode plate of the controller disc. The controller disc comprises an integrated circuit in a printed circuit board or in a silicon wafer. Fluid flow in the bio-disc device is induced by the centrifugal

force generated as the bio-disc engaged with the controller disc rotates and by the opening and closing of the valve.

The controller disc may further comprise a non-contact interface selected from among an infrared interface, an optical interface, and a wireless interface to transmit the result of a detection from the assay site by the detector to an external central control system, a storage unit, or an output unit via the non-contact interface.

Alternatively, the bio-disc and the controller disc may be integrated as a single body to form a controller disc-combined bio-disc. In this case, the controller disc-combined bio-disc has a monolithic circuit structure integrated into a silicon wafer via photolithography and etching processes, the monolithic circuit structure including the controller, the integrated circuit card, a non-contact interface, an electrode plate or electromagnet for valve control, various circuit patterns, chambers, and channels. The controller disc-combined bio-disc may be further combined with a general optical disc selected from among an audio CD, a CD-RW, a DVD-RW, a CD, and a DVD to form an optical disc-combined bio-disc.

In accordance with another aspect of the present invention, there is provided a bio-driver apparatus comprising: a controller disc including a controller which outputs a power signal and/or a control signal to control power supply to and the operation of the above-described non-optical bio-disc according to the present invention and/or an optical bio-disc; a motor which drives the controller disc and the bio-disc to rotate; a power supply unit which supplies power to the controller of the controller disc; an interface via which the control signal and/or the power signal are transmitted from the controller to the bio-disc; and a body which supports the bio-driver apparatus.

A bio-driver apparatus according to the present invention may further comprise a detector including a light transmission type device to

detect an analyte-specific signal from the assay site. A bio-driver apparatus according to the present invention may further comprise a non-contact interface via which the result of a detection from the assay site is transmitted to a central control system, a storage unit, or an output unit and via which a command signal from the central control system is transmitted to the controller disc. A bio-driver apparatus according to the present invention may further comprise a central control system and a storage or output unit installed on a printed circuit board connected as a base to the body, the central control system controlling the operation of the motor to rotate the bio-disc and the controller disc and stop their rotation and to push the controller disc and the bio-disc to be closer together so that the controller disc and the bio-disc mechanically and/or electrically combine together via their interfacing zones and rotate together. In this embodiment, the output unit may be a Universal Serial Bus or IEEE1394.

Another bio-disc device according to the present invention comprises: the above-described non-optical bio-disc according to the present invention or an optical bio-disc; a turntable on which the bio-disc or a general optical disc is loaded; and a controller disc including a controller which outputs a power or control signal to control the bio-disc, the controller disc being fixed to the turntable.

In specific embodiments of the above bio-disc device, the controller disc may further comprise an electromagnet which controls the movement of a microbead in the bio-disc. The bio-disc is loaded on the turntable with a gap of 0.1-5 mm, preferably, about 1 mm, from the controller disc fixed to the turntable. The controller disc supplies to the bio-disc the power provided via frictional contact between a rotating annular electrode plate and blushes connected to an external power supply unit. The controller disc comprises an integrated circuit in a printed circuit board or in a silicon wafer. The controller disc may

further comprise a non-contact interface selected from among an infrared interface, an optical interface, and a wireless interface to transmit the result of a detection from the assay site by the detector to an external central control system, a storage unit, or an output unit via the non-contact interface.

Another bio-driver apparatus according to the present invention comprise: a turntable on which the above-described non-optical bio-disc according to the present invention or a general optical disc is loaded; a controller disc fixed to the turntable and including a controller and an electromagnet, the controller controlling power supply to the bio-disc and the opening and closing of the valve installed in the bio-disc; a motor which drives the controller disc and the bio-disc to rotate; a power supply unit which supplies power to the controller of the controller disc; and a body which supports the bio-driver apparatus.

In specific embodiments of the above bio-driver apparatus according to the present invention, the power supply unit supplies a positive voltage via frictional contact between a rotating annular electrode and blushes and a negative voltage via electrical connection with the motor or its shaft, which are grounded, to the controller disc. The bio-driver apparatus may further comprise a detector including a light transmission type device to detect an analyte-specific signal from the assay site. The bio-driver apparatus may further comprise a non-contact interface via which the result of a detection from the assay site is transmitted to a central control system, a storage unit, or an output unit and via which a command signal from the central control system is transmitted to the controller disc. The bio-driver apparatus may further comprise a central control system and a storage or output unit installed on a printed circuit board connected as a base to the body, the central control system controlling the operation of the motor to rotate the bio-disc and the control disc and stop their rotation.

Regarding the bio-driver apparatuses according to the present invention, the general optical disc is selected from among an audio CD, a CD-R, a game CD, and a DVD, and the bio-driver apparatus further comprises an optical pickup to read information from the general optical disc. It is preferable that the controller comprises a bio-disc detection unit determining whether a currently loaded disc is a bio-disc or a general optical disc selected from among an audio CD, a CD-R, a game CD, and a DVD. In this case, the bio-disc detection unit measures a predetermined voltage across some or all resistors arranged in the bio-disc as a bio-disc detection signal and wirelessly transmits the bio-disc detection signal via a non-contact interface to a central control system to inform the central control system that the currently loaded disc is a bio-disc.

Alternatively, the bio-disc may have a groove pattern or a data pattern at a particular area on its surface for the optical pickup to be able to detect whether a currently loaded disc is a bio-disc from the groove pattern or the data pattern of the currently loaded disc and inform a central control system of the result of the detection.

Alternatively, a central control system may determine whether a currently loaded disc is a bio-disc or a general optical disc selected from among an audio CD, a CD-R, a game CD, and a DVD; transmit information read from the general optical disc using the optical pickup to a storage or output unit, transmit to the optical pickup information to be written, or output various read/write control signals if the currently loaded disc is determined to be a general optical disc; and transmit various control signals for the bio-disc via a non-contact interface to the controller if the currently loaded disc is determined to be a bio-disc.

It is preferable that the non-optical bio-disc according to the present invention loaded into the bio-driver apparatus further comprises a memory or an integrated circuit card storing a protocol of the bio-disc,

assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, bio-driver software, educational information for patients on clinical assays, a variety of web sites and links enabling a patient to communicate with a doctor or hospital at a remote location based on his/her diagnosis result, or encrypted personal information.

Regarding the bio-driver apparatuses according to the present invention, a signal indicative of bio-discs may be wirelessly transmitted to a central control system upon loading of a bio-disc, via a non-contact interface or an integrated circuit card of the bio-disc, to inform the central control system of the current loading of the bio-disc into the bio-driver apparatus.

In accordance with another aspect of the present invention, there is provided a PCR bio-disc device for polymerase chain reaction (PCR), comprising: a solid substrate in which channels as fluid flow paths, a chamber as a buffer reservoir, and a hole connecting the channels are integrated; and a valve used to open and close the hole connecting the channels, wherein the chamber comprises: at least one preparation chamber for preparing a DNA sample from blood, cells, or RNA; at least one PCR chamber reserving various enzymes, including a polymerase and a primer, required to amplify the DNA sample through polymerase chain reaction, in a buffer; and a plurality of out-chambers into which PCR products are discharged, the at least one preparation chamber, the at least one PCR chamber, and the plurality of out-chambers being sequentially connected with each other in the solid substrate.

In specific embodiments of the PCR bio-disc device according to the present invention, the plurality of out-chambers have outlets via which the PCR products can be extracted by means of a pipette or a syringe. A ladder marker reservoir, a positive control and negative control reservoir, and a stain reservoir are further integrated into the solid

substrate. The PCR bio-disc device may be combined with an electrophoresis bio-disc. The electrophoresis bio-disc may comprise: gel plates made of agarose gel and/or polyacrylamide gel; and annular electrodes across which a voltage is applied to the gel plates. The PCR bio-disc device may further comprise a UV radiator and a camera to identify, store, and transmit bands appearing on the gel plates.

In accordance with another aspect of the present invention, there is provided a nucleic acid assay method using the above PCR bio-disc device, the method comprising: preparing a DNA sample from blood, cells, or RNA; amplifying the prepared DNA sample through polymerase chain reaction; flowing PCR products into an out-chamber; moving the contents in the out-chamber into the electrophoresis bio-disc; incubating the electrophoresis bio-disc while applying a voltage across its annular electrodes; and identifying, storing, and transmitting bands appearing on the gel plates.

The present invention also provides a nucleic acid assay method using the bio-disc recited in claim 3, the method comprising: preparing a DNA sample from blood, cells, or RNA; amplifying the prepared DNA through polymerase chain reaction (PCR); hybridizing amplified DNA products from the PCR to the assay and diagnostic probe array immobilized on the assay site; and detecting a cleavable signal element remaining in the assay site using the detector including the light transmission type device, the electrochemical device, or the capacitance and impedance measurement device.

In specific embodiments of the above nucleic acid assay methods according to the present invention, preparing the DNA sample comprises: injecting blood via a sample inlet into the preparation chamber; incubating the preparation chamber to allow ferroelectric beads in the preparation chamber to attract DNA extracted through lysis; fixing the ferrroelectric beads and slowly rotating the bio-disc to wash out and

flow the cell debris into the trash chamber; and separating the DNA from the ferroelectric beads or resuspending the DNA in a resuspension buffer.

Amplifying the prepared DNA sample through PCR comprises: slowly rotating the bio-disc to allow the prepared DNA sample to flow into the PCR chamber; and repeating a PCR cycle several times using a heater and a thermosensor installed in the PCR chamber to amplify the DNA sample. The nucleic acid assay methods may further comprise, after amplifying the prepared DNA sample: slowly rotating the bio-disc and allowing a DNAse to flow into the PCR chamber; and heating the PCR chamber to deactivate the DNAse and obtain single-stranded DNA fragments. For the nucleic acid assay method, each PCR chamber may comprise a heater which is controlled independently from the heaters of the other PCR chambers to give single-stranded DNA fragments which vary in lengths.

In accordance with another aspect of the present invention, there is provided an immunoassay method using the bio-disc recited in claim 6, the method comprising: slowly rotating the bio-disc and allowing blood to pass through a filter to extract serum or an antigen; slowly rotating the bio-disc to allow the antigen to enter a conjugate antibody chamber and incubating the conjugate antibody chamber for 1-2 minutes to bind the antigen to conjugate antibodies and form a conjugate-antigen complex; slowly rotating the bio-disc to allow the conjugate-antigen complex to flow into the assay site and incubating the bio-disc in a stationary state to induce an antigen-antibody reaction between the conjugate-antigen complex and the capture antibodies; and rotating the bio-disc to allow a washing buffer to flow into and wash the analyte site.

In the bio-discs according to the present invention, the assay site may comprise an immunoassay sector and a nucleic acid probe assay sector arranged in an angular or radial direction to enable an immunoassay and a nucleic acid probe assay to be performed

concurrently.

The bio-driver apparatuses according to the present invention may send an eject message or a warning message to a user if a bio-disc into which a sample has not be injected yet is loaded.

In the bio-discs according to the present invention, an additional impedance measurement device may be installed in the preparation chamber so as to determine whether a sample has been injected into a bio-disc. In this case, the additional impedance measurement device may comprise interdigitated array electrodes.

The bio-driver apparatuses according to the present invention may continue assay or diagnosis even when an unloading or a stop command is input, and optionally send a warding message or requesting a user's password, and stopping the assay or diagnosis or ejecting the bio-disc if a user enters the correct password.

The bio-driver apparatuses according to the present invention may further comprise a memory storing information on how many times a bio-disc has been used, its validation period, and kinds of diseases which it can diagnose, so as to provide a user with the stored information on the bio-disc or the availability of the bio-disc whenever the bio-disc is loaded.

The bio-driver apparatuses according to the present invention may comprise: a play and search button and a stop button for general optical discs; and a light emitting diode that indicates a bio-disc has been loaded. Alternative indicative means, instead of LEDs, can be used.

The bio-driver apparatuses according to the present invention comprises a liquid crystal display to display the status of progress in sample preparation, PCR, hybridization, and antigen-antibody reaction, which are main processes conducted in the bio-disc, in percentages or as a bar graph.

The bio-driver apparatuses according to the present invention are

connected to a computer monitor to display the status of progress in sample preparation, PCR, hybridization, and antigen-antibody reaction, which are main processes conducted in the bio-disc, in percentages or as a bar or pie graph.

Brief Description of the Drawings

FIGS. 1A and 1B are sectional views of a valve apparatus using microbeads, which is installed in a bio disc according to the present invention;

FIG. 1C illustrates an embodiment of a bio-disc, in which a lab-on-a-chip is integrated, and its controller disc;

FIG. 1D is a sectional view illustrating an exemplary structure of a conductive arm;

FIG. 1E illustrates an exemplary spiral arrangement of grooves which allows spontaneous alignment and insertion of the conductive arm;

FIG. 1F illustrates an embodiment of a bio-driver apparatus according to the present invention in which a controller disc is installed;

FIG. 1G illustrates another example of a bio-disc with a lab-on-a-chip and its controller disc;

FIGS. 1H and 1I illustrate an example of an auxiliary substrate which supplies power to the controller disc via frictional contact between blushes and a rotary electrode shown in FIG. 1G;

FIG. 1J illustrates another embodiment of a bio-driver apparatus according to the present invention in which a controller disc is installed;

FIGS. 2A and 2B illustrate an embodiment of a controller disc-combined bio-disc device and a bio-driver apparatus according to the present invention according to the present invention;

FIG. 2C illustrates an embodiment of an electrochemical device or a capacitance and impedance measurement device using interdigitated array electrodes;

FIG. 2D illustrates an embodiment of an optical disc-combined bio-disc device according to the present invention;

FIG. 3A illustrates an embodiment of how to determine whether a currently loaded disc is a non-optical bio-disc;

FIG. 3B illustrates an embodiment of informing a central control system that a disc currently loaded into a bio-driver apparatus is a bio-disc;

FIGS. 4A through 6D illustrate alternative embodiments of optical assay detectors;

FIGS. 7A through 7G illustrate examples of electrochemical detectors or capacitance and impedance measurement devices;

FIGS. 8A through 8F illustrate embodiments of bio-discs according to the present invention;

FIGS. 9A and 9B illustrate alternative embodiments of bio-discs according to the present invention, in which sample preparation and PCR or further electrophoresis can be conducted in a single disc;

FIGS. 10A and FIG. 10B illustrate embodiments of assay devices according to the present invention that include an immunoassay sector and a nucleic acid probe hybridization sector for simultaneous immunoassays and DNA assays; and

FIGS. 11A and 11B illustrate exemplary appearances of bio-driver apparatuses according to the present invention.

Best mode for carrying out the Invention

The present invention will be described in detail in the following embodiments with reference to the appended drawings.

A bio-disc according to the present invention includes a valve which controls fluid flow or the flow rate in a lab-on-a-chip integrated in the bio-disc. The valve opens or closes a channel formed in the bio-disc using a microbead that is movable by the magnetic force generated by

an electromagnet disposed on the top and/or bottom surface of the bio-disc. International Patent Application No. PCT/KR02/01035 filed 31 May 2002 and its priority Korean Application No. 10-2001-0031284 filed 31 May 2002, which are entitled "Micro valve apparatus using microbead and method for controlling the same", can be referred to for the detailed structure of the valve.

In exemplary embodiments of the bio-disc according to the present invention, the microbead may include, for example, a magnetic ball, ferroelectric particles, paramagnetic particles, diamagnetic particles, a stainless steel ball. Alternatively, the microbead may be made of a solid metal, plastic, or glass bead. When the microbead is made of a plastic or glass bead, the microbead is further coated with a metal. Solid metals for the microbead may be metal alloys. The microbead may be charged. In which case, instead of electromagnets, electrode plates are arranged on the top and bottom surfaces of the bio-disc. The microbead is charged and moved in the direction in which a voltage is applied to the electrode plates, to open or close a hole connecting channels in the lab-on-a-chip. The microbead has a diameter of 1 μm-1 mm, preferably, 100μm-500μm. When the diameter of the microbead is larger, the hole can be opened or plugged with higher reliability due to an increase in the contact area between the hole and the microbead. The microbead may be a spherical permanent magnet or a film-like cylindrical or rectangular permanent magnet. The microbead may be a wound wire having a diameter of, preferably, 0.01-0.1 mm, with an air core or a non-magnetic core.

FIGS. 1A and 1B are sectional views of a bio-disc showing a valve apparatus therein using a permanent magnetic microbead.

As shown in FIGS. 1A and 1B, a bio-disc 100 includes an upper substrate 1, an intermediate substrate 2, and a lower substrate 3. Channels as flow paths, chambers as buffer reservoirs, and holes

connecting the channels are formed in each of the upper, intermediate, and lower substrates 1, 2, and 3 by injection molding. Next, the upper, intermediate, and lower substrates 1, 2, and 3 are bound together to form a body of the bio-disc 100.

FIG. 1A illustrates a state where a hole 10 is plugged by a permanent magnetic microbead 70a to block a channel 16a. FIG. 1B illustrates a state where the permanent magnetic microbead 70a is removed from the hole 10 to interconnect the channel 16a. To plug the hole 10 with the permanent magnetic microbead 70a and block the channel 22, as shown in FIG. 1A, power is applied to upper and lower electromagnets 4a and 5a such as to attract the permanent magnetic microbead 70a downward. In particular, power is supplied to cause repulsion between the upper electromagnet 4a and the permanent magnetic microbead 70a and attraction between the lower electromagnet 4b and the permanent magnetic microbead 70a. In contrast, to open the hole 10 and interconnect the channel 16a, power is applied to the upper and lower electromagnets 4a and 5a such as to attract the permanent magnetic microbead 70a upward. In other words, power is applied to cause attraction between the upper electromagnet 4a and the permanent magnetic microbead 70a and repulsion between the lower electromagnet 5a and the film-like cylindrical permanent magnet 70a.

Preferred examples of the upper and lower electromagnets 4a and 5a include film-like electromagnets with an air core and bobbinless coils. Since the bio-disc 100 according to the present invention includes the channel 16a, which is relatively narrow, as a fluid path, a ventilating hole 12 is formed in the upper substrate 1 to reduce the air pressure and allow a fluid to smoothly flow through the channel 16a.

FIG. 1C illustrates a bio-disc 100 and a controller disc 200 for controlling the bio-disc 100, in which chambers as various assay buffer reservoirs and places for various reactions, channels as flow paths of a

fluid sample and buffers, and valve apparatuses for controlling the opening and closing of the channels are integrated to form a lab-on-a-chip.

Suitable materials for the bio-disc 100 according to the present invention include plastics, polymethylmethacrylate (PMMA), glass, mica, silica, any material for semiconductor wafers, etc. However, among these materials, plastics are most preferred for economical reasons and the convenience of processing. Suitable examples of plastics include polypropylenes, polyacrylates, polyvinyl alcohols, polyethylenes, polymethylmethacrylates, and polycarbonates, with polypropylenes and polycarbonates being preferred and polycarbonates being more preferred.

As described above with reference to FIGS. 1A and 1C, the bio-disc 100 of FIG. 1C includes the upper substrate 1, the intermediate substrate 2, and the lower substrate 3. Channels as flow paths, chambers as buffer reservoirs, and holes connecting the channels are formed in each of the upper, intermediate, and lower substrates 1, 2, and 3 by injection molding. Next, the upper, intermediate, and lower substrates 1, 2, and 3 are bound together to form a body of the bio-disc 100.

International Patent Application No. PCT/KR02/01035 filed 31 May 2002 and its priority Korean Patent Application No. 10-2001-0031284 filed 31 May 2001, which are entitled "Micro valve apparatus using microbead and method for controlling the same," can be referred to for the detailed structure of the valve.

Suitable materials for the controller disc 200 include plastics, PMMA, glass, mica, silica, silicon, materials for printed circuit board (PCB), etc., in which PCB materials and any material for semiconductor wafers are preferred for their easy applicability in designing circuits.

The bio-disc 100 is built of the upper substrate 1, the intermediate

substrate 2, and the lower substrate 3 stacked upon one another. Permanent magnetic microbeads 70a, 70b, and 70c are individually moved up and down by the magnetic force generated by respective upper and lower electromagnet pairs 4a and 5a, 4b and 5b, and 4c and 5c to close and open holes connecting channels. In FIG. 1C, reference numeral 120 denotes a pipette or syringe for sample injection, reference numeral 121 denotes a sample inlet, and reference numeral 170 denotes a disk hole. Reference numeral 171a denotes an interfacing zone for electrical connection with the controller disc 200, which includes a plurality of control signal nodes 173 via which control signals are input to the bio-disc 100, and power nodes 33a for power supply. In practice, the controls signal nodes 173 and the power nodes 33a are formed by coating grooves 33 with conductive materials.

Referring to the enlarged plan view of the bio-disc 100 in FIG. 1C, reference numeral 130 denotes a preparation chamber for preparing a DNA sample directly from blood or cells or from RNA through reverse transcription (RT) or for preparing a serum sample from blood, reference numeral 131 denotes a PCR chamber for polymerase chain reaction (PCR), and reference numeral 132 denotes a chamber for hybridization or antigen-antibody reaction, which is an assay site with capture probes for analyzing and diagnosing amplified DNA products from the PCR or with immuno arrays immobilized thereon. Reference numeral 133 denotes a trash chamber for collecting wastes generated during washing. Reference numeral 140 denotes a chamber for reserving a buffer containing various enzymes, including polymerase, primer, etc., required for PCR, and reference numerals 141, 142, and 143 denote chambers for reserving various enzymes required for hybridization.

Opening and closing of the valve apparatuses at the start and ending points of time of each of the processes (preparation, PCR, hybridization, antigen-antibody reaction, and washing) are controlled by

on/off control of the power supplied to the electromagnet pair 4a and 5a, 4b and 5b, or 4c and 5c arranged above and below each of the permanent magnetic microbeads 70a, 70b, and 70c. Fluid flow in the bio-disc 100 is induced by the centrifugal force generated as it is rotated.

Power is supplied to a controller 63 of the controller disc 200 and a non-contact interface 107 serving as a wireless transmission and/or reception unit, through frictional contact with brushes 108 and 109. An annular electrode plate 223, which frictionally contacts the brushes 108 and 109, is formed on an upper substrate of the controller disc 200. Power and the control signals of the controller 63 are supplied to conductive arms 13 via a circuit pattern integrated in an interfacing zone 171b of the controller disc 200.

Power and the control signals of the controller 63 are transmitted from the controller disc 200 to the bio-disc 100 via a plurality of conductive arms 13 fitted into the control signal nodes 173 and the power nodes 33a, actually the grooves 33 coated with a conductive material. The conductive arms 13 and the grooves 33 act as connectors between the bio-disc 100 and the controller disc 200. When rotation starts, the controller disc 200 is pushed close to the bio-disc 100, the conductive arms 13 of the controller disc 200 engage the grooves 33 of the bio-disc 100, and the controller disc 200 and the bio-disc 100 are rotated together.

The power provided by the blushes 108 and 109 is supplied to the bio-disc 100 via power nodes 33b and the conductive arms 13 of the controller disc 200 and the power nodes 33a of the bio-disc 100. Since the grooves 33 of the bio-disc 100, which engage the conductive arms 13, are electrically connected to the circuit pattern of the bio-disc 100, various control signals and power can be supplied from the controller disc 200 to the bio-disc 100.

In FIG. 1C, reference numeral 188 denotes an integrated circuit

(IC) card storing a protocol of the lab-on-chip, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, and the like. The IC card 188 may include bio-driver software, educational information for patients on clinical assays and may be adapted for users. The IC card 188 may include a variety of web sites and links, for example, a web site enabling a patient to communicate with a doctor or hospital based on his/her diagnosis result, and encrypted personal information to prevent unauthorized user access.

A preferred example of the IC card 188 is a RAM or ROM embedded smart IC card. The information stored in the IC card 188 may be wirelessly transmitted to a central control system to allow for remote analysis and diagnosis and encryption for personal information security.

FIG. 1D is a sectional view illustrating the detailed structure of a conductive arm 13. An end of the conductive arm 13 is fixed to the interfacing zone 171b of the controller disc 200, and the other end of the conductive arm 13 is formed to protrude and be able to smoothly fit into each groove 33 of the bio-disc 100 when the controller disc 200 and the bio-disc 100 are rotated and become closer together. In addition, a spring 13c is installed inside the body of the conductive arm 13. In FIG. 1D, reference numeral 13a denotes the body of the conductive arm 13, whose one end is fixed to the interfacing zone 171b of the controller disc 200, reference numeral 13b denotes the protruding end of the conductive arm 13 that is inserted into the groove 33 of the bio-disc 100, reference numeral 13d denotes a support plate which elastically supports the spring 13c and links the protruding end 13b to the body 13a of the conductive arm.

FIG. 1E illustrates an exemplary spiral arrangement of grooves 33 in the bio-disc 100 that allows spontaneous insertion of the conductive

arm 13 protruding from the interfacing zone 171b of the controller disc 200 into each groove 33 upon rotation. When the bio-disc 100 continues to rotate and becomes closer to the controller disc 200, the conductive arm 12 fit into and is electrically connected to each groove 33.

In FIG. 1E, reference numeral 170 denotes a disc hole of the bio-disc 100. As is apparent in FIG. 1E, control signal nodes 173 and power nodes 33a, which are formed by coating the grooves 33 with conductive materials, are arranged around the disc hole 170. A circuit pattern 888 electrically connecting each groove 33 to a corresponding part, chamber or channel, of the bio-disc 100 to supply power or a control signal to that corresponding part is shown.

FIG. 1F illustrates an embodiment of a bio-driver apparatus according to the present invention, which includes the controller disc 200 for controlling the operation of the bio-disc 100.

The bio-driver apparatus of FIG. 1F includes a power supply unit 110 for supplying power to the controller 63 of the controller disc 200 via the blushes 108 and 109. Reference numeral 300 denotes a body of the bio-driver apparatus. A printed circuit board (PCB) 140 is connected to the body 300 of the bio-driver apparatus as a base. A central control system 101 for controlling the bio-driver apparatus and a storage or output unit 111 are arranged on the PCB 140.

The central control system 101 controls a motor 102 to rotate the bio-disc 100 and the controller disc 200 or stop their rotation, and in particular, to push the controller disc 200 and the bio-disc 100 to be closer together such that the conductive arms 13 of the controller disc 200 spontaneously fit into the grooves 33 of the bio-disc 100. The central control system 101 also controls the movement of an optical pickup 103. The bio-driver apparatus includes a lower rotor 105 which rotates in contact with the bottom of the bio-disc 100 and an upper rotor

104 which rotates above the controller disc 200. The upper rotor 104 has a plurality of connectors 143 extending to the controller disc 200 and a grooved circumference 111 ensuring free spinning without contacting the body 300 of the bio driver apparatus.

The central control system 101 determines whether a disc currently loaded into the bio-driver apparatus is a general optical disc, for example, an audio CD, a CD-R, a game CD, or a DVD, or a non-optical bio-disc. If the currently loaded disc is determined to be a general optical disc, the central control system 101 transmits information read from the optical disc using the optical pickup 103 to the storage or output unit 111 or transmits information to be written to the optical pickup 103 and controls the operation of the optical disc using read/write control signals. If the currently loaded disc is determined to be a bio-disc, the central control system 101 sends various control signals for controlling a lab-on-a-chip of the bio-disc to the controller 63 of the controller disc 200 via non-contact interfaces 106 and 107 or the IC card 188 of the bio-disc 100.

The controller 63 of the controller disc 200 transmits the received control signals via the conductive arms 13 or the IC card 188 to the bio-disc 100.

The controller 63 transmits the result of a detection from the array chamber (assay site) 132 of the bio-disc 100 by a detector including an optical device, a non-optical device, an electrochemical device, or a capacitance and impedance measurement device, via the conductive arms 13 and the non-contact interfaces 106 and 107, which may be implemented with an infrared interface, optical interface, or wireless interface, to the central control system 101 or the storage or output unit 111. Alternatively, the controller 36 transmits the result of a detection from the array chamber (assay site) 132 of the bio-disc 100 by a detector including an optical device, a non-optical device, an electrochemical

device, or a capacitance and impedance measurement device, via the IC card 188 and a wireless transmission/reception unit (not shown), to the central control system 101 or the storage or output unit 111.

The detector including such a transmission type device and used to detect information from the array chamber (assay site) 132 is discriminated from the optical pickup 103. In practice, the detector is implemented with dedicated optical assay detectors 99a and 99b. In other words, the optical pickup 103 is used to read information from a general optical disc, whereas the optical assay detectors 99a and 99b are used to detect information from the assay site 132 of the non-optical bio-disc 100. In practice, the non-contact interfaces 106 and 107 are reception and/or transmission units for non-contact interfacing. The central control system 101 may transmit control commands via the non-contact interfaces 106 and 107 to the controller 63.

The non-contact interfaces 106 and 107 may be implemented with infrared sensors for infrared interfacing, photosensors for optical interfacing, or combinations of a stripe antenna and a modulator/demodulator for wireless interfacing.

As described above, the memory embedded IC card 188 of the bio-disc 100 stores a protocol of the lab-on-chip, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, and the like. The IC card 188 may include bio-driver software, educational information for patients on clinical assays and may be adapted for users. The IC card 188 may include a variety of web sites and links, for example, a web site enabling a patient to communicate with a doctor or hospital based on his/her diagnosis result, and encrypted personal information to prevent unauthorized user assess.

A preferred example of the IC card 188 is a RAM or ROM embedded smart IC card. The information stored in the IC card 188

may be wirelessly transmitted to the central control system 101 to allow for remote analysis and diagnosis and encryption for personal information security.

A preferred example of the output unit 111 is a Universal Serial Bus (USB) or IEEE1394.

FIG. 1G illustrates another example of the bio-disc 100 and the controller disc 200 for controlling the bio-disc 100, in which chambers as various assay buffer reservoirs and places for various reactions, channels as flow paths of a fluid sample and buffers, and valve apparatuses for controlling the opening and closing of the channels are integrated to form a lab-on-a-chip.

The bio-disc 100 is built of the upper substrate 1, the intermediate substrate 2, and the lower substrate 3 stacked upon one another. Permanent magnetic microbeads 70a, 70b, and 70c are individually moved up and down by the magnetic force generated by respective electromagnets 4a, 4b, and 4c to close and open holes connecting channels. In FIG. 1G, reference numeral 120 denotes a pipette or syringe for sample injection, reference numeral 121 denotes a sample inlet, and reference numeral 170 denotes a disk hole. Reference numeral 130 denotes a preparation chamber for preparing a DNA sample directly from blood or cells or from RNA through reverse transcription (RT) or for preparing a serum sample from blood, reference numeral 131 denotes a PCR chamber for polymerase chain reaction (PCR), and reference numeral 132 denotes a chamber for hybridization or antigen-antibody reaction, which is an assay site with capture probes for analyzing and diagnosing amplified DNA products from the PCR or with immuno arrays immobilized thereon. Reference numeral 133 denotes a trash chamber for collecting wastes generated during washing. Reference numeral 140 denotes a chamber for reserving a buffer containing various enzymes, including polymerase, primer, etc., required

for PCR, and reference numerals 141, 142, and 143 denote chambers for reserving various enzymes required for hybridization.

Opening and closing of the valve apparatuses at the start and ending points of time of each of the processes (preparation, PCR, hybridization, antigen-antibody reaction, and washing) are controlled by on/off control of the power supplied to the electromagnet 4a, 4b, or 4c arranged above and below each of the permanent magnetic microbeads 70a, 70b, and 70c. Fluid flow in the bio-disc 100 is induced by the centrifugal force generated as it is rotated.

In FIG. 1G, reference numeral 55 denotes a rotary electrode coated with a conductive material and fixed to the motor 102. Reference numeral 110 denotes a power supply unit which supplies a direct current (DC) voltage and has a grounded negative port connected to the motor 102 and a positive port connected via blushes 108 and 109 to the rotary electrode 55 and supplies a positive voltage to the rotary electrode 55.

A positive voltage is supplied to the controller 63 and the wireless transmission and/or reception unit 107 of the controller disc 200 by frictional contact between the rotary electrode 55 and the brushes 108 and 109, whereas a negative voltage is supplied to the controller disc 200 via a motor shaft 57 connected to the motor 102 and an auxiliary substrate 201. Reference numerals 240 and 241 denote positive and negative power ports, respectively.

Reference numeral 181 denotes a turntable on which the bio-disc 100 or a general optical disc, such as an audio CD, a CD-R, a game CD, or a DVD, is loaded and which engages the disc hole 170 of the bio-disc 100 or a general optical disc. In FIG. 1G, the controller disc 200 is fixed to the turntable 181, and the bio-disc 100 is loaded on the turntable 181 with a gap of about 1 mm from the controller disc 200.

As described above, the memory embedded IC card 188 of the

bio-disc 100 stores a protocol of the lab-on-chip, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, and the like. The IC card 188 may include bio-driver software, educational information for patients on clinical assays and may be adapted for users. The IC card 188 may include a variety of web sites and links, for example, a web site enabling a patient to communicate with a doctor or hospital based on his/her diagnosis result, and encrypted personal information to prevent unauthorized user assess.

A preferred example of the IC card 188 is a RAM or ROM embedded smart IC card. The information stored in the IC card 188 may be wirelessly transmitted to the central control system 101 to allow for remote analysis and diagnosis and encryption for personal information security.

Power nodes 240a and 241a of the bio-disc 100 are coated with a conductive material and are coupled with the respective power ports 240 and 241 of the controller disc 200, so that power is supplied to the bio-disc 100 from the controller disc 200.

FIGS. 1H and 1I illustrate an example of the auxiliary substrate 201 which supplies the power generated by frictional contact between the blushes 108 and 109 and the rotary electrode 55, shown in FIG. 1G, to the controller disc 200. A preferred auxiliary substrate is a double-sided PCB. Exemplary upper and lower surfaces of the auxiliary substrate 201 are shown in FIGS. 1H and 1I, respectively. Reference numeral 91 denotes a grounded pattern, and reference numeral 92 denotes a positive voltage pattern.

Referring to FIG. 1H, the motor 102 is grounded, and the motor shaft 57 connected to the motor 102 is also grounded. Accordingly, as the motor shaft 57 is inserted into a through (via) hole 203 of the auxiliary substrate 201, the grounded pattern 91 takes on a negative voltage.

Referring to FIG. 1I, a positive voltage supplied from the power supply unit 110 is transmitted to the rotary electrode 55 via the blushes 108 and 109, which frictionally contact the rotary electrode 55. In addition, since the rotary electrode 55 contacts the lower surface of the auxiliary substrate 201, the positive voltage supplied to the rotary electrode 55 is transmitted via the positive voltage pattern 92 formed on the lower substrate of the auxiliary substrate 201. In other words, a positive voltage and a negative voltage are supplied via the positive voltage pattern 92 and the grounded pattern 91, respectively, of the auxiliary substrate 201 to the controller disc 200.

FIG. 1J illustrates an embodiment of a bio-driver apparatus assembled from the bio-disc 100 and the controller disc 200 of FIG. 1G, in which the controller disc 200 is fixed to the turntable 181.

Positive and negative voltages are supplied to the bio-disc 100 via the conductive arms 13, as shown in FIG. 1D, of the controller disc 200. The conductive arms 13 are comprised of the positive and negative power ports 240 and 241 and fit into the power nodes 240a and 241a, which are formed by coating with a conductive material, of the bio-disc 100 when the bio-disc 100 is loaded.

The bio-driver apparatus of FIG. 1J includes a power supply unit 110 for supplying power to the controller 63 of the controller disc 200 via the blushes 108 and 109. Reference numeral 300 denotes a body of the bio-driver apparatus. A printed circuit board (PCB) 140 is connected to the body 300 of the bio-driver apparatus as a base. A central control system 101 for controlling the bio-driver apparatus and a storage or output unit 111 are arranged on the PCB 140. The central control system 101 controls a motor 102 to rotate the bio-disc 100 and the controller disc 200 or stop their rotation and controls the movement of an optical pickup 103.

The central control system 101 determines whether a disc

currently loaded into the bio-driver apparatus is a general optical disc, for example, an audio CD, a CD-R, a game CD, or a DVD, or a non-optical bio-disc. If the currently loaded disc is determined to be a general optical disc, the central control system 101 transmits information read from the optical disc using the optical pickup 103 to the storage or output unit 111 or transmits information to be written to the optical pickup 103 and controls the operation of the optical disc using read/write control signals. If the currently loaded disc is determined to be a bio-disc, the central control system 101 sends various control signals for controlling the lab-on-a-chip of the bio-disc to the controller 63 of the controller disc 200 via non-contact interfaces 106 and 107 or the IC card 188 of the bio-disc 100.

The controller 63 of the controller disc 200 transmits the received control signals to the bio-disc 100 and controls the opening and closing of the valve apparatuses by on/off control of the power supplied to the electromagnet 4a, 4b, or 4c arranged on the controller disc 200. The electromagnet 4a, 4b, and 4c of the controller disc 200 is arranged so close to the bio-disc 100 that the repulsive or attractive force of the permanent magnetic microbeads 70a, 70b, and 70c reaches the electromagnet 4a, 4b, and 4c. The controller disc 200 fixed to the turntable 181 has a gap 182 of about 1 mm from the bio-disc 100 loaded on the turntable 181.

As described above, the non-contact interfaces 106 and 107 are reception and/or transmission units for non-contact interfacing.

The controller 63 transmits the result of a detection from the array chamber (assay site) 132 of the bio-disc 100 by a detector including an optical device, a non-optical device, an electrochemical device, or a capacitance and impedance measurement device, via the non-contact interfaces 106 and 107, which may be implemented with an infrared interface, optical interface, or wireless interface, to the central control

system 101 or the storage or output unit 111. Alternatively, the controller 36 transmits the result of a detection from the array chamber (assay site) 132 of the bio-disc 100 by a detector including an optical device, a non-optical device, an electrochemical device, or a capacitance and impedance measurement device, via the IC card 188 and a wireless transmission/reception unit (not shown), to the central control system 101 or the storage or output unit 111.

FIGS. 2A and 2B illustrate an example of a controller disc-combined bio-disc device 700 in which the controller disc 200 and the bio-disc 100 as described above are integrated as a single body. In FIGS. 2A and 2B, reference numeral 700a denotes a bio-disc portion, and reference numeral 700b denotes a controller disc portion. Any material for semiconductor wafers is preferable for the controller disc-combined bio-disc device 700. A common silicon wafer is suitable to highly integrate a monolithic structure including, for example, the controller 63, the IC card 188, the non-contact interface 107, the electrode plates or electromagnets for valve control, and electronic circuit patterns, and is highly compatible with common photolithography and etching techniques applied to form chambers and channels of the bio-disc according to the present invention. Integrating circuits into a wafer using semiconductor manufacturing processes, and photolithography and etching processes are well known to one of skill in the art.

The bio-disc portion 700a is built of an upper substrate 1, an intermediate substrate 2, and a lower substrate 3. Channels as fluid flow paths, chambers 130, 131, 132, 133, 140, 141, 142, and 143 as buffer reservoirs, and holes connecting the channels are formed in the upper, intermediate, and lower substrates 1, 2, and 3 using photolithography and etching processes. The blushes 108 and 109 for power supply and an annular electrode plate 223, which frictionally

contacts the blushes 108 and 109, are formed in the controller disc portion 700b of the controller disc-combined bio-disc device 700. Interfacing zones 171a and 171b include a plurality of control signal nodes 173 via which the controller 63 of the controller disc portion 700b provides control signals to valve apparatuses and electronic circuits of the bio-disc portion 700a and power nodes 33a and 33b for power supply. The control signal nodes 173 and the power nodes 33a and 33b are formed as via or through holes and are interconnected with one another in the interfacing zones 171 and 171b. Although the interfacing zones 171a and 171b are illustrated as being around the disc hole, they may be formed at any position on the disc as far as they are interconnected with one another, for example, as via or through holes. How to form via or through holes are well known to one of skill in the art.

Reference numeral 555 denotes an optional opening filled with a transparent material, for example, glass, to enable a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device to detect the assay site 132.

FIG. 2B illustrates an example of a bio-driver apparatus for driving the controller disc-combined bio-disc device 700. The controller 63 transmits the result of a detection from the array chamber (assay site) 132 of the controller disc-combined bio-disc device 700 by a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device, via the non-contact interfaces 106 and 107, which may be implemented with an infrared interface, optical interface, or wireless interface, to the central control system 101 or the storage or output unit 111. Alternatively, the controller 36 transmits the result of a detection from the array chamber (assay site) 132 of the controller disc-combined bio-disc device 700 by a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device, via the IC card 188 and a wireless

transmission/reception unit (not shown), to the central control system 101 or the storage or output unit 111.

As described above, the non-contact interfaces 106 and 107 are reception and/or transmission units for non-contact interfacing. The central control system 101 may transmit control commands via the non-contact interfaces 106 and 107 or the IC card 188 to the controller 63.

The non-contact interfaces 106 and 107 may be implemented with infrared sensors for infrared interfacing, photosensors for optical interfacing, or combinations of a stripe antenna and a modulator/demodulator for wireless interfacing.

The bio-driver apparatus of FIG. 2B includes a power supply unit 110 for supplying power to the controller 63 of the controller disc-combined bio-disc device 700 via the blushes 108 and 109. Reference numeral 300 denotes a body of the bio-driver apparatus. A printed circuit board (PCB) 140 is connected to the body 300 of the bio-driver apparatus as a base. A central control system 101 for controlling the bio-driver apparatus and a storage or output unit 111 are arranged on the PCB 140.

The central control system 101 controls a motor 102 to rotate the controller disc-combined bio-disc device 700 or stop its rotation and controls the movement of an optical pickup 103. The central control system 101 controls an upper rotor 104 and a lower rotor (turntable) 105 to become closer to the disc hole 170 of the controller disc-combined bio-disc device 700 when the controller disc-combined bio-disc device 700 starts to rotate.

The central control system 101 determines whether a disc currently loaded into the bio-driver apparatus is a general optical disc, for example, an audio CD, a CD-R, a game CD, or a DVD, or a combined bio-disc. If the currently loaded disc is determined to be a general optical

disc, the central control system 101 transmits information read from the optical disc using the optical pickup 103 to the storage or output unit 111 or transmits information to be written to the optical pickup 103 and controls the operation of the optical disc using read/write control signals. If the currently loaded disc is determined to be a combined bio-disc, the central control system 101 sends various control signals for controlling the lab-on-a-chip of the controller disc-combined bio-disc device 700 to the controller 63 via the non-contact interfaces 106 and 107 or the IC card 188 of the controller disc-combined bio-disc device 700. A detector for detecting the assay site 132 of the controller disc-combined bio-disc device 700, which may include an optical device, is discriminated from the optical pickup 103 used to read information from a general optical disc and may be implemented, for example, with dedicated optical assay detectors 99a and 99b. In other words, the optical pickup 103 is used to read information from a general optical disc, whereas the optical assay detectors 99a and 99b are used to detect information from the assay site 132 of the non-optical, controller disc-combined bio-disc device 700. For example, the optical assay detectors 99a and 99b may be implemented as electrochemical detectors or capacitance and impedance measurement devices.

As described above, the IC card 188 of the controller disc-combined bio-disc device 700 stores a protocol of the lab-on-a-chip, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, and the like. The IC card 188 may include bio-driver software, educational information for patients on clinical assays and may be adapted for users. The IC card 188 may include a variety of web sites and links, for example, a web site enabling a patient to communicate with a doctor or hospital based on his/her diagnosis result, and encrypted personal information to prevent unauthorized user assess.

A preferred example of the IC card 188 is a RAM or ROM embedded IC card. The information stored in the IC card 188 may be wirelessly transmitted to the central control system 101 to allow for remote analysis and diagnosis and encryption for personal information security.

FIG. 2C illustrates an embodiment of a detector used in the controller disc-combined bio-disc device 700 to detect analyte signals from the analyte site 312, the detector being implemented with an electrochemical device or a capacitance and impedance measurement device which use interdigitated array electrodes. International Patent Application No. PCT/KR02/00126 filed 27 January 2002 and its priority Korean Patent Application No. 10-2001-0003956 filed 27 January 2001, which are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or single strand of nucleic acids or oligonucleotides", can be referred to for the detailed structure of this type of detector.

In FIG. 2C, reference numerals 371, 372, 373, and 374 denote individual analyte sites on which cleavable signal elements or capture antibodies specific to analytes are immobilized and which are arrayed in the array chamber 132. Reference numeral 271 denotes a frequency generator which applies an alternating current (AC) with a given bandwidth to the individual analyte sites. AC signals detected from the individual analyte sites are input to input ports of the interdigitated array electrodes to measure their frequency response characteristics and measure the electrochemical properties or the capacitance and impedance of the analyte sites based on the frequency response characteristics.

In particular, the frequency response characteristics of the analyte sites are provided to the controller 63 via a multiplexer 68, and the controller 63 measures the electrochemical properties or the capacitance

and impedance of the analyte sites. The multiplexer 68 is controlled by the controller 63, as indicated by reference numeral 64 in FIG. 2C.

The electrochemical device or the capacitance and impedance measurement device of FIG. 2C is integrated into the controller disc-combined bio-disc device 700 together with the controller 63.

The electrochemical device or the capacitance and impedance measurement device of FIG. 2C, which serve as a detector with interdigitated array electrodes, can also be applied to such a bio-disc device as illustrated in FIGS. 1C and 1G. In this case, the multiplexer 68 and the frequency generator 271 can be arranged in the bio-disc 100 and integrated with the IC card 188.

FIG. 2D illustrates an example of an optical disc-combined bio-disc device 1000 assembled from a general optical disc 900 and the controller disc-combined bio-disc device 700. The optical disc 900 of the optical disc-combined bio-disc device 1000 stores assay interpretive algorithms, bioinformatics information, self-diagnostics, and the like. The optical disc 900 may include software enabling remote assay information storage, bio-driver software, and educational information for patients on clinical assays and may be adapted for users. The optical disc 900 may include a variety of web sites and links, for example, a web site enabling a patient to communicate with a doctor or hospital based on his/her diagnosis result. The optical disc 900 may store various contents from, for example, audio CDs, game CDs, CD-Rs, DVDs, etc.

The optical pickup 103 is used to read information from the optical disc 900, whereas a dedicated assay detector including a transmissional optical device, an electrochemical device, or a capacitance and impedance measurement device is used to detect information from the assay site 132 of the controller disc-combined bio-disc device 700. The optical disc 900 may be a recordable empty CD or DVD, such as CD-RW or DVD-RW.

In the optical disc-combined bio-disc device 1000, the optical disc 900 and the controller disc-combined bio-disc device 700 can be read concurrently or at differing points in time by the optical pickup 103 and the dedicated assay detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device, respectively.

FIG. 3A illustrates an embodiment of how the controller 63 of the bio-driver apparatus of FIGS. 1F and 1J determines whether a currently loaded disc is a general optical disc, such as an audio CD, a CD-R, a game CD, a DVD, etc., or a non-optical bio-disc 100.

The controller 63 of the controller disc 200 measures a predetermined voltage across one or both of resistors R1 and R2 arranged in the bio-disc 100 as a bio-disc detection signal, via the conductive arms 13 and the grooves 33, and determines a currently loaded disc to be a bio-disc. In contrast, a general optical disc does not include resistors R1 and R2, and no voltage is generated from the general optical disc. Next, the controller 63 wirelessly transmits the bio-disc detection signal to the central control system 101 via the non-contact interfaces 106 and 107 or the IC card 188 to inform the central control system 101 that the currently loaded disc is a bio-disc.

The controller 36 operates in a normal mode when a general optical disc is loaded. However, when a bio-disc 100 is loaded, the controller 63 transmits various control signals for controlling its lab-on-a-chip to the bio-disc 100.

FIG. 3B illustrates an embodiment of informing the central control system 101 that a disc currently loaded into a bio-driver apparatus is a bio-disc, which can be any one of the bio-disc 100, the controller disc-combined bio-disc device 700, and the optical disc-combined bio-disc 100.

When a bio-disc is loaded and the controller 63 is turned on, the

bio-disc wirelessly transmits a signal indicative of bio-discs to the central control system 101 via the non-contact interfaces 106 and 107 or the IC card 188. In contrast, since a general optical disc does not include such a controller 63, no signal is transmitted to the central control system 101.

Alternatively, the bio-disc 100, the controller disc-combined bio-disc device 700, and the optical disc-combined bio-disc 100 may have a groove pattern or data pattern at a particular area on their surface to enable a bio-disc driver to determine whether or not a currently loaded disc is a bio-disc from the groove pattern or data pattern and inform the central control system 100 of the loading of the bio-disc. In which case, the groove pattern or data pattern formed at a particular area on the surface of a disc is detected by the optical pickup 103. In this way, a determination as to whether a disc currently loaded into a bio-driver is a general optical disc, such as an audio CD, a CD-R, a game CD, a DVD, etc., or a bio-disc, such as the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device, can be made.

A user may selectively load the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000 that is appropriate for his/her assay or diagnostic purpose into a bio-driver.

FIGS. 4A through 6D illustrate various embodiments of the optical assay detectors 99a and 99b used to detect analyte-specific signals from the assay site 132 of a bio-disc according to the present invention.

FIG. 4A illustrates an embodiment of the optical assay detectors which detect analyte-specific signals from the assay site 132 using light transmission through metal microspheres. This light transmission method differs from conventional detection methods applied to general optical discs which are based on differential light reflection from indentation and flat areas formed on the surface of the disc, for example,

a CD, due to its physical pits.

The left sectional view of FIG. 4A shows a state where numerous cleavable signal elements 557 are immobilized on the surface of an upper substrate 1 of the bio-disc 100, and the right sectional view of FIG. 4A shows a state where only a few cleavable signal elements 557 remain on the upper substrate 1 after cleavage reaction.

For the detailed information on the cleavable signal elements 557, International Patent Application No. PCT/KR02/00126 filed 27 January 2002 and its Korean Patent Application No. 10-2001-0003956 filed 27 January 2001, which are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or single strand of nucleic acids or oligonucleotides", can be referred to.

In the embodiment of FIG. 4A, the optical assay detectors 99 and 99b are implemented with a laser device, which emits a laser beam onto the cleavable signal elements 557, and a photodetector, which detects a differential light transmission signal.

FIG. 4B illustrates another embodiment of the optical assay detectors which detect analyte-specific signals from the assay site 132 using light transmission through metal microspheres.

The left sectional view of FIG. 4B shows a state where numerous cleavable signal elements 557 are immobilized on the surface of the upper substrate 1 of the bio-disc 100, and the right sectional view of FIG. 4B shows a state where only a few cleavable signal elements 557 remain on the upper substrate 1 after cleavage reaction.

In the embodiment of FIG. 4B, the optical array detectors 99a and 99b are implemented with a laser device, which emits a laser beam onto the cleavable signal elements 557, and a photodetector, which detects a differential light transmission signal. Unlike the embodiment of FIG. 4A, a transparent opening 555 is further formed for higher sensitivity of the

photodetector 99b.

FIG. 5A illustrates a modification of the optical array detectors of FIG. 4B based on light transmission, in which the photodetector 99b is integrated into the upper substrate 1. In this embodiment, a plurality of photodetectors 99b are arrayed one-to-one corresponding to a plurality of assay sites. This arrangement of the plurality of photodetectors 99b is distinguished from a modular light transmission and reception unit used in the general optical pickup 103, the modular light transmission and reception unit causing a low sensitivity problem at a receiving site due to its longer reflection path.

FIG. 5B illustrates an embodiment of a bio-disc with a plurality of photodetectors 99b arrayed along its outer perimeter region. As the bio-disc is rotated, individual analyte sites in the bio-disc are sequentially detected by the corresponding photodetectors 99b.

FIG. 6A illustrates another embodiment of a detector for detecting analyte sites using light transmission, in which both the laser device 99a and the photodetector 99b are integrated into a lower substrate 3. FIG. 6C illustrate still another embodiment of a detector for detecting analytes sites using light transmission, in which the laser device 99a is integrated into the lower substrate 3, whereas the photodetector 99b is integrated into the upper substrate 1. In either case, the laser device 99a and the photodetector 99b may be arrayed one-to-one corresponding to a plurality of assay sites for higher detection sensitivity.

The left sectional views of FIGS. 6A and 6C show a state where numerous cleavable signal elements 557 are immobilized on the surface of the upper substrate 1 of the bio-disc 100, and the right sectional views of FIG. 6A and 6C show a state where only a few cleavable signal elements 557 remain on the upper substrate 1 after cleavage reaction.

FIG. 6B illustrates an example of an array structure of the detector of FIG. 6A, in which the laser device 99a and the photodetector 99b are

alternately arrayed along an outer perimeter region of the bio-disc 100. FIG. 6D illustrates an example of an array structure of the detector of FIG. 6C, in which the laser device 99a and the photodetector 99b, which face each other, are arrayed along an outer perimeter region of the bio-disc 100. As in the embodiments of FIGS. 6B and 6D, an optical assay detector may include a combination of a laser device and a photodetector for each assay.

Alternatively, an optical assay detector for detecting assay sites of a bio-disc may be configured, based on the arrangement of FIG. 6B, such that at least two sets of a laser device and a photodetector are integrated for each assay site for higher detection sensitivity.

The optical array detectors of FIGS. 6A through 6D, which detect assay sites using light transmission, allow for concurrent detections of assay sites 312 as well as direct detection without need to rotate the bio-disc. In other words, non-scanning detection of assay results using light transmission can be obtained with the structures of FIGS. 6A through 6D. This assay detection method requires neither rotating the bio-disc to allow an optical pickup to access to individual assay sites nor predetermined site location information therefor, unlike laser scanning detection methods which use an optical pickup to read information from general optical discs.

FIGS. 7A through 7G illustrate examples of electrochemical detectors or capacitance and impedance measurement devices for detecting analyte-specific signals from the assay site 132 of the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000. Some of the electrochemical detectors or capacitance impedance measurement devices illustrated in FIGS. 7A through 7G are implemented with interdigitated array electrodes 702 and 703 arranged on a substrate 701 and a metal microsphere 40 or horse radish peroxidase (HRP) 41 attached as signal

responsive moiety to each cleavable signal element immobilized as a probe on the substrate 701. Some of the electrochemical detectors or capacitance impedance measurement devices illustrated in FIGS. 7A through 7G are based on antigen-antibody reaction mainly used for immunochromatography.

FIG. 7A illustrates an example of an electrochemical detector or a capacitance and impedance measurement device with interdigitated array electrodes 702 and 703.

The controller 63 applies an AC signal having a given bandwidth to two input ports 704 and 705 of the respective interdigitated array electrodes 702 and 703 to measure the frequency response characteristics of assay sites and then the capacitance and impedance of the assay sites from the frequency response characteristics. Alternatively, the controller 63 may be able to measure a voltage or a current induced as a result of the reduction/oxidation (REDOX) of analytes by HRP in H_2O_2 solution, thereby enabling electrochemical detection of assay sites. For the detailed structure of such a capacitance and impedance measurement device using interdigitated array electrodes, International Patent Application No. PCT/KR02/00126 filed 27 January 2002 and its priority Korean Patent Application No. 10-2001-0003956 filed 27 January 2001, which are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or single strand of nucleic acids or oligonucleotides," can be referred to.

FIGS. 7B and 7C illustrate an example of an electrochemical detector or a capacitance and impedance measurement device for detecting analyte-specific signals from the assay site 132 of the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000. The electrochemical detector or the capacitance and impedance measurement device of FIGS. 7B and

7C is implemented with the interdigitated array electrodes 702 and 703 arranged on the substrate 701 and HRP 41 attached as signal responsive moiety to each cleavable signal element immobilized as a probe on the substrate 701. Electrons are generated as a result of successive REDOX reactions by the HRP 41 and induce a current and a voltage across the interdigitated array electrodes 702 and 703.

The sensitivity of the interdigitated array electrodes 702 and 703 becomes higher with more digits.

The assay site 132 of the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000 is manufactured by aminating the surface of the substrate 701, forming a non-reactive monolayer, for example, of alkane chains $(CH_2)_n$ on the aminated surface of the substrate 701, and immobilizing cleavable signal elements labeled with biotin 50, wherein the non-reactive layer is for preventing direct contact of the cleavable signal elements with the substrate 701.

After sample injection, cleavable signal elements which are not hybridized with a sample remain as single strands are cleaved by a nuclease and removed through washing. Meanwhile, cleavable signal elements which are hybridized with the sample and form double strands 43 remain uncleaved after the cleavage and washing processes. Next, streptavidin-labeled HRP is injected to bind the streptavidin 51 to the biotin labeled to the uncleaved signal elements.

Next, a series of REDOX reactions of the uncleaved signal elements are caused by the HRP in H_2O_2 solution to induce a voltage and a current across the interdigitated array electrodes 701 and 703. The controller 63 measures the voltage and the current across the interdigitated array electrodes 701 and 703. In this way, a differential electrochemical signal between the cleaved and uncleaved signal elements can be detected.

The left sectional view of FIG. 7C shows a state where cleavable signal elements remain uncleaved on the bio-disc 100, 700, or 1000, so that the uncleaved signal elements are highly likely to be oxidized and reduced by the HRP in H_2O_2 solution. The right sectional view of FIG. 7C shows a state where most cleavable signal elements are cleaved and removed through washing so that REDOX reaction is unlikely to occur. A differential electrochemical signal between the two states is detected.

FIGS. 7D and 7E illustrate another example of an electrochemical detector or a capacitance and impedance measurement device for detecting analyte-specific signals from the assay site 132 of the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000. The electrochemical detector or the capacitance and impedance measurement device of FIGS. 7D and 7E is implemented with the interdigitated array electrodes 702 and 703 arranged on the substrate 701 and HRP 41 and metal microspheres 40 attached as signal responsive moiety to cleavable signal elements immobilized as probes on the substrate 701. Electrons are generated as a result of successive REDOX reactions by the HRP 41, contact the metal microspheres 40, and induce a current and a voltage across the interdigitated array electrodes 702 and 703. The sensitivity of the detector is determined by the ratio of HRP-labeled probes and metal microsphere-labeled probes. More metal microspheres, which act as a carrier of electrons generated from a series of REDOX reactions by the HRP, lead to higher detection sensitivity.

After sample injection into the assay site 132 in which biotin-labeled cleavable signal elements are immobilized, cleavable signal elements which are not hybridized with a sample remain as single strands are cleaved by a nuclease and removed through washing. Meanwhile, cleavable signal elements which are hybridized with the sample and form double strands 43 remain uncleaved after the cleavage

and washing processes. Next, streptavidin-labeled HRP and streptavidin-labeled metal microspheres 40 are provided to bind the streptavidin 51 to the biotin labeled to the uncleaved signal elements.

Next, a series of REDOX reactions of the uncleaved signal elements are caused by the HRP in H_2O_2 solution to induce a voltage and a current across the interdigitated array electrodes 701 and 703. The controller 63 measures the voltage and the current across the interdigitated array electrodes 701 and 703. In this way, a differential electrochemical signal between the cleaved and uncleaved signal elements can be detected.

FIG. 7D illustrates the concept of REDOX reactions induced by the HRP. In FIG. 7D, the biotin 50 labeled to the end of the uncleaved signal elements prior to the hybridization and the HRP 41 and the metal microsphere 40 which are labeled with the streptavidin 51 appear. The coupling of the streptavidin 51 of the HRP 41 and the metal microsphere 40 to the biotin 50 at the ends of the uncleaved signal elements, which is formed through simple contact, also appear.

The left sectional view of FIG. 7E shows a state where cleavable signal elements remain uncleaved on the bio-disc 100, 700, or 1000, so that the uncleaved signal elements are labeled with the HRP 41 and the metal microsphere 40 and are highly likely to be oxidized and reduced by the HRP 41 in H_2O_2 solution. The right sectional view of FIG. 7E shows a state where most cleavable signal elements are cleaved and removed through washing so that REDOX reaction is unlikely to occur. A differential electrochemical signal between the two states is detected.

FIGS. 7F and 7G illustrate another example of an electrochemical detector or a capacitance and impedance measurement device for detecting analyte-specific signals from the assay site 132 of the bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000. The electrochemical detector or

the capacitance and impedance measurement device of FIGS. 7F and 7G is implemented with the interdigitated array electrodes 702 and 703 arranged on the substrate 701 and a conjugate antibody 471 which forms a conjugate-antigen complex with a target sample (analyte or antigen) to be assayed. The conjugate-antigen complex is applied to an assay site 312 in which capture antibodies 473 are immobilized on the substrate 701. The electrochemical detector or the capacitance and impedance measurement device of FIGS. 7F and 7G are based on antigen-antibody reaction between the conjugate-antigen complex and the capture body 473.

The conjugate antibody 471 is labeled with colorimetric moiety 474 made of, preferably, gold or latex.

When the conjugate-antigen complex reacts with the capture antibody 473, the antigen-antibody reaction product remains an uncleaved signal element after washing. When the conjugate-antigen complex does not react with the capture antibody 473, the capture antibody 473, which remains unreacted, serves as a cleaved signal element. The capacitances and impedances of the uncleaved and cleaved signal elements are measured from their frequency response characteristics.

The left sectional view of FIG. 7G shows a state where the uncleaved signal elements labeled with gold or latex, which are products of antigen-antibody reactions in the bio-disc 100, 700, or 1000, remain on the substrate 701 after washing. The right sectional view of FIG. 7G shows a state where no antigen-antibody reaction takes place and only the capture antibody remains unreacted after washing. A differential capacitance and impedance signal between the two states is detected.

Embodiments of bio-discs according to the present invention are illustrated in FIGS. 8A through 8F. FIGS. 8A through 8C illustrate various examples of labs-on-a-chip which can be integrated into the

bio-disc 100, the controller disc-combined bio-disc device 700, or the optical disc-combined bio-disc device 1000 according to the present invention.

In FIGS. 8A through 8C, reference numeral 170 denotes a disc hole, and reference numeral 171 denotes an interfacing zone for electrical connection with the controller disc 200. Reference numeral 130 denotes a preparation chamber for preparing a DNA sample or a serum sample from blood, cells, or RNA; reference numerals 131 and 131a denote PCR chambers for polymerase chain reaction (PCR), in which a buffer containing various enzymes, such as polymerase and primers, is reserved; reference numeral 132 denotes a chamber for hybridization or antigen-antibody reaction, which is an assay site with biotin-labeled capture probes for analyzing and diagnosing amplified DNA products from the PCR or with immuno arrays immobilized thereon; and reference numeral 133 denotes a trash chamber for collecting wastes generated during washing.

The chambers for the main processes, such as sample preparation, PCR, hybridization or antigen-antibody reaction, and washing, are arranged in a spiral formation from the center to the outer perimeter and are interconnected with each other, so as to induce natural fluid flow by centrifugal force to allow for sequential processes. In addition, reagent reservoir chambers are arranged in a spiral formation near the corresponding reaction chambers.

Reference numeral 129 denotes a washing buffer reservoir; reference numeral 129a denotes a distilled water reservoir; reference numeral 144 denotes a hybridization buffer reservoir; reference numeral 136 denotes a reservoir of a DNAse used in DNA fragmentation into appropriate size; and reference numerals 141, 142, and 143 denote reservoirs of various enzymes used in hybridization. Reference numeral 141 denotes a reservoir of a nuclease used in single strand

cleavage; reference numeral 142 denotes a reservoir of streptavidin-labeled metal microspheres; and reference numeral 143 denotes a reservoir of phosphate buffered saline (PBS).

Reference numerals 150, 151, 152, 153, 154, 155, 156, 157, 158, 160, 161, and 162 denote valves. Fluid flow in the bio-discs 100, 700, and 1000 is controlled by the centrifugal force generated as the bio-disc is rotated and by opening and closing the valves. Reference numeral 177 denotes an electromagnet embedded in the bio-disc 100, 700, or 1000, which may be disposed above or below the preparation chamber 130, instead of be embedded in the bio-disc 100, 700, or 1000.

Opening and closing of the valves at the start and ending points of time of each of the main processes, including sample preparation, PCR, hybridization, antigen-antibody reaction, and washing, are controlled by the controller 63 controlling the on/off of the power applied to the electromagnets arranged above and below each film-like cylindrical permanent magnet of the valves. Reference numeral 128 denotes a distilled water reservoir, and reference numeral 135 denotes a trash chamber.

FIG. 8A illustrates an embodiment of a bio-disc including one PCR chamber in its lab-on-a-chip. FIG. 8B illustrates an embodiment of a bio-disc including a plurality of PCR chambers in its lab-on-a-chip. In the structure of FIG. 8B, each PCR chamber reserves one type of primer. Alternatively, all of the PCR chambers reserves the same type of primer. The amplified DNA products from each of the PCR chambers combine in a chamber 131b.

FIG. 8C illustrates an embodiment of a lab-on-a-chip designed for antigen-antibody reaction, which can be integrated into the bio-disc 100, 700, or 1000. In FIG. 8C, reference numeral 130 denotes a preparation chamber for preparing a serum sample from blood injected via a sample inlet; cells, or RNA; reference numeral 132 denotes a chamber for

hybridization, which is an assay site with immuno arrays immobilized thereon so as to analyze and diagnose an antigen, i.e., sample or analyte; and reference numeral 133 denotes a trash chamber for collecting wastes generated during washing.

The chambers for the main processes, such as sample preparation, antigen-antibody reaction, and washing, are arranged in a spiral formation from the center to the outer perimeter of the disc and are interconnected with each other, so as to induce natural fluid flow by centrifugal force to allow for sequential processes. In addition, reagent reservoir chambers are arranged in a spiral formation near the corresponding reaction chambers.

Reference numeral 129 denotes a washing buffer reservoir, and reference numeral 142a denotes a conjugate antibody reservoir. Conjugate antibodies in reservoir 142a are labeled with colorimetric moiety made of, for example, gold or latex. Reference numerals 150, 152, 153, and 156 denote valves. Fluid flow in the bio-discs 100, 700, and 1000 is controlled by the centrifugal force generated as the bio-disc is rotated and by opening and closing the valves. Reference numeral 177a denotes a filter embedded in the bio-disc 100, 700, or 1000, which is used to filter a blood sample to extract serum.

FIGS. 8D and 8E are sectional views of the bio-discs of FIGS. 8A and 8B or 8C, illustrating the main assay processes conducted therein.

Permanent magnetic microbeads 150, 151, 153, and 156 are individually moved up and down to close and open channels by the magnetic force generated by respective electromagnet pairs 4d and 5d, 4a and 5a, 4b and 5b, and 4c and 5c. Reference numeral 121 denotes a sample inlet.

In the preparation chamber 130, a DNA or serum sample is prepared from blood, cells, or RNA. For this purpose, the preparation chamber 130 reserves a lysis buffer solution for DNA extraction through

lysis and ferroelectric beads having affinity to extracted DNA.

The PCR chamber 131 contains various enzymes, including a polymerase and a primer such as dNTP, which are required for PCR, in a buffer. In the assay site 132 where hybridization or antigen-antibody reaction takes place, capture probes for analyzing and diagnosing amplified DNA products from the PCR or immuno arrays are immobilized. Wastes from washing are collected in the trash chamber 133. A blood sample injected via the sample inlet 121 is passed through the filter 177a to extract serum.

An embodiment of how to conduct main assay processes in the labs-on-a-chip of FIGS. 8A and 8B will be described.

< Sample Preparation Process >

DNA is extracted from a sample in the preparation chamber 130 in the following way.

1) 10 μL (EDTA, ACD Tube) or 5 μL (heparin tube) of blood is injected via the sample inlet 121 into the preparation chamber 130 containing a lysis buffer solution and ferroelectric beads having affinity to extracted DNA.

2) Five-min incubation is performed to extract DNA from the blood and allow the ferroelectric beads to attract the extracted DNA.

3) Power is applied to the electromagnet 177 of FIG. 8a to fix the ferroelectric beads, followed by 1-3 min suspension.

4) The bio-disc is slowly rotated, the valve 161 is opened to allow the cell debris to flow into the trash chamber 153, followed by closing the valve 161 and stopping rotation of the bio-disc.

5) The power applied to the electromagnet 177 is cut off.

6) The valve 150 is opened and the bio-disc is slowly rotated to allow a washing buffer in the washing buffer reservoir 129 to flow into the preparation chamber 130.

7) Processes 2) through 6) are repeated twice, the bio-disc is slowly rotated, and the valve 161 is opened to fully wash the cell debris out and collect it in the trash chamber 135, followed by closing the valve 161 and stopping rotation of the bio-disc.

8) The power applied to the electromagnet 177 is cut off, the bio-disc is slowly rotated, and the valve 151 is opened to allow the distilled water in the reservoir 129a to flow into the preparation chamber 130.

9) A heater 960 (refer to FIG. 8D) installed in the preparation chamber 130 is turned on to separate DNA from the electromagnetic beads or resuspend it in a resuspension buffer.

< PCR process >

DNA amplification is conducted in the PCR chamber 131 (131a) in the following way.

1) The bio-disc is slowly rotated, the valve 152 is opened to allow the DNA separated from the electromagnetic beads in the preparation chamber 130 to flow into the PCR chamber 131.

2) Once the DNA reaches the PCR chamber 131, the valve 152 is closed, followed by stopping rotation of the bio-disc.

3) Thirty cycles of PCR are conducted using a heater 961 (refer to FIG. 8D) and a thermosensor 520 installed in the PCR chamber 131 to amplify DNA.

4) The PCR products were cooled for 1-2 minutes.

For a bio-disc with the structure of FIG. 8B, the bio-disc is slowly rotated, the vale 152a is opened to migrate the PCR products from each of the PCR chambers 131a into the chamber 131b.

< Fragmentation process >

Fragmentation, which is optional, is conducted to cut the amplified

DNA products from the PCR to proper size for hybridization. The amplified DNA products may be fragmented as follows.

1) The bio-disc is slowly rotated, and the valve 158 is opened to allow a DNAse in the reservoir 136 to flow into the PCR chamber 131 (131b) for fragmentation.

2) The valve 158 is closed, followed by stopping rotation of the bio-disc.

3) After 1-2 min incubation, the heater 961 is turned on to deactivate the DNAse and stop the fragmentation. As a result, the DNA is denaturated into single strands.

The length of DNA fragments may be varied depending on the duration of incubation process 3). For the bio-disc of FIG. 8B, which includes a plurality of PCR chambers 131b with a separate heater in each PCR chamber 131b, the heaters are individually controlled during fragmentation to obtain DNA fragments which vary in length. It will be appreciated that the duration of the incubation can be varied in each PCR chamber 131b.

< Hybridization process >

Single-stranded DNA from the PCR, which has undergone high-temperature denaturation, optionally, has further undergone fragmentation into a proper size, is hybridized to biotin-labeled capture probes previously immobilized on the assay site 132 in the following way.

1) The bio-disc is slowly rotated, the valve 153 is opened to allow the single-stranded DNA to enter the assay site 132.

2) After the single-stranded DNA is allowed to spread over the assay site, the valve 153 is closed, rotating the bio-disc is stropped, and the bio-disc is incubated in a stationary state at room temperature for 3-5 minutes. Hybridization reaction is controlled by varying the electric field strength of an external electrode pattern 962 and an electrode plate 963

and the amount of heat generated by a heater 962. For reference, the electrode pattern 962 acts as a heater when operated alone but can also serve as an electrode plate generating a perpendicular electric field when operated in combination with the electrode plate 963.

3) The bio-disc is rotated, the valve 157 is opened to allow a hybridization buffer to flow into the assay site 132 for washing, with or without the application of an external electric field vertically through the bio-disc (first wash process). The valve 157 is closed. The valve 156 is opened during washing and closed after washing.

4) The bio-disc is slowly rotated, and the valve 154 is opened to allow a nuclease solution to enter and spread over the assay site 132. The valve 154 is closed, and the bio-disc is incubated in a stationary state for 1-2 minutes to cleave single-stranded DNA (cleavage process).

5) The bio-disc is slowly rotated, and the valve 160 is opened to allow a PBS solution to enter the assay site 132 to wash out cleaved DNA fragments at 80℃, with or without the application of an external electric field to the bio-disc. After washing, the valve 160 is closed.

6) The bio-disc is slowly rotated, and the valve 155 is opened to allow a streptavidin-labeled metal microsphere suspension to enter and spread over the assay site 132 ("uncleaved probe-label complex" formation). In particular, the biotin-labeled capture probes are bound with the streptavidin-labeled metal microspheres 40, forming a biotin-streptavidin binding structure. Next, the valve 155 is closed. During this process, the reaction temperature and the electric field strength may be controlled using the external electrode pattern 962 and the electrode plate 963. As described above, the electrode pattern 962 acts as a heater when operated alone but can also serve as an electrode plate generating a perpendicular electric field when operated in combination with the electrode plate 963.

7) The bio-disc is rotated at a higher speed, and the valve 162 is

opened to allow distilled water in the reservoir 128 to enter the assay site for washing, with or without the application of an electric field to the bio-disc (second wash process). During this wash process, the valve 156 is opened.

< Detection process >

Uncleaved signal elements remaining in the assay site 132 are detected using a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device, which have the above-described structure, the detector being programmed to be able to selectively detect assay sites with cleavable signal elements.

The diagnostic data and a prescription based on the result of the detection are displayed on a computer monitor, and optionally automatically or manually transmitted through the Internet to a specialist at a remote location. The patient waits for a prescription from the specialist.

For the detailed descriptions on the cleavage, first wash, second wash, and remote diagnosis processes, International Patent Application No. PCT/KR02/00126 filed 27 January 2002 and its priority Korean Patent Application No. 10-2001-0003956 filed 27 January 2001, which are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or single strand of nucleic acids or oligonucleotides," can be referred to.

FIG. 8D illustrates an embodiment of a bio-disc in which an electrochemical detector or a capacitance and impedance measurement device using the interdigitated array electrodes on the substrate 701 is installed as a detector in the assay site 132. FIG. 8E illustrates an embodiment of a bio-disc in which a pair of optical assay detectors 99a and 99b are integrated into the same silicon wafer via semiconductor manufacturing processes to detect analyte-specific signals.

The optical assay detectors 99a and 99b of FIG. 8E may be any modification from the structures of FIGS. 5A, 5B, 6A, and 6B.

An embodiment of how to conduct main assay processes in the lab-on-a-chip of FIG. 8C will be described.

< Sample Preparation Process >

Serum is extracted from blood in the preparation chamber 130 in the following way.

1) 10 μL (EDTA, ACD Tube) of blood is injected via the sample inlet 121 into the preparation chamber 130 with the filter 177a at its outlet.

2) The valve 152 is opened, and the bio-disc is slowly rotated to allow the blood to flow out the preparation chamber 130 through the filter 177a and enter the conjugate antibody reservoir 142a.

3) Rotation of the bio-disc is stopped, and the valve 152 is closed.

< Antigen-antibody reaction >

The conjugate antibody reservoir 142a of FIG. 8C reserves conjugate antibodies labeled with colorimetric moiety, such as gold or latex, and the assay site 132 contains capture antibodies immobilized on a substrate.

Antigen-antibody reactions in a bio-disc according to the present invention involve binding an antigen in the serum extracted via the sample preparation to the labeled conjugate antibodies in the conjugate antibody reservoir 142a to form a conjugate-antigen complex and binding the conjugate-antigen complex to the capture antibodies in the assay site 132. These antigen-antibody reactions are induced in the following way.

1) After the serum enters the conjugate reservoir chamber 142,

the conjugate reservoir chamber 142 is incubated for 1-2 minutes to induce a reaction between an antigen and conjugate antibodies to form a conjugate-antigen complex.

2) The valve 153 is opened, the bio-disc is slowly rotated to allow the conjugate-antigen complex in the conjugate antibody reservoir 142a to flow into the assay site 132.

3) Rotation of the bio-disc is stopped, and the valve 153 is closed.

4) The bio-disc is incubated in a stationary state at room temperature for 3-5 minutes and left for a reaction between the conjugate-antigen antibody and the capture antibodies in the assay site 132.

5) The bio-disc is rotated, and the valves 150, 153, and 156 are opened to allow the washing buffer in the washing buffer reservoir 129 to enter and wash the assay site 132.

< Detection process >

Uncleaved signal elements remaining in the assay site 132 are detected using a detector including an optical device, an electrochemical device, or a capacitance and impedance measurement device, which have the above-described structure, the detector being programmed to be able to selectively detect assay sites with cleavable signal elements.

The diagnostic data and a prescription based on the result of the detection are displayed on a computer monitor, and optionally automatically or manually transmitted through the Internet to a specialist at a remote location. The patient waits for a prescription from the specialist.

FIG. 8F illustrates an embodiment of a heater and an electric field generation used in sample preparation, PCR, and hybridization. The heaters 960, 961, and 962 in FIGS. 8D and 8E are formed as an

electrode pattern. As described above, the electrode pattern 962 acts as a heater when operated alone but can also serve as an electrode plate generating a perpendicular electric field when operated in combination with the electrode plate 963.

The reaction temperature and the electric field strength are controlled by the controller 63. As shown in FIG. 8F, the electrode pattern 962 as a heater have two input ports 962a and 962b. A voltage is applied across the input ports 962a and 962b to induce current flow in the electrode pattern 961 and enable the electrode pattern 961 to act as a resistive or thermal coil.

The controller 63 supplies a current to the electrode pattern 962 via its input ports 962a and 962b and controls the amount of current supplied to the electrode pattern 962 and its temperature using the temperatures of the electrode pattern 962 periodically measured by the thermosensor 520. To operate the electrode pattern 962 as an electrical field generator in combination with the electrode pattern 963, an equal voltage is applied across the two input ports 962a and 962b of the electrode pattern 962 to handle them as one port, while a voltage is applied to the electrode plate 962 as the other port. In other words, the controller 63 applies an AC voltage across the electrode pattern 962 and the electrode plate 963 to generate an AC electric field. Since DNA has negative charges, the AC electric field strength between the electrode pattern 962 and the electrode plate 963 can be varied to control the stringency of DNA hybridization and for higher sensitivity in detecting single nucleotide polymorphism (SNP).

For the detailed description on SNP detection, International Patent Application No. PCT/KR02/00126 filed 27 January 2002 and its priority Korean Patent Application No. 10-2001-0003956 filed 27 January 2001, which are entitled "Nucleic acid hybridization assay method and device using cleavage technique responsive to complementary double strand or

single strand of nucleic acids or oligonucleotides," can be referred to.

Although the thermosensor 520 of FIGS. 8D and 8E is described as being used for precise temperature control during PCR, it can be used in any process which requires thermal detection.

An assay automatically starts as soon as a bio-disc is loaded into a bio-driver apparatus. When a bio-disc into which a sample has not been injected yet via the sample inlet is loaded, the bio-driver apparatus sends an "eject" message or a warning message to a user.

To determine whether a sample has been injected or not, an additional impedance measurement device may be installed in the preparation chamber 130. Whether a sample has been injected or not can be determined from different impedance characteristics between two states, one containing a sample and one without a sample.

Such an impedance measurement device for detecting the presence of a sample may be implemented with interdigitated array electrodes, like the capacitance and impedance measurement device installed in the assay site 132.

When an unloading or a stop command is input to the bio-driver apparatus during assay or diagnosis, the bio-driver apparatus sends a warning message or requests a user's password while continuing assay and diagnosis.

If the user enters the correct password, the bio-driver apparatus stops the assay or diagnosis and ejects the bio-disc.

Once the assay or diagnosis is completed, the bio-driver apparatus ejects the bio-disc at the request of the user.

The bio-disc stores in its IC card 188 information on how many times it has been used, its validation period, and kinds of diseases which it can diagnose.

For example, when an eject command is input to a disposable bio-disc during an assay or after the completion of an assay, the history

of its use is written to its IC card 188 to later inform a user who loads the disposable bio-disc that it cannot be reused.

When a bio-disc which has an expired validation term is loaded, the bio-driver apparatus informs the user that the bio-disc is no longer valid.

FIGS. 9A and 9B illustrate alternative embodiments of bio-discs according to the present invention, in which sample preparation and PCR or further electrophoresis can be conducted in a single disc.

FIG. 9A illustrates an example of a PCR bio-disc capable of sample preparation and PCR therein. In FIG. 9A, reference numeral 170 denotes a disc hole, and reference numeral 171 denotes an interfacing zone for electrical connection with its controller disc. Reference numeral 130 denotes a preparation chamber for preparing a DNA sample or a serum sample from blood, cells, or RNA; reference numeral 131a denotes a PCR chamber in which a buffer containing various enzymes, such as polymerase and primers, is reserved; reference numeral 88a denotes an out-chamber into which PCR products are discharged; reference numeral 129 denotes a washing buffer reservoir; reference numeral 129a denotes a distilled water reservoir; reference numerals 144a and 88b denote a ladder marker reservoir and its out-chamber, respectively; reference numerals 141a and 88c denote a positive or negative control reservoir and its out-chamber, respectively; reference numerals 142a and 143a denote electrophoretic reagent reservoirs for storing various reagents used in electrophoresis, including strains; reference numerals 88d and 88e denote out-chambers of the respective electrophoretic reagent reservoirs 142a and 143a; and reference numerals 150, 151, 152, 153, 154a, 155a, 156a, and 157a denote valves. The out-chamber 88a may have an outlet via which PCR products can be extracted by means of a pipette or a syringe for manual electrophoresis.

FIG. 9B illustrates an example of an electrophoresis bio-disc device for automated electrophoresis that is assembled from an upper PCR bio-disc, which can be the PCR bio-disc of FIG. 9A, and a lower electrophoresis bio-disc.

The lower electrophoresis bio-disc includes gel plates 155 made of agarose gel and/or polyacrylamide gel and annular electrodes 555a and 555b across which a voltage is applied to the gel plates 155.

The PCR product out-chamber 88a, the ladder marker out-chamber 88b, the positive/negative control out-chamber 88c, and the strain out-chamber 88e are interconnected with respective in-chambers 99a, 99b, 99c, 99d, and 99e of the electrophoresis bio-disc. After the valves 152a, 157a, 154a, 155a, and 156a are opened to allow the contents in their corresponding output-chamber to flow into the corresponding in-chamber of the electrophoresis disc, electrophoresis starts with the application of a voltage across the electrodes 555a and 555b. After a predetermined amount of time, the voltage applied to the electrodes 555a and 555b is cut off to stop electrophoresis.

The controller 63 controls voltage level and the opening and closing of the valves. The PCR bio-disc and the electrophoresis bio-disc are electrically connected via the interfacing zone 171 of their controller disc.

A bio-disc device including such an electrophoresis disc as described above may further include a UV radiator and a camera to identify, store, and transmit bands appearing on the gel plate 555c.

FIGS. 10A and FIG. 10B illustrate embodiments of assay devices according to the present invention, in which an immunoassay sector for antigen-antibody reaction and a nucleic acid probe hybridization sector are arranged in an angular or radial direction. An immunoassay and a DNA assay can be conducted simultaneously with the assay devices of FIGS. 10A and 10B. In addition, the number of assay sites can be

reduced through proper combination, and diagnostic reliability is doubled.

FIGS. 11A and 11B illustrate exemplary appearances of bio-driver apparatuses according to the present invention. Reference numeral 751 denotes a case, reference numeral 750 denotes a bio-disc loading tray, and reference numerals 745 and 746 denote a play/search button and a stop button, respectively, for general optical discs.

In particular, the bio-driver apparatus of FIG. 11A is an embodiment of indicating the status of proceeding with an assay using light emitting diodes (LEDs). A LED 741 indicates that a currently loaded disc is a bio-disc, a LED 742 indicates the current status of proceeding with an assay, and a LED 743 indicates that a general optical disc has been loaded. Alternative indicative means instead of LEDs can be used for the same purpose.

The bio-driver apparatus of FIG. 11B is an embodiment of indicating the status of proceeding with an assay through a liquid crystal display (LCD) 760. In this embodiment, the status of progress in each main process, such as sample preparation, PCR, hybridization, and antigen-antibody reaction, can be expressed in percentages or as a bar graph.

The status of proceeding with an assay in the bio drive apparatus according to the present invention can be displayed through a computer monitor. The status of progress in each main process, such as sample preparation, PCR, hybridization, and antigen-antibody reaction, can be expressed in percentages or as a bar or pie graph.

While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit and scope of the present invention as defined by the following claims.

Industrial Applicability

As described above, a bio-disc device including an optical and/or non-optical disc, a bio-driver apparatus, and an assay method using the same according to the present invention are suitable for labs-on-a-chip for various diagnostic assay devices, nucleic acid hybridization assay devices, and immunoassays. A particularly important feature of the present invention is that the bio-driver apparatus is compatible with general optical discs, including audio CDs, CD-Rs, game CDs, DVDs, etc., and the assay method is compatible with general optical disc drivers, including CD-ROMs, DVD players, etc. Thus, the present invention offers an economical and convenient alternative to conventional products. In addition, the bio-driver apparatus can be readily and easily applied in connection with a computer for remote diagnosis via the Internet.

What is claimed is:

1. A non-optical bio-disc comprising:

a solid substrate in which channels as fluid flow paths, a chamber as a buffer reservoir, a hole connecting the channels, and an assay site with biomolecular arrays immobilized thereon are integrated; and

a valve used to open and close the hole connecting the channels,

wherein an analyte-specific signal from the assay site is detectable using a detector including a light transmission type device, an electrochemical device, or a capacitance and impedance measurement device.

2. The non-optical bio-disc of claim 1, wherein the biomolecular arrays are made from at least one selected from the group consisting of DNA, RNA, PNA, and protein probes.

3. The non-optical bio-disc of claim 1, wherein the chamber comprises at least one chamber selected from the group consisting of: a preparation chamber for preparing a DNA sample from blood, cells, or RNA; a PCR chamber for amplifying the DNA sample through polymerase chain reaction (PCR); a hybridization chamber in which assay and diagnostic probes are arrayed for hybridization with the amplified DNA from the PCR; and a trash chamber for collecting wastes generated from washing.

4. The non-optical bio-disc of claim 3, wherein the preparation chamber reserves a lysis buffer solution used to extract a DNA through lysis and ferroelectric beads having affinity to the extracted DNA.

5. The non-optical bio-disc of claim 3, wherein the chamber comprises a plurality of PCR chambers, and either each PCR chamber

reserves one type or several types of primer or all of the PCR chambers reserves the same type of primer.

6. The non-optical bio-disc of claim 1, wherein the chamber comprises at least one chamber selected from the group consisting of: at least one preparation chamber for preparing a serum sample, an antigen, or an antibody from blood or cells; at least one antigen-antibody reaction chamber in which immuno probes are arrayed for antigen-antibody reaction with the prepared antigen or antibody; and a trash chamber for collecting waste generated from washing.

7. The non-optical bio-disc of claim 6, wherein the chamber further comprises a filter at an outlet of the preparation chamber and a conjugate antibody chamber as a conjugate antibody reservoir.

8. The non-optical bio-disc of claim 7, wherein conjugate antibodies reserved in the conjugate antibody chamber have colorimetric moiety selected from gold and latex.

9. The non-optical bio-disc of claim 1, wherein the valve comprises:

a microbead which plugs or opens the hole connecting channels; and

electromagnets with an air core or a non-magnetic core, which are arranged above and below the microbead.

10. The non-optical bio-disc of claim 9, wherein the microbead is a film-like cylindrical permanent magnet.

11. The non-optical bio-disc of claim 1, wherein the light

transmission type device comprises:

a laser device which emits a laser beam onto an uncleaved signal element and a cleaved signal element; and

a photodetector which detects a differential light transmission signal between the uncleaved signal element and the cleaved signal element.

12. The non-optical bio-disc of claim 11, wherein at least one photodetector is arrayed along an outer perimeter region of the bio-disc to correspond to each assay site.

13. The non-optical bio-disc of claim 11, wherein at least one set of a laser device and a photodetector is arrayed along an outer perimeter region of the bio-disc to correspond to each assay site.

14. The non-optical bio-disc of claim 1, wherein the detector detects the analyte-specific signal from the assay site in a non-scanning manner without need to rotate the bio-disc.

15. The non-optical bio-disc of claim 1, wherein the electrochemical device or the capacitance and impedance measurement device comprises:

interdigitated array electrodes on the substrate of the assay site; and

a horse radish peroxidase and/or a metal microsphere attached to the end of cleavable signal elements.

16. The non-optical bio-disc of claim 15, wherein the electrochemical device or the capacitance and impedance measurement device using the interdigitated array electrodes further comprises a

multiplexer and/or a frequency generator.

17. The non-optical bio-disc of claim 1, further comprising a memory or an integrated circuit card storing a protocol of the bio-disc, assay interpretive algorithms, standard control values for analysis, positional information on analysis sites, bioinformatics information, self-diagnostics, bio-driver software, educational information for patients on clinical assays, a variety of web sites and links enabling a patient to communicate with a doctor or hospital at a remote location based on his/her diagnosis result, or encrypted personal information.

18. A bio-disc device comprising;

the non-optical bio-disc of any one of claims 1 through 17 or an optical bio-disc;

a controller disc including a controller which supplies power or a control signal to the bio-disc; and

an interfacing zone for connecting the bio disc and the controller disc.

19. The bio-disc device of claim 18, wherein the interfacing zone comprises:

a plurality of control signal nodes via which the control signal is supplied; and/or

a power node via which power is supplied.

20. The bio-disc device of claim 18, wherein the interfacing zone comprises:

grooves formed in the bio-disc and coated with a conductive material; and

conductive arms protruding from the controller disc and engaging

the grooves.

21. The bio-disc device of claim 18, wherein power is supplied to the controller disc via frictional contact between brushes connected to an external power supply and an annular electrode plate of the controller disc.

22. The bio-disc device of claim 19, wherein the controller disc comprises an integrated circuit in a printed circuit board or in a silicon wafer.

23. The bio-disc device of claim 18, wherein fluid flow in the bio-disc device is induced by the centrifugal force generated as the bio-disc engaged with the controller disc rotates and by the opening and closing of the valve.

24. The bio-disc device of claim 18, wherein the controller disc further comprises a non-contact interface selected from among an infrared interface, an optical interface, and a wireless interface to transmit the result of a detection from the assay site by the detector to an external central control system, a storage unit, or an output unit via the non-contact interface.

25. The bio-disc device of claim 18, wherein the bio-disc and the controller disc are integrated as a single body to form a controller disc-combined bio-disc.

26. The bio-disc device of claim 25, wherein the controller disc-combined bio-disc has a monolithic circuit structure integrated into a silicon wafer via photolithography and etching processes, the monolithic

circuit structure including the controller, the integrated circuit card, a non-contact interface, an electrode plate or electromagnet for valve control, various circuit patterns, chambers, and channels.

27. The bio-disc device of claim 25, wherein the controller disc-combined bio-disc is combined with a general optical disc selected from among an audio CD, a CD-RW, a DVD-RW, a CD, and a DVD to form an optical disc-combined bio-disc.

28. A bio-driver apparatus comprising:

a controller disc including a controller which outputs a power signal and/or a control signal to control power supply to and the operation of the non-optical bio-disc of any one of claims 1 through 17 and/or an optical bio-disc;

a motor which drives the controller disc and the bio-disc to rotate;

a power supply unit which supplies power to the controller of the controller disc;

an interface via which the control signal and/or the power signal are transmitted from the controller to the bio-disc; and

a body which supports the bio-driver apparatus.

29. The bio-driver apparatus of claim 28, further comprising a detector including a light transmission type device to detect an analyte-specific signal from the assay site.

30. The bio-driver apparatus of claim 28, further comprising a non-contact interface via which the result of a detection from the assay site is transmitted to a central control system, a storage unit, or an output unit and via which a command signal from the central control system is transmitted to the controller disc.

31. The bio-driver apparatus of claim 28, further comprising a central control system and a storage or output unit installed on a printed circuit board connected as a base to the body, the central control system controlling the operation of the motor to rotate the bio-disc and the controller disc and stop their rotation and to push the controller disc and the bio-disc to be closer together so that the controller disc and the bio-disc mechanically and/or electrically combine together via their interfacing zones and rotate together.

33. The bio-driver apparatus of claim 31, wherein the output unit is a Universal Serial Bus or IEEE1394.

33. A bio-disc device comprising:

the non-optical bio-disc of any one of claims 1 through 17 or an optical bio-disc;

a turntable on which the bio-disc or a general optical disc is loaded; and

a controller disc including a controller which outputs a power or control signal to control the bio-disc, the controller disc being fixed to the turntable.

34. The bio-disc device of claim 33, wherein the controller disc further comprises an electromagnet which controls the movement of a microbead in the bio-disc.

35. The bio-disc device of claim 33, wherein the bio-disc is loaded on the turntable with a gap of 0.1-5 mm from the controller disc fixed to the turntable.

36. The bio-disc device of claim 33, wherein the controller disc supplies to the bio-disc the power provided via frictional contact between a rotating annular electrode plate and blushes connected to an external power supply unit.

37. The bio-disc device of claim 33, wherein the controller disc comprises an integrated circuit in a printed circuit board or in a silicon wafer.

38. The bio-disc device of claim 33, wherein the controller disc further comprises a non-contact interface selected from among an infrared interface, an optical interface, and a wireless interface to transmit the result of a detection from the assay site by the detector to an external central control system, a storage unit, or an output unit via the non-contact interface.

39. A bio-driver apparatus comprising:

a turntable on which the non-optical bio-disc of any one of claims 1 through 17, an optical bio-disc, or a general optical disc is loaded;

a controller disc fixed to the turntable and including a controller and an electromagnet, the controller controlling power supply to the bio-disc and the opening and closing of the valve installed in the bio-disc;

a motor which drives the controller disc and the bio-disc to rotate;

a power supply unit which supplies power to the controller of the controller disc; and

a body which supports the bio-driver apparatus.

40. The bio-driver apparatus of claim 39, wherein the power supply unit supplies a positive voltage via frictional contact between a rotating annular electrode and blushes and a negative voltage via

electrical connection with the motor or its shaft, which are grounded, to the controller disc.

41. The bio-driver apparatus of claim 39, further comprising a detector including a light transmission type device to detect an analyte-specific signal from the assay site.

42. The bio-driver apparatus of claim 39, further comprising a non-contact interface via which the result of a detection from the assay site is transmitted to a central control system, a storage unit, or an output unit and via which a command signal from the central control system is transmitted to the controller disc.

43. The bio-driver apparatus of claim 39, further comprising a central control system and a storage or output unit installed on a printed circuit board connected as a base to the body, the central control system controlling the operation of the motor to rotate the bio-disc and the control disc and stop their rotation.

44. The bio-driver apparatus of claim 28 or 39, wherein the general optical disc is selected from among an audio CD, a CD-R, a game CD, and a DVD, and the bio-driver apparatus further comprises an optical pickup to read information from the general optical disc.

45. The bio-driver apparatus of claim 44, wherein the controller comprises a bio-disc detection unit determining whether a currently loaded disc is a bio-disc or a general optical disc selected from among an audio CD, a CD-R, a game CD, and a DVD.

46. The bio-driver apparatus of claim 45, wherein the bio-disc

detection unit measures a predetermined voltage across some or all resistors arranged in the bio-disc as a bio-disc detection signal and wirelessly transmits the bio-disc detection signal via a non-contact interface to a central control system to inform the central control system that the currently loaded disc is a bio-disc.

47. The bio-driver apparatus of claim 45, wherein the bio-disc has a groove pattern or a data pattern at a particular area on its surface, and the optical pickup detects whether a currently loaded disc is a bio-disc from the groove pattern or the data pattern of the currently loaded disc and informs a central control system of the result of the detection.

48. The bio-driver apparatus of claim 45, wherein a central control system determines whether a currently loaded disc is a bio-disc or a general optical disc selected from among an audio CD, a CD-R, a game CD, and a DVD; transmits information read from the general optical disc using the optical pickup to a storage or output unit, transmits to the optical pickup information to be written, or outputs various read/write control signals if the currently loaded disc is determined to be a general optical disc; and transmits various control signals for the bio-disc via a non-contact interface to the controller if the currently loaded disc is determined to be a bio-disc.

49. The bio-driver apparatus of claim 28 or 39, wherein a signal indicative of bio-discs is wirelessly transmitted to a central control system upon loading of a bio-disc, via a non-contact interface or an integrated circuit card of the bio-disc, to inform the central control system of the current loading of the bio-disc into the bio-driver apparatus.

50. A PCR bio-disc device for polymerase chain reaction, comprising:

a solid substrate in which channels as fluid flow paths, a chamber as a buffer reservoir, and a hole connecting the channels are integrated; and

a valve used to open and close the hole connecting the channels,

wherein the chamber comprises: at least one preparation chamber for preparing a DNA sample from blood, cells, or RNA; at least one PCR chamber reserving various enzymes, including a polymerase and a primer, required to amplify the DNA sample through polymerase chain reaction (PCR), in a buffer; and a plurality of out-chambers into which PCR products are discharged, the at least one preparation chamber, the at least one PCR chamber, and the plurality of out-chambers being sequentially connected with each other in the solid substrate.

51. The PCR bio-disc device of claim 50, wherein the plurality of out-chambers have outlets via which the PCR products can be extracted by means of a pipette or a syringe.

52. The PCR bio-disc device of claim 50, wherein a ladder marker reservoir, a positive control and negative control reservoir, and a stain reservoir are further integrated into the solid substrate.

53. The PCR bio-disc device of claim 50, being combined with an electrophoresis bio-disc.

54. The PCR bio-disc device of claim 50, wherein the electrophoresis bio-disc comprises: gel plates made of agarose gel and/or polyacrylamide gel; and annular electrodes across which a

voltage is applied to the gel plates.

55. The PCR bio-disc device of claim 50, further comprising a UV radiator and a camera to identify, store, and transmit bands appearing on the gel plates.

56. A nucleic acid assay method using the PCR bio-disc device of claim 53, the method comprising:

preparing a DNA sample from blood, cells, or RNA;

amplifying the prepared DNA sample through polymerase chain reaction (PCR);

flowing PCR products into an out-chamber;

moving the contents in the out-chamber into the electrophoresis bio-disc;

incubating the electrophoresis bio-disc while applying a voltage across its annular electrodes; and

identifying, storing, and transmitting bands appearing on the gel plates.

57. A nucleic acid assay method using the bio-disc of claim 3, the method comprising:

preparing a DNA sample from blood, cells, or RNA;

amplifying the prepared DNA through polymerase chain reaction (PCR);

hybridizing amplified DNA products from the PCR to the assay and diagnostic probe array immobilized on the assay site; and

detecting a cleavable signal element remaining in the assay site using the detector including the light transmission type device, the electrochemical device, or the capacitance and impedance measurement device.

58. The nucleic acid assay method of claim 56 or 57, wherein preparing the DNA sample comprises:

injecting blood via a sample inlet into the preparation chamber;

incubating the preparation chamber to allow ferroelectric beads in the preparation chamber to attract DNA extracted through lysis;

fixing the ferrroelectric beads and slowly rotating the bio-disc to wash out and flow the cell debris into the trash chamber; and

separating the DNA from the ferroelectric beads or resuspending the DNA in a resuspension buffer.

59. The nucleic acid assay method of claim 56 or 57, wherein amplifying the prepared DNA sample through PCR comprises:

slowly rotating the bio-disc to allow the prepared DNA sample to flow into the PCR chamber; and

repeating a PCR cycle several times using a heater and a thermosensor installed in the PCR chamber to amplify the DNA sample.

60. The nucleic acid assay method of claim 59, after amplifying the prepared DNA sample, further comprising:

slowly rotating the bio-disc and allowing a DNAse to flow into the PCR chamber; and

heating the PCR chamber to deactivate the DNAse and obtain single-stranded DNA fragments.

61. The nucleic acid assay method of claim 60, wherein each PCR chamber comprises a heater which is controlled independently from the heaters of the other PCR chambers to give single-stranded DNA fragments which vary in lengths.

62. An immunoassay method using the bio-disc of claim 6, the method comprising:

slowly rotating the bio-disc and allowing blood to pass through a filter to extract serum or an antigen;

slowly rotating the bio-disc to allow the antigen to enter a conjugate antibody chamber and incubating the conjugate antibody chamber for 1-2 minutes to bind the antigen to conjugate antibodies and form a conjugate-antigen complex;

slowly rotating the bio-disc to allow the conjugate-antigen complex to flow into the assay site and incubating the bio-disc in a stationary state to induce an antigen-antibody reaction between the conjugate-antigen complex and the capture antibodies; and

rotating the bio-disc to allow a washing buffer to flow into and wash the analyte site.

63. The bio-disc of any one of claims 1 through 17, wherein the assay site comprises an immunoassay sector and a nucleic acid probe assay sector arranged in an angular or radial direction to enable an immunoassay and a nucleic acid probe assay to be performed concurrently.

64. The bio-driver apparatus of claim 28 or 39, which sends an eject message or a warning message to a user if a bio-disc into which a sample has not be injected yet is loaded.

65. The bio-disc of any one of claims 1 through 17, wherein an additional impedance measurement device is installed in the preparation chamber so as to determine whether a sample has been injected into a bio-disc.

66. The bio-disc of claim 65, wherein the additional impedance measurement device comprises interdigitated array electrodes.

67. The bio-driver apparatus of claim 28 or 39, which continues assay or diagnosis even when an unloading or a stop command is input, and optionally sends a warding message or requesting a user's password, and stopping the assay or diagnosis or ejecting the bio-disc if a user enters the correct password.

68. The bio-driver apparatus of claim 28 or 39, further comprising a memory storing information on how many times a bio-disc has been used, its validation period, and kinds of diseases which it can diagnose, so as to provide a user with the stored information on the bio-disc or the availability of the bio-disc whenever the bio-disc is loaded.

69. The bio-driver apparatus of claim 28 or 39, comprising:

a play and search button and a stop button for general optical discs; and

a light emitting diode that indicates a bio-disc has been loaded.

70. The bio-driver apparatus of claim 28 or 39, comprising a liquid crystal display to display the status of progress in sample preparation, PCR, hybridization, and antigen-antibody reaction, which are main processes conducted in the bio-disc, in percentages or as a bar graph.

71. The bio-driver apparatus of claim 28 or 39, being connected to a computer monitor to display the status of progress in sample preparation, PCR, hybridization, and antigen-antibody reaction, which are main processes conducted in the bio-disc, in percentages or

as a bar or pie graph.

72. The bio-driver apparatus of claim 28 or 39, comprising:

a play and search button and a stop button for general optical discs; and

an indicator that indicates a bio-disc has been loaded.

FIG. 1A

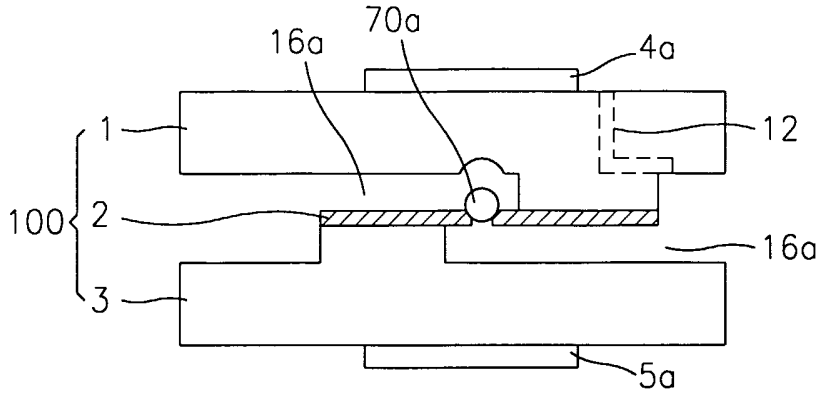


FIG. 1B

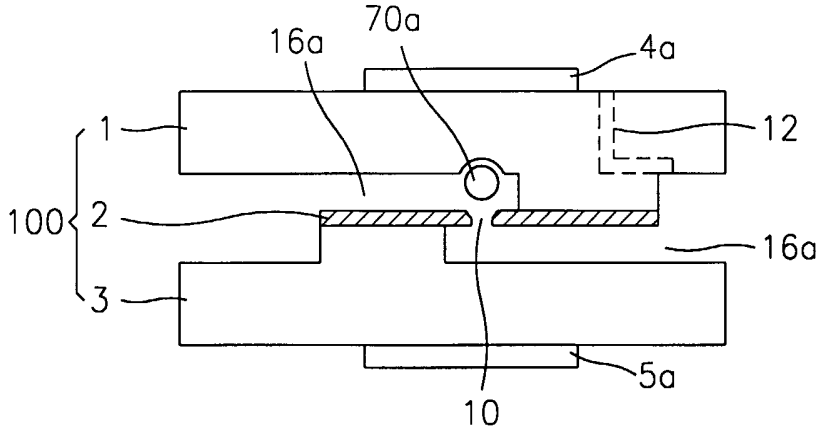


FIG. 1C

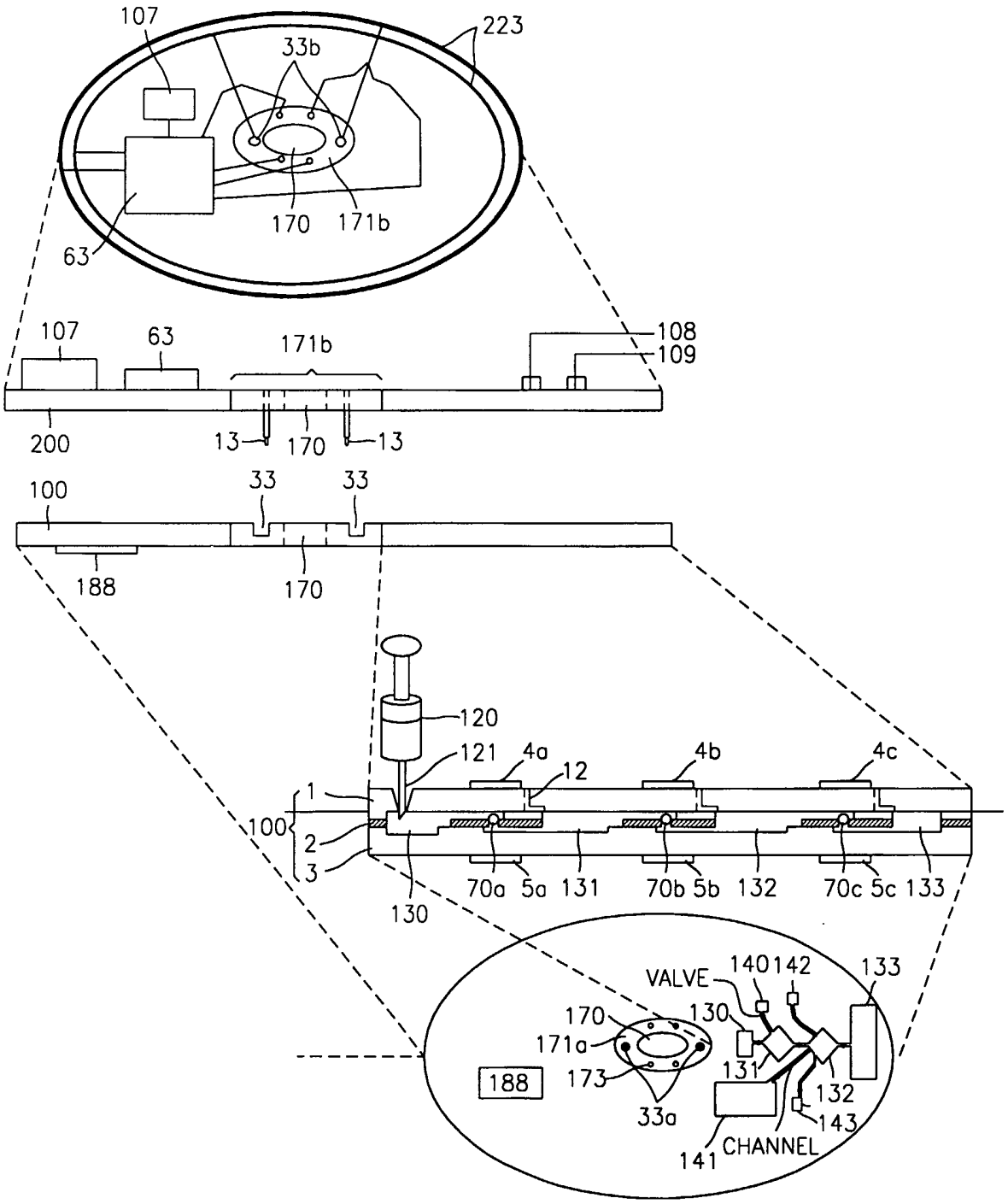

107
223
33b
170
171b
63
107
63
171b
108
109
200
13
170
13
100
33
33
188
170
120
121
4a
4b
4c
12
1
100
2
3
130
70a
5a
131
70b
5b
132
70c
5c
133
VALVE
140
142
133
170
130
171a
173
188
131
132
143
33a
141
CHANNEL

FIG. 1D

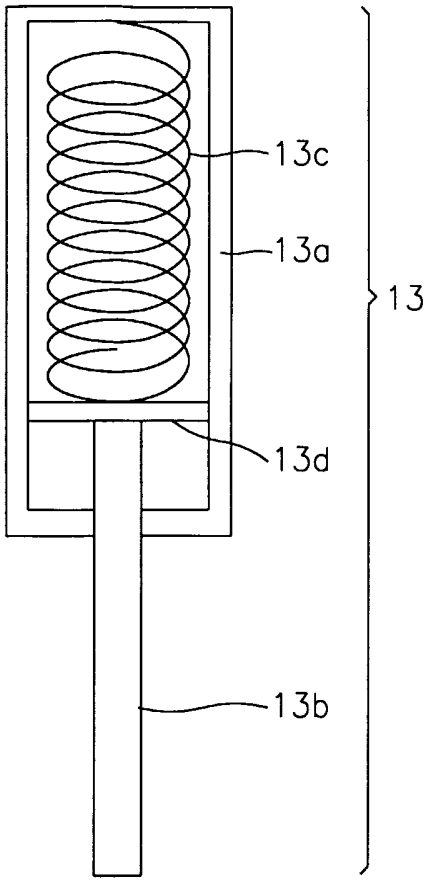
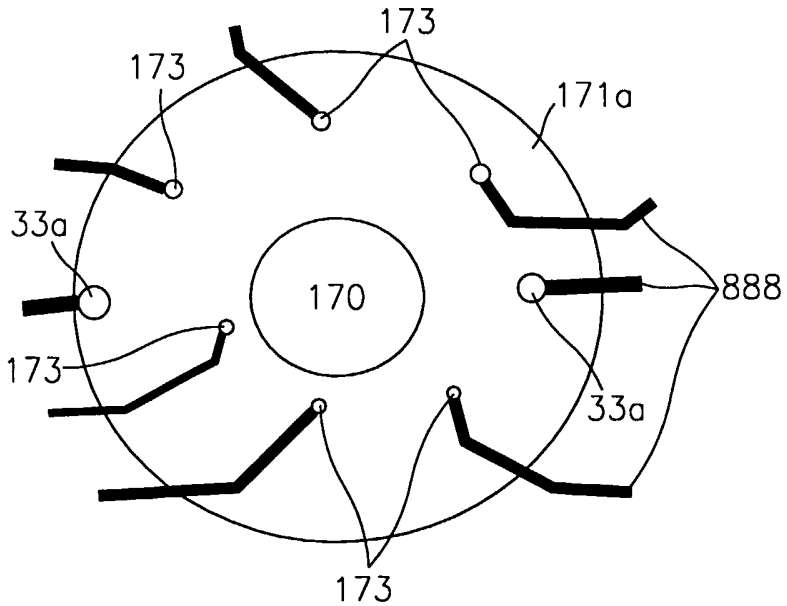


FIG. 1E



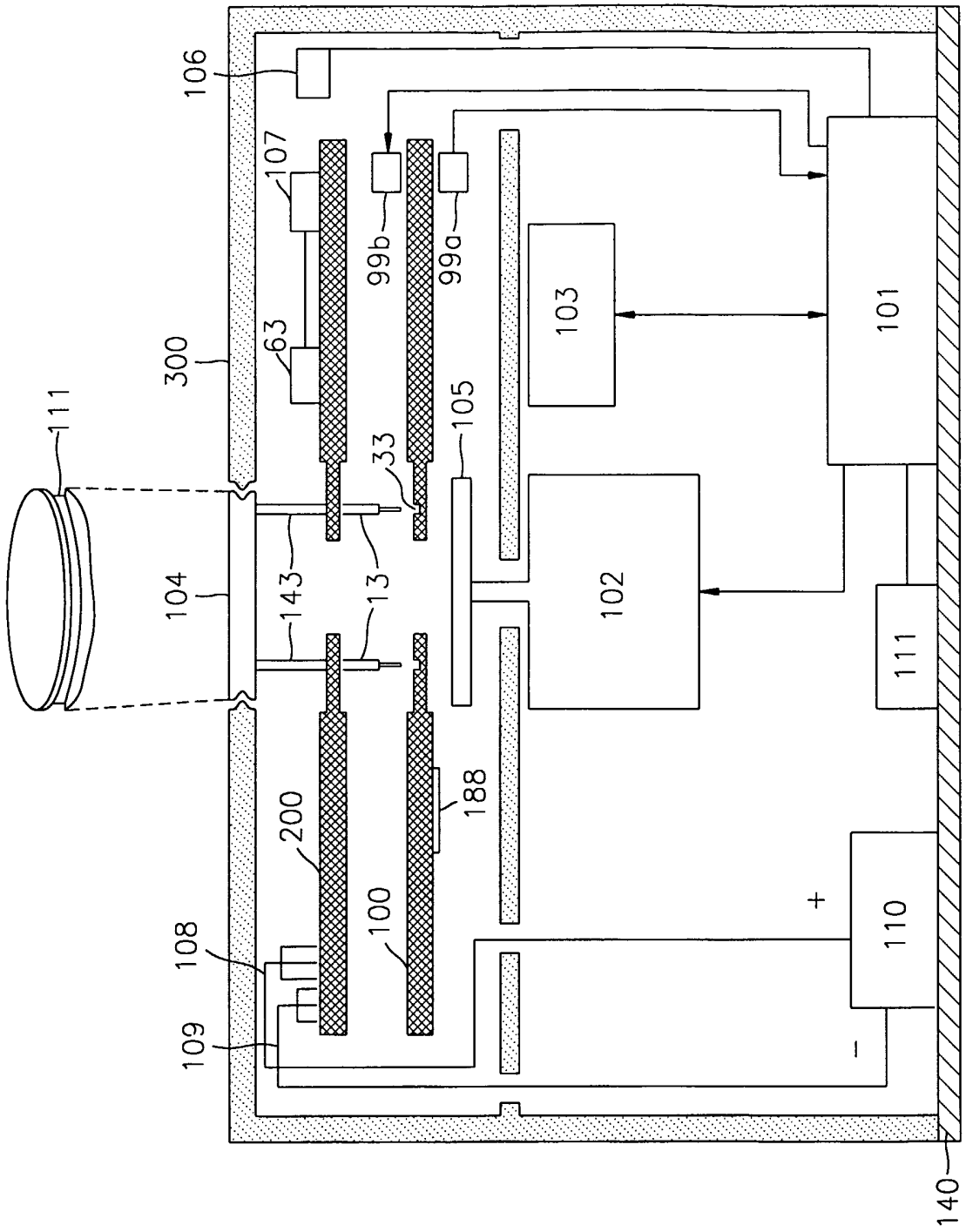

106
107
99b
99a
63
300
111
105
33
103
101
104
143
13
102
111
188
200
100
108
109
110
+
-
140

FIG. 1F

FIG. 1G

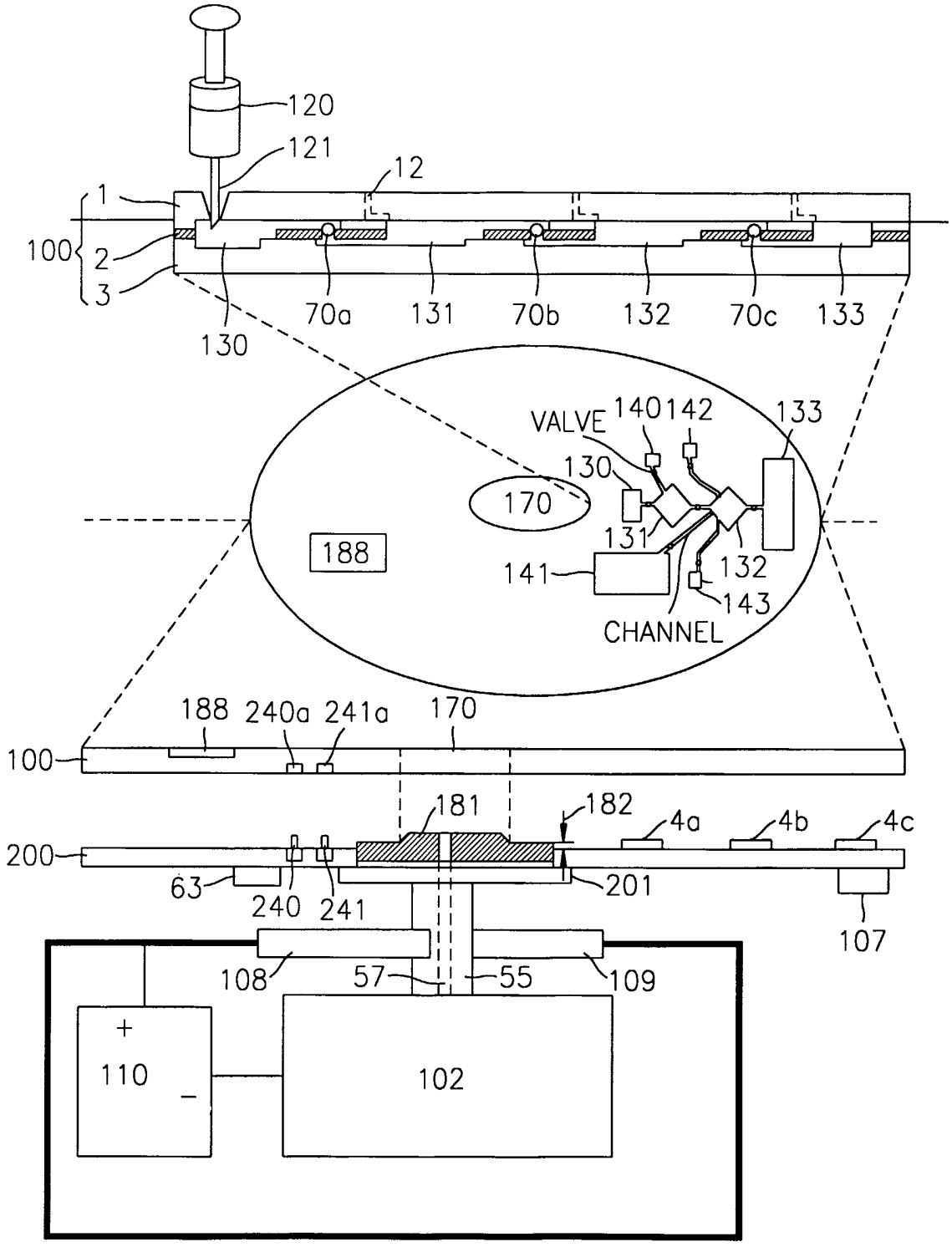

120
121
12
1
100
2
3
130
70a
131
70b
132
70c
133
VALVE
140
142
133
130
170
188
131
141
132
143
CHANNEL
188
240a
241a
170
100
181
182
4a
4b
4c
200
63
240
241
201
107
108
57
55
109
+
110
−
102

FIG. 1H

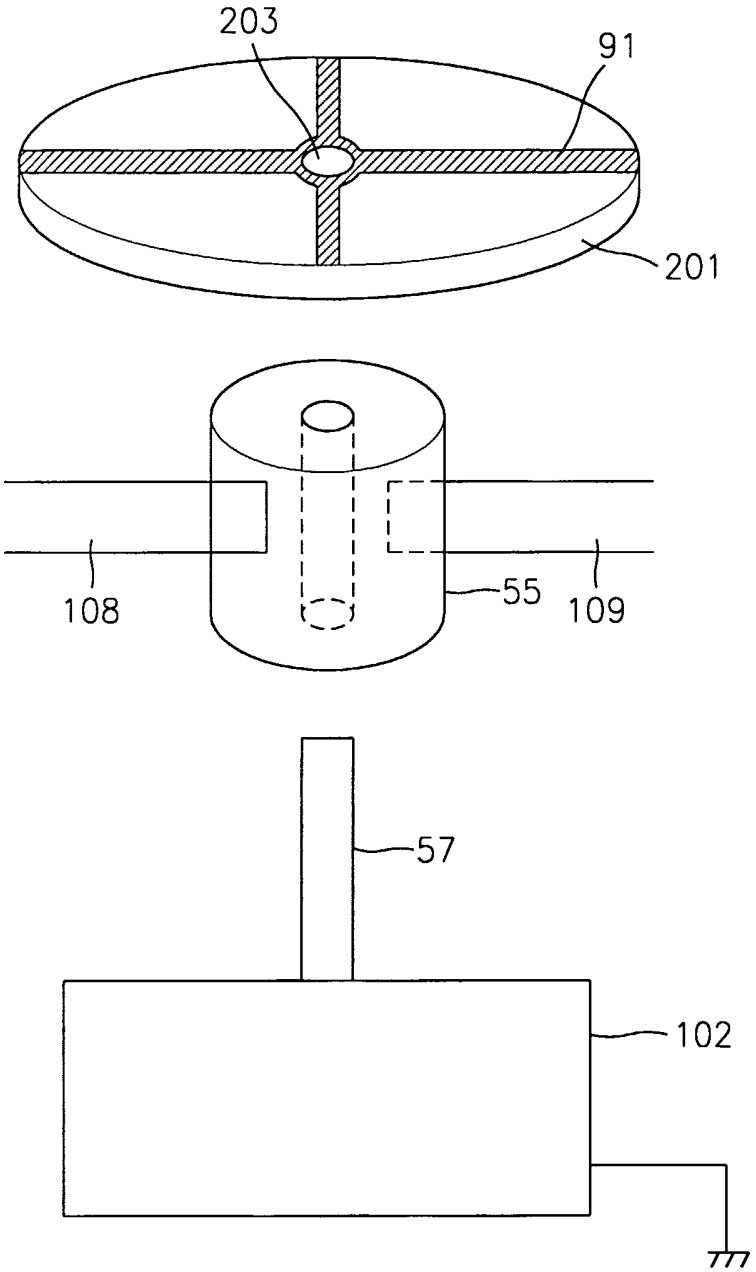


FIG. 1I

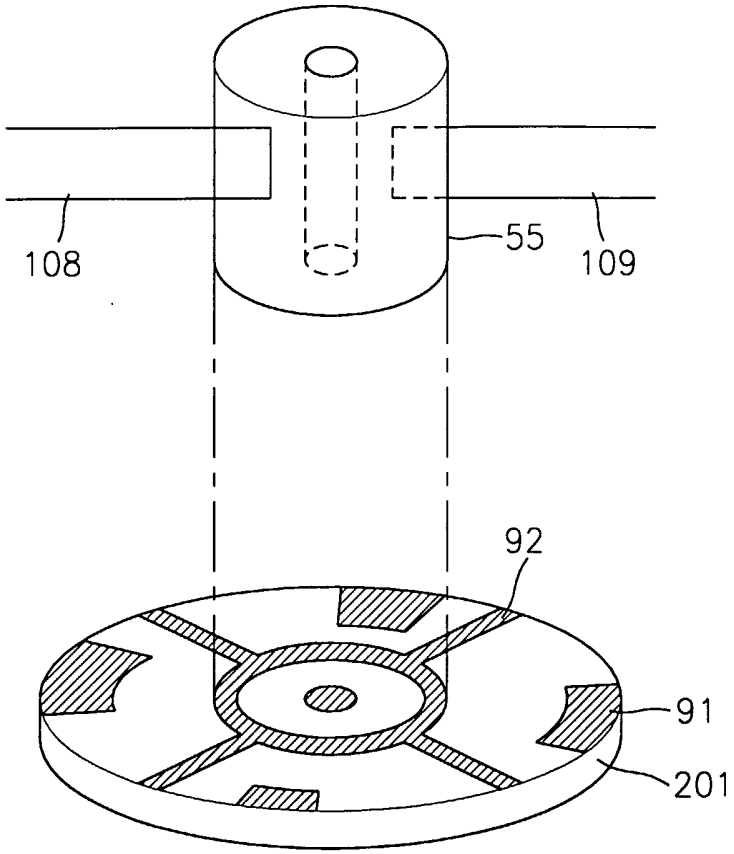


FIG. 1J

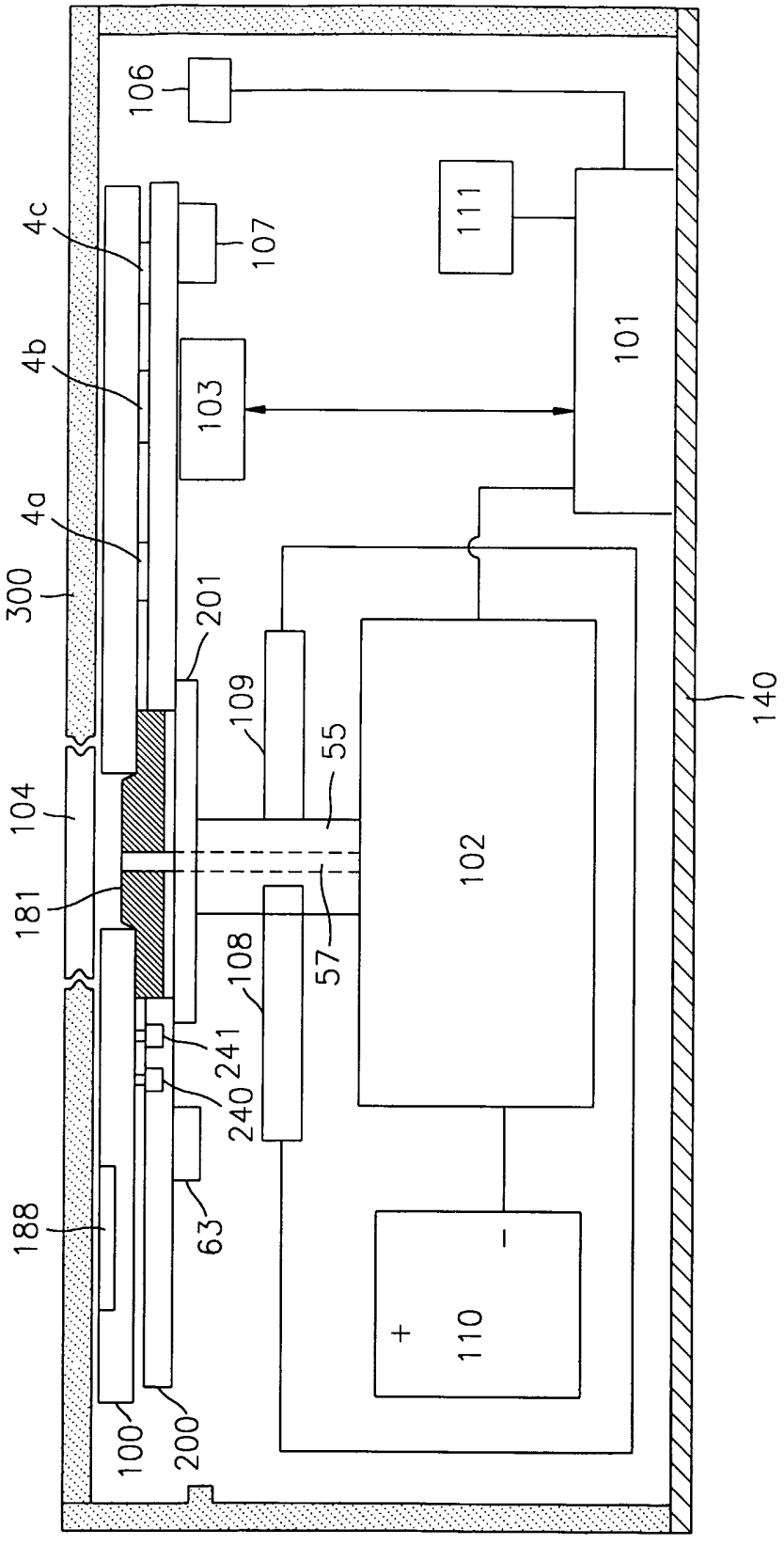

106
111
4c
107
101
4b
103
4a
300
201
109
55
140
104
102
181
57
108
241
240
188
63
110
+
−
100
200

FIG. 2A

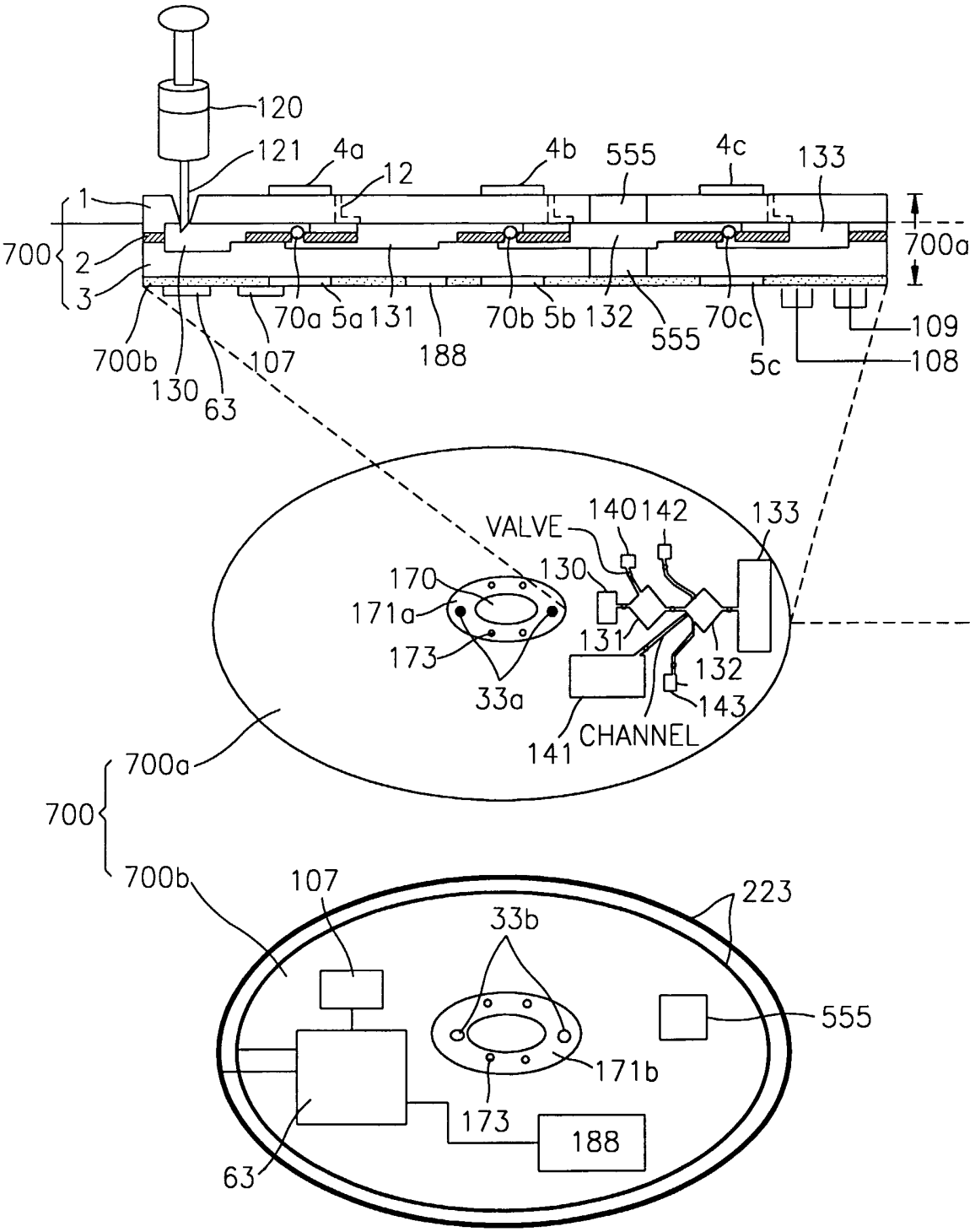

120
121
4a
12
4b
555
4c
133
1
700
2
3
700a
700b
130
63
107
70a
5a
131
188
70b
5b
132
555
70c
5c
109
108
VALVE
140
142
133
170
171a
173
33a
130
131
132
143
141
CHANNEL
700a
700
700b
107
223
33b
555
171b
173
188
63

FIG. 2B

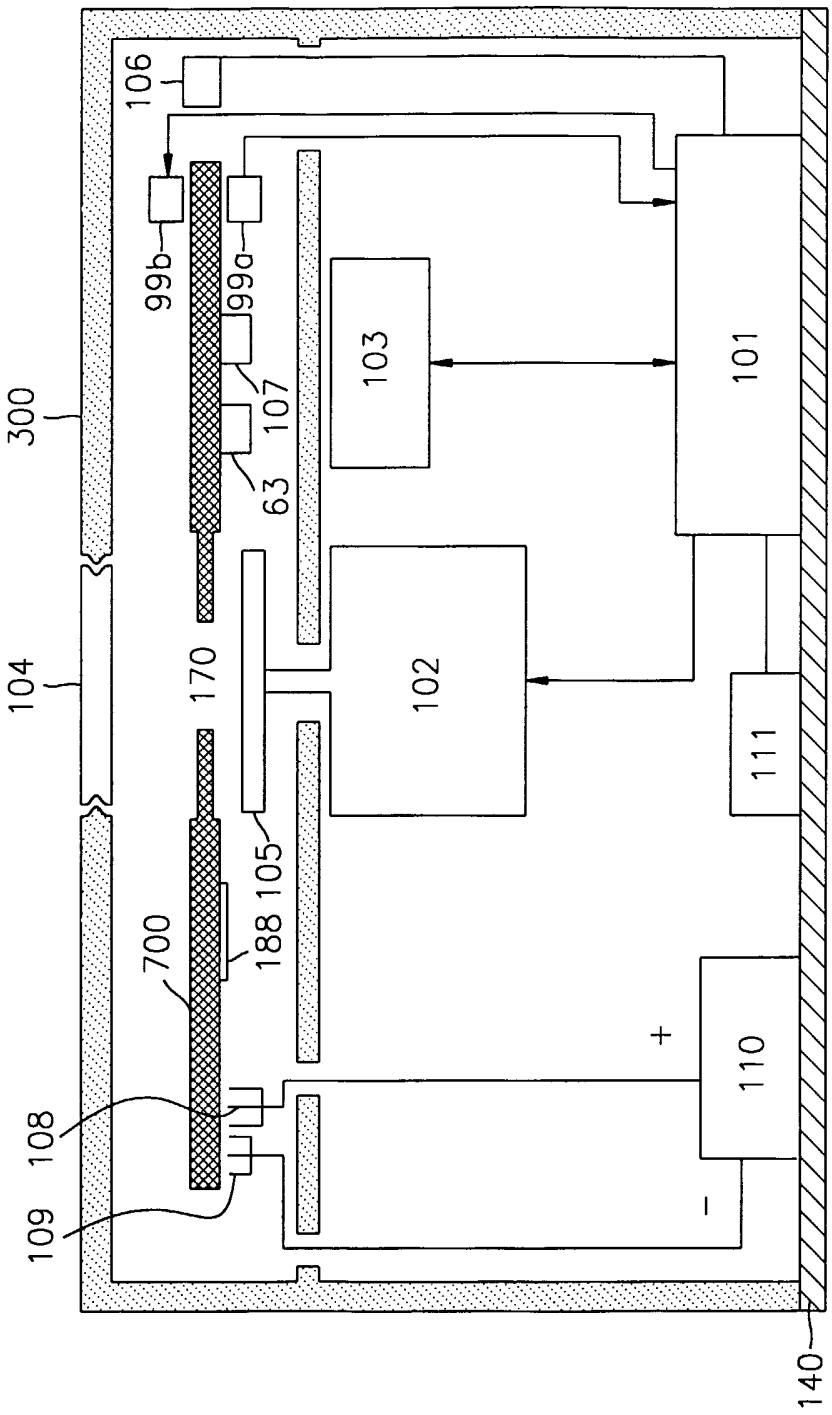

106
99b
99a
107
63
103
101
300
104
170
102
111
105
188
700
108
109
110
+
-
140

FIG. 2C

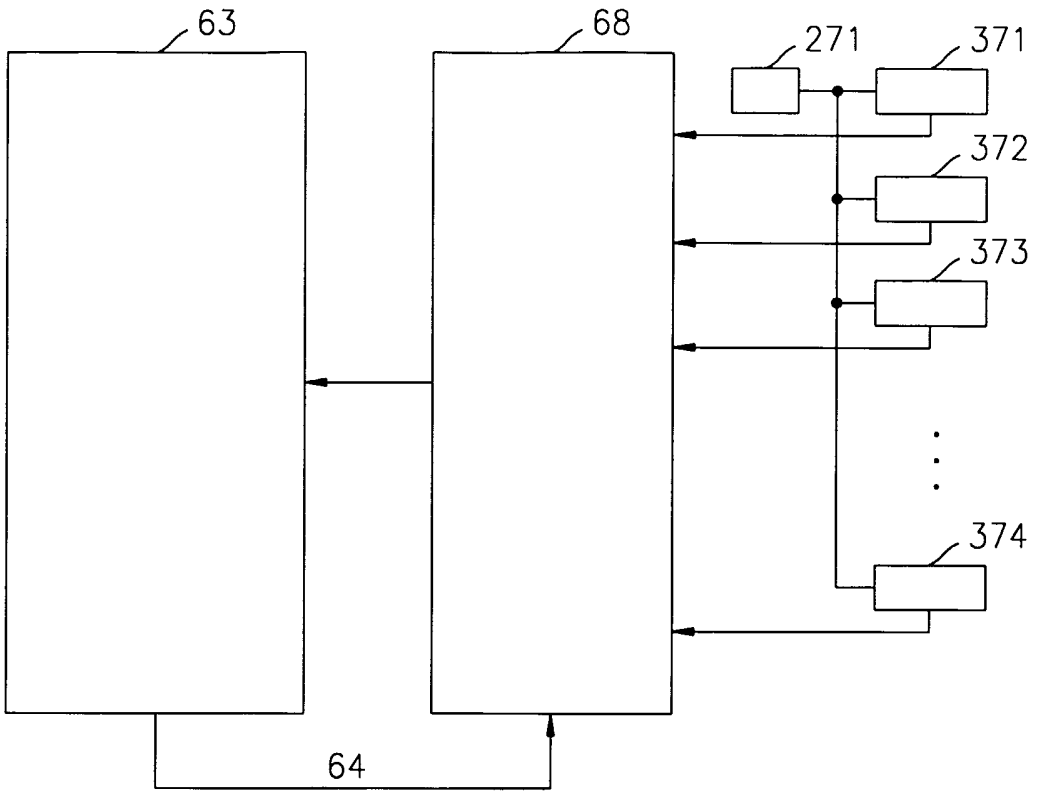


FIG. 2D

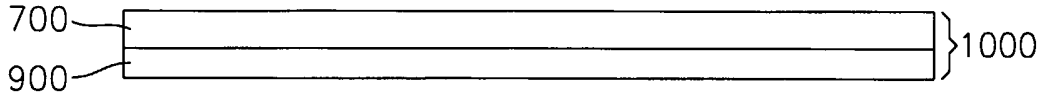


FIG. 3A

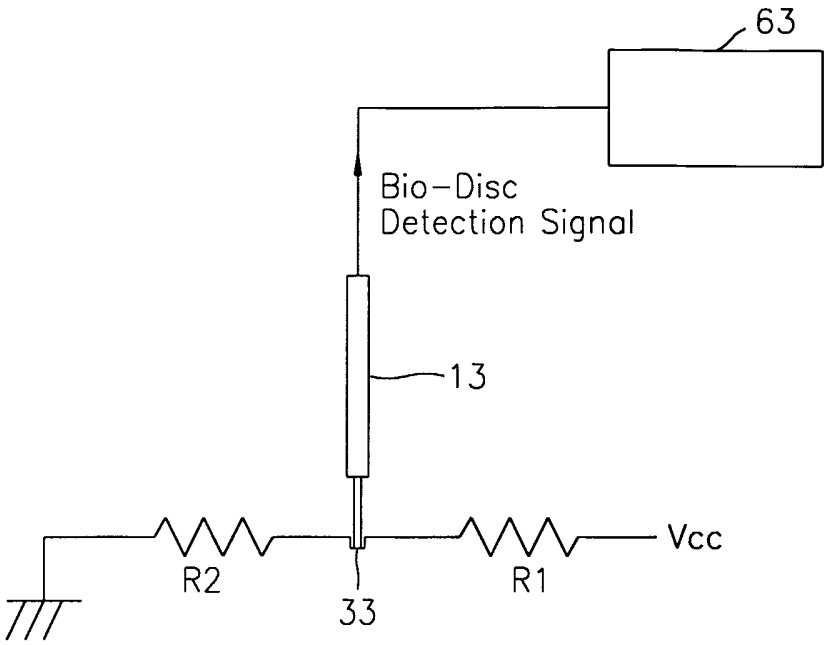


FIG. 3B

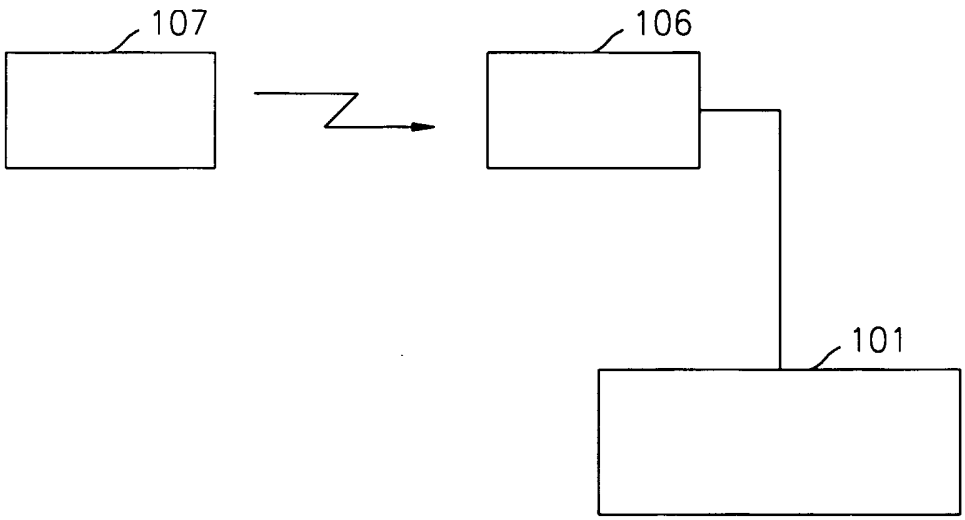
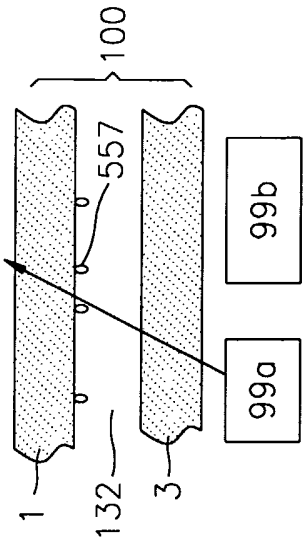


FIG. 4A


100
557
99b
99a
1
132
3

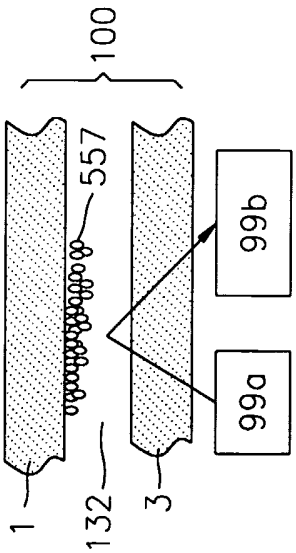
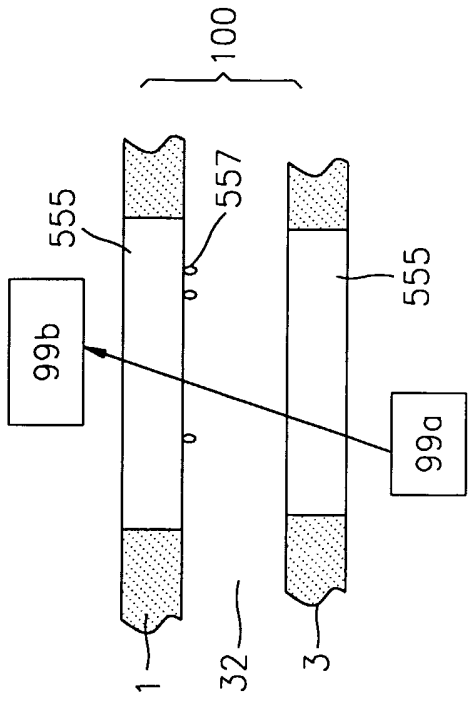

100
557
99b
99a
1
132
3

FIG. 4B


100
555
557
99b
555
99a
1
132
3

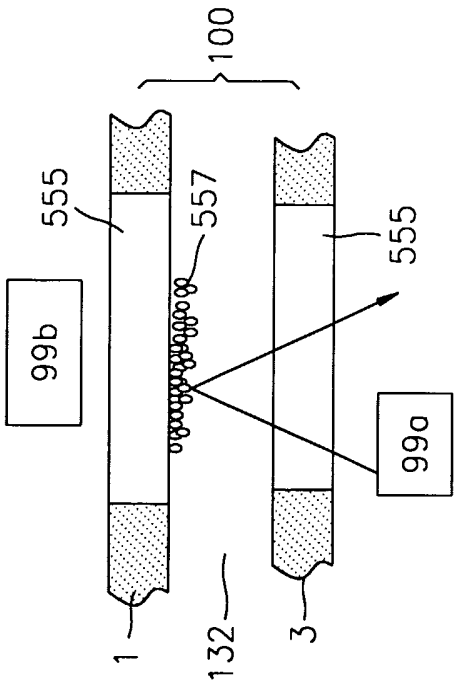

100
555
557
99b
555
99a
1
132
3

FIG. 5A

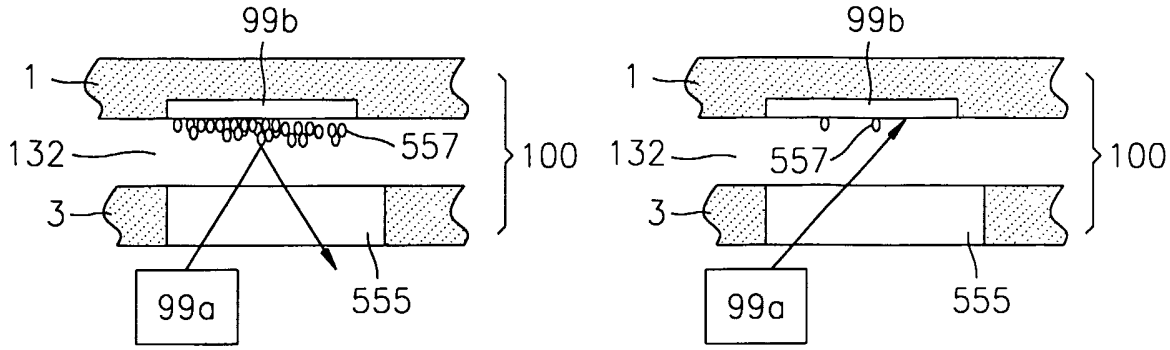

99b
1
132
557
100
3
99a
555
99b
1
132
557
100
3
99a
555

FIG. 5B

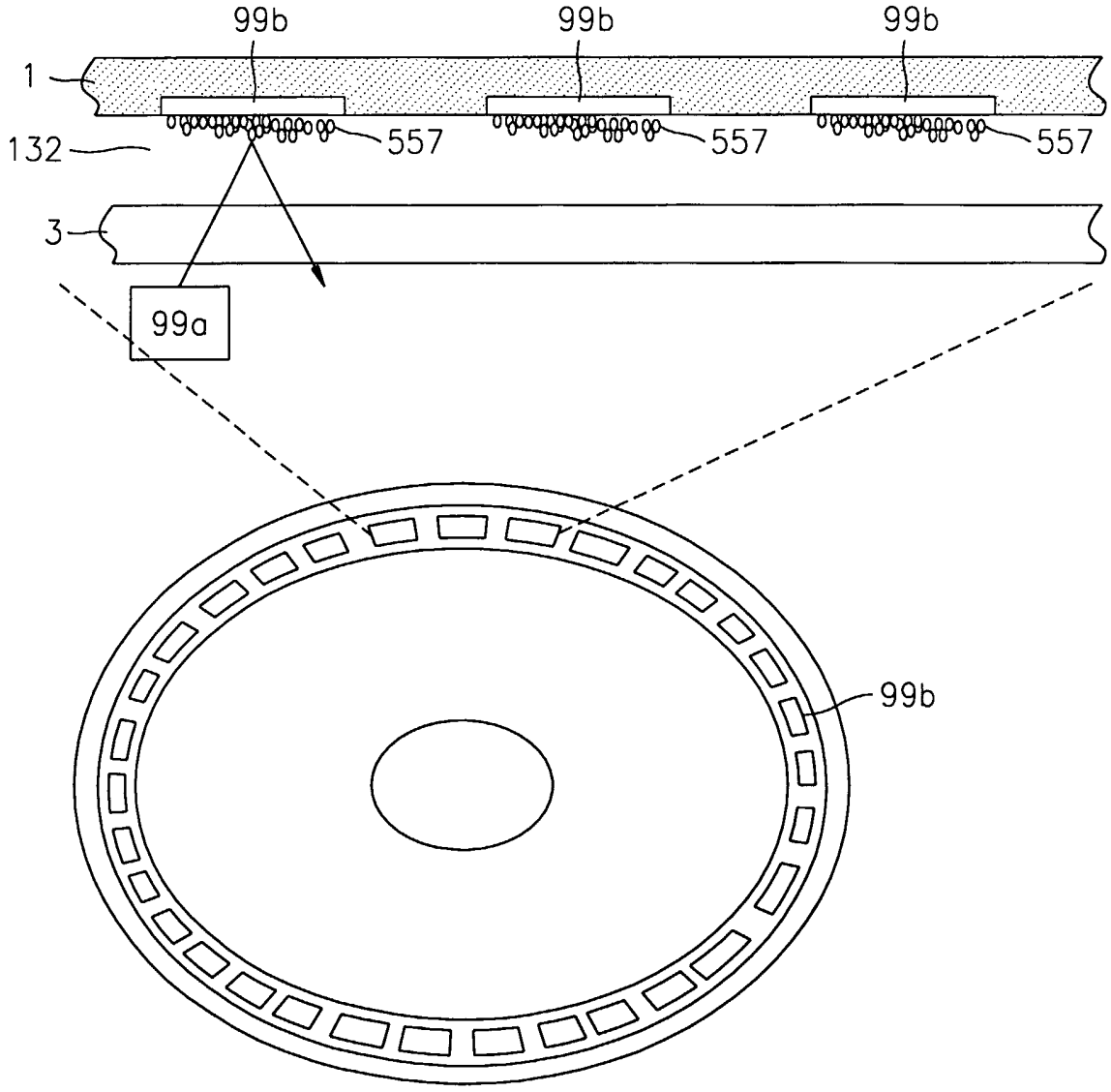

99b
99b
99b
1
132
557
557
557
3
99a
99b

FIG. 6A

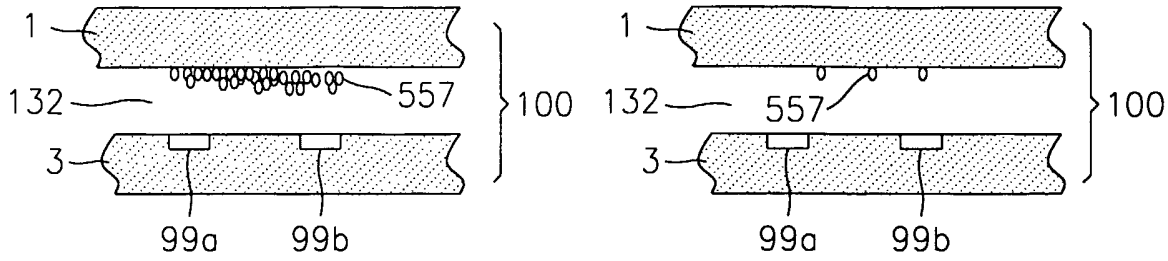

1
132
557
100
3
99a
99b
1
132
557
100
3
99a
99b

FIG. 6B

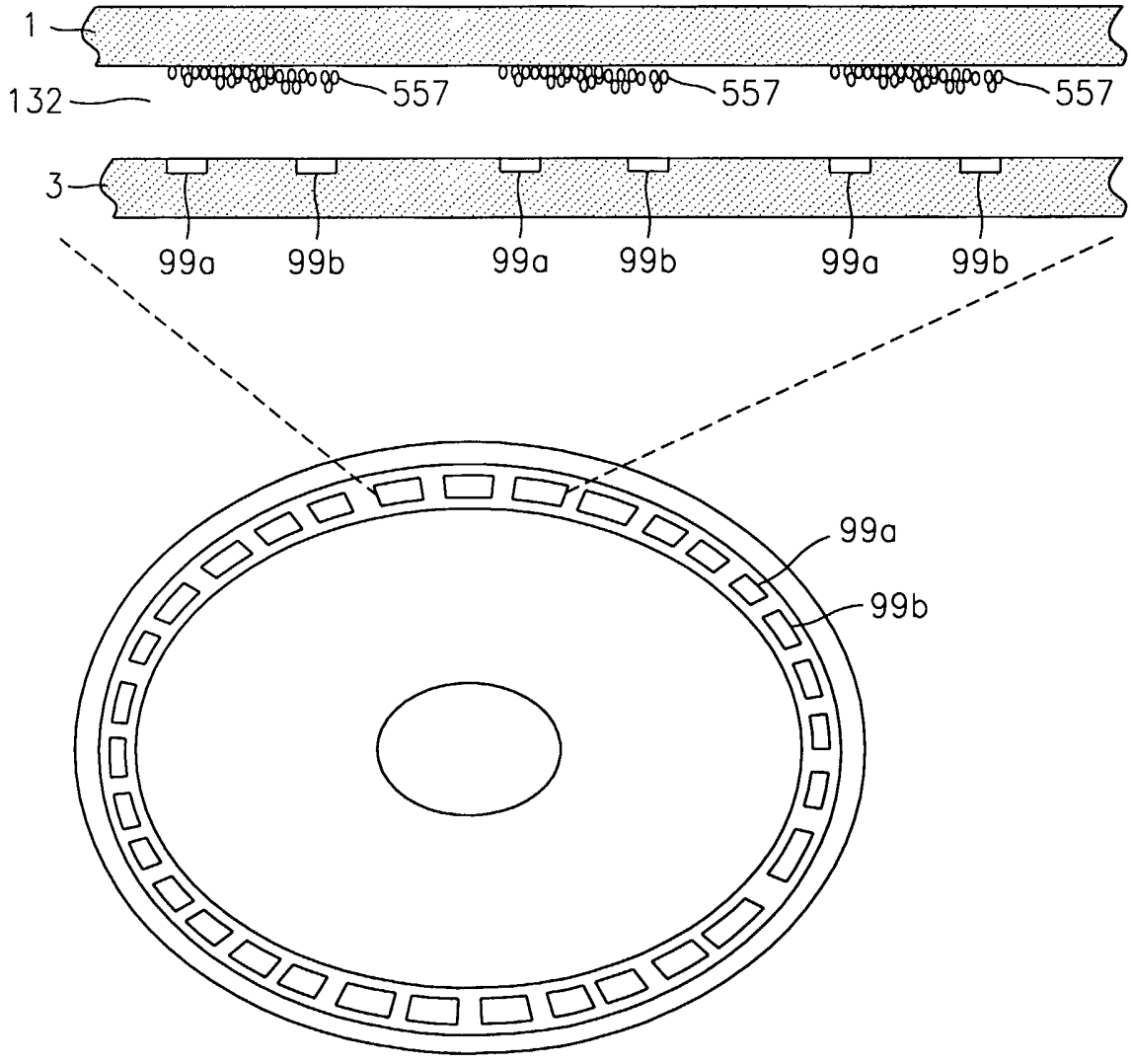

1
132
557
557
557
3
99a
99b
99a
99b
99a
99b
99a
99b

FIG. 6C

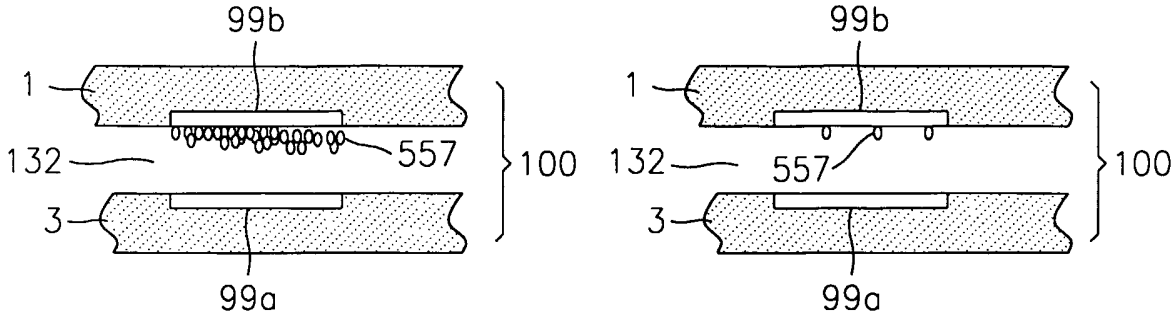

99b
1
132
557
100
3
99a
99b
1
132
557
100
3
99a

FIG. 6D

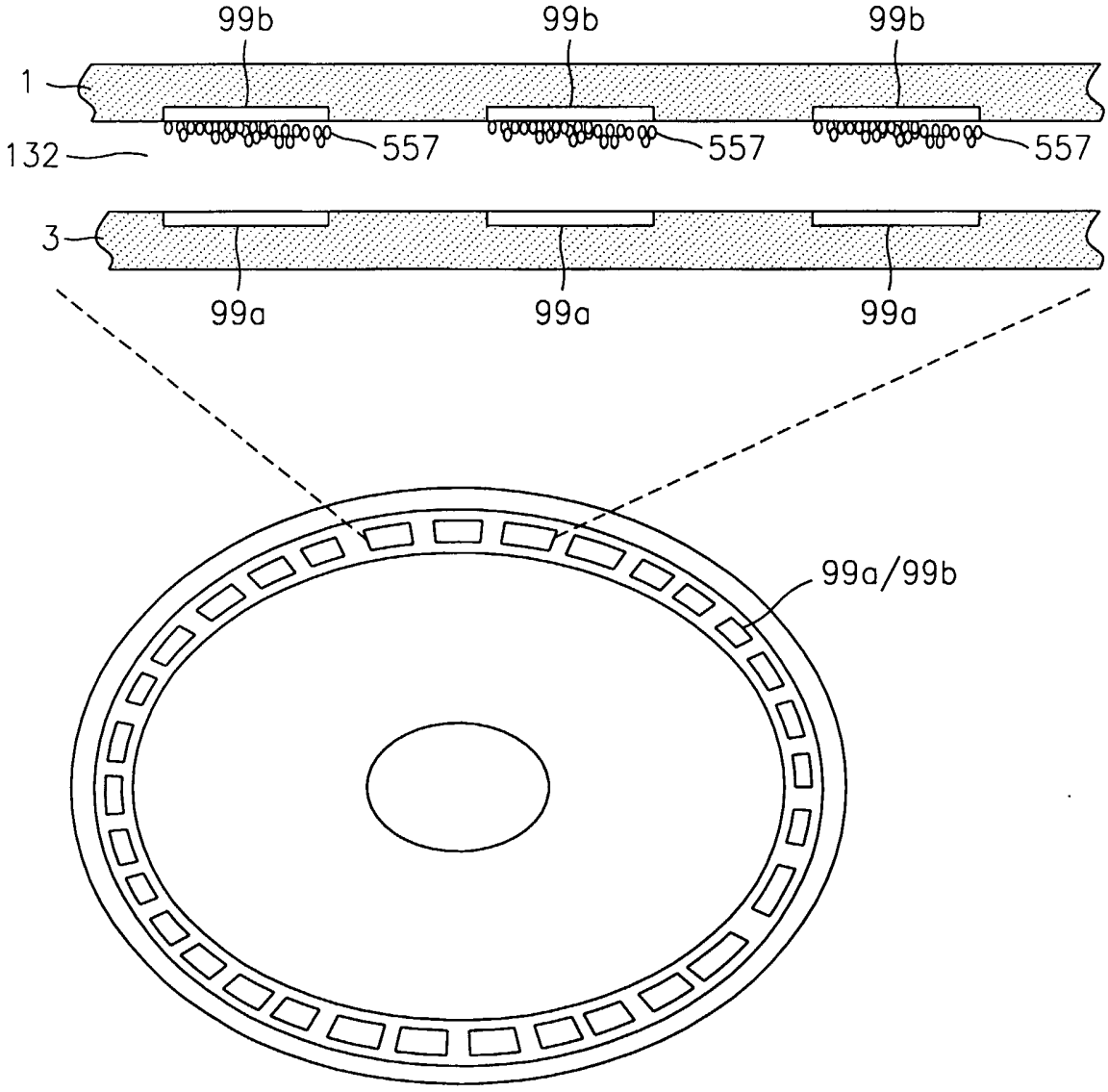

99b
99b
99b
1
132
557
557
557
3
99a
99a
99a
99a/99b

FIG. 7A

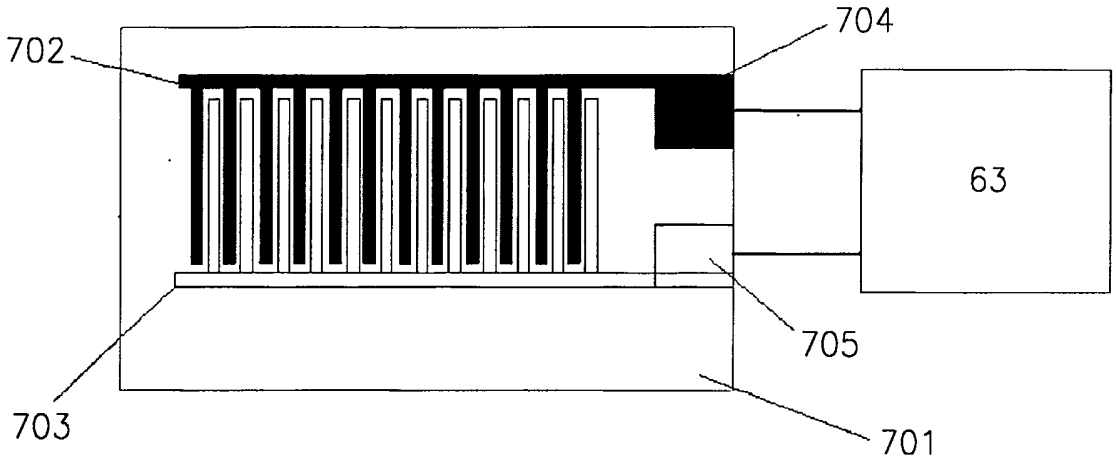

702
704
63
705
703
701

FIG. 7B

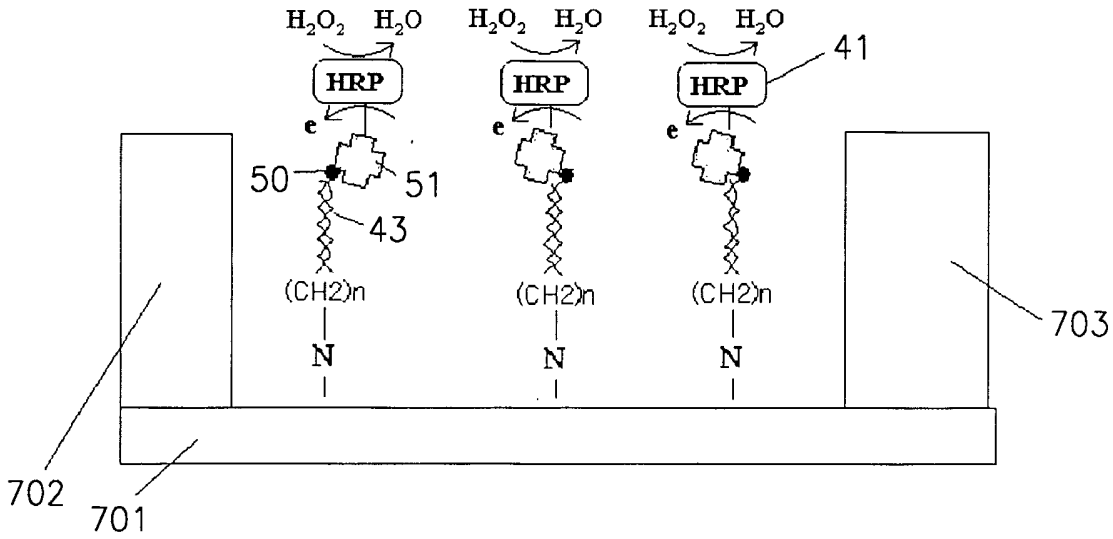

H_2O_2 H_2O
HRP
e
50
51
43
(CH2)n
N
41
703
702
701

FIG. 7C

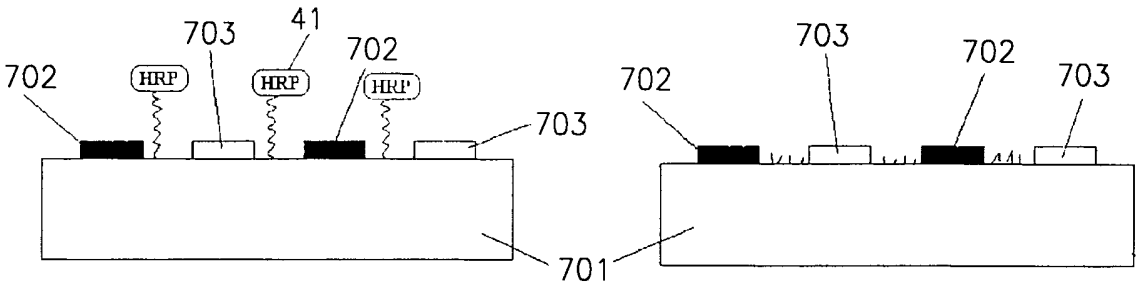

702
703
41
702
HRP
HRP
HRP
703
701
703
702
702
703

FIG. 7D

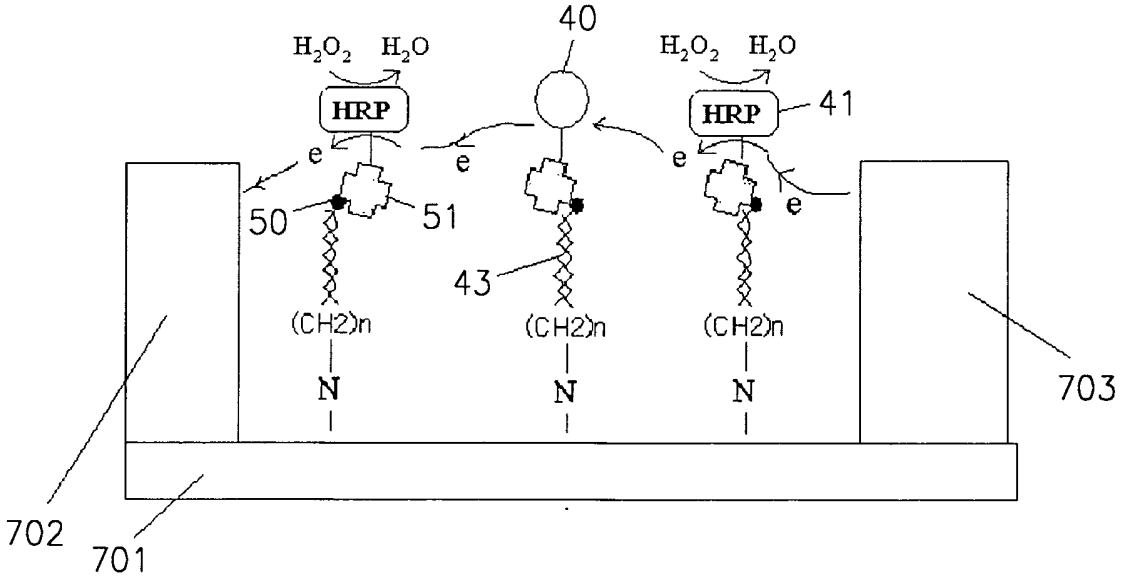

40
H_2O_2 H_2O
H_2O_2 H_2O
HRP
HRP
41
e
e
e
e
50
51
43
(CH2)n
(CH2)n
(CH2)n
N
N
N
703
702
701

FIG. 7E

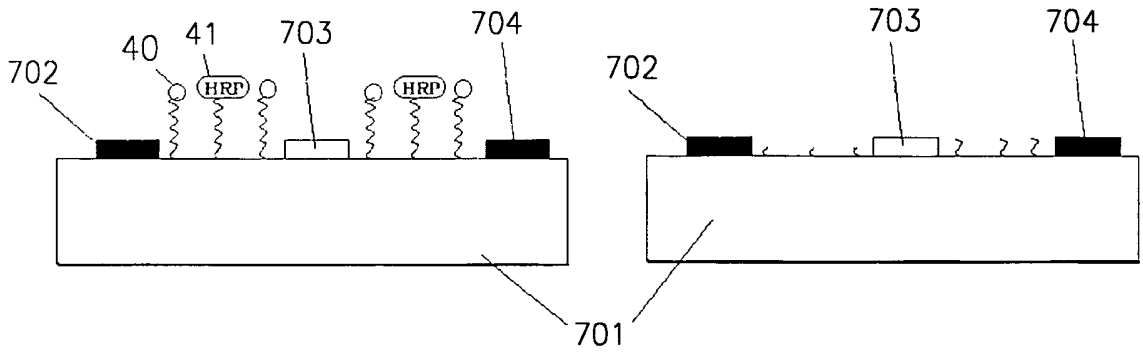

702
40
41
HRP
703
704
HRP
702
703
704
701

FIG. 7F

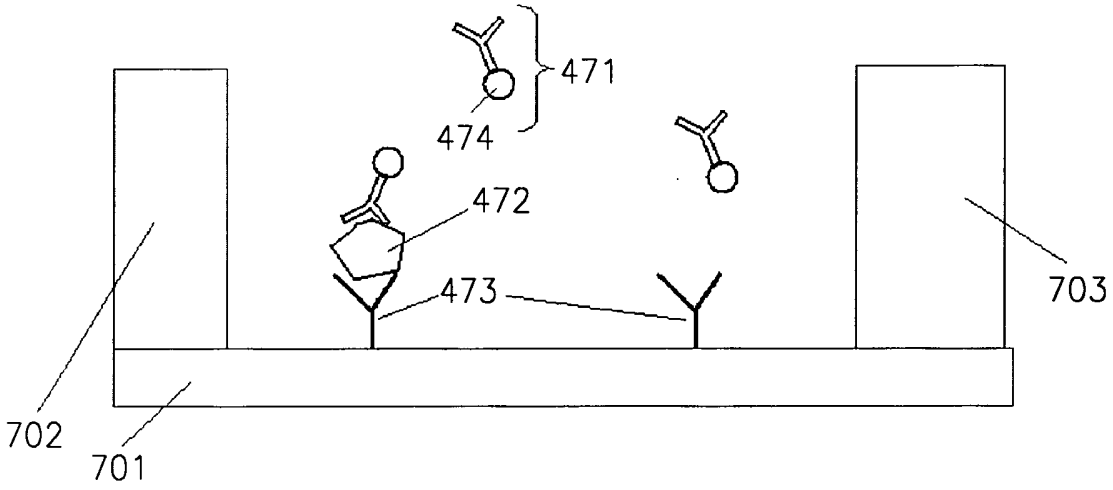

471
474
472
473
703
702
701

FIG. 7G

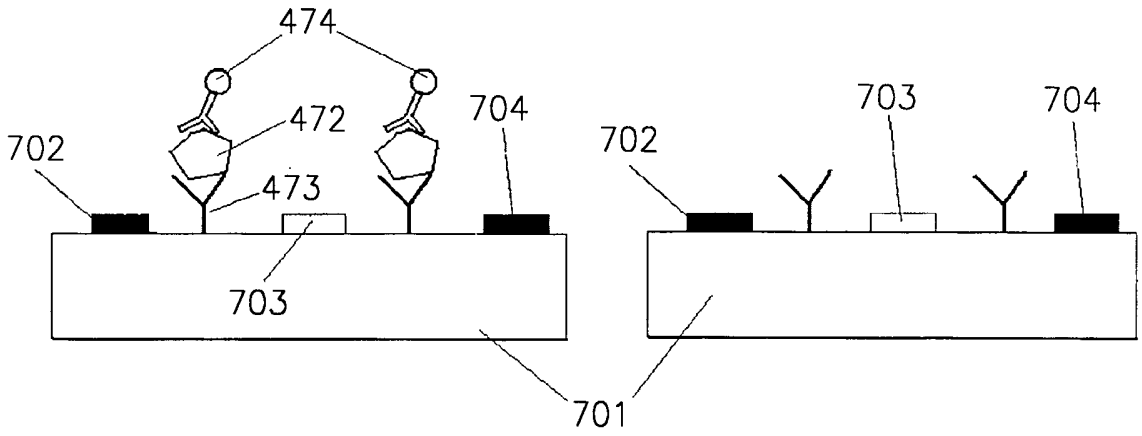


FIG. 8A

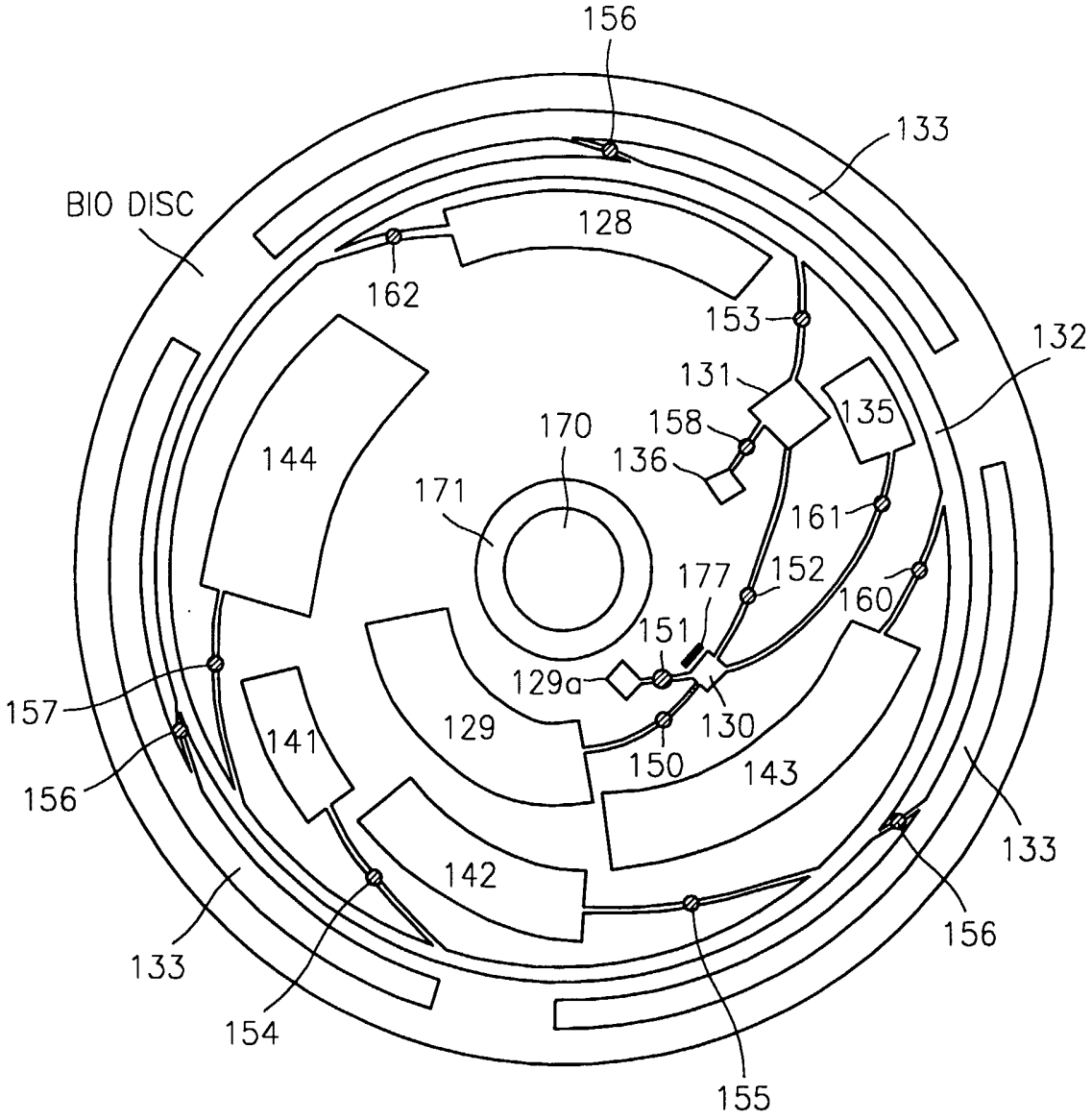

156
133
BIO DISC
128
162
153
132
131
135
158
170
136
144
171
161
177
152
160
151
129a
157
141
129
130
150
143
156
133
142
133
156
154
155

FIG. 8B

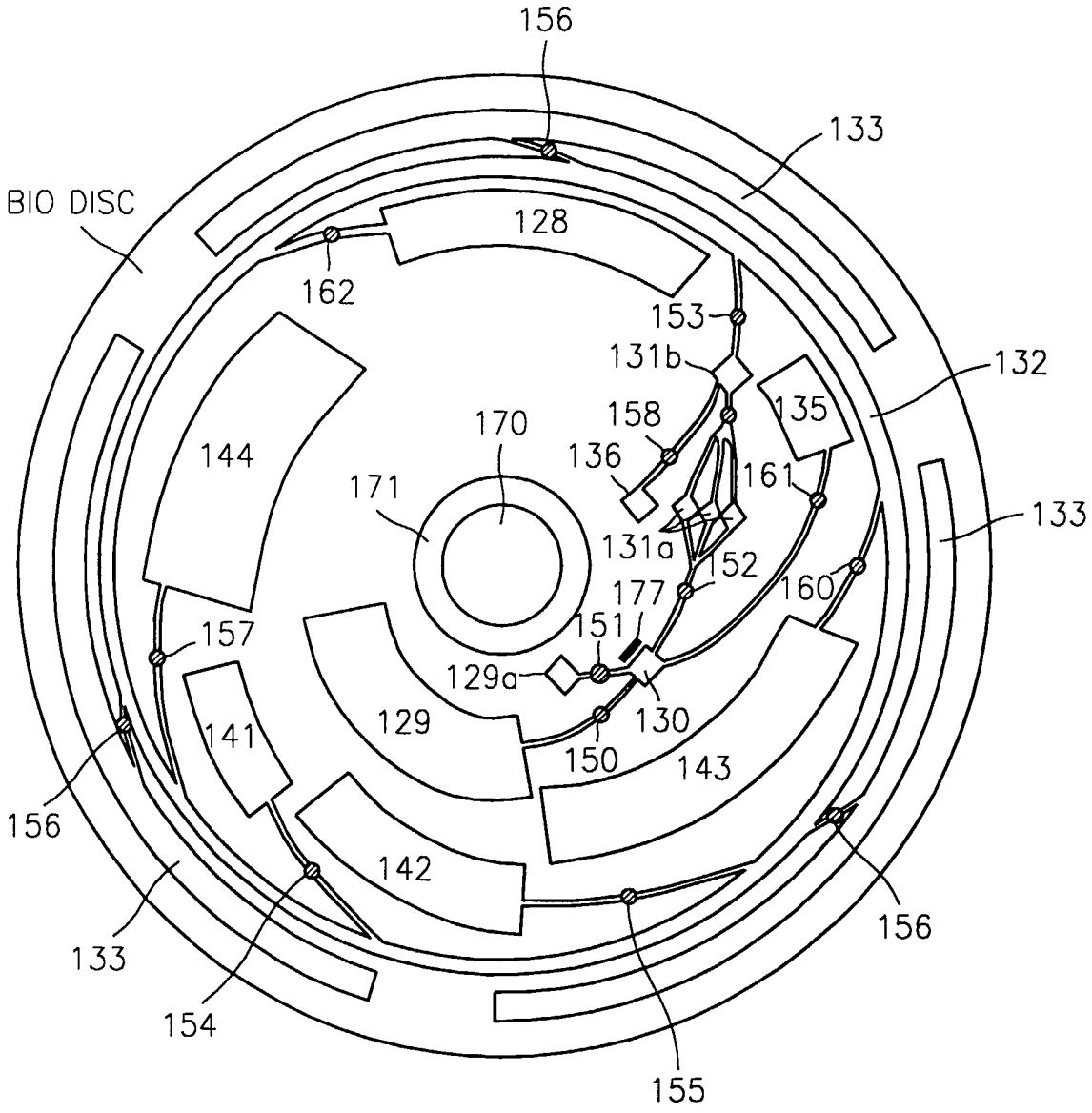

156
133
BIO DISC
128
162
153
131b
132
158
135
170
136
144
161
171
133
131a
152
177
160
157
151
129a
130
141
129
150
143
156
142
156
133
154
155

FIG. 8C

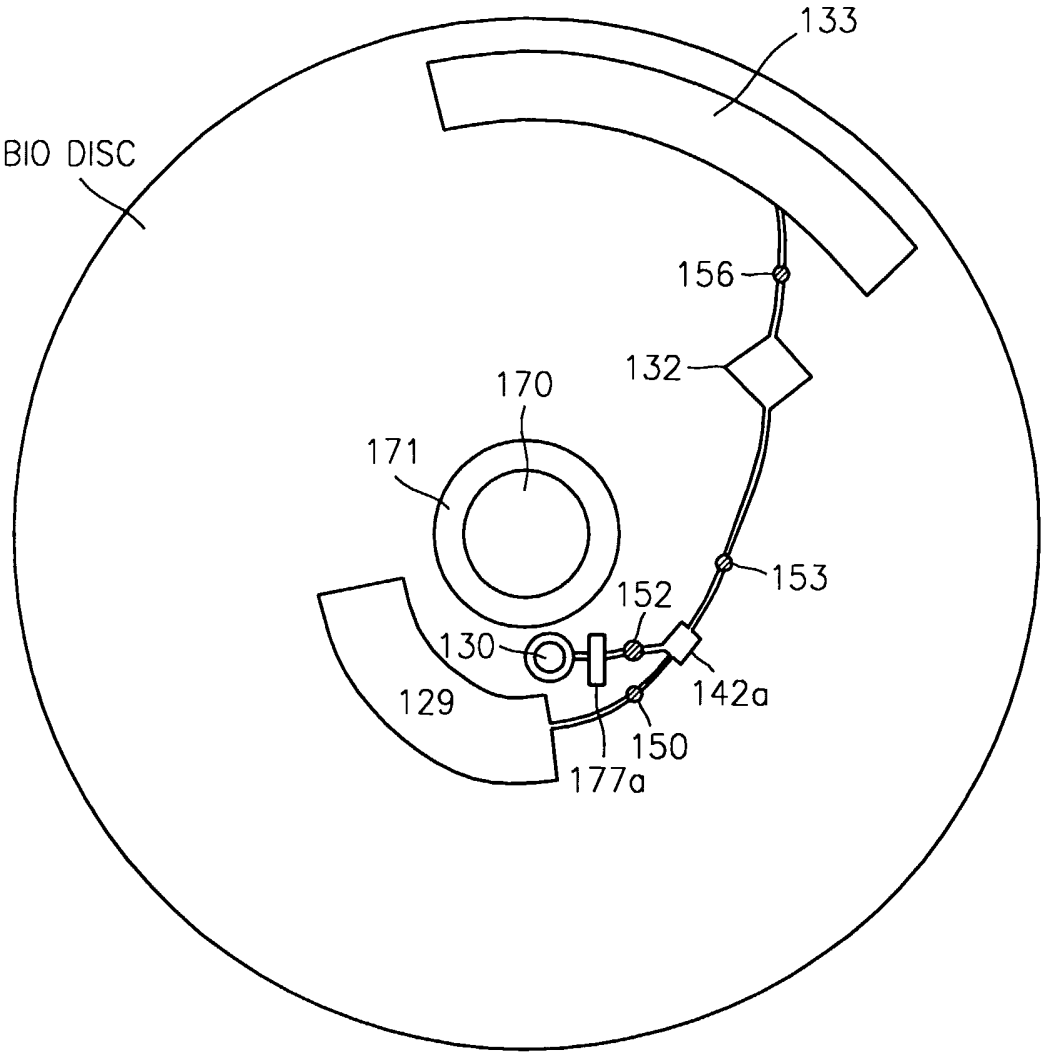


FIG. 8D

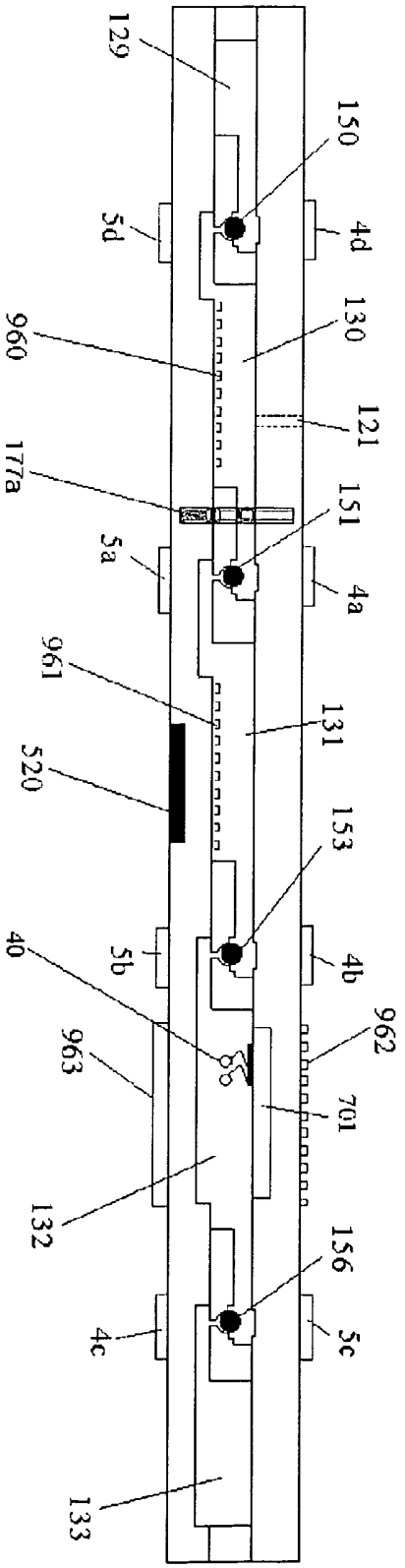

129
150
5d
4d
130
960
121
177a
151
5a
4a
961
131
520
153
40
5b
4b
962
963
701
132
156
4c
5c
133

FIG. 8E

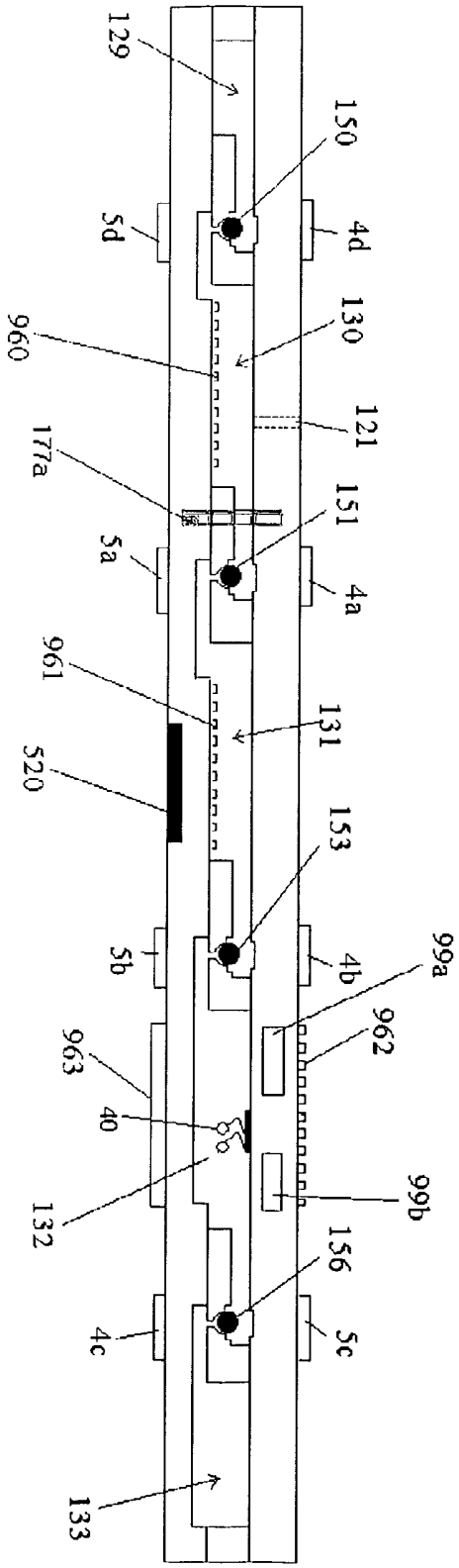

129
150
5d
4d
130
960
121
177a
151
5a
4a
961
131
520
153
5b
4b
99a
962
963
40
99b
132
156
4c
5c
133

FIG. 8F

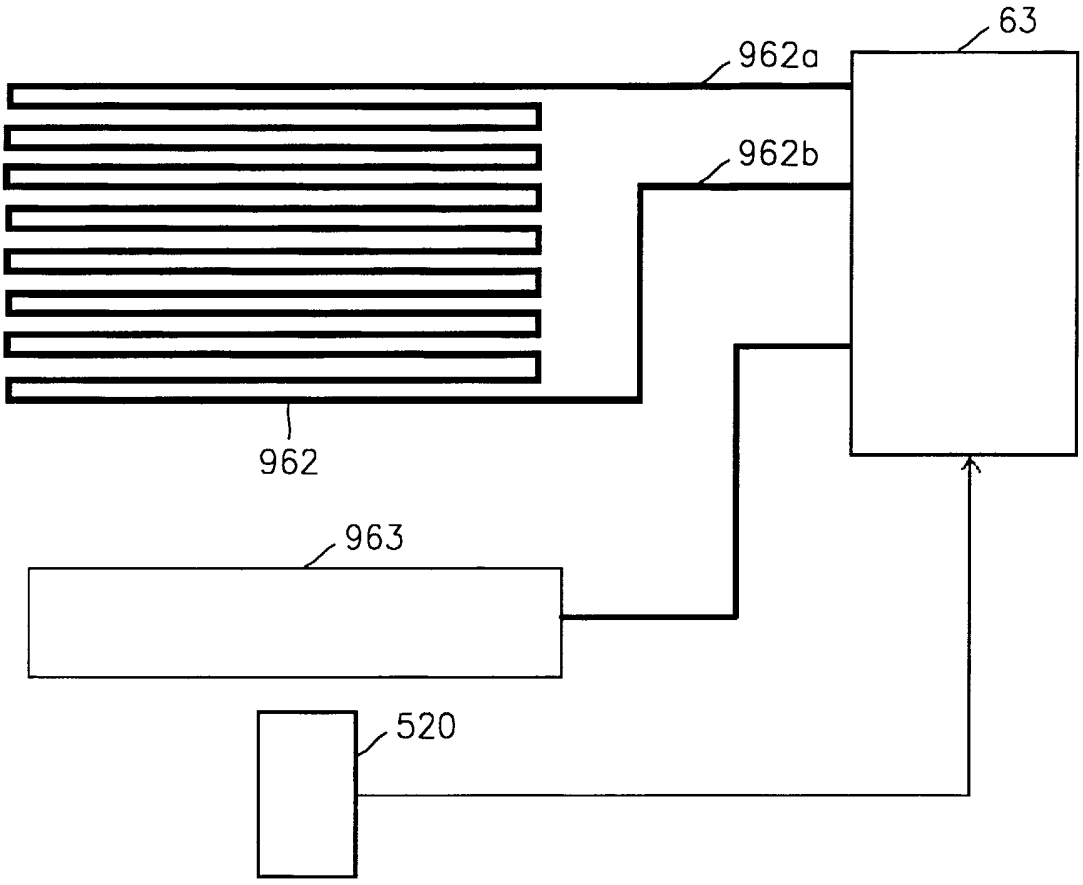


FIG. 9A

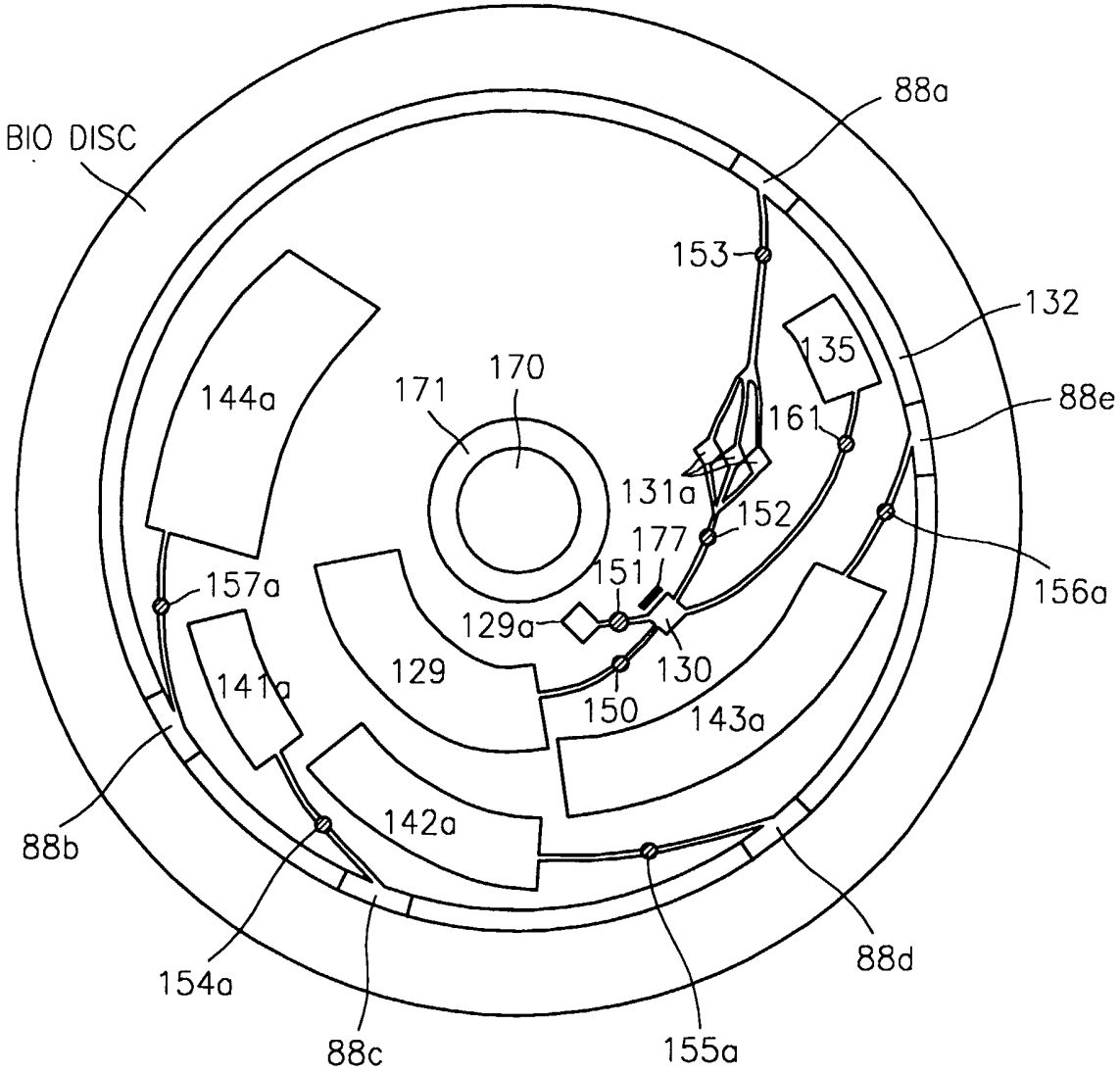

BIO DISC
88a
153
132
135
144a
171
170
88e
161
131a
152
177
151
157a
156a
129a
130
129
150
141a
143a
142a
88b
154a
88c
155a
88d

FIG. 9B

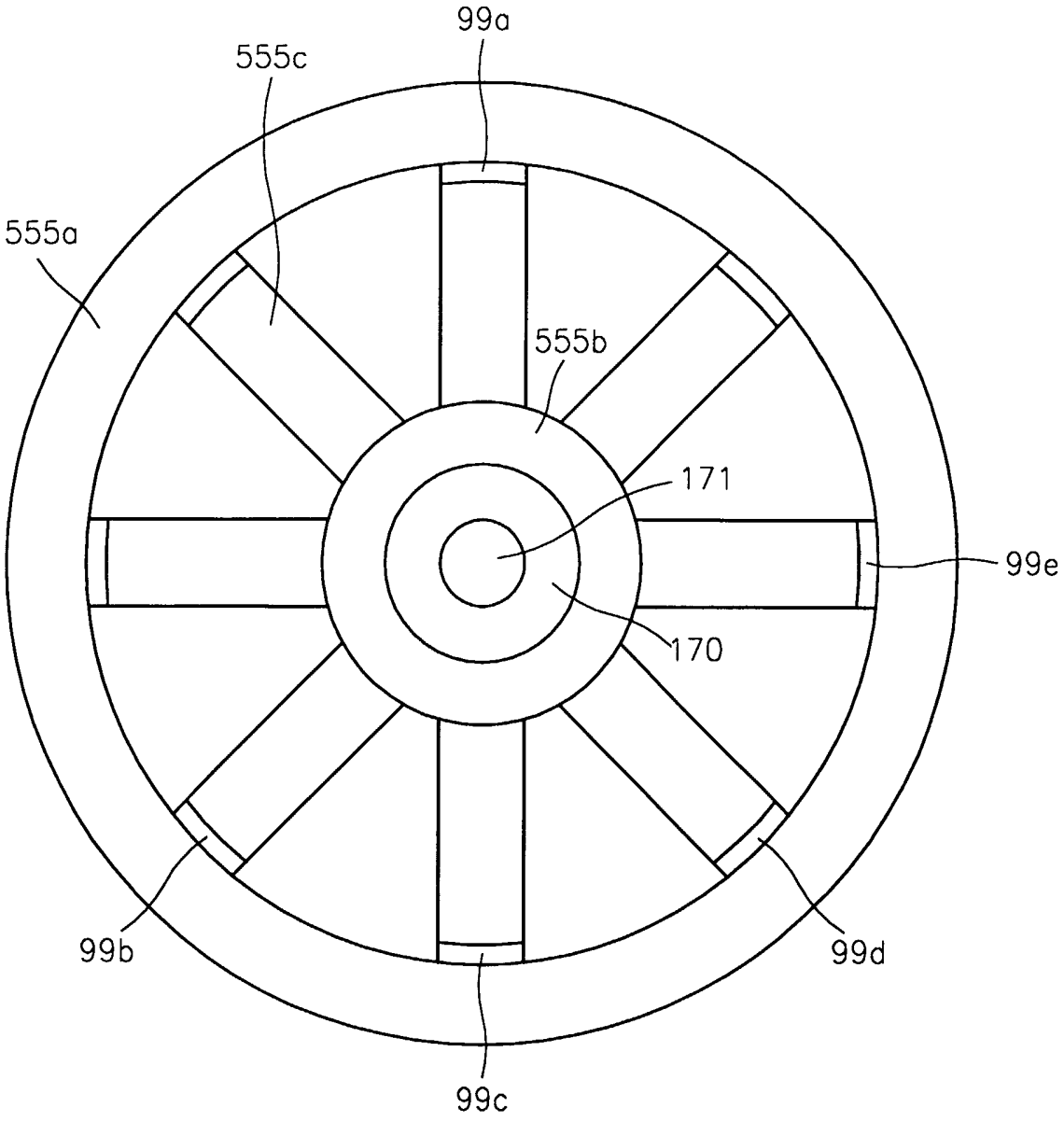


FIG. 10A

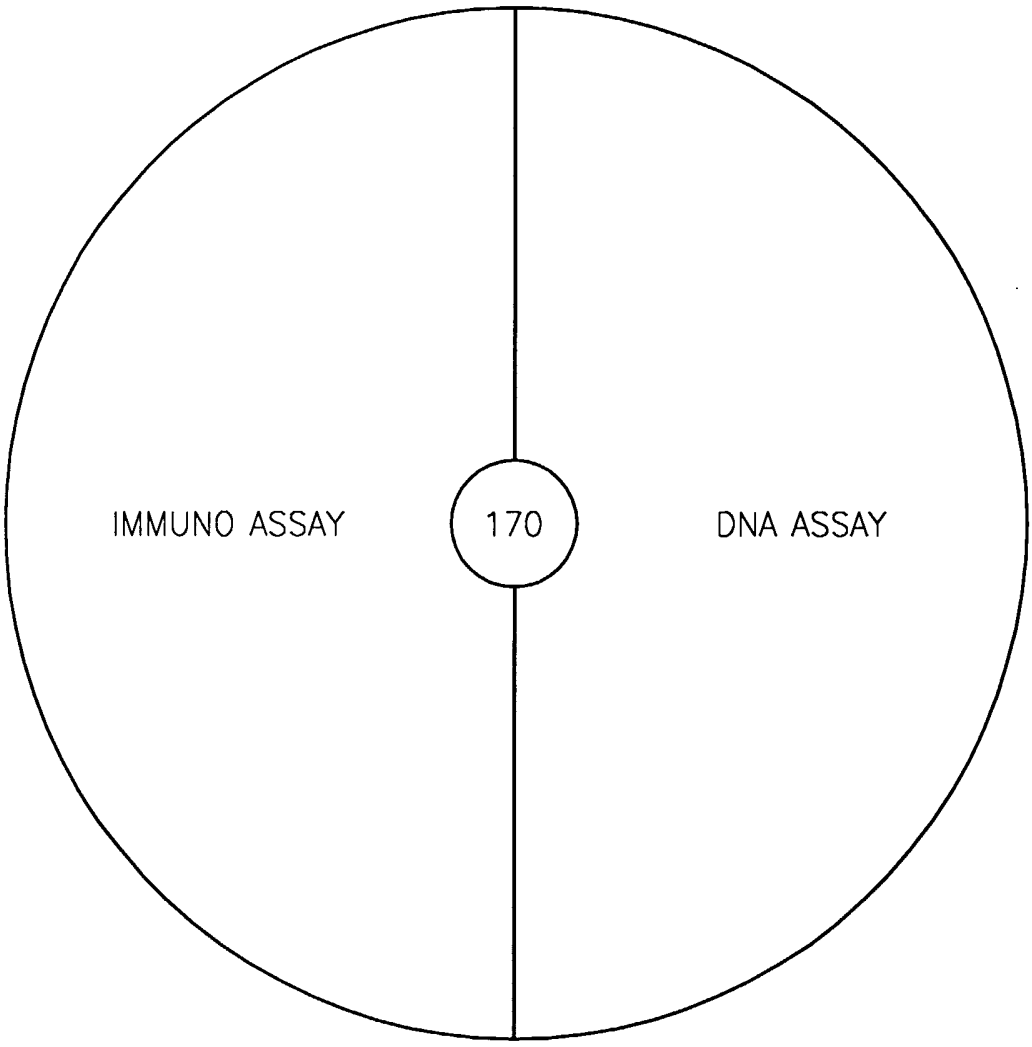


FIG. 10B

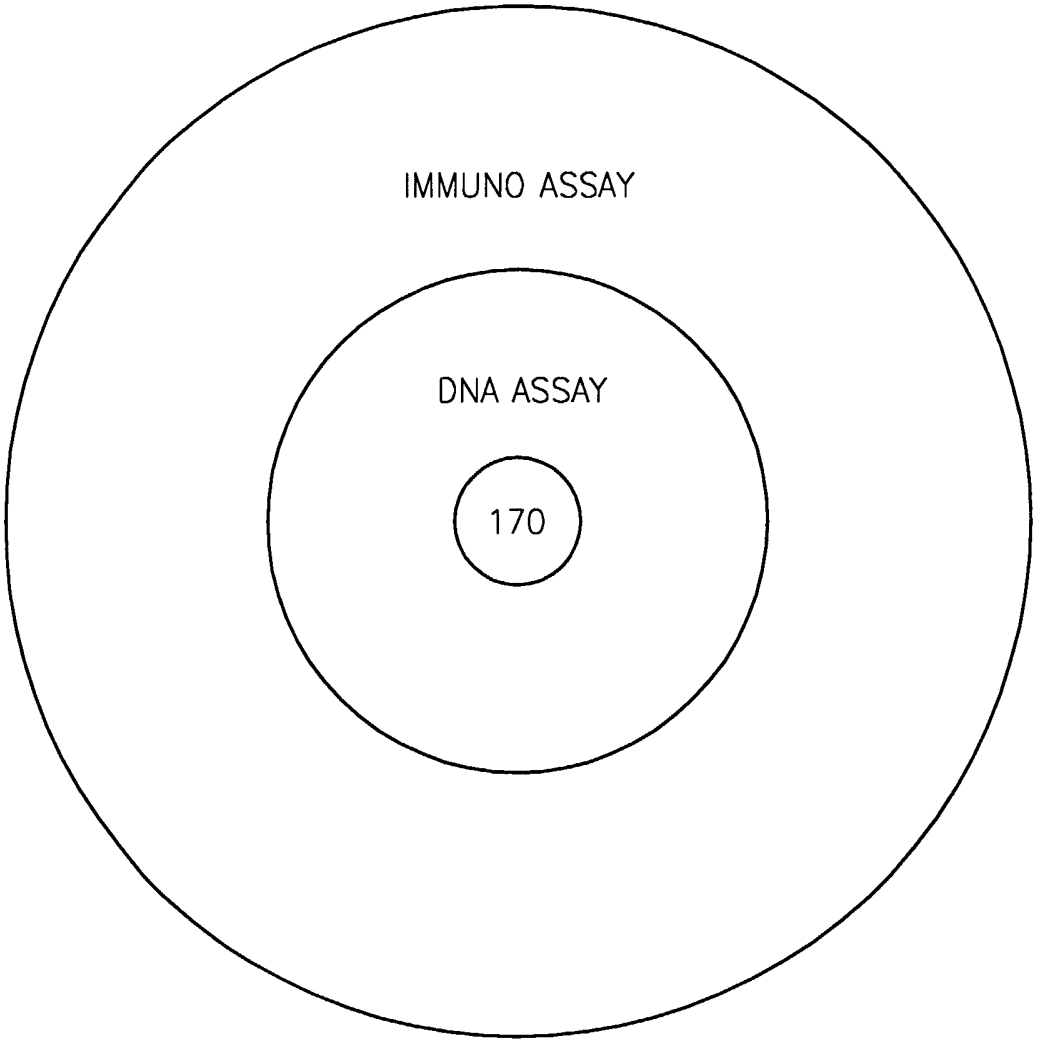


FIG. 11A

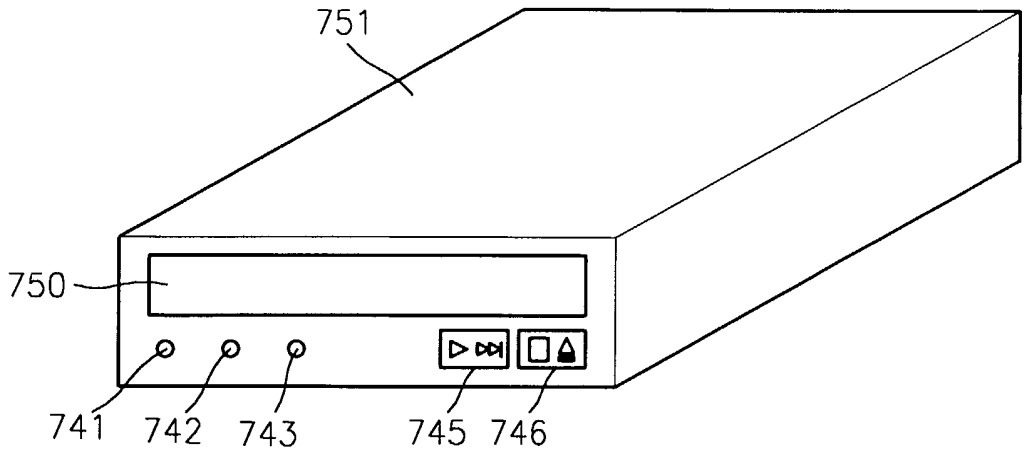
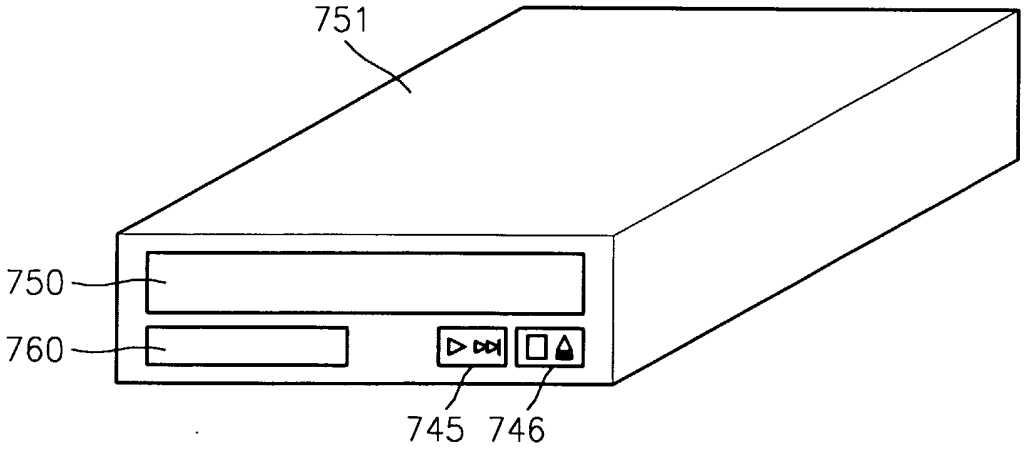


FIG. 11B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00613

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C12Q 1/68, G11B 17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C12Q, G11B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)

CAPLUS, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03021223 A2 (Burstein Technologies, Inc.), 13. 03. 2003, see entire document.	1-72
A	WO 02018655 A2 (Board of Regents, the University of Texas System), 07. 03. 2002, see entire document.	1-72
A	Nagai H. et al., "High-throughput PCR in silicon based microchamber array." In: Biosensors and Bioelectronics, 2001, 16(9-12): pages 1015-1019, see entire document.	1-72
A	Lenigk R. et al., "Surface characterization of a silicon-chip-based DNA microarray." In: Langmuir, 2001, 17(8): pages 2497-2501, see entire document.	1-72
A	WO 00037163 A1 (Nanogen, Inc.), 29. 06. 2000, see entire document.	1-72
A	JP 10-103558 A (Tokyo Gas Co. Ltd.), 21. 04. 1998, see entire document.	1-72

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 JULY 2003 (22.07.2003)	23 JULY 2003 (23.07.2003)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00613

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03021223 A2	13. 03. 2003	US 2003104486 A1	05. 06. 2003
		US 2003096324 A1	22. 05. 2003
		US 2003133840 A1	17. 07. 2003
WO 02018665 A2	07. 03. 2002	AU 2001086929 A	13. 03. 2002
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		BR 9916840 A	09. 10. 2001
JP 10-103558 A	21. 04. 1998	None	