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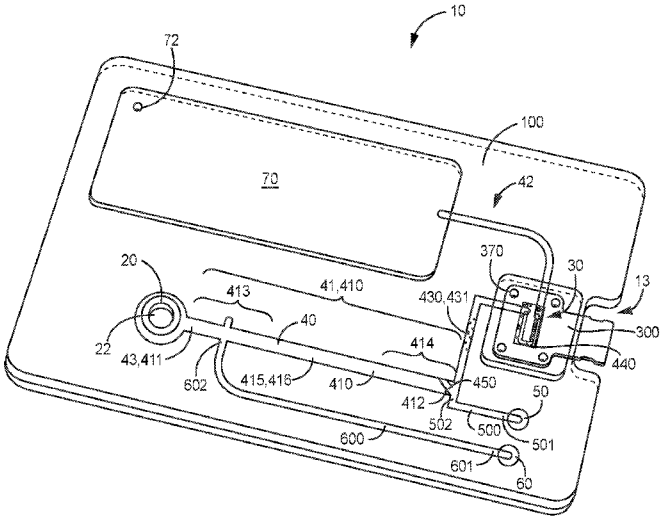

FIG. 4

(57) Abstract: A cartridge for sample handling and sensing includes a sample port connected to a sample reservoir having a proximal end, a proximal region adjacent the proximal end, and a distal end opposite of the proximal end. The cartridge also includes a first fluid port connected to the sample reservoir in the distal region via a first fluid channel; and a second fluid port connected to the sample reservoir in the proximal region via a second fluid channel. In addition, the cartridge includes a sensor platform comprising a bulk acoustic wave (BAW) resonator and a fluid flow path comprising a sensing region extending across a sensing surface of the BAW resonator. The cartridge further includes a fluid valve between the distal end of the sample reservoir and the sensing region. A sample may be applied to the sample port; first volume of fluid may be injected through the first fluid port; and then a second volume of fluid may be injected through the second fluid port to drive the sample into the sensing region of the fluid flow path.

WO 2018/022778 A1

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CARTRIDGES FOR INTEGRATED BAW BIOSENSORS AND METHODS FOR USING THE SAME

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 62/366,831, filed on 26 July 2016; to U.S. Provisional Application Serial No. 62/368,261, filed on 29 July 2016; and to U.S. Provisional Application Serial No. 62/370,788, filed on 4 August 2016, the contents of which are hereby incorporated herein their entireties to the extent that they do not conflict with the disclosure presented herein.

FIELD

The present disclosure relates to bulk acoustic wave (BAW) resonators and their use as biosensors. In particular, the present disclosure relates to cartridges containing bulk acoustic wave resonators.

BACKGROUND

Numerous instruments and measurement techniques exist for diagnostic testing of materials for medical, veterinary medical, environmental, biohazard, bioterrorism, agricultural, and food safety purposes. Diagnostic testing traditionally requires long response times to obtain meaningful data, involves expensive, remote, or cumbersome laboratory equipment, requires large sample size, utilizes multiple reagents, demands highly trained users, and can involve significant direct and indirect costs. For example, in both the human and veterinary diagnostic markets, most tests require that a sample be collected from a patient and then be sent to a laboratory, where the results are not available for several hours or days. As a result, the caregiver must wait to treat the patient.

Point of use (or point of care when discussing human or veterinary medicine) solutions for diagnostic testing and analysis, although capable of solving most of the noted drawbacks, remain somewhat limited. Even some of the point of use solutions that are available, are limited in sensitivity and reproducibility compared to in-laboratory testing. There are also often significant costs involved as separate systems may be needed for different point of use tests.

Bulk acoustic wave (BAW) sensors have been described for use as biosensors. Fluidic devices having BAW sensors for detecting the presence of an analyte in a sample often have biomolecules, such as antibodies or other proteins such as receptors, polynucleic acids, or the like, attached to their surfaces. The analyte may bind to the biomolecule attached to the surface of the sensor and increase the mass bound to the sensor. The increased mass alters the wave propagation characteristics (e.g., magnitude, frequency, phase, etc.) of the sensor. The change in propagation characteristics due to analyte binding may be correlated with the amount of bound analyte and, thus, the amount of analyte in the sample.

It would be desirable to provide a biosensor platform for point of use testing that is simple and cost-effective to manufacture, allows for flexibility to test for various analytes on the same platform, and is convenient and reliable.

SUMMARY

Disclosed herein are cartridges containing BAW resonators as sensors. The cartridges are designed to flow sample across sensing surfaces of the resonators. The cartridges provide for effective manipulation of flow of fluid through the cartridge to cause a sample to flow of a sample across sensing surfaces of the resonators.

The cartridges may be used with external devices, such as readers, that may fluidly connect with the cartridges to manipulate flow of the sample through the cartridge, precondition a flow path for sample flow, and the like.

In one aspect, a cartridge for handling and sensing a liquid sample is disclosed herein. The cartridge includes a sensor comprising a bulk acoustic wave (BAW) resonator having a sensing surface; a sample port; and a fluid flow path from the sample port to the sensor for carrying a sample introduced into the sample port across the sensing surface of the resonator. The fluid flow path includes a sample reservoir defining a proximal portion of the fluid flow path and defining an inner surface. The sample reservoir has a proximal end connected to the sample port, a proximal region adjacent the proximal end, a distal end, a distal region adjacent the distal end, and a volume extending between the proximal end and the distal end. The fluid flow path further includes a sensing portion downstream of the sample reservoir and extending across the sensing surface of the resonator. The sensing surface of the resonator defines at least a portion of

a surface of the sensing portion. The flow path further comprises a valve disposed between the distal end of the sample reservoir and the sensing portion. The cartridge also includes a first fluid port, a first fluid channel, a second fluid port, and a second fluid channel. The first fluid channel has a proximal end connected to the first fluid port and a distal end connected to the distal region of the sample reservoir. The second fluid channel has a proximal end connected to the second fluid port and a distal end connected to the proximal region of the sample reservoir.

In another aspect, a method of sample handling and sensing using a cartridge is disclosed. The cartridge includes a sample port connected to a sample reservoir having a proximal end, a proximal region adjacent the proximal end, and a distal end opposite of the proximal end. The cartridge also includes a first fluid port connected to the sample reservoir in the distal region via a first fluid channel; and a second fluid port connected to the sample reservoir in the proximal region via a second fluid channel. In addition, the cartridge includes a sensor platform comprising a bulk acoustic wave (BAW) resonator and a fluid flow path comprising a sensing region extending across a sensing surface of the BAW resonator. The cartridge further includes a fluid valve between the distal end of the sample reservoir and the sensing region. The method includes applying a sample to the sample port; injecting a first volume of fluid through the first fluid port; and then injecting a second volume of fluid through the second fluid port to drive the sample into the sensing region of the fluid flow path.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a schematic perspective view of a system according to an embodiment.

FIGS. 2A and **2B** are schematic cross-sectional views of bulk acoustic wave resonators.

FIG. 3 is a perspective view of a cartridge according to an embodiment.

FIG. 4 is a perspective view of the cartridge of **FIG. 3** with its cover removed.

FIG. 5A is a top perspective view of a sensor platform for the cartridge of **FIG. 3**.

FIG. 5B is a bottom perspective view of the sensor platform of **FIG. 5A**.

FIG. 6 is a close-up of a sensing region on the sensor platform of **FIG. 5A**.

The drawings are not necessarily to scale. Like numbers used in the figures refer to like parts. However, the use of different numbers to refer to components is not intended to indicate that the different numbered components cannot be the same or similar.

DETAILED DESCRIPTION

In the following detailed description, several specific embodiments of compounds, compositions, products and methods are disclosed. It is to be understood that other embodiments are contemplated and may be made without departing from the scope or spirit of the present disclosure. The following detailed description, therefore, is not to be taken in a limiting sense.

The present disclosure relates to bulk acoustic wave (BAW) resonators and their use as biosensors. In particular, the present disclosure relates to devices, such as cartridges, containing bulk acoustic wave resonators.

As shown schematically in **FIG. 1**, the cartridge **10** may be used as part of a system **1** with a device or reader **2** constructed to receive the cartridge **10**. The reader **2** may provide solutions used in sample handling in the cartridge **10**, and may be used to read and optionally interpret the results from the BAW sensor in the cartridge **10**.

The cartridge **10** of the present disclosure embodies the integrated components necessary to convert a BAW resonator, or array of BAW resonators, into a biosensor. This allows for a collection of the tools integrated into a single cartridge that can be tailored for the detection of one or more analytes, such as proteins, DNA, bacteria, fungi, viruses, and other biological or non-biological materials.

The disclosed cartridges can accommodate a large breadth of testing protocols without requiring the platform to be entirely redesigned. The disclosed cartridges may also provide for the use of the same configuration for different protocols, meaning that only the materials would need to be different to afford different protocols to be undertaken with the device. The cartridges may be manufactured with a selectable or interchangeable sensor platform that allows for even more flexibility. The cartridges or parts of the cartridges may be reusable, recyclable, or disposable. The cartridges may be offered as "dry" cartridges, meaning that no liquid reagents are stored on the device, making the cartridges simpler and more cost-effective to manufacture, and improving storage life of the device. The cartridges are portable and can be used at the sampling location or transported into a laboratory or other secondary site for analysis.

The cartridges of the present disclosure are constructed to receive a liquid sample, to at least temporarily store the sample, to provide sample handling and conditioning, and to transfer and meter the sample to a sensor for analysis of one more parameters of the sample. Examples of typical samples include biological samples, such as urine, plasma, serum, blood, saliva, tears, sweat, and the like, and environmental samples, such as air or other gases, water, and aqueous solutions. However, the device can be modified to accommodate various types of fluid samples, and is not particularly limited by sample type.

The cartridges of the present disclosure utilize sensors with bulk acoustic wave (BAW) resonators. According to an embodiment, the cartridge contains a BAW array in a fluid flow path. BAW resonators generally include a piezoelectric crystal resonator that can be used to detect changes in material (e.g., changes in the mass of the material) deposited (e.g., bound) on the surface of the resonator. The BAW resonator may have biomolecules, such as antibodies or other proteins such as receptors, polynucleic acids, or the like, attached to its surface such that when the target analyte passes over the surface, it binds onto the biomolecule. The cartridge may be prepared with various select biomolecules based on the desired target analyte or analytes.

BAW devices typically involve transduction of an acoustic wave using electrodes arranged on opposing top and bottom surfaces of a piezoelectric material. In a BAW device, three wave modes may propagate, namely, one longitudinal mode (embodying longitudinal waves, also called compressional/extensional waves), and two shear modes (embodying shear waves, also called transverse waves), with longitudinal and shear modes respectively identifying vibrations where particle motion is parallel to or perpendicular to the direction of wave propagation. The longitudinal mode is characterized by compression and elongation in the direction of the propagation, whereas the shear modes consist of motion perpendicular to the direction of propagation with no local change of volume. Longitudinal and shear modes propagate at different velocities. In practice, these modes are not necessarily pure modes as the particle vibration, or polarization, is neither purely parallel nor purely perpendicular to the propagation direction. The propagation characteristics of the respective modes depend on the material properties and propagation direction respective to the crystal axis orientations. The ability to create shear displacements is beneficial for operation of acoustic wave devices with fluids (e.g., liquids) because shear waves do not impart significant energy into fluids. BAW devices include bulk acoustic resonators deposited on one or more reflective layers, such as Bragg mirror, and film bulk acoustic resonators having an air-gap.

The BAW sensor described herein may employ any suitable piezoelectric thin film. Certain piezoelectric thin films are capable of exciting both longitudinal and shear mode resonance, such as hexagonal crystal structure piezoelectric materials including (but not limited to) aluminum nitride (AlN) and zinc oxide (ZnO). To excite a wave including a shear mode using a piezoelectric material layer arranged between electrodes, a polarization axis in a piezoelectric thin film is generally non-perpendicular to (e.g., tilted relative to) the film plane. In sensing applications involving liquid media, the shear component of the resonator is preferably used. In such applications, piezoelectric material may be grown with a c-axis orientation distribution that is non-perpendicular relative to a face of an underlying substrate to enable a BAW resonator structure to exhibit a dominant shear response upon application of an alternating current signal across electrodes thereof. Conversely, a piezoelectric material grown with a c-axis orientation that is perpendicular relative to a face of an underlying substrate will exhibit a

dominant longitudinal response upon application of an alternating current signal across electrodes thereof.

FIG. 2A is a schematic cross-sectional view of a portion of a bulk acoustic wave (BAW) Microelectromechanical system (MEMS) resonator structure **3100** useable with embodiments disclosed herein. The resonator structure **3100** includes a substrate **3130** (e.g., typically silicon or another semiconductor material), an acoustic reflector **3140** arranged over the substrate **3130**, a piezoelectric material **3160**, and bottom and top side electrodes **3151**, **3152**. The bottom side electrode **3151** is arranged along a portion of a lower surface **3161** of the piezoelectric material **3160** (between the acoustic reflector **3140** and the piezoelectric material **3160**), and the top side electrode **3152** is arranged along a portion of an upper surface **3162** of the piezoelectric material **3160**. An area in which the piezoelectric material **3160** is arranged between overlapping portions of the top side electrode **3152** and the bottom side electrode **3151** is considered an active region **3110** of the resonator device **3100** to which a biomolecule is preferably applied. The acoustic reflector **3140** serves to reflect acoustic waves and therefore reduce or avoid their dissipation in the substrate **3130**. In certain embodiments, the acoustic reflector **3140** includes alternating thin layers **3141**, **3142** of materials (e.g., silicon oxicarbide [SiOC], silicon nitride [Si_3N_4], silicon dioxide [SiO_2], aluminum nitride [AlN], tungsten [W], and molybdenum [Mo]) having different acoustic impedance values, optionally embodied in a quarter-wave Bragg mirror, deposited over the substrate **3130**. In certain embodiments, other types of acoustic reflectors may be used. Steps for forming the resonator device **30** may include depositing the acoustic reflector **3140** over the substrate **3130**, followed by deposition of the bottom side electrode **3151**, followed by growth (e.g., via sputtering or other appropriate methods) of the piezoelectric material **3160**, followed by deposition of the top side electrode **3152**.

In certain embodiments, the piezoelectric material **3160** comprises a hexagonal crystal structure piezoelectric material (e.g., aluminum nitride or zinc oxide) that includes a c-axis having an orientation distribution that is predominantly non-parallel (and may also be non-perpendicular to) to normal of a face of the substrate **3130**. Under appropriate conditions, presence of a c-axis having an orientation distribution that is predominantly non-parallel to normal of a face of a substrate enables a BAW resonator structure to be configured to exhibit a dominant shear response upon application of an alternating current signal across a distal

electrode and a proximal electrode thereof (e.g., as may be desirable in the context of a BAW resonator structure providing sensing utility). Methods for forming hexagonal crystal structure piezoelectric materials including a c-axis having an orientation distribution that is predominantly non-parallel to normal of a face of a substrate are disclosed in U.S. Patent Application No. 15/293,063 filed on October 13, 2016. Additional methods for forming piezoelectric materials having an inclined c-axis orientation are disclosed in U.S. Patent No. 4,640,756 issued on February 3, 1987.

The bulk acoustic wave MEMS resonator structure **3100** shown in **FIG. 2A** lacks any layers (e.g., including functionalization material) overlying the active region **3110** that maypermit the resonator device **3100** to be used as a biochemical sensor. If desired, at least portions of the resonator device **3100** shown in **FIG. 2A** (e.g., including the active region **3110**) may be overlaid with various layers, such as one or more of: a hermeticity layer, an interface layer, a self-assembled monolayer (SAM), and/or a functionalization material layer (which may include specific binding material or non-specific binding material).

FIG. 2B is a schematic cross-sectional view of an upper portion of a BAW resonator device including a piezoelectric material **3160** and a top side electrode **3152** overlaid with a hermeticity layer **3171**, an interface layer **3172**, a self-assembled monolayer (SAM) **3173**, and a layer **3120** comprising a biomolecule. In certain embodiments, one or more blocking materials (not shown) may be applied during fabrication, such as over portions of an interface layer to prevent localized attachment of one or more subsequently deposited layers, or (if applied over selected regions of a SAM or a functionalization material) to prevent analyte capture in regions not overlying an active region of the BAW resonator device.

In certain embodiments incorporating electrode materials subject to corrosion, a hermeticity layer may be applied between a top side electrode and an interface layer. If provided, a hermeticity layer preferably includes a dielectric material with a low water vapor transmission rate (e.g., no greater than 0.1 $g/m^2/day$). Following deposition of a hermeticity layer and an interface layer, a SAM may be formed over the interface layer, with the SAM including an organosilane material in certain embodiments. The hermeticity layer protects a reactive electrode material (e.g., aluminum or aluminum alloy) from attack in corrosive liquid environments, and the interface layer facilitates proper chemical binding of the SAM.

Following deposition of an interface layer (optionally arranged over an underlying hermeticity layer), a SAM is preferably formed over the interface layer. SAMs are typically formed by exposure of a solid surface to amphiphilic molecules with chemical groups that exhibit strong affinities for the solid surface. When an interface layer comprising a hydroxylated oxide surface is used, then organosilane SAMs are particularly preferred for attachment to the hydroxylated oxide surface. Organosilane SAMs promote surface bonding through silicon-oxygen (Si-O) bonds.

When an electrode and/or interface layer comprising gold or another noble metal is used, then thiol-based (e.g., alkanethiol-based) SAMs may be used. Alkanethiols are molecules with an alkyl chain as the back bone, a tail group, and an S-H head group. Thiols may be used on noble metal interface layers due to the strong affinity of sulfur for these metals.

Following formation of a SAM, the SAM may be biologically functionalized, such as by receiving at least one specific binding material. In certain embodiments, specific binding materials may be applied on or over a SAM using a microarray spotting needle or other suitable methods. In certain embodiments, an interface layer may be patterned (e.g., using photolithography for defining the interface layer) with a high dimensional tolerance over only a portion of a resonator structure (which includes a substrate), a SAM may be applied over the interface layer, and a subsequently applied specific binding material may be attached only to the SAM. In certain embodiments, patterning of an interface layer may provide a higher dimensional tolerance for positioning of the specific binding material than could be attained by microarray spotting alone. Examples of specific binding materials include, but are not limited to, antibodies, receptors, ligands, oligopeptides, DNA or RNA strands, and the like. A specific binding material is preferably configured to receive a predefined target species (e.g., molecule, protein, DNA, virus, bacteria, etc.). A functionalization material including specific binding material may include a thickness in a range of from about 5 nm to about 1000 nm, or from about 5 nm to about 500 nm. In certain embodiments, an array of different specific binding materials may be provided over different active areas of a multi-resonator structure (i.e., one or more resonator structures including multiple active regions), optionally in combination with one or more active areas that are devoid of specific binding materials to serve as comparison (or

"reference") regions. In certain embodiments, a functionalization material (e.g., chemical functionalization material) may provide non-specific binding utility.

Certain embodiments of the present disclosure are directed to a cartridge including multiple BAW resonators as disclosed herein and including a fluidic passage (e.g., a channel, a chamber, or the like) arranged to conduct a liquid to contact at least one functionalization (e.g., specific binding) material arranged over at least one active sensing surface of the resonators. Such a device may be microfluidic in scale, and comprise at least one microfluidic passage (e.g., having at least one dimension, such as height and/or width, of no greater than about 1000 microns, no greater than about 500 microns, or no greater than about 250 microns, or no greater than about 100 microns).

Referring now to **FIG. 3**, a cartridge **10** housing a BAW resonator sensor **30** is shown. According to an embodiment, the cartridge **10** contains a fluid flow path **40** with a sample port **20** that is constructed to guide the sample across the sensing surface of a BAW array **320** arranged in the fluid flow path **40**. The fluid flow path **40**, the BAW sensor **30**, and other parts discussed in more detail below, are housed in a cartridge housing **100**. The shape and size of the cartridge housing **100** is not particularly limited, and the cartridge **10** may have any suitable shape and size. In the embodiment shown, the cartridge **10** has a width **W10** and length **L10** approximately similar to those of a standard size credit card (e.g., about 50 to 60 mm wide and 80 to 90 mm long), and a thickness **T10** of about 5-7 mm. The cartridge includes a sample port **20**, a first fluid port **50**, a second fluid port **60**, and an electrical interconnect **13**. The first **50** and second **60** fluid ports and the electrical interconnect **13** may interface and operably couple with a reader (such as reader **2** depicted in **FIG. 1**) or another suitable device.

The description provided above regarding BAW resonators is fairly generic regarding a resonator structure. Some of the description provided with regard to **FIGS. 2A** and **2B** details embodiments of bulk acoustic resonators that may be employed as a resonator structure. In at least some embodiments, the resonator structure incorporated in the cartridge **10** comprises a BAW resonator arranged over at least a portion of a substrate, and a biomolecule arranged over at least a portion of an active region of the BAW resonator structure. Various layers may be arranged between the biomolecule and a top side electrode (which is coincident with an active region of a BAW resonator structure), such as: a hermeticity layer (e.g., to protect the top side

electrode from corrosion in a liquid environment), an interface layer, and/or a self-assembled monolayer (SAM), with the interface layer and/or the SAM being useful to facilitate attachment of at least one overlying material layer, ultimately including functionalization material. In certain embodiments, the interface layer facilitates attachment of an overlying SAM, and the SAM facilitates attachment of an overlying functionalization material.

FIGURE **4** shows a view of the fluid flow path **40** and sensor platform **300** (BAW sensor **30**) with the top layer or cover of the cartridge **10** removed. According to an embodiment, the cartridge houses a BAW sensor **30** comprising at least one BAW resonator having a sensing surface. The BAW sensor **30** may include an array of BAW resonators. The cartridge also includes a sample port **20** for introducing a liquid sample to the flow path **40**. The fluid flow path **40** extends from the sample port **20** to the sensor **30** and carries a sample introduced into the sample port **20** across the sensing surface of the sensor **30**.

The fluid flow path **40** includes a proximal portion **41** and a distal portion **42**, and a sample reservoir **410** defining the proximal portion **41** of the fluid flow path **40**. The sample reservoir **410** has a proximal end **411** connected to the sample port **20**, and a distal end **412** opposite of the proximal end **411**. A proximal region **413** is disposed adjacent the proximal end **411**, and a distal region **414** adjacent the distal end **412**. The sample reservoir **410** has a wall **415** defining an inner surface **416** and a volume extending between the proximal end **411** and the distal end **412**.

The fluid flow path **40** further includes a sensing portion **440** downstream of the sample reservoir **410**. The sensing portion **440** extends across the sensing surface of one or more resonators of the sensor **30** such that the sensing surface **311** defines at least a portion of a surface **441** of the sensing portion **440**.

The fluid flow path **40** includes a valve **450** disposed between the distal end **412** of the sample reservoir **400** and the sensing portion **440**. Any suitable valve can be used. Preferably, the valve **450** is a passive valve. In one embodiment, the valve **450** is a hydrophobic valve formed by a hydrophobic surface of the fluid flow path **40** in the area where the valve is formed to prevent hydrophilic sample fluid from flowing past the valve **450** at, for example, ambient

pressure. Other embodiments of the cartridge **10** may also include additional valves and fluid flow management features, such as pumps.

The valve **450** may be a hydrophobic valve formed by a hydrophobic surface of the fluid flow path **40**. For example, the valve **450** may be formed from a hydrophobic material, such as polyether ether ketone (PEEK), polycarbonate, polyurethane, perfluoroalkoxy alkanes (PFA), polytetrafluoroethylene (PTFE), polythermide (PEI), cyclic olefin copolymers, etc., or may be coated by a hydrophobic coating of the fluid flow path **40**. Examples of suitable hydrophobic coatings include silanes modified to include a hydrophobic end group (e.g., an aliphatic or fluorinated hydrocarbon), such as long chain alkylsilanes.

According to an embodiment, the cartridge **10** includes a first fluid port **50** and a first fluid channel **500** extending from a proximal end **501** at the first fluid port **50** to a distal end **502**. The distal end **502** of the first fluid channel **500** is connected to the distal region **414** of the sample reservoir **410** via valve **450**. In one embodiment, the distal end **502** of the first fluid channel **500** is connected to the distal end **412** of the sample reservoir **410**.

According to an embodiment, the cartridge **10** includes a second fluid port **60** and a second fluid channel **600** extending from a proximal end **601** at the second fluid port **60** to a distal end **602**. The distal end **602** of the second fluid channel **600** is connected to the proximal region **413** of the sample reservoir **400**. For example, the distal end **602** of the second fluid channel **600** may be connected to the proximal end **411** of the sample reservoir **410**, or downstream of the proximal end **411** by a distance of up to 15 %, up to 20 %, up to 25 %, up to 30 %, or up to 40 % of the length of the sample reservoir **410**.

As the sample handling fluids can be provided through the first and second fluid ports **50**, **60**, the cartridge **10** may be stored and transported "dry" without liquid reagents stored on the cartridge **10** prior to use. In an alternative embodiment, some liquid reagents (e.g., a buffer) may be stored on the cartridge **10** (e.g., in connection with the first fluid channel **500** or second fluid channel **600**).

The sample port **20** may be closed by a closure **22**. For example, the sample port **20** may be closed by a film, a cap, a septum, or any other suitable closure that can accommodate delivery of the sample into the sample port **20** and keep the sample from inadvertently flowing out of the

sample port **20**. In an embodiment, the closure **22** comprises a septum or a similar closure that self-closes after being punctured, and the sample can be delivered by a needle and syringe. In an embodiment, the closure **22** comprises a cap that may be removed to introduce the sample into the sample port **20** and reattached after the sample has been introduced.

The sample reservoir **410** is constructed to receive and house the sample and to deliver the sample into the sensing portion **440**. In one embodiment, the sample reservoir **410** is defined by walls **415** that have a hydrophilic surface that can draw an aqueous sample into the sample reservoir **410**. The walls **415** may be constructed from a hydrophilic material, such as glass or quartz, or may be coated with a hydrophilic coating. For example, the walls **415** may be coated by polyethylene glycol (PEG), ethylene glycol, polyacrylate, polyvinyl pyrrolidone (PVP). If a polymeric material, such as polyacrylate, is used as the hydrophilic coating, the material may be selected to have hydrophilic properties (e.g., hydroxyethylmethacrylate or "HEMA").

The sample reservoir **410** may have any suitable volume. For example, the volume of the sample reservoir **410** may be about 1 μL or greater, about 4 μL or greater, or about 10 μL or greater. The volume may be about 200 μL or less, about 150 μL or less, about 100 μL or less, about 50 μL or less, or about 20 μL or less. The volume is defined by the walls **415** and the proximal end **411** and distal end **412** of the sample reservoir **410** or the proximal end **411** of the reservoir **410** and a proximal end of valve **450**. In one embodiment, the sample port **20** and the sample reservoir **410** are designed to receive a liquid sample of about 10 μL.

According to an embodiment, at least two fluid ports (e.g., first and second fluid ports **50**, **60**) may deliver fluids into the fluid flow path **40** through fluid channels (e.g., first and second fluid channels **500**, **600**). The fluids can be used, for example, to prepare the fluid flow path for receiving the sample, such as to prepare the walls of the fluid flow path so that the sample does not get absorbed or adsorbed into the walls, to remove any air bubbles, to stop the sample from getting to the sensor prematurely, or to open the hydrophobic valve. The fluids may also be used to push or advance the sample forward in the fluid flow path, to dilute and buffer the sample, and to deliver and mix chemical agents into the sample.

One or both of the first and second fluid ports **50**, **60** may include a valve. The first and second fluid ports **50**, **60** may be constructed to independently connect to external pumps and

fluid reservoirs. For example, the fluid ports may be constructed to couple with corresponding valves or fluid ports connected to pumps, fluid lines, and/or fluid reservoirs on a reader (such as reader **2** depicted in **FIG. 1**) that receives the cartridge **10**.

The first fluid channel **500** (e.g., the distal end **502** of the first fluid channel **500**) is connected to the distal region **414** of the sample reservoir **410**. In one embodiment, the first fluid channel **500** connects to the fluid flow path **40** at the juncture of the sample reservoir **410** and the mixing region **430**. Alternatively, the first fluid channel **500** connects to the sample reservoir **410** upstream of its distal end **412**. The first fluid channel **500** may also connect to the fluid flow path **40** downstream of the distal end **412** of the sample reservoir **410**.

The second fluid channel **600** (e.g., the distal end **602** of the second fluid channel **600**) is connected to the proximal region **413** of the sample reservoir **410**. The point where the second fluid channel **600** connects to the sample reservoir **410** can vary within the proximal region **413** such that the fluid (e.g., air or an aqueous solution) injected from the second fluid port **60** can push or deliver at least a part of the sample from the sample reservoir **410** into the sensing portion **440** of the fluid flow path **40**. In one embodiment, the second fluid channel **600** connects to the sample reservoir **410** at its proximal end **411**. The second fluid channel **600** may also connect to the sample reservoir **410** downstream of the proximal end **411**. For example, the second fluid channel **600** may connect to the sample reservoir **410** downstream from the proximal end **411** at up to 15 %, up to 20 %, up to 25 %, up to 30 %, or up to 40 % down the length of the sample reservoir **410**.

The second fluid channel **600** or a portion thereof may include hydrophobic walls or a hydrophobic coating to prevent an aqueous sample from entering the second fluid channel **600**.

The fluid flow path **40** may further include a mixing region **430** downstream of the sample reservoir **410**. A mixing region can be used to mix the sample with one or more of the fluids provided through the first and second fluid ports **50**, **60**. The mixing region **430** may include one or more static features **431** constructed to induce mixing within the fluid flow path **40**. The static mixing features **431** may include, for example, protrusions that narrow the inside diameter of the fluid flow path or multiple tight turns of the fluid flow path. Such static mixing features **431** may induce turbulence in the mixing region **430**.

The cartridge **10** may further include a waste reservoir **70**. The waste reservoir **70** may be located at the distal end **42** of the fluid flow path **40**. The waste reservoir **70** may be constructed to receive the sample and any fluids used to process the sample (e.g., fluids injected through the first and second fluid ports **50**, **60**) after the sample and the fluids have progressed through the sensing portion **440**. The volume of the waste reservoir **70** is not particularly limited and can range from about 100 μL to about 2 mL. The waste reservoir **70** may also include a vent **72** that allows air or gases but not fluids to escape from the waste reservoir **70**. The vent **72** may, for example, be covered by a hydrophobic membrane.

According to some embodiments, the BAW sensor **30** is mounted onto a sensor platform **300**. The sensor platform **300** may comprise, for example, a printed circuit board. The sensor platform **300** may be inserted into a cavity on the cartridge **10**, such that electrical interconnect **13** extends outside the housing **100** of the cartridge **10**, and may include features, such as mounting and registration apertures **370** that aid with placement of the sensor platform **300** in the correct location and can be used to secure the sensor platform **300** in place. The registration apertures **370** may couple with corresponding registration posts on the cartridge **10**. Alternatively, the sensor platform **300** may include posts, and the cartridge **10** may include corresponding apertures. The sensor platform **300** can be interchangeable such that a sensor platform with a specific, desired sensor can be selected and installed into the cartridge **10** which in turn can be generic and capable of housing various sensor platforms.

Referring now to **FIGS.** 5A, 5B and 6, the BAW sensor **30** provided on the sensor platform **300** may be provided as a BAW die **330**, as shown in **FIGS. 5A** and **5B**. A close-up view of a BAW die **330** is shown in **FIG. 6**. The sensor platform **300** may also include a RF switch **340** and other circuit components, such as a control and memory unit **350** and other electronic components to stimulate the BAW, condition the signal, and to communicate with the with the various electronics. The electronic component may be operably coupled to electrical interconnect **13** for coupling to an external device, such as a reader.

According to an embodiment, the BAW die **330** defines the sensing portion **440** of the fluid flow path **40**. The BAW die **330** includes BAW resonators **310** disposed along the sensing portion **440**. The BAW resonators **310** may have a sensing surface **311**, where biomolecules **312** are attached to the sensing surface **311**. When a sample flows through the sensing portion **440** of

the fluid flow path **40**, it comes into contact with the BAW resonators **310** and their sensing surfaces **311**. The BAW resonators **310** can be arranged in an array that includes multiple BAW resonators **310** of either the same or different types (i.e., including the same or different biomolecules). In the embodiment shown, the BAW array **320** includes six BAW resonators that are divided into three BAW resonators **310** that are used for testing, and three BAW resonators that are used as references (e.g., two non-specific BAW references **313** and an isolated environmental BAW reference **314)**. However, the sensor is not limited to six BAW resonators, and could include any number, such as from one to 20 resonators. The number of resonators on the sensor **30** can also be divided into testing resonators and reference resonators in various ways and is not limited to the 3-2-1 split of the example cartridge. Typically, the BAW die **330** includes one or more non-specific BAW references **313** and may also include an isolated environmental BAW reference **314**. The sensing portion **440** of the fluid flow path **40** may be configured so that the sample (or other fluid) in the fluid flow path **40** does not come into contact with the isolated environmental BAW reference **314**. The BAW die **330** also includes an electrical interface **334** for connecting the die to the electrical components of the sample platform **300** and/or a reader through electrical interconnect **13**.

Still referring to **FIGS. 5A**, **5B** and **6** and in accordance with an embodiment, a system including a cartridge described herein may include various temperature control mechanisms to help improve precision of the analysis. For example, the system may include multiple stages of temperature control, where one or more stages provide more approximate temperature control and/or insulation, and one or more stages provide finer temperature control. The reader may include a temperature control unit, and may also insulate the cartridge. The housing of the cartridge also provides insulation to the BAW sensor **30** inside the housing. The printed circuit board of the sensor platform **300** may include an electrically resistive heater **361** operated in a closed loop with an integrated resistive temperature device, or resistance temperature detector ("RTD"). The electrically resistive heater **361** may provide temperature control of about ±0.1 K. The BAW die **330** itself may also include a second electrically resistive heater **362** and RTD **363**, which may provide temperature control of about ±0.001 K. The second electrically resistive heater **362** may affect temperature of fluid flowing within the sensing portion **440** of the fluid flow path **40**. Examples of such temperature control systems are discussed in more detail in co-

pending International Patent Application No. PCT/US17/43958, titled BAW BIOSENSOR INCLUDING HEATER AND TEMPERATURE SENSOR AND METHODS FOR USING THE SAME, filed on 26 July 2017, which is incorporated here by reference in its entirety to the extent that it does not conflict with the present disclosure.

The cartridge can be manufactured from any suitable materials, such as polymeric materials, metals, semimetals, semiconductors, ceramics, and combinations thereof. For example, the housing of the cartridge may be manufactured from polypropylene, polyethylene, PEEK, perfluoroalkoxy alkanes (PFA), polytetrafluoroethylene (PTFE), polystyrene, cyclic olefin copolymers, or the like. The surfaces inside the cartridge, such as the walls of the fluid flow path, may be made selectively made from or coated with hydrophobic or hydrophilic materials. The sensor platform can be manufactured from materials suitable for printed circuit boards (PCBs), such as rigid laminated PCB materials including polyimides and epoxies, or flexible materials, such as polyimide, polyethylene terephthalate (PET), and combinations thereof. In one embodiment, the sensor platform is manufactured from high dielectric PCB material available from Rogers Corp. in Chandler, AZ.

Following fabrication of the BAW resonators and deposition of a SAM over portions thereof (optionally preceded by deposition of a hermeticity layer and an interface layer), the microfluidic channel of the sensing portion may be fabricated by forming one or more walls defining lateral boundaries of the microfluidic channel over the BAW resonators, such that the active region of the BAW resonators is arranged along the bottom surface of the microfluidic passage. The microfluidic passage can then be enclosed using a cap or cover layer that may define fluidic ports (e.g., an inlet and an outlet) enabling fluid communication with the rest of the fluid flow path.

Walls of the microfluidic channels may be formed of any suitable material, such as laser-cut "stencil" layers of thin polymeric materials and/or laminate materials, optionally including one or more self-adhesive surfaces (e.g., adhesive tape). Optionally such walls may be formed prior to deposition of a SAM layer, functionalization material, and/or blocking layers. The walls may be made with a SU-8 negative epoxy resist or other photoresist material. In certain embodiments, a cover or cap layer may be integrally formed with one or more walls (e.g., via molding or another suitable process) to define a portion of an upper boundary as well as lateral

boundaries of at least one fluidic channel, and the integrally formed partial cover-and-wall structure may be applied (e.g., adhered or otherwise bonded) over at least a portion of a BAW sensor to enclose the at least one fluidic channel.

In certain embodiments, functionalization (e.g., specific binding) material may be pre-applied to the sensing surface before formation of a microfluidic passage; in other embodiments, functionalization material may be applied over an active region of a bulk acoustic wave resonator structure following formation of the microfluidic passage. The cartridge or parts of the cartridge (such as the sensor platform and BAW die) may be manufactured and/or assembled using low-temperature methods. In some embodiments, the cartridge and its parts are assembled at temperatures below 40 °C. The cartridge may be assembled without the use of UV curing, welding, or other process steps that may damage the biomolecules on the sensing surface of the BAW resonators. This allows the biomolecules to be patterned on the sensing surface prior to assembly.

A chemical or biological blocking material may be applied over a portion of a SAM to prevent attachment of a functionalization (e.g., specific binding) material over one or more selected regions of a BAW resonator structure (e.g., one or more regions apart from an active region). The proper choice of a chemical or biological blocking material (e.g., blocking buffer) for a given analysis depends on the type of target species or analyte present in a sample. Various types of blocking buffers such as highly purified proteins, serum, or milk may be used to block free sites on a SAM. Additional blockers include ethanolamine or polyethylene oxide (PEO)–containing materials. An ideal blocking buffer would bind to all potential sites of non-specific interaction away from an active region. To optimize a blocking buffer for a particular analysis, empirical testing may be used to determine signal-to-noise ratio. No single chemical blocking material is ideal for every situation, since each antibody-antigen pair has unique characteristics.

The walls of the fluid flow path may be treated with chemical or biological blocking materials to prevent attachment of analytes in regions other than the BAW sensors. Such blocking materials may be applied ahead of time, or may be provided in one of the solutions used to prime the fluid flow path prior to applying the sample (e.g., a solution or buffer injected through the first fluid port).

According to an embodiment, at least some of the fluid channels of the cartridge may be microfluidic channels. For example, the first and second fluid channels may be microfluidic channels. The distal portion of the fluid flow path may also include microfluidic channels, such as in the mixing region and the sensing portion. The microfluidic channels may have a hydraulic cross-sectional area of about 0.01 mm^2 to about 4.0 mm^2.

In general, movement of the sample and the analytes contained in the sample in the fluid flow path is primarily affected by hydrophobic/hydrophilic forces or fluid pressure (e.g., fluid from the second fluid port). However, the cartridge may also include other mechanisms to either enhance or retard the movement of certain compounds in the sample. For example, the cartridge may utilize electrophoresis to enhance the sensitivity of the BAW sensor. Examples of such electrophoretic systems are discussed in more detail in co-pending International Patent Application No. PCT/US17/43959, titled MICROFLUIDIC SENSORS USING ELECTROPHORESIS, filed on 26 July 2017, which is incorporated here by reference in its entirety to the extent that it does not conflict with the present disclosure.

The cartridge may include various features for interfacing with the reader. For example, the first and second fluid ports may interface with valves, pumps, or other fluidic interfaces for pneumatic or liquid-based fluid transfer systems on the reader. The cartridge may also include mechanical registrations to position the cartridge within the reader, and interfaces for electrical current (e.g., direct current or alternating current) and power and digital communication signals, magnetic interfaces, thermal interfaces, and/or optical interfaces.

The cartridges of the present disclosure are constructed to receive a liquid sample, to at least temporarily store the sample, to provide sample handling and conditioning, and to transfer and meter the sample to a sensor for analysis of one more parameters of the sample. Examples of typical samples include biological samples, such as urine, plasma, serum, blood, saliva, tears, sweat, and the like, and environmental samples, such as air or other gases, water, and aqueous solutions.

According to an embodiment and with reference to **FIG. 4**, the sample is applied to the sample port **20** using any suitable application method. For example, the sample can be applied using a syringe or a pipette or some other applicator. The hydrophilic walls **415** of the sample

reservoir **410** at least partially draw the sample into the sample reservoir **410**. However, the valve **450**, which may be a hydrophobic valve, prevents the sample from advancing past the sample reservoir **410** in the fluid flow path **40**.

Once the sample has been applied to the sample port **20**, the cartridge **10** may be inserted into the reader to electrically couple the reader with the cartridge **10** through electrical interconnect **13**. A fluid interface within the reader may engage the first fluid port **50**, injecting a first volume of a first fluid in the first fluid channel **500**. The first volume of the first fluid may be from about 100 μL to about 1000 μL. The first fluid may include a buffer or another solution that pre-fills and wets the distal portion **42** of the fluid flow path **40** and opens the hydrophobic valve **450**. The first fluid may also include a blocker compound that prevents the sample or the analyte from attaching to the walls of the fluid flow path **40**. Injecting the first fluid may also remove any unwanted bubbles in the fluid flow path **40** and stop the sample from getting to the sensor prematurely. The various functions of the first fluid may be understood as "priming" the fluid flow path **40**.

A fluid interface within the reader may engage the second fluid port of the cartridge **10** when the cartridge **10** is inserted into the reader. After fluid is moved through the first fluid channel **500** through the first port **50**, a second fluid (which may be a liquid or gas) may be injected through the second fluid port **60** to push at least a portion of the sample from the sample reservoir **410** into the sensing portion **440** of the fluid flow path **40**. Increased pressure due to the second fluid in the sample reservoir **410** may permit the sample to flow past the valve **450**. The sample may mix with a volume of the first fluid in the mixing region **430** of the fluid flow path **40** prior to entering the sensing portion **440**. The sample may be mixed with the first fluid to, for example, dilute the sample or to mix the sample with buffering agents or reagents.

In the sensing portion **440** the sample comes into contact with the sensing surface of resonators, and analytes of the sample may selectively bind with biomolecules on the sensing surfaces of the BAW resonators. Multiple analytes can be sensed simultaneously by including, for example, BAW resonators with different biomolecules. In alternative embodiments, the BAW sensor does not include biomolecules and is used to detect physical characteristics of the sample, such as changes in viscosity or density. Signals from the BAW array are received by signal processing and storing units (e.g., control and memory units) on the sensor platform **300**

and/or the reader. The reader may to read and optionally interpret the results from the BAW sensor **30**, and may deliver results in a desired format, such as display results on a user interface, send results remotely, or produce a print-out.

The volume of the second fluid may be determined by the desired volume of sample that is to be pushed through the sensing portion **440**. For example, the volume of the second fluid may be from about 100 μL to about 1000 μL. In one embodiment, the sensing sequence may be interrupted by injecting the first fluid through the first fluid port **50** again before the sample has passed all the way through the sensing portion **440**.

The method may further include controlling the temperature of the sample. For example, the sample may be heated to a predetermined temperature using electrically resistive heaters on the sample platform and/or the BAW die.

A further volume of fluid can be injected to drive the sample into the waste reservoir. The method may further include discarding the cartridge after sensing one or more parameters of the sample.

The method can be used to detect various analytes in the sample, or to detect physical characteristics of the sample. For example, the method can be used to detect proteins, DNA, bacteria, fungi, viruses, and other analytes. The sample may be a biological sample, such as urine, plasma, serum, blood, saliva, tears, sweat, or the like, or an environmental sample, such as air or other gas, water, or other aqueous solution.

All scientific and technical terms used herein have meanings commonly used in the art unless otherwise specified. The definitions provided herein are to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

As used in this specification and the appended claims, the singular forms “a”, “an”, and “the” encompass embodiments having plural referents, unless the content clearly dictates otherwise.

As used in this specification and the appended claims, the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. The term

"and/or" means one or all of the listed elements or a combination of any two or more of the listed elements.

As used herein, "have", "having", "include", "including", "comprise", "comprising" or the like are used in their open-ended sense, and generally mean "including, but not limited to." It will be understood that "consisting essentially of," "consisting of," and the like are subsumed in "comprising" and the like. As used herein, "consisting essentially of," as it relates to a composition, product, method or the like, means that the components of the composition, product, method or the like are limited to the enumerated components and any other components that do not materially affect the basic and novel characteristic(s) of the composition, product, method or the like.

The words "preferred" and "preferably" refer to embodiments of the invention that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the disclosure, including the claims.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc. or 10 or less includes 10, 9.4, 7 .6, 5, 4.3, 2.9, 1.62, 0.3, etc.). Where a range of values is "up to" a particular value, that value is included within the range.

Any direction referred to herein, such as "top," "bottom," "left," "right," "upper," "lower," and other directions and orientations are described herein for clarity in reference to the figures and are not to be limiting of an actual device or system or use of the device or system. Devices or systems as described herein may be used in a number of directions and orientations.

Those skilled in the art will recognize improvements, variations, and modifications to the exemplary embodiments of the present disclosure. All such improvements and modifications are considered within the scope of the concepts disclosed here and the claims that follow.

CLAIMS

1. A cartridge for handling and sensing a liquid sample, the cartridge comprising:
a sensor comprising a bulk acoustic wave (BAW) resonator having a sensing surface;
a sample port;
a fluid flow path from the sample port to the sensor for carrying a sample introduced into the sample port across the sensing surface of the resonator, the fluid flow path comprising:
a sample reservoir defining a proximal portion of the fluid flow path and defining an inner surface, the sample reservoir having a proximal end connected to the sample port, a proximal region adjacent the proximal end, a distal end, a distal region adjacent the distal end, and a volume extending between the proximal end and the distal end;
a sensing portion downstream of the sample reservoir and extending across the sensing surface of the resonator, wherein the sensing surface of the resonator defines at least a portion of a surface of the sensing portion;
a valve disposed between the distal end of the sample reservoir and the sensing portion;
a first fluid port;
a first fluid channel having a proximal end connected to the first fluid port and a distal end connected to the distal region of the sample reservoir;
a second fluid port; and
a second fluid channel having a proximal end connected to the second fluid port and a distal end connected to the proximal region of the sample reservoir.

2. The cartridge of claim 1, wherein the valve is disposed at the distal end of the sample reservoir.

3. The cartridge of claim 1 or claim 2, wherein the valve comprises a hydrophobic valve.

4. The cartridge of any one of claims 1 to 3, wherein the valve comprises a hydrophobic coating of the fluid flow path.

5. The cartridge of any one of claims 1 to 4, wherein the sensor comprises a second BAW resonator having a sensing surface, wherein the sensing surface of the second resonator defines at least a portion of the surface of the sensing portion of the flow path.

6. The cartridge of any one of claims 1 to 5, wherein the volume of the sample reservoir is from about 1 μL to about 20 μL.

7. The cartridge of any one of claims 1 to 6, wherein the sample reservoir volume is defined by walls having a hydrophilic surface.

8. The cartridge of claim 7, wherein the walls comprise a hydrophilic coating.

9. The cartridge of any one of claims 1 to 8, wherein the first fluid port and the second fluid port are constructed to couple with an external pump.

10. The cartridge any one of claims 1 to 9, wherein the first fluid port and the second fluid port are constructed to couple with an external fluid reservoir.

11. The cartridge of any one of claims 1 to 10, wherein the first fluid port and the second fluid port comprise a first valve and a second valve, respectively.

12. The cartridge of any one of claims 1 to 11, wherein the fluid flow path comprises a mixing region downstream of the sample reservoir.

13. The cartridge of claim 12, wherein the mixing region comprises one or more static features constructed to induce mixing in the fluid flow path.

14. The cartridge of claim 13, wherein the one or more static features comprise a protrusion narrowing an inside diameter of the fluid flow path.

15. The cartridge of any one of claims 1 to 14, wherein the first and second fluid channels are microfluidic channels.

16. The cartridge of any one of claims 1 to 15, wherein the sensing portion of the fluid flow path is a microfluidic channel.

17. The cartridge of any one of claims 1 to 16, wherein the sample port comprises a closure.

18. A method of sample handling and sensing using a cartridge,
the cartridge comprising:
a sample port connected to a sample reservoir having a proximal end, a proximal region adjacent the proximal end, and a distal end opposite of the proximal end;
a first fluid port connected to the sample reservoir in the distal region via a first fluid channel;
a second fluid port connected to the sample reservoir in the proximal region via a second fluid channel;
a sensor platform comprising a bulk acoustic wave (BAW) resonator and a fluid flow path comprising a sensing region extending across a sensing surface of the BAW resonator; and
a fluid valve between the distal end of the sample reservoir and the sensing region;
the method comprising:
applying a sample to the sample port;
injecting a first volume of fluid through the first fluid port; and
then injecting a second volume of fluid through the second fluid port to drive the sample into the sensing region of the fluid flow path.

19. The method of claim 18, wherein the first volume of fluid comprises a buffer.

20. The method of claim 18 or 19, wherein the second volume of fluid comprises a buffer or a gas.

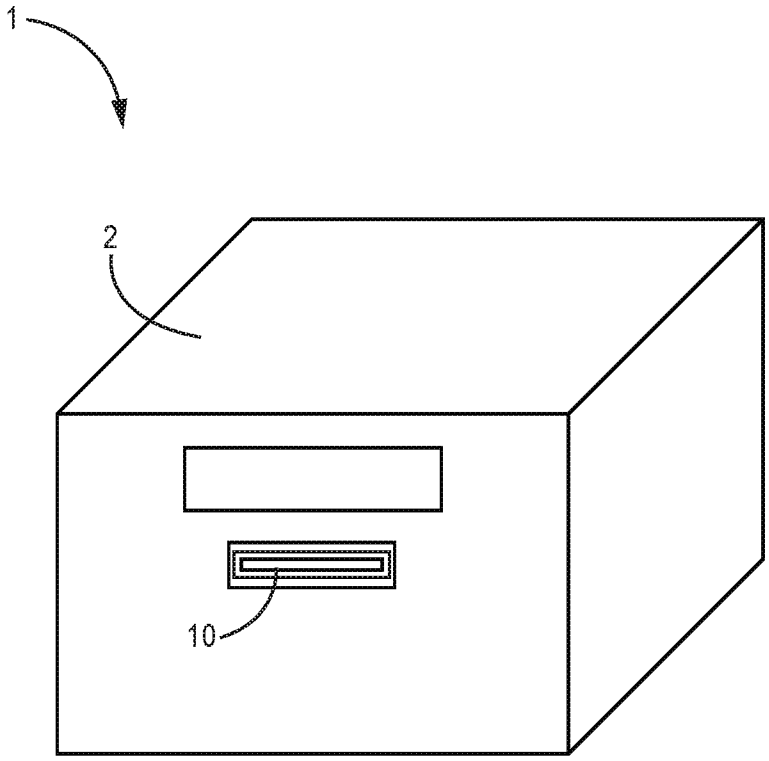

FIG. 1

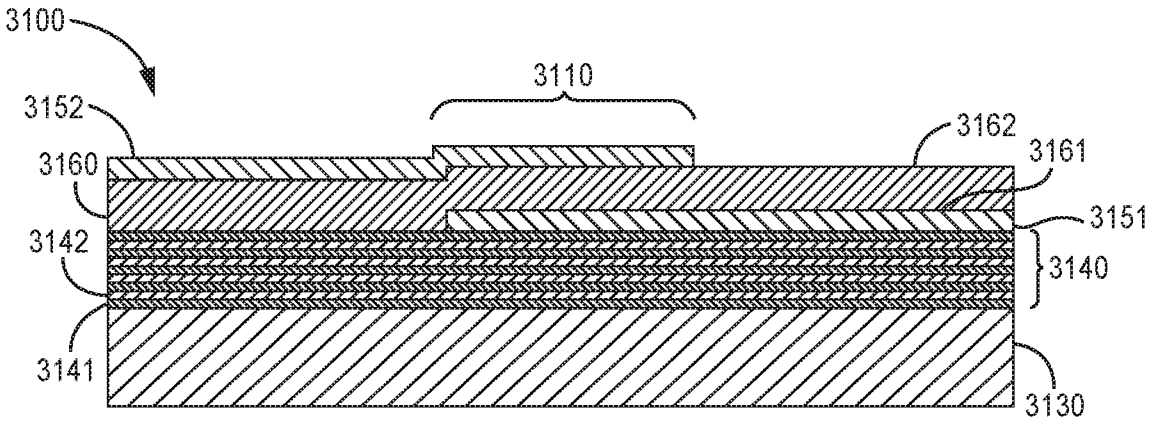
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FIG. 2A

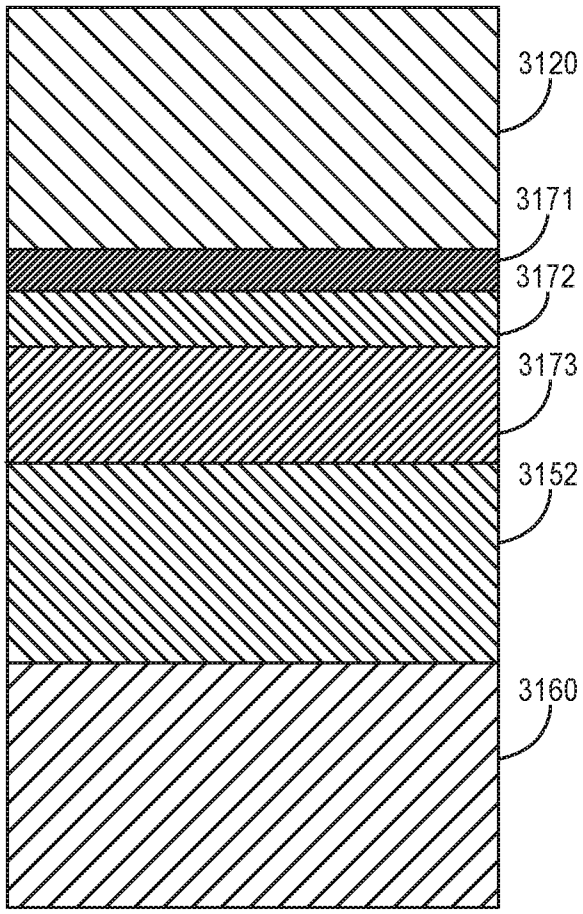
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FIG. 2B

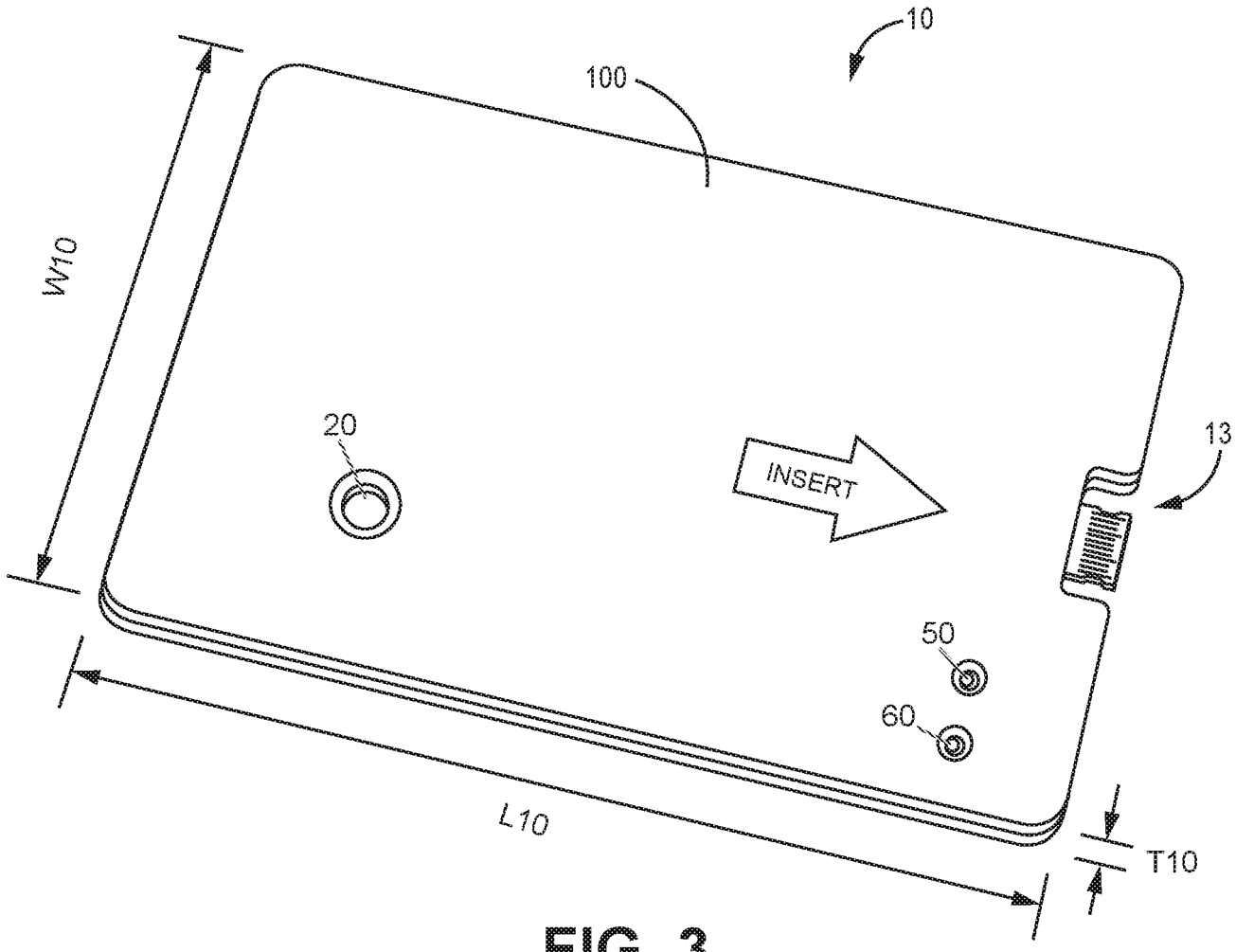
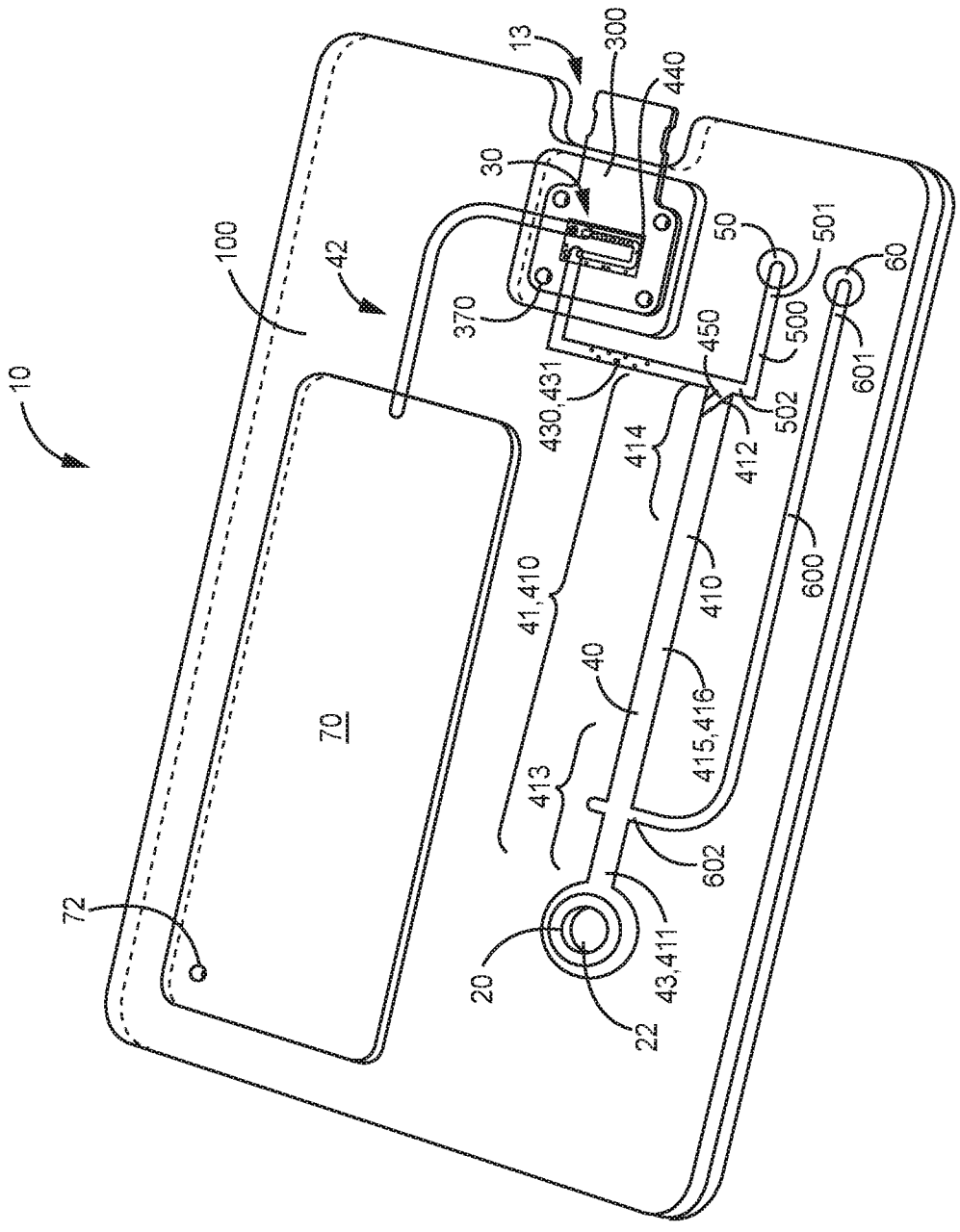


FIG. 3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100
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13
300
440
30
370
50
501
60
500
601
450
430,431
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410
600
40
415,416
413
602
72
70
20
43,411
22

FIG. 4

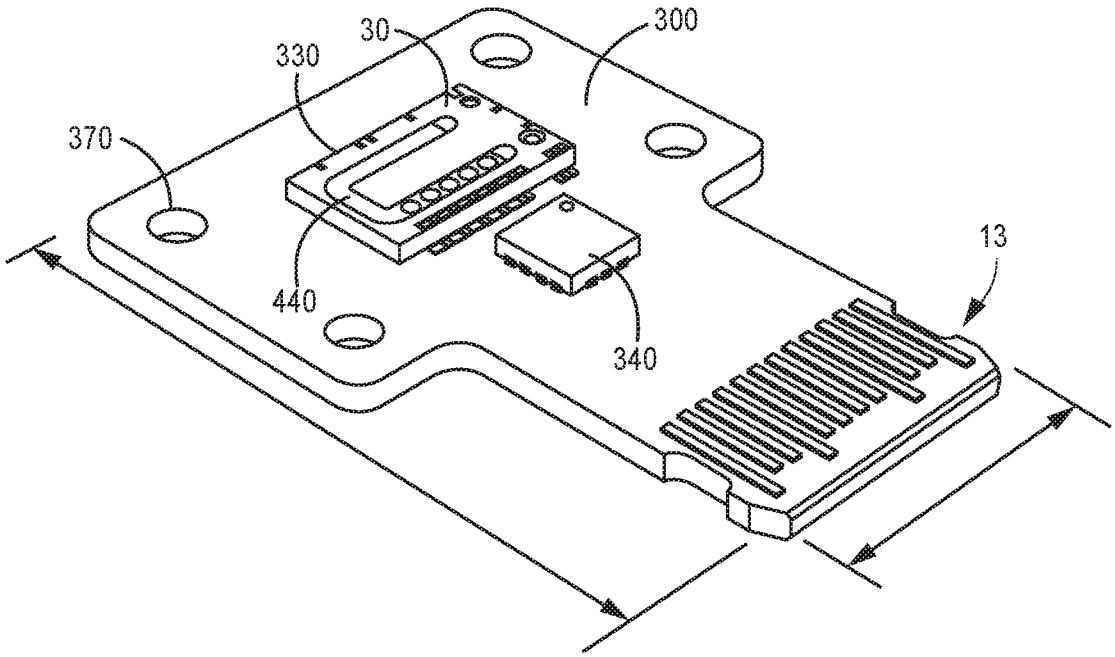

FIG. 5A

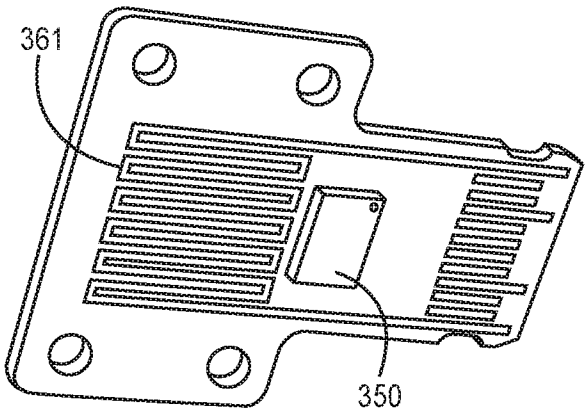

FIG. 5B

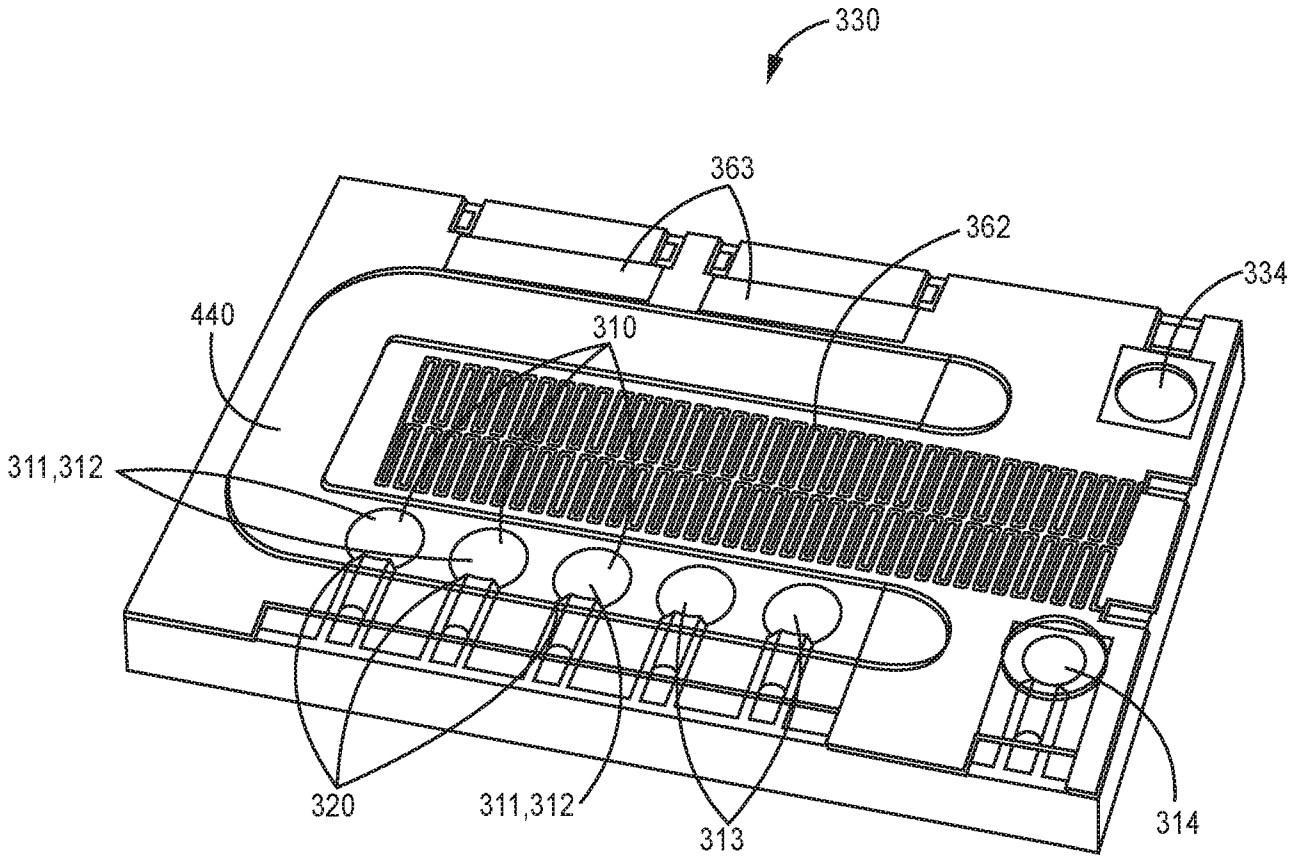

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/043992

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 29/02; G01N 27/00; G01N 29/036; G01N 29/22; G01N 33/543; H03H 9/17 (2017.01)
CPC - G01N 29/022; G01N 2291/0256; G01N 29/036; G01N 33/54373; G01N 2291/0255; G01N 2291/0426 (2017.08)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 310/365; 333/187; 422/69; 435/287.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2006/0216812 A1 (OKADA et al) 28 September 2006 (28.09.2006) entire document	1-3, 18-20
Y	US 20120164753 A1 (JOHNSTON et al) 28 June 2012 (28.06.2012) entire document	1-3, 18-20
A	US 7,943,388 B2 (BAETZOLD et al) 17 May 2011 (17.05.2011) entire document	1-3, 18-20
A	US 7,473,551 B2 (WARTHOE) 06 January 2009 (06.01.2009) entire document	1-3, 18-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2017	06 OCT 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/043992

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.