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54 **CARTRIDGE WITH LAMINATED MANIFOLD**

57 A circuit with electrical interconnect for external electronic connection and sensor(s) on a die are combined with a laminated manifold to deliver a liquid reagent over an active surface of the sensor(s). The laminated manifold includes fluidic channel(s), an interface between the die and the fluidic channel(s) being sealed. Also disclosed is a method, the method including assembling a laminated manifold including fluidic channel(s), attaching sensor(s) on a die to a circuit, the circuit including an electrical interconnect, and attaching a planarization layer to the circuit, the planarization layer including a cut out for the die. The method further includes placing sealing adhesive at sides of the die, attaching the laminated manifold to the circuit, and sealing an interface between the die and fluidic channel(s).

CARTRIDGE WITH LAMINATED MANIFOLD

BACKGROUND

[0001] Current cartridges for biological or chemical analysis do not handle liquid reagents in an efficient manner. For example, the fluidic path is long, going from the reagent storage area through a conventional manifold to the die, the die including semiconductor sensor(s). The arrangement may slow the analysis and results in large volumes of wash reagent used for each cycle.

[0002] Therefore, there is a need for a more efficient fluidic path design.

SUMMARY

[0003] The shortcomings of pre-existing approaches may be overcome and additional advantages are provided through the provision, in one aspect, of an apparatus. The apparatus comprises a circuit and at least one sensor on a die coupled to the circuit, the circuit comprising an electrical interconnect for external electrical connection, and a laminated manifold attached to the circuit to deliver a liquid reagent over an active surface of the at least one sensor, the laminated manifold comprising at least one fluidic channel, an interface between the die and the at least one fluidic channel being sealed.

[0004] In accordance with yet another aspect, a method is provided. The method comprises assembling a laminated manifold, the laminated manifold comprising at least one fluidic channel, attaching at least one sensor on a die to a circuit, the circuit comprising an electrical interconnect, and attaching a planarization layer to the circuit, the planarization layer comprising a cut out for the die. The method further comprises placing sealing adhesive at sides of the die, attaching the laminated manifold to the circuit, and sealing an interface between the die and the at least one fluidic channel, the laminated manifold and attached circuit together comprise an assembly.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] These, and other objects, features and advantages of this disclosure will become apparent from the following detailed description of the various aspects thereof taken in conjunction with the accompanying drawings, in which:

[0006] FIG. 1 is a perspective view of one example of a cartridge with a sensor and laminated manifold, useable for, e.g., biological or chemical analysis, in accordance with one or more aspects of the present disclosure.

[0007] FIG. 2 is a blown-up view of one example of the laminated manifold of FIG. 1, showing the various layers of the laminated manifold, in accordance with one or more aspects of the present disclosure.

[0008] FIG. 3 is a perspective view of one example of the sensor in relation to the laminated manifold and the circuit, in accordance with one or more aspects of the present disclosure.

[0009] FIG. 4 is a perspective view of one example of a cross-section of the sensor area taken across a line of FIG. 3, in accordance with one or more aspects of the present disclosure.

[0010] FIGs. 5-10 depict various stages of constructing the cartridge of FIG. 1. FIG. 5 is a perspective view of one example of the circuit with the sensor attached thereto, in accordance with one or more aspects of the present disclosure.

[0011] FIG. 6 depicts attaching a planarization layer to the circuit of FIG. 5 via, for example, using a bonding layer including a pressure-sensitive adhesive, in accordance with one or more aspects of the present disclosure.

[0012] FIG. 7 depicts dispensing and curing a bridge adhesive to the structure of FIG. 6, in accordance with one or more aspects of the present disclosure.

[0013] FIG. 8 depicts one example of attaching a laminated manifold (e.g., as described with respect to FIG. 2) to the circuit of FIG. 7 via, for example, a bonding layer (FIG. 2) including a pressure-sensitive adhesive, in accordance with one or more aspects of the present disclosure.

[0014] FIG. 9 depicts one example of forming wire bonding to the structure of FIG. 8,

encapsulating the wire bonding and attaching a flow cell channel, in accordance with one or more aspects of the present disclosure.

[0015] FIG. 10 depicts one example of connecting the structure of FIG. 9 to the reagent rotor and the cartridge body, in accordance with one or more aspects of the present disclosure.

DETAILED DESCRIPTION

[0016] Aspects of the present disclosure and certain features, advantages, and details thereof, are explained more fully below with reference to the non-limiting examples illustrated in the accompanying drawings. Descriptions of well-known materials, fabrication tools, processing techniques, etc., are omitted so as not to unnecessarily obscure the relevant details. It should be understood, however, that the detailed description and the specific examples, while indicating aspects of the disclosure, are given by way of illustration only, and are not by way of limitation. Various substitutions, modifications, additions, and/or arrangements, within the spirit and/or scope of the underlying inventive concepts will be apparent to those skilled in the art from this disclosure.

[0017] Approximating language, as used herein throughout the specification and claims, may be applied to modify any quantitative representation that may permissibly vary without resulting in a change in the basic function to which it is related. Accordingly, a value modified by a term or terms, such as “about” or “substantially,” is not limited to the precise value specified. In some instances, the approximating language may correspond to the precision of an instrument for measuring the value.

[0018] The terminology used herein is for the purpose of describing particular examples only and is not intended to be limiting. As used herein, the singular forms “a”, “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms “comprise” (and any form of comprise, such as “comprises” and “comprising”), “have” (and any form of have, such as “has” and “having”), “include (and any form of include, such as “includes” and “including”), and “contain” (and any form of contain, such as “contains” and “containing”) are open-ended linking verbs. As a result, a method or device that “comprises,” “has,” “includes” or “contains” one or more steps or elements possesses those one or more steps or elements, but is not limited to possessing only those one or more steps or elements. Likewise, a step of a method or an element of a device that “comprises,” “has,” “includes” or “contains” one or more features possesses those one or more features, but is not limited to possessing only those one or more features. Furthermore, a device or structure that is configured in a certain way is configured in at least that way, but may also be configured in ways that are not listed.

[0019] As used herein, the term “connected,” when used to refer to two physical elements, means a direct connection between the two physical elements. The term “coupled,” however, can mean a direct connection or a connection through one or more intermediary elements.

[0020] As used herein, the terms “may” and “may be” indicate a possibility of an occurrence within a set of circumstances; a possession of a specified property, characteristic or function; and/or qualify another verb by expressing one or more of an ability, capability, or possibility associated with the qualified verb. Accordingly, usage of “may” and “may be” indicates that a modified term is apparently appropriate, capable, or suitable for an indicated capacity, function, or usage, while taking into account that in some circumstances the modified term may sometimes not be appropriate, capable or suitable. For example, in some circumstances, an event or capacity can be expected, while in other circumstances the event or capacity cannot occur – this distinction is captured by the terms “may” and “may be.”

[0021] As used herein, unless otherwise specified, the approximating terms “about,” “substantially” and the like, used with a value, such as measurement, size, etc., means a possible variation of plus or minus ten percent of the value.

[0022] As used herein, the terms “bond,” “bonded” and “bonding” refer to two things being joined securely together using an adhesive or bonding agent together with a heat process or pressure. As used herein, the term “attach” refers to joining two things together, with or without the use of a fastener (e.g., screw, adhesive or bonding agent, etc.) Thus, the term “bond” is a subset of the term “attach.”

[0023] Reference is made below to the drawings, which are not drawn to scale for ease of understanding, wherein the same reference numbers are used throughout different figures to designate the same or similar components.

[0024] The present disclosure relates to biological or chemical analysis, and more particularly, to a circuit with sensor(s) connected to a laminated manifold for efficient delivery of a liquid reagent to an active surface of the sensor(s).

[0025] FIG. 1 is a perspective view of one example of a cartridge 100, which may be used for, e.g., biological or chemical analysis. In one example, the cartridge may be used to enable sequencing, for example, DNA sequencing, e.g., sequencing-by-synthesis or next-generation sequencing (also known as high-throughput sequencing). In another example, the cartridge may be used to enable genotyping. As one skilled in the art will know, genotyping involves determining differences in the genetic make-up (genotype) of an individual by examining the individual's DNA sequence using biological assays and comparing it to another individual's sequence or a reference sequence. The cartridge, which may be consumable or reusable, includes a reagent rotor 102, a cartridge body 104 (with pump 107 internal to cartridge body), a laminated manifold 106 for delivering the reagent and a circuit 108 with passive electronics 109 for various functions of the cartridge and electrical interconnect 110 for external electrical connection. The laminated manifold is used to deliver a liquid reagent to an active surface of a sensor (134, FIG. 2), in accordance with one or more aspects of the present disclosure. Although the pump in this example is internal to the cartridge, it will be understood that the pump may instead be on a surface of the cartridge or external to the cartridge.

[0026] The fluid flow of the reagent from storage (rotor 102 in this example) is active via pump 107. The pump draws the liquid reagent from the rotor, through the laminated manifold 106 and to flow cell 119 over the active surface (138, FIG. 3) of the sensor (134, FIG. 2) through fluidic opening 103. The liquid reagent exits the flow cell to the arms of what looks like a candelabra (channels 117). The liquid reagent returns to the pump through the array of pinch valves 111 located, for example, at the bottom of the cartridge. The pinch valves may normally be closed, such that which pinch valve is open when the pump aspirates determines which arm of the candelabra is used for the return. Any excess fluid from channels 117 return to the pump through fluidic path 115 and fluidic opening 105. The microfluidic pump maintains a flow of reagent(s) through the cartridge for sensing. In one example, the pump takes the form of a self-priming micro-pump.

[0027] Non-limiting examples of the function(s) of the sensor include, for example, light sensing (e.g., having a predetermined range of wavelengths sensed), detecting the presence of one or more substances (e.g., biological or chemical substance) and detecting a change in concentration of something (e.g., ion concentration). The sensor may be, for example, semiconductor-based

(e.g., an integrated circuit), the individual devices of which may be planar or non-planar (e.g., Fin Field Effect Transistor (FinFET) based). In one example, the sensor may be a CMOS (Complementary Metal-Oxide Semiconductor) image sensor. As one skilled in the art will know, the circuitry of a CMOS image sensor includes passive electronic elements, such as a clock and timing generation circuit, an analog-to-digital converter, etc., as well as an array of photodetectors to convert photons (light) to electrons, which is then converted to a voltage. In another example, the sensor may be a CCD (Charge Coupled Device), another type of image sensor.

[0028] As one skilled in the art will understand, “CMOS” refers to a technology used to fabricate integrated circuits. As used herein, “CMOS sensor” and “CMOS image sensor” refer to sensors fabricated using CMOS technology. The “complementary” aspect of the name refers to the inclusion of both n-type and p-type metal-oxide semiconductor field effect transistors (MOSFETs) in integrated circuits (ICs) fabricated using CMOS technology. Each MOSFET has a metal gate with a gate dielectric, such as an oxide (hence, the “Metal-Oxide” part of the name) and a semiconductor material below the gate (corresponds to “Semiconductor” in the name). ICs are fabricated on a die, which is a portion of a semiconductor substrate or wafer that is cut out after fabrication, and ICs fabricated using CMOS technology are characterized by, for example, high noise immunity and low static power consumption (one of the transistors is always off).

[0029] In one example, a CMOS image sensor may include, for example, millions of photodetectors, also called pixels. Each pixel includes a photosensor, which accumulates charge from the light, an amplifier to convert the accumulated charge into a voltage, and a pixel-select switch. Each pixel may also include, for example, an individual microlens to capture more of the light, or have other enhancements to improve the image such as, for example, noise reduction.

[0030] One example of the fabrication of a semiconductor device fabricated using CMOS technology will now be provided. Starting, for example, with a p-type semiconductor substrate, the NMOS region may be protected while an n-type well is created in the PMOS region. This may be accomplished using, for example, one or more lithographic processes. A thin gate oxide and gate (e.g., polysilicon) may then be formed in both the NMOS and PMOS regions. N+ type dopant regions may be formed in the p-type substrate of the NMOS region on either side of the dummy gate (i.e., the source and drain are formed), and one region of the n+ type dopant as the body (here, the well) contact in the PMOS region. This may be accomplished using, for example, a mask. The same process of masking and doping may then be used to form the source and drain in the PMOS region and the body contact in the NMOS region. Metallization to form the terminals to the various regions of the NMOS and PMOS transistors (i.e., body, source, drain and gate) may then be performed. Unlike CCDs, CMOS image sensors may include other circuits on the same chip at little to no extra cost, providing functions such as image stabilization and image compression on-chip.

[0031] FIG. 2 is an exploded view of one example of the laminated manifold 106 of FIG. 1. The laminate includes a lidding layer 112, which may be, for example, a polymer film (e.g., polyethylene terephthalate (PET) or poly(methyl methacrylate (PMMA)), and may have a thickness of, e.g., about 100 microns to about 700 microns in one example, and about 100 microns to about 400 microns in another example. The laminated manifold also includes a fluidic distribution layer 116 for distributing the liquid reagent(s), which may have a thickness of, for example, about 200 microns to about 1000 microns in one example, and about 300 microns to about 700 microns in another example. Fluidic distribution layer 116 may be, for example, a material with low or no autofluorescence, e.g., a thin plastic film or glass. Non-limiting examples of materials for layer 116 include: PMMA, commercially available from, for example, Evonit Corporation, Parsippany, New Jersey; a Cobalt Phosphide (CoP) film, commercially available from, for example, American Elements, Los Angeles, California; a Cyclic Olefin Copolymer (COC), commercially available from, for example, Zeon Chemicals L.P., Louisville, Kentucky; and borosilicate glass, commercially available from, for example, Schott North America, Inc., Elmsford, New York. A fluidic path through channels 117 for bulk or relatively thick fluid is defined by layer 116. The channels are sized to enable fluid flow with low impedance, for example, having a width of between about 0.25mm and about 1mm. Between the lidding and fluidic distribution layers is an adhesive layer 114, which may have a thickness of, for example, about 20 microns to about 50 microns in one example, and about 25 microns in another example. In one example, the adhesive layer may include a pressure-sensitive adhesive for securely attaching under pressure the layers directly above and below the pressure-sensitive adhesive. Non-limiting examples of the adhesive of layer 114 include an acrylic or silicone adhesive. The pressure-sensitive adhesive may be part of, for example, a single-sided adhesive tape that may include, for example, a rigid plastic liner (e.g., PET) with the adhesive thereon. Such adhesive tapes are commercially available from, for example, 3M in St. Paul, Minnesota, or Adhesives Research, Inc. in Glen Rock, Pennsylvania. As one skilled in the art will know, a pressure-sensitive adhesive, when under pressure, creates a bond without the need for solvent, water or heat.

[0032] The laminated manifold of FIG. 2 further includes a substrate layer 120, and the substrate layer may include an aperture 121, along with layers 118 and 122, which overlap openings 123 and 125 in layer 116, allowing reagent(s) to reach the active surface (138, FIG. 3) of the sensor from the channels in layer 116. In one example, the openings are sized similar to the channels. The substrate layer may have a thickness of, for example, about 50 microns to about 70 microns in one example, and about 60 microns in another example. Substrate layer 120 may be, for example, a polymer film (e.g., PET or PMMA). The fluid flow over the sensor transitions from the relatively thick flow in the channels of the fluidic distribution layer to a relatively thin fluid flow, which provides an efficient use of the fluid. The fluidic path over the sensor is shown

through flow line 156 in FIG. 4. In one example, a chemical reaction of only the fluid passing over the sensor, for example, fluorescence, may be observable to a user. Between the fluidic distribution layer and the substrate layer is an adhesive layer 118, which may have a thickness of, for example, about 20 microns to about 50 microns in one example, and about 25 microns in another example. In one example, layer 118 may include a pressure-sensitive adhesive for securely attaching under pressure the layers directly above and below the pressure-sensitive adhesive. Non-limiting examples of the adhesive of layer 118 include an acrylic or silicone adhesive. The pressure-sensitive adhesive may be part of, for example, a double-sided adhesive tape that may include, for example, a rigid plastic liner (e.g., PET) with the adhesive thereon. Such adhesive tapes are commercially available as described above. The structure further includes a planarization layer 124 to provide support to the laminated manifold and to present an even surface to the circuit 108, which may have a thickness of, for example, about 500 microns to about 700 microns in one example, and about 600 microns in another example, in accordance with one or more aspects of the present disclosure. In one example, the planarization layer is about the same thickness as the die.

In one example, the material of the planarization layer 124 may include extruded plastic, for example, PET, polypropylene or polycarbonate. Between substrate layer 120 and planarization layer 124 is an adhesive layer 122, which may have a thickness of, for example, about 20 microns to about 50 microns in one example, and about 25 microns in another example. In one example, layer 122 may include a pressure-sensitive adhesive for securely attaching under pressure the layers directly above and below the pressure-sensitive adhesive. Non-limiting examples of the adhesive of layer 122 include an acrylic or silicone adhesive. The pressure-sensitive adhesive may be part of, for example, a double-sided adhesive tape that may include, for example, a rigid plastic liner (e.g., PET) with the adhesive thereon. Such adhesive tapes are commercially available as described above.

[0033] The laminated manifold 106 may be bonded to circuit 108, for example, via bonding layer 126, which may include, for example, a pressure-sensitive adhesive with a thickness of, e.g., about 50 microns to about 70 microns in one example, and about 60 microns in another example. Non-limiting examples of the adhesive of layer 126 include an acrylic or silicone adhesive. The pressure-sensitive adhesive may be part of, for example, a single-sided adhesive tape that may include, for example, a rigid plastic liner (e.g., PET) with the adhesive thereon. Such adhesive tapes are commercially available as described above. The circuit may be flexible or rigid (e.g., PCB board) and have a thickness of, for example, about 200 microns to about 300 microns in one example, and about 250 microns in another example.

[0034] Both the planarization layer 124 and bonding layer 126 include a cut-out 132 for a sensor 134 on the circuit such that the active surface (138, FIG. 3) may be substantially planar with the laminated manifold when the reagent is in contact with the active surface. Finally, the circuit is

bonded to the cartridge body 104 via bonding layer 130, which may include a pressure-sensitive adhesive and may have a thickness of, for example, about 50 microns to about 150 microns in one example, and about 100 microns in another example. Non-limiting examples of the adhesive of layer 130 include an acrylic or silicone adhesive. The pressure-sensitive adhesive may be part of, for example, a double-sided adhesive tape that may include, for example, a rigid plastic liner (e.g., PET) with the adhesive thereon. Such adhesive tapes are commercially available as described above.

[0035] FIG. 3 is a perspective view of one example of sensor 134 in relation to the laminated manifold 106 and circuit 108. The active surface of the sensor and the laminated manifold structure surrounding and above the sensor (i.e., fluidic distribution layer 116, FIG. 2) where the reagent(s) are introduced, constitutes a flow cell. A flow cell channel 136 delivers liquid reagent(s) to an active surface 138 of the sensor(s), situated on die 140, and then carries the liquid reagent(s) away from the sensor. Substance(s), for example, biological or chemical substances(s), may be introduced into the space for on-chip sensing by the active surface of the sensor. Where semiconductor based, the sensor may be fabricated on a silicon substrate (e.g., a silicon wafer), which becomes the die when cut from the silicon wafer. The thickness of the die depends on the size (diameter) of the silicon wafer. For example, a standard silicon wafer with a 51mm diameter may have a thickness of about 275 microns, while a standard silicon wafer with a diameter of 300mm may have a thickness of about 775 microns. As used herein, the active area of the sensor(s) refers to the sensor surface that will come into contact with the reagent(s) for sensing. There may be more than one sensor on the die, and different sensors may be included on the same die. The flow cell channel may include, for example, silicate glass (e.g., aluminosilicate glass). The die is sealed at sealing areas 142. In one example, each sealing area includes, for example, a bridge adhesive 144, structural adhesive 146 and wire bonding 148 using, for example, gold wire, which is covered by a wire bond encapsulate 150, in accordance with one or more aspects of the present disclosure. The die may be attached to circuit 108 by an adhesive, for example, a dispersed ultraviolet-curable adhesive or a pressure-sensitive adhesive tape (e.g., acrylic or silicon adhesive). Electrical connection between the circuit and the sensor may be accomplished a number of ways, for example, low-temperature wire bonding, which prevents exposure of the die to high temperatures. The wire bonds are relatively small and may be ultrasonically welded wires that make electrical connections between the sensor and the circuit. These electrical connections may be protected with, for example, an adhesive dispersed on the wires (e.g., an ultraviolet (UV)-curable adhesive), which completely encapsulates the wires when cured with UV light, transforming into a solid form. A commercially available UV-curable adhesive may be obtained from, for example, Dymax Corporation, Torrington, Connecticut. The interface 141 between the die 140 and the manifold's fluidic channel is sealed so that the active surface of the sensor comes

into contact with the fluid(s) in the laminated manifold, while also isolating the liquid from electrical interconnects and other aspects of the circuit that may be shorted out by the presence of electrically conductive liquid.

[0036] FIG. 4 is a perspective view of one example of a cross-section of the sensor area taken across line 152 of FIG. 3. As shown, an inlet 103 from a reagent reservoir (e.g., within reagent rotor 102 shown in FIG. 1) distributes the reagent via force of the pump (107, FIG. 1) to a flow line 156 connected to flow cell channel 136 over active surface 138 of the sensor, in accordance with one or more aspects of the present disclosure.

[0037] FIGs. 5-10 depict various stages of constructing the cartridge 100 of FIG. 1. FIG. 5 is a perspective view of one example of circuit 108 with sensor 134 attached thereto, for example, bonded together, in accordance with one or more aspects of the present disclosure.

[0038] FIG. 6 depicts attaching planarization layer 124 to the circuit 108 of FIG. 5 by, for example, using a bonding layer 126, in accordance with one or more aspects of the present disclosure.

[0039] FIG. 7 depicts dispensing and curing bridge adhesive 144 to the structure of FIG. 6, in accordance with one or more aspects of the present disclosure.

[0040] FIG. 8 depicts one example of attaching a laminated manifold 106 (e.g., as described with respect to FIG. 2) to the planarization layer 124 on circuit 108 of FIG. 7 via, for example, using bonding layer 122 (FIG. 2), in accordance with one or more aspects of the present disclosure.

[0041] FIG. 9 depicts one example of wire bonding 148 the structure of FIG. 8, for example, low-temperature wire bonding, encapsulating the wire bonding via, for example, wire bond encapsulant 150 and attaching flow cell channel 136, a V-shaped extension of the fluidic pathway on opposite sides of the sensor delivering the reagent(s) to the active surface of the sensor for sensing, in accordance with one or more aspects of the present disclosure. The wire bond may include a metal, for example, aluminum, copper, silver or gold.

[0042] FIG. 10 depicts one example of attaching the structure of FIG. 9 to the reagent rotor 102 and cartridge body 104, for example, by bonding using bonding layer 130 (FIG. 2), which may include an adhesive (e.g., a pressure-sensitive adhesive as previously described), in accordance with one or more aspects of the present disclosure.

[0043] In a first aspect, disclosed above is an apparatus. The apparatus includes a circuit and sensor(s) on a die attached to the circuit, the circuit including an electrical interconnect for external electrical connection, and a laminated manifold attached to the circuit to deliver a liquid reagent over an active surface of the sensor(s), the laminated manifold including fluidic channel(s), an interface between the die and the fluidic channel(s) being sealed.

[0044] In one example, the sensor(s) may include, for example, a semiconductor. In another example, the sensor(s) may take the form of, for example, a Complementary Metal-Oxide Semiconductor (CMOS) sensor (e.g., a CMOS image sensor).

5 [0045] In one example, the laminated manifold in the apparatus of the first aspect may include, for example, multiple layers that may include, for example, a top lidding layer, a fluidic distribution layer, a substrate layer, and a bottom planarization layer. In one example, the circuit may be, for example, bonded to the planarization layer, and the planarization layer may have, for example, a thickness that is about a collective thickness of the sensor(s) and die.

10 [0046] In one example, a pressure-sensitive adhesive may be, for example, between adjacent layers of the multiple layers of the laminated manifold.

[0047] In one example, adjacent layers of the laminated manifold may be, for example, mechanically connected, for example, via fasteners or screws.

[0048] In one example, the apparatus of the first aspect may be, for example, part of a cartridge, such as that used for biological analysis.

15 [0049] In one example, the apparatus of the first aspect may be, for example, part of a cartridge, such as that used for chemical analysis.

[0050] In one example, the apparatus of the first aspect may be, for example, part of a cartridge, and the cartridge may further include, for example, a reagent storage and delivery system coupled to the laminated manifold, and a cartridge body and a reagent pump coupled to the reagent storage and delivery system.

20 [0051] In one example, the laminated manifold in the apparatus of the first aspect may have, for example, cut-out(s) for the die. In one example, the die may be, for example, wire bonded to the circuit.

[0052] In one example, the apparatus of the first aspect, when in use, a reagent may be, for example, delivered via the laminated manifold over an active surface of the sensor(s). In one example, only the active surface(s) of the sensor(s) is (are) exposed to the reagent.

30 [0053] In a second aspect, disclosed above is a method. The method includes assembling a laminated manifold, the laminated manifold including fluidic channel(s), attaching a die with sensor(s) to a circuit, the circuit including an electrical interconnect. The method further includes attaching a planarization layer to the circuit, the planarization layer including a cut out for the die, placing sealing adhesive at sides of the die, attaching the laminated manifold to the circuit, and sealing an interface between the die and the fluidic channel(s), the laminated manifold and attached circuit together being an assembly.

35 [0054] In one example, the method may further include, for example, attaching the assembly to a cartridge.

[0055] In one example, assembling the laminated manifold in the method of the second aspect may include, for example, laminating layers, and the layers may include, for example, a top lidding layer, a fluidic distribution layer, a substrate layer, and a bottom planarization layer. In one example, the laminating may include, for example, using an adhesive between adjacent layers (e.g., a pressure-sensitive adhesive).

[0056] In one example, the method of the second aspect may further include, for example, using the assembly for sequencing.

[0057] In one example, the method of the second aspect may further include, for example, using the assembly for genotyping.

[0058] While several aspects of the present disclosure have been described and depicted herein, alternative aspects may be effected by those skilled in the art to accomplish the same objectives. Accordingly, it is intended by the appended claims to cover all such alternative aspects.

[0059] It should be appreciated that all combinations of the foregoing concepts (provided such concepts are not mutually inconsistent) are contemplated as being part of the inventive subject matter disclosed herein. In particular, all combinations of claimed subject matter appearing at the end of this disclosure are contemplated as being part of the inventive subject matter disclosed herein.

[0060] The disclosure also includes the following clauses:

1. Apparatus, comprising:
a circuit and at least one sensor on a die attached to the circuit, the circuit comprising an electrical interconnect for external electrical connection; and
a laminated manifold attached to the circuit to deliver a liquid reagent over an active surface of the at least one sensor, the laminated manifold comprising at least one fluidic channel, wherein an interface between the die and the at least one fluidic channel is sealed.
2. The apparatus of clause 1, wherein the at least one sensor comprises a semiconductor.
3. The apparatus of clause 2, wherein the at least one sensor comprises a Complementary Metal-Oxide Semiconductor (CMOS) sensor.
4. The apparatus of any of the clauses 1-3, wherein the laminated manifold comprises a plurality of layers, the plurality of layers comprising:

a top lidding layer;
 a fluidic distribution layer;
 a substrate layer; and
 a bottom planarization layer.

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5. The apparatus of clause 4, wherein the circuit is bonded to the planarization layer, and wherein the planarization layer has a thickness that is about a collective thickness of the at least one sensor and die.

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6. The apparatus of clauses 4 or 5, wherein between adjacent layers of the plurality of layers is a pressure-sensitive adhesive.

7. The apparatus of clause 4, wherein adjacent layers of the plurality of layers are mechanically connected.

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8. The apparatus of any of the clauses 4-6 wherein the apparatus is part of a cartridge for biological analysis.

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9. The apparatus of any of the preceding clauses wherein the apparatus is part of a cartridge for chemical analysis.

10. The apparatus of any of the preceding clauses wherein the apparatus is part of a cartridge, and wherein the cartridge further comprises:

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a reagent storage and delivery system coupled to the laminated manifold; and
 a cartridge body and a reagent pump coupled to the reagent storage and delivery system.

11. The apparatus of any of the preceding clauses wherein the laminated manifold has at least one cut-out for the die.

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12. The apparatus of clause 11, wherein the die is wire bonded to the circuit.

13. The apparatus of any of the preceding clauses wherein when in use, a reagent is delivered via the laminated manifold over an active surface of the at least one sensor.

14. The apparatus of clause 13, wherein only the active surface of the at least one sensor is exposed to the reagent.

15. A method, comprising:

5 assembling a laminated manifold, the laminated manifold comprising at least one fluidic channel;

attaching at least one sensor on a die to a circuit, the circuit comprising an electrical interconnect;

10 attaching a planarization layer to the circuit, the planarization layer comprising a cut out for the die;

placing sealing adhesive at sides of the die;

attaching the laminated manifold to the circuit; and

sealing an interface between the die and the at least one fluidic channel;

15 wherein the laminated manifold and attached circuit together comprise an assembly.

16. The method of clause 15, further comprising attaching the assembly to a cartridge.

17. The method of clause 15 or 16, wherein assembling the laminated manifold
20 comprises laminating a plurality of layers, the plurality of layers comprising:

a top lidding layer;

a fluidic distribution layer;

a substrate layer; and

a bottom planarization layer.

25

18. The method of clause 17, wherein the laminating comprises using a pressure-sensitive adhesive between adjacent layers of the plurality of layers.

19. The method of any of the clauses 15-18 further comprising using the assembly for
30 sequencing.

20. The method of any of the clauses 15-19 further comprising using the assembly for genotyping.

CONCLUSIES

1. Toestel omvattende:
een schakeling en ten minste één sensor op een chip bevestigd aan de schakeling, de schakeling omvattende een elektrische onderlinge verbinding voor een externe elektrische
5 verbinding;
een gelamineerde verdeler bevestigd aan de schakeling om een vloeistofreagens over een actief oppervlak van de ten minste ene sensor te leveren, de gelamineerde verdeler omvattende ten minste één fluïdumkanaal, waarin een interface tussen de chip en het ten minste ene fluïdumkanaal afgedicht is.
10
2. Toestel volgens conclusie 1, waarin de ten minste ene sensor een halfgeleider omvat.
3. Toestel volgens conclusie 2, waarin de ten minste ene sensor een complementaire
15 Metaal-Oxide Halfgeleider (Complementary Metal-Oxide Semiconductor, CMOS) sensor omvat.
4. Toestel volgens conclusies 1-3, waarin de gelamineerde verdeler een aantal lagen omvat, waarin het aantal lagen omvat:
een bovenste bedekkingslaag;
20 een fluïdumverdelingslaag;
een substraatlaag; en
een onderste planarisatielaag.
5. Toestel volgens conclusie 4, waarin de schakeling gebonden is met de
25 planarisatielaag, en waarin de planarisatielaag een dikte heeft die ongeveer gelijk is aan de collectieve dikte van de ten minste ene sensor en de chip.
6. Toestel volgens conclusie 4 of 5, waarin tussen naburige lagen van het aantal lagen zich een drukgevoelig kleefmiddel bevindt.
30
7. Toestel volgens conclusie 4, waarin de naburige lagen van het aantal lagen mechanisch verbonden zijn.
8. Toestel volgens één van de conclusies 1-7, waarin het toestel deel is van een
35 cartridge voor biologische analyse.

9. Toestel volgens één van de voorgaande conclusies, waarin het toestel een deel is van een cartridge voor chemische analyse.

10. Toestel volgens één van de voorafgaande conclusies, waarin het toestel een deel is van een cartridge, en waarin de cartridge verder omvat:
5 een reagensopslag en leveringssysteem gekoppeld aan de gelamineerde verdeler; en een cartridgelichaam en een reagenspomp gekoppeld aan de reagensopslag en het leveringssysteem.

10 11. Toestel volgens één van de voorafgaande conclusies, waarin de gelamineerde verdeler ten minste één uitsparing voor de chip heeft.

12. Toestel volgens conclusie 11, waarin de chip met draad verbonden is (wire bonded) aan de schakeling.

15 13. Toestel volgens één van de voorafgaande conclusies, waarin, wanneer dit in gebruik is, een reagens via de gelamineerde verdeler over een actief oppervlak van de ten minste ene sensor geleverd wordt.

20 14. Toestel volgens conclusie 13, waarin slechts het actieve oppervlak van de ten minste ene sensor blootgesteld wordt aan het reagens.

15. Werkwijze, omvattende:
het samenstellen van een gelamineerde verdeler, waarbij de gelamineerde verdeler ten
25 minste één fluïdumkanaal omvat;

het bevestigen van ten minste één sensor op een chip aan een schakeling, de schakeling omvattende een elektrische onderlinge verbinding;

het bevestigen van een planarisatielaag aan de schakeling, waarbij de planarisatielaag een uitsparing voor de chip omvat;

30 het plaatsen van afdichtingskleefmiddel aan de zijden van de chip;

het bevestigen van de gelamineerde verdeler aan de schakeling; en

het afdichten van de interface tussen de chip en het ten minste ene fluïdumkanaal;

waarin de gelamineerde verdeler en de bevestigingsschakeling samen een samenstel omvatten.

16. Werkwijze volgens conclusie 15, verder omvattende het bevestigen van het samenstel aan een cartridge.

5 17. Werkwijze volgens conclusie 15 of 16, waarin het samenstellen van de gelamineerde verdeler omvat het lamineren van een aantal lagen, waarbij het aantal lagen omvat:
een bovenste verdelingslaag;
een fluïdumverdelingslaag;
een substraatlaag; en
10 een onderste planarisatielaag.

18. Werkwijze volgens conclusie 17, waarin het lamineren omvat het gebruiken van een drukgevoelig kleefmiddel tussen naburige lagen van het aantal lagen.

15 19. Werkwijze volgens één van de conclusies 15-18, verder omvattende het gebruik van het samenstel voor het sequencen.

20. Werkwijze volgens één van de conclusies 15-19, verder omvattende het gebruik van het samenstel voor genotypering.

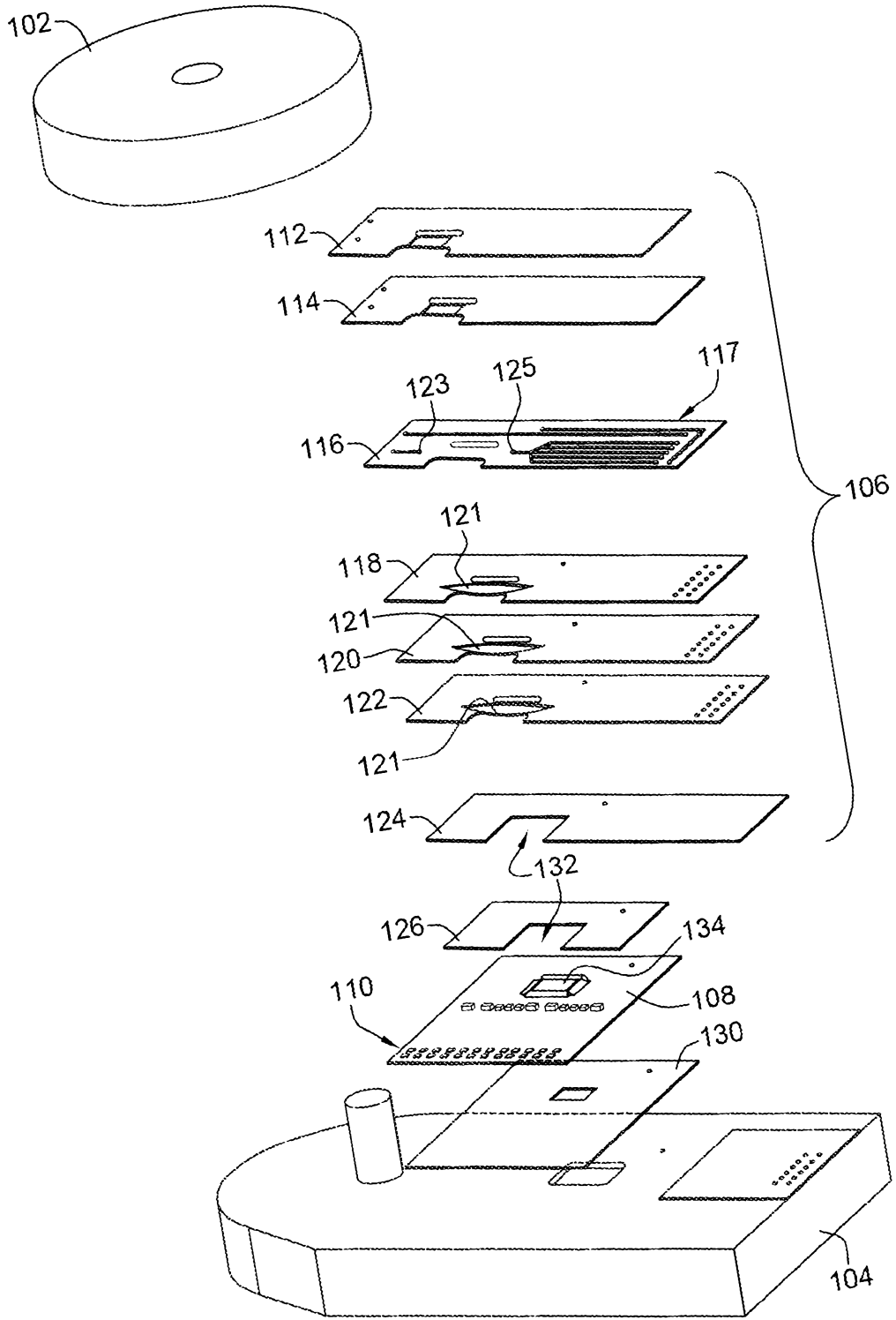


FIG. 2

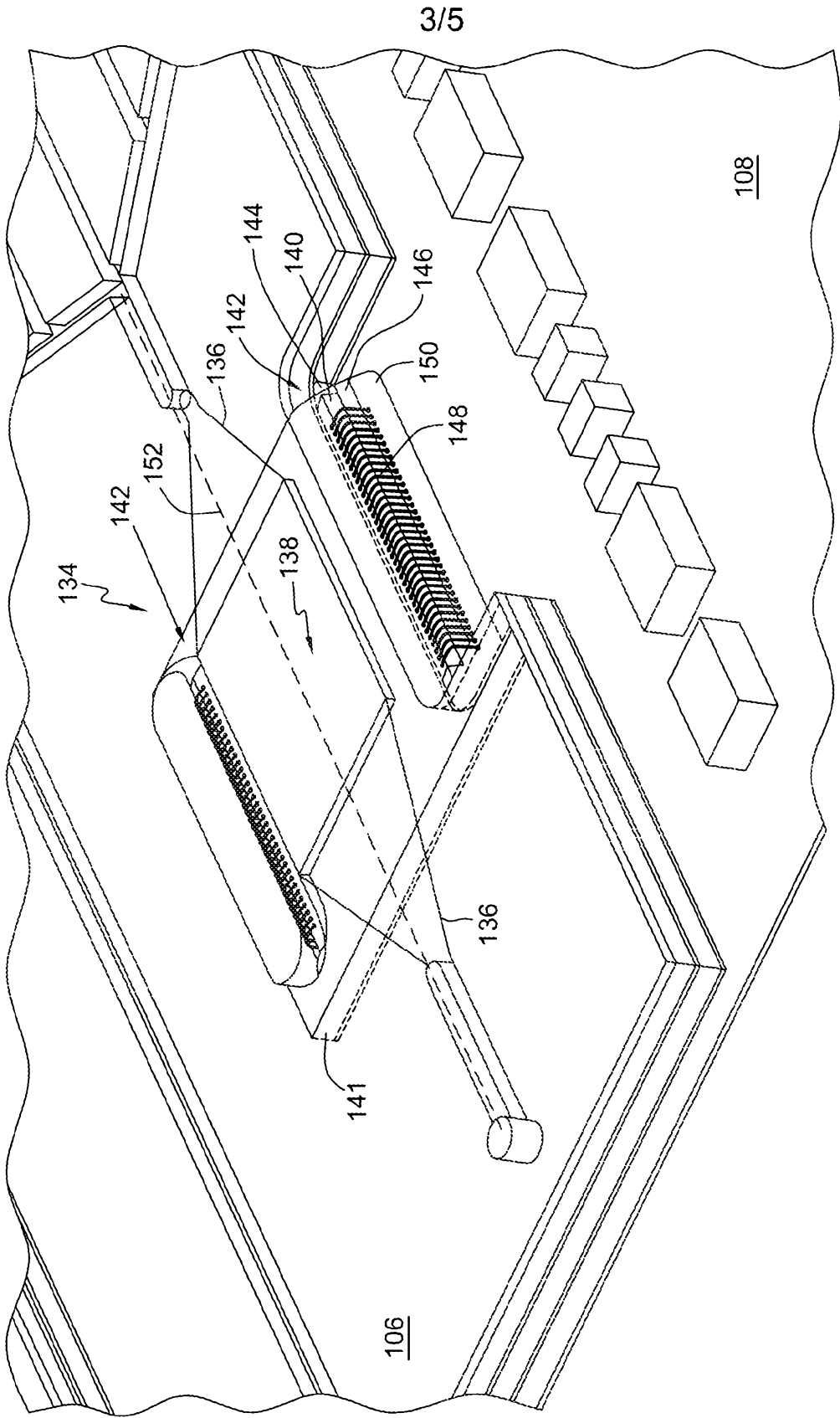


FIG. 3

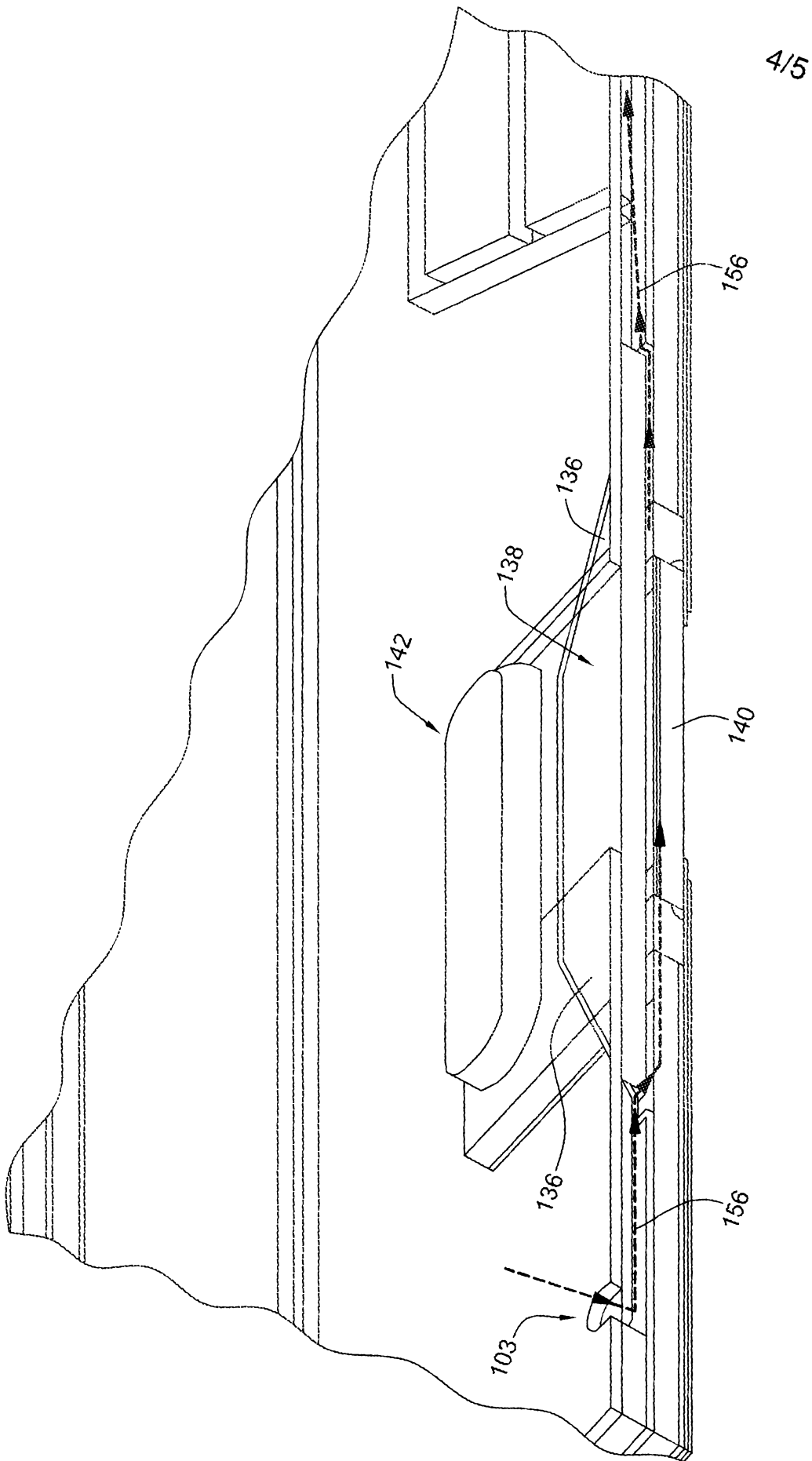
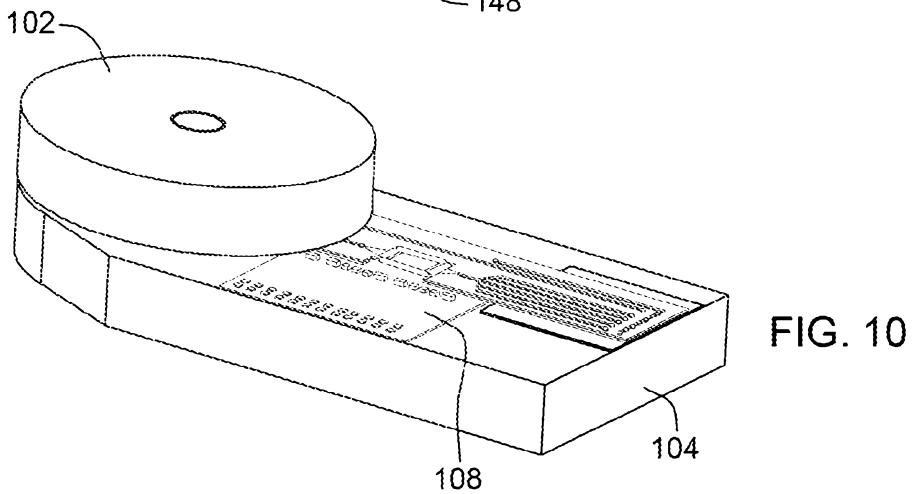
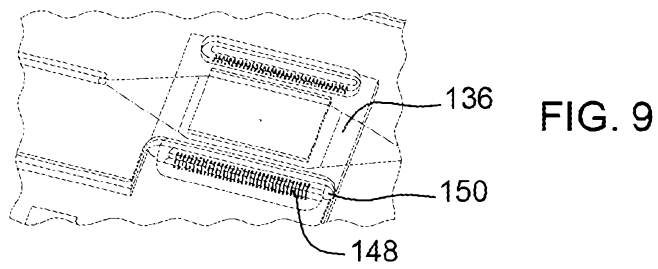
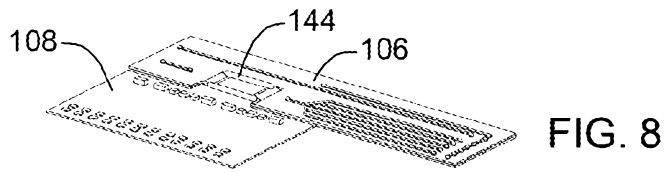
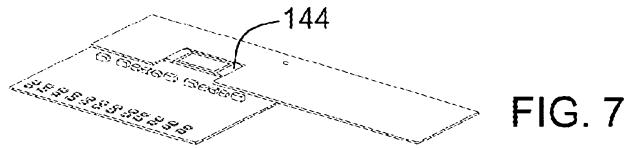
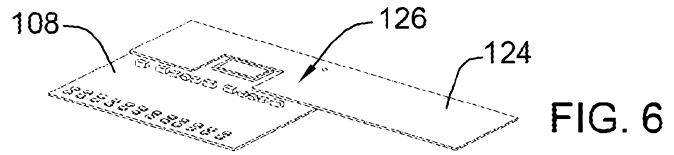
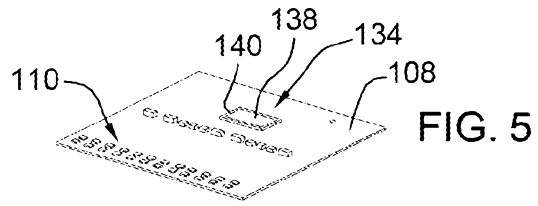


FIG. 4



ABSTRACT

A circuit with electrical interconnect for external electronic connection and sensor(s) on a die are combined with a laminated manifold to deliver a liquid reagent over an active surface of the sensor(s). The laminated manifold includes fluidic channel(s), an interface between the die and the fluidic channel(s) being sealed. Also disclosed is a method, the method including assembling a laminated manifold including fluidic channel(s), attaching sensor(s) on a die to a circuit, the circuit including an electrical interconnect, and attaching a planarization layer to the circuit, the planarization layer including a cut out for the die. The method further includes placing sealing adhesive at sides of the die, attaching the laminated manifold to the circuit, and sealing an interface between the die and fluidic channel(s).

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
	4A/2WR91/3
Nederlands aanvraag nr.	Indieningsdatum
2020616	19-03-2018
	Ingeroepen voorrangsdatum
Aanvrager (Naam)	
illumina, Inc.	
Datum van het verzoek voor een onderzoek van internationaal type	Door de instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr.
05-05-2018	SN71202
I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)	
Volgens de internationale classificatie (IPC)	
C12Q1/6837;B01L3/00	
II. ONDERZOCHE GEBIEDEN VAN DE TECHNIEK	
Onderzochte minimumdocumentatie	
Classificatiesysteem	Classificatiesymbolen
IPC	C12Q;B01L
Onderzochte andere documentatie dan de minimum documentatie, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen	
III.	GEEN ONDERZOEK MOGELIJK VOOR BEPAALDE CONCLUSIES (opmerkingen op aanvullingsblad)
IV.	GEBREK AAN EENHEID VAN UITVINDING (opmerkingen op aanvullingsblad)

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Nummer van het verzoek om een onderzoek naar
de stand van de techniek

NL 2020616

<p>A. CLASSIFICATIE VAN HET ONDERWERP INV. C12Q1/6837 B01L3/00 ADD.</p>		
<p>Volgens de Internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC.</p>		
<p>B. ONDERZOCHETE GEBIEDEN VAN DE TECHNIEK</p>		
<p>Onderzochte minimum documentatie (classificatie gevolgd door classificatiesymbolen) C12Q B01L</p>		
<p>Onderzochte andere documentatie dan de minimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen.</p>		
<p>Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden) EPO-Internal, WPI Data, EMBASE, BIOSIS</p>		
<p>C. VAN BELANG GEACHTE DOCUMENTEN</p>		
Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	US 6 772 513 B1 (FRYE-MASON GREGORY C [US] ET AL) 10 augustus 2004 (2004-08-10) * conclusies 1-20; figuren 1-6 *	1-20
A	WO 2009/102688 A2 (ILLUMINA INC [US]) 20 augustus 2009 (2009-08-20) * conclusies 1-31; figuren 2-10 *	1-20
A	US 2013/044431 A1 (KOENEMAN PAUL B [US]) 21 februari 2013 (2013-02-21) * conclusies 1-21; figuren 1-11 *	1-20
A	WO 2015/183871 A1 (ILLUMINA INC [US]) 3 december 2015 (2015-12-03) * alinea's [0088], [0170] - [0192]; conclusies 1-60; figuren 14-21, 40, 53-60 * ----- -/--	1-20
<p><input checked="" type="checkbox"/> Verdere documenten worden vermeld in het vervolg van vak C. <input checked="" type="checkbox"/> Leden van dezelfde octrooifamilie zijn vermeld in een bijlage</p>		
<p>* Speciale categorieën van aangehaalde documenten</p> <p>"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft</p> <p>"D" in de octrooiaanvraag vermeld</p> <p>"E" eerdere octrooiaanvraag, gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven</p> <p>"L" om andere redenen vermelde literatuur</p> <p>"O" niet-schriftelijke stand van de techniek</p> <p>"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur</p> <p>"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwerend is voor de octrooiaanvraag, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding</p> <p>"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur</p> <p>"Y" de conclusie wordt als niet inventief beschouwd ten opzichte van de combinatie van deze literatuur met andere geciteerde literatuur van dezelfde categorie, waarbij de combinatie voor de vakman voor de hand liggend wordt geacht</p> <p>"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie</p>		
<p>Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid</p> <p>31 mei 2018</p>		<p>Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type</p>
<p>Naam en adres van de instantie</p> <p>European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016</p>		<p>De bevoegde ambtenaar</p> <p>Moreno de Vega, C</p>

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Nummer van het verzoek om een onderzoek naar
de stand van de techniek

NL 2020616

C. (Vervolg) VAN BELANG GEACHTE DOCUMENTEN		
Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	WO 2017/072513 A1 (RANDOX LABORATORIES LTD [GB]) 4 mei 2017 (2017-05-04) * conclusies 1-24; figuren 1-9 * -----	1-20

**ONDERZOEKSRAPPORT BETREFFENDE HET
RESULTAAT VAN HET ONDERZOEK NAAR DE STAND
VAN DE TECHNIEK VAN HET INTERNATIONALE TYPE**

Informatie over leden van dezelfde octrooifamilie

Nummer van het verzoek om een onderzoek naar
de stand van de techniek

NL 2020616

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
US 6772513	B1	10-08-2004	GEEN
WO 2009102688	A2	20-08-2009	EP 2260284 A2 15-12-2010 US 2011072914 A1 31-03-2011 US 2012195794 A1 02-08-2012 WO 2009102688 A2 20-08-2009
US 2013044431	A1	21-02-2013	US 2013044431 A1 21-02-2013 WO 2013025982 A1 21-02-2013
WO 2015183871	A1	03-12-2015	AU 2015267189 A1 08-12-2016 CA 2949984 A1 03-12-2015 CN 106536055 A 22-03-2017 EP 3148697 A1 05-04-2017 JP 2017522545 A 10-08-2017 KR 20170012367 A 02-02-2017 US 2017189904 A1 06-07-2017 WO 2015183871 A1 03-12-2015
WO 2017072513	A1	04-05-2017	GEEN

WRITTEN OPINION

File No. SN71202	Filing date (day/month/year) 19.03.2018	Priority date (day/month/year)	Application No. NL2020616
International Patent Classification (IPC) INV. C12Q1/6837 B01L3/00			
Applicant Illumina, Inc.			

This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the application
- Box No. VIII Certain observations on the application

Examiner Moreno de Vega, C

WRITTEN OPINION

NL2020616

Box No. I Basis of this opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - on paper
 - in electronic form
 - c. time of filing/furnishing:
 - contained in the application as filed.
 - filed together with the application in electronic form.
 - furnished subsequently for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes: Claims	1-20
	No: Claims	
Inventive step	Yes: Claims	1-20
	No: Claims	
Industrial applicability	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

Application number

NL2020616

Box No. VIII Certain observations on the application

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2015/183871 A1 (ILLUMINA INC [US]) 3 december 2015 (2015-12-03)
- D2 WO 2017/072513 A1 (RANDOX LABORATORIES LTD [GB]) 4 mei 2017 (2017-05-04)

- 1 If the objections of lack of clarity mentioned under Item VIII were overcome, the subject-matter of claims 1-20 is considered to be new:
 - 1.1 Document D1, see especially figures 14-21, 40, and 53-60, claims 1-60 and paragraphs 88, 170-192, discloses systems and methods for conducting designated reactions, e.g. sequencing, utilizing a base instrument and a removable cartridge. The removable cartridge includes a fluidic network that receives and fluidically directs a biological sample to conduct the designated reactions. The removable cartridge also includes a flow-control valve that is operably coupled to the fluidic network and is movable relative to the fluidic network to control flow of the biological sample therethrough. The removable cartridge is configured to separably engage a base instrument. The base instrument includes a valve actuator that engages the flow-control valve of the removable cartridge. A detection assembly held by at least one of the removable cartridge or the base instrument may be used to detect the designated reactions.

- 1.2 Document D2, see figures 1-9 and claims 1-24, discloses a fluidic card assembly comprising a fluidic card housing and a biochip located in the fluidic card housing. The fluidic card housing includes a chamber with a base wall, into which at least one fluidic channel extends. The biochip is at least partially located in the chamber. A seal is provided for sealing the biochip in the chamber when the biochip is urged into the chamber. The fluidic channel has a serpentine form.
- 1.3 None of the documents above discloses the apparatus of present claims 1-20.
- 2 Considering D2 as the most relevant prior art to present claims 1-20, the problem to be solved by the present invention may be regarded as the provision of an alternative and efficient fluidic path design for cartridges for biological or chemical analysis.

The solution to this problem proposed in claims 1 and 15 of the present application is considered as involving an inventive step for the following reasons: there is no hint in the D1 or in other known prior art documents, to modify the design of the apparatus of D2 to include the fluidic channel in a laminated manifold that is attached to a circuit comprising sensors on a die, so that the liquid reagent can be delivered over an active surface of the sensor, as depicted in present figures.

Claims 2-14 and 16-20 are dependent on claims 1 resp. 15 and as such also meet(s) the requirements of inventive step.

Re Item VIII

Certain observations on the application

- 3 The features of claims 1-20 are not provided with reference signs to the figures placed in parentheses. For the sake of clarity, said features should include reference signs to the corresponding parts in the figures.

- 4 It is clear from the description and the figures that the features of how the laminated manifold is attached to the circuit, that the laminated manifold has at least one cut-out for the die (claim 11), and the different plural layers that the manifold comprises (claim 4), are essential to the definition of the invention.

Since independent claims 1 and 15 do not contain these features they do not meet the requirement of clarity that any independent claim must contain all the technical features essential to the definition of the invention.

In the absence of said features the subject-matter of present claims 1 and 15 is not clearly defined.