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(54) **FLOW CELL WITH FLEXIBLE CONNECTION**

(57) An instrument includes a reagent management system (RMS). The RMS includes a plurality of reagent wells, each reagent well operable to contain a reagent of a plurality of reagents positioned therein. The RMS is operable to select a flow of reagent from one of the plurality of reagents. A flexible connection includes a 1st flexible channel in fluid communication with the RMS. The 1st flexible channel is operable to route the flow of reagent therethrough. A flow cell includes a flow channel in fluid communication with the 1st flexible channel. The flow channel is operable to route the flow of reagent over analytes positioned in the flow channel. The flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

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FLOW CELL WITH FLEXIBLE CONNECTION

BACKGROUND

[0001] Many instruments that use microfluidic devices may include a reagent management system (RMS) that is capable of selecting and routing a plurality of reagents to a flow cell, wherein the RMS and the flow cell may be rigidly connected (i.e. connected such that the positions of the RMS and flow cell are held substantially fixed relative to each other). For example, the reagent management system may include a plurality of reagent wells that contain a variety of reagents, wherein each reagent well may be connected to a rotary selector valve. The rotary valve aligns with each reagent well in order to select any one of the reagents. A common line is then utilized to route the selected reagents from the rotary valve to an inlet port of a flow cell.

[0002] Analytes, such as DNA segments, nucleic-acid chains or the like, may be positioned in the flow channel. The selected reagents may flow through the flow cell in order to perform various controlled chemical reactions on the analytes. The chemical reactions may affect certain detectable properties related to the analytes. For example, one such detectable property may be light photons emitted from the analytes.

[0003] A detection module (such as an imaging module) may be positioned within the instrument. The detection module may be operable to scan the flow cell in order to detect the detectable properties. Device circuitry within the instrument may then process and transmit data signals derived from those detected properties. The data signals may then be analyzed to reveal properties of the analytes.

[0004] However, flow cells in many instruments are very sensitive to vibrations during a detection process. Additionally, in order to detect small features (such as light photons from the analytes) in the flow cell, the detection module may often be positioned relative to the flow cell with micron precision (e.g., plus or minus 100 microns or less).

[0005] Since the RMS and flow cell may be rigidly connected and may not move within the instrument, it is the detection module that may be moved relative to the flow cell as it scans over the flow cell. However, the detection module may be several orders of magnitude heavier and larger than the flow cell. As such, positioning the detection module with precision may be difficult. Additionally, the relatively large handling equipment needed to position the detection module may inadvertently vibrate the flow cell. Moreover, due to the size of the detection module and its associated handling equipment, scanning over several positions across the entire flow cell is costly and time consuming.

BRIEF DESCRIPTION

[0006] The present disclosure offers advantages and alternatives over the prior art by providing a flow cell connected in fluid communication to a reagent management system (RMS) with a flexible connection. The flexible connection enables the flow cell to be moved relative to a reference point on an instrument while the RMS is fixed relative to the reference point. As such, the flow cell may be moved relative to a detection module of the instrument while the detection module is also held stationary relative to the reference point. Additionally, because the flow cell is not rigidly coupled to the RMS, the flow cell may be positioned more precisely relative to a fixed reference point on the instrument than either the RMS or the detection module.

[0007] The RMS and flow cell may be included in a cartridge that is detachable from an instrument, wherein the flow cell may, or may not, be detachable from the cartridge Alternatively, the RMS may be rigidly attached to an instrument while the flow cell is detachable from the instrument.

[0008] Additionally, the flow cell and the flexible connection may be assembled together and included in a flexible connection module. The flexible connection module may be connected to a cartridge or to an instrument. The module may, or may not, be operable to detachably connect to an RMS in a cartridge or an instrument.

[0009] Since the flow cell is much lighter and smaller than a detection module, moving the flow cell may involve smaller and less costly handling equipment than that which may be involved for movement of the detection module. Further, movement of the flow cell, rather than the detection module, reduces vibrations that may affect the accuracy of detection of light photons, or other forms of detectable properties, related to analytes positioned in the flow cell. Additionally, the flow cell may be moved to various positions more quickly than a detection module may be moved in order to scan and detect the detectable properties.

[0010] Additionally, even if the detection module is mobile and the flow cell is fixed relative to a reference point of an instrument, the flexible connection may advantageously reduce vibrations transmitted to the flow cell by the RMS. This is because the flexible connection may dampen the vibrations produced by the RMS as they are transmitted through the flexible connection.

[0011] An instrument in accordance with one or more aspects of the present disclosure includes a reagent management system (RMS) operable to be positioned in the instrument. The RMS includes a plurality of reagent wells, each reagent well is operable to contain a reagent of a plurality of reagents positioned therein. The RMS is operable to select a flow of reagent from one of the plurality of reagents. A

flexible connection is also operable to be positioned in the instrument. The flexible connection includes a 1st flexible channel in fluid communication with the RMS. The 1st flexible channel is operable to route the flow of reagent therethrough. A flow cell is also operable to be positioned in the instrument. The flow cell includes a flow channel in fluid communication with the 1st flexible channel. The flow channel is operable to route the flow of reagent over analytes positioned in the flow channel. The flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

[0012] A cartridge of an instrument in accordance with one or more aspects of the present disclosure includes a reagent management system (RMS) operable to select a flow of reagent from one of a plurality of reagents contained in the RMS. A flexible connection is operable to be positioned in the cartridge. The flexible connection includes a 1st flexible channel in fluid communication with the RMS. The 1st flexible channel is operable to route the flow of reagent therethrough. A flow cell is operable to be positioned in the cartridge. The flow cell includes a flow channel in fluid communication with the 1st flexible channel. The flow channel is operable to route the flow of reagents over analytes positioned in the flow channel. When the cartridge is engaged with the instrument, the flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

[0013] A flexible connection module in accordance with one or more aspects of the present disclosure includes a flexible connection and a flow cell. The flexible connection includes a 1st channel inlet via, a 1st channel outlet via and a 1st flexible channel in fluid communication therebetween. The 1st channel inlet via includes a fluidic seal operable to connect to an RMS outlet port and to enable a flow of reagent therethrough. The flow cell includes an inlet port, an outlet port and a flow channel in fluid communication therebetween. The inlet port is in fluid communication with the 1st channel outlet via of the flexible connection. The flow channel is operable to route the flow of reagent over analytes positioned in the flow channel.

DRAWINGS

[0014] The disclosure will be more fully understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

[0015] FIG. 1 depicts an example of a schematic block diagram of an instrument according to aspects disclosed herein;

[0016] FIG. 2 depicts an example of a schematic block diagram of an instrument having a cartridge according to aspects disclosed herein;

[0017] FIG. 3 depicts an example of a more detailed schematic diagram of the instrument of FIG. 2 according to aspects disclosed herein;

[0018] FIG. 4 depicts an example of a schematic block diagram of the instrument of FIG. 3 according to aspects disclosed herein;

[0019] FIG. 5A depicts an example of a simplified perspective view of a flexible connection module and a portion of an RMS that the module is operable to connect to according to aspects disclosed herein;

[0020] FIG. 5B depicts an example of a cross sectional side view of the flexible connection module of FIG. 5A according to aspects disclosed herein;

[0021] FIG. 6 depicts an example of an exploded view of a flexible connection having a top layer, a bottom layer and an intermediate layer according to aspects disclosed herein;

[0022] FIG. 7A depicts an example of a perspective view of the flexible connection of FIG. 6 according to aspects disclosed herein;

[0023] FIG. 7B depicts an example of a front side view of the flexible connection of FIG. 6 according to aspects disclosed herein;

[0024] FIG. 8 depicts an example of a graph of burst pressure vs. the ratio of wall width to channel width according to aspects disclosed herein;

[0025] FIG. 9A depicts an example of a front side view of a flexible connection having an intermediate stack of sublayers, wherein 50 percent by volume of the sublayers is adhesive according to aspects disclosed herein;

[0026] FIG. 9B depicts an example of a front side view of a flexible connection having an intermediate stack of sublayers, wherein 25 percent by volume of the sublayers is adhesive according to aspects disclosed herein;

[0027] FIG. 10 depicts an example of a pair of graphs of force vs. displacement for a straight flexible connection without a slit and a straight flexible connection with a slit respectively according to aspects disclosed herein;

[0028] FIG. 11 depicts an example of a pair of graphs of force vs. displacement for a straight flexible connection and an S-curve flexible connection respectively according to aspects disclosed herein;

[0029] FIG. 12A depicts an example of a pair of graphs of force vs. displacement for a laser bonded flexible connection and an adhesive bonded flexible connection respectively according to aspects disclosed herein;

[0030] FIG. 12B depicts an exploded perspective view of the laser bonded flexible connection of FIG. 12A in accordance with aspects disclosed herein; and

[0031] FIG. 12C depicts an exploded perspective view of the adhesive bonded flexible connection of FIG. 12A in accordance with aspects disclosed herein.

DETAILED DESCRIPTION

[0032] Certain examples will now be described to provide an overall understanding of the principles of the structure, function, manufacture, and use of the methods, systems, and devices disclosed herein. One or more examples are illustrated in the accompanying drawings. Those skilled in the art will understand that the methods, systems, and devices specifically described herein and illustrated in the accompanying drawings are non-limiting examples and that the scope of the present disclosure is defined solely by the claims. The features illustrated or described in connection with one example may be combined with the features of other examples. Such modifications and variations are intended to be included within the scope of the present disclosure.

[0033] The terms "substantially", "approximately", "about", "relatively," or other such similar terms that may be used throughout this disclosure, including the claims, are used to describe and account for small fluctuations, such as due to variations in processing, from a reference or parameter. Such small fluctuations include a zero fluctuation from the reference or parameter as well. For example, they can refer to less than or equal to ± 10%, such as less than or equal to ± 5%, such as less than or equal to ± 2%, such as less than or equal to ± 1%, such as less than or equal to ± 0.5%, such as less than or equal to ± 0.2%, such as less than or equal to ± 0.1%, such as less than or equal to ± 0.05%.

[0034] Referring to FIG. 1, an example of a schematic block diagram of an instrument 100 according to aspects disclosed herein is depicted. The instrument 100 may be a sequencing instrument or other instrument that utilizes microfluidic devices.

[0035] The instrument 100 includes a flow cell 102 in fluid communication with a reagent management system (RMS) 104, wherein the RMS 104 and the flow cell 102 are mechanically and flexibly connected together by a flexible connection 106. The RMS 104 is capable of selecting and routing a plurality of reagents 108, 109, 110, 111, 112, 114, 116, 118 (herein 108-118) (best seen in FIG. 3) to the flow cell 102. For purposes herein, the term "flexible" and its derivatives include the capability of being turned, bowed, or twisted without breaking or losing functionality.

[0036] The flow cell 102 includes an inlet port 120 and an outlet port 122 connected therebetween by a flow channel 124 (best seen in FIG. 3). Analytes 140 (best seen in FIG. 3), such as DNA segments, nucleic-acid chains or the like, may be positioned in the flow channel 124.

[0037] The selected reagents 108-118 may flow through the flow channel 124 of the flow cell 102 and be routed over the analytes 140 in order to perform various controlled chemical reactions on the analytes with a predetermined sequence of the reagents 108-118. One example of a chemical reaction between a reagent and analytes in a flow cell is where a reagent delivers an identifiable label (such as a fluorescently labeled nucleotide molecule or the like) that may be used to tag the analytes. Thereafter, an excitation light may be radiated through the top layer of the flow cell and onto the analytes, causing the fluorescent label tagged to the analytes to fluoresce emissive light photons. The emissive light photons may be scanned and detected by a detection module 126 (such as an imaging module) of the instrument 100 during a detection process.

[0038] During the detection process, the detection module may, or may not, be movable relative to fixed reference point on the instrument. For example, the detection module may be moved and the flow cell held fixed relative to the reference point in order to scan the flow channel for the emissive light photons. Alternatively, by way of example, the detection module may be held fixed and the flow cell moved relative to the instrument's reference point in order to scan the flow channel of the flow cell.

[0039] Device circuitry within the instrument 100 may then process and transmit data signals derived from those detected photons. The data signals may then be analyzed to reveal properties of the analytes.

[0040] Though the detection module 126 has been illustrated in this example as being an imaging module used for detecting photons of light, other forms of detection modules and detection schemes may be used to detect other forms of detectable properties related to the analytes. For example, the detectable properties related to the analytes may include photons of light, electric charges, magnetic fields, electrochemical properties, pH changes or the like. Moreover, the detection module 126 may, without limitation, include sensing devices that may be either embedded in the flow cell 102, mounted in the

instrument 100 external to the flow cell 100 or any combination thereof. The chemical reactions between the reagents and the analytes induce the analytes to affect the detectable properties.

[0041] For purposes herein, the term "affecting detectable properties", and its derivatives, includes causing such detectable property to initiate or change in such a way that its initiation or change is detectable by the detection module. For example, affecting a detectable property may include: causing fluorescent labels tagged to the analytes to fluoresce emissive light photons, changing or initiating an electromagnetic field, changing a pH or the like.

[0042] The detection module 126 may be equipped with all cameras and/or sensors suitable and/or needed to detect the affected detectable properties. Alternatively, some sensors may be embedded in the flow cell itself, wherein the sensors communicate with the detection module.

[0043] The flexible connection 106 enables the flow cell 102 to be moved relative to a fixed reference point 128 in the instrument 100 while the detection module 126 is held stationary relative to the reference point 128 in order to detect the photons of light, or other forms of detectable properties. Alternatively, the flow cell 102 may be held stationary, and the detection module 126 moved, relative to the reference point 128 in order to detect the detectable properties. More specifically, the flow channel 124 of the flow cell 102 is moved past the focal areas of the sensing devices and/or cameras of the stationary detection module 126 to allow the detection module to scan the flow channel 124 for photons of light, or other forms of detectable properties, related to the analytes 140.

[0044] The flow cell 102 may be moved in any of three directions (as indicated by the X, Y and Z arrows) relative to the reference point 128. Additionally, the flow cell may be moved such that is may be rotated in anyone or any combination of the axes (i.e., X, Y, and Z) as rotational axes. In this example, the flow cell may be moved with 6 degrees of freedom in three dimensional space (i.e., any combination of linear movement in the X, Y and Z directions plus any combination of rotational movement about the X, Y, Z axes). It is important to note, however, that regardless of which direction the flow cell 102 is moved in, the flow cell 102 may be able to be positioned in each of those three directions (i.e., in the X direction, the Y direction or the Z direction) relative to the reference point 128 within a precise tolerance range, for example, within plus or minus 100 microns or less.

[0045] The reference point 128 may be anyone or any number of stationary structures on the instrument 100. For example, the reference point may be one or more mechanical registration holes or protrusions located throughout the instrument. Further the reference point may include separate reference

points that the RMS 104, flow cell 102 and/or detection module 126 are aligned or positioned to, wherein those separate reference points may be aligned to a common reference point.

[0046] For purposes herein, various reference points or groups of reference points may be referred to as one or more registration systems. Additionally, the positioning or aligning of a component, such as a flow cell 102, an RMS 104 or a detection module 126, to a registration system may be referred to herein as registering the component.

[0047] Additionally, the flow cell 102 may be positioned indirectly to the reference point 128. For example, the detection module 126 may be positioned relative to the reference point 128 and the flow cell 102 may be positioned relative to a fixed reference point on the detection module 126. Alternatively, by way of example, the detection module 126 may be positioned relative to the reference point 128 and the detection module 126 may then be utilized to detect the relative position of the flow cell 102 to the detection module 126.

[0048] The flow cell 102 is moved relative to the detection module 126 in order for the detection module 126 to scan and detect light photons, or other forms of detectable properties, being affected by the analytes positioned over a majority of the area of the flow channel 124. Advantageously, the flow cell 102 is at least an order of magnitude lighter and smaller than the detection module 126. Therefore, precise positioning of the flow cell 100 relative to a stationary detection module 126 may be done with smaller handling equipment, less expensively and in less time than such positioning of a detection module 126 relative to a stationary flow cell 102. Additionally, the movement of the flow cell 102 causes less vibration than movement of the detection module 126.

[0049] Additionally, even if the detection module 126 is mobile and the flow cell 102 is fixed relative to a reference point 128 of an instrument 100, the flexible connection 106 may advantageously reduce vibrations transmitted to the flow cell 102 by the RMS 104. This is because the flexible connection 106 separates the RMS 104 from the flow cell 102 and, therefore, may dampen the vibrations produced by the RMS 104 as they are transmitted through the flexible connection 106.

[0050] Moreover, whether the detection module 126 is movable or fixed, the flexible connection 106 advantageously enables independent registration (i.e., positioning) of the RMS 104 and flow cell 102 to separate registration systems (i.e., to separate reference points). As such, both the RMS 104 and the flow cell 102 may be more precisely registered to their associated reference points.

[0051] For example, the reference point 128 may include a 1st reference point for the RMS 104 and a 2nd reference point for the flow cell 102. As such, the RMS 104 may be positioned relative to the 1st reference point and the flow cell 102 may be positioned relative to the 2nd reference point. Wherein, the positioning of the RMS 104 and the flow cell 102 to their respective 1st and 2nd reference points respectively may be independent of each other.

[0052] Referring to FIG. 2, an example of a schematic block diagram of a cartridge-based instrument, wherein the instrument 100 includes a cartridge 130 according to aspects disclosed herein is depicted. The cartridge 130 includes the flow cell 102, the RMS 104 and the flexible connection 106. Further, the cartridge 130 may be detachable from the instrument 100. Still further, the flow cell 102 may, or may not, be detachable from the cartridge 130. When the cartridge 130 is engaged with the instrument 100 and the flow cell 102 is engaged with the cartridge 130, the RMS 104 is fixed relative to the reference point 128 of the instrument 100 while the flow cell 100 is movable relative to the reference point 128 of the instrument 100.

[0053] During the engagement process of the cartridge 130 to the instrument 100, the tolerance ranges of positioning requirements (i.e., registration requirements) of the RMS 104 and the flow cell 102 may be very different. More specifically, in order for the cartridge 130 to be engaged with the instrument 100, the RMS 104 may be positioned relative to the reference point 128 within about a predetermined 1st tolerance range. That 1st tolerance range may be in the millimeter range, for example, plus or minus 2 millimeters or less. On the other hand when the flow cell 102 is registered relative to the detection module 126 and/or moved to a predetermined position in the instrument 100 in order to be scanned by the detection module 126, the flow cell's position may be positioned relative to the reference point 128 within about a 2nd predetermined tolerance range. That 2nd tolerance range may be in the micrometer range, for example, plus or minus 100 microns or less. As such the 1st tolerance range may to be at least 10 times greater than the 2nd tolerance range.

[0054] This is because the RMS 104 may align with certain mechanical components, such as valves and drive motors, in order to be operated by the instrument 100. On the other hand, the flow cell 102 may be more precisely positioned relative to the detection module 126 in order to be optically scanned over a majority of the surface of the flow channel 124.

[0055] If the RMS 104 were rigidly connected to the flow cell 102 (i.e., connected such that the positions of the RMS and the flow cell are held substantially fixed relative to each other), then both the RMS 104 and the flow cell 102 may have to be positioned within the smaller of the two tolerance ranges (i.e., the 2nd tolerance range). However, the flexible connection 106 decouples the positioning requirements

of the RMS 104 and flow cell 102. Therefore, the RMS 104 and flow cell 102 may be independently aligned to their separate positioning requirements, making it much easier to engage the cartridge 130 to the instrument 100 and to position the flow cell 102 relative to the detection module 126.

[0056] Even though the example of this FIG. 2 illustrates a cartridge-based instrument 100 having an RMS 104 and flow cell 102 contained in a cartridge 130, other instruments 100 may not include such a cartridge-based system. Rather in some instruments 100, the components of the RMS 104 may be integrally and rigidly mounted within the instrument 100, and only the flow cell 102 may be detachable from the instrument 100. However, even in such non-cartridge-based instruments 100, the flexible connection 106 still advantageously facilitates the precise positioning of the flow cell 102 relative to a detection module 126 during a detection process.

[0057] Referring to FIG. 3, an example of a more detailed schematic diagram of the cartridge-based instrument 100 of FIG. 2 having the cartridge 130 engaged therein is depicted. The cartridge 130 includes the flow cell 102 and the RMS 104 connected with the flexible connection 106 therebetween.

[0058] The RMS includes a plurality of reagent wells 132. Each reagent well 132 is operable to contain a reagent of a plurality of reagents 108-118 positioned therein. The RMS 104 is operable to select a flow of reagent 134 from one of the plurality of reagents 108-118.

[0059] The reagents 108-118 may be any of several types or combinations of reagents depending on the type and sequence of the chemical reactions that are to be performed at the flow cell. For example, the reagents 108-118 may be of the following types:

- Reagent 108 and 109 may be different formulations of an incorporation mix, which is a mixture of chemicals that incorporates fluorescently-labeled nucleotides into DNA strands.
- Reagent 110 and 111 may be different formulations of a scan mix, which is a mixture of chemicals that stabilize DNA strands during a detection process.
- Reagent 112 may be a cleave mix, which is a mixture of chemicals that enzymatically cleave fluorescently-labeled nucleotides from DNA strands.
- Reagent 114 and 116 may be different formulations of a wash buffer, which is a mixture of wash reagents to remove the active reagents from a flow cell.
- Reagent 118 may be air.

[0060] The flexible connection 106 includes a 1st flexible channel 136 in fluid communication with the RMS 104 through an RMS inlet port 156. The 1st flexible channel 136 is operable to route the flow of reagent 134 through an inlet port 120 of the flow cell 102 and into the flow channel 124. The flexible

connection 106 also includes a 2nd flexible channel 138 in fluid communication with the flow channel 124 through an outlet port 122 of the flow cell 102. The 2nd flexible channel 138 is operable to route the flow of reagent 134 from the flow cell 102, through an RMS inlet port 158 and back into the RMS 104 after the flow of reagent 134 has passed through the flow channel 124.

[0061] The flow cell 102 of the cartridge 130 includes the flow channel 124 in fluid communication with the 1st flexible channel 136 through its inlet port 120, and in fluid communication with the 2nd flexible channel 138 through its outlet port 122. The flow channel 124 is operable to perform a variety of chemical reactions between the various flows of reagent 134 from the plurality of reagents 108-118 and analytes 140 positioned in the flow channel 124. The flexible connection 106 enables the flow cell 102 to be moved relative to a fixed reference point 128 in the instrument 100.

[0062] The fixed reference point 128 is, in this example, a registration hole. However, the reference point 128 may be any number of fixed structures in the instrument 100. For example, the reference point 128 may be a plurality of registration pegs or holes located at various places on a stationary frame of the instrument 100.

[0063] The cartridge 130, in this example, includes a rotary valve 142 for selecting the reagents 108-118. The rotary valve has an internal rotary valve body 144. The valve body 144 includes a center port 146 and a rotatable port 148, which are connected by a rotary channel 150. The valve body 144 pivots around the center port 146 to move the rotatable port 148.

[0064] The plurality of reagent wells 132, which contain the reagents 108-118, are disposed around the periphery of the rotary valve 142. Each well 132 is in fluid communication with a well channel 152. Each well channel 152 includes a well channel port 154 that the rotatable port 148 of the rotary valve 142 may align with in order to receive the flow of reagent 134 from any given well 132.

[0065] When the rotatable port 148 aligns with one of the well channel ports 154, a reagent flow path 134 is established that allows a flow of reagent 134 to flow from the selected well 132, through the well channel 152, through the rotary valve 142, through a common line 155 and out the RMS outlet port 156. The reagent flow 134 then continues through the 1st flexible channel 136, into the inlet port 120 of the flow cell 102 and through the flow channel 124, where the reagents 108-118 may react with the analytes 140.

[0066] The unreacted reagents and/or by products of the reaction, may then flow out the outlet port 122 of the flow cell 102 and through the 2nd flexible channel 138. The reagent flow 134 may then re-enter the RMS 104 through the RMS inlet port 158.

[0067] The RMS inlet port 158 of the RMS 104 is in fluid communication with a 1st pinch valve 160. The 1st pinch valve 160 is in fluid communication with a 2nd pinch valve 162. The 1st and 2nd pinch valves 160, 162 include a resilient central portion that may be mechanically or pneumatically actuated to pinch off or release the flow of reagent 134 through the pinch valves 160, 162. Additionally, though pinch valves 160, 162 are illustrated in this example, other types of valves may be utilized to perform the same function. For example, the valves 160, 162 may be rotary valves.

[0068] An onboard pump 164 (such as a syringe pump, or similar) is also disposed on the RMS 104. Even though the onboard pump 164 may be other types of pumps, it will be referred to herein as the syringe pump 164. The syringe pump 164 is connected in a tee formation between the 1st and 2nd pinch valves 160, 162. Both pinch valves 160, 162 are opened and closed by the instrument 100 to engage or disengage the syringe pump 164 from the flow cell 102.

[0069] The syringe pump 164 includes a reciprocating plunger 166 disposed in a cylinder 168, which has a cylinder bore 170. The plunger 166 is received within the cylinder bore 170 to form a plunger-cylinder bore seal. The plunger 166 is driven by the instrument 100 to reciprocate within the cylinder bore 170 and to pump the reagents 108-118 from the reagent wells 132 to a vented waste tank 172.

[0070] The instrument 100 also includes the detection module 126, which is operable to detect photons of light, or other forms of detectable properties, when a chemical reaction caused by the reagents 108-118 induces the analytes 140 to affect such detectable properties. The flexible connection 106 enables the flow cell 102 to be moved relative to the fixed reference point 128 in the instrument 100 while the detection module 126 is held stationary relative to the reference point 128 in order to facilitate detection of the detectable properties.

[0071] Alternatively, the detection module 126 may be movable relative to the fixed reference point 128 while the flow cell 102 is held fixed relative to the reference point 128. As such, the flexible connection 106 may enable the flow cell 102 to be more precisely positioned relative to the reference point 128 than that of a flow cell that is rigidly connected to the RMS.

[0072] Further, vibrations transmitted to the flow cell 102 by the RMS 104 may also be advantageously reduced even if the detection module 126 is movable and the flow cell 102 is held fixed relative to the reference point 128. This is because the flexible connection 106 separates the RMS 104 from the flow cell 102 and, therefore, may dampen the vibrations produced by the RMS 104 as they are transmitted through the flexible connection 106.

[0073] Additionally, because the flexible connection 106 decouples the RMS 104 from the flow cell 102, the flexible connection 106 enables independent registration (i.e., positioning) of the RMS 104 and flow cell 102 to separate registration systems (i.e., to separate reference points). As such, both the RMS 104 and the flow cell 102 may be more precisely registered to their associated reference points.

[0074] Though the example illustrated in FIG. 3 is that of an instrument 100 utilizing a rotary valve 142 that routes the various reagents 108-118 through a common line 155 and into the flow cell 102, other instruments 100 may not utilize a rotary valve 142. For example, the well channels 152 from each reagent well 132 may extend directly to one of a plurality of separate RMS outlet ports 156.

[0075] In that case, the well channels 152 may each include a valve (not shown) to control the reagent flow 134 from each reagent well 132. Additionally, the 1st flexible channel 136 may be a plurality of 1st flexible channels to receive the various reagent flows 134 from each RMS outlet port 156. Moreover, the inlet port 120 of the flow cell 102 may be a plurality of inlet ports 120 to receive the various reagent flows 134 from each 1st flexible channel 136.

[0076] Referring to FIG. 4, an example of a schematic block diagram of the instrument 100 of FIG. 3 is depicted. The instrument 100 includes a docking station 174 to receive the cartridge 130. Various electrical and mechanical assemblies within the instrument 100 interact with the cartridge 130 to operate the cartridge during a microfluidics analysis operation of the various chemical reactions that are performed in the flow cell 102.

[0077] The instrument 100 may include, among other things, one or more processors 176 that are to execute program instructions stored in a memory 178 in order to perform the microfluidics analysis operations. The processors are in electronic communication to a rotary valve drive assembly 180, a syringe pump drive assembly 182, a pinch valve assembly 184, the detection module 126 and a movable temperature regulation assembly 206.

[0078] A user interface 186 is provided for users to control and monitor operation of the instrument 100. A communications interface 188 conveys data and other information between the instrument 100 and remote computers, networks and the like.

[0079] The rotary valve drive assembly 180 includes a drive shaft 190, which is mechanically coupled to a rotary valve interface bracket 192. The rotary valve interface bracket 192 is mechanically coupled to the rotary valve 142. The rotary valve drive assembly 180 includes a rotation motor 194 and a translation motor 196. The translation motor 196 moves the drive shaft 190 in a translational direction

between an engaged state and a disengaged state with the rotary valve 142. The rotary motor 194 manages rotation of the rotary valve body 144 of the rotary valve 142.

[0080] The rotary valve drive assembly 180 also includes a position encoder 198 that monitors the position of the drive shaft 190. The encoder 198 provides position data to the processor 176.

[0081] The syringe pump drive assembly 182 includes a syringe pump motor 200 coupled to an extendable shaft 202. The shaft 202 is driven by the motor 200 between an extended position and a retracted position to reciprocate the plunger 166 within the cylinder bore 170 of the cylinder 168 on the syringe pump 164.

[0082] The pinch valve drive assembly 184 includes a set of two pneumatically driven pinch valve drive motors 204. The two pinch valve drive motors 204 are mechanically coupled to the 1st and 2nd pinch valves 160, 162. The drive motors 204 may utilize air pressure to pinch off or release a resilient central portion of the pinch valves 160, 162 to pneumatically open and close the pinch valves. Alternatively, the drive motors 204 may be electrically driven.

[0083] The detection module 126 may contain all of the cameras and/or detecting sensors suitable and/or needed to enable the detection of emissive light photons, or other forms of detectable properties, related to analytes 140 in the flow cell 102. Device circuitry (not shown) within the instrument 100 may then process and transmit data signals derived from those detected emissions. The data signals may then be analyzed to reveal properties of the analytes.

[0084] A temperature regulation assembly 206 (or other environmental control device) may also be included in the instrument 100. The temperature regulation assembly 206 may be utilized to provide temperature control of the flow cell 102 during the various chemical reactions. More specifically, the temperature regulation assembly 206 may provide both heating and cooling of the flow cell 102, thereby enabling thermocycling of the flow cell 102. An environmental control device may control or regulate parameters other than just temperature (e.g., pressure). As will be seen in more detail in FIGS. 5A and 5B, the temperature regulation assembly 206 may be movable relative to the reference point 128 and may provide a platform upon which the flow cell 102 may be positioned in order to move the flow cell 102 relative to the detection module 126.

[0085] Referring to FIGS. 5A and 5B, an example of a flexible connection module 300 is depicted. More specifically, FIG. 5A depicts an example of a simplified perspective view of the flexible connection module 300 and a portion of the RMS 104 that the module 300 is operable to connect to. Also more

specifically, FIG. 5B depicts an example of a cross sectional side view of the module 300 connected in fluid communication to the portion of the RMS 104, wherein the cross sectional side view is taken along the 1st flexible channel 136 of the flexible connection 106.

[0086] The flexible connection module 300 includes a flexible connection 106, a flow cell 102 and a support fixture 302. The flexible connection 106 is assembled in fluid communication to the flow cell 102, wherein the flexible connection 106 and flow cell 102 assembly are framed and supported by the support fixture 302. The module 300 may be connected to an RMS 104 within an instrument 100 or a cartridge 130.

[0087] The flexible connection 106 of module 300 includes a 1st channel inlet via 304, a 1st channel outlet via 306 and a 1st flexible channel 136 in fluid communication therebetween. The 1st flexible channel 136 is operable to route a flow of reagent 134 from an RMS outlet port 156 of the RMS 104 to an inlet port 120 of the flow cell 102.

[0088] The flexible connection 106 also includes a 2nd channel inlet via 308, a 2nd channel outlet via 310 and a 2nd flexible channel 138 in fluid communication therebetween. The 2nd flexible channel 138 is operable to route the flow of reagent 134 from an outlet port 122 of the flow cell 102 to an RMS inlet port 158 of the RMS 104.

[0089] Both the 1st channel inlet via 304 and the 2nd channel outlet via 310 include a fluidic seal 312. The fluidic seal 312 of the 1st channel inlet via 304 is operable to connect to an RMS outlet port 156 of the RMS 104 and to enable the flow of reagent 134 therethrough such that the flow of reagent 134 passes from the RMS 104 to the 1st flexible channel 136. The fluidic seal 312 of the 2nd channel outlet via 310 is operable to connect to an RMS inlet port 158 of the RMS 104 and to enable the flow of reagent 134 therethrough such that the flow of reagent 134 passes from the 2nd flexible channel 138 back into the RMS 104.

[0090] The fluidic seals 312 in the specific example illustrated in FIGS. 5A and 5B are detachable O-rings. However, other forms of detachable fluidic seals 312 may be utilized. For example, various elastomeric gaskets may be used to provide a detachable fluidic seal.

[0091] Additionally, the fluidic seals 312 may not be detachably connectable to the RMS 104 of a cartridge or an instrument. For example, the fluidic seals may be a layer of adhesive that bonds to the RMS 104, or the fluidic seal may be operable to be laser bonded to form a permanent bond to the RMS 104.

[0092] The flow cell 102 of module 300 includes the inlet port 120, the outlet port 122 and a flow channel 124 in fluid communication therebetween. The flow channel 124 is operable to route the flow of reagent 134 over analytes 140 positioned in the flow channel 124.

[0093] The 1st channel outlet via 306 is connected in fluid communication with the inlet port 120 of the flow cell 102. Additionally the 2nd channel inlet via 308 is connected in fluid communication with the outlet port 122 of the flow cell 102. The fluidic connections from outlet via 306 to inlet port 120, and from inlet via 308 to outlet port 122, are sealed together with a layer of adhesive 314 (best seen in FIG. 5B). The adhesive 314 forms a permanent bond between via 306 and port 120, and between via 308 and port 122.

[0094] The adhesive 314 may be composed of several different materials that are suitable to handle the application parameters, including application temperatures, application pressures and chemical compatibility with the reagents. For example, the adhesive 314 may be composed of an acrylic based adhesive, a silicone based adhesive, a heat activated adhesive, a pressure activated adhesive, a light activated adhesive, an epoxy adhesive, and the like, or a combination thereof.

[0095] Alternatively, other forms of bonding may be utilized to seal the connections between via 306 and port 120, and between via 308 and port 122. For example, vias and ports may be laser bonded together. Further, vias and ports may be detachably connected with a detachable fluidic seal, such as with an O-ring or an elastomeric gasket.

[0096] The support fixture 302 of the module 300 includes an inner border 316 that surrounds the flow cell 102. The fixture 302 is operable to contain the flow cell 102 within its inner border 316. The fixture 302 also enables the flow cell to move laterally in the Y direction and longitudinally in the X direction. Additionally, the fixture 302 may also allow some movement of the flow cell 102 vertically in the Z direction.

[0097] One way the fixture 302 may provide such movement in the X, Y and Z directions, while containing the flow cell 102 within its inner border 316, is with a plurality of support fingers 318 disposed on the upper 320 and lower 322 surfaces of the fixture 302. The support fingers 318 may extend inwardly from the inner border 316 and partially across the top and bottom surfaces of the flow cell 102. However, the support fingers disposed on the upper surface 320 may be sized such that they do not extend over the flow channel 124 of the flow cell 102 in order to not interfere with a scan of a detection module 126 over the flow channel 124 during a detection process. The support fingers 318 may prevent the flow cell 102 and flexible connection 106 from falling out from within the inner border 316 of the fixture 302 during shipment of the module 300.

[0098] Additionally, the support fingers 318 may allow movement of the flow cell 102 both laterally (Y direction) and longitudinally (X direction) within the inner border 316. Additionally, the support fingers 318 disposed on the bottom surface 322 of the support fixture 302 and the support fingers 318 disposed on the top surface 320 of the support fixture 302 may be spaced apart enough to allow some movement of the flow cell 102 in the vertical (Z) direction, while still containing the flow cell 102 within the inner border 316.

[0099] During operation, the flexible connection module 300 may be assembled to the RMS 104 (best seen in FIG. 5B) by aligning the fluidic seals 312 with the RMS outlet port 156 and the RMS inlet port 158. Thereafter, the support fixture 302 may be clamped to the RMS 104 such that the fluidic seals 312 are sandwiched between the support fixture 302 and the RMS 104. This may be accomplished with any number of clamping techniques, such as by bolting, or by using C-clamps or various other forms of clamping devices.

[00100] Once the support fixture 302 is attached to the RMS 104 such that the RMS is in fluid communication with the flexible connection module 300, the flow cell 102 may be affixed to the movable temperature regulation assembly 206 (best seen in FIG. 5B). This is because, the support fingers 318 disposed on the lower surface 322 of the support fixture 302 only extend partially across the bottom surface of the flow cell 102. As such enough of the bottom surface of the flow cell 102 is exposed for the temperature regulation assembly 206 to be affixed against the flow cell 102, and to allow for longitudinal and lateral movement within the inner border 316 of the support fixture 302.

[00101] The temperature regulation assembly 206 is operable to position the flow cell 102 within a few microns of the detection module 126 in the vertical (i.e., Z) direction. Additionally, the temperature regulation assembly 206 may move the flow cell 102 in both the X and Y directions to enable the detection module 126 to scan the flow channel 124 of the flow cell 102 during a detection process.

[00102] Alternatively, even if the detection module 126 is moved and the flow cell 102 is held fixed relative to a reference point 128 during a scan of the flow cell 102, the temperature regulation assembly may still precisely position the flow cell 102 relative to the detection module 126 prior to initiating the scan. This is because the flexible connection 106 decouples the movements of the flow cell 102 from the movements of the RMS 104. As such, the initial starting position of the flow cell 102 relative to the detection module 126 prior to a scan may be precisely maintained by moving just the flow cell 102. If the flow cell 102 did not connect to a flexible connection 106 and was rigidly connected to the RMS 104, then both the flow cell 102 and portions of the RMS 104 may have to be moved, making such precise positioning of the flow cell 102 relative to the detection module 126 more difficult.

[00103] Additionally, whether the detection module is movable or fixed relative to a reference point, the flexible connection 106 decouples the RMS 104 from the flow cell 102. Therefore, the flexible connection 106 enables independent registration (i.e., positioning) of the RMS 104 and flow cell 102 to separate registration systems (i.e., to separate reference points). As such, both the RMS 104 and the flow cell 102 may be more precisely registered to their associated reference points.

[00104] Referring to FIG.6, an example of an exploded view of the flexible connection 106 having a top layer 210, a bottom layer 212 and an intermediate layer 214 is depicted. The layers 210, 212, 214 are bonded together using an adhesive 216 to form a laminated stack or laminate 218.

[00105] The 1st and 2nd flexible channels 136, 138 are cut into the intermediate layer 214 using, for example, a laser cutting process. Accordingly, the intermediate layer 214 defines a geometry of the flexible channels 136, 138. More specifically the intermediate layer 214 defines a wall width 220 and a channel width 222 (best seen in FIGS 7A and 7B) of the flexible channels 136, 138.

[00106] The top layer 210 defines a top 224 (best seen in FIGS. 7A and 7B) of the 1st and 2nd flexible channels 136, 138. The bottom layer defines a bottom 226 (best seen in FIGS. 7A and 7B) of the 1st and 2nd flexible channels 136, 138.

[00107] A 1st via 228 and a 2nd via 230 are positioned in the bottom layer 212 of the flexible connection 106. The 1st and 2nd vias 228, 230 are in fluid communication with opposing distal ends 232, 234 of the 1st flexible channel 136 in the intermediate layer 214. Additionally, a 3rd via 236 and a 4th via 238 are positioned in the bottom layer 212 of the flexible connection 106. The 3rd and 4th vias 236, 238 are in fluid communication with opposing distal ends 240, 242 of the 2nd flexible channel 138 in the intermediate layer 214. Though vias 228, 230, 236, 238 are illustrated in FIG. 6 as being disposed in the bottom layer 212, they may also be positioned in the top layer 210 as well. More specifically, the 1st and 4th vias may be positioned together in either the bottom layer 212 or top layer 210. Additionally, the 2nd and 3rd vias also may be positioned together in either the bottom layer 212 or top layer 210.

[00108] The 1st via 228 is bonded to the RMS outlet port 156 of the RMS 104 to route the flow of reagent 134 from the RMS 104 to the 1st flexible channel 136 (and therefore, the 1st via may be considered an inlet via of the 1st flexible channel 136). The 2nd via 230 is bonded to the inlet port 120 of the flow cell 102 to route the flow of reagent 134 from the 1st flexible channel 136 to the flow channel 124 (and therefore, the 2nd via may be considered an outlet via of the 1st flexible channel 136). The 4th via 238 is bonded to the outlet port 122 of the flow cell 102 to route the flow of reagent 134 from the flow cell to the 2nd flexible channel 138 (and therefore, the 4th via may be considered an inlet via of the 2nd flexible channel

138). The 3rd via 236 is bonded to the RMS inlet port 158 of the RMS 104 to route the flow of reagent 134 from the 2nd flexible channel 138 back into the RMS 104 (and therefore, the 3rd via may be considered an outlet via of the 2nd flexible channel 138).

[00109] The layers 210, 212, 214 may be composed of several different materials that are suitable to handle the application parameters, including application temperatures, application pressures and chemical compatibility with the reagents. For example, the layers 210, 212, 214 may be composed of polyethylene terephthalate, polyimide, cyclic olefin copolymer, polycarbonate, polypropylene and the like.

[00110] Additionally, an additive of carbon black may be added to such materials as polyethylene terephthalate to provide a black polyethylene terephthalate or similar. The materials where the carbon black additive is added may have a relatively lower auto-florescence characteristic. Further, the carbon black additive may facilitate laser bonding of the layers 210, 212, 214.

[00111] The adhesive 216 may be composed of several different materials that are suitable to handle the application parameters, including application temperatures, application pressures and chemical compatibility with the reagents. For example, the adhesive 216 may be composed of an acrylic based adhesive, a silicone based adhesive, a heat activated adhesive, a pressure activated adhesive, a light activated adhesive, an epoxy adhesive, and the like, or a combination thereof. Such adhesives 216 may be utilized to adhesive bond the layers 210, 212, 214 together.

[00112] In addition to the layers 210, 212, 214 being adhesively bonded together with an adhesive (216), they may be bonded together in other ways as well. For example, the layers 210, 212, 214 may be bonded together using direct bonding techniques, such as thermal (fusion) bonding or laser bonding. Additionally, the layers 210, 212, 214 may be bonded together utilizing any combination of adhesive bonding or direct bonding techniques.

[00113] Additionally, with regards to adhesive bonding or direct bonding techniques, surface treatments of the layers 210, 212, 214 may be utilized to enhance the strength of the various bonds. Such surface treatments may include, for example, chemical surface treatments, plasma surface treatments or the like.

[00114] One simplified manufacturing method of building the flexible connection 106 may be to start by cutting each layer 210, 212, 214 to a predetermined specification using, for example, a laser cutting process. The method may continue by aligning the layers 210, 212, 214 together and bonding them with manual pressure only just to get the layers to stick together and form a laminate 218. Thereafter, the

laminate 218 may be put through a laminator to activate the adhesive 216 by applying a predetermined pressure. Thereafter the laminate 218 may be heated to a predetermined temperature (for example, above about 50 degrees C or above about 90 degrees C) for a predetermined amount of time (for example, about 2 hours or more), to fully form the flexible connection 106.

[00115] Thereafter, a bottom liner (not shown) that was disposed over the adhesive 216 of the bottom layer 212 is removed to expose that adhesive 216. The flexible connection 106 is then bonded to the RMS 104 and flow cell 102 by applying an appropriate force to the flexible connection 106 in order to activate the adhesive 216 disposed on the bottom of the flexible connection 106.

[00116] Referring to FIGS 7A and 7B, an example of a perspective view (FIG. 7A) and a front side view (FIG. 7B) of the flexible connection 106 of FIG. 6 is depicted. For purposes of clarity, in this particular example, only the 1st flexible channel 136 is illustrated.

[00117] The three layers 210, 212, 214 are bonded together to form the laminate 218. The three layers 210, 212, 214 are thin, for example, in some cases, from about 10 microns to about 1000 microns each. As such, the laminate 218 is flexible.

[00118] The laminate height (or flexible connection height) 244 may range, for example, from about 30 microns to about 3000 microns. The channel height 246 is the distance between the top 224 and bottom 226 of the 1st flexible channel 136. The channel height may range, for example, from about 10 microns to about 1000 microns. The channel width 222 is the distance between the two opposing inside walls 248, 250. The wall widths 220 may be any practical size depending on the design parameters. For example, the wall widths 220 may range from about 250 microns to about 650 microns. As will be discussed in greater detail in FIG. 8, the ratio of the wall width 220 to channel width 222 is often designed to be about 2.5 or greater.

[00119] Referring to FIG. 8, an example of a graph 252 of burst pressure vs. the ratio 254 of wall width 220 to channel width 222 is depicted. The ratio of wall width to channel width 254 is shown on the horizontal axis of the graph 252. The burst pressure 256 (in pounds per square inch gage (psig)) is shown on the vertical axis. Each plotted point 258 represents the intersection of the burst pressure 256 for any given ratio 254. Note that 1 pound per square inch (English units) is equal to about 0.069 bar (metric units).

[00120] The ratio 254 of wall width 220 to channel width 222 is a parameter that significantly affects burst pressure 256 of a flexible channel (for example, the 1st or 2nd flexible channels 136, 138) in the

flexible connection 106. The larger the ratio 254, the higher the burst pressure 256 tends to be. Burst pressure, in this case, means a pressure at which leaks will develop in the flexible channel.

[00121] The desired burst pressure 256 for an application may vary depending on application parameters. However, a burst pressure of 40 psig or greater in the 1st and 2nd channels 136, 138 is often adequate for most reagent flow 134 applications. From the plotted points 258 on the graph 252, it may be seen that a ratio 254 of about 2.5 or greater may often result in a burst pressure 256 of about 40 psig or greater.

[00122] Referring to FIG. 9A, an example of a front side view of a flexible connection having an intermediate stack of sublayers is depicted. In this FIG. 9A, 50 percent by volume of the sublayers is adhesive.

[00123] Referring to FIG. 9B, an example of a front side view of a flexible connection having an intermediate stack of sublayers is also depicted. In this FIG. 9B, 25 percent by volume of the sublayers is adhesive.

[00124] The flexible connections 106 of FIGS. 9A and 9B both include a top layer 210, a bottom layer 212 and an intermediate layer 214. However, the intermediate layer 214 is a plurality of intermediate sublayers 260 that are bonded together by an adhesive 262.

[00125] In FIG. 9A, there is about 50 percent by volume of adhesive 262 to that of the total volume of adhesive 262 plus intermediate sublayers 260, which may be composed of, for example, a polyimide. However, in FIG. 9B, there is only about 25 percent by volume of adhesive 262 to that of the total volume of adhesive 262 plus intermediate sublayers 260, which are composed of the same material (for example, polyimide).

[00126] The percentage of adhesive (such as pressure sensitive adhesive) relative to a total of adhesive plus intermediate sublayers by volume is also a parameter that significantly affects burst pressure. The smaller the percentage, the larger the burst pressure tends to be. In the specific case of FIGS. 9A and 9B, the only difference between the two structures of flexible connections 106 is the percentage of adhesive relative to the total of the adhesive and intermediate sublayers by volume. In FIG. 9A, the percentage is 50 percent and the burst pressure is 50 psig. In FIG. 9B, the ratio is 25 percent and the burst pressure is 130 psig.

[00127] Referring to FIG.10, an example of a pair of graphs 264 and 266 of force (in newtons) vs. displacement (in millimeters) for a respective pair of straight flexible connections 106A, 106B is depicted. In graph 264, the associated flexible connection 106A includes only the 1st and 2nd flexible channels 136, 138 dispose therein. In graph 266, the associated flexible connection 106B includes the 1st and 2nd flexible channels 136, 138, but additionally includes a slit 268 disposed between the flexible channels 136, 138.

[00128] Decoupling the reagent management system (RMS) 130 from the flow cell 102 may come at a cost of applying an additional mechanical stress to both the RMS 130 and the flow cell 102. This is because the RMS 130 and the flow cell 102 may now move with respect to each other due to the bending of the flexible connection 106. However, there are a number of ways to relieve that additional mechanical stress. One such way to reduce such stress (i.e., the force involved to move, or displace, the flow cell 102 and/or the flexible connection 106) is to position a slit 268 between the 1st and 2nd flexible channels 136, 138.

[00129] As shown in a comparison of graphs 264 and 266, the slit 268 reduces the force involved to move the flexible connection 106. More specifically, a first distal end 263 of the flexible connections 106A and 106B is anchored and a second distal end 265 of the flexible connections 106A and 106B is moved a predetermined distance (e.g., about 1 to 20 percent of the overall length of the flexible connection) in the X direction toward the first distal end 263. Thereafter, the second distal end 265 is moved in a direction perpendicular to the X direction (i.e., the Y direction) and the force (in newtons) needed to move a given displacement (in millimeters) in the Y direction is then measured to plot graphs 264 and 266.

[00130] The slit 268 reduces the force (as shown in graph 266) by at least about 2 times the force involved to move the flexible connection without the slit (as shown in graph 264). More specifically, the force applied to move the flexible connection 106 (and therefore, the flow cell 102) a distance of one millimeter is greater than 0.2 newtons without the slit 268 (see graph 264) while it is reduced to less than 0.1 newtons with the slit 268 (see graph 266). Additionally, the force applied to move the flexible connection 106 a distance of four millimeters is greater than 0.6 newtons without the slit 268 (see graph 264) while it is reduced to less than 0.2 newtons with the slit 268 (see graph 266).

[00131] Referring to FIG.11, an example of a pair of graphs 270, 272 of force vs. displacement for a straight flexible connection 106C (graph 270) and an S-curve flexible connection 106D (graph 272) is depicted. Another way to reduce the additional mechanical stress caused by decoupling the RMS 130 from the flow cell 102 via the flexible connection 106 is to design a sinuous shape into the flexible connection 106. In this particular example, the sinuous shape is an S-curve 274 designed into the flexible connection 106D of graph 272.

[00132] As shown in a comparison of graphs 270 and 272, the S-curve 274 reduces the force involved to move the flexible connection 106. More specifically, a first distal end 271 of the flexible connections 106C and 106D is anchored and a second distal end 273 of the flexible connections 106C and 106D is moved a predetermined distance (e.g., about 1 to 20 percent of the overall length of the flexible connection) in the X direction toward the first distal end 271. Thereafter, the second distal end 273 is moved in a direction perpendicular to the X direction (i.e., the Y direction) and the force (in newtons) needed to move a given displacement (in millimeters) in the Y direction is then measured to plot graphs 270 and 272.

[00133] The S-curve 274 reduces the force (as shown in graph 272) by at least about 2 times the force involved to move the flexible connection without the S-curve (as shown in graph 270). More specifically, the force applied to move the flexible connection 106 (and therefore, the flow cell 102) a distance of one millimeter is greater than 0.2 newtons without the S-curve 274 (see graph 270) while it is reduced to less than 0.1 newtons with the S-curve 274 (see graph 272). Additionally, the force applied to move the flexible connection 106 a distance of four millimeters is greater than 0.6 newtons without the S-curve 274 (see graph 270) while it is reduced to less than 0.1 newtons with the S-curve (see graph 272).

[00134] Referring to FIGS. 12A, 12B and 12C, an example of a pair of graphs 276, 278 of force vs. displacement for a laser bonded flexible connection 106E (graph 276 of FIG. 12A and FIG. 12B) and an adhesive bonded flexible connection 106F (graph 278 of FIG. 12A and FIG. 12C) is depicted. Both flexible connections 106E and 106F include an S-curve 274.

[00135] Another way to reduce the additional mechanical stress caused by decoupling the RMS 130 from the flow cell 102 via the flexible connection 106 is in the choice of bonding processes between layers 210, 212, 214. In this particular example, the only significant difference between the structures of the flexible connections 106E and 106F for each graph 276, 278 respectively is in the bonding process.

[00136] More specifically, the flexible connection 106E for graph 276 has been laser bonded. Accordingly, as illustrated in the exploded perspective view of FIG. 12B, the top layer 210, bottom layer 212 and intermediate layer 214 of flexible connection 106E are in direct contact with each other and do not include an adhesive layer 216 between them. In contrast, the flexible connection 106F for graph 278 has been adhesive bonded. Accordingly, as illustrated in the exploded perspective view of FIG. 12C, the top layer 210, bottom layer 212 and intermediate layer 214 of flexible connection 106F include a layer of adhesive 216 between them.

[00137] As shown in a comparison of graphs 276 and 278, the adhesive bonding reduces the force involved to move the flexible connection 106. More specifically, a first distal end 275 of the flexible connections 106E and 106F is anchored and a second distal end 277 of the flexible connections 106E and 106F is moved a predetermined distance (e.g., about 1 to 20 percent of the overall length of the flexible connection) in the X direction toward the first distal end 275. Thereafter, the second distal end 277 is moved in a direction perpendicular to the X direction (i.e., the Y direction) and the force (in newtons) needed to move a given displacement (in millimeters) in the Y direction is then measured to plot graphs 276 and 278.

[00138] The adhesive bonding reduces the force (as shown in graph 278) by at least about 6 times the force involved to move the flexible connection that has been laser bonded (as shown in graph 276). More specifically, the force applied to move the flexible connection 106 (and therefore, the flow cell 102) a distance of one millimeter is greater than 0.6 newtons when laser bonded (see graph 276) while it is reduced to less than 0.1 newtons when adhesive bonded (see graph 278). Additionally, the force applied to move the flexible connection 106 a distance of four millimeters is greater than 0.8 newtons when laser bonded (see graph 276) while it is reduced to less than 0.1 newtons when adhesive bonded (see graph 278).

[00139] It should be appreciated that all combinations of the foregoing concepts and additional concepts discussed in greater detail herein (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.

[00140] Although the forgoing disclosure has been described by reference to specific examples, it should be understood that numerous changes may be made within the spirit and scope of the inventive concepts described. Accordingly, it is intended that the disclosure is not be limited to the described examples, but that it has the full scope defined by the language of the claims.

[00141] The disclosure also includes the following clauses:

1. An instrument comprising:

a reagent management system (RMS), operable to be positioned in the instrument, the RMS comprising a plurality of reagent wells, each reagent well operable to contain a reagent of a plurality of reagents positioned therein, the RMS operable to select a flow of reagent from one of the plurality of reagents;

a flexible connection, operable to be positioned in the instrument, the flexible connection comprising a 1st flexible channel in fluid communication with the RMS, the 1st flexible channel being operable to route the flow of reagent therethrough; and

a flow cell, operable to be positioned in the instrument, the flow cell comprising a flow channel in fluid communication with the 1st flexible channel, the flow channel operable to route the flow of reagent over analytes positioned in the flow channel;

wherein the flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

2. The instrument of clause 1, wherein the flexible connection enables the flow cell to be moved relative to a fixed reference point in the instrument while the detection module is held stationary relative to the reference point.

3. The instrument of clause 1 or 2, comprising:

a cartridge, the cartridge comprising the RMS, the flow cell and the flexible connection therebetween;

wherein, when the cartridge is engaged with the instrument and the flow cell is engaged with the cartridge, the RMS is fixed relative to the reference point of the instrument while the flow cell is movable relative to the reference point of the instrument.

4. The instrument of any of the preceding clauses, wherein:

the RMS is positioned relative to the reference point within about a predetermined 1st tolerance range; and the flow cell is positioned relative to the reference point within about a 2nd predetermined tolerance range, the 1st tolerance range being at least 10 times greater than the 2nd tolerance range.

5. The instrument of any of the preceding clauses, wherein the flexible connection comprises a 2nd flexible channel in fluid communication with the flow channel of the flow cell, the 2nd flexible channel operable to route the flow of reagent from the flow cell to the RMS after the flow of reagent has passed through the flow channel.

6. The instrument of clause 5, wherein the flexible connection comprises a slit positioned between the 1st and 2nd flexible channels to reduce a force involved to move the flexible connection.

7. The instrument of any of the preceding clauses, wherein the flexible connection has a sinuous shape to reduce a force involved to move the flexible connection.

8. The instrument of any of the preceding clauses, wherein the flexible connection comprises:
a top layer defining a top of the 1st flexible channel;
a bottom layer defining a bottom of the 1st flexible channel; and
an intermediate layer defining a wall width and a channel width of the 1st flexible channel;
wherein the ratio of the wall width to the channel width is about 2.5 or greater.

9. The instrument of any of the preceding clauses, comprising:
a detection module;
wherein, as the flow of reagent is routed over the analytes, a chemical reaction is performed between the flow of reagent and the analytes, the chemical reaction inducing the analytes to affect detectable properties related to the analytes; and
wherein the detection module is operable to detect the detectable properties as the flow cell moves relative to the detection module.

10. The instrument of clause 8, wherein the intermediate layer is a plurality of sublayers.

11. The instrument of clause 8 or 10, wherein the top, intermediate and bottom layers are bonded together utilizing one of an adhesive bonding process, a thermal bonding process and a direct laser bonding process.

12. A cartridge comprising:
a reagent management system (RMS) operable to select a flow of reagent from one of a plurality of reagents contained in the RMS;
a flexible connection, operable to be positioned in the cartridge, the flexible connection comprising a 1st flexible channel in fluid communication with the RMS, the 1st flexible channel being operable to route the flow of reagent therethrough; and
a flow cell, operable to be positioned in the cartridge, the flow cell comprising a flow channel in fluid communication with the 1st flexible channel, the flow channel operable to route the flow of reagents over analytes positioned in the flow channel;
wherein, when the cartridge is engaged with an instrument, the flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

13. The cartridge of clause 12, wherein the flexible connection comprises a 2nd flexible channel in fluid communication with the flow channel of the flow cell, the 2nd flexible channel operable to route the flow of reagent from the flow cell to the RMS after the flow of reagent has passed through the flow channel.

14. The cartridge of clause 12 or 13, wherein the flexible connection comprises a slit positioned between the 1st and 2nd flexible channels to reduce a force involved to move the flexible connection.

15. The cartridge of clause 12, 13 or 14, wherein the flexible connection has a sinuous shape to reduce a force involved to move the flexible connection.

16. The cartridge of any of clauses 12-15, wherein the flexible connection comprises:

a top layer defining a top of the 1st flexible channel;

a bottom layer defining a bottom of the 1st flexible channel; and

an intermediate layer defining a wall width and a channel width of the 1st flexible channel;

wherein the ratio of the wall width to the channel width is about 2.5 or greater.

17. A flexible connection module comprising:

a flexible connection comprising a 1st channel inlet via, a 1st channel outlet via and a 1st flexible channel in fluid communication therebetween, wherein the 1st channel inlet via comprises a fluidic seal operable to connect to an RMS outlet port and to enable a flow of reagent therethrough; and

a flow cell comprising an inlet port, an outlet port and a flow channel in fluid communication therebetween, wherein the inlet port is in fluid communication with the 1st channel outlet via of the flexible connection, the flow channel operable to route the flow of reagent over analytes positioned in the flow channel.

18. The module of clause 17, wherein the flexible connection comprises:

2nd channel inlet via, a 2nd channel outlet via and a 2nd flexible channel in fluid communication therebetween;

wherein the 2nd channel inlet via is in fluid communication with the outlet port of the flow cell; and

wherein the 2nd channel outlet via comprises a fluidic seal operable to connect to an RMS inlet port and to enable the flow of reagent therethrough.

19. The module of clause 17 or 18, wherein the fluidic seal is a detachable fluidic seal operable to detachably connect to the RMS outlet port and to enable the flow of reagent therethrough.

20. The module of clause 17, 18 or 19, comprising:

a support fixture comprising an inner border surrounding the flow cell, the fixture operable to contain the flow cell within the border and to enable the flow cell to move laterally and longitudinally therein.

CONCLUSIES

1. Instrument omvattende:

een reagens beheersingssysteem (reagent management system (RMS)), werkzaam om gepositioneerd te worden in het instrument, waarbij het RMS een aantal reagensputten omvat, waarbij elke reagensput werkzaam is om een reagens te bevatten van een aantal reagentia die daarin gepositioneerd zijn, waarbij het RMS werkzaam is om een stroom van reagens van een van het aantal reagentia te selecteren;

een flexibele verbinding, werkzaam om gepositioneerd te worden in het instrument, waarbij de flexibele verbinding een eerste flexibel kanaal in fluïdumcommunicatie met het RMS omvat, waarbij het eerste flexibele kanaal werkzaam is om de stroom van reagens daardoor te zenden; en

een stroomcel, werkzaam om gepositioneerd te worden in het instrument, waarbij de stroomcel een stroomkanaal in fluïdumcommunicatie met het eerste flexibele kanaal omvat, waarbij het stroomkanaal werkzaam is om de stroom van reagens te zenden over in het stroomkanaal gepositioneerde analyten;

waarin de flexibele verbinding het mogelijk maakt dat de stroomcel door het instrument ten opzichte van een vast referentiepunt in het instrument verplaatst wordt.

2. Instrument volgens conclusie 1, waarin de flexibele verbinding het de stroomcel mogelijk maakt om verplaatst te worden ten opzichte van een vast referentiepunt in het instrument terwijl de detectiemodule stationair ten opzichte van het referentiepunt gehouden wordt.

3. Instrument volgens conclusie 1 of 2, omvattende:

een cartridge, waarbij de cartridge het RMS, de stroomcel en de flexibele verbinding daartussen omvat;

waarin, wanneer de cartridge aangegrepen wordt met het instrument en de stroomcel aangrijpt met de cartridge, het RMS gefixeerd is ten opzichte van het referentiepunt van het instrument terwijl de stroomcel beweegbaar is ten opzichte van het referentiepunt van het instrument.

4. Instrument volgens een van de voorafgaande conclusies, waarin:

het RMS gepositioneerd is ten opzichte van het referentiepunt binnen ongeveer een eerste tolerantiebereik; en de stroomcel gepositioneerd is ten opzichte van het referentiepunt binnen en tweede voorafbepaald tolerantiebereik, waarbij het eerste tolerantiebereik en minste tien keer groter is dan het tweede tolerantiebereik.

5. Instrument volgens een van de voorafgaande conclusies, waarin de flexibele verbinding een tweede flexibel kanaal in fluïdumcommunicatie met het stroomkanaal van de stroomcel omvat, waarbij het tweede flexibele kanaal werkzaam is om de stroom van reagens vanaf de stroomcel naar het RMS nadat de stroom van reagens door het stroomkanaal gestroomd is, te zenden.

6. Instrument volgens conclusie 5, waarin de flexibele verbinding een sleuf omvat die gepositioneerd is tussen de eerste en tweede flexibele kanalen teneinde een kracht te reduceren die gemoeid is bij de verplaatsing van de flexibele verbinding.

7. Instrument volgens een van de voorafgaande conclusies, waarin de flexibele verbinding een sinusvorm heeft teneinde een kracht te reduceren die betrekking heeft op het verplaatsen van de flexibele verbinding.

8. Instrument volgens een van de voorafgaande conclusies, waarin de flexibele verbinding omvat:

een toplaag die een top van het eerste flexibele kanaal definieert;

een bodemlaag die een bodem van het eerste flexibele kanaal definieert; en

een tussenliggende laag die een wanddikte en een kanaaldikte van het eerste flexibele kanaal definieert;

waarin de verhouding van de wanddikte ten opzichte van de kanaalbreedte ongeveer 2,5 of meer is.

9. Instrument volgens een van de voorafgaande conclusies, omvattende:

een detectiemodule, waarin wanneer de stroom van reagens gezonden wordt over de analyten, een chemische reactie uitgevoerd wordt tussen de stroom van reagens en de analyten, waarbij de chemische reactie de analyten induceert om detecteerbare eigenschappen gerelateerd aan de analyten te beïnvloeden; en

waarin de detectiemodule werkzaam is om de detecteerbare eigenschappen te detecteren wanneer de stroomcel ten opzichte van de detectiemodule verplaatst wordt.

10. Instrument volgens conclusie 8 of 9, waarin de tussenliggende laag een aantal sublagen is.

11. Instrument volgens een van de conclusies 8-10, waarin de top, tussenliggende en bodemlagen samen gebonden zijn door gebruik te maken van een van een

kleefverbindingsproces, een thermisch verbindingsproces en een directe laserverbindingsproces.

12. Cartridge omvattende:

een reagens managementsysteem (reagent management system (RMS)) werkzaam om een stroom van reagens van een van een aantal reagentia in het RMS te selecteren;

een flexibele verbinding werkzaam om gepositioneerd te worden in de cartridge, waarbij de flexibele verbinding een eerste flexibel kanaal in fluïdumcommunicatie met het RMS omvat, waarbij het eerste flexibele kanaal werkzaam is om de stroom van reagens daardoor te zenden;

een stroomcel, werkzaam om gepositioneerd te worden in de cartridge, waarin de stroomcel een stroomkanaal in fluïdumcommunicatie met het eerste flexibele kanaal omvat, waarbij het stroomkanaal werkzaam is om de stroom van reagentia over analyten die in het stroomkanaal gepositioneerde analyten te zenden;

waarin, wanneer de cartridge een instrument aangrijpt, de flexibele verbinding het de stroomcel mogelijk maakt om verplaatst te worden door het instrument ten opzichte van een vast referentiepunt in het instrument.

13. Cartridge volgens conclusie 12, waarin de flexibele verbinding een tweede flexibel kanaal in fluïdumcommunicatie met het stroomkanaal van de stroomcel omvat, waarbij het tweede flexibele kanaal werkzaam is om de stroom van reagens vanaf de stroomcel naar de RMS te zenden nadat de stroom van reagens door het kanaal gestroomd is.

14. Cartridge volgens conclusie 12 of 13, waarin de flexibele verbinding een sleuf omvat die gepositioneerd is tussen het eerste en tweede flexibele kanaal teneinde een kracht te reduceren die betrokken is bij het verplaatsen van de flexibele verbinding.

15. Cartridge volgens conclusie 12, 13 of 14, waarin de flexibele verbinding een sinusvorm heeft teneinde de kracht te reduceren die betrokken is bij de verplaatsing van de flexibele verbinding.

16. Cartridge volgens een van de conclusies 12-15, waarin de flexibele verbinding omvat:

een toplaag die een top van het eerste flexibele kanaal definieert,

een bodemlaag die een bodem van het eerste flexibele kanaal definieert; en

een tussenliggende laag die een wanddikte en een kanaalbreedte van het eerste flexibele kanaal definieert;

waarin de verhouding van de wanddikte ten opzichte van de kanaalbreedte ongeveer 2,5 of meer is.

17. Flexibele verbindingsmodule omvattende:

een flexibele verbinding omvattende een eerste kanaalinlaat via, een eerste kanaaluitlaat via en een eerste flexibel kanaal in fluïdumcommunicatie daartussen, waarin de eerste kanaalinlaat via een fluïdidumafdichting heeft die werkzaam is om een RMS uitlaatpoort te verbinden en om een stroom van reagens daardoor mogelijk te maken; en

een stroomcel omvattende een inlaatpoort, een uitlaatpoort en een stroomkanaal in fluïdumcommunicatie daartussen, waarin de inlaatpoort in fluïdumcommunicatie is met de eerste kanaaluitlaat via van de flexibele verbinding, waarbij het stroomkanaal werkzaam is om de stroom van reagens over in het stroomkanaal gepositioneerde analyten te zenden.

18. Module volgens conclusie 17, waarin de flexibele verbinding omvat:

een tweede kanaalinlaat via, een tweede kanaaluitlaat via en een tweede flexibel kanaal in fluïdumcommunicatie daartussen;

waarin de tweede kanaalinlaat via in fluïdumcommunicatie is met de uitlaatpoort van de stroomcel; en

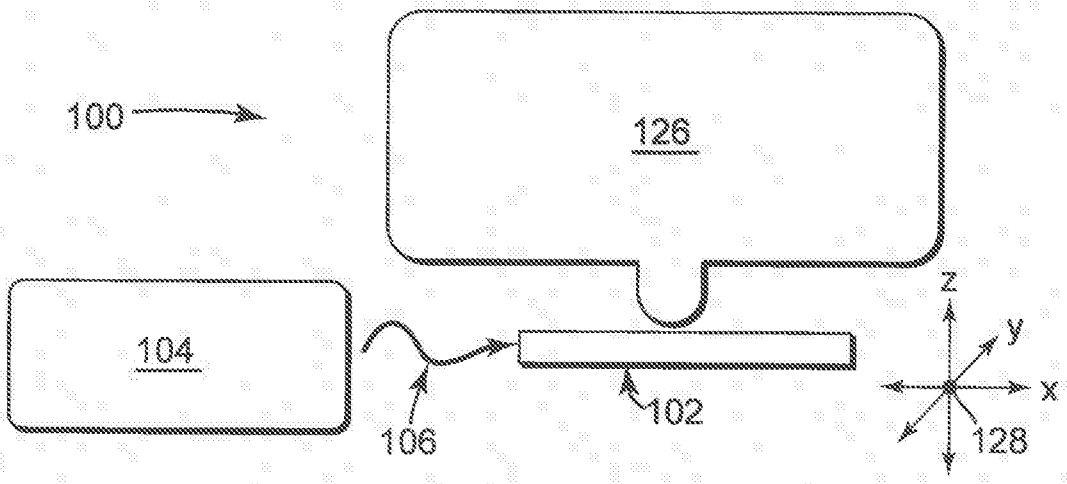
waarin de tweede kanaaluitlaat via een fluïdumafdichting omvat die werkzaam is om verbonden te worden met een RMS inlaatpoort en om de stroom van reagens daardoor mogelijk te maken.

19. Module volgens conclusie 17 of 18, waarin de fluïdumafdichting een losmaakbare fluïdumafdichting is die werkzaam is om losmaakbaar verbonden te worden met de RMS uitlaatpoort en om de stroom van reagens daardoor mogelijk te maken.

20. Module volgens conclusie 17, 18 of 19, omvattende:

een ondersteuningsvoorziening omvattende een binnenste rand die de stroomcel omgeeft, waarbij de voorziening werkzaam is om de stroomcel binnen de rand te houden en om het de stroomcel mogelijk te maken om zich lateraal en longitudinaal daarin te verplaatsen.

FIG. 1



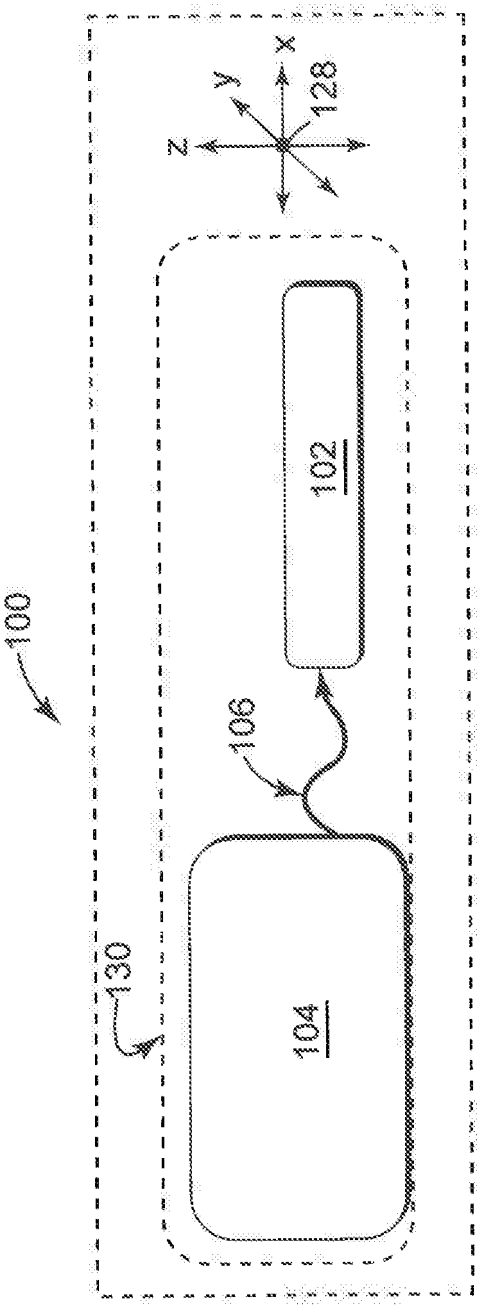


FIG. 2

FIG. 3

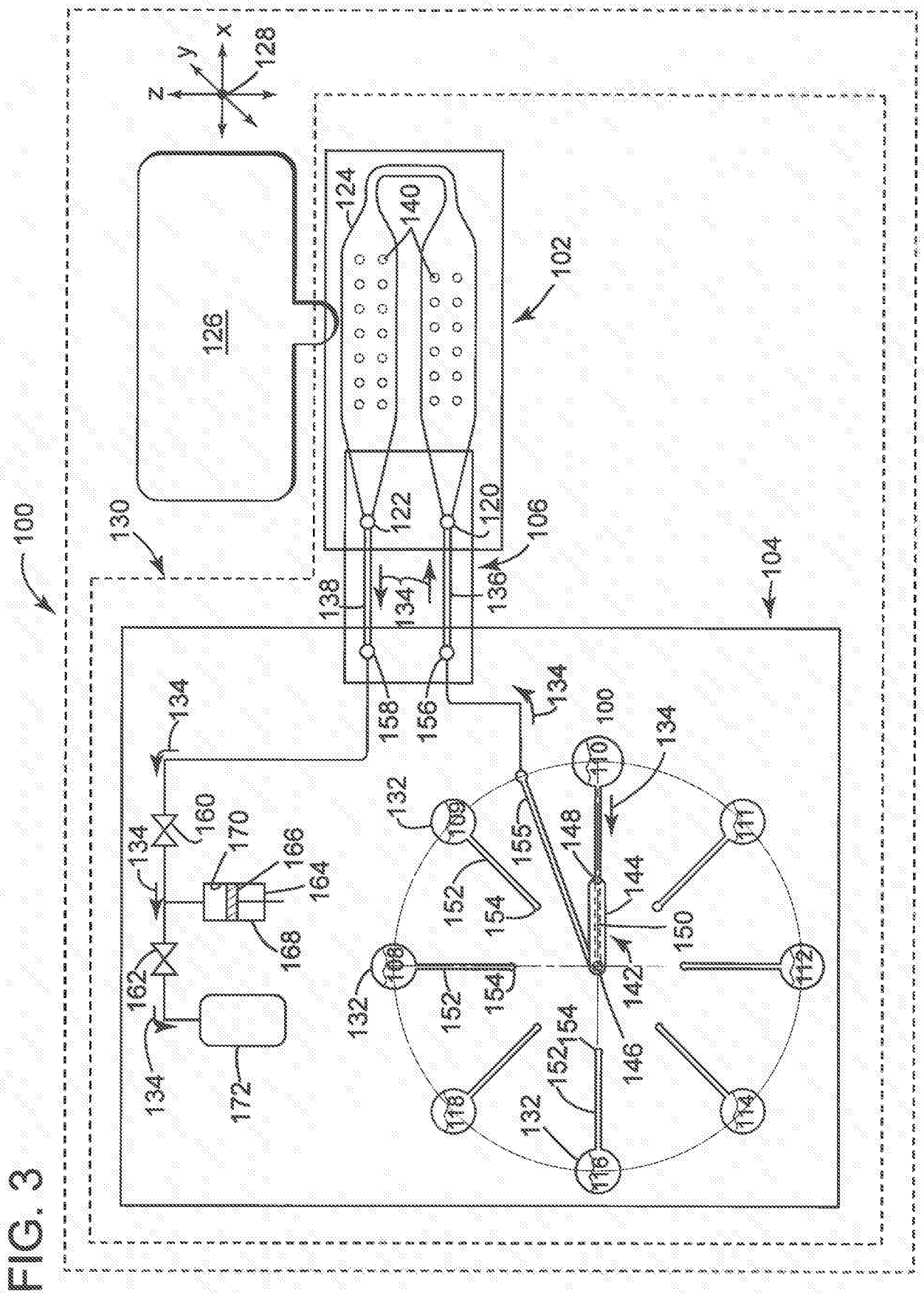
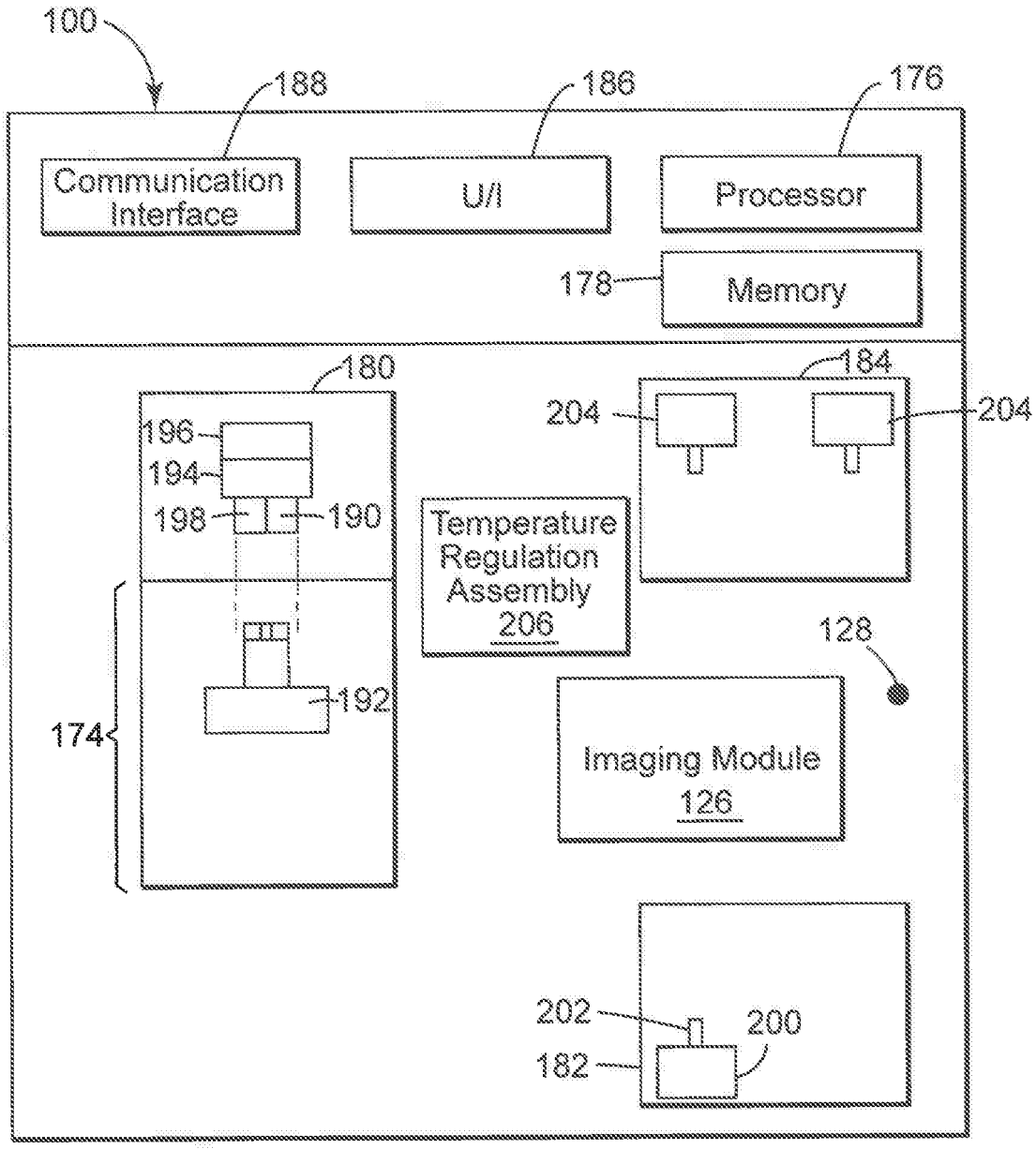
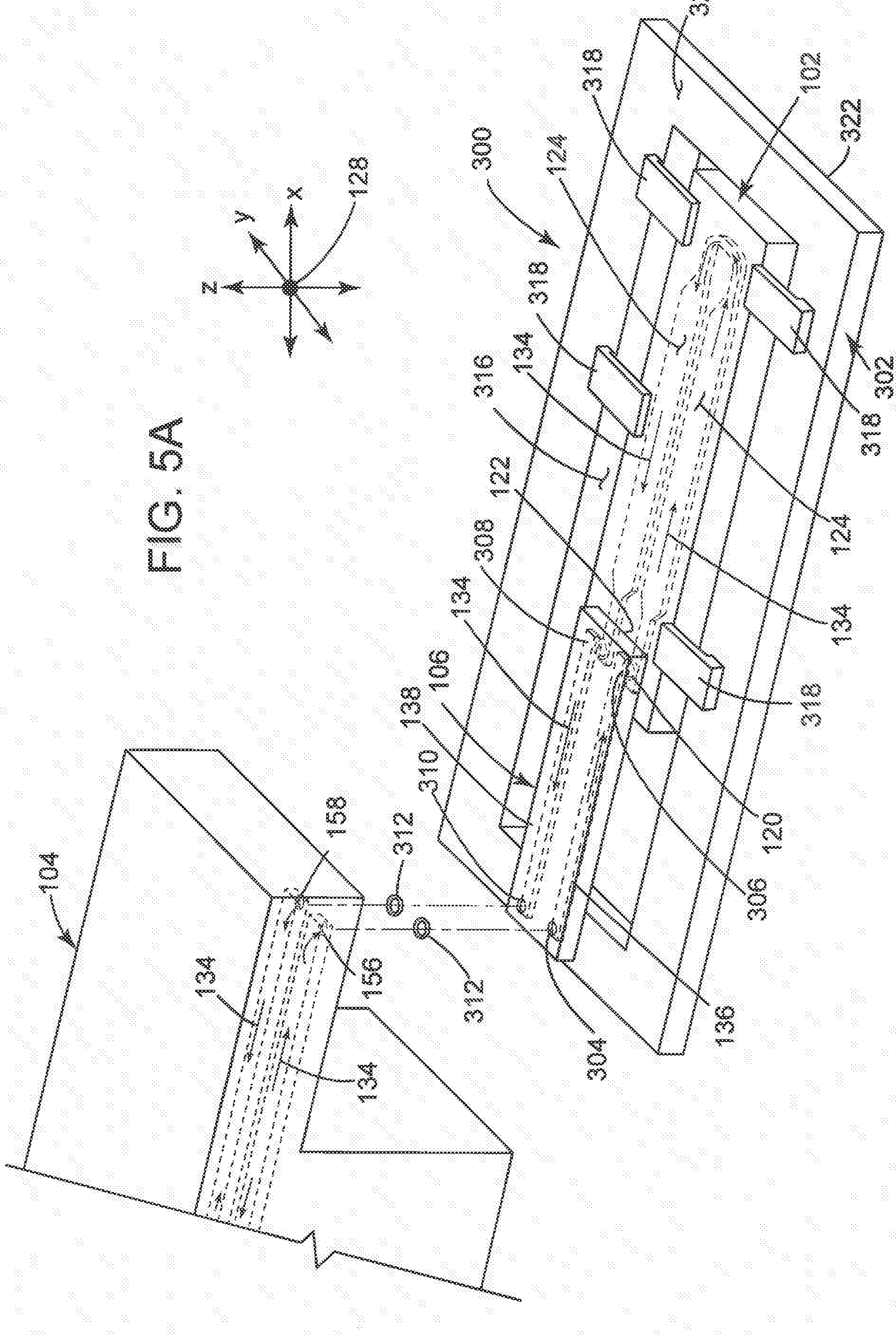

100
130
126
128
z
y
x
124
140
102
122
120
106
104
138
134
136
158
156
160
170
166
164
168
162
172
132
108
110
111
112
114
116
118
152
154
155
148
144
150
142
146

FIG. 4


100
188
186
176
Communication Interface
U/I
Processor
178
Memory
180
184
196
194
198
190
204
204
Temperature Regulation Assembly 206
128
192
174
Imaging Module 126
202
200
182



128
x
y
z
300
320
318
102
322
124
318
318
302
134
316
124
122
308
134
134
106
138
318
310
312
158
104
156
312
134
134
304
136
306
120

FIG. 5A

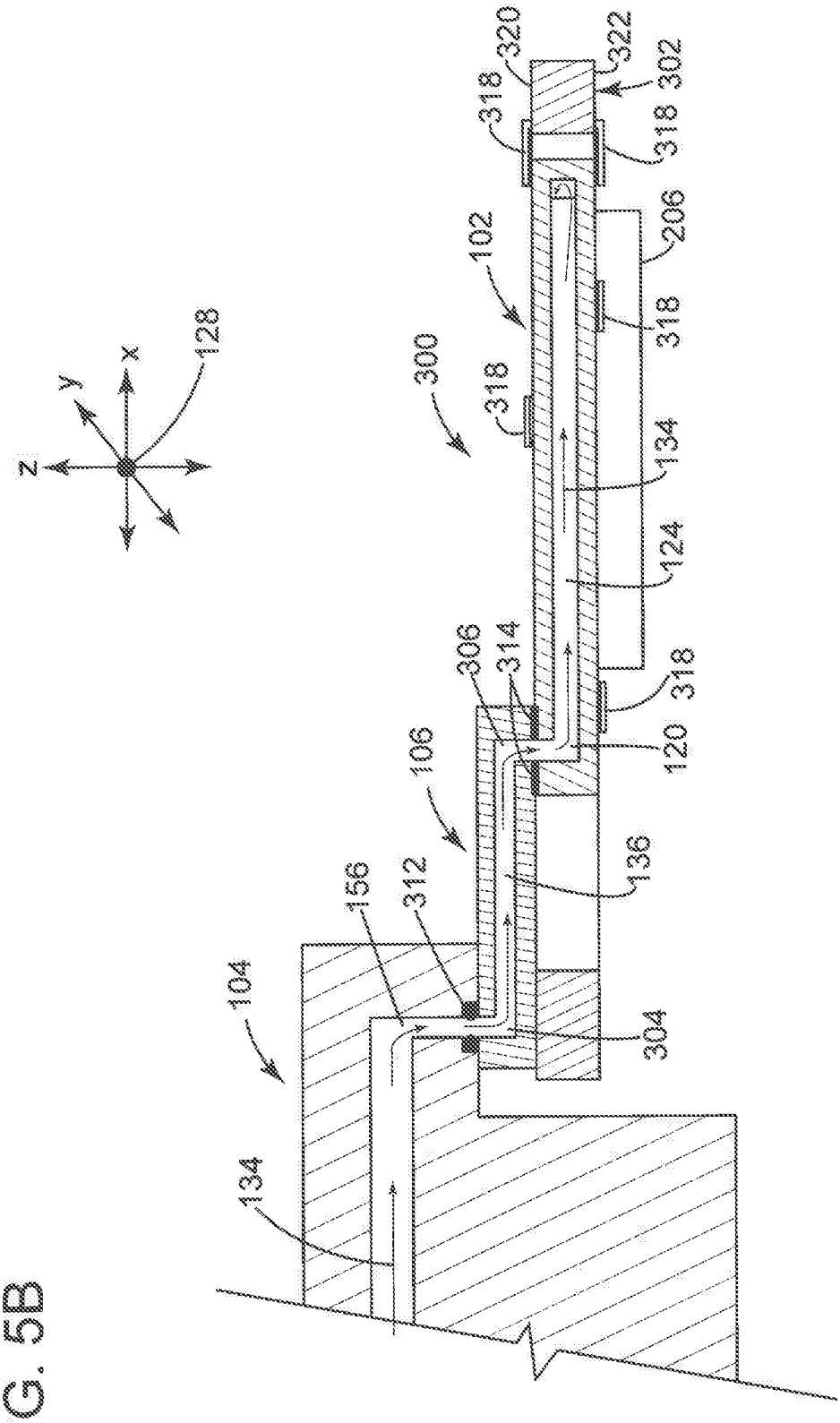
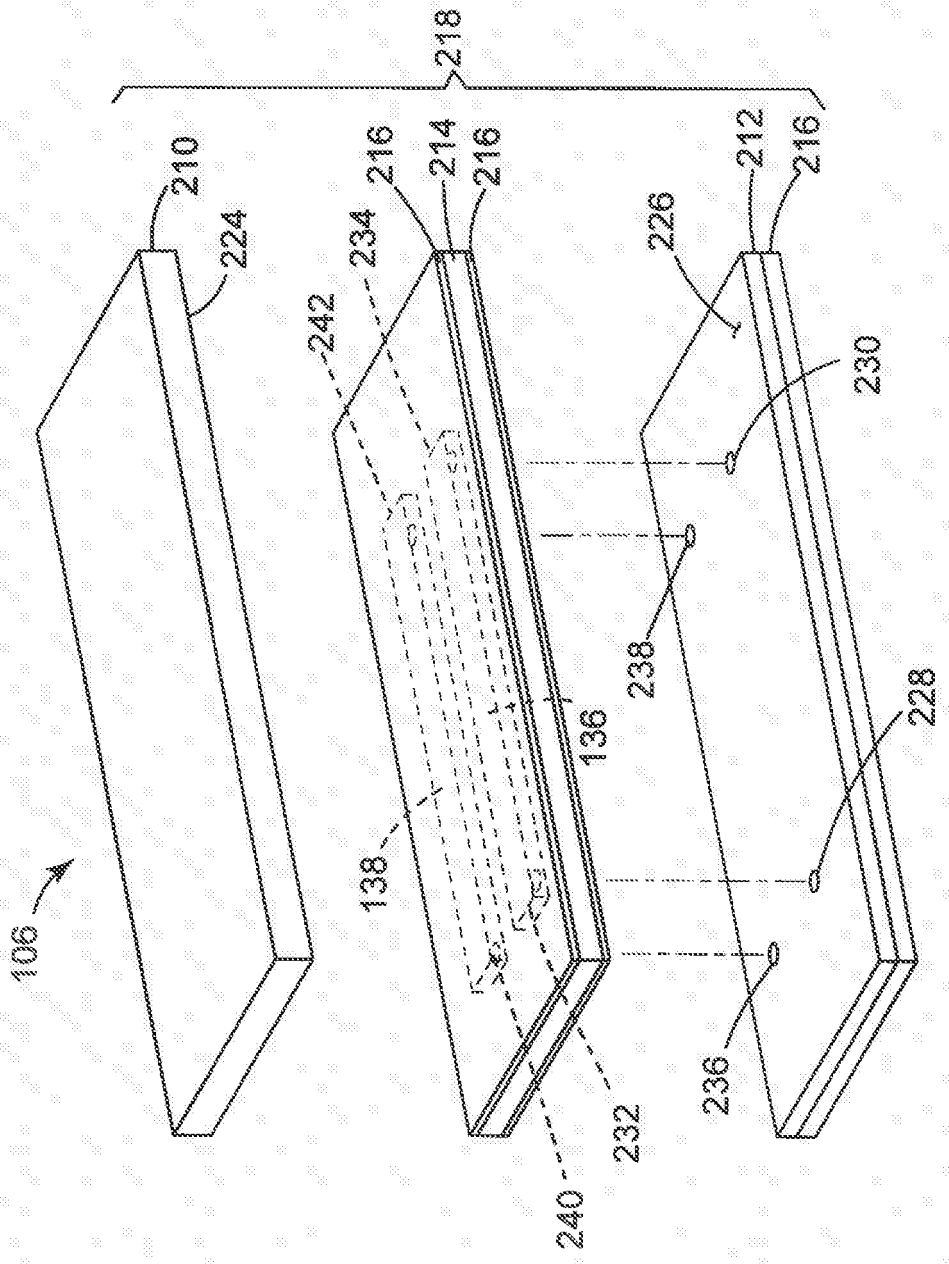

128
y
x
z
300
102
104
106
134
156
312
304
136
306
314
318
120
124
206
322
320
302

FIG. 5B

FIG. 6


218
210
224
216
234
214
216
242
212
216
226
230
238
228
136
138
106
236
232
240

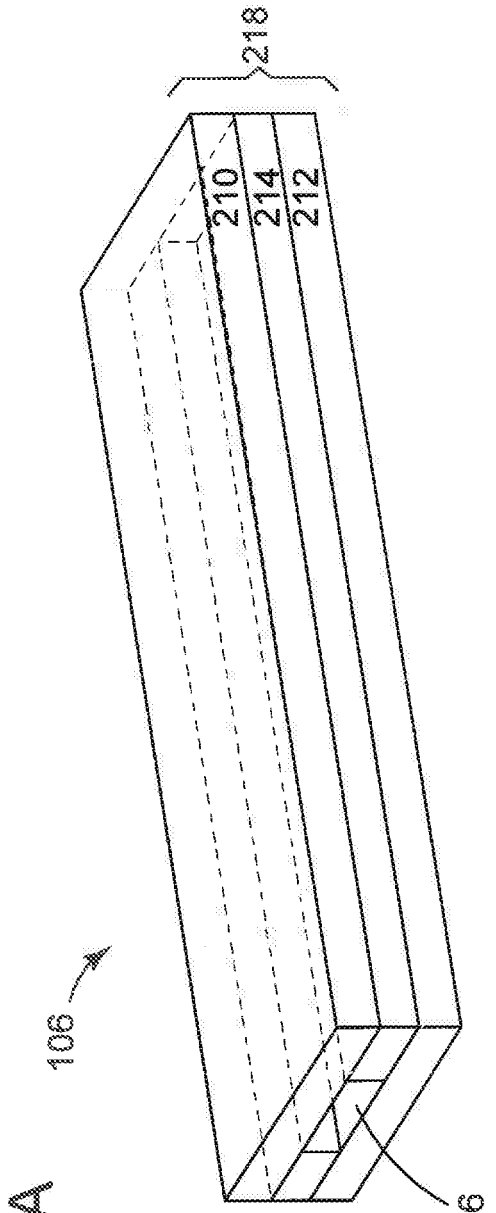

218
210
214
212
106
136

FIG. 7A

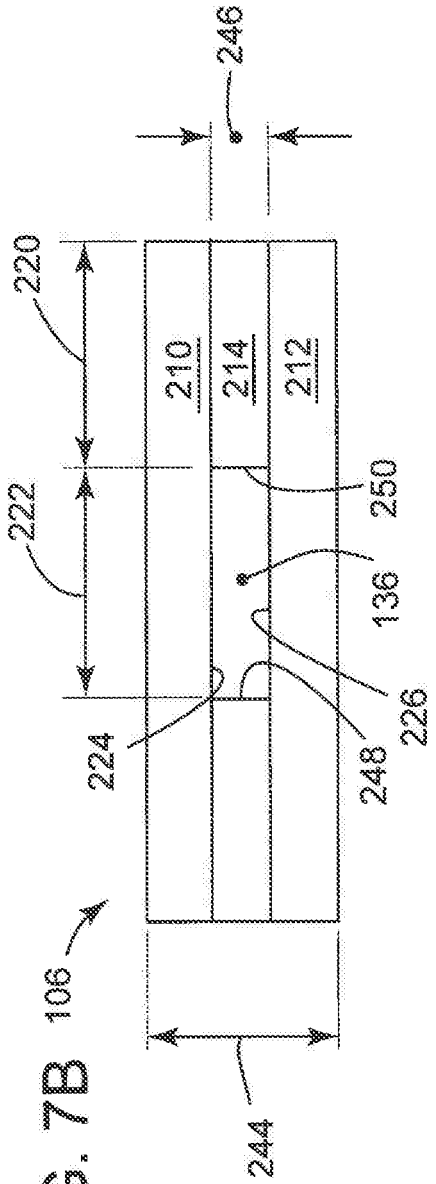

246
220
210
214
212
222
250
136
226
224
248
106
244

FIG. 7B

FIG. 8

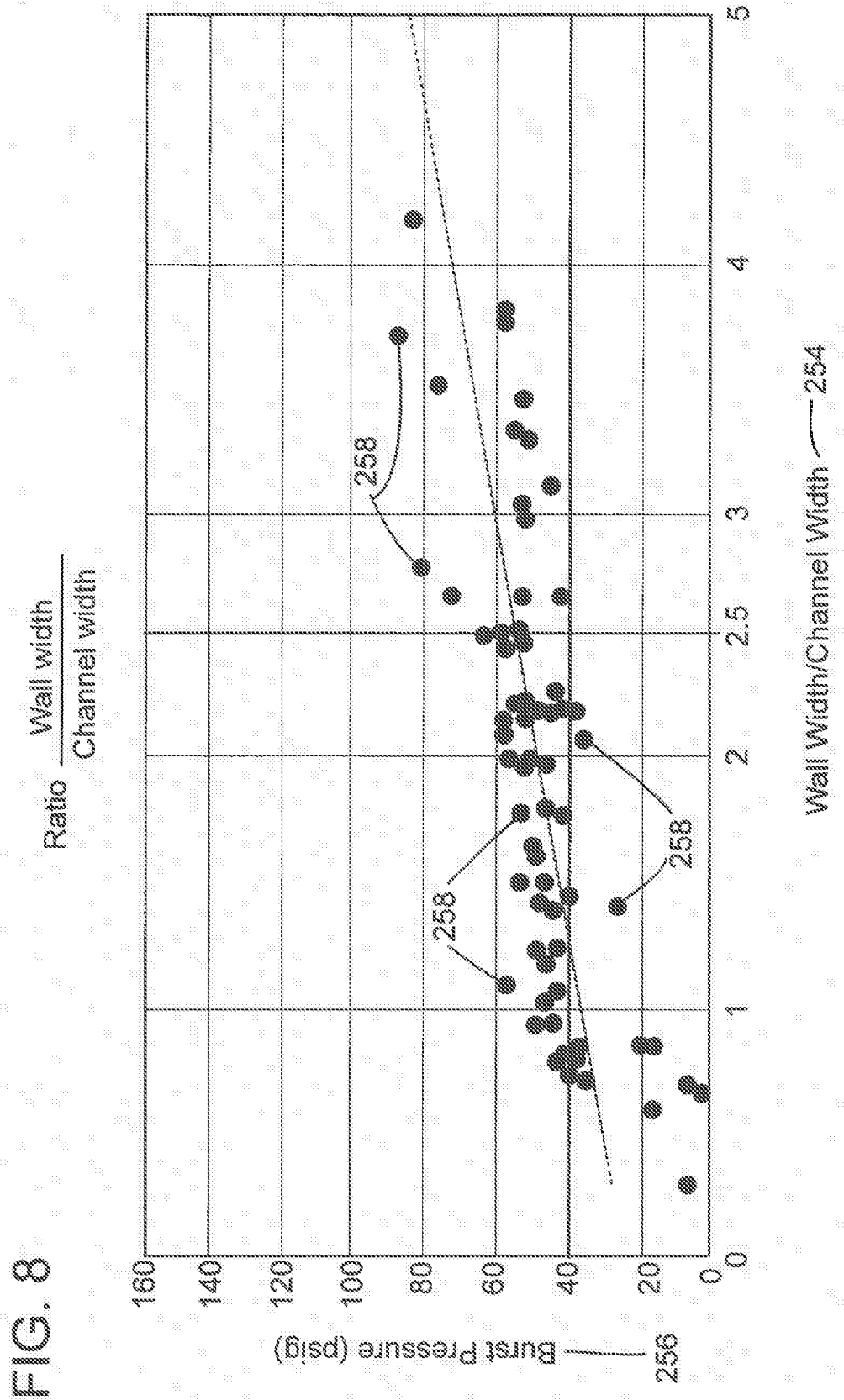

252
Ratio Wall width / Channel width
160
140
120
100
80
60
40
20
0
Burst Pressure (psig)
256
0
1
2
2.5
3
4
5
Wall Width/Channel Width
254
258
258
258

FIG. 9A

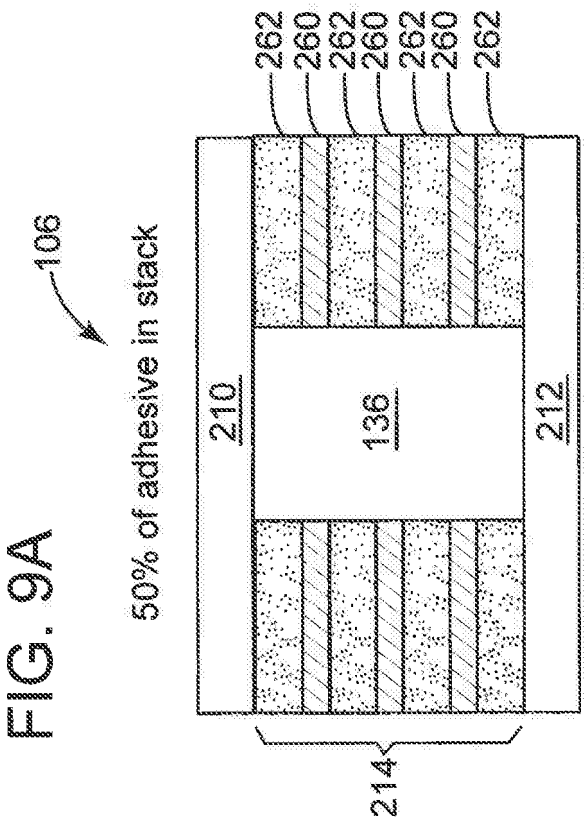

106
50% of adhesive in stack
210
136
212
214
262
260
262
260
262
260
262
Burst Pressure
50psi

FIG. 9B

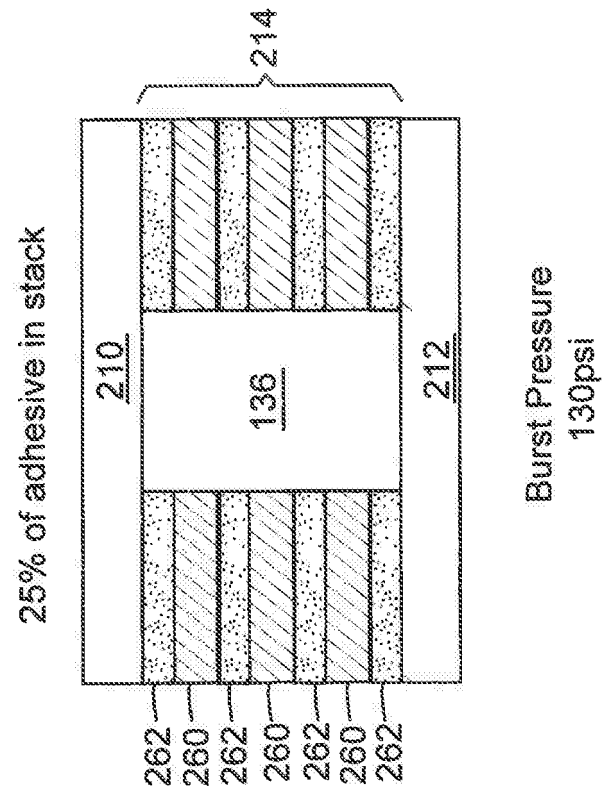
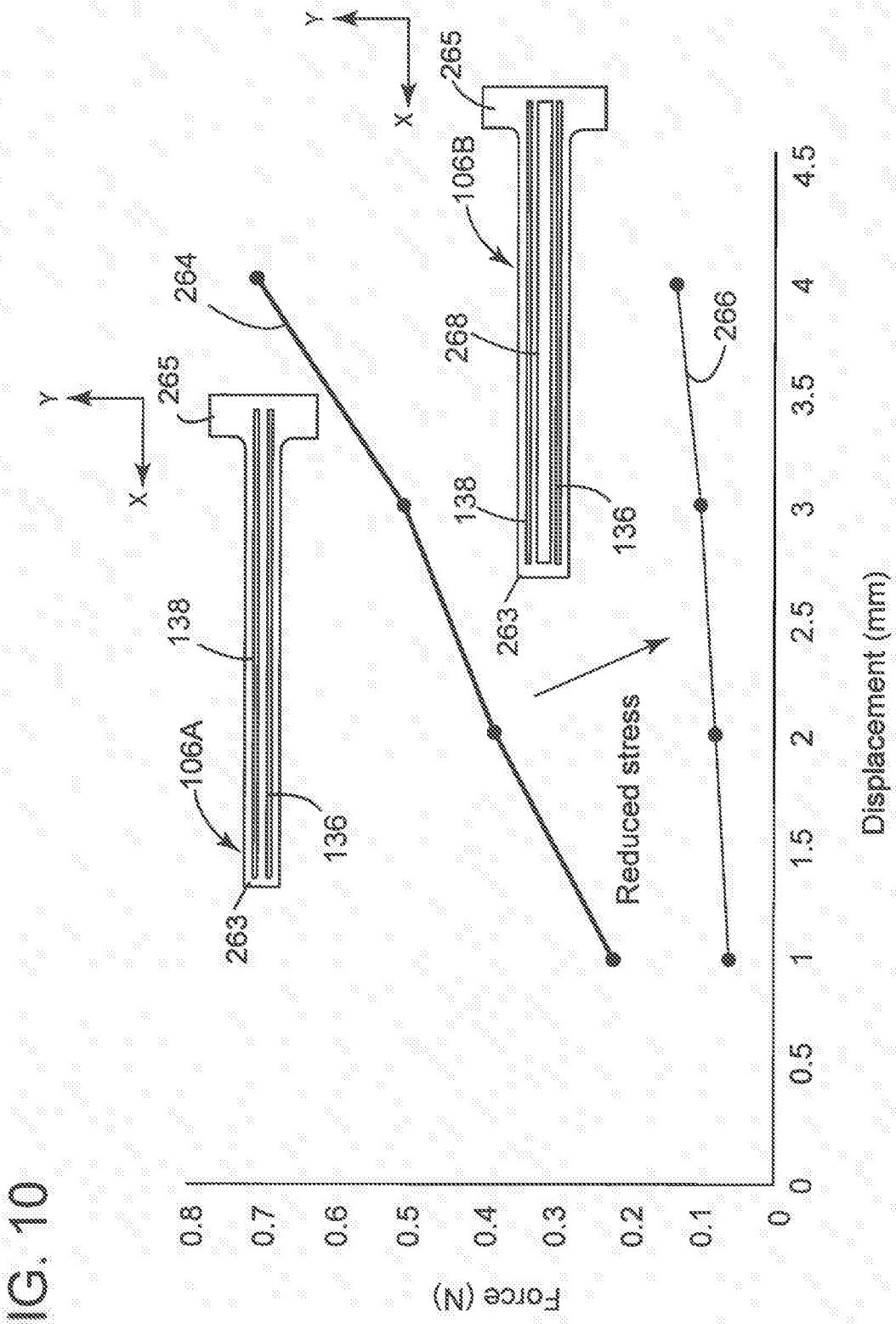

106
25% of adhesive in stack
210
136
212
214
262
260
262
260
262
260
262
Burst Pressure
130psi

FIG. 10


Force (N)
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Displacement (mm)
Reduced stress
263
264
265
106A
138
136
Y
X
263
265
106B
268
138
136
266
Y
X

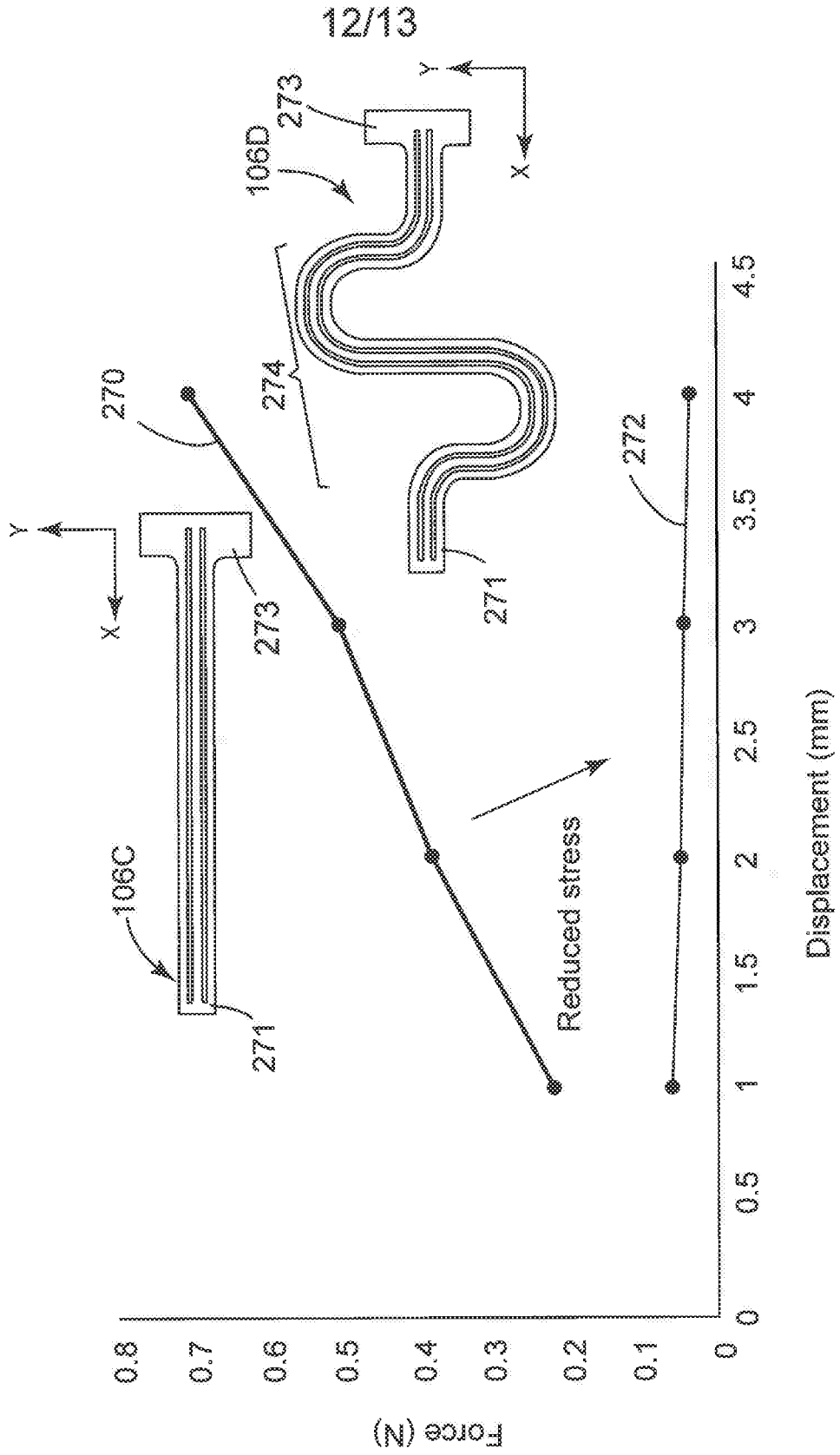

106C
271
273
270
Y
X
106D
273
274
271
272
Reduced stress
Force (N)
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Displacement (mm)

FIG. 11

FIG. 12A

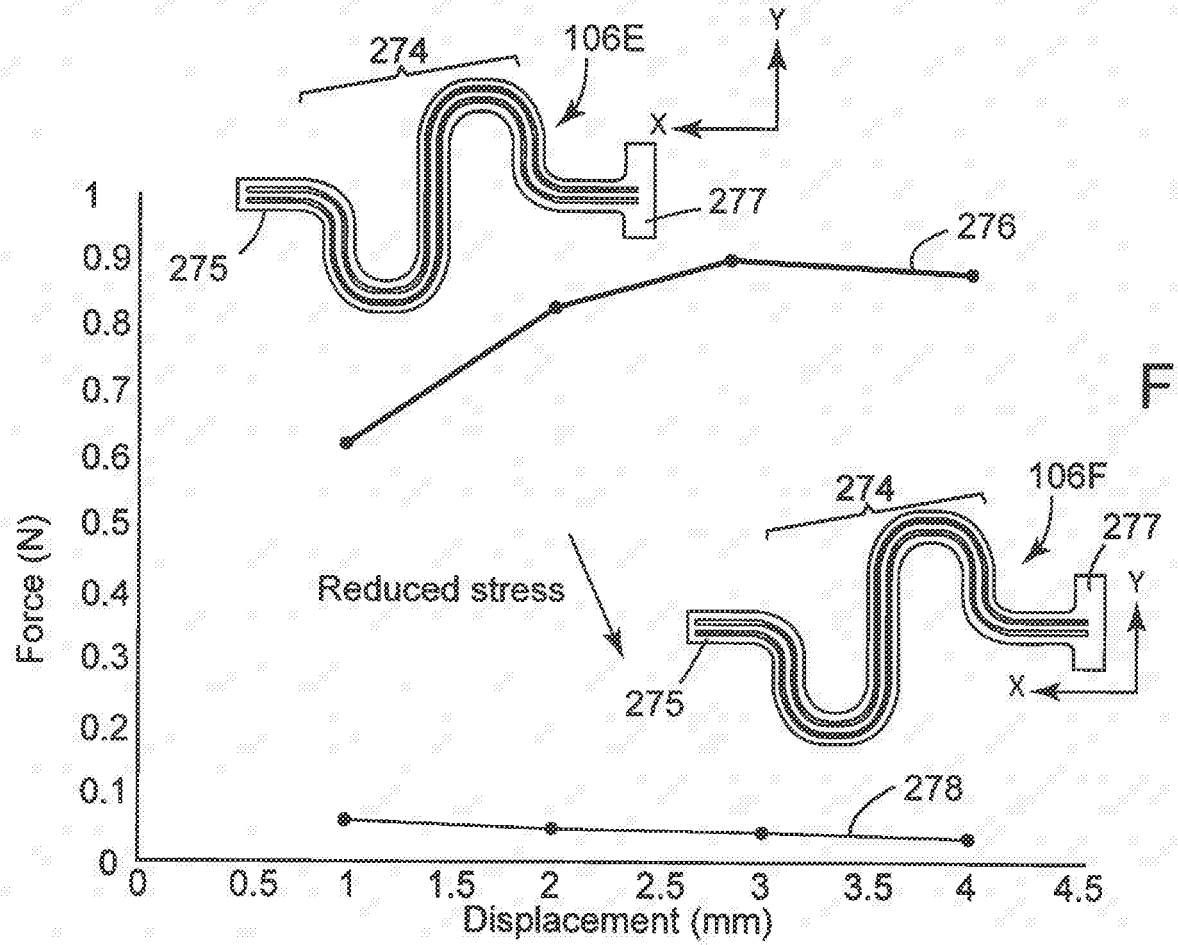


FIG. 12B

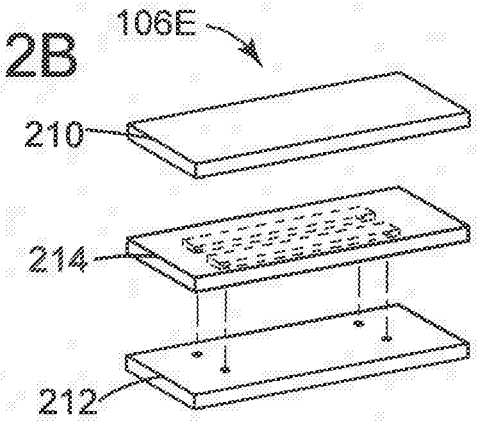
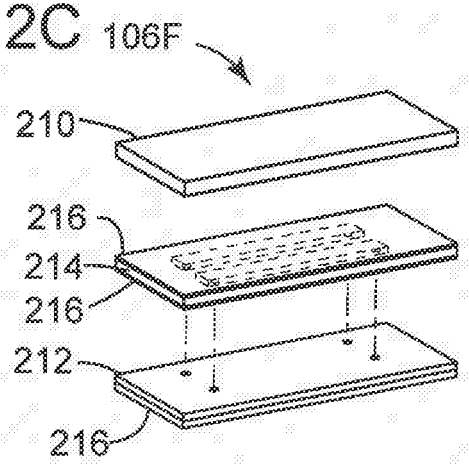


FIG. 12C



ABSTRACT

An instrument includes a reagent management system (RMS). The RMS includes a plurality of reagent wells, each reagent well operable to contain a reagent of a plurality of reagents positioned therein. The RMS is operable to select a flow of reagent from one of the plurality of reagents. A flexible connection includes a 1st flexible channel in fluid communication with the RMS. The 1st flexible channel is operable to route the flow of reagent therethrough. A flow cell includes a flow channel in fluid communication with the 1st flexible channel. The flow channel is operable to route the flow of reagent over analytes positioned in the flow channel. The flexible connection enables the flow cell to be moved by the instrument relative to a fixed reference point in the instrument.

SAMENWERKINGSVERDRAG (PCT)

RAPPORT BETREFFENDE NIEUWHEIDSONDERZOEK VAN INTERNATIONAAL TYPE

IDENTIFICATIE VAN DE NATIONALE AANVRAGE	KENMERK VAN DE AANVRAGER OF VAN DE GEMACHTIGDE
	4A/2XD42/15
Nederlands aanvraag nr. **2021147**	Indieningsdatum **18-06-2018**
	Ingeroepen voorrangsdatum
Aanvrager (Naam) **Illumina, Inc.**	
Datum van het verzoek voor een onderzoek van internationaal type **21-07-2018**	Door de Instantie voor Internationaal Onderzoek aan het verzoek voor een onderzoek van internationaal type toegekend nr. **SN71631**

I. CLASSIFICATIE VAN HET ONDERWERP (bij toepassing van verschillende classificaties, alle classificatiesymbolen opgeven)

Volgens de internationale classificatie (IPC)

B01L3/00;F16L11/22

II. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimumdocumentatie

Classificatiesysteem	Classificatiesymbolen
IPC	**B01L;F16L**

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 2021147

A. CLASSIFICATIE VAN HET ONDERWERP
INV. B01L3/00
ADD. F16L11/22

Volgens de Internationale Classificatie van octrooien (IPC) of zowel volgens de nationale classificatie als volgens de IPC

B. ONDERZOCHTE GEBIEDEN VAN DE TECHNIEK

Onderzochte minimum documentatie (classificatie gevolgd door classificatiesymbolen)
B01L F16L

Onderzochte andere documentatie dan de minimum documentatie, voor dergelijke documenten, voor zover dergelijke documenten in de onderzochte gebieden zijn opgenomen

Tijdens het onderzoek geraadpleegde elektronische gegevensbestanden (naam van de gegevensbestanden en, waar uitvoerbaar, gebruikte trefwoorden)
EPO-Internal, WPI Data

C. VAN BELANG GEACHTE DOCUMENTEN

Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
X	US 2017/199210 A1 (ANG BENG KEONG [SG] ET AL) 13 juli 2017 (2017-07-13) * alineas [0085], [0088] - [0090], [0095], [0124]; figuren 1,2,4A *	1,12,17
X	US 2013/260372 A1 (BUERMANN DALE [US] ET AL) 3 oktober 2013 (2013-10-03)	1-5, 7-13, 15-20
Y	* alineas [0034], [0110]; figuren 1,2 *	6,14
X	US 2011/052446 A1 (HIRANO KIRK [US] ET AL) 3 maart 2011 (2011-03-03) * alineas [0028], [0074], [0078], [0102] - [0103]; conclusies; figuren 1,3,4,6,23,28 *	1,17

-/--

[X] Verdere documenten worden vermeld in het vervolg van vak C.

[X] Leden van dezelfde octrooifamilie zijn vermeld in een bijlage

* Speciale categorieën van aangehaalde documenten

"A" niet tot de categorie X of Y behorende literatuur die de stand van de techniek beschrijft

"D" in de octrooiaanvrage vermeld

"E" eerdere octrooi(aanvrage), gepubliceerd op of na de indieningsdatum, waarin dezelfde uitvinding wordt beschreven

"L" om andere redenen vermelde literatuur

"O" niet-schriftelijke stand van de techniek

"P" tussen de voorrangsdatum en de indieningsdatum gepubliceerde literatuur

"T" na de indieningsdatum of de voorrangsdatum gepubliceerde literatuur die niet bezwarend is voor de octrooiaanvrage, maar wordt vermeld ter verheldering van de theorie of het principe dat ten grondslag ligt aan de uitvinding

"X" de conclusie wordt als niet nieuw of niet inventief beschouwd ten opzichte van deze literatuur

"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

"&" lid van dezelfde octrooifamilie of overeenkomstige octrooipublicatie

Datum waarop het onderzoek naar de stand van de techniek van internationaal type werd voltooid	Verzenddatum van het rapport van het onderzoek naar de stand van de techniek van internationaal type
18 januari 2019	

Naam en adres van de instantie	De bevoegde ambtenaar
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Veefkind, Victor

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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 2021147

C.(Vervolg) VAN BELANG GEACHTE DOCUMENTEN

Categorie *	Geciteerde documenten, eventueel met aanduiding van speciaal van belang zijnde passages	Van belang voor conclusie nr.
A	US 2012/270305 A1 (REED MARK T [US] ET AL) 25 oktober 2012 (2012-10-25) * het gehele document *	1-20
Y	GB 2 156 033 A (FESTO KG) 2 oktober 1985 (1985-10-02) * het gehele document *	6,14
Y	US 2 301 207 A (GARRETSON CORNELIUS D) 10 november 1942 (1942-11-10) * het gehele document *	6,14

Formulier PCT/ISA/201 (vervolg tweede blad) (Januari 2004)

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 2021147

In het rapport genoemd octrooigeschrift	Datum van publicatie	Overeenkomend(e) geschrift(en)	Datum van publicatie
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WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
SN71631	18.06.2018		NL2021147

International Patent Classification (IPC)
INV. B01L3/00 ADD. F16L11/22

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
Veefkind, Victor

WRITTEN OPINION

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	6-8, 10, 11, 13-16
	No:	Claims	1-5, 9, 12, 17-20
Inventive step	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

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	US 2017/199210 A1 (ANG BENG KEONG [SG] ET AL) 13 juli 2017 (2017-07-13)
D2	US 2013/260372 A1 (BUERMANN DALE [US] ET AL) 3 oktober 2013 (2013-10-03)
D3	US 2011/052446 A1 (HIRANO KIRK [US] ET AL) 3 maart 2011 (2011-03-03)
D4	US 2012/270305 A1 (REED MARK T [US] ET AL) 25 oktober 2012 (2012-10-25)

1 Document D1 discloses a flow cell (having an inlet and outlet) with an array of analytes in it ([0124], fig. 4A), which is connected via flexible tubing ([0095]) to a fluidics automation module FAM (a "reagent management system (RMS)") having wells with reagents. Since the connection is flexible, it will enable movement of the flow cell relative to a fixed point in the instrument.

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new.

2 Document D2 discloses a cartridge comprising a flow cell with analytes (an array of nucleic acid features) that is to be presented to a detection unit, the cartridge optionally also containing reagent reservoirs ([0034]), i.e. a reagent management system. In [0110] it is explained that the flow cell may be moveable (to "float") within the instrument or cartridge, which is advantageous to align it with an optical instrument (i.e. detection module). In this passage it is explained that in that case the tubing will generally be flexible. For example flexible tubing will connect a flow cell to fixed fluidic components of a cartridge. The flexible tubing will inherently have a fluidic seal operable to connect to an RMS outlet port since it is connected to the fluidic devices.

As can be seen from the above, document D2 discloses in combination all the features defined in independent claims 1, 12 and 17. Hence the subject-matter of these independent claims is not new.

3 Document D3 describes (see cited passages) at least a flow cell with flexible tubes connected to the inlet and outlet ports, the flexible tubes having valves (100, 102) and ports (96, 98) which would be operable to connect to an RMS. The flow-cell defines a number of reaction sites (see [0102]-[0103] and figs.1 and 23). The flexible tubes allow movement of the flow cell, see figure 4
The document (see e.g. [0028] and figure 3) furthermore discloses a reagent delivery system (RMS) with wells and a cartridge having these elements disposed thereon/in.

As can be seen from the above, document D3 discloses in combination all the features defined in independent claims 1,12 and 17. Hence the subject-matter of these claims is not new.

3.1 The features of dependent claims 2-4 (inherent, for claim 4 also see below), 5 (the inlet and outlet tubes together can be labeled "the flexible connection"), 9, 18, 19 and 20 (cartridge) also appear to already have been disclosed in the above-mentioned documents (see cited passages), in particular in D2.

Furthermore, double tubing with a slit between the two vias is well known in the art, see e.g. D5 or D6. Hence, the skilled person would consider applying this. In addition, when wishing to move the flow cell back-and-forth, the skilled person would a priori consider using a sinusoidal shape hose, as it allows easy movement back and forth. Hence, claims 6,7,14,15 lack an inventive step over D2.
At present, over the whole scope of these claims, the surprising effect of the features of claims 8 and 16 is unclear. it would seem unsurprising that thicker walls give stronger tubing. Hence, they are considered as merely obvious alternatives.

Re Item VIII

Certain observations on the application

4 There is a multiplicity of independent claims in the same category overlapping to a very large extent. this gives rise to an objection for lack of conciseness.

5 The following claims are not clear:

5.1 **Claim 1** describes an instrument comprising essentially a number of modules. However, these modules are not described as comprised in the instrument, but merely as operable to be positioned in the instrument. this throws doubt upon the features of this claim. Does the instrument now comprise the RMS or not?
The same applies to the cartridge of independent **claim 12**.

5.2 **Claim 2** mentions "the detection module". This detection module lacks an antecedent basis.

5.3 **Claim 4** seems to describe an apparatus in terms of process features (positioning). If these are not process features then the "tolerance" can be arbitrarily defined for features which are simply in a certain place. For a device it cannot be determined if a certain tolerance for the position of a subunit had or had not been "predetermined".

5.4 **Claim 10** refers to claims 8 or 9 as well as to "the intermediate layer", however, claims 9 and 1 (to which claim 9 *inter alia* refers) do not mention such intermediate layer. This layer seems only mentioned in claim 8. The same applies to **claim 11**.