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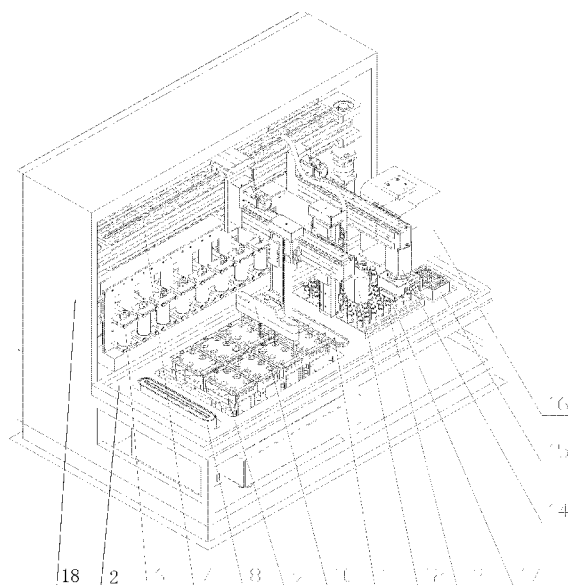
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(54) Title: SYSTEM FOR EXTRACTING BIOMOLECULES FROM A SAMPLE AND RELATED METHODS

FIG. 1



(57) Abstract: An automated system for isolating biomolecules from a biological sample is described herein. Further described are methods for operating such systems. Also described are components of the automated system, such as a liquid handling system, a robotic arm, sample tube racks, an analytical instrument, a barcode reader, and sample processing modules, which can include a shaker, a magnetic bead biomolecule isolation system, an endotoxin control system, a heated incubator, or a chilled incubator.

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SYSTEM FOR EXTRACTING BIOMOLECULES FROM A SAMPLE AND RELATED METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of International patent application PCT/CN2018/083155, filed April 16, 2018, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to automated sample processing systems and components thereof, including liquid handling systems, sample tube racks adapted to be used with liquid handling systems, and magnetic bead isolation systems, as well as methods of use thereof.

BACKGROUND

[0003] Automated systems have been previously used for isolating nucleic acids in biological samples. Such systems allow for increased efficiency and quality control compared to manual benchtop isolation techniques. The automated system sold under the trade name QIAasymphony® SP system from QIAGEN is an exemplary system that automatically processes biological samples for nucleic acid isolation. The automated systems generally utilize a liquid handling system and bead isolation technology to mix reagents with the biological sample, remove non-target components from the sample, and isolate the target biomolecules.

[0004] Despite the benefits of known automated systems for isolating biomolecules from a biological sample, such systems frequently suffer from incomplete biomolecule recover and cross-contamination, have limited sample processing throughput, and are generally limited to processing quite small sample volumes. These deficiencies can result in inaccurate diagnostic assays or poor research results. There continues to be a need in the art for the development of automated systems for isolating biomolecules from a sample with increased quantity and quality of biomolecule recovery, increased sample processing throughput, processing of larger sample volumes, and limited cross-contamination.

[0005] The disclosures of all publications, patents, and patent applications referred to herein are each hereby incorporated by reference in their entireties. To the extent that any reference incorporated by reference conflicts with the instant disclosure, the instant disclosure shall control.

SUMMARY OF THE INVENTION

[0006] An automated system for isolating biomolecules from a biological sample is described herein. Also described are components of the automated system, such as a liquid handling system and/or a biomolecule isolation system, which may employ one or more magnets. Further described are methods for operating such systems.

[0007] In some embodiments, the liquid handling system comprises: at least one pipette system, comprising: a multiple-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; and a pump fluidly connected to the control valve. The multiple-channel pipette can have two or more (e.g., three, four, five, or more) channels. In some embodiments, the multiple-channel pipette is a dual-channel pipette.

[0008] In some embodiments, the second channel of the multiple-channel pipette passes through and parallel to the first channel of the multiple-channel pipette. In some embodiments, the second channel of the multiple-channel pipette is adjacent to the first channel of the multiple-channel pipette.

[0009] In some embodiments, the second liquid port comprises a concave cutout.

[0010] In some embodiments, the first liquid port is configured to spray liquid onto an inner wall of a container.

[0011] In some embodiments, at least a portion of the pipette is coated with a hydrophobic layer.

[0012] In some embodiments, the second channel is fluidly connected to a liquid storage loop positioned between the multiple-channel pipette and the control valve. In some embodiments, the liquid storage loop has a liquid storage capacity of about 2 mL or more.

[0013] In some embodiments, the liquid handling system comprises a liquid waste management system connected to the second channel of the multiple-channel pipette. In some

embodiments, the liquid handling system comprises a valve between the second channel of the multiple-channel pipette and the liquid waste management system.

[0014] In some embodiments, the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid pump fluidly connected to a wash liquid container.

[0015] In some embodiments, the liquid handling system comprises a plurality of reagent tanks fluidly connected to a reagent valve configured to select a reagent from the plurality of reagent tanks, wherein the reagent valve is fluidly connected to the control valve.

[0016] In some embodiments, the support structure is attached to a robotic arm. In some embodiments, the robotic arm is configured to move at least in the direction of the vertical axis.

[0017] In some embodiments, the multiple-channel pipette is attached to a support block, and wherein the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette. In some embodiments, the liquid handling system comprises a plurality of pipette systems, wherein each pipette system comprises a multiple-channel pipette attached to the support block. In some embodiments, the elastic mechanism comprises two or more springs and two or more guide mechanisms.

[0018] In some embodiments, the liquid handling system further comprises a pipette cleaning system comprising a container having an open top and at least one cleaning tube vertically positioned within the container. In some embodiments, the cleaning tube is sized and shaped to receive the multiple-channel pipette. In some embodiments, the container comprises a bottom comprising a drain.

[0019] Also provided herein is a method of operating the liquid handling system described above, comprising drawing liquid into the pipette through the second liquid port. In some embodiments, the method comprises lowering the pipette into a sample tube comprising the liquid. In some embodiments, the method comprises contacting the pipette to the bottom of the sample tube. In some embodiments, the liquid comprises magnetic beads. In some embodiments, the liquid comprises a target biomolecule. In some embodiments, the liquid is stored in a liquid storage loop. In some embodiments, the method comprises dispensing the liquid through the second liquid port.

[0020] Further provided herein is a method of operating the liquid handling system described above, further comprising spraying a liquid from the first liquid port onto an inner wall of a

container. In some embodiments, the method comprises washing beads off of the inner wall of the container using the sprayed liquid. In some embodiments, the beads are magnetic beads.

[0021] Also provided herein is an automated system for isolating biomolecules from a sample, comprising the liquid handling system described above, further comprising one or more of a magnetic bead regeneration system, a second liquid handling system, a shaker, a sample tube rack, a biomolecule isolation system, a magnetic bead regeneration system, a cold-storage unit, a barcode reader, or an analytical instrument.

[0022] Further provided herein is an automated system for isolating biomolecules from a biological sample, comprising (a) a liquid handling system comprising a pipette operable to move in at least a vertical axis; (b) a sample tube rack; and (c) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube.

[0023] In some embodiments of the automated system, the sealable port comprises two or more connected slits. In some embodiments, the sealable port comprises an elastomer or rubber.

[0024] In some embodiments of the automated system, the sample tube rack comprises a base that fits into a sample tube rack mount attached to a surface. In some embodiments, the base comprises a groove or a protrusion, and the receiving block comprises a complementary groove or protrusion. In some embodiments, the surface is part of a biomolecule isolation system comprising a magnet configurable in an active configuration and an inactive configuration, wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.

[0025] In some embodiments of the automated system, the system further comprises one or more of a magnetic bead regeneration system, a shaker, a magnetic bead isolation system, a pipette cleaning system, a cold-storage unit, a barcode reader, or an analytical instrument.

[0026] Also provided herein is an automated system for isolating biomolecules from a biological sample, comprising: (a) a first liquid handling system, comprising at least one pipette

system, comprising (i) a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; (ii) a control valve that controls liquid flow through the first channel or the second channel of the pipette; and (iii) a pump fluidly connected to the control valve; (b) a second liquid handling system comprising at least one pipette, wherein the second liquid handling system is configured to handle liquid volumes smaller than the first liquid handling system; (c) a sample tube rack; (d) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of a pipette from the first liquid handling system or the second liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube; and (e) a biomolecule isolation system configured to bond magnetic beads to the side of a sample tube through a magnetic field in an active configuration.

[0027] In some embodiments of the automated system, the biomolecule isolation system is operable to configure a magnet in an active configuration and an inactive configuration, wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.

[0028] In some embodiments, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector.

[0029] In some embodiments of the automated system, the system is contained within a housing. In some embodiments, the housing is sealed. In some embodiments, the housing comprises a sterilization system. In some embodiments, the sterilization system comprises an air filter or an ultraviolet light.

[0030] In some embodiments of the automated system, the automated system is operated using a computer system.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] FIG. 1 illustrates an exemplary automated system for isolating biomolecules. FIG. 1A shows a zoomed-in view of the robotic arms of the system illustrated in FIG. 1.

[0032] FIG. 2 illustrates an exemplary consumable transfer system that can be used with the automated system.

[0033] FIG. 3 illustrates an exemplary incubator, which can be heated or chilled, which can be used with the automated system.

[0034] FIG. 4 illustrates an exemplary automated system enclosed in an exemplary housing.

[0035] FIG. 5 illustrates an exemplary biomolecule isolation system that can be used with the automated system.

[0036] FIG. 6 illustrates an exemplary sample tube rack that can be used with the biomolecule isolation system.

[0037] FIG. 7 illustrates an exemplary magnetic bead regeneration system the can be used with the automated system.

[0038] FIG. 8A and FIG. 8B illustrates an embodiment of the dispensing region of the dual-channel pipette, with FIG. 8A showing a perspective image and FIG. 8B showing a profile image. FIG. 8C shows a cross-sectional view of the dual-channel pipette, showing the second channel passing through the first channel. FIG. 8D shows a cross-sectional view of the dual-channel pipette from the line marked "A-A" in FIG. 8C.

[0039] FIG. 9A illustrates a schematic for an exemplary liquid handling system that can be used with the automated system equipped with a single dual-channel pipette. FIG. 9B shows a schematic for a liquid handling system with a similar configuration applied to a liquid handling system comprising a plurality of dual-channel pipettes.

[0040] FIG. 10A illustrates an exemplary liquid handling system attached to the robotic arm, and FIG. 10B illustrates the support structure connected to a plurality of pipettes in detail.

[0041] FIG. 11A and FIG. 11B illustrate an exemplary small volume liquid handling system.

[0042] FIG. 12 illustrates a schematic of an exemplary setup of the small volume liquid handling system.

[0043] FIG. 13 illustrates a schematic of an exemplary large volume liquid handling system integrated with a small volume liquid handling system.

[0044] FIG. 14A illustrates an exemplary pipette cleaning system, and FIG. 14B illustrates a cross-sectional view of the pipette cleaning system shown in FIG. 14A.

[0045] FIG. 15 illustrates an exemplary rack that can be used for a sample input module and/or sample output module.

[0046] FIG. 16 depicts an exemplary computer system configured to operate the automated system described herein or perform any one of the processes described herein.

[0047] FIG. 17A showing an alignment view illustrates an embodiment of an exemplary dual-channel pipette. FIG. 17B shows a perspective image of the dispensing region of an exemplary dual-channel pipette of the liquid handling system. FIG. 17C shows a cross-section of an exemplary dual-channel pipette viewed upward.

DETAILED DESCRIPTION OF THE INVENTION

[0048] Described herein is an automated system for isolating biomolecules from a biological sample, as well as methods for operating such systems. The automated system can include a liquid handling system, a robotic arm, one or more sample tube racks, and/or sample processing modules (for example, a shaker, a magnetic bead biomolecule isolation system, an endotoxin control system, a heated incubator, and/or a chilled incubator). Optionally, the automated system can include a barcode reader, which can be used to track samples in the system, or an analytical instrument, such as an optical detector for analyzing the samples.

[0049] Further described is a liquid handling system, which can be a component of the automated system. The liquid handling system can include at least one multiple-channel pipette attached to a liquid handling system support structure. The multiple-channel pipette can have two or more (e.g., three, four, five, or more) channels. In some embodiments, the multiple-channel pipette is a dual-channel pipette. The multiple-channel pipette includes a dispensing region with a first liquid port on the side of the dispensing region, and a second liquid port at a tip of the dispensing region. In some embodiments, the multiple-channel pipette further includes additional channels (e.g., a third channel and/or a fourth channel), which can also be used to disperse and/or withdraw liquids. For example, there can be two or more channels for dispersing liquids and/or two or more channels for withdrawing liquids in a multiple-channel pipette. The liquid handling system includes a valve that controls liquid flow through the first channel or the second channel. Liquid that flows through the first channel is dispensed through the first liquid

port on the side of the dispensing region of the pipette, which causes the liquid to spray sideward. The sideward spray of the liquid allows the liquid to wash an inner wall of a container, for example to detach beads that may be stuck to the side of a sample tube. The second liquid port may be larger than the first liquid port, and can be used to withdraw or dispense larger liquid volumes. In some embodiments, the second liquid port includes a concave cutout. A valve, which may be automatically operated by a computer system, controls liquid flow through the first channel of the pipette or the second channel of the pipette.

[0050] Some embodiments of the liquid handling system include one or more single channel pipettes in place of or in addition to a multiple-channel pipette (e.g., a dual-channel pipette or a pipette with three or more channels). In a single-channel pipette, the same channel can be used to dispense liquid and/or withdraw liquid.

[0051] The automated system can include a sample tube rack and one or more covers configured to fit over one or more sample tubes contained within the sample tube rack. The one or more covers allow the liquid handling system to access the inside of the sample tube without substantially exposing the contents of the sample tube to an outside environment, thereby limiting cross-contamination of the sample tube contents. The cover or covers include a sealable port above each of the sample tubes contained within the rack that allows passage of the pipette from the liquid handling system through the sealable port into the sample tube. When the pipette is withdrawn from the sample tube, the sealable port is sealed. In some embodiments, the cover is configured to cover a plurality of sample tubes, and is optionally attached to the sample tube rack, for example by a hinge.

Definitions

[0052] As used herein, the singular forms “a,” “an,” and “the” include the plural reference unless the context clearly dictates otherwise.

[0053] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[0054] It is understood that aspects and variations of the invention described herein include “consisting” and/or “consisting essentially of” aspects and variations.

[0055] Where a range of values is provided, it is to be understood that each intervening value between the upper and lower limit of that range, and any other stated or intervening value in that stated range, is encompassed within the scope of the present disclosure. Where the stated range includes upper or lower limits, ranges excluding either of those included limits are also included in the present disclosure.

[0056] It is to be understood that one, some or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Automated System

[0057] FIG. 1 illustrates an exemplary automated system for isolating biomolecules. System components can be mounted on a work platform 2 or within a hutch 18 positioned behind the work platform 2. The hutch 18 can store components that do not actively engage in sample processing, such as reagent tanks 6, extra sample tubes or multi-well plates, or structural support for one or more robotic arms 7. The automated system includes a liquid handling system 10, and optionally a second liquid handling system 12, each of which may be connected to a robotic arm 7. The automated system can also include a biomolecule isolation system 9, which can be used to separate target biomolecules from the source sample, for example by using magnetic bead affinity purification, and a magnetic bead regeneration system 8. A sample input/output module 13 can be disposed on the work platform 2, which can receive sample obtained from a subject, or can receive biomolecules isolated by the automated system for retrieval by a user. In some embodiments of the automated system, the system includes an additional robotic arm that can transfer system consumables, such as multi-well plates or sample tubes, which may be transferred individually or in a group contained within a sample tube rack. A barcode reader 17 can optionally be included in the automated system, which can scan a barcode or other identifier on sample tubes to track the location of the samples or consumables within the system. In some embodiments, the automated system includes an analytical instrument 16, which can analyze biomolecules isolated by the system.

[0058] The robotic arms can maneuver systems components attached to the arm in two or three dimensions, depending on the arrangement of the other components in the system. In the

automated system shown in FIG. 1, the robotic arms 7 maneuver a first liquid handling system 10, a second liquid handling system 12, and a consumable transfer system 14 in three dimensions. FIG. 1A shows a zoomed-in view of the robotic arms of the system illustrated in FIG. 1. The robotic arm can include a lateral track, which allows for movement of the component at the end of the robotic arm to move along the length of the system, and a depth track attached to the lateral track, which allows for movement of the component along the depth of the system. The component can be directly attached to a vertical track, which connects to the depth track. Robotic arms can have shared tracks or separate tracks. In some embodiments, the robotic arm allows for rotational movement, for example at the connection of the robotic arm to the system component. As shown in FIG. 1A the lateral track 24 is positioned in the hutch behind the work platform, and is elevated above the work platform. In the illustrated example, two depth track 19 and 20 share the same lateral track 24. To move along the length of the system, the depth track 19 and 20 can independently travel along the lateral track 24. In some embodiments, each depth track is connected to a separate lateral track. Depth track 19 is connected to a first vertical track 21 connected to a first liquid handling system 10, and a second vertical track 22 connected to a second liquid handling system 12. Vertical track 21 and vertical track 22 can independently travel along depth track 19 to move in the depth dimension of the system. Liquid handling system 10 can move vertically by adjusting vertical track 21, and liquid handling system can independently move vertically by adjusting vertical track 22. Depth track 20 is connected to a consumable transfer system 23. The consumable transfer system 23 can travel along the depth track 20 to move in a depth dimension, and the depth track 20 can travel along the lateral track 24 to move along the length of the system. Consumable transfer system 23 can also have one or two axes of rotation, which allow greater maneuverability of the consumable transfer system 23. The consumable transfer system 23 is configured to transport consumables, such as plates or sample tubes in the system, and may include movable fingers that are operable to handle and transport consumables, for example from a consumable storage to a desired location within in the system. The robotic arms shown in the system in FIG. 1A is exemplary, and other robotic arms that can be used with an automated system are known in the art.

[0059] FIG. 2 illustrates an exemplary consumable transfer system. The consumable transfer system includes a body 24, which houses an operation system 25 that controls fingers 26. The operation system 25 can operate the fingers 26 between a closed configuration, wherein the

figures are spaced to grip a consumable such as a multi-well plate or a sample tube, and an open configuration, wherein the fingers are spaced to release the consumable. The operation system 25 can include a power system, such as a hydraulic cylinder, a gas cylinder, or an electric motor, which can power movement of the fingers 26. The operation system 25 can also include a guiding component, such as a linear guide rail, guide shaft, or guide sleeve, which can align the directional movement of the fingers 26. The consumable transfer system further includes a bearing 27 and a rotation control mechanism 28, which can rotate the body 24. In some embodiments, the body can rotate between about 0° and about 270°.

[0060] The automated system can optionally include a sample tracking device, which may be, for example, a barcode scanner or radiofrequency identification (RFID) scanner. In some embodiments, the sample tracking device is connected to the consumable transfer system, for example in FIG. 2, the sample tracking device 17 is connected to the body 24 of the consumable transfer system. Sample tubes can be tagged with a barcode or RFID tag, and the sample tracking device can scan the tag to track the position of the sample within the system. The tracked position can be transmitted to computer system that operates the automated system.

[0061] The system can include a sample input module and a sample output module. In some embodiments, the sample input module and the sample output module are the same module. The sample input module and the sample output module are configured for holding sample tubes. Input biological samples, for example saliva, urine, stool, or blood samples, contained in sample tubes are placed in the sample input module. Such biological samples can be used by the system to isolate biomolecules, such as nucleic acids, proteins, and/or antibodies. In some embodiments, the sample tubes are contained within a sample tube rack. A cover with one or more sealable ports can cover the sample tubes, which allow the sample to be accessed by a liquid handling module while remaining sealed when the liquid handling module is not accessing the contents of the sample tube. The cover can be an individual cap for the sample tube, or can be a joined cover comprising a sealable port for each sample tube in the sample tube rack. During processing of the sample, the robotic arm can position a liquid handling system over the sample tube containing the biological sample, and a pipette can be lowered to access the biological sample in the sample tube. Reagents can be added to the sample and/or the sample can be drawn into the pipette for transport to another location of the system, such as a sample processing tube. Once the target biomolecule has been isolated by the automated system, the composition

containing the target biomolecule can be dispensed in a sample tube in the sample output module. Once the sample is in a sample tube in the sample output module, the sample can be retrieved by a user for further process, or may be analyzed using an analytical instrument. For example, a liquid handling system may draw a sample from the sample processing tube in the sample output module and dispense the sample in a multi-well plate. The multi-well plate can be transported to an analytical instrument, for example using the consumable transfer system attached to a robotic arm.

[0062] Exemplary analytical instruments that may be used with the automated system include, but are not limited to, a fluorometer, an optical detector, a mass spectrometer, a calorimeter, or a nucleic acid sequencer. Other analytical instruments that can be used with the automated system are known. The analytical instrument may be used, for example, to determine a biomolecule (e.g., protein or nucleic acid) concentration, an antibody titer, a nucleic acid sequence, or the presence or amount of one or more analytes.

[0063] The sample input and/or output module is configured to hold a plurality of sample tubes, such about 6 or more, about 12 or more, about 24 or more, about 48 or more, about 96 or more, or about 192 or more sample tubes. In some embodiments, the input module and/or output module comprises a chiller, and can cool the sample tube to about 0 °C to about 20 °C, such as about 0 °C to about 4 °C, about 4 °C to about 10 °C, about 10 °C to about 15 °C, or about 15 °C to about 20 °C. In some embodiments, the input module and/or output module comprises an insulating block, which resists heating of the sample tubes. The input module and/or output module can optionally be configured to lift and/or laterally move a sample tube or a row of sample tubes. The sample tubes may be lifted or moved, for example so that the sample tube tag (e.g., RFID or barcode) can be read by the tracking device. In some embodiments, the input module and/or the output module comprises a lift system, which can include a drive system (such as an electric motor, a hydraulic cylinder, or a gas cylinder) and a guide (such as a guide rail, guide shaft, or guide sleeve). The lift system can be operated to lift the sample tube or row of sample tubes. In some embodiments, the input module and/or output module comprises a lateral transporter, which can transport sample tubes or a row of sample tubes laterally. The lateral transporter can include a drive system (such as an electric motor, a hydraulic cylinder, or a gas cylinder) and a guide (such as a guide rail, guide shaft, or guide sleeve).

[0064] FIG. 15 illustrates an exemplary rack that can be used for a sample input module and/or sample output module. The rack is configured to hold one or more sample tubes 127, which may be arranged in rows and/or columns. The rack includes a chiller 128, which chills the sample tubes in the module. The module further includes a lift system 129, which includes a drive system 129a and a guide 129b that allows the sample tubes to be moved in a vertical dimension. The module also includes a lateral transport system 130 for horizontal movement of the sample tubes, which includes a drive system 130a and a guide rail 130b.

[0065] In some embodiments, the automated system includes a heated incubator and/or a chilled incubator. Sample tubes may be placed in the heated or chilled incubator before, during or after processing. For example, in some embodiments the sample input module and/or the sample output module are chilled. In some embodiments, a heated incubator may be used to pretreat the biological sample. In some embodiments, the heated incubator is heated to a temperature of about 25 °C to about 100 °C, such as about 25 °C to about 30 °C, about 30 °C to about 37 °C, about 37 °C to about 42 °C, about 42 °C to about 60 °C, about 60 °C to about 80 °C, or about 80 °C to about 100 °C. In some embodiments, the chilled incubator is chilled to a temperature of about -20 °C to about 20 °C, such as about -20 °C to about -10 °C, about -10 °C to about 0 °C, about 0 °C to about 10 °C, or about 10 °C to about 20 °C. FIG. 3 illustrates an exemplary incubator, which can be heated or chilled. The incubator includes a base 29, which can be secured to the work platform of the system, and a temperature control unit 30, which can be heated or chilled. The temperature control unit 30 includes a plurality of receptacles, which can receive sample tubes or mini tubes.

[0066] In some embodiments, the automated system includes a shaker, rocker, or other mixing device. Sample tubes may be placed on the shaker, rocker or other mixing device using the consumable transfer system during sample processing. In some embodiments, the shaker, rocker, or other mixing device is configured to hold one or more individual sample tubes, or to hold a sample tube rack, which may hold one or more sample tubes.

[0067] Contamination of samples processed by the system can be limited by including a housing that encloses the system. The system may further include one or more additional anti-contamination features, such as a UV light for sterilization and/or an air filtration system. The automated system can be enclosed in a housing, for example as shown in FIG. 4. The housing protects the samples and components of the system from outside sources of contamination. The

housing can include a door 3, which can be opened by a user to place samples in the sample input module, remove samples from the sample output module, add or replace consumables, or otherwise maintain the system. The door 3 can include a window, which allows a user to observe operation of the system. The housing further includes a housing top 4 and sidewalls 31, which can optionally include a window 32. In some embodiments, can include an air filtration system 5, which may be disposed on the top 4 of the housing, a sidewall 31 of the housing, or any other suitable location. Optionally, the air filtration system 5 maintains a positive pressure within the housing. In some embodiments, the automated system includes a UV light, which can be used to sterilize surfaces on the system to avoid cross contamination. In some embodiments, the UV light is positioned on an inner surface of the housing, such as the inner surface of the housing top 4 or the inner surface of the sidewall 31. In some embodiments, the system is positioned on a base unit 1, which can optionally include castors 33. Other methods for limiting cross-contamination or removing endotoxins are described herein, such as a cover for a sample tube that includes a sealable port.

[0068] In some embodiments, the automated system for isolating biomolecules from a biological sample comprises a liquid handling system, the liquid handling system comprising (a) at least one pipette system, comprising a multiple-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; (b) a control valve that controls liquid flow through the first channel or the second channel of the pipette; and (c) a pump fluidly connected to the control valve. In some embodiments, the multiple-channel pipette is a dual-channel pipette. In some embodiments, the multiple-channel pipette has three or more (e.g., three, four, five, or more) channels. It is also contemplated in the present application that, in certain embodiments, the pipette system described herein comprises a single-channel pipette. The liquid handling system comprising such a pipette system can accommodate relatively large or small sample volumes.

[0069] In some embodiments, the automated system for isolating biomolecules from a biological sample comprises a liquid handling system, the liquid handling system comprising at least one pipette system, comprising a single-channel pipette comprising an upper region

attached to a support structure, and a lower dispensing region. In some embodiments, the single-channel pipette may be configured to both dispense liquids and withdraw liquids.

[0070] In some embodiments, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector. In some embodiments, the automated system is contained within a housing, which optionally includes a sterilization system (such as a UV light and/or an air filter). In some embodiments, the automated system is operated using a computer system.

[0071] In some embodiments, the automated system for isolating biomolecules from a biological sample comprises (a) a liquid handling system, comprising (i) at least one pipette system, comprising: a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; (ii) a control valve that controls liquid flow through the first channel or the second channel of the pipette; and (iii) a pump fluidly connected to the control valve; (b) a sample tube rack; and (c) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the cover comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette from the liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube. In some embodiments, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector. In some embodiments, the automated system is contained within a housing, which optionally includes a sterilization system (such as a UV light and/or an air filter). In some embodiments, the automated system is operated using a computer system.

[0072] In some embodiments, the automated system for isolating biomolecules from a biological sample comprises (a) a liquid handling system, comprising (i) at least one pipette system, comprising: a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; (ii) a control valve that controls liquid flow through the first channel or the second channel of the

pipette; and (iii) a pump fluidly connected to the control valve; (b) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the cover comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette from the liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube; and (c) a biomolecule isolation system configured to bond magnetic beads to the side of a sample tube through a magnetic field in an active configuration. In some embodiments, the biomolecule isolation system is operable to configure a magnet in an active configuration and an inactive configuration, wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration. Optionally, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector. In some embodiments, the automated system is contained within a housing, which optionally includes a sterilization system (such as a UV light and/or an air filter). In some embodiments, the automated system is operated using a computer system.

[0073] In some embodiments, the automated system for isolating biomolecules from a biological sample comprises (a) a first liquid handling system, comprising at least one pipette system, comprising: (i) a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; (ii) a control valve that controls liquid flow through the first channel or the second channel of the pipette; and (iii) a pump fluidly connected to the control valve; (b) a second liquid handling system comprising at least one pipette, wherein the second liquid handling system is configured to handle liquid volumes smaller than the first liquid handling system; (c) a sample tube rack; (d) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the cover comprising a sealable port above each of the one or more sample tubes that allows passage of a pipette from the first liquid handling

system or the second liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube; and (e) a biomolecule isolation system configured to bond magnetic beads to the side of a sample tube through a magnetic field in an active configuration. In some embodiments, the biomolecule isolation system is operable to configure a magnet in an active configuration and an inactive configuration, wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration. Optionally, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector. In some embodiments, the automated system is contained within a housing, which optionally includes a sterilization system (such as a UV light and/or an air filter). In some embodiments, the automated system is operated using a computer system.

Biomolecule Isolation System and Magnetic Bead Regeneration

[0074] The automated system can isolate target biomolecules, such as proteins, antibodies, or nucleic acids (such as DNA or RNA), depending on the reagents used in the system. Bead separation technology can be used to bind target biomolecules to beads, and separate the target biomolecules bound to the beads from other biological sample components to isolate the target biomolecule. In some embodiments, the automated system includes a bead regeneration system, which allows for continuous reuse of the beads in the automated system. Beads, which may be coated with an affinity molecule (such as an oligonucleotide, an antigen, or an antibody) or charged to provide electrostatic affinity, are mixed with a sample, and target biomolecules bind to the beads.

[0075] In some embodiments, the beads are magnetic. Once bound to the target biomolecule, the magnetic beads can be separated from the remaining sample component liquid in a sample using a biomolecule isolation system. The biomolecule isolation system is configured to selectively apply a magnetic field to the sample tube, which pulls the magnetic beads bound to the target biomolecule to the inner wall of the sample tube. Liquid is withdrawn from the sample

tube using a liquid handling system, leaving the magnetic beads attached to the sample tube walls. The magnetic beads can be washed using the liquid handling system, and the magnetic field can be removed from the sample tube, thereby releasing the magnetic beads. In some embodiments, the liquid handling system washes beads stuck to the walls of the sample tube, thereby suspending them in liquid.

[0076] The biomolecule isolation system can comprise one or more magnets that can be configured in an active configuration that applies a magnetic field to one or more sample tubes, and an inactive position that does not apply a magnetic field to the one or more sample tubes. In some embodiments, the magnetic is a permanent magnet. A permanent magnet can be configured in an active configuration by positioning the permanent magnet adjacent to the one or more sample tubes, and can be configured in an inactive configuration by moving the permanent magnet away from the one or more sample tubes. In some embodiments, the magnet is a transient magnet, for example by applying an electric current to the transient to produce a magnetic field in the active configuration, and stopping the electric current to turn off the magnetic field in the inactive configuration. The magnets should be positioned close to the sample tubes, for example within about 5 mm of the sample tubes. In some embodiments, the magnets are positioned within about 5 mm, about 4 mm, about 3 mm, about 2 mm, or about 1 mm of the sample tubes. In some embodiments, the magnets are positioned about 0.5 mm to about 5 mm from the sample tubes.

[0077] The biomolecule isolation system can accommodate relatively large sample tubes and sample volumes in the sample tubes. In some embodiments, the volume of the sample tube used with the biomolecule isolation system is between about 1 mL and about 500 mL, such as between about 1 mL and about 5 mL, between about 5 mL and about 15 mL, between about 15 mL and about 40 mL, between about 40 mL and about 60 mL, between about 60 mL and about 80 mL, between about 80 mL and about 100 mL, between about 100 mL and about 250 mL, or between about 250 mL and about 500 mL. In some embodiments, the volume of the sample tube used with the biomolecule isolation system is about 78 mL. The volume of liquid in the sample tube is preferably sufficiently small to avoid spillage during sample processing. Nevertheless, the liquid volume in the sample tube can be large, depending on the size of the sample tube. For example, in some embodiments, the liquid volume is up to about 80 mL, such as between about 1 mL and about 5 mL, between about 5 mL and about 15 mL, between about 15 mL and about 40

mL, between about 40 mL and about 60 mL, or between about 60 mL and about 80 mL. In some embodiments, the volume of liquid is about 50 mL. In some embodiments, the volume of the sample tube is about 78 mL and the volume of liquid in the sample tube is up to about 50 mL. In some embodiments, the volume of input biological sample processed by the automated system is up to about 80 mL, such as between about 1 mL and about 5 mL, between about 5 mL and about 15 mL, between about 15 mL and about 40 mL, between about 40 mL and about 60 mL, or between about 60 mL and about 80 mL. In some embodiments, the volume of input biological sample processed by the automated system is about 50 mL.

[0078] FIG. 5 illustrates an exemplary biomolecule isolation system. The biomolecule isolation system includes a base 34, and a sample tube rack mount 35 attached to the base 34. In some embodiments, the base 34 is a shaker, and can include a shaking platform 36. The sample tube rack mount 35 can be attached to the shaking platform 36 such that liquids in the sample tubes held by the racks secured to the sample tube rack mount 35 can be mixed by shaking or rocking the sample tubes. Optionally, one or more cushions 37 can be attached to the underside of the base, which can stabilize the base during shaking or rocking. One or more sample tube racks 38 can be secured to the sample tube rack mount 35. The sample tube rack mount 35 can include one or more guides 39 and 40 (e.g., a groove or protrusion), which can fit with one or more guides (e.g., a complementary groove or protrusion) on the bottom of the sample tube racks 38 to hold the test tube rack 38 in place upon shaking.

[0079] In some embodiments, the sample tube rack mount 35 is configured to hold one or more sample tube racks such as about 1 to about 20, about 2 to about 18, about 4 to about 16, about 6 to about 12, or about 8 to about 10. The sample tube racks 38 can be arranged in one or more columns and one or more rows. Between each of the rows, there is a space or a groove 41. In some embodiments, there is a space or a groove 42 on the outer edge of the sample tube rack mount 35 parallel to the space or groove 41 separating the rows.

[0080] In some embodiments, the biomolecule isolation system further includes one or more magnetic placement plates 43 that are configured to slide within the space or groove under the control of a drive system. A plurality of magnetic placement plates 43 can be connected at a distal end to a support element 45. The plurality of magnetic placement plates 43 are unconnected at the proximal end, which allows the magnetic placement plates 43 to slide in the spaces or grooves without directly contacting the sample tubes. The magnetic placement plates

43 each comprise a plurality of magnets 44, which may be permanent magnets. When the magnets 44 are configured in an active position, the magnets are placed adjacent to the sample tubes, for example by sliding the magnetic placement plates 43 in the spaces or grooves. To switch the magnets 44 in an inactive configuration, the magnetic placement plates 43 slide in the groove such that the magnets 44 are no longer adjacent to the sample tubes. The support element 45 can fit onto guides 46, which prevent the support element 45 and the magnetic placement plates 43 from becoming dislodged. When the shaker stops, the magnetic placement plates 43 can move away or be positioned adjacent to the sample tube racks 38. When the shaker is working, the magnetic placement plates 43 can stay away so that the liquid contents of the sample tube racks 38 are mixed, or magnetic placement plates 43 in an active configuration can be positioned adjacent to the sample tube racks 38 so that magnetic beads adhering to the inner wall of the sample tube racks 38 are washed.

[0081] In an alternative embodiment, the biomolecule isolation system includes magnetic placement plates in a fixed position on either side of the rows of test tube racks, for example by permanently attaching the magnets to the shaker. The magnetic placement plates can include a plurality of transient magnets, wherein the magnet is activated by passing electricity through the magnet.

[0082] The sample tube rack that can be used with the biomolecule isolation system is configured to hold a plurality of sample tubes, which may be arranged in one or more rows or one or more columns. In some embodiments, the sample tube rack is configured to arrange sample tubes in two rows, which allows a magnet to be positioned adjacent to each sample tube. In some embodiments, the sample tube rack is configured to arrange sample tubes in a single tube, which allows two magnets to be positioned adjacent to each sample tube, which the magnets being positioned on opposite sides of the sample tube. The sample tube rack can hold about 4 to about 12 sample tubes, such as about 6, 8, or 10 sample tubes.

[0083] FIG. 6 illustrates an exemplary sample tube rack that can be used with the biomolecule isolation system. Although this sample tube rack is described in the context of the biomolecule isolation system, it is understood that the sample tube rack can be used with any other system, or can be used without a corresponding system. In the illustrated embodiment, the sample tube rack is configured to hold 6 sample tubes 47 in two rows and three columns, although it is understood that the sample tube rack can be configured to hold an alternative

numbers of sample tubes in alternative arrangements. The sample tube rack includes a cover 48 that fits over the sample tubes 47 contained within the sample tube rack. The cover includes a sealable port 49 above each of the sample tubes 47. The sealable port 49 is made from a flexible material, such as a rubber or elastomer (such as silicon or an elastomeric plastic), which is preferably resistant to chemicals used in the system. The sealable port 49 allows passage of a pipette from a liquid handling system into the sample tube, and is sealed with the pipette is withdrawn from the sample tube. The sealable port 49 includes two or more connected slits. When the pipette is lowered, the pipette separates flaps formed by the connected slits, thereby allowing the pipette to enter into the sample tube. The pipette can then be raised, which allows the flaps to join together, thereby sealing the sample tube.

[0084] The base 50 of the sample tube rack can include one or more guides than fit into the guides of the sample tube rack mount of the biomolecule isolation system. In some embodiments, the guides of the sample tube rack and the sample tube rack are arranged to require mounting of the sample tube rack to the sample tube rack mount in a predetermined orientation. In some embodiments, the cover 48 includes a hinge 51 that connects the cover 48 to side supports 52 of the sample tube rack. Sample tubes can be removed or added to the sample tube rack by lifting the cover. The hinge connection, if present, allows for convenient access to add or remove sample tubes. Optionally, a closing mechanism, such as a fitting snap 53 and receiving slot 54 can be positioned on the opposite side of the sample tube rack as the hinge 51. The sitting snap 53 can be positioned on the cover, and the receiving slot 54 can be positioned on the side support, and cover can be locked in place upon closing the cover 48.

[0085] In some embodiments, there is an automated system for isolating biomolecules from a biological sample, comprising a liquid handling system comprising a pipette operable to move in at least a vertical axis; and a sample tube rack comprising a cover configured to fit over one or more sample tubes contained within the sample tube rack, the cover comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube. In some embodiments, the sample tube rack comprises a base that fits into a sample tube rack attached to a surface, which may be part of a biomolecule isolation system. The biomolecule isolation system can comprise a magnet configurable in an active configuration and an inactive configuration, wherein the magnet applies a magnetic field

to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration. In some embodiments, the automated system further comprises one or more of a magnetic bead regeneration system, a shaker, a magnetic bead isolation system, a pipette cleaning system, a cold-storage unit, a barcode reader, or an analytical instrument.

[0086] In some embodiments of the automated system, the magnetic beads used to isolate the target biomolecule are regenerated. The automated system can include a magnetic bead regeneration system accessible by the liquid handling system. The magnetic bead regeneration system includes a cleaning chamber, a magnet, and a mixer. The cleaning chamber includes an opening at the top of the chamber. One or more pipettes from the liquid handling system can be lowered into the cleaning chamber through the opening to dispense liquids and/or used magnetic beads, or to withdraw used liquids or regenerated magnetic beads. The opening can include a seal, which may be a flexible material such as rubber, silicon, or an elastomeric plastic. The one or more pipettes lowered into the cleaning chamber displace the seal to allow access to the chamber. When the pipettes are raised away from the cleaning chamber, the seal closes the opening thereby limiting liquid spilling from the cleaning chamber during mixing. The magnet can be selectively operated in an active configuration that applies a magnetic field to the cleaning chamber, and an inactive configuration that does not apply a magnetic field to the cleaning chamber. The magnet may be a transient magnet that is configured into the active configuration by passing an electric current through the transient magnet, and the deactivated configuration by switching off the electric current. In some embodiments, the magnet is a permanent magnet is positioned adjacent to the cleaning chamber in the active configuration and moved away from the cleaning chamber in the inactive configuration.

[0087] The liquid handling system can transfer used magnetic beads from the biomolecule isolation system to the cleaning chamber of the magnetic bead regeneration system. Once the magnetic beads are dispensed in the cleaning chamber, the magnetic beads can adhere to the inner wall of the cleaning chamber when the magnet is in the active configuration. In some embodiments, the inner wall of the cleaning chamber is coated with a hydrophobic material, such as polytetrafluoroethylene. With the magnetic beads adhering to the inner wall of the cleaning

chamber, the liquid handling system can withdraw liquid in the cleaning chamber without substantial loss of the magnetic beads. The liquid handling system can then dispense a cleaning solution in the cleaning chamber, and the magnet can be operated in the inactive configuration, thereby releasing the magnetic beads into the solution. The mixer can then mix the beads with the cleaning solution. The cycle can be repeated as desired using any combination of desired liquid reagents. For example, the magnet can be operated in the active configuration so that the magnetic beads adhere to the side of the cleaning chamber, the liquid handling system can withdraw the used cleaning solution from the cleaning chamber, the liquid handling system can dispense a wash solution to the cleaning chamber, and the magnet can be operated in the inactive configuration to allow the magnetic beads to become suspended in the wash solution. In some embodiments, the magnetic beads are washed one, two, three or more times. After the desired number of cleaning cycles, the liquid handling system can withdraw the regenerated magnetic beads from the cleaning chamber with the magnet in the inactive configuration. The regenerated magnetic beads can then be used in the biomolecule isolations system.

[0088] In some embodiments, the mixer of the magnetic bead regeneration system is a shaker. For example, the cleaning chamber can be attached to the shaker, and the contents of the cleaning chamber are mixed by shaking the cleaning chamber. In some embodiments, the mixer is an agitator comprising an agitator motor and an impeller disposed within the cleaning chamber. In such an embodiment, the impeller can be operated to mix the liquid contents of the cleaning chamber.

[0089] FIG. 7 illustrates an exemplary magnetic bead regeneration system that can be used with the automated system. The magnetic bead regeneration system includes a cleaning chamber 55 attached to a shaker 56. When activated, the shaker 56 can mix the liquid contents of the cleaning chamber 55. The cleaning chamber includes an opening 57 at the top of the cleaning chamber 55. As illustrated, the cleaning chamber 55 is elongated with an elongated opening 57, but it is understood that there can be more than one openings, for example, 2, 3, 4, 5, 6, or more openings. The opening 57 can be sized and shaped to allow minimal clearance of the pipettes in the liquid handling system. The opening 57 can further include a seal that is displaced with the pipettes press down on the seal when passing through the opening 57 into the cleaning chamber 55. A selectively operable magnet 58 is positioned along an outer elongated wall of the cleaning chamber 55. In an optional configuration, the magnet 58 is attached to the shaker 56. The

magnet 58 can be selectively operated in an active configuration or an inactive configuration during the magnetic bead regeneration process. For example, when the shaker 56 stops, the magnet 58 can move away or be positioned adjacent to the cleaning chamber 55. When the shaker 56 is working, the magnet 58 can stay away such that the liquid contents of the cleaning chamber 55 are mixed, or the magnet 58 in an active configuration can be positioned adjacent to the cleaning chamber 55 such that magnetic beads adhering to the inner wall of the cleaning chamber 55 are washed.

Liquid Handling System

[0090] The automated system includes a liquid handling system, which is used to transfer liquids throughout the system. The liquid handling system can include a large volume liquid handling system, a small volume liquid handling system, or both a large volume liquid handling system and a small volume liquid handling system. In some embodiments, the small volume liquid handling system and the large volume liquid handling system are integrated. In some embodiments, the small volume liquid handling system and the large volume liquid handling system are separately operated systems.

[0091] The large volume liquid handling system can be used to transfer relatively large volumes of liquid, such as between about 10 microliters (μL) to about 100 mL, for example between about 10 μL and about 100 μL , between about 100 μL and about 1 mL, between about 1 mL and about 10 mL, between about 10 mL and about 50 mL, or between about 50 mL and about 100 mL. The small volume liquid handling system can be used to transfer relatively small volumes of liquid, such as about 1 μL to about 10 mL, such as between 1 μL and about 10 μL , between about 10 μL and about 100 μL , between about 100 μL and about 500 μL , between about 500 μL and about 1 mL, between about 1 mL and about 5 mL, or between about 5 mL and about 10 mL. Other transfer volumes for the large volume liquid handling system and/or the small volume liquid handling system can be contemplated.

[0092] The large volume liquid handling system includes one or more multiple-channel pipettes (for example, one or more dual-channel pipettes). In some embodiments, the large volume liquid handling system includes 2, 3, 4, 5, 6, 7, 8 or more multiple-channel pipettes. The multiple-channel pipettes each have an upper region attached to a support structure, and a dispensing region. The dispensing region includes multiple (e.g., two or more) liquid ports. In

some embodiments, the dispensing region includes at least a first liquid port on the side of the dispensing region fluidly connected to a first channel in the multiple-pipette, and a second liquid port at the tip of the dispensing region fluidly connected to a second channel. A control valve for each multiple-channel pipette controls liquid flow through the first channel or the second channel of the pipette. In some embodiments, the second liquid port includes a concave cutout. The concave cutout ensures that substantially all of the liquid in the sample tube is removed when the tip of the pipette is lowered to the bottom of the sample tube. In some embodiments, the one or more multiple-channel pipettes are non-magnetic. In some embodiments, at least a portion of the multiple-channel pipette is coated with a hydrophobic layer, such as a polytetrafluoroethylene layer. In some embodiments, the first channel or the second channel is coated with the hydrophobic later. In some embodiments, the outside surface of the multiple-channel pipette is coated with the hydrophobic layer. In some embodiments, the entire multiple-channel pipette is coated with the hydrophobic layer. In some embodiments, the outer surfaces of the multiple-channel pipettes are coated with a hydrophobic layer and are non-magnetic.

[0093] The diameter of the first liquid port may be smaller than the diameter of the second liquid port, which can control the velocity of the liquid dispensed form the first liquid port or the second liquid port. This allows, for example, liquid dispensed through the first liquid port on the side of the dispensing region to be sprayed with sufficient velocity to wash beads that adhere to the inner surface of containers within the automated system. The second channel may pass through the first channel so that the first channel can access the liquid ports on the side of the pipette and the second channel can access the liquid port at the tip of the pipette. As one example, the second channel may be about 0.6 mm to about 1 mm in diameter (such as about 0.8 mm in diameter), can pass through the first channel that has a diameter between about 1.4 mm to about 2.5 mm in diameter. In another example, the first channel and the second channel are adjacent, and optionally parallel, to each other.

[0094] FIG. 8A and FIG. 8B illustrates an embodiment of the dispensing region of the dual-channel pipette, with FIG. 8A showing a perspective image and FIG. 8B showing a profile image. The pipette includes a first channel that spans the length of the pipette and fluidly connects to the control valve. At the dispensing region of the dual-channel pipette, the first channel terminates at the first liquid port 59 disposed on the side of the dispensing region of the pipette. In some embodiments, the first channel terminates at two or more liquid ports disposed on the side of the

dispensing region. The ports can partially or completely surround the diameter of the pipette. The first liquid port 59 is disposed at an angle (preferably a 90° angle) compared to the first liquid channel. With this orientation, liquid that flows out of the first liquid port 59 is sprayed outwardly. When the pipette is positioned within a sample tube or cleaning chamber of the magnetic bead regeneration system, liquid that flows out of the first liquid port 59 can wash the inner wall of the sample tube or the inner wall of the cleaning chamber. The second channel also spans the length of the pipette and fluidly connects to the control valve, and can run parallel to the first channel. The second channel terminates at the second liquid port 60, which is positioned at the tip of the pipette. In some embodiments, the tip of the pipette is tapered. The second liquid port 60 can include a concave cutout, which prevents the second liquid port 60 from forming a seal with a container bottom and allows efficient liquid flow when liquid is dispensed from the pipette or withdrawn into the pipette.

[0095] FIG. 8C illustrates a cross-sectional view of the dual-channel pipette of the liquid handling system, and shows how the two channels are connected to the liquid ports. In the embodiment illustrated in FIG. 8C, the first channel 59a is connected to two openings of the first liquid port 59b and 59c. The first channel 59a of the dual-channel pipette includes connects to other components of the liquid handling system (for example, the control valve) in the upper region at 59d. The second channel 60a passes through the first channel 59a, and fluidly connects to the second liquid port 60b. The second channel 60a connects to the other components of the liquid handling system in the upper region at 60c. FIG. 8D illustrates a cross-section of the dual-channel pipette along line A-A of FIG. 8C viewed upward. As shown in FIG. 8D, the openings of the first liquid port 59b and 59c are fan shaped to increase spray of liquids flowing from the first liquid port. As illustrated, openings 59b and 59c each have an opening arc angle of about 80°, although in some embodiments the angle is about 60° to about 120°. Although the pipette illustrated in FIGS. 8A-8D is shown with two openings of the first liquid port, it is contemplated that the first liquid port can have 1, 2, 3, 4, 5, or more openings. The height of the openings can be, for example, about 0.1 mm to about 0.5 mm, such as about 0.2 mm to about 0.4 mm, or about 0.3 mm.

[0096] FIGS. 17A-17C illustrate another exemplary embodiment of the dual-channel pipette. FIG. 17A illustrates an alignment view of the dual-channel pipette, and FIG. 17B illustrates a perspective image of the dispensing region of the dual-channel pipette of the liquid handling

system. The dual-channel pipette includes a first channel 131 for dispensing liquid and a second channel 132 for withdrawing liquid from a pipette. At the dispensing region of the dual-channel pipette, the first channel terminates at the first liquid port 133 disposed on the side of the dispensing region of the pipette. The first channel may terminate at one or more liquid port openings, for example two liquid port openings 133a and 133b, as illustrated in FIG. 17C. In some embodiments, the first liquid port can have 1, 2, 3, 4, 5, or more openings. The height of the openings can be, for example, about 0.1 mm to about 0.5 mm, such as about 0.2 mm to about 0.4 mm, or about 0.3 mm. The tip 134 of the first channel 131 is generally sealed so that dispensed liquid flows out of the one or more ports 133 on the side of the first channel 131. When the pipette is positioned within a sample tube or cleaning chamber of the magnetic bead regeneration system, liquid that flows out of the first liquid port 133 can wash the inner wall of the sample tube or the inner wall of the cleaning chamber. The second channel 132 also spans the length of the pipette and fluidly connects to the control valve, and can run parallel to the first channel 131. The second channel terminates at the second liquid port 135, which is positioned at the tip of the pipette. In some embodiments, the tip of the pipette is tapered. The second liquid port 135 can include a concave cutout, which prevents the second liquid port from forming a seal with a container bottom and allows efficient liquid flow when liquid is dispensed from the pipette or withdrawn into the pipette.

[0097] FIG. 17C illustrates a cross-section of the dual-channel pipette viewed at cross-section A—A of FIG. 17A. The first channel 131 of the illustrated embodiment includes two first liquid port openings 133a and 133b on opposite sides of the first channel 131 within the dispensing region of the two-channel pipette. The second channel 132 does not include openings on the side of the channel.

[0098] In some embodiments, the second channel is fluidly connected to a liquid storage loop, which may be disposed between the second channel of the dual channel pipette and the control valve. Liquid drawn into the multiple-channel pipette (which may be, for example, a dual-channel pipette) through the second channel can be stored in the liquid storage loop during transfer. For example, isolated biomolecules can be withdrawn from the sample tube in the biomolecule isolation system into the liquid storage loop and transferred to a second sample tube in the sample output module. In another example, magnetic beads can be drawn into the liquid storage loop from the sample tube in the biomolecule isolation system and dispensed in the

magnetic bead regeneration system. In some embodiments, the liquid storage loop has a capacity of about 100 μ L to about 100 mL, for example between about 100 μ L and about 1 mL, between about 1 mL and about 10 mL, between about 10 mL and about 50 mL, or between about 50 mL and about 100 mL. In some embodiments, the liquid storage loop has a capacity of about 2 mL or more, 5 mL or more, or 10 mL or more.

[0099] In some embodiments, the liquid handling system includes a liquid waste management system fluidly connected to the second channel. The liquid waste management system receives liquid waste, which can be drawn into second channel of the multiple-channel pipette. A connector for the waste management system can be disposed along a conduit between the control valve and the second channel of the multiple-channel pipette. The connector fluidly connects the second channel of the pipette to a waste management conduit that is fluidly connected to the waste management system. A valve is disposed along the waste management conduit to control liquid waste flow into the waste management system. The valve can be, for example, a two-way valve. In some embodiments, the valve is an electromagnetic valve. The waste management system can include a pump or a vacuum and, by opening the valve for the waste management system, liquid waste in the second channel of the dual channel pipette or in the liquid storage loop can flow into the liquid waste management system. The pump for the waste management system can be, for example, a syringe pump or a plunger pump. In some embodiments, the liquid waste management system includes a waste container to receive the waste liquid.

[0100] Each multiple-channel pipette is connected to a liquid pump, which powers liquid flowing through the system. The pump can be, for example, a syringe pump or a plunger pump. The pump is fluidly connected to the control valve for the pipette, and the control valve is fluidly connected to a reagent valve that is fluidly connected to a plurality of reagent tanks. The reagent valve can be operated to select the desired reagent from the reagent tanks, and the control valve can be operated to fluidly connect the pump to the selected reagent. The pump can then be operated to draw the selected reagent into the pump through a pump port. The control valve can be operated to fluidly connect the pump to the first channel or the second channel of the multiple-channel pipette, and the pump can operate to dispense the reagent through the selected channel.

[0101] In another mode of operate, the control valve can be operated to connect the pump to the second channel, and the pump can operate to draw liquid into the liquid storage loop. The liquid handling system can be transported within the sample using the robotic arm, and the pump can operate to dispense the liquid in the liquid storage loop through the second channel.

[0102] In some embodiments, the pump is fluidly connected to a wash liquid. Optionally, the wash liquid may bypass the reagent valve and the control valve. In some embodiments, the wash fluid is connected to the pump through a second pump port. To wash the pump, the wash fluid can be drawn into the pump through the second pump port and pumped out of the pump through the first pump port. By opening the waste management valve connecting the pipette to the waste management system, wash fluid can flow through the pump and into the waste management system. In another embodiment, the wash fluid is dispensed from the pipette into the pipette cleaning system or a waste container, which may be connected to the waste management system.

[0103] FIG. 9A illustrates a schematic for a liquid handling system that can be used with the automated system equipped with a single dual-channel pipette. The illustrated schematic indicates an exemplary configuration, but it is understood that variations may be made for effective liquid handling within the system. A similar configuration can be applied to a liquid handling system comprising a plurality of pipettes, for example as shown in FIG. 9B. As before, the illustrated liquid path is exemplary, and variations may be made for effective liquid handling. The liquid handling system includes a dual-channel pipette 61, wherein the first channel is fluidly connected to a control valve 62 through a first channel conduit 63, and the second channel is fluidly connected to the control valve 62 through a second channel conduit 64. The dual-channel pipette may be configured as illustrated in FIG. 8A-8D or 9A, but other variations of the dual-channel pipette may be used, such as the dual-channel pipette shown in FIG. 17A-17C. The control valve 62 in the illustrated liquid handling system is a four-way valve, but it is understood that the control valve can be a few two-way electromagnetic valves in other embodiments. A liquid storage loop 65 is disposed along the second channel conduit 64 between the control valve 62 and the dual-channel pipette 61. Also disposed along the second channel conduit 64 is a three-way connector 66, which fluidly connects the second channel conduit 64 to a waste management conduit 67. The waste management conduit 67 leads to a waste management system 68, which can include pump or vacuum, and a waste tank. Disposed along the waste management conduit

67 is a two-way electromagnetic valve 69, which controls flow into the waste management system 68. A plurality of reagent tanks 70 are fluidly connected to a reagent valve 71, which is configured to select a desired reagent. The reagent valve 71 in the illustrated liquid handling system is an eight-way valve, but it is understood that it can be a multi-channel intercom splitter in other embodiments. Optionally, compressed air 72 is also fluidly connected to the reagent valve 71, and the reagent valve 71 can be configured to allow air to flow through the liquid handling system. The reagent valve 71 is fluidly connected to the control valve 62 through a reagent supply conduit 73. The control valve 62 is fluidly connected to a pump 74 through a first pump port 75. Optionally, a wash tank 76 comprising a washing liquid is fluidly connected to the pump at second pump port 77 through a washing liquid conduit 78. To wash the system, pump 74 can draw washing liquid through the second pump port 77 and out through the first pump port 75 into the waste management system 68. The pump 74 is not limited to a syringe pump, but also can be a plunger pump or other liquid delivery devices.

[0104] FIG. 9B illustrates the liquid handling system illustrated in FIG. 9A expanded to include a plurality of dual-channel pipettes. In the illustrated example, the liquid handling system comprises six pipettes, but it is understood that the system include additional or fewer pipettes. Each dual channel pipette 79a, 79b, 79c, 79e, and 79f is fluidly connected to an individual control valve 80a, 80b, 80c, 80d, 80e, and 80f. For each pipette, the first channel is fluidly connected to the control valve with an individual first channel conduit 81a, 81b, 81c, 81d, 81e, and 81f, and the second channel separately fluidly connected to the control valve through an individual second channel conduit 82a, 82b, 82c, 82d, 82e, and 82f. An individual liquid storage loop 83a, 83b, 83c, 83d, 83e, and 83f is fluidly connected to each second channel conduit. That is, liquid storage loop 83a is fluidly connected to second channel conduit 82a, liquid storage loop 83b is fluidly connected to second channel conduit 82b, etc. Additionally, each pipette is independently connected to the waste management system through an independent waste management conduit 84a, 84b, 84c, 84d, 84e, and 84f and valve disposed on each independent waste management conduit. The waste management system may be shared among the individual pipettes or may be separate. Each control valve is further fluidly connected to an independent pump 85a, 85b, 85c, 85d, 85e, and 85f for each pipette. A plurality of reagent tanks 86 fluidly connected to a reagent valve 87 can provide reagents or air to the liquid handling system. The reagent tanks can be shared among the pumps and pipettes in the system. A reagent supply line

88 fluidly connects the reagent valve 87 to each of the individual control valves. The reagent supply line 88 can branch at three-way connectors 89a, 89b, 89c, 89d, and 89e to provide reagent to each control valve. The reagent supply line 88 can terminate at the last control valve 80f in the series, as no additional branch is needed at this location. Washing liquid in a washing liquid tank 90 can be fluidly connected to the pumps through a washing liquid conduit 91. The washing liquid conduit 91 can branch at three-way connectors 92a, 92b, 92c, 92d, and 92e to provide washing fluid to the pumps. The washing fluid conduit 91 can terminate at pump 85f, as no additional branching is needed at this location.

[0105] The upper regions of the pipettes of the liquid handling system are attached to a support block, which is connected to a support structure from below the support structure. The support structure can be connected to a robotic arm through an attachment region of the support structure. In some embodiments, the pipettes pass through holes in the support block, and in some embodiments the pipettes are attached to the side of the support block. The upper portion of each pipette is therefore positioned above the support block, and the lower portion of each pipette, including the dispensing region, is positioned below the support block. The support block can help limit lateral or spinning movement of the pipettes during operation. Conduits for each of the first channel and the second channel of the each pipette enter the support structure, and can connect to the control valve. In some embodiments, one or both of the control valve and liquid storage loops are housed within the support structure. In some embodiments, one or both of the control valve and the liquid storage loop is housed outside of the support structure.

[0106] The support block is connected to the support structure through an elastic mechanism. The support structure of the liquid handling system can be lowered by the robotic arm to position the tips of the pipettes at the bottom of sample tubes. The elastic mechanism allows force pushing upward on pipettes to be buffered upon contact of the pipettes with the bottom of the sample tubes. The upper regions of the pipettes are pushed toward the support structure if the robotic arm continues to push the support structure downward. The elastic mechanism can include two or more springs that connect the support block to the support structure. When the support structure is lifted (i.e., the pipette tips are not being forced down against a surface), the springs are fully extended. When the pipettes are forced towards the support structure, the springs are compressed. The elastic mechanism can further include two or more guides (such as two or more guide rails, guide shafts, or guide sleeves), which limit lateral movement of the

support block. The guide rails can include vertical rail directed downward from the bottom of the support structure. The guide rail fits into an opening in the support block. When the pipettes (which are attached to the support block) are pushed towards the support structure, the guide rails can slide vertically within the openings in the support block.

[0107] FIG. 10A illustrates a liquid handling system attached to the robotic arm, and FIG. 10B illustrates the support structure connected to six pipettes. Although the liquid handling system is illustrated in FIG. 10A and FIG. 10B as having six pipettes, it is understood that in some embodiments the liquid handling system includes more or fewer pipettes. The support structure 94 is connected to the vertical arm 95 of a robotic arm through an attachment region 96. The attachment region 96 may be the upper portion of the support structure 94 or may be the along the side of the support structure 94. The vertical arm 95 of the robotic arm can vertically position the support structure 94, including the attached pipettes 97a, 97b, 97c, 97d, 97e, and 97f. The vertical arm can include a limit mechanism 98, which can include a limit switch and a limit block. The limit switch operates the vertical arm 95 to move the support structure 94 vertically, and the limit block puts a hard limit on the range of motion for the vertical arm 95.

[0108] FIG. 10B provides further detail of the support structure, support block, and elastic mechanism. The illustrated liquid handling system includes a support block 99 connected to a support structure 94 through an elastic mechanism that includes a first spring 100 and a second spring 101. A first guide rail 102 and a second guide rail 103 extend vertically downward from the support structure 94 into an opening in the support block 99. The pipettes 97a, 97b, 97c, 97d, 97e, and 97f pass through the support block 99, which holds the pipettes in place.

[0109] The automated system can also include a small volume liquid handling system, which can be used to transfer smaller volumes of liquid throughout the system. For example, the small volume liquid handling system may be used to adjust the pH of a sample or to transfer a sample from a sample tube to a multi-well plate, for example for analysis by an analytical instrument. The small volume liquid handling system includes one or more (such as two, three, four or more) pipettes. In contrast to the pipettes in the large volume liquid handling system, the pipettes in the small volume liquid handling system may be single-channel pipettes. The pipettes are attached to a support structure, which attached to a robotic arm, such as a vertical arm of a robotic arm. Similar to the large volume liquid handling system, the robotic arm connected to the small volume liquid handling system can include a limit mechanism, which can include a limit switch

and a limit block to control movement and movement range of the robotic arm. In some embodiments, the small volume liquid handling system is configured to adjust a distance between two or more pipettes connected to the support structure. This may be useful, for example, when transferring liquids from a plurality of sample tubes to a plurality of wells in a micro-well plate, as the spacing between the sample tubes and the wells may be different. To adjust the spacing between the pipettes, the small volume liquid handling system can include an adjustable spacer and a drive system that controls the adjustable spacer. The drive system can include a hydraulic cylinder, a gas cylinder, or an electric motor to provide power to control the adjustable spacer. In some embodiments, the adjustable spacer includes a limit switch, which is operated upon by the drive system to adjust the spacing of the pipettes, and a limit block that provides a limit on the range of motion of the adjustable spacer. In some embodiments, the upper region of each pipette is connected to an elastic mechanism. In some embodiments, the elastic mechanism includes a spring and/or guides (such as a guide rail, guide shaft, or guide sleeve).

[0110] FIG. 11A and FIG. 11B illustrate an exemplary small volume liquid handling system. The illustrated embodiment shows three pipettes, but it is understood that more or fewer pipettes can be used with the system. The liquid handling system includes a support structure 104 connected to a robotic arm through an attachment region. The robotic arm can include a vertical arm 105 configured to move the support structure 104 in a vertical dimension. The vertical arm can include a limit mechanism 106, which can include a limit switch and a limit block. The limit switch operates the vertical arm 105 to move the support structure 104 vertically, and the limit block puts a hard limit on the range of motion for the vertical arm 105. Referring to FIG. 11B, the support structure 104 is connected to pipettes 107a, 107b, and 107c. The pipettes are connected to an adjustable spacer 108 through elastic mechanisms 109a, 109b, and 109c. The adjustable spacer 108 can slide along a guide 110 under control of the drive system 111 to reposition the pipettes. The elastic mechanism includes a spring and a guide (such as a guide rail, guide shaft, or guide sleeve). The robotic arm can lower the pipettes into sample tubes, wells in a multi-well plate, or other container to withdraw or dispense liquid. When the pipette reaches the bottom of the container, an upward force may be applied on the pipettes, which is absorbed by the elastic mechanism.

[0111] The small volume liquid handling system includes a pump fluidly attached to each pipette. In some embodiments, the pump has a capacity of about 1 mL to about 10 mL, such as about 1 mL to about 2 mL, about 2 mL to about 5 mL, or about 5 mL to about 10 mL. The pump has at least two pump ports. The first pump port is fluidly connected to the pipette, and the pump can be activated to draw liquid into the pipette from the tip of the pipette and to dispense liquid from the pipette tip. The second pump port is fluidly connected to a washing liquid conduit, which is fluidly connected to a washing liquid tank that contains washing liquid. Washing liquid can be drawn into the pump through the second pump port via the washing liquid conduit, and then dispensed through the pipette via the first pump port. By cycling washing fluid through the pipette, the pipette can be washed. In some embodiments, washing of the pipette uses a pipette cleaning system, as described herein.

[0112] FIG. 12 illustrates a schematic of an exemplary setup of the small volume liquid handling system. The illustrated system includes three pipettes, but it is understood that additional or fewer pipettes can be included in the system. Pipettes 112a, 112b, and 112c are each connected to the first port 113a, 113b, and 113c of a pump 114a, 114b, and 114c through pipette conduit 115a, 115b, and 115c. A washing liquid tank 116 is fluidly connected to a washing liquid conduit 117, which supplies washing fluid to the pumps. The second port 118a and 118b are fluidly connected to the washing liquid conduit 117 at three-way connectors 119a and 119b. The washing liquid conduit 117 fluidly connects to second port 118c of pump 114c, but no three-way connector is needed in the final pump.

[0113] In some embodiments, the automated system includes a large volume liquid handling system and a small volume liquid handling system, wherein the system shares a washing liquid tank and a washing liquid conduit. Such an embodiment of the liquid handling system is illustrated in FIG. 13.

[0114] In some embodiments, the automated system includes a pipette cleaning system configured to clean the pipettes of the large volume liquid handling system and/or the small volume liquid handling system. The pipette cleaning system comprises a container with an open top and one or more vertically positioned cleaning tubes. Each pipette can pair with a cleaning tube in the pipette cleaning system. The container of the pipette cleaning system can have an elongated shape configured to receive the linearly arranged pipettes in the liquid handling system. The cleaning tubes are open at the top end and are sized and shaped to receive at least a portion

of the paired pipette. The bottom end of the cleaning tubes are fluidly connected to a drain, which is fluidly connected to a waste management system. In some embodiments, there is a drain at the bottom of the container outside of the cleaning tubes, which can receive liquid that overflows from the cleaning tubes. The drain at the bottom of the container is also fluidly connected to the waste management system.

[0115] To clean a pipette, the at least a portion of the pipette (for example, at least the dispensing region of the pipette) is inserted into the cleaning tube of the pipette cleaning system. Accordingly, the inner diameter of the cleaning tube is wider than the outer diameter of the pipette. Washing liquid is pumped through the pipette into the cleaning tube, which drains through the drain at the bottom of the cleaning tube. The washing liquid can be pumped into the cleaning tube faster than the drain at the bottom of the cleaning tube can drain the liquid, causing the washing liquid to overflow from the top of the cleaning tube into the container, thereby washing the outer surface of the pipette. Washing liquid that overflows can then be drained from the container through the drain at the bottom of the container.

[0116] FIG. 14A illustrates an exemplary pipette cleaning system. The pipette cleaning system includes an elongated container 120 with an open top 121. The inside of the container includes vertically positioned cleaning tubes 122a, 122b, 122c, 122d, 122e, and 122f. Optionally, the cleaning tubes are stabilized by attaching the cleaning tube to the inner surface 123 of the container 120 via brace 124a, 124b, 124c, 124d, 124e, and 124f. FIG. 14B illustrates a cross-sectional view of the pipette cleaning system shown in FIG. 14A. The bottoms of the cleaning tubes are joined to the bottom of the container 120. A drain 125a, 125b, 125c, 125d, 125e, and 125f at the base of each cleaning tube are fluidly connected to a waste management system. The bottom of the container 120 further includes a drain 126 fluidly connected to the waste management system.

[0117] In an exemplary embodiment, a liquid handling system comprises at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; and a pump fluidly connected to the control valve. The second liquid port can comprise

a concave cutout, and the liquid port can be configured to spray liquid onto an inner wall of a container. In some embodiments, the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid port fluidly connected to a wash liquid container. In some embodiments, the support structure is attached to a robotic arm, which may be configured to move at least in a direction of the vertical axis. In some embodiments, the multiple-channel pipette is attached to a support block, and the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

[0118] In some embodiments, the liquid handling system comprises at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; a pump fluidly connected to the control valve; and a liquid storage loop fluidly connected to the second channel of the pipette positioned between the multiple-channel pipette and the control valve. The second liquid port can comprise a concave cutout, and the liquid port can be configured to spray liquid onto an inner wall of a container. In some embodiments, the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid port fluidly connected to a wash liquid container. In some embodiments, the support structure is attached to a robotic arm, which may be configured to move at least in a direction of the vertical axis. In some embodiments, the multiple-channel pipette is attached to a support block, and the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

[0119] In some embodiments, the liquid handling system comprises at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; a pump fluidly connected to the control valve; a liquid storage loop fluidly connected to

the second channel of the pipette positioned between the multiple-channel pipette and the control valve; and a plurality of reagent tanks fluidly connected to a reagent valve configured to select a reagent from the plurality of reagent tanks, wherein the reagent valve is fluidly connected to the control valve. The second liquid port can comprise a concave cutout, and the liquid port can be configured to spray liquid onto an inner wall of a container. In some embodiments, the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid port fluidly connected to a wash liquid container. In some embodiments, the support structure is attached to a robotic arm, which may be configured to move at least in a direction of the vertical axis. In some embodiments, the multiple-channel pipette is attached to a support block, and the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

[0120] In some embodiments, the liquid handling system comprises at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; a pump fluidly connected to the control valve; a liquid storage loop fluidly connected to the second channel of the pipette positioned between the multiple-channel pipette and the control valve; a plurality of reagent tanks fluidly connected to a reagent valve configured to select a reagent from the plurality of reagent tanks, wherein the reagent valve is fluidly connected to the control valve; and a waste management system connected to the second channel of the multiple-channel pipette. Optionally, there is a valve between the second channel of the dual channel pipette and the liquid waste management system. The second liquid port can comprise a concave cutout, and the liquid port can be configured to spray liquid onto an inner wall of a container. In some embodiments, the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid port fluidly connected to a wash liquid container. In some embodiments, the support structure is attached to a robotic arm, which may be configured to move at least in a direction of the vertical axis. In some embodiments, the multiple-channel pipette is attached to a support block, and the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

Methods of Use

[0121] The automated system described herein can be used to isolate biomolecules (such as proteins, antibodies, or nucleic acids) from a biological sample. Methods can include adding a biological samples to the system, methods for controlling contaminants (such as endotoxins), isolating the target biomolecules, regenerating magnetic beads, or methods of operating a liquid handling system. The methods described herein allow for high-throughput processing of large-volume biological samples while minimizing contamination.

[0122] The automated system can be operated for high-throughput processing of biological samples for target biomolecule isolation. Generally, the system operates to process input biological samples in about 3 to 4 hours, and the number of input biological samples that can be processed during this time depends on the number of input samples and capacity of the system. For example, in some embodiments, the system can process up to about 128 samples within about 3 to about 4 hours. The system can also be operated in a continuous operating mode, with new input samples being added as the input samples are being processed. In some embodiments, the system is configured to continuously operate for about 1 day or more, 1 week or more, 1 month or more, or up to about 1 year.

[0123] In one embodiment, a method of isolating a target biomolecule from a biological sample comprises loading the biological sample contained within a sample tube in an automated system (such as the automated system described herein); transferring magnetic beads to the biological sample using a liquid handling system (such as the liquid handling system described herein); complexing the target biomolecule to the magnetic beads; attaching the magnetic beads complexed to the target biomolecule to an inner surface of the sample tube using a magnetic field applied to the magnetic beads (for example, using the biomolecule isolation system described herein); washing the magnetic beads using the liquid handling system (for example, by dispensing a reagent in the sample tube); eluting the target biomolecule from the washed magnetic beads; attaching the magnetic beads to the inner surface of the sample tube after the target biomolecule has been eluted from the magnetic beads; and transferring the target biomolecule to a container. In some embodiments, the method includes regenerating the magnetic beads, for example using a magnetic bead regeneration system described herein. In some embodiments, the method further includes analyzing the target biomolecule using an

automated analytic instrument, for example to determine a biomolecule concentration or an antibody titer.

[0124] To load a biological sample in the automated system, the biological sample (for example, a saliva, blood, stool, or urine sample from a subject) is dispensed in an open sample tube. The sample tube is then placed in a sample tube rack and covered with a cover configured to allow a liquid handling system to access the inside of the sample tube. The sample can include, for example, a sealable port above the sample tube that allows a pipetted from a liquid handling system to access the biological sample. In some embodiments, a plurality of sample tubes containing a biological sample is placed in the sample tube rack. The cover can cover each of the sample tubes in the plurality of sample tubes. The rack comprising the covered sample tubes are then mounted on a surface within the automatic system, such as a surface on the biomolecule isolation system.

[0125] Contaminants, such as endotoxins, can be minimized by activating the air filtration system or the UV light. In some embodiments, the air filter system generates a positive air pressure within the automated system enclosed by a housing. This can prevent contaminants from entering the housing. The UV light can destroy contaminating biomolecules, bacteria or virus that might enter the system. Additionally, the housing can seal the automated system, thereby inhibiting contaminants from entering the system. The housing may be sealed, for example, by closing a door to the housing after samples are loaded in the automated system. Methods for minimizing contamination in the automated system can therefore include sealing the automated system in a housing; activating an ultraviolet light, and/or activating an air filtration system

[0126] Contaminants can also be minimized by cleaning the liquid handling system, which optionally includes washing the pipettes using the pipette cleaning system. Cleaning the liquid handling system includes drawing washing liquid into a pump, and pumping the washing liquid through the pipette. In some embodiments, the washing liquid is pumped through the liquid storage loop. In some embodiments, the washing liquid is pumped through a first channel and a second channel of the pipette. In addition or alternatively, the washing liquid can be pumped through an additional channel (e.g., a third channel) of the pipette. When a pipette cleaning system is used, a pipette of the liquid handling system can be at least partially inserted into a cleaning tube. Washing liquid pumped out of the pipette enters the cleaning tube. In some

embodiments, the washing liquid drains from the bottom of the cleaning tube and/or overflows from the top of the cleaning tube. When the washing liquid overflows from the top of the cleaning tube, the outer surface of the pipette is cleaned.

[0127] In some embodiments, there is a method of removing endotoxins from an automated biomolecule isolation system (such as the automated system described herein), comprising pumping an alkaline disinfecting solution through a multiple-channel pipette (for example, a dual-channel pipette) of a liquid handling system (for example, as described herein), and washing the multiple-channel pipettes using a washing buffer (for example, using the pipette cleaning system described herein). In some embodiments, the method further comprises activating an air filter. In some embodiments, the method further comprises activating a UV light.

[0128] In some embodiments, a pipette in the liquid handling system is primed with a selected reagent. To prime a pipette, the reagent valve is configured to select the desired reagent, and the control valve is configured to fluidly connect the pump to the reagent valve. In some embodiments, the desired reagent is pumped into the pump, and the control valve is configured to select the first channel or the second channel of the pipette. In addition or alternatively, the desired reagent can be pumped into the pump, and the control valve can be configured to select an additional channel (e.g., a third channel) of the pipette. The desired reagent is then pumped through the pipette. If the control valve is configured to select the first channel, the reagent is sprayed from the side of the dispensing region. If the control valve is configured to select the second channel, the reagent flows from the tip of the pipette. The pipette cleaning module may be used when priming the pipette. For example, the pipette can be at least partially inserted into a cleaning tube, and the desired reagent can be pumped into the cleaning tube. Use of the cleaning module provides a convenient method for collecting and disposing of reagent used to prime the pipette.

[0129] Magnetic beads can be prepared for use by dispensing the magnetic beads suspended in solution in a cleaning chamber of a magnetic bead regeneration system. The magnet is configured in the active configuration, which causes the magnetic bead regeneration system to bond to the inner surface of the cleaning chamber. The liquid handling system withdraws liquid in the cleaning chamber, and a pipette of the liquid handling system is primed with a desired reagent. The magnet is then configured in an inactive configuration and the liquid handling system dispenses the desired reagent into the cleaning chamber. In some embodiments, the

desired reagent is dispensed from the side of the dispensing region of the pipette, thereby washing the inner surface of the cleaning chamber to dislodge any magnetic particles that adhere to the inner surface. The magnetic beads are then mixed with the desired reagent in the cleaning chamber. In some embodiments, the liquid handling system withdraws the magnetic beads from the cleaning chamber, and the magnetic beads are transported to a desired location, such as a magnetic bead storage container or a sample tube. In some embodiments, the magnetic beads are washed. For example, the magnet can be configured in the active configuration thereby bonding the magnetic beads to the inner surface of the cleaning chamber, and the liquid handling system can dispense additional desired reagent into the cleaning chamber. The additional desired reagent may be the same or different as the first desired reagent. The magnet can be configured in the inactive configuration, and the additional desired reagent can be mixed with the magnetic beads before being transported to a desired location within the system by the liquid handling system, such as a magnetic bead storage container or a sample tube.

[0130] To regenerate used magnetic beads, magnetic beads are transferred using a liquid handling system into the cleaning chamber of the magnetic bead regeneration system. Magnetic beads from one or more sample tubes can be transferred to the cleaning chamber. The large-volume liquid handling system, for example, can be used by drawing the magnetic beads into the liquid storage loop through the liquid port at the tip of the pipette. In some embodiments, prior to transferring the magnetic beads into the cleaning chamber, a desired reagent can be dispensed through the first channel and the liquid port at side of the dispensing region of the pipette into a sample tube after removal of isolated target biomolecules, thereby washing the magnetic beads from the inner surface of the sample tube. The magnetic beads in the sample tube can be mixed in the desired reagent using the biomolecule isolation system to ensure the magnetic beads are suspended. The magnet of the magnetic bead regeneration system can be configured in the active configuration, thereby bonding the magnetic beads to the inner surface of the cleaning chamber. The liquid handling system then withdraws the reagent from the cleaning chamber, and the magnet is configured in the inactive configuration to release the magnetic beads from the inner surface of the cleaning chamber. The liquid handling system dispenses an additional desired reagent into the cleaning chamber, which may be the same or different from the prior desired reagent. In some embodiments, the liquid handling system dispenses the additional desired reagent from the side of the dispensing region of the pipette, thereby washing the

magnetic beads from the inner surface of the cleaning chamber. The additional desired reagent can be mixed with the magnetic beads, for example by shanking the cleaning chamber. The reagent may be replaced one, two, three, or four or more time using the same process, with reagents that may be the same or different, to regenerate the magnetic beads. Once the magnetic beads are regenerated the liquid handling system may transport the magnetic beads to a magnetic bead storage container or a new biological sample.

[0131] To isolate a target biomolecule, magnetic beads are transferred to a sample tube containing a biological sample. The magnetic beads may be transferred, for example, from a magnetic bead storage container or from a cleaning chamber of a magnetic bead regeneration system. Preferably, the magnetic beads are mixed in a reagent prior to transfer to ensure uniform suspension of the magnetic beads. The magnetic beads can be transferred using a liquid handling system, which can draw the magnetic beads into a liquid storage loop through a liquid port at the tip of a pipette, and then dispense the magnetic beads into the sample tube through the liquid port. The biological sample and the magnetic beads are mixed together using a biomolecule isolation system, thereby bonding the target biomolecules to the magnetic beads. In some embodiments, the magnetic beads and the biological sample are incubated for a period of time. A magnetic field is applied to the sample tube, thereby binding the magnetic beads to the inner wall of the sample tube. The liquid in the sample tube is removed, for example using the liquid handling system, and the magnetic field is removed from the sample tube. The pipettes of the liquid handling system can be cleaned, for example using the pipette cleaning system, and a desired reagent can be added to the sample tubes. In some embodiments, the reagent is dispensed from a liquid port on the side of the dispensing region of the pipette to wash the magnetic beads from the side of the sample tubes. The contents of the sample tubes can be mixed, and the magnetic field can be reapplied to the sample tube to bond the magnetic beads to the inner surface of the sample tubes. The liquid can be removed from the sample tubes, and the magnetic field can be removed from the sample tubes. The magnetic beads are optionally washed two, three, or more times using a similar process. To remove the isolated target biomolecules, an elution reagent is added to the magnetic beads and mixed. The magnetic field is applied to the sample tube to bond the magnetic beads to the inner surface of the sample tube, and the liquid containing the eluted target biomolecule is removed and transported to a separate sample tube, which may be located in a sample output module.

[0132] Isolated target molecules can be analyzed by an analytical instrument, for example to determine protein concentration, an antibody titer, or other analytical measurement. A biological sample can be transferred to a multi-well plate, for example using a small-volume liquid handling system, and the multi-well plate can be transported to the analytical instrument for analysis of the isolated target biomolecule.

[0133] In some embodiments, a liquid handling system comprising at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; and a pump fluidly connected to the control valve; is operated by drawing liquid (which may comprise, for example, magnetic beads or a target biomolecule) into the second liquid port. In some embodiments, the method comprises lowering the multiple-channel pipette into a sample tube comprising the liquid. In some embodiments, the tip of the multiple-channel pipette contacts the bottom of the sample tube. In some embodiments, the method further comprises dispensing the liquid through the second liquid port.

[0134] In some embodiments, a liquid handling system comprising at least one pipette system, comprising a multiple-channel pipette (for example, a dual-channel pipette) comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel; a control valve that controls liquid flow through the first channel or the second channel of the pipette; and a pump fluidly connected to the control valve; is operated by spraying a liquid from the first liquid port onto an inner wall of a container. In some embodiments, the method comprises washing beads (which may be magnetic beads) off of the inner wall of the container using the sprayed liquid.

Computer Systems for Operating the Automated System

[0135] The automated system for isolating target biomolecules from the biological samples can include a computer system, which is configured to operate components of the system. The

computer system can be use, for example, to operate the automated system to perform the methods described herein. For example, the computer system can include instructions for operating the liquid handling system, the robotic arm, the biomolecule isolating system, the magnetic bead regeneration system, the analytical instrument, the pipette cleaning system, or any other system component described herein.

[0136] In some embodiments, the computer system tracks the location of one or more samples within the automated system. A sample source tube inputted into the system can include a sample identifier associated with the sample contained therein. The sample identifier scanner can scan the sample identifier at a known location (e.g., within the sample source tube holder), and the sample location can be communicated to the computer system by the sample identifier scanner. The computer system can then operate the liquid handling system or robotic arm(s) to transfer the sample to a sample tube or micro-well plate at a known location.

[0137] The computer system operates the liquid handling system to withdraw and dispense liquids according to a predetermined workflow. Liquids can be withdrawn by the pipette at a first system component and dispensed at a different system component. Additionally, the computer system can operate the one or more valves in the liquid handling system, for example to select channels or conduits for liquid flow, or to select reagents.

[0138] The computer system can include a user interface (which may be a graphical user interface (GUI)), which can be displayed by the display. The user interface can be used to operate and/or monitor the automated system, such as by managing or reviewing sample inputs or data outputs, reviewing alerts or alarms, suspending or initiating the automated system, or controlling temperatures or incubation times. FIG. 16 depicts an exemplary computer system 1600 configured to perform any one of the processes described herein, including the various exemplary processes for operating the automated system. In this context, computing system 1600 may include, for example, a processor, non-transitory computer readable medium (e.g., memory), storage, and input/output devices (e.g., monitor, keyboard, disk drive, Internet connection, etc.). However, computing system 1600 may include circuitry or other specialized hardware for carrying out some or all aspects of the processes. In some operational settings, computing system 1600 may be configured as a system that includes one or more units, each of which is configured to carry out some aspects of the processes either in software, hardware, or some combination thereof. FIG. 16 depicts computing system 1600 with a number of

components that may be used to perform the above-described processes. The main system 1602 includes a motherboard 1604 having an input/output (“I/O”) section 1606, one or more central processing units (“CPU”) 1608, and a memory section 1410, which may have a flash memory card 1612 related to it. The I/O section 1606 is connected to a display 1624, a keyboard 1614, a disk storage unit 1616, and a media drive unit 1618. The media drive unit 1618 can read/write a computer-readable medium 1620, which can contain programs 1622 and/or data. At least some values based on the results of the above-described processes can be saved for subsequent use. Additionally, a non-transitory computer-readable medium can be used to store (e.g., tangibly embody) one or more computer programs for performing any one of the above-described processes by means of a computer. The computer program may be written, for example, in a general-purpose programming language (e.g., Pascal, C, C++, Java, Python, JSON, etc.) or some specialized application-specific language.

EXEMPLARY EMBODIMENTS

[0139] Embodiment 1. A liquid handling system, comprising:

at least one pipette system, comprising:

a dual-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel;

a control valve that controls liquid flow through the first channel or the second channel of the pipette; and

a pump fluidly connected to the control valve.

[0140] Embodiment 2. The liquid handling system of embodiment 1, wherein the second channel of the dual-channel pipette passes through and parallel to the first channel of the dual-channel pipette.

[0141] Embodiment 3. The liquid handling system of embodiment 1, wherein the second channel of the dual-channel pipette is adjacent to the first channel of the dual-channel pipette.

[0142] Embodiment 4. The liquid handling system of any one of embodiments 1-3, wherein the second liquid port comprises a concave cutout.

[0143] Embodiment 5. The liquid handling system of any one of embodiments 1-4, wherein the first liquid port is configured to spray liquid onto an inner wall of a container.

[0144] Embodiment 6. The liquid handling system of any one of embodiments 1-5, wherein at least a portion of the pipette is coated with a hydrophobic layer.

[0145] Embodiment 7. The liquid handling system of any one of embodiments 1-6, wherein the second channel is fluidly connected to a liquid storage loop positioned between the dual-channel pipette and the control valve.

[0146] Embodiment 8. The liquid handling system of embodiment 7, wherein the liquid storage loop has a liquid storage capacity of about 2 mL or more.

[0147] Embodiment 9. The liquid handling system of any one of embodiments 1-8, wherein the liquid handling system comprises a liquid waste management system connected to the second channel of the dual-channel pipette.

[0148] Embodiment 10. The liquid handling system of embodiment 9, wherein the liquid handling system comprises a valve between the second channel of the dual-channel pipette and the liquid waste management system.

[0149] Embodiment 11. The liquid handling system of any one of embodiments 1-9, wherein the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid pump fluidly connected to a wash liquid container.

[0150] Embodiment 12. The liquid handling system of any one of embodiments 1-11, comprising a plurality of reagent tanks fluidly connected to a reagent valve configured to select a reagent from the plurality of reagent tanks, wherein the reagent valve is fluidly connected to the control valve.

[0151] Embodiment 13. The liquid handling system of any one of embodiments 1-12, wherein the support structure is attached to a robotic arm.

[0152] Embodiment 14. The liquid handling system of embodiment 13, wherein the robotic arm is configured to move at least in the direction of the vertical axis.

[0153] Embodiment 15. The liquid handling system of any one of embodiments 1-14, wherein the dual-channel pipette is attached to a support block, and wherein the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

[0154] Embodiment 16. The liquid handling system of embodiment 15, wherein the liquid handling system comprises a plurality of pipette systems, wherein each pipette system comprises a dual-channel pipette attached to the support block.

[0155] Embodiment 17. The liquid handling system of embodiment 15 or 16 wherein the elastic mechanism comprises two or more springs and two or more guide mechanisms.

[0156] Embodiment 18. The liquid handling system of any one of embodiments 1-17, further comprising a pipette cleaning system comprising a container having an open top and at least one cleaning tube vertically positioned within the container.

[0157] Embodiment 19. The liquid handling system of embodiment 18, wherein the cleaning tube is sized and shaped to receive the dual-channel pipette.

[0158] Embodiment 20. The liquid handling system of embodiment 18 or 19, wherein the container comprises a bottom comprising a drain.

[0159] Embodiment 21. A method of operating the liquid handling system of any one of embodiments 1-20, comprising drawing liquid into the pipette through the second liquid port.

[0160] Embodiment 22. The method of embodiment 21, comprising lowering the pipette into a sample tube comprising the liquid.

[0161] Embodiment 23. The method of embodiment 21, comprising contacting the pipette to the bottom of the sample tube.

[0162] Embodiment 24. The method of any one of embodiments 21-23, wherein the liquid comprises magnetic beads.

[0163] Embodiment 25. The method of any one of embodiments 21-23, wherein the liquid comprises a target biomolecule.

[0164] Embodiment 26. The method of any one of embodiments 21-25, wherein the liquid is stored in a liquid storage loop.

[0165] Embodiment 27. The method of any one of embodiments 21-26, comprising dispensing the liquid through the second liquid port.

[0166] Embodiment 28. A method of operating the liquid handling system of any one of embodiments 1-20, comprising spraying a liquid from the first liquid port onto an inner wall of a container.

[0167] Embodiment 29. The method of embodiment 28, comprising washing beads off of the inner wall of the container using the sprayed liquid.

[0168] Embodiment 30. The method of embodiment 29, wherein the beads are magnetic beads.

[0169] Embodiment 31. An automated system for isolating biomolecules from a sample, comprising the liquid handling system of any one of embodiments 1-20, further comprising one or more of a magnetic bead regeneration system, a second liquid handling system, a shaker, a sample tube rack, a biomolecule isolation system, a magnetic bead regeneration system, a cold-storage unit, a barcode reader, or an analytical instrument.

[0170] Embodiment 32. An automated system for isolating biomolecules from a biological sample, comprising:

a liquid handling system comprising a pipette operable to move in at least a vertical axis;
and

a sample tube rack;

one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube.

[0171] Embodiment 33. The automated system of embodiment 32, wherein the sealable port comprises two or more connected slits.

[0172] Embodiment 34. The automated system of embodiments 32 or 33, wherein the sealable port comprises an elastomer or rubber.

[0173] Embodiment 35. The automated system of any one of embodiments 32-34, wherein the sample tube rack comprises a base that fits into a sample tube rack mount attached to a surface.

[0174] Embodiment 36. The automated system of embodiment 35, wherein the base comprises a groove or a protrusion, and the receiving block comprises a complementary groove or protrusion.

[0175] Embodiment 37. The automated system of embodiment 35 or 36, wherein the surface is part of a biomolecule isolation system comprising a magnet configurable in an active configuration and an inactive configuration,

the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and

wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.

[0176] Embodiment 38. The automated system of any one of embodiments 31-37, further comprising one or more of a magnetic bead regeneration system, a shaker, a magnetic bead isolation system, a pipette cleaning system, a cold-storage unit, a barcode reader, or an analytical instrument.

[0177] Embodiment 39. An automated system for isolating biomolecules from a biological sample, comprising:

(a) a first liquid handling system, comprising:

at least one pipette system, comprising:

a dual-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel;

a control valve that controls liquid flow through the first channel or the second channel of the pipette; and

a pump fluidly connected to the control valve;

(b) a second liquid handling system comprising at least one pipette, wherein the second liquid handling system is configured to handle liquid volumes smaller than the first liquid handling system;

(c) a sample tube rack;

(d) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of a pipette from the first liquid handling system or the second liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube; and

(e) a biomolecule isolation system configured to bond magnetic beads to the side of a sample tube through a magnetic field in an active configuration.

[0178] Embodiment 40. The automated system of embodiment 39, wherein the biomolecule isolation system is operable to configure a magnet in an active configuration and an inactive configuration,

wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and

wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.

[0179] Embodiment 41. The automated system of embodiment 39 or 40, further comprising one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector.

[0180] Embodiment 42. The automated system of any one of embodiments 39-41, wherein the system is contained within a housing.

[0181] Embodiment 43. The automated system of embodiment 42, wherein the housing is sealed.

[0182] Embodiment 44. The automated system of embodiment 42 or 43, wherein the housing comprises a sterilization system.

[0183] Embodiment 45. The automated system of embodiment 44, wherein the sterilization system comprises an air filter or an ultraviolet light.

[0184] Embodiment 46. The automated system of any one of embodiments 39-45, wherein the automated system is operated using a computer system.

EXAMPLES

Example 1 - Automated System Preparation

[0185] Forty-eight 50 mL sample tubes (e.g., 48 centrifugation tubes or eight 6-well plates), each containing a biological sample, are placed in eight sample tube racks. A cover is placed over the sample tubes, which each sample tube rack having its own cover. The cover includes six sealable ports that align with the sample tubes in the sample tube rack. The sample tube racks are then secured to a sample tube rack mount within a biomolecule isolation system.

[0186] Separately, 48 clean 15 mL sample tubes or a 96-well plate is placed within a sample output module.

Example 2 – Endotoxin Control

[0187] The sterilize the sample tubes, a sterilization fluid (Reagent D) is added to a sample tube in the biomolecule isolation system using a large volume liquid handler and allowed to soak for a period of time.

[0188] To sterilize the system components and area within the system housing, the ultraviolet light and the air filtration system are activated.

[0189] To clean the liquid handling systems (either or both of the large volume liquid handling system and the small volume liquid handling system), the pipettes of the liquid handling system are inserted into the pipette cleaning system. Reagent D is pumped through the pipettes into the cleaning tubes, and is allowed to drain through the pipette cleaning system drains. A basic (alkaline) disinfecting solution, Reagent B, is then pumped through the pipettes into the cleaning tubes, and is allowed to drain through the pipette cleaning system drains.

Example 3 - Magnetic Bead Preparation

[0190] Magnetic beads suspended in liquid are manually placed into a cleaning chamber of the magnetic bead regeneration system. The magnet of the magnetic bead regeneration system is activated to induce a magnetic field within the cleaning chamber that causes the magnetic beads to bond to the inner surface of the cleaning chamber. The large volume liquid handling system is used to remove the supernatant, and the magnet is inactivated.

[0191] Pipettes from the large volume liquid handling system are cleaned using a pipette cleaning system. The pipettes from the liquid handling system are inserted into the cleaning tubes of the pipette cleaning system, and a magnetic bead buffer, Reagent A, is pumped through the pipettes. The large volume liquid handling system then dispenses Reagent A into the cleaning chamber of the magnetic bead regeneration system through a port on the side of the dispensing region of the pipette. Reagent A sprays onto the inner surface of the cleaning chamber, dislodging magnetic beads that are stuck to the inner surface. The magnetic beads and Reagent A are mixed in the cleaning chamber, and the magnet is reconfigured in the active configuration to induce a magnetic field within the cleaning chamber that causes the magnetic beads to bond to the inner surface of the cleaning chamber. The supernatant is then removed using the large volume liquid handling system using the liquid port at the tip of the pipette, and

the supernatant is disposed of using the liquid waste management system. Once the reagent has been withdrawn from the cleaning chamber, the magnet is configured in the inactive configuration.

[0192] The pipettes from the liquid handling system are cleaned by inserting the pipettes into the cleaning tubes of the pipette cleaning system, and fresh Reagent A is pumped through the pipettes. The large volume liquid handling system then dispenses Reagent A through the liquid port on the side of the dispensing region of the pipettes into the cleaning chamber of the magnetic bead regeneration system by spraying the inner surface of the cleaning chamber, thereby dislodging magnetic beads that are stuck to the inner surface.

Example 4 – pH Adjustment of Isolated Target Biomolecules

[0193] The small volume liquid handling system is used to adjust the pH of isolated target biomolecules in 15 mL centrifuge tubes held in a sample output module. The pipettes from the small volume liquid handling system are inserted into cleaning tubes of a pipette cleaning system, and Reagent E (which may be an acid or base to adjust pH) is pumped through the pipettes until the cleaning tubes overflow. The small volume liquid handling system then dispenses a desired amount of Reagent E into sample tubes containing the isolated target biomolecules.

Example 5 – Isolating Target Biomolecules

[0194] Magnetic beads in a cleaning chamber of a magnetic bead regeneration system are mixed in a liquid to ensure uniformity. A fixed amount of the magnetic bead suspension is transferred from the cleaning chamber to 48 sample tubes (e.g., 48 centrifugation or the wells of 8 6-well plates) held in a biomolecule isolation system, each sample tube containing a biological sample, using a large volume liquid handling system. The biological samples are mixed with the magnetic beads and incubated for a period of time to allow the target biomolecules to bond to the magnetic beads.

[0195] Several magnets are positioned adjacent to the sample tubes, thereby bonding the magnetic beads bound to the target molecules to the inner surface of the sample tubes. The supernatant is removed from the sample tubes by drawing the liquid through a liquid port at the tip of a pipette from the large volume liquid handling system, which transfers the liquid into the liquid waste management system. The magnets are then removed from the position adjacent to

the sample tubes to disrupt the magnetic field in the sample tubes, thereby releasing the magnetic beads.

[0196] Pipettes from the large volume liquid handler are inserted into cleaning tubes of a pipette cleaning system, and Reagent A is pumped through the pipette until the cleaning tubes overflow. Reagent A is then sprayed into the sample tubes through a liquid port on the side of the dispensing region of the pipette, thereby washing magnetic beads from the inner surfaces of the sample tubes. The magnetic beads are mixed with Reagent A in the sample tubes, and the magnets are repositioned in the active configuration, thereby bonding the magnetic beads to the inner surface of the sample tubes. The supernatant is removed from the sample tubes by drawing the liquid through a liquid port at the tip of a pipette from the large volume liquid handling system, which transfers the liquid into the liquid waste management system. The magnets are then removed from the position adjacent to the sample tubes to disrupt the magnetic field in the sample tubes, thereby releasing the magnetic beads.

[0197] Pipettes from the large volume liquid handler are inserted into cleaning tubes of a pipette cleaning system, and elution buffer, Reagent C, is pumped through the pipette until the cleaning tubes overflow. Reagent C is then sprayed into the sample tubes through a liquid port on the side of the dispensing region of the pipette, thereby washing magnetic beads from the inner surfaces of the sample tubes. The magnetic beads are mixed with Reagent C in the sample tubes, and the magnets are repositioned in the active configuration, thereby bonding the magnetic beads to the inner surface of the sample tubes. The target biomolecules are eluted from the magnetic beads using Reagent C, and the isolated biomolecules then remain in solution when the magnetic beads are bonded to the inner surface of the sample tubes.

[0198] The large volume liquid handling system draws the solution containing Reagent C and the target biological molecule into the liquid storage loop, and dispenses the isolated target biomolecules into 15 mL sample tubes (such as 15 mL centrifugation tubes or wells in a multi-well plate) in a sample output module. Since there are more sample tubes than pipettes, the pipettes can be cleaned using the pipette cleaning module using Reagent C between transfer of different samples.

[0199] The magnets are then removed from the position adjacent to the sample tubes to disrupt the magnetic field in the sample tubes, thereby releasing the magnetic beads. Reagent C is then sprayed into the sample tubes through a liquid port on the side of the dispensing region of

the pipette, thereby washing magnetic beads from the inner surfaces of the sample tubes. The magnetic beads are mixed with Reagent C in the sample tubes, and the magnets are repositioned in the active configuration, thereby bonding the magnetic beads to the inner surface of the sample tubes. The additional solution is then transferred to the corresponding sample tube in the sample output module.

[0200] When a solution containing the isolated biomolecules is transferred to a sample tube in the output module, the sample tube is raised and a barcode on the sample tube is scanned to track the sample.

Example 6 – Optical Detection of Isolated Target Biomolecules

[0201] Pipettes from the small-volume liquid handling system are cleaned using a pipette cleaning system. The pipettes are inserted in cleaning tubes, and Reagent C is pumped through the pipettes until the cleaning tubes overflow and the reagent is drained from the pipette cleaning system.

[0202] 100 μ L of isolated target biomolecule in from 36 sample tubes in the sample output module is transferred to 36 wells of a 96-well plate. The small volume liquid handling system includes three pipettes, which are cleaned using the pipette cleaning system with Reagent B before transferring a new sample.

[0203] The 96-well plate is then transported to an optical detection system using a consumable transfer system configured to transport a 96-well plate to detect concentration of the isolated target biomolecule in the sample.

Example 7 – Magnetic Bead Regeneration

[0204] Once the isolated target biomolecules have been transferred from the sample tubes in the biomolecule isolation system, the magnetic in the biomolecule isolation system is positioned in an inactive configuration to remove the magnetic field in the sample tubes, thereby releasing most of the magnetic particles from the inner surface of the sample tubes. Reagent A is sprayed from a liquid port on the side of a dispensing region of a pipette of the large-volume liquid handling system to wash any magnetic beads that remain on the inner surface of the sample tube.

The magnetic beads and Reagent A are mixed using the biomolecule isolation system, and the large volume liquid handling system draws the suspended magnetic beads into the liquid storage loop through the liquid port at the tip of the pipette.

[0205] The magnetic beads are transferred to a cleaning chamber of a magnetic bead regeneration system by dispensing the magnetic bead suspension through the liquid port at the tip of the pipette. The magnet of the magnetic bead regeneration system is configured in an active configuration to induce a magnetic field within the cleaning chamber and bond the magnetic beads to the inner surface of the cleaning chamber. The large volume liquid handling system then removes the supernatant through the liquid port at the tip of the pipette, and transfers the liquid to the liquid waste management system. The magnet is then configured in the inactive position, which releases most of the magnetic beads from the inner surface of the cleaning chamber.

[0206] Pipettes of the large volume liquid handling system are cleaned using the pipette cleaning system. The pipettes are inserted into the cleaning tubes of the pipette cleaning system, and Reagent A is pumped through the pipettes until the cleaning tube overflows. Reagent A is sprayed from a liquid port on the side of a dispensing region of a pipette of the large-volume liquid handling system to wash any magnetic beads that remain on the inner surface of the sample tube. The magnetic beads and Reagent A are mixed using the magnetic bead regeneration system, and the magnet of the magnetic bead regeneration system is configured in an active configuration to induce a magnetic field within the cleaning chamber and bond the magnetic beads to the inner surface of the cleaning chamber. The large volume liquid handling system then removes the supernatant through the liquid port at the tip of the pipette, and transfers the liquid to the liquid waste management system. The magnet is then configured in the inactive position, which releases most of the magnetic beads from the inner surface of the cleaning chamber.

[0207] The pipettes are again inserted into the cleaning tubes of the pipette cleaning system, and Reagent D is pumped through the pipettes until the cleaning tube overflows. Reagent D is sprayed from a liquid port on the side of a dispensing region of a pipette of the large-volume liquid handling system to wash any magnetic beads that remain on the inner surface of the sample tube. The magnetic beads and Reagent D are mixed using the magnetic bead regeneration system, and the magnet of the magnetic bead regeneration system is configured in an active

configuration to induce a magnetic field within the cleaning chamber and bond the magnetic beads to the inner surface of the cleaning chamber. The large volume liquid handling system then removes the supernatant through the liquid port at the tip of the pipette, and transfers the liquid to the liquid waste management system. The magnet is then configured in the inactive position, which releases most of the magnetic beads from the inner surface of the cleaning chamber.

[0208] The pipettes are again inserted into the cleaning tubes of the pipette cleaning system, and Reagent A is pumped through the pipettes until the cleaning tube overflows. Reagent A is sprayed from a liquid port on the side of a dispensing region of a pipette of the large-volume liquid handling system to wash any magnetic beads that remain on the inner surface of the sample tube. The magnetic beads and Reagent A are mixed using the magnetic bead regeneration system, and the magnet of the magnetic bead regeneration system is configured in an active configuration to induce a magnetic field within the cleaning chamber and bond the magnetic beads to the inner surface of the cleaning chamber. The large volume liquid handling system then removes the supernatant through the liquid port at the tip of the pipette, and transfers the liquid to the liquid waste management system. The magnet is then configured in the inactive position, which releases most of the magnetic beads from the inner surface of the cleaning chamber.

[0209] The pipettes are again inserted into the cleaning tubes of the pipette cleaning system, and magnetic bead storage buffer, Reagent F, is pumped through the pipettes until the cleaning tube overflows. Reagent F is sprayed from a liquid port on the side of a dispensing region of a pipette of the large-volume liquid handling system to wash any magnetic beads that remain on the inner surface of the sample tube. The magnetic beads and Reagent F are mixed using the magnetic bead regeneration system to complete regeneration of the magnetic beads. The magnetic beads can then be re-used for isolation of target biomolecules from new biological samples.

[0210] Various exemplary embodiments are described herein. Although examples of this disclosure have been fully described with reference to the accompanying drawings, it is to be noted that various changes and modifications will become apparent to those skilled in the art. Such changes and modifications are to be understood as being included within the scope of examples of this disclosure as defined by the appended claims. In addition, modifications may be made to adapt a particular situation, material, composition of matter, process, process act(s) or

step(s) to the objective(s), spirit or scope of the various embodiments. Further, as will be appreciated by those with skill in the art, each of the individual variations described and illustrated herein has discrete components and features that may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the various embodiments. All such modifications are intended to be within the scope of claims associated with this disclosure.

CLAIMS

What is claimed is:

1. A liquid handling system, comprising:
 - at least one pipette system, comprising:
 - a multiple-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a second liquid port at a tip of the dispensing region fluidly connected to a second channel;
 - a control valve that controls liquid flow through at least the first channel or the second channel of the pipette; and
 - a pump fluidly connected to the control valve.
2. The liquid handling system of claim 1, wherein the second channel of the multiple-channel pipette passes through and parallel to the first channel of the channel pipette.
3. The liquid handling system of claim 1, wherein the second channel of the multiple-channel pipette is adjacent to the first channel of the multiple-channel pipette.
4. The liquid handling system of any one of claims 1-3, wherein the second liquid port comprises a concave cutout.
5. The liquid handling system of any one of claims 1-4, wherein the first liquid port is configured to spray liquid onto an inner wall of a container.
6. The liquid handling system of any one of claims 1-5, wherein at least a portion of the pipette is coated with a hydrophobic layer.
7. The liquid handling system of any one of claims 1-6, wherein the second channel is fluidly connected to a liquid storage loop positioned between the multiple-channel pipette and the control valve.

8. The liquid handling system of claim 7, wherein the liquid storage loop has a liquid storage capacity of about 2 mL of or more.
9. The liquid handling system of any one of claims 1-8, wherein the liquid handling system comprises a liquid waste management system connected to the second channel of the multiple-channel pipette.
10. The liquid handling system of claim 9, wherein the liquid handling system comprises a valve between the second channel of the multiple-channel pipette and the liquid waste management system.
11. The liquid handling system of any one of claims 1-9, wherein the pump comprises a first liquid port fluidly connected to the control valve, and a second liquid pump fluidly connected to a wash liquid container.
12. The liquid handling system of any one of claims 1-11, comprising a plurality of reagent tanks fluidly connected to a reagent valve configured to select a reagent from the plurality of reagent tanks, wherein the reagent valve is fluidly connected to the control valve.
13. The liquid handling system of any one of claims 1-12, wherein the support structure is attached to a robotic arm.
14. The liquid handling system of claim 13, wherein the robotic arm is configured to move at least in the direction of the vertical axis.
15. The liquid handling system of any one of claims 1-14, wherein the multiple-channel pipette is attached to a support block, and wherein the support block is attached to the support structure through an elastic mechanism configured to at least partially absorb an upward force applied to the pipette.

16. The liquid handling system of claim 15, wherein the liquid handling system comprises a plurality of pipette systems, wherein each pipette system comprises a multiple-channel pipette attached to the support block.
17. The liquid handling system of claim 15 or 16 wherein the elastic mechanism comprises two or more springs and two or more guide mechanisms.
18. The liquid handling system of any one of claims 1-17, further comprising a pipette cleaning system comprising a container having an open top and at least one cleaning tube vertically positioned within the container.
19. The liquid handling system of claim 18, wherein the cleaning tube is sized and shaped to receive the multiple-channel pipette.
20. The liquid handling system of claim 18 or 19, wherein the container comprises a bottom comprising a drain.
21. The liquid handling system of any one of claims 1-20, wherein the lower dispensing region further comprises a third port fluidly connected to a third channel.
22. The liquid handling system of any one of claims 1-20, wherein the multiple-channel pipette is a dual-channel pipette.
23. A method of operating the liquid handling system of any one of claims 1-22, comprising drawing liquid into the pipette through the second liquid port.
24. The method of claim 23, comprising lowering the pipette into a sample tube comprising the liquid.
25. The method of claim 23, comprising contacting the pipette to the bottom of the sample tube.
26. The method of any one of claims 23-25, wherein the liquid comprises magnetic beads.

27. The method of any one of claims 23-25, wherein the liquid comprises a target biomolecule.
28. The method of any one of claims 23-27, wherein the liquid is stored in a liquid storage loop.
29. The method of any one of claims 23-28, comprising dispensing the liquid through the second liquid port.
30. A method of operating the liquid handling system of any one of claims 1-22, comprising spraying a liquid from the first liquid port onto an inner wall of a container.
31. The method of claim 30, comprising washing beads off of the inner wall of the container using the sprayed liquid.
32. The method of claim 31, wherein the beads are magnetic beads.
33. An automated system for isolating biomolecules from a sample, comprising the liquid handling system of any one of claims 1-22, further comprising one or more of a magnetic bead regeneration system, a second liquid handling system, a shaker, a sample tube rack, a biomolecule isolation system, a magnetic bead regeneration system, a cold-storage unit, a barcode reader, or an analytical instrument.
34. An automated system for isolating biomolecules from a biological sample, comprising:
a liquid handling system comprising a pipette operable to move in at least a vertical axis;
and
a sample tube rack;
one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of the pipette through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube.

35. The automated system of claim 34, wherein the sealable port comprises two or more connected slits.
36. The automated system of claims 34 or 35, wherein the sealable port comprises an elastomer or rubber.
37. The automated system of any one of claims 34-36, wherein the sample tube rack comprises a base that fits into a sample tube rack mount attached to a surface.
38. The automated system of claim 37, wherein the base comprises a groove or a protrusion, and the receiving block comprises a complementary groove or protrusion.
39. The automated system of claim 37 or 38, wherein the surface is part of a biomolecule isolation system comprising a magnet configurable in an active configuration and an inactive configuration,
wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and
wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.
40. The automated system of any one of claims 33-39, further comprising one or more of a magnetic bead regeneration system, a shaker, a magnetic bead isolation system, a pipette cleaning system, a cold-storage unit, a barcode reader, or an analytical instrument.
41. An automated system for isolating biomolecules from a biological sample, comprising:
(a) a first liquid handling system, comprising:
at least one pipette system, comprising:
a multiple-channel pipette comprising an upper region attached to a support structure, and a lower dispensing region comprising at least a first liquid port on the side of the dispensing region fluidly connected to a first channel, and a

second liquid port at a tip of the dispensing region fluidly connected to a second channel;

a control valve that controls liquid flow through at least the first channel or the second channel of the pipette; and

a pump fluidly connected to the control valve;

(b) a second liquid handling system comprising at least one pipette, wherein the second liquid handling system is configured to handle liquid volumes smaller than the first liquid handling system;

(c) a sample tube rack;

(d) one or more covers configured to fit over one or more sample tubes contained within the sample tube rack, the one or more covers comprising a sealable port above each of the one or more sample tubes that allows passage of a pipette from the first liquid handling system or the second liquid handling system through the sealable port into the sample tube, wherein the sealable port is sealed when the pipette is withdrawn from the sample tube; and

(e) a biomolecule isolation system configured to bond magnetic beads to the side of a sample tube through a magnetic field in an active configuration.

42. The automated system of claim 41, wherein the biomolecule isolation system is operable to configure a magnet in an active configuration and an inactive configuration,

wherein the magnet applies a magnetic field to the one or more sample tubes to bond magnetic beads in the sample tube to an inner surface of the one or more sample tubes when the magnet is in the active configuration, and

wherein the magnetic field is removed to release most of the magnetic beads from the inner surface of the one or more sample tubes when the magnet is in the inactive configuration.

43. The automated system of claim 41 or 42, further comprising one or more of a magnetic bead regeneration system, a shaker, a pipette cleaning system, a cold-storage unit, a barcode reader, or an optical detector.

44. The automated system of any one of claims 41-43, wherein the system is contained within a housing.

45. The automated system of claim 44, wherein the housing is sealed.
46. The automated system of claim 44 or 45, wherein the housing comprises a sterilization system.
47. The automated system of claim 46, wherein the sterilization system comprises an air filter or an ultraviolet light.
48. The automated system of any one of claims 41-47, wherein the automated system is operated using a computer system.

FIG. 1

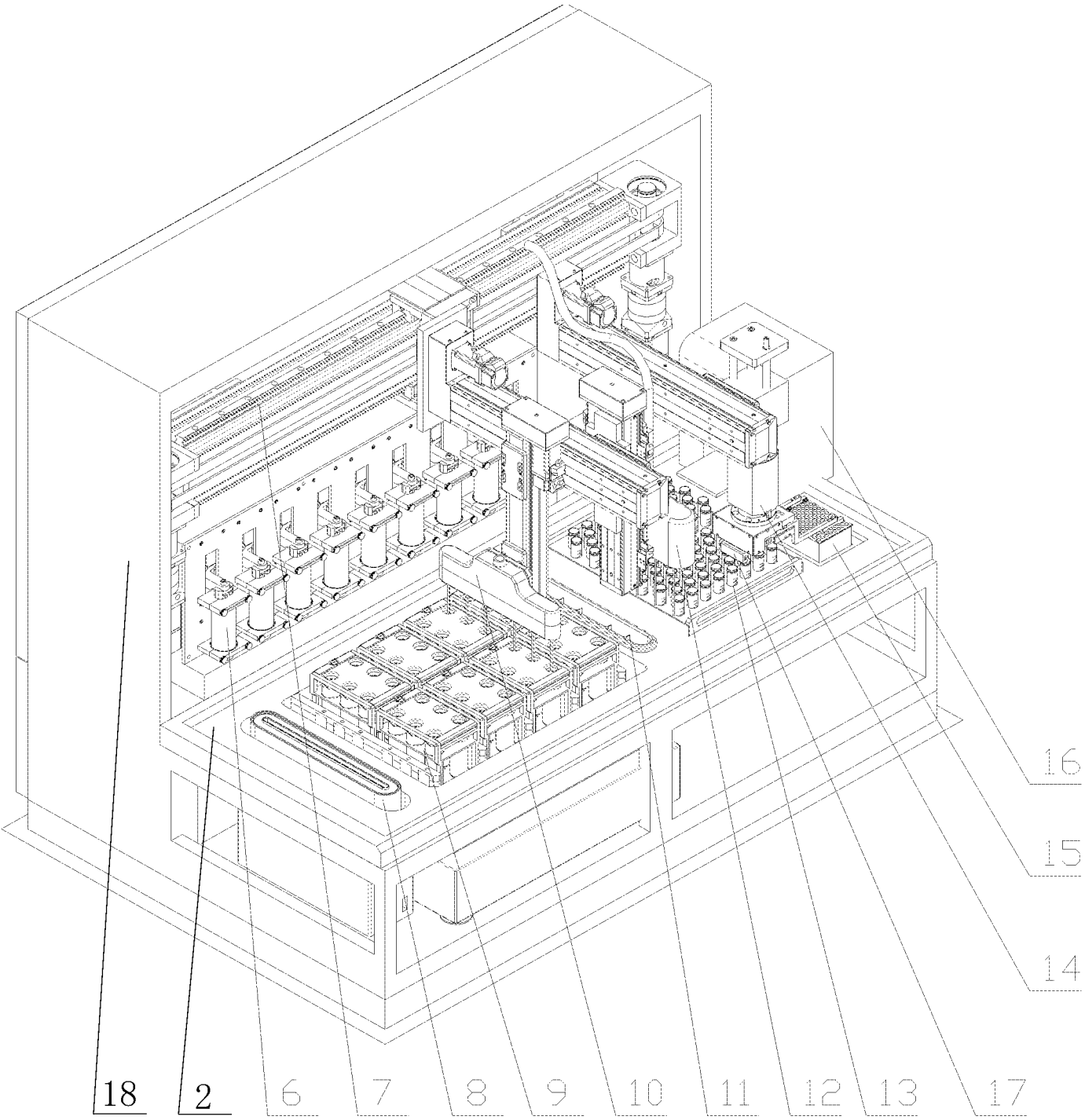


FIG. 1A

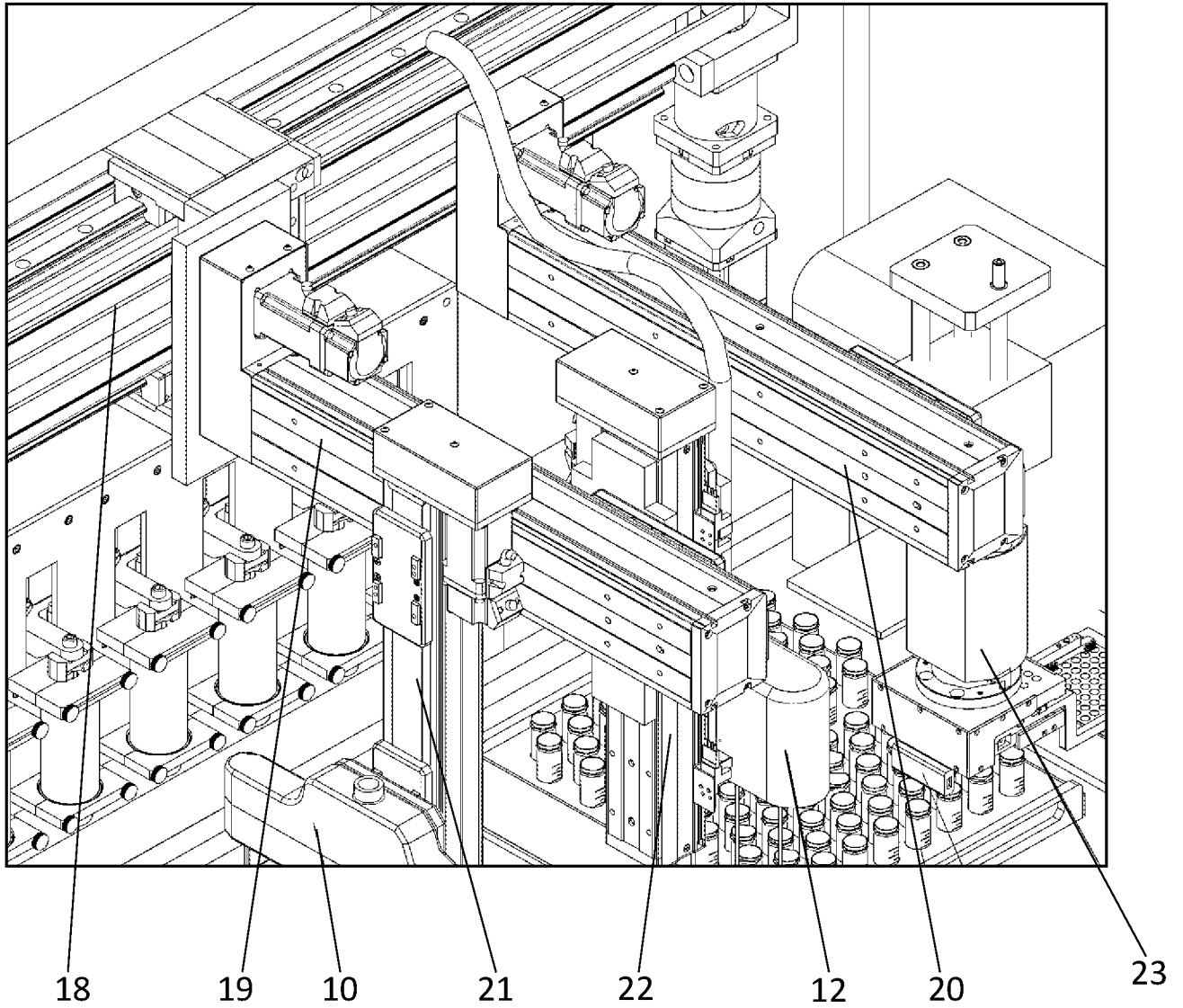


FIG. 2

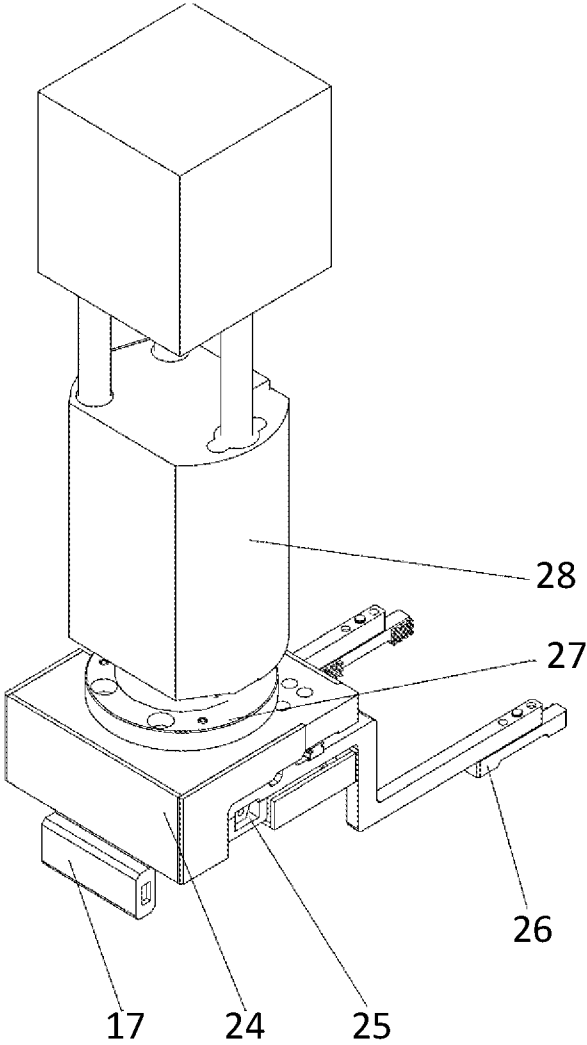


FIG. 3

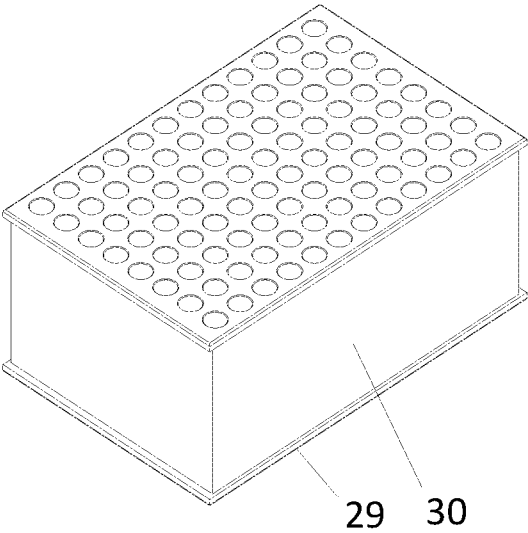


FIG. 4

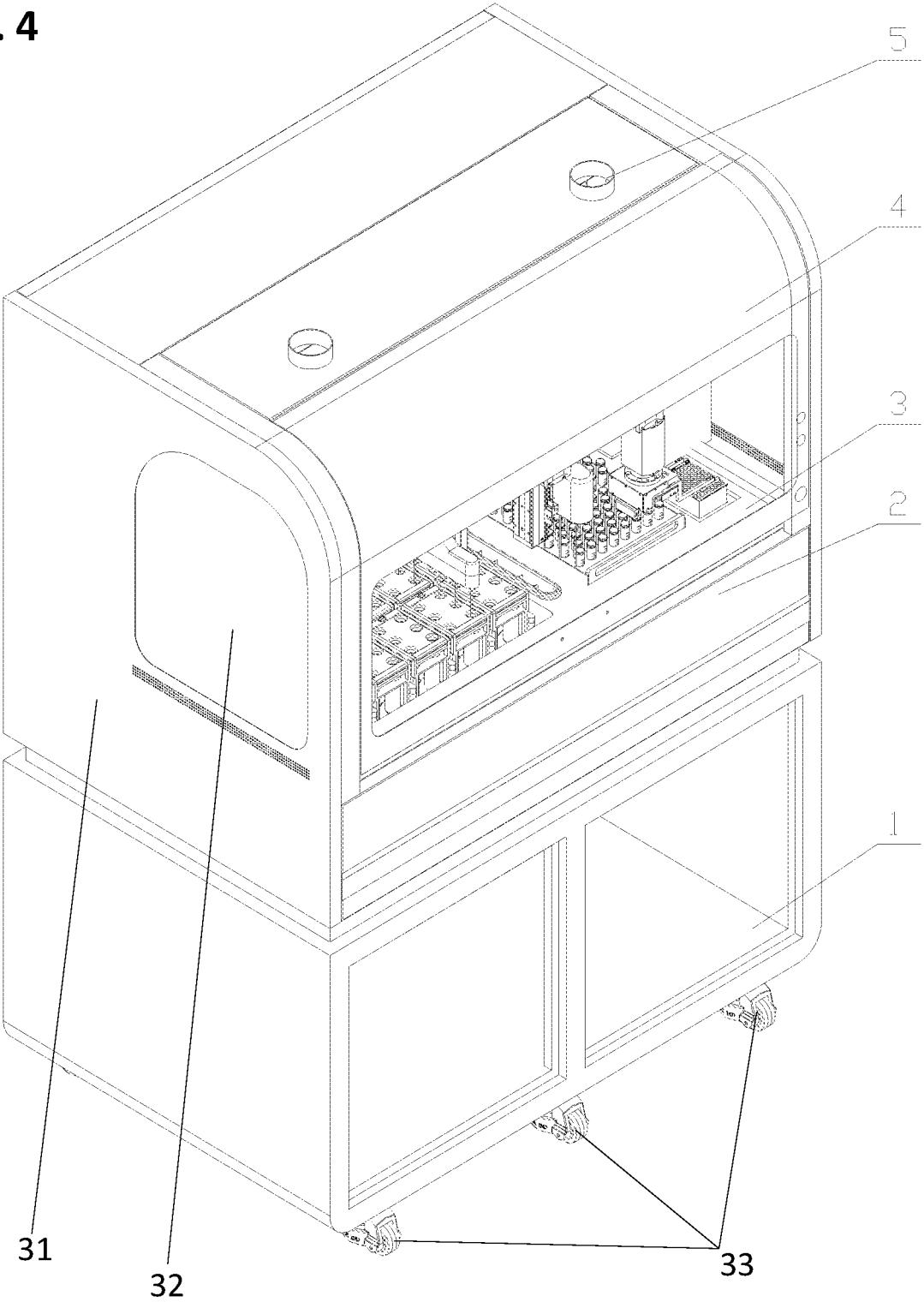


FIG. 5

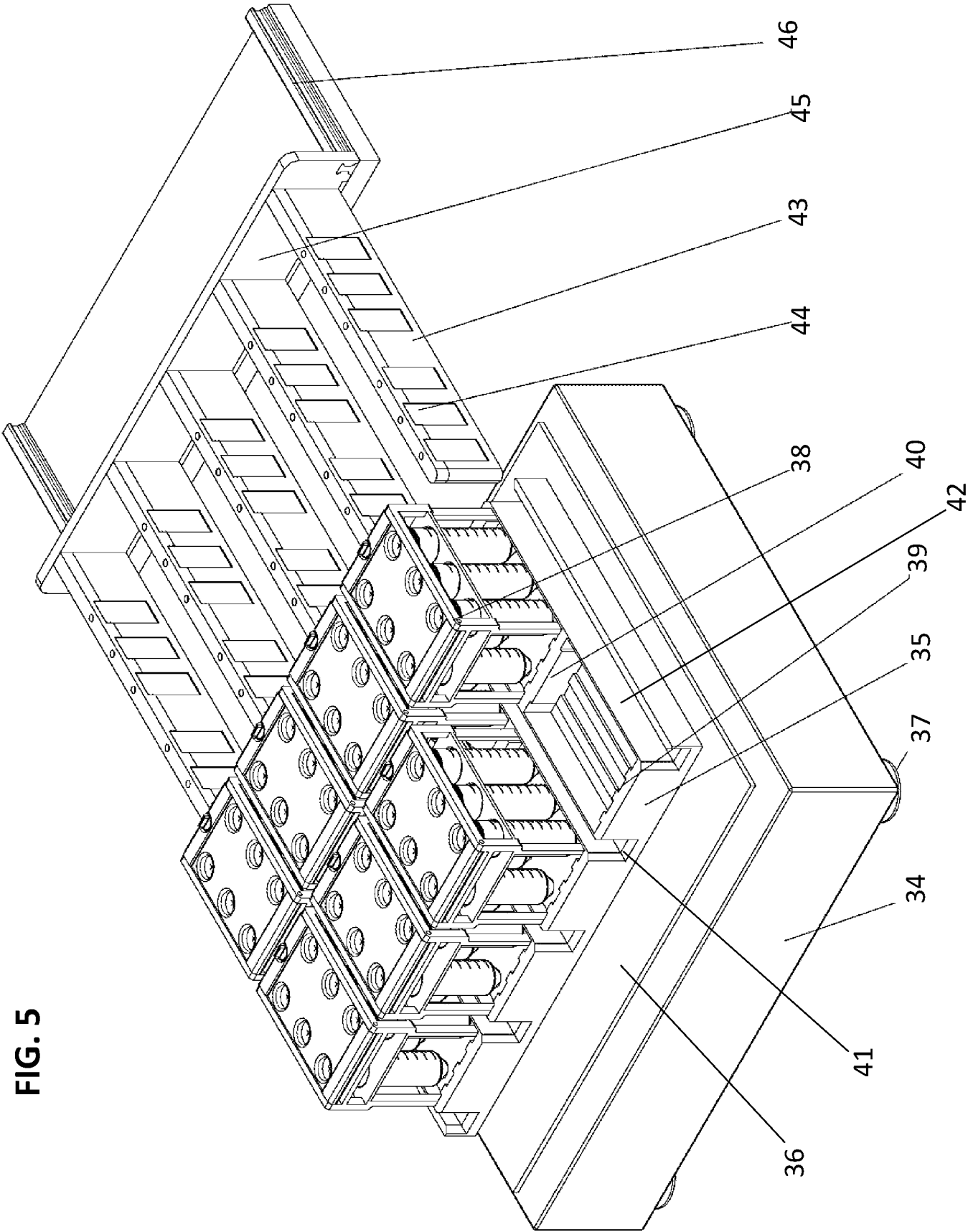


FIG. 6

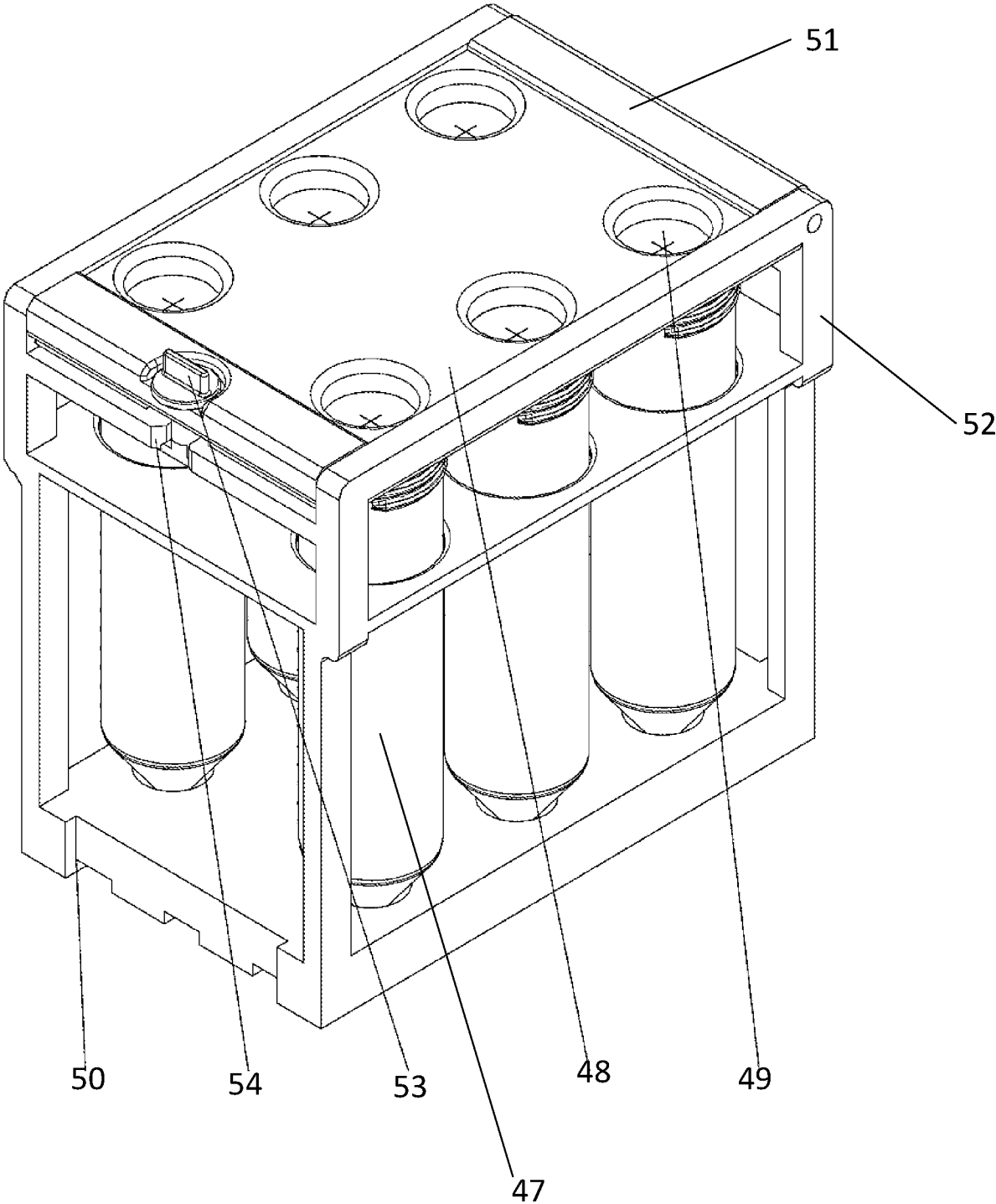


FIG. 7

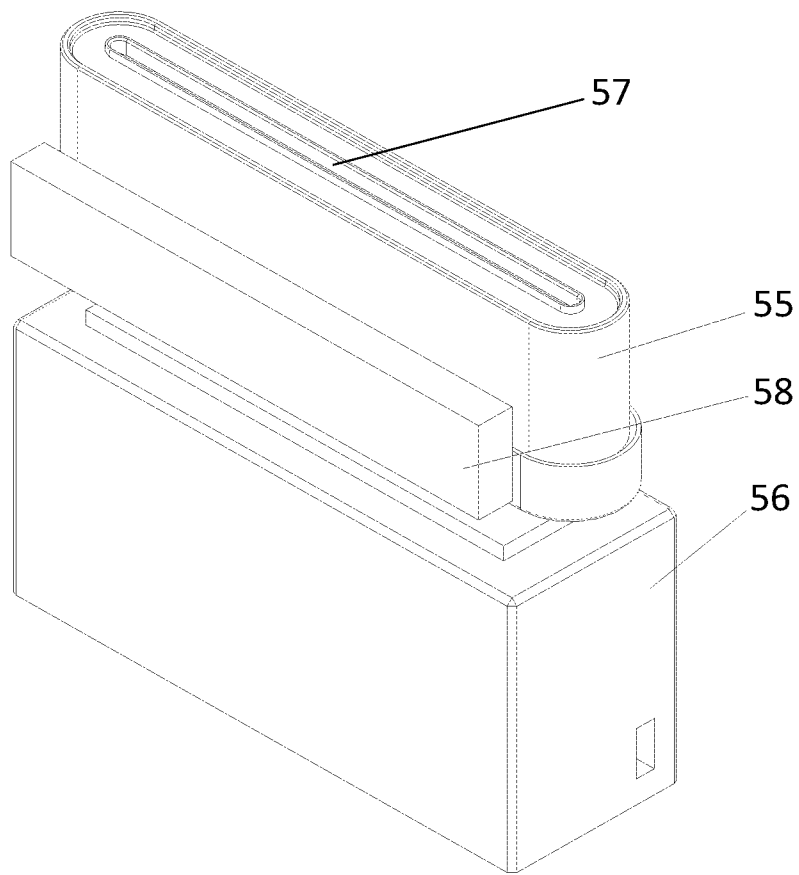


FIG. 8A

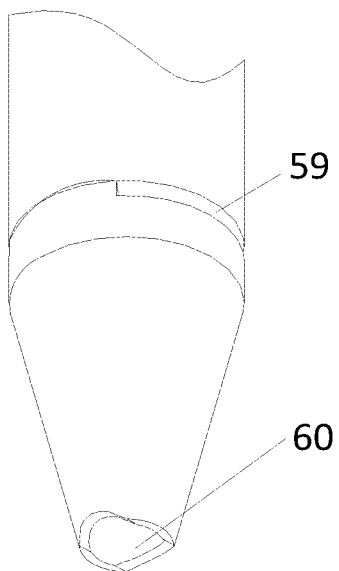


FIG. 8B

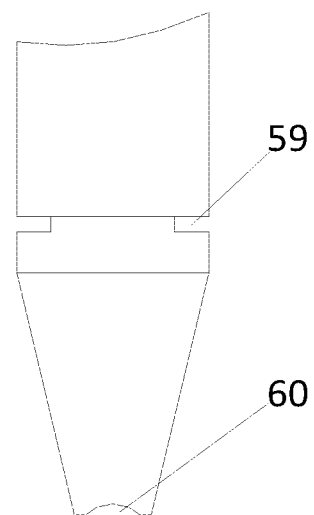


FIG. 8C

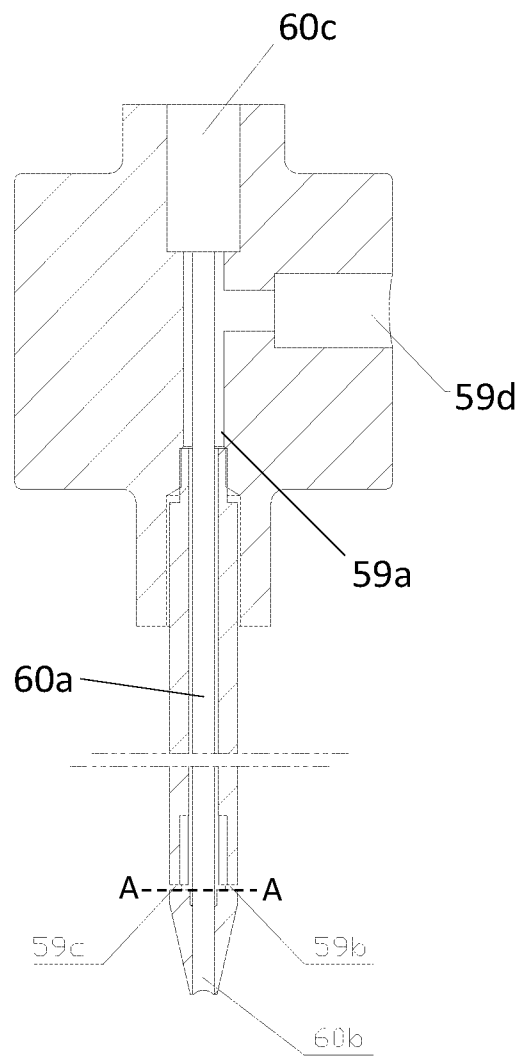


FIG. 8D

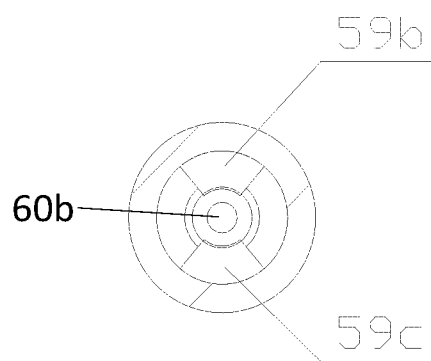


FIG. 9A

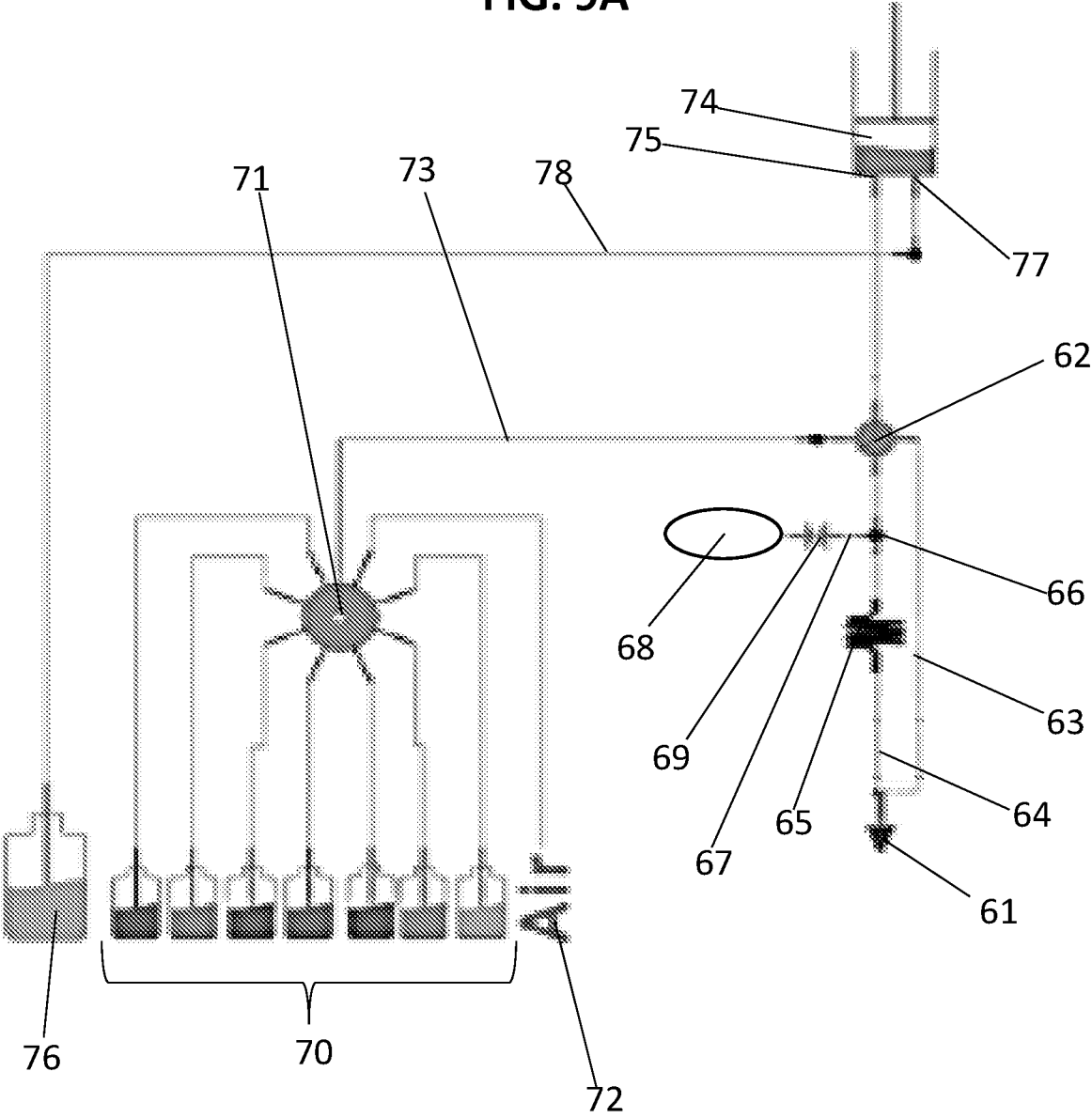
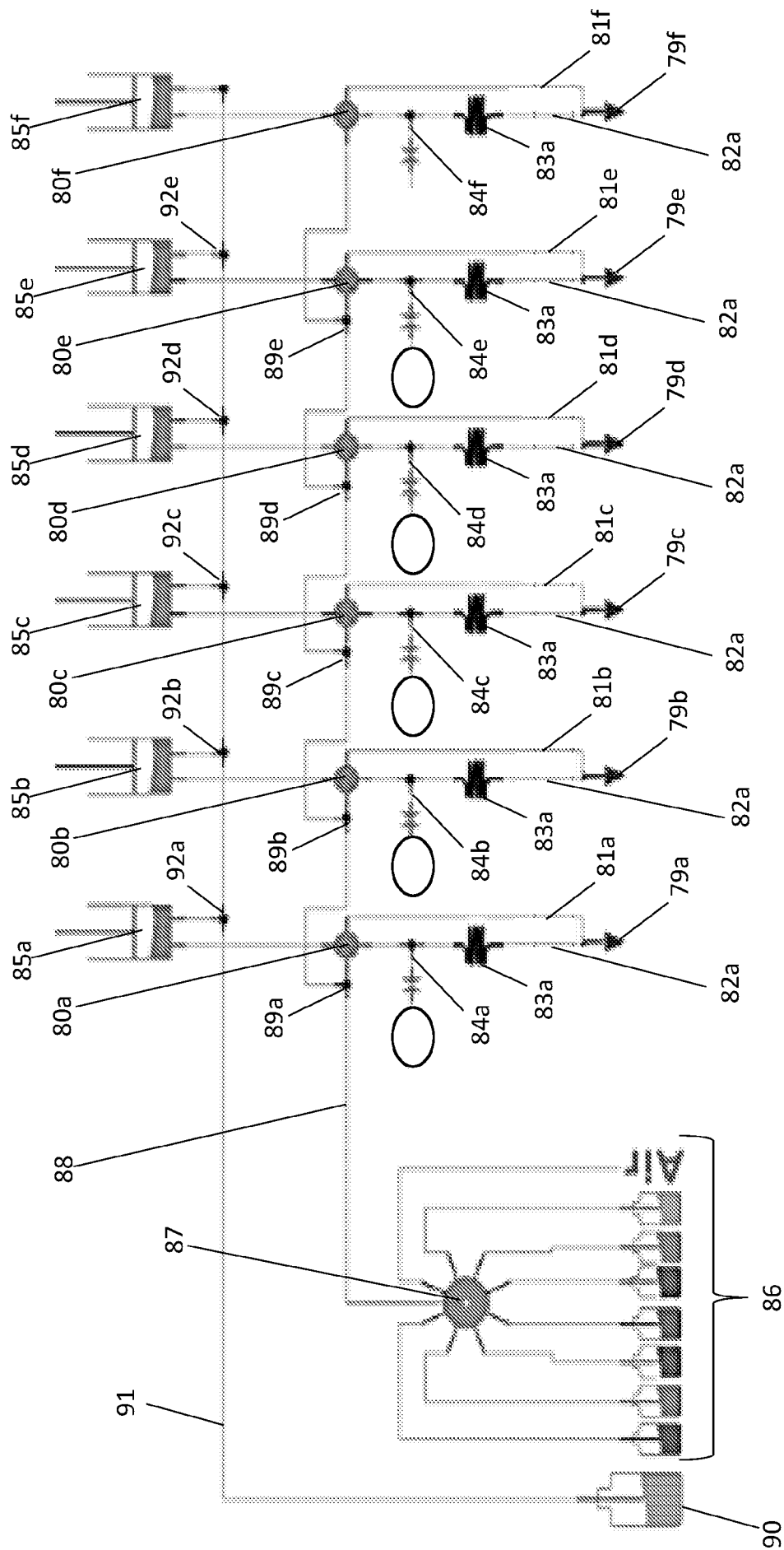


FIG. 9B



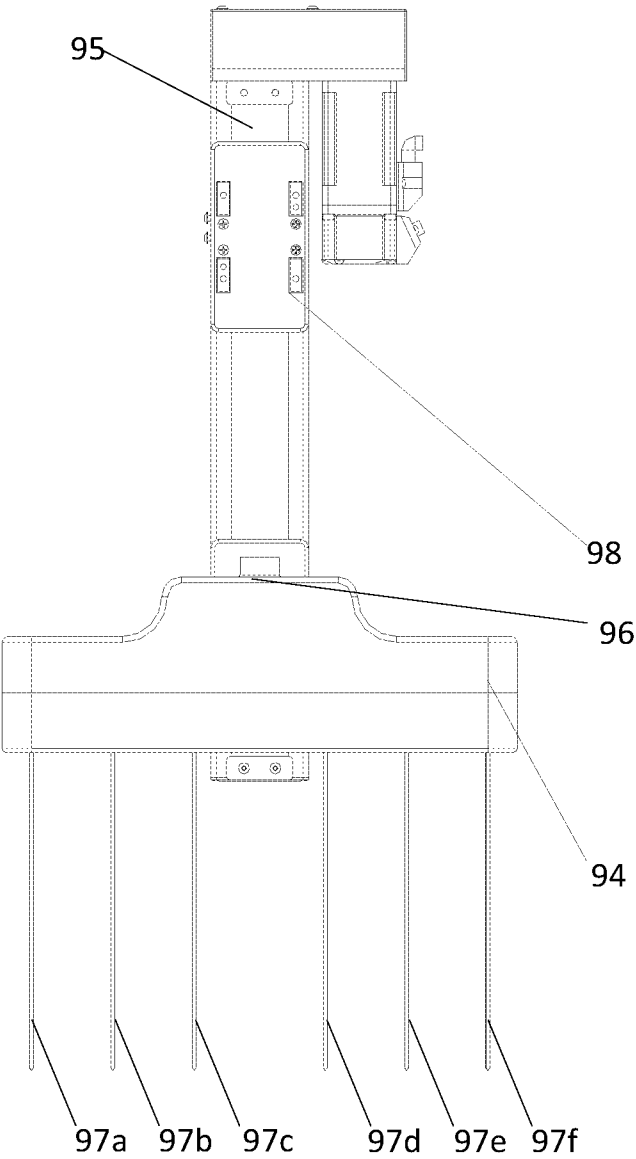


FIG. 10A

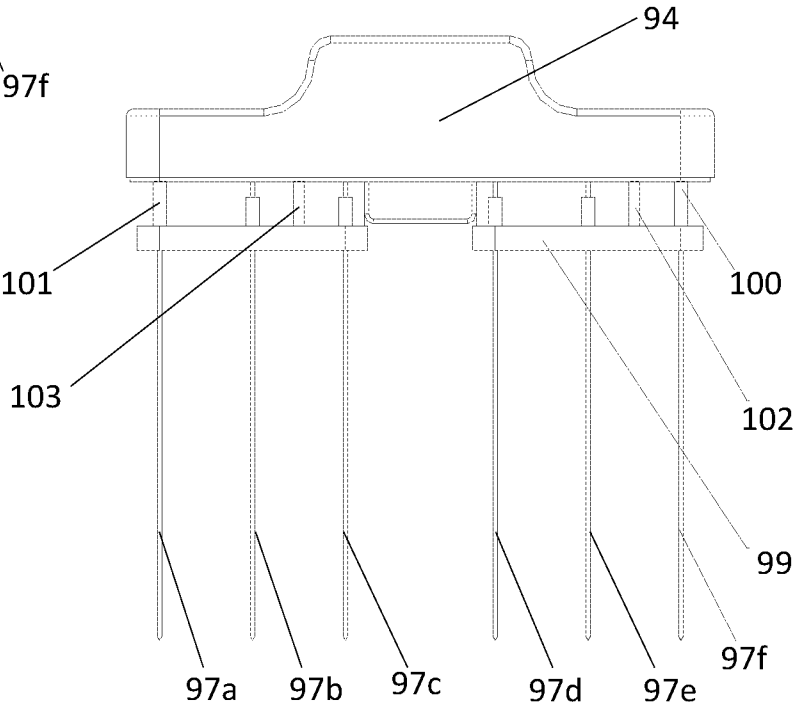


FIG. 10B

FIG. 11A

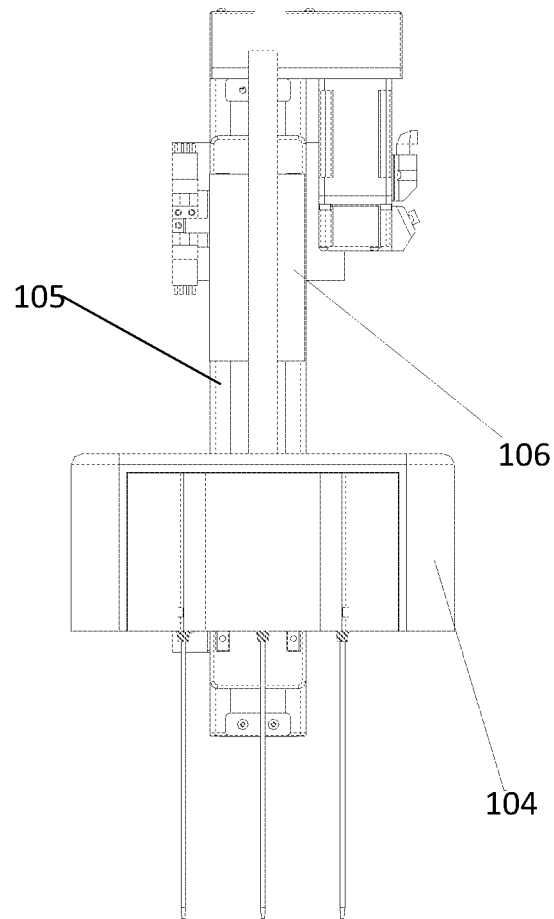


FIG. 11B

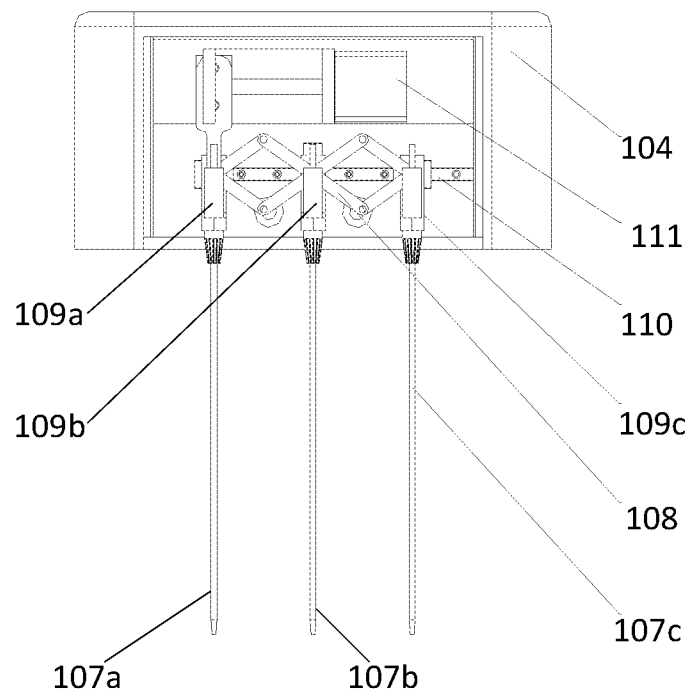


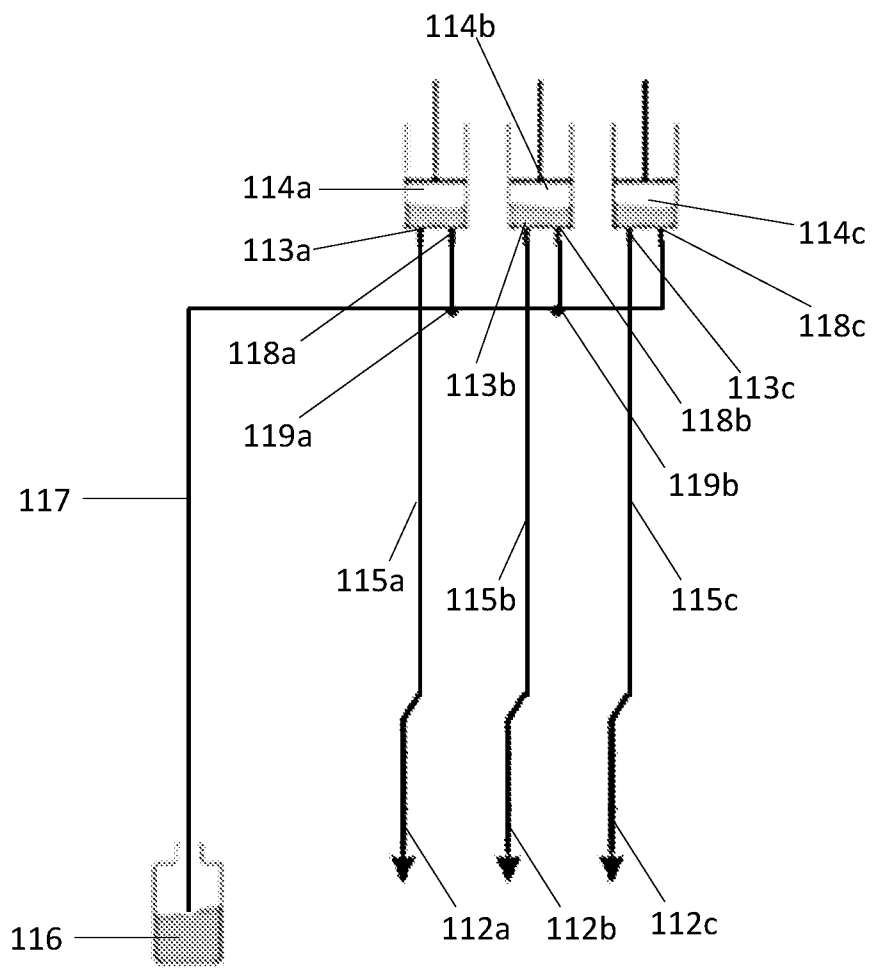
FIG. 12

FIG. 13

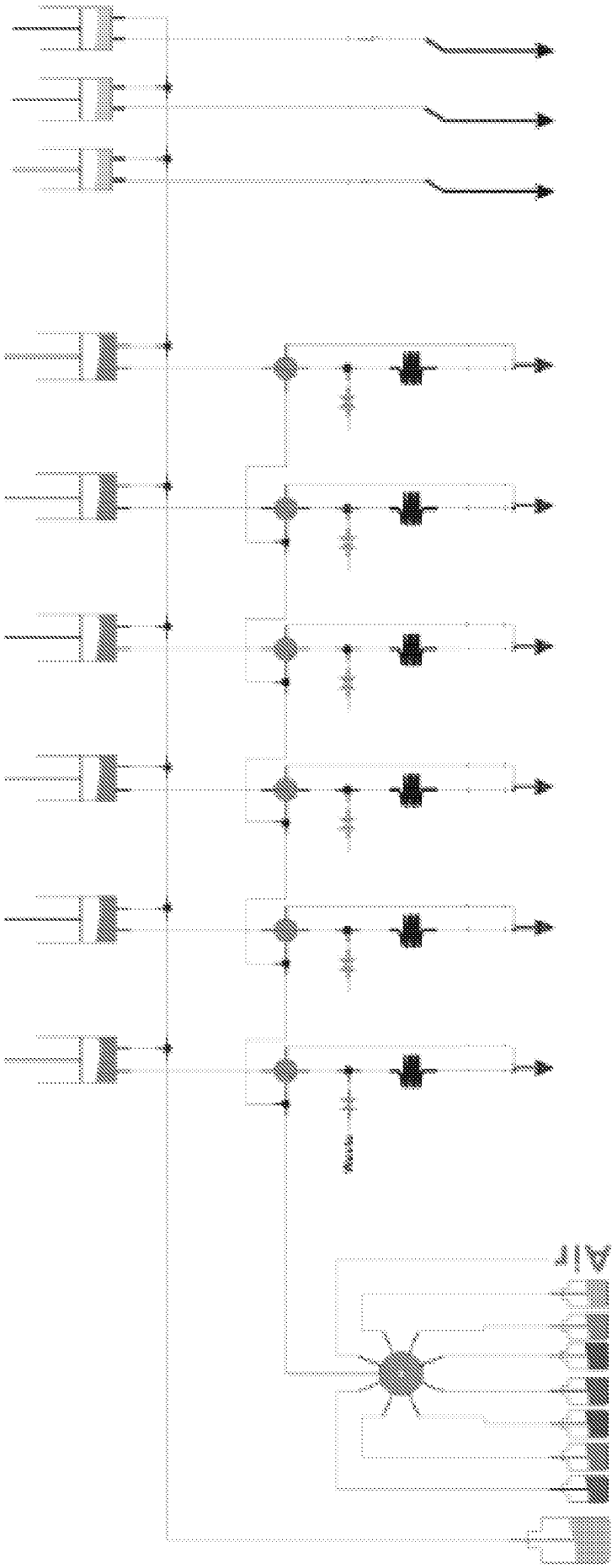


FIG. 14A

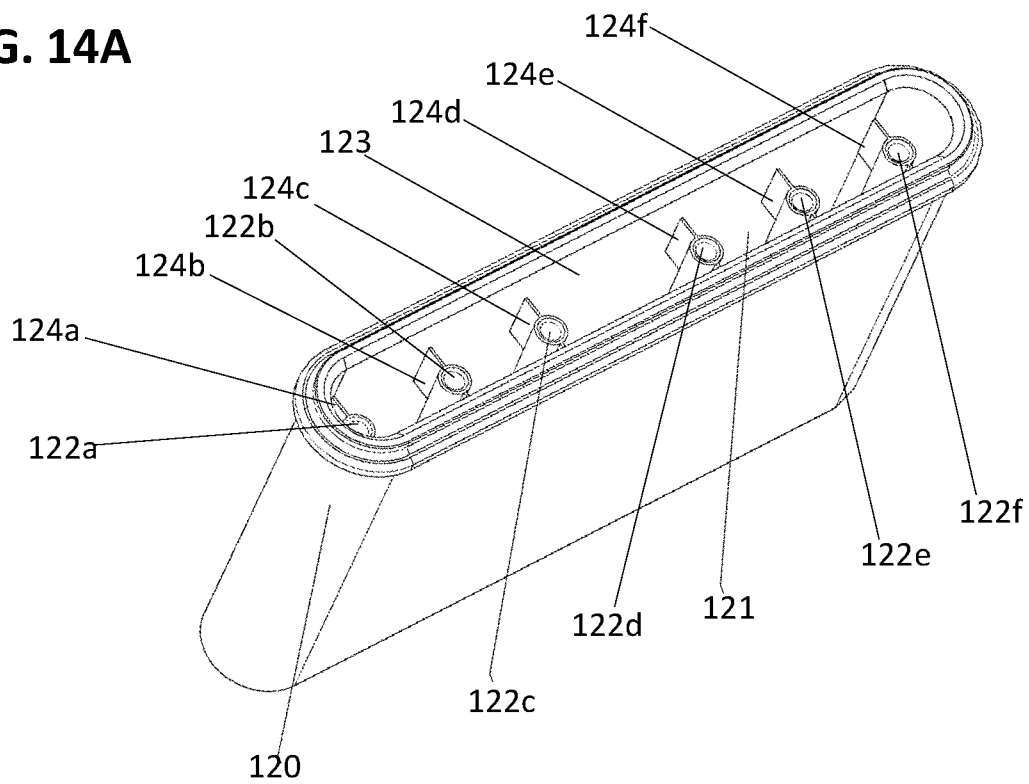


FIG. 14B

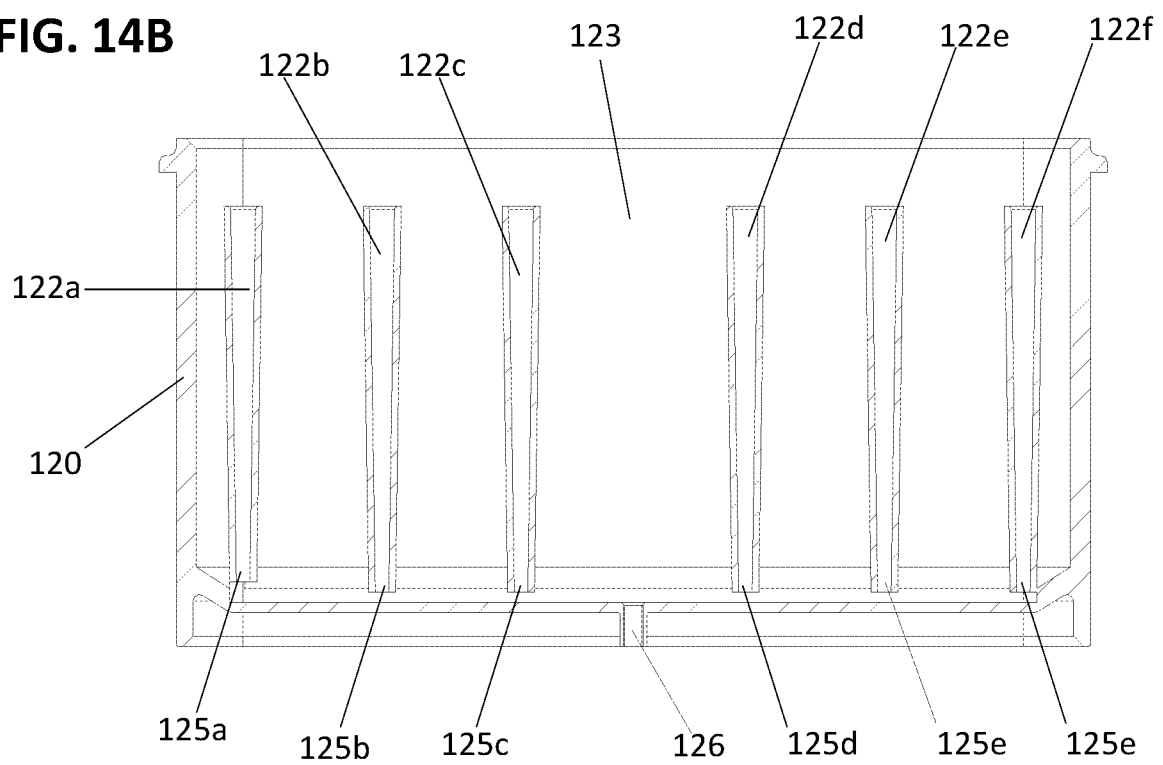


FIG. 15

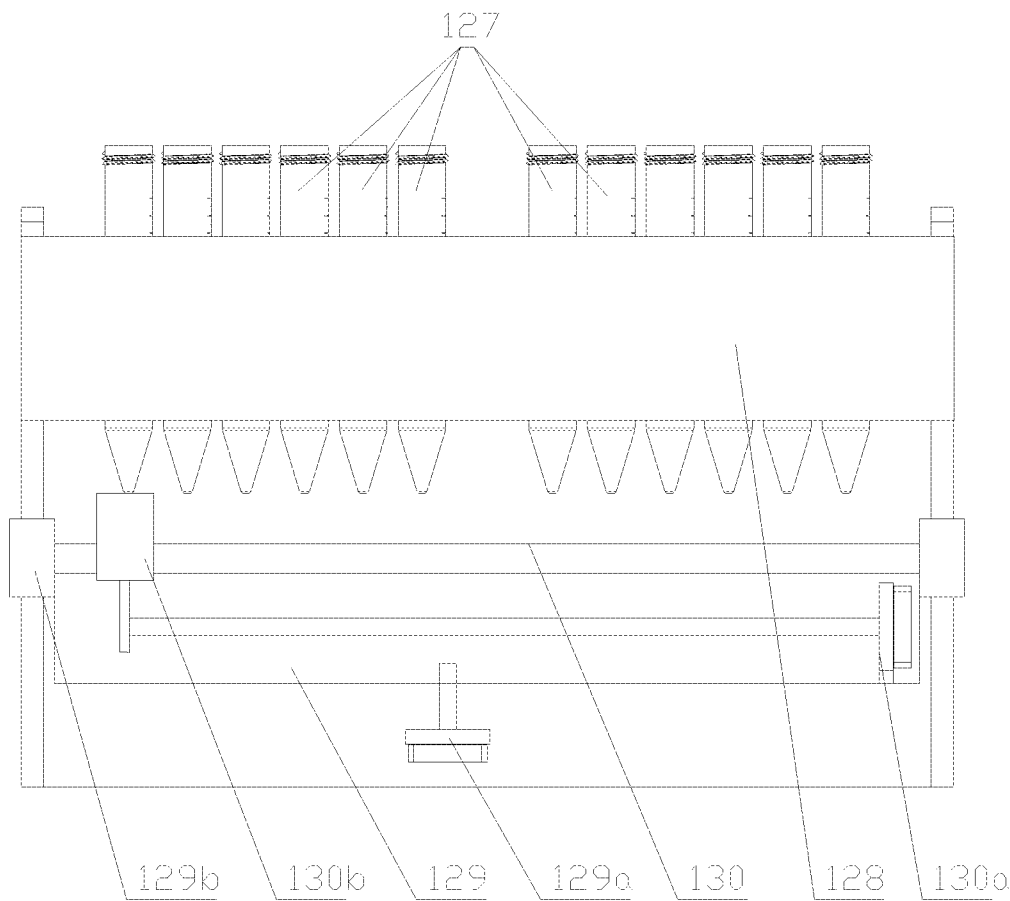


FIG. 16

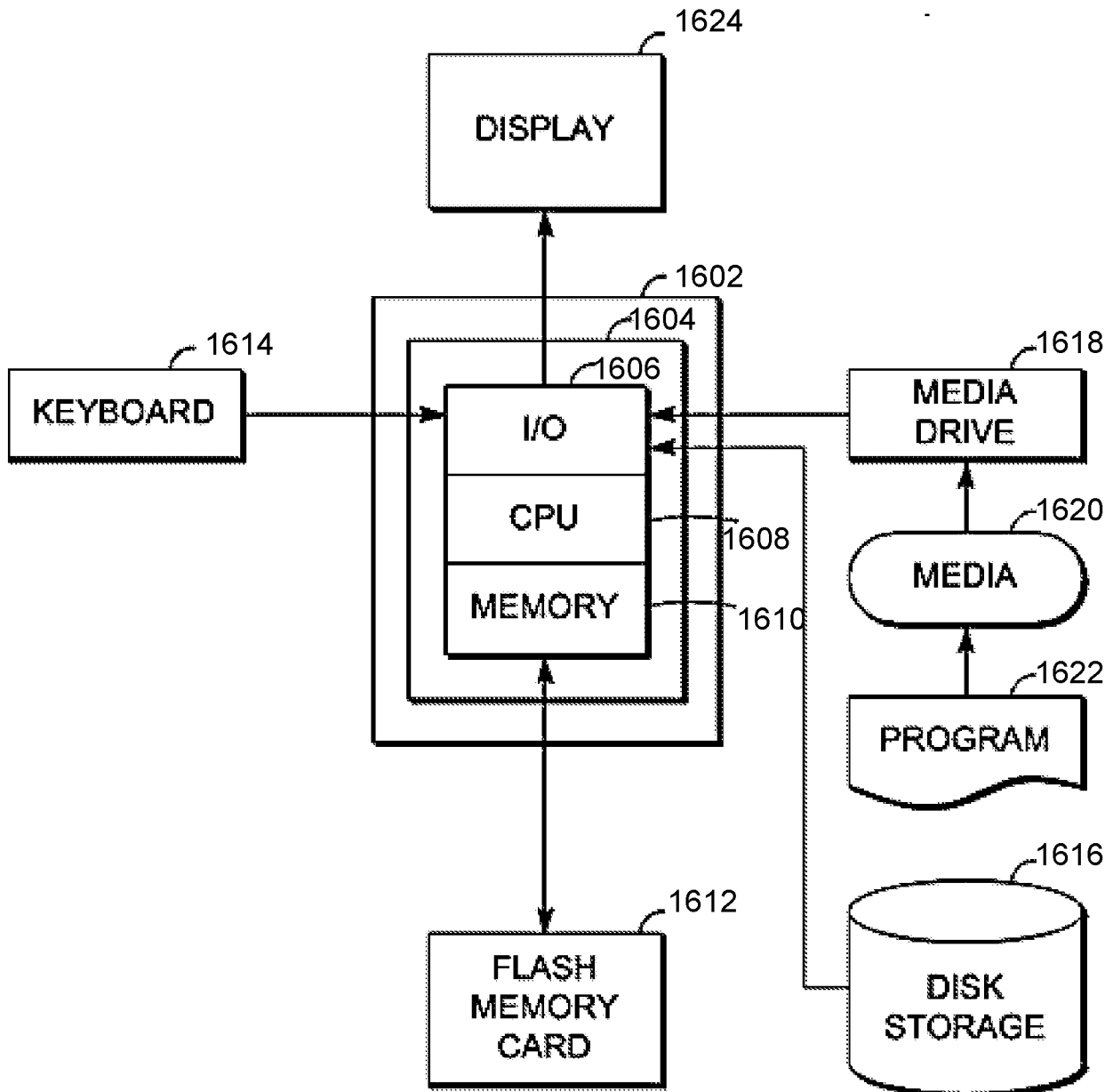


FIG. 17A

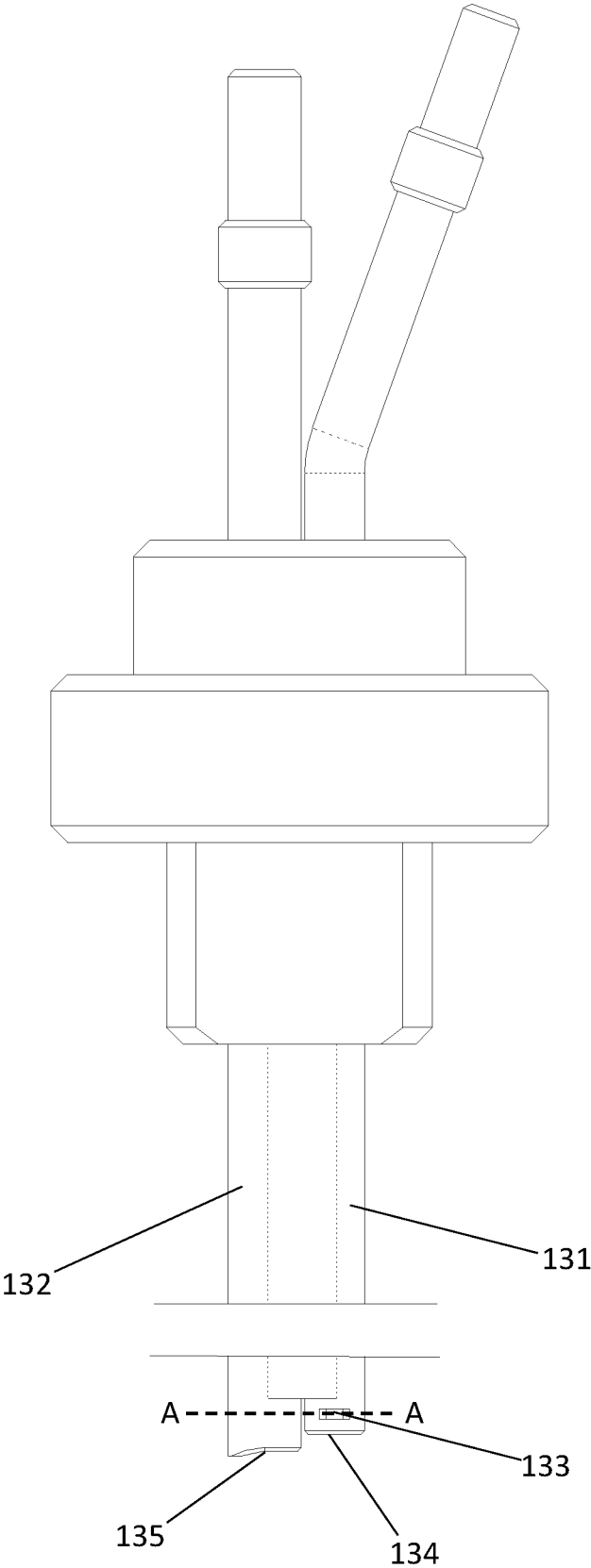


FIG. 17B

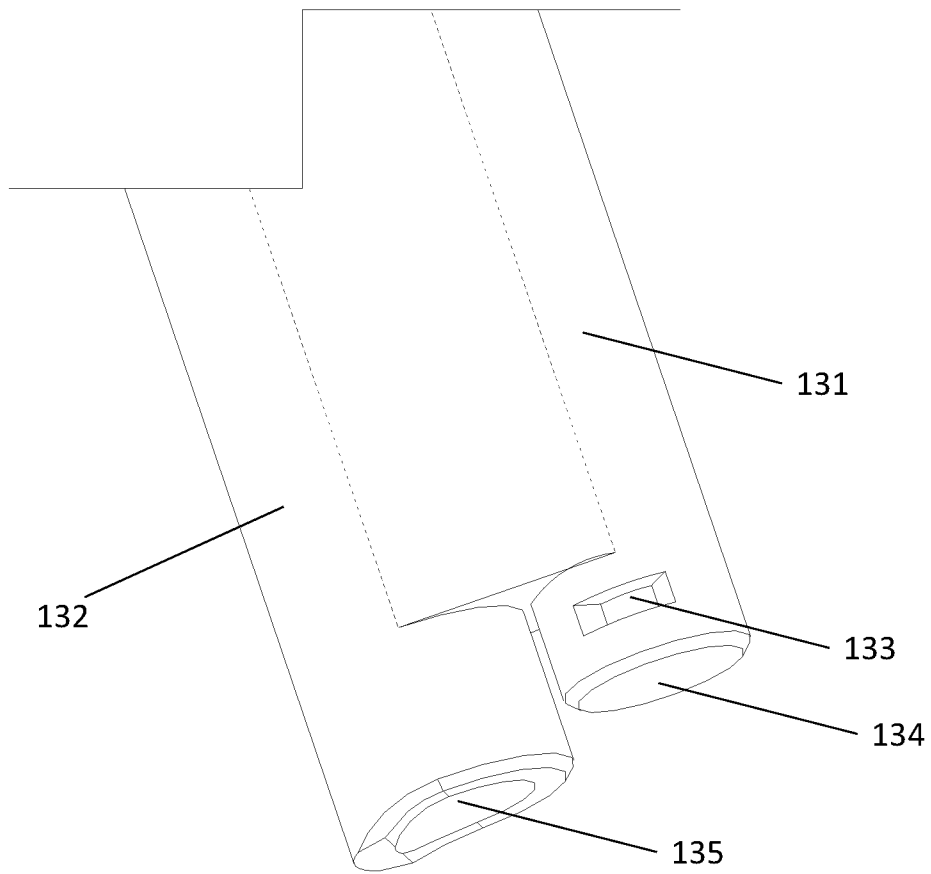
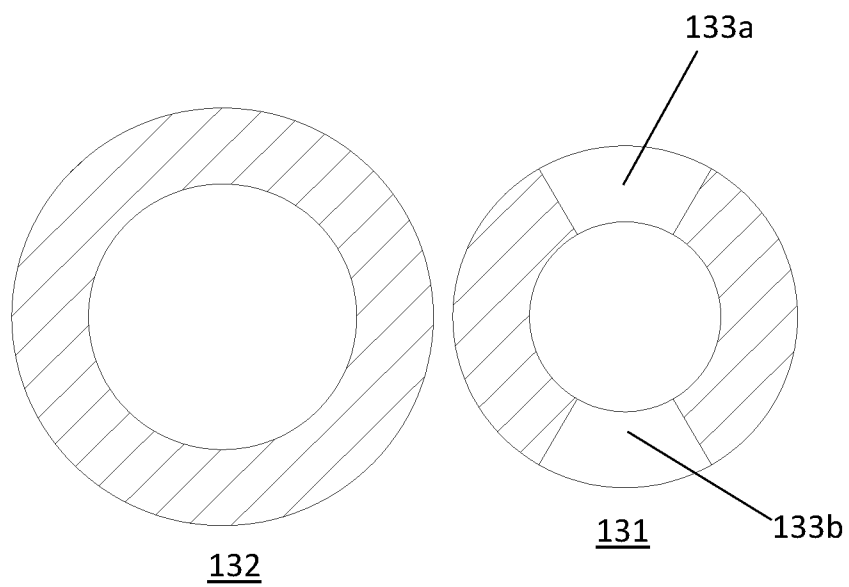


FIG. 17C



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2019/082837

A. CLASSIFICATION OF SUBJECT MATTER

C12M 1/00(2006.01)i; C12M 1/26(2006.01)i; B01L 9/00(2006.01)i; B01L 9/06(2006.01)i

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)

C12M B01L

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

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

CPRSABS; CNKI; CNTXT; DWPI; SIPOABS; EPTXT; USTXT; WOTXT; JPTXT; ELSEVIER; PUBMED and search terms: multiple channel?, pipette, wash+, clean+, liquid, port, pump, etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001005489 A1 (AMERSHAM BIOSCIENCES SV CORP ET AL.) 28 June 2001 (2001-06-28) see abstract, claims 1-40, description, paragraphs [0061]-[0087]	34-38
Y	US 2001005489 A1 (AMERSHAM BIOSCIENCES SV CORP ET AL.) 28 June 2001 (2001-06-28) see abstract, claims 1-40, description, paragraphs [0061]-[0087]	1-32
Y	CN 105665385 A (LIU XIN) 15 June 2016 (2016-06-15) see abstract, claims 1-10, description, paragraphs [0013]-[0032]	1-32
A	CN 1315913 A (CARTESIAN TECHNOLOGIES INC) 03 October 2001 (2001-10-03) see the whole document	1-48
A	CN 103842794 A (ROCHE DIAGNOSTIC HEMATOLOGY INC) 04 June 2014 (2014-06-04) see the whole document	1-48
A	CN 101978273 A (OBISO RICHARD, MCKEEN BRIAN, MESSINA MARK) 16 February 2011 (2011-02-16) see the whole document	1-48

☐ 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

24 June 2019

Date of mailing of the international search report

18 July 2019

Name and mailing address of the ISA/CN

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Facsimile No. (86-10)62019451

Telephone No. (86-10)62412295

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2019/082837

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				DE	60138300	D1	20 May 2009
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				AU	2002239584	A1	18 November 2002
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				AU	4861099	A	24 January 2000
				EP	1129008	A4	05 December 2001
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