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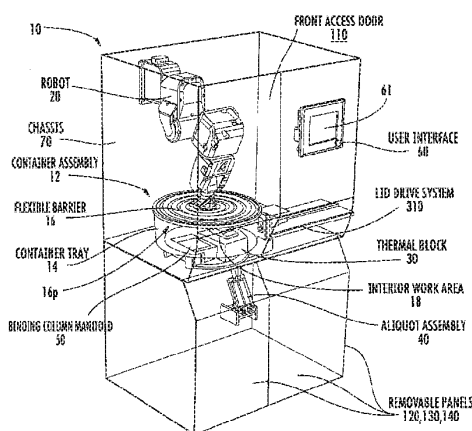
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[Continued on next page]

(54) Title: SYSTEMS AND METHODS FOR PROCESSING SAMPLES IN A CLOSED CONTAINER, AND RELATED DEVICES



(57) Abstract: A system and method for automated processing of nucleic acids and other samples includes a disposable container comprising a tray and a flexible barrier. The barrier is configured to seal with a top edge of the tray, providing a closed, aseptic work area within the sealed tray. A pipette head and/or other sample manipulation device can be attached to the inside of the barrier, and the barrier can include an interface for a robotic arm or other device. When the barrier is sealed over the tray, the barrier separates the contents of the tray from the robot or other manipulation device. The barrier can be flexible, and allow the robotic arm to move the pipette head throughout the work area of the tray. All samples, reagents, pipette tips and other tools or devices for processing nucleic acid samples may remain within the closed compartment provided by the container during processing.

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SYSTEMS AND METHODS FOR PROCESSING SAMPLES IN A CLOSED CONTAINER, AND RELATED DEVICES

RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial Number 60/760,087, filed January 18, 2006, the contents of which are hereby incorporated by reference as if recited in full herein.

FIELD OF THE INVENTION

[0002] The present invention relates to automated processing of samples and materials, and may be particularly suitable for processing nucleic acids in a closed environment.

BACKGROUND OF THE INVENTION

[0003] Nucleic acid based amplification reactions are widely used in research and clinical laboratories to aid in the diagnosis of disease and/or identification of pathogenic organisms in a test sample. Such amplification reactions may also be used for development of vaccines, including, for example, autologous vaccines derived from a patient's own tumor cells. Amplification of nucleic acids isolated from tumor tissue allows for autologous vaccine production even from small tumors, and therefore affords the opportunity to treat patients with minimal tumor burden.

[0004] Generally stated, the currently known amplification schemes can be broadly grouped into two classes based on whether the enzymatic amplification reactions are driven by continuous cycling of the temperature between the denaturation temperature, the primer annealing temperature, and the amplicon (product of enzymatic amplification of nucleic acid) synthesis temperature, or whether the temperature is kept constant throughout the enzymatic amplification process (isothermal amplification). Typical cycling nucleic acid amplification technologies (thermal cycling) are polymerase chain reaction (PCR), and ligase chain reaction (LCR). Specific protocols for such reactions are discussed in, for example, Short Protocols in Molecular Biology, 2nd Edition, *A Compendium of Methods from Current Protocols in Molecular Biology*, (Eds. Ausubel et al., John Wiley & Sons, New York, 1992) chapter 15. Isothermal reactions

include transcription-mediated amplification (TMA), nucleic acid sequence-based amplification (NASBA), and strand displacement amplification (SDA).

[0005] Nucleic acid amplification is discussed in, for example, U.S. Pat. Nos. 4,683,195; 4,683,202; 5,130,238; 4,876,187; 5,030,557; 5,399,491; 5,409,818; 5,485,184; 5,409,818; 5,554,517; 5,437,990 and 5,554,516. It is well-known that methods such as those described in these patents permit the amplification and detection of nucleic acids without requiring cloning, and are responsible for sensitive assays for nucleic acid sequences. However, it is equally well recognized that, along with the sensitivity of detection possible with nucleic acid amplification, the risk of contamination by minute amounts of unwanted exogenous nucleic acid sequences is extremely great. The utility of amplification reactions may be enhanced by methods to control the introduction of unwanted exogenous nucleic acids and other contaminants.

[0006] In particular, for processing of biological samples, including for example the production of therapeutic agents, like vaccines for autologous therapy, current good manufacturing practice (GMP) typically requires manufacture in an aseptic environment.

[0007] Accordingly, there remains a need in the art to provide automated systems and methods for processing nucleic acids and other samples.

SUMMARY OF EMBODIMENTS OF THE INVENTION

[0008] Embodiments of the present invention are directed to systems, apparatus and methods for automated processing of one or more samples. The systems can be used to manipulate items in a closed environment, and may be particularly useful in the fields of medicine, diagnostics, biotechnology, electronics and nanotechnology. Embodiments of the invention may be particularly relevant for processing biological samples, including, but not limited to, tissues, blood, blood products, nucleic acids (*e.g.*, RNA, DNA), proteins, cell cultures, and the like.

[0009] Embodiments of the present invention provide an apparatus for manipulating one or more items in a closed container. The container, also referred to herein as an "isolation container", comprises a tray defining an interior chamber, which is configured to hold any number of items to be manipulated, and a flexible barrier configured and dimensioned to cover the interior area and seal with the container tray. A

tool for manipulating items within the interior area is attached to or integrated with or within the flexible barrier.

[0010] The tool can have a first interface that is accessible from an exterior side of the barrier that is configured to attach to a robotic device. The tool can also include a second interface that can extend from an opposite side of the barrier, such that it is disposed within the interior area when the flexible barrier is sealed with the container. The tool can be configured to manipulate items within the container when the robotic device is attached to the first interface. In some embodiments, the one or more items in the closed container comprise, for example, any of nucleic acids, other samples, reagents, wash fluids, pipette tips, vessels, other consumables and/or any combination thereof. Other tools or devices may also be disposed within the container, for example tools or devices for processing, manipulating, measuring, analyzing, sampling and/or storing samples or other items within the container.

[0011] In some embodiments, systems and methods for automated processing of nucleic acids and other samples include a single-use disposable isolation container assembly with a tray and a flexible barrier configured to seal with the tray, thereby providing a closed work area within the sealed tray. The closed work area may be aseptic.

[0012] A pipette head and/or other sample manipulation device can be attached to the inside of the barrier, and the barrier can include an interface for a robotic arm or other device that is used to manipulate items within the sealed work area. When the barrier is sealed over the tray, the barrier separates the contents of the tray from the robot or other manipulation device. The barrier is flexible, and allows the robotic arm to move the pipette head or other sample manipulation devices throughout the work area of the tray. All samples, reagents, pipette tips and other consumables, tools or devices for processing nucleic acid samples may remain within the closed compartment provided by the isolation container during processing.

[0013] In another embodiment, methods of processing nucleic acids, (*e.g.*, RNA and/or DNA) utilize a disposable (single-use) isolation container to reduce the risk of contaminating subject material with undesired biological matter, *e.g.*, from an operator, another subject or the external environment. In some embodiments, the isolation container is designed for RNA isolation from a biological sample, including but not limited to one or more of the following: tumor tissue, blood, blood products, cells, pathogens, etc. In particular embodiments, the biological sample comprises a tumor

homogenate, and the system provides all the features and functionality to convert clarified tumor homogenate into *in vitro* transcribed (IVT) RNA.

[0014] Typically, only the inside of the isolation container is exposed to the subject material, thereby preventing possible contamination of the processing system and reducing cleaning requirements between consecutive subject samples processed by the system. In some embodiments, the processing system processes samples in one isolation container at a time. In other embodiments, the systems can be configured to process samples in two or more isolation containers substantially concurrently.

[0015] In some embodiments, the present invention provides an apparatus for the transfer of fluid comprising working fluid and a working fluid pump that are separated from a sample device by a diaphragm. In use, a sample or other fluid may be drawn into or expelled from the sample device by a change in pressure which is transmitted across the diaphragm, *e.g.*, by movement of the diaphragm when the working fluid pump changes pressure of the working fluid. In one embodiment, the sample device is a pipette tip or other tube for uptaking, dispensing and/or mixing fluidic samples, and/or for transferring a sample, reagent or other fluid from one location to another location. The pipette tip or tube may be of any suitable shape and size.

[0016] In yet other embodiments, the present invention provides an apparatus for measuring the volume of a fluid comprising: at least one light source or emitter and at least one receiver; a cuvette configured with a light path through which the receiver can detect a change in the light path associated with whether the cuvette contains fluid or is empty; and a fluid transfer device in communication with the receiver to determine the volume of fluid that has been removed from the cuvette.

[0017] Other embodiments are directed to biological sample processing containers. The containers include a single-use disposable tray having a substantially rigid body with a first workstation configured to hold a vessel for incubation in a thermal block (*e.g.*, a single tube, multi-well plate or strips, a PCR plate, etc.), a second workstation configured to hold reagents, and a third workstation configured to hold pipettes.

[0018] Some embodiments are directed to flexible barriers having an outer edge portion configured to seal to a tray to define a sealed closed interior chamber. The flexible barrier includes an elastomer and is sealably attached to a robotic arm interface at a medial portion of the barrier.

[0019] Yet other embodiments are directed to an automated pipette tip disengagement system. The system includes: (a) a tray having a sidewall; and (b) a robotic arm merging into a manipulation tool having an outwardly extending lever configured to contact the tray sidewall, whereby contact with the sidewall forces the lever to pivot and release a respective used pipette tip held by the manipulation tool. In some embodiments, the tray has an angled sidewall that contacts the manipulation tool lever.

[0020] Some embodiments are directed to systems for processing liquids. The systems include: (a) a robotic arm; and (b) a manipulation tool that cooperates with the robotic arm, the tool configured to releasably engage a pipette tip and automatically translate to pierce a cover on a vessel a plurality of times in different spaced apart locations before withdrawing fluid from the vessel through one of the pierced openings in the cover.

[0021] Other embodiments are directed to elution trays. The trays are sterile biocompatible elution trays having a plurality of spaced apart receptacles, a plurality on a first side of an upwardly extending barrier and a plurality on an opposing side of the barrier. The receptacles have a channel that extends on each side of and tapers down in the direction of a primary tubular portion.

[0022] Still other embodiments are directed to kits for use with an automated processing system. The kits include: (a) a single-use disposable container comprising a tray and a flexible barrier configured to sealably attach thereto; (b) a single-use disposable reagent rack configured to reside in the container at a first workstation; (c) a single-use disposable binding column manifold configured to reside in the container; and (d) a single-use disposable pipette rack configured to reside in the container.

[0023] Some embodiments are directed to methods of transferring liquids. The methods include: (a) programmatically directing a robotic arm to move an interface tool releasably holding a pipette tip; (b) automatically piercing a sealant on a vessel holding a target liquid a plurality of times using the pipette tip; then (c) automatically withdrawing liquid from the vessel with the pierced sealant using the pipette tip.

[0024] Some embodiments are directed to methods of releasing liquids from pipettes. The methods include: (a) programmatically directing a robotic arm to move an interface tool releasably holding a pipette to orient the pipette in a downwardly extending angled orientation with the tip proximate to a receiving surface in a closed container; (b)

then automatically moving the downwardly oriented angled pipette in a substantially straight line along a plane, while releasing a flowable substance from the pipette.

[0025] Yet other embodiments are directed to methods of aspirating liquids into pipettes. The methods include: (a) programmatically directing a robotic arm to move an interface tool releasably holding a pipette to engage a vessel holding a target fluid in a closed container; then (b) automatically moving the pipette inside the vessel to mix the liquid in the vessel; then (c) aspirating the mixed liquid into the pipette.

In some embodiments, the method can include aspirating and dispensing the liquid to mix the liquid (once or multiple times).

[0026] Still other embodiments are directed to automated methods of processing a sample in a closed system. The methods include: (a) providing a sample in a sealably closed container having a flexible barrier; and (b) programmatically directing a robotic arm to cooperate with the flexible barrier to move an interface tool inside the closed container through a series of operations while the closed container remains sealed to process the sample.

[0027] The method may optionally also include one or more of the following: (c) electronically and automatically measuring volume and concentration of the sample at a plurality of times during the amplification; (d) electronically and automatically monitoring seal integrity of the closed container before, after, and/or during use; and (e) capturing at least one amplified RNA sample in an aliquot vessel without disrupting the sealed status of the closed system.

[0028] Still other embodiments of the invention are directed to apparatus for manipulating items in a closed container. The apparatus include: (a) a container having an interior region configured to hold a plurality of items to be manipulated; and (b) a recirculating vacuum system configured to circulate air sealed within the interior region of the container in a closed loop.

[0029] Although described in some embodiments herein with respect to method aspects of the present invention, it will be understood that the present invention may also be embodied as systems and computer program products. Also, it is noted that any of the features claimed with respect to one type of claim, such as a system, apparatus, method or computer program, may be claimed or carried out as any of the other types of claimed operations or features.

[0030] Other systems, methods, system components and/or computer program products according to embodiments of the invention will be or become apparent

to one with skill in the art upon review of the following drawings and detailed description. It is intended that all such additional systems, methods, and/or computer program products be included within this description, be within the scope of the present invention, and be protected by the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] Other features of the present invention will be more readily understood from the following detailed description of exemplary embodiments thereof when read in conjunction with the accompanying drawings, wherein like reference numerals represent like elements. The drawings are merely exemplary to illustrate certain features that may be used singularly or in combination with other features and the present invention should not be limited to the embodiments shown. Features shown with respect to one embodiment or figure may be used with other embodiments or figures.

[0032] **Figure 1** is a perspective view of a processing system according to embodiments of the present invention;

[0033] **Figure 2** is a side view of the upper portion of the system of **Figure 1**, including an isolation container on a work surface;

[0034] **Figure 3** is a perspective view of one embodiment of the work surface of the system of **Figure 1**, illustrated without the isolation container;

[0035] **Figure 4** is a perspective view of an isolation container assembly with the flexible barrier not yet attached according to embodiments of the present invention;

[0036] **Figure 5** is a cutaway perspective illustration of an isolation container assembly according to embodiments of the present invention;

[0037] **Figure 6** is a cutaway perspective view of the isolation container assembly of **Figure 5**;

[0038] **Figures 7A and 7B** are side views of a syringe pump system according to embodiments of the present invention;

[0039] **Figures 8A and 8B** are cross-sectional side views of a pipette head adapted to cooperate with a fluid pump system according to embodiments of the present invention;

[0040] **Figure 8C** is a top view of a flexible isolation diaphragm used in the pipette head of **Figure 8A**, according to embodiments of the present invention;

[0041] **Figure 8D** is a cross-sectional view of the flexible isolation diaphragm shown in **Figure 8C**;

[0042] **Figures 9A and 9B** are perspective and cross-sectional views, respectively, of a flexible barrier according to embodiments of the present invention;

[0043] **Figures 9C and 9D** are perspective and cross-sectional side views, respectively, of other embodiments of a flexible barrier;

[0044] **Figure 9E** is a perspective view of a flexible barrier with an integral coupler, the coupler in the barrier shown in partial section view, according to embodiments of the invention;

[0045] **Figure 9F** is a perspective view of a portion of a robotic arm having a coupler configured to engage the barrier coupler shown in **Figure 9E** according to embodiments of the present invention;

[0046] **Figure 9G** is a perspective view of the assembly of the components shown in **Figures 9E and 9F** (without the flexible barrier) and with the outer housing over the internal components shown transparent and in broken line;

[0047] **Figure 9H** is a perspective view of the assembly shown in **Figure 9G** with the flexible barrier attached according to embodiments of the present invention;

[0048] **Figure 10** is a cross-sectional view of a PCR plate and thermal cycler lid assembly according to embodiments of the present invention;

[0049] **Figure 11** is a perspective view of a thermal cycler assembly with a thermal cycler lid drive system according to embodiments of the present invention;

[0050] **Figure 12** is a perspective view of the thermal cycler lid drive system of **Figure 11** in use with a flexible thermal cycler lid seal of a container according to embodiments of the present invention;

[0051] **Figures 13A and 13B** are cross-sectional views of the lid seal of **Figure 12** during movement of the thermal lid into and out of the work space of the container according to embodiments of the present invention;

[0052] **Figure 13C** is a partial cutaway side perspective view of the lid seal and container shown in **Figures 13A and 13B**.

[0053] **Figure 14** is a perspective view of a manifold for housing DNA and RNA binding columns according to embodiments of the present invention;

[0054] **Figure 15** is a perspective view of the manifold of **Figure 14** during engagement with a pipette head to move the manifold between stations according to embodiments of the present invention;

[0055] **Figure 16** is a schematic side view depicting a closed vacuum system prior to use with an isolation container according to embodiments of the present invention;

[0056] **Figure 17** is a schematic side view of the vacuum system of **Figure 16** during use with the isolation container according to embodiments of the present invention;

[0057] **Figure 18** is a perspective view of a processing system work surface with a cutaway of an isolation tray, showing cooling units for controlling humidity and vapor concentrations according to embodiments of the present invention;

[0058] **Figure 19A** is a cross-sectional perspective view of a cuvette attached to an isolation tray according to embodiments of the present invention;

[0059] **Figure 19B** is a side perspective view of cooperating components of a spectrophotometer cuvette measuring system according to embodiments of the present invention.

[0060] **Figures 20A – 20D** are examples of operations of a system to measure volume in a volumetric cuvette according to embodiments of the present invention, each figure being a section view of the volumetric cuvette measuring system;

[0061] **Figure 20E** is a top, side perspective view of a multi-cuvette volume measurement system that can operate as described with respect to **Figures 20A-20D** according to embodiments of the invention;

[0062] **Figure 20F** is a bottom perspective view of the container shown in **Figures 4 and 5** illustrating cuvettes extending below the bounds of the container according to embodiments of the present invention;

[0063] **Figure 21A** is a perspective view of a reagent rack according to embodiments of the present invention;

[0064] **Figure 21B** is a schematic top perspective view of the reagent rack shown in **Figure 21A** illustrating a piercing technique according to embodiments of the present invention.

[0065] **Figure 22** is a series of schematic illustrations showing operation of an aliquot tube mechanism according to embodiments of the present invention;

[0066] **Figure 23A** is an illustration showing components that may be loaded into an isolation container tray according to embodiments of the present invention;

[0067] **Figure 23B** is a top perspective view of a partially assembled container using the kit components shown in **Figure 23A** according to embodiments of the present invention;

[0068] **Figure 23C** is a bottom view of the partially assembled kit shown in **Figure 23B**;

[0069] **Figure 23D** is a top view of the container in the kit shown in **Figure 23A** before kit components are attached at a use site according to embodiments of the invention;

[0070] **Figure 24** is an exploded view of the isolation container tray of **Figure 23A** illustrating sealing of the tray with a flexible barrier according to embodiments of the present invention;

[0071] **Figure 25** is a flow chart of operations that can be carried out according to embodiments of the present invention;

[0072] **Figures 26A and 26B** are enlarged side perspective views of the pipette head with lever according to embodiments of the present invention;

[0073] **Figure 26C** is a side perspective view of the lever shown in **Figures 26A and 26B** shown engaging with an interior surface of the container to release a pipette tip according to embodiments of the present invention;

[0074] **Figure 27** is a top perspective view of a trolley that can be used to load the container onto an instrument according to embodiments of the present invention;

[0075] **Figure 28A** is an enlarged side perspective view of a work surface with a biasing assembly configuration that can force the container into alignment with the robotic arm according to embodiments of the present invention;

[0076] **Figure 28B** is a bottom perspective view of a portion of the work surface shown in **Figure 28A** illustrating a spring used to force the container in a desired direction according to embodiments of the present invention;

[0077] **Figure 29A** is a top view of an elution tray according to embodiments of the present invention;

[0078] **Figure 29B** is a bottom perspective view of the tray shown in **Figure 29A**;

[0079] **Figure 29C** is a top perspective view of the tray shown in **Figure 29A**;

[0080] **Figure 30A** is a top perspective view of a waste tray cover;

[0081] **Figure 30B** is a bottom perspective view of the tray cover shown in **Figure 30A**;

[0082] **Figure 31** is a block diagram of a circuit used in automated systems contemplated by the present invention; and

[0083] **Figure 32** is a block diagram of a data processing system according to embodiments of the present invention.

DETAILED DESCRIPTION

[0084] While the invention may be made in modified and alternative forms, specific embodiments thereof are shown by way of example in the drawings and will be described in detail. It should be understood, however, that there is no intent to limit the invention to the particular forms disclosed, but on the contrary, the invention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention. Like reference numbers signify like elements throughout the description of the figures.

[0085] In the figures, the thickness of certain lines, layers, components, elements or features may be exaggerated for clarity. Broken lines illustrate optional features or operations or hidden components unless specified otherwise. In the claims, the claimed methods are not limited to the order of any steps recited unless so stated thereat.

[0086] The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" and/or "comprising," when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. As used herein, phrases such as "between X and Y" and "between about X and Y" should be interpreted to include X and Y. As used herein, phrases such as "between about X and Y" mean "between about X and about Y." As used herein, phrases such as "from about X to Y" mean "from about X to about Y."

[0087] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. Well-known functions or constructions may not be described in detail for brevity and/or clarity.

[0088] It will be understood that, although the terms first, second, etc. may be used herein to describe various elements, components, regions, layers and/or sections, these elements, components, regions, layers and/or sections should not be limited by these terms. These terms are only used to distinguish one element, component, region, layer or section from another region, layer or section. Thus, a first element, component, region, layer or section discussed below could be termed a second element, component, region, layer or section without departing from the teachings of the present invention. The sequence of operations (or steps) is not limited to the order presented in the claims or figures unless specifically indicated otherwise.

[0089] The terms "closed system" or "closed container" refers to systems and containers, respectively, that are sealed and operate in a substantially, if not totally, closed manner to inhibit or prevent the introduction of exogenous or external materials into (or out of) the system or container during processing. The closed systems can be configured to inhibit or prevent contamination. In some embodiments, components of the closed systems or containers can be pre-sterilized prior to use at a manufacture site, sterilized at the point of use, and/or sterilized after a respective closed system is assembled and closed prior to use. The closed systems or containers can be pressure- or vacuum-tight to some target or predefined leak rate at certain atmospheric conditions. The leak rate may be detected by an internal and/or external sensor using a vacuum or pressure sensor test or other leak check system and the like. The typical atmospheric conditions may change with location of the apparatus, from sea level to higher altitudes. However, the closed systems contemplated by embodiments of the invention may be used in marine (subsurface, deep sea), flight, and/or space environments as well, with the seal being sufficient to substantially maintain the target leak rate at those atmospheric conditions. The closed systems or containers can be utilized for their respective intended purpose without breach to the integrity of the closed system. The closed systems or

containers may be adapted for fluid transfers of target fluid samples in or out while maintaining asepsis, and/or can be connectable to other closed systems while maintaining the integrity of the closed systems. Filters may optionally be used in a flow path that may be open to atmosphere or other components during process. The filters may be configured to filter to a desired clean level or class, to facilitate the closed state, such as class 100,000, class 10,000, class 1000 filters or even class 100 filters.

[0090] The term "isolation container" refers to a container configured to hold, enclose and/or isolate internal components and the processing of one or more items or samples held therein from external pathogens, microorganisms and the like and/or other materials that may exist in an external environment. The isolation container may be a single-use disposable container. In some embodiments, the samples in the isolation container are or comprise nucleic acids, *e.g.*, for processing nucleic acids in tissues (*e.g.*, clarified tumor homogenate) into IVT RNA.

[0091] The term "single-use disposable" refers to a component that is not reused. That is, after completing its intended use, *i.e.*, processing or production of a target sample or sample(s), it is disposed of. The isolation container can be single-use disposable (and may be labeled as such), such that the isolation container remains a closed system that is disposed of in the closed sealed state with its internal components held therein, to inhibit any inadvertent external release or exposure of its internal content(s) after processing/production of the target product.

[0092] The term "aliquot" refers to a desired amount of a target fluid; the amount of fluid may be in a predetermined and/or specific range. The term "aliquot tube" refers to a tube that permits removal of a fluid aliquot from the container. Typically, the term "aliquot tube" refers to a tube that is in communication with the interior of the isolation container to receive at least one (and typically a plurality of) fluid aliquot without breaching the closed status or sealed integrity of the isolation container. The aliquot tube can be flexible and sterile and may comprise an elastomer, such as PVC.

[0093] The term "cuvette" refers to a vessel configured to permit mechanical, electrical or optical measurement(s) of a substance, typically a fluid, and typically concentration or volume measurements, contained within that vessel. The cuvette may be sized to hold a relatively small amount of fluid, typically, in the range between about 0.001 mL to about 5.0 mL.

[0094] The term "pipette tip" refers to a tube open at both ends to be able to intake and/or discharge fluid, typically liquids in small volumes, and typically in amounts between about 0.1 μ L to about 1000 μ L. The tube may have an irregular or constant perimeter shape or size, typically tapering down at a lower tip from the head. A "pipette" can be defined by a plurality of matable components. That is, a pipette can include a tip portion and a head portion. The head portion can be defined on a manipulation tool attached to a robotic device (indirectly) that releasably attaches to different pipette tips during processing. Pipettes of different volumetric sizes may be used in a single container/processing system.

[0095] The term "Human Machine Interface (HMI)" is well known to those in the art and refers to an interface which allows an operator to input, direct, interact with or machines, and typically includes an electronic display with a "Graphic User Interface (GUI)" that programmatically provides information to and accepts control instructions from an operator.

[0096] The term "aseptic" refers to processing conditions that inhibit or prevent contamination of a target sample in an interior processing space of a container by external pathogenic microorganisms and/or undesired exogenous materials, and/or to inhibit or prevent contamination of the proximal exterior environment with the contents of the container.

[0097] The term "binding column" refers to a filtration/elution column that can be used for separating components of a sample or derivatives thereof. In some embodiments, the binding column can be used for nucleic acid (*e.g.*, DNA and/or RNA) isolation or purification. In some embodiments, the binding column may contain a silica membrane.

[0098] The term "tray" refers to a substrate having sufficient rigidity to hold one or more components. The tray may be substantially flat or may have a bowl-like shape. The tray may also have other shapes and configurations. The tray can be configured to define integral wells or holding regions or may be configured to sealably mate with and/or hold devices or containers, typically those components associated with at least one processing workstation.

[0099] The term "user" is a generic term for an operator, programmer, and/or maintainer.

[0100] The term "robot" refers to an automated device that can be programmatically directed to translate in desired directions to carry out defined

processing steps or operations. The term "robot" is used broadly and includes a stationary mounted robotic arm with a multi-axis translation as well as a fully mobile robot and other appropriate robotic devices.

[0101] The present invention may be embodied as systems, methods, and/or computer program products. Accordingly, the present invention may be embodied in hardware and/or in software (including firmware, resident software, micro-code, *etc.*). Furthermore, the present invention may take the form of a computer program product on a computer-usable or computer-readable storage medium having computer-usable or computer-readable program code embodied in the medium for use by or in connection with an instruction execution system. In the context of this document, a computer-usable or computer-readable medium may be any medium that can contain, store, communicate, propagate, or transport the program for use by or in connection with the instruction execution system, apparatus, or device.

[0102] The computer-usable or computer-readable medium may be, for example but not limited to, an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system, apparatus, device, or propagation medium. More specific examples (a non-exhaustive list) of the computer-readable medium would include the following: an electrical connection having one or more wires, a portable computer diskette, a random access memory (RAM), a read-only memory (ROM), an erasable programmable read-only memory (EPROM or Flash memory), an optical fiber, and a portable compact disc read-only memory (CD-ROM). Note that the computer-usable or computer-readable medium could even be paper or another suitable medium, upon which the program is printed, as the program can be electronically captured, via, for instance, optical scanning of the paper or other medium, then compiled, interpreted, or otherwise processed in a suitable manner, if necessary, and then stored in computer (electronic) memory.

[0103] Apparatus and methods for automated processing in a closed environment are discussed below. The systems can be used, for example, to process, fabricate, assemble or otherwise manipulate anything in a closed environment, and is particularly useful in the fields of medicine, forensics, therapeutics, diagnostics, biotechnology, electronics and nanotechnology. For convenience of description, various aspects and features of the invention are described herein in the context of a system for processing nucleic acids. One skilled in the art will appreciate, however, that the following descriptions are intended to be merely illustrative of the invention and not

restrictive. Various other applications are intended within the scope of the present invention, including, for example, systems and methods for fabricating, assembling, processing or otherwise manipulating any items in a closed container.

Overview of Exemplary Automated Systems

[0104] In overview, referring to **Figure 1**, the system **10** can be configured with a robotic arm **20** that manipulates one or more items within a closed container assembly **12** with an interior chamber (also described as an interior work area or region, where the word "area" is used broadly and not in a two-dimensional mathematical manner). In some embodiments, the container assembly **12** has an interior region **18** configured to hold a plurality of items to be processed and/or otherwise manipulated. A flexible barrier **16** can be configured and dimensioned to cover the interior of and seal with a container tray **14**. A tool for manipulating items within the chamber is attached to or integrated within the flexible barrier **16** and can extend into the interior region when the barrier **16** is attached to the tray **14**. The tool can have an adapter or other interface that is accessible from an exterior side of the barrier, such that the tool may be manipulated by a robotic device from outside of the container when the barrier is sealed with or otherwise attached to the container tray. The tray **14** may be configured to include one or more workspaces, areas, stations, racks, holders, receptacles, wells or other devices for holding one or more items or process components or fluids in the closed container. Other tools or devices may also be disposed or otherwise accessible from within the container; for example, tools or devices for processing, manipulating, measuring, analyzing, sampling and/or storing samples or other items may reside within the chamber of the container.

[0105] Turning now to the figures, **Figure 1** shows an exemplary automated nucleic acid processing system **10**. System **10** may include a container assembly **12**. The container assembly **12** may be an isolation container **12**. The system **10** also includes a robot **20** (typically a robotic arm) or other automated or manually directable device for manipulating items within and/or associated with the container assembly **12**. The container assembly **12** comprises the tray **14** and the flexible barrier **16**. The barrier **16** is configured to seal with or otherwise attach to the tray **14**. An outer perimeter edge portion **16p** of the barrier **16** can sealably engage the container tray **14**, providing a closed, aseptic work area **18** within the container assembly **12**. In some embodiments,

the container assembly 12, or any portion thereof, is single-use disposable. In particular embodiments, the sample can be discharged, collected or captured outside of the container without opening the sealed container, and the sealed container 12 can be disposed of "intact" with the remainder internal contents.

[0106] The tray 14 can be substantially rigid and may be a molded body. In some embodiments, the tray 14 comprises a medical grade (such as USP Class VI or other suitable grade) molded polymer. The body of the tray 14 may comprise one or more substantially clear, translucent or transparent polished regions for optic visibility that provides for internal viewability. The tray 14 can be molded in a clean room mold and in a clean room molding facility to inhibit and/or minimize bioburden and particulates. The tray 14 may be sterilized prior to or after sealing the flexible barrier 16, by using conventional sterilization techniques, such as, for example, surface decontamination with VHP (vaporous hydrogen peroxide), gamma irradiation or ethylene oxide vapor hydrogen peroxide. For shipment, the tray 14 may be enclosed in double elastomeric sterile packaging material, such as such as sealed double plastic wrapping/bagging.

[0107] The barrier 16 can be configured to allow the robot 20 to move a tool inside the work area 18 of the sealed container assembly 12 between about 4-24 inches vertically, and horizontally at least about the width and length of the tray 14, without destroying the sealed integrity of the container assembly 12. In some embodiments, the robot 20 can direct an internal interface to have between 6-12 inches of vertical movement in the sealed container assembly 12 without destroying the sealed integrity of the seal. The barrier 16 can be sized and configured relative to the tray 14 to provide for a sufficient volume of air to allow the desired range of movement of the robot 20 without overly compressing or decompressing the interior volume of the container 12.

[0108] In some embodiments, the system 10 is used to process biological samples, including, but not limited to tissues, blood, blood products, nucleic acids, proteins, cell cultures, and the like inside the container assembly 12. In such embodiments, the container 12 may comprise, for example, items such as biological samples, reagents, wash fluids, pipettes, pipette tips, vessels, other consumables or any combination thereof.

[0109] As shown, the system 10 can be a self-standing, self-contained unit. The system 10 can include a housing or chassis 70 for supporting an isolation container assembly 12 and other components of the automated system 10, such as, for example, the

robot 20, a thermal block 30 (e.g., a heat block and/or cooling block, etc...), an aliquot retrieval assembly 40 and related mechanisms for collecting processed samples, a user interface 60, and various other components and mechanisms as described in the sections that follow. The thermal block 30 may cooperate with a thermal block assembly 1000 as shown, for example, in **Figures 10, 11**.

[0110] In some embodiments of a processing system 10, an operator or maintainer may only need to access the front of the system 10 for normal operation. As shown in **Figure 1**, one or more access doors 110 may open, e.g., by lifting substantially vertically or opening to a side or in another direction, to provide accessibility while installing or removing an isolation container 12.

[0111] In some embodiments, due to the automated nature of system 10, the door 110 may protect the operator from moving parts of the system during operation. The system 10 may incorporate an electronically controlled interlock or other mechanism to inhibit or prevent the operator from opening the door 110 while the system is in operation. A manual override may be provided to allow opening of the interlocked guards, and such an override may be employed, for example, if no power is available. The user interface 60, also referred to as an HMI (Human Machine Interface), can be configured to allow an operator to initiate a processing operation or otherwise control the system 10, and can be mounted on the front of the chassis 70 next to the access door 110. In one embodiment, the display screen 61 and controls (touchscreen, keypad or other input) of the HMI may be positioned to allow the user to view and operate them while standing. In some embodiments, the rear and sides of the system 10 do not need to be routinely accessed by operators. Consequently the system can be positioned against a wall or another system.

[0112] In some embodiments, a lower section of the chassis 70 can contain electronic control systems, power supplies and other components, which may not require operator interaction. These components can be housed in dedicated enclosures that protect the components from accidental fluid ingress and protect the operator from possible electrical hazards. Removable panels 120, 130, 140 may be included to provide access to the electrical components and/or other components inside the enclosures. In some embodiments, only trained service personnel are permitted or required to access the insides of these enclosures. The service access panels may or may not be interlocked, for example, to allow or disallow the system to continue to operate with the panels removed.

[0113] **Figure 2** shows an enlarged side view of an upper portion of system 10, including isolation container 12 on a work surface 200. A pipette head 220 and/or other manipulation device can be attached to or integrated with or within the barrier 16, for example, such that at least a portion of a pipette head 220 extends into the interior work area 18 of container 12 when the barrier is attached to the tray 14 as shown. The pipette head 220 can include an interface on an opposite side of barrier 16 that is configured to releasably connect with an adapter 210 on an end portion of arm 230 of robotic device 20. In some embodiments, a pipette head 220 or other manipulation device does not physically pass through the barrier 16, and may not necessarily couple to a robot or other device through an adapter. Rather, such a pipette head may attach to or otherwise integrate with the inside of the barrier, and may be operated or manipulated from the opposite side of the barrier 16, for example, using the robotic arm 230 attached to the opposite side of the barrier. In other embodiments, a pipette head or other sample manipulation device integrated with the barrier 16 (which can be substantially impermeable) may be operated by a magnet or other device that supports and/or communicates with the manipulation device through the barrier 16.

[0114] When the barrier 16 is sealed over the tray 14, the barrier 16 separates the contents of the tray 14 from the robot 20 or other device that manipulates the pipette head 220. The seal between barrier 16 and tray 14 can be airtight, thereby providing a closed environment within the container 12. In some embodiments, the barrier 16 is flexible and allows the robotic arm 230 to move the pipette head 220 throughout the work area 18 within tray 14. All items or materials involved in processing the nucleic acid samples, including for example biological samples, reagents, pipette tips, or other consumables, and other tools or devices for processing the samples, can remain within the closed work area 18 during processing. The tray 14 may include a number of features or stations 242 which may be molded, formed, attached or otherwise integrated with base 240 of the tray 14, or another portion of the tray 14, to accommodate such items.

[0115] As shown, robotic device 20 may be attached to a wall of the chassis 70. In other embodiments, robotic device 20 may comprise an arm, gantry or linkage system attached to work surface 200 or to another support structure. Suitable robotic devices are known in the art. Non-limiting examples include Stäubli TX90 robot, Epson E2L Scara robot, Kawasaki F Series robots, Yamaha YKL Scara robot, ST Robotics R17 Robot, etc. In some embodiments, the robotic device 20 is a FANUC LR MATE 200iB

5C, 6-axis robot or other suitable multi-axis robotic device, and is used to automatically perform the desired manipulations inside the closed container 12, such as, for example, aspiration and transfer of fluids using pipette tips and sliding or lifting a binding column manifold during processing of samples.

[0116] The multi-axis robotic arm can be used to move an interface tool releasably holding a pipette to orient the pipette in a number of different directions to help mix the liquid upon aspiration or dispensing. For example, the pipette can be oriented in a downwardly extending angled orientation with the tip proximate to a receiving surface in a receiving vessel in the closed container, then, automatically, the downwardly oriented angled pipette can be moved in a substantially straight line along a plane (similar to a typically layering or dispensing of mustard), while releasing a flowable substance from the pipette. In other embodiments, the robotic arm can automatically move the pipette to mix the liquid in the vessel prior to aspiration, then aspirate the mixed liquid into the pipette. Alternatively or additionally, in some embodiments, the liquid can be aspirated and dispensed at least once to mix the liquid. In some embodiments, the receiving or dispense vessel has a lip, and the robotic arm is configured to direct the pipette tip to move around the perimeter of the lip.

[0117] As shown in Figure 3, the horizontal work surface 200, which may be located inside of front access door 110, for example, supports various components and mechanisms that interact with an isolation container 12. The work surface 200 can include one or more guides 390, that may include guide slots 390s that engage components on an assembly support trolley 399 (Figure 27) to align the container, or other location features to orient and releasably clamp to the isolation container 12 (e.g., to base 240 of Figure 2) during processing.

[0118] As shown in Figure 27, a container assembly 12 can be prepared on a trolley 399 that can dock with the system 10. The trolley 399 can include slots 399s that align with slots 390s defined by guide 390 on a support surface of the system 10. To transfer the container assembly 12 to the system 10, an operator can roll the trolley adjacent to the system 10, so that the trolley 399 is aligned with the guide 390 of the system 10. The container assembly 12 can slide into the slots 390s of the system 10 into proper operative position without requiring that an operator lift the container assembly 12.

[0119] As shown in Figures 28A and 28B, the work surface 200 can include roller guides 381, 382 that contact the lower portion of the container 12 when it is in

position. The roller guide 382 can be in communication with a spring 383 that can bias the container 12 inwardly so as to fit snugly against the innermost slot wall 390 to be in the desired alignment with the robotic arm for registration of workstation locations.

[0120] Referring again to **Figure 3**, the work surface 200 may support a temperature control device, such as an incubation device for heating and/or cooling regions, vessels, or target objects or locations within the container. Such devices are known to those of skill in the art. In one embodiment, the system 10 includes a thermal cycler 30 for controlling temperature of a PCR plate 610 (**Figure 6**) or other vessel or component during some nucleic acid amplification reactions or other reactions or processes, for example, and a thermal cycler lid mechanism 310 for selectively covering the thermal cycler 30 during such reactions. In one embodiment, a vacuum pump assembly 320 and a pinch valve assembly 330 provide for control of vacuum and circulation of air within the isolation container 12 during processing. The vacuum pump assembly 320 can releasably engage a single-use disposable vacuum head 1602 and associated tubing 1650 (**Figure 23B**). The work surface 200 can also hold the container assembly 12 so as to allow a spectrophotometer 1900s to communicate with components held by the container assembly 12 as will be discussed further herein.

[0121] One or more syringe pumps 350 (shown, for example, as two pumps) may be used to drive aspiration and dispense actions of pipette head 220 (**Figure 2**). In some embodiments, syringe pumps 350 may be used to pump a working fluid, *e.g.*, from a reservoir 340, through the pipette head adapter 210 shown in **Figure 2** to provide vacuum and pressure for operation of pipette head 220. The working fluid may be substantially incompressible, and can, for example, comprise an aqueous solution of about 50% ethanol. Other fluids, even air, may be used. Additional details of an exemplary embodiment of a pump mechanism and pipette head 220 are described in greater detail below in connection with **Figures 7 and 8**.

[0122] Returning to **Figure 3**, a cuvette holder 360 (see also spectrophotometer cuvette in **Figure 19A**) can be coupled with a spectrophotometer 1900s typically residing in a lower portion of the chassis 70, to provide automatic concentration measurements at desired operations during processing. Optionally, the work surface 200 may include one or more cooling features, *e.g.*, a heat exchanger such as a chiller or Peltier cooling plates 370 and 372 are positioned to engage certain portions of the isolation container 12 and help control humidity and vapor concentrations within

the sealed container 12. A lever 380 or other mechanism or device may be used to secure the isolation container into place on the work surface 200.

[0123] In some embodiments, an RNA processing system may operate in a stand-alone fashion isolated from a larger production system and any data management tools or systems. An internal or external computer system may control and/or monitor the automated components of the subsystem. Users may interact with the interface 60, for example, to operate the system and monitor status. In other embodiments, the system 10 can communicate with other systems or a monitoring station (which may be in a different room or even in a different facility).

[0124] Additional details of the various components and assemblies, and exemplary methods of use, are described in sections that follow.

Exemplary Isolation Containers

[0125] Referring to the isolation container assembly 12, tray 14 and flexible barrier 16 are described in greater detail. The tray 14 includes an interior work area 18 and may comprise a number of inserts, recesses, racks, or rack mounting features and/or stations 242 for holding items within container 12, *e.g.*, including one or more racks, manifolds or other holders for holding vessels, pipette tips, binding columns, other substrates and/or other consumables or devices for a desired assay or process. All items used to process the material to a desired finished state or product can be held within the container, *i.e.*, the consumables for the system can be self-contained and sealed during processing to minimize the risk of contaminating the interior of the container, or to prevent a sample from contaminating the environment or user. The barrier 16 can have an outermost perimeter portion 16p (Figure 5) that can be configured to releasably or permanently seal with the tray 14, for example about an annular edge 452 of tray 14 as shown in Figure 5. When the barrier 16 is sealed with the tray 14, at least a portion of pipette head 220 and/or another sample manipulation tool or device extends from the barrier 16 into the work area 18.

[0126] In some embodiments, the barrier 16 engages the tray 14 along a rigid top edge 452 (Figure 5). The outermost perimeter portion 16p of the barrier 16 can reside against the top edge 452 (Figure 5). The top edge 452 may be configured as an upstanding lip with a gap space that receives an O-ring (not shown) that pinches against the barrier 16 to seal the barrier against the tray 14.

[0127] To create a closed system or environment, the isolation container tray 14 and barrier 16 may be configured to form a physical barrier between items within the container 12 and external devices, mechanisms and pieces of equipment used for processing the items in the container. For example, a flexible thermal cycler lid seal 430 may be integrated within a wall 450 of the tray 14 as shown in Figure 4. Such a seal 430 may enclose and define a sleeve or closed channel that receives the lid 1010 (Figure 11) and be used to allow the thermal cycler lid mechanism 310 to extend the lid into an aperture 14a (Figure 5) in the sidewall of the tray 14 to cover samples during heating by a thermal cycler block 30, while providing a physical barrier between the lid mechanism 310 and items within the interior area 18 of container 12.

[0128] Also, cooling plates 370, 372 may engage portions of an external surface of the tray 14 to impart changes in temperature within the container 12 while not contacting any items within the isolated work area. In some embodiments, cooling plates may engage with portions of the external surface of the tray 14 and/or container 12 to control the temperature of items (such as reagents) held inside the isolated work area/space.

[0129] Similarly, as shown in Figure 3, a cuvette holder 360 can selectively engage a cuvette 660 (Figure 6) extending from base 240 of tray 14 to perform measurements of concentration and/or volume, but the holder 360 may not contact any items within container 12. Thus, in some embodiments, only the reagents, consumables and tools or devices that are required to directly contact the sample are contained within the isolation container. Such a configuration may have several benefits. For example, a sample can be processed in its own isolated environment and/or the processing equipment residing outside the container will not contact the sample and so is protected from possible contamination. At the conclusion of processing, a desired number of aliquots may be collected in aliquot tubes 440 (Figure 4) and removed from the container 12, *e.g.*, without compromising the integrity of the collected samples or the isolation container, as will be discussed further below. In some embodiments, for example, the sealed isolation container 12, along with the components contaminated by sample material, can be discarded after a processing cycle.

[0130] Figures 5 and 6 show additional details of some components of exemplary isolation containers 12, including the isolation tray 14 and the flexible barrier 16. The interior work area 18 may be surrounded, for example, by base 240 and one or more walls 450. The barrier 16 can include a pipette head 220 or other device or tool,

which is described in more detail in a separate section below. The barrier **16** can be configured to cover and seal with the tray **14**, for example at a seal **510** along an annular edge **452** of the tray **14**, such that the work area **18** is a closed, typically air-tight, compartment when the barrier **16** is sealed with the tray **14**.

[0131] The tray **14** can be substantially rigid and includes a number of features and/or stations **242** which may be molded, formed, attached or otherwise integrated with tray to accommodate. Some or all of the following components are examples of features that may be integrated into the tray **14**:

- elution **630** and waste **632** stations;
- vacuum inlets and outlets;
- spectrophotometer (concentration) cuvettes **660** (Figure 19A);
- other vessels or cuvettes, *e.g.*, volume measurement cuvettes **2060** (Figures 20A-E);
- a thermal cycler PCR plate **610** and/or other substrate or vessel that may be heated and/or cooled with a temperature control device;
- reagent vessels **622** in a rack **620**;
- pipette tips **651** in a rack **650**;
- one or more additional tip racks **650** or other disposal container, *e.g.*, for used pipette tips **653**;
- a binding column manifold **50**, *e.g.*, which may include one or more binding columns for nucleic acid processing; and
- one or more aliquot tubes **440** for processing outputs: *e.g.*, nucleic acids, such as (*e.g.*, DNA, RNA, tumor total RNA and/or amplified tumor *in vitro* transcribed RNA and the like), microorganisms, cells, medicaments, etc.

[0132] In some embodiments, the flexible barrier **16** seals with and supports a manipulation tool that interfaces with the robotic device **20** on one side of the barrier and interfaces with internal components on the inside of the barrier **16**. The tool can include the pipette head **220** and additional manipulation features, such as handles **520** or other features or mechanism for engaging internal components, such as, for example, handles **50h** (Figure 5) on a binding column manifold **50** for transferring the manifold between the waste and elution stations **632**, **630**, respectively. The flexible barrier **16** can allow the pipette head **220** to move sufficiently to access all desired internal components housed by the tray **14**. The head **220** can also engage the binding column manifold **50** to

be able to transfer the binding column manifold to and/or from the waste 632 and elution 630 stations. Although not shown, the internal interface may be a plurality of serially attachable interfaces. That is, the pipette head or first interface can be releasably held and interchanged for another manipulation tool inside the closed container. The selection of manipulation tools can be held by tray 14 and/or an internal manipulation tool rack (not shown).

[0133] A mixer and/or centrifuge may cooperate with or be integrated into the tray to mix, homogenize, separate or otherwise blend or process a liquid or sample, such, as for example, a biological sample or other materials as desired (not shown). In other embodiments, the starting material may be pre-mixed, and then placed in the rack 620 or at another location. The mixer may be a rotating head mixer, a magnetic mixer or a homogenizer that can mix the desired material.

Exemplary Pipetting Systems

[0134] Referring to Figures 7A and B, a pipetting system 700 comprising a pipette head 220 and adapter 210 assembly may be used to perform fluid transfers inside the isolation container 12. In keeping with a closed isolation container design, the pipette head 220 can be configured to maintain a barrier between the fluid being transferred and the pipette pump mechanism. A filter and/or a flexible diaphragm 710 can provide the physical contamination-resistant barrier between the interior of the isolation container 12 and the outside.

[0135] In some embodiments, to provide high volumetric accuracy, the pipetting system 700 may use two positive displacement syringe pumps 350-1, 350-2, e.g., one for low volume transfers (e.g., between about 1 μ l and about 50 μ l) and one for the higher volumes (e.g., between about 51 μ l and about 1000 μ l). In other embodiments, a single pump chamber with different reservoirs or a single reservoir with a means of metering the working fluid can be employed. The pump chambers may be hydraulically connected to the flexible diaphragm 710 via (substantially rigid) tubing and a buffer solution (working fluid). The buffer solution can be a substantially or totally incompressible hydraulic fluid that can reduce or minimize the elasticity of the pipetting system 700. The robotic arm 230 is used to position the pipette head 220 at desired

locations in the workspace. To reduce the potential for reagent carryover during pipette transfers, disposable tips 651 may be used for fluid handling. That is, after each transfer, the used tip can be discharged into a "trash" receptacle, typically into a used rack, and a new sterile different tip from a sterile rack or supply station may be used for the next transfer. Other components of an exemplary embodiment of the pipetting system 700 are shown in **Figures 7A and 7B**.

[0136] In some embodiments, the pipetting system 700 is primed to introduce liquid and remove air from the pipette line prior to initial use, and may be primed prior to each time a different pipette head 220 is connected to the pipette head adapter 210, such as at the beginning of processing of a new closed container 12. For example, a bleed line connects a bleed port in the pipette head to the working fluid reservoir via a solenoid valve 741. The valve 741 may be opened during the priming sequence to allow air to be bled from the pumps 350, through the fluid lines 222,223 (**Figure 8A**) and pipette head 220, and back to the working fluid reservoir 340. The robotic arm 230 can be directed to orient the fluid lines in the pipette head 220 so that they are angled during the priming. Once the system 700 is primed, the bleed valve 741 may be closed and the pipette head 220 is ready to perform fluid transfers. At the completion of the RNA process, the bleed valve 741 may be used to drain the fluid lines 222,223 and pipette head 220. Filling the fluid lines with air may prevent the possibility of fluid spills during disconnection of the pipette head.

[0137] **Figures 8A and 8B** show a cross-sectional view of the operation of a pressure transfer mechanism 800 for transferring pressure through the pipette head 220 and to the pipette tips 651, 653. In some embodiments, the hydraulic working fluid, *e.g.*, from reservoir 340, actuates the flexible isolation diaphragm 710 (*see also Figures 8C and 8D*) and drives the pipetting action while maintaining physical separation between the working fluid and the fluids to be aspirated by the pipette. A reservoir of working fluid can reside on one side of the diaphragm 710, which is sealed from working air on the other side. The flexible diaphragm 710 resides in the head 220 between the working fluid 340 and the internal pipette tip adapter 220a (*i.e.*, pipette head) and aspirated fluid. **Figure 15** illustrates the adapter 220a without the diaphragm and upper assembly.

[0138] Referring again to **Figures 8A and 8B**, displacement of the diaphragm 710 affects the working air volume 700a under the diaphragm 710 and in the pipette tip adapter 220, thereby causing the pipette tip to intake or discharge (typically metered) amounts of liquid. The overall elasticity of the pipetting system 700 may be directly

related to dispense accuracy. In some embodiments, reducing the air volume 700a can improve both the pipetting accuracy and precision.

[0139] In some embodiments, to facilitate thorough mixing of fluids within reagent vessels, spectrophotometer cuvettes 660 and PCR wells, a repeated aspirate/dispense cycle can be employed and/or the robotic arm 230 can be directed to move the tip of the pipette in multi-axis translation.

[0140] In some embodiments, the tray 14 and/or pipette head 220 may include one or more features to allow used tips 653 to be removed from the pipette tip adapter 220a (Figure 8B). As shown in Figures 26A-26C, the pipette head 220 can include a lever 221 that pivots upon contact with a portion of the container proximate to the used pipette rack 650. As shown in Figure 26C, the container sidewall 14w or a member held thereon can be angled so that upon contact with the outer end of the lever 221, the lever 221 pivots and pushes the used pipette tip 653 off the adapter 220a and into a receiving space in the rack 650. That is, as the pipette head 220 moves downward toward the used rack 650, the lever 221 contacts the wall 14w, which forces one end of the lever upward and the end over the pipette tip 653 downward to push the used tip into the rack 650. Other release configurations may also be used. For example, the used rack 650 may be configured to restrict upward movement of the pipette tip 653 to pull, push or otherwise force or strip the tip from the adapter 220a.

[0141] The pipette head 220 and/or adapter 210 may attach to fluid lines and load cell wiring which can be elevated to clear the flexible barrier 16, and a flexible conduit back to the chassis 70. The load cell wiring communicates with a load sensor in communication with the sterile or new pipette tips. The load cell provides data used to control the loading of new pipettes onto adapter 220a. For example, the robotic arm can cause the pipette head 220 to advance down with a force between about 5N to about 50N to indicate the pipette tip 651 is properly attached. Adapter 210 can also include a collar for locking and unlocking the adapter 210 to the pipette head 220, e.g., as a non-limiting alternative to an engage/release handle mechanism.

Exemplary Flexible Barriers

[0142] Figures 9A-9E illustrate exemplary flexible barriers 16 according to embodiments of the present invention. Any suitable material can be used for the barrier. The barrier 16 can be substantially impermeable to air, moisture, and ethanol vapor. The

barrier 16 may be moldable without losing sufficient flexibility or impacting permeability. In some embodiments, the barrier 16 comprises a low-density polyethylene, but other alternatives could include a range of urethane materials. In particular embodiments, the flexible barrier is or comprises an "ARMORFLEX" material, available from ILC Dover Company, located in Frederica, Delaware.

[0143] The formed shape of the flexible barrier 16 can allow sufficient robot movement and give the pipette head (or other internal interface) access to the interior of the isolation container 12 without restriction or otherwise pinching or catching the flexible barrier. The shape of the molded flexible barrier 16 can be substantially self-supporting (e.g., it will not collapse into the isolation container) once the flexible barrier 16 is sealed to the tray 14 forming the isolation container 12.

[0144] In some embodiments, a portion 910 of the barrier 16 may be adapted to integrate with, receive, hold, attach to, mate with, seal with, support, or otherwise interact with a device for manipulating samples within the container, such as, for example a pipette head 220, another fluid transfer device, and/or another manipulation tool. The portion 910 can be a substantially medial portion. The barrier 16 may include one or more folds, pleats or undulations described as "convolutions" 920, some of which may be substantially concentric with others. Figure 9B illustrates that the portion 910 may include at least one stepped portion 17, shown as a series of substantially vertically oriented stepped portions 17₁, 17₂, 17₃.

[0145] In some embodiments, as shown for example in Figures 9C and 9D, the barrier 16 may include one or more radial convolutions 930. The radial and/or concentric convolutions may help facilitate a full range of movement of the pipette head (or other internal manipulation tool interface), and help control the barrier shape during movement of the pipette head. A rim 940, flange or other feature may provide a surface for clamping, sealing, fixing, adhering, or otherwise attaching the barrier 16 to the tray 14.

[0146] As shown in Figures 9C and 9D, the flexible barrier 16 can comprise a unitary sheet of material that is stretched or formed into a series of substantially concentric folds, pleats or convolutions that can allow for the desired movement of head 220. Outer perimeter regions of the barrier sheet 16f may have a different thickness than a center region 16c. In some particular embodiments, during fabrication, thicker material can be drawn down to the center during vacuum forming causing thinner central regions and thicker perimeter regions of the barrier sheet 16. The center region 16c may include

a series of columnated steps 17₁-17₃, arranged smaller to larger as the barrier 16 moves away from the workspace 18. In other embodiments, rather than a unitary sheet of material, the flexible barrier 16 may comprise a plurality of co-joined sealed segments of the same or different suitable materials (not shown).

[0147] Figure 9E illustrates the flexible barrier 16 sealably attached to a lower portion of the pipette head 220 for subsequent engagement to the robotic arm 20. A robotic arm coupler 910c resides outside the barrier 16. Figure 9F illustrates a cooperating coupler 210c that is configured to engage the coupler 910c. As shown in Figure 9G, fingers 211 are configured to enter apertures in the coupler body 910a to releasably engage the barrier 16. The assembly is shown in Figure 9H (without the lower container tray 14).

Exemplary Thermal Block Assemblies

[0148] As shown in Figure 10, a nucleic acid processing system may incorporate a thermal block assembly 1000 or any other temperature control device. For example, a nucleic acid processing system can incorporate a thermal cycler for synthesizing and amplifying nucleic acids. The thermal block assembly 1000 may include, for example, a thermal (heater) block 30, which may be configured to receive a multiwell strip or plate such as a PCR plate 610, and a thermal cycler heated lid 1010 which may be actuated by a lid mechanism 310 to cover the PCR plate 610. For example, in some embodiments, the thermal cycler assembly is used for cDNA synthesis, cDNA amplification, IVT RNA synthesis and DNA removal steps of the process. Various types of thermal blocks and/or thermal cycler devices are available.

[0149] As shown in Figure 10, the PCR plate 610 may be incorporated into the isolation container tray 14. In some embodiments, the perimeter of the PCR plate 610 can be sealed to an open (substantially rectangular) region formed in the base of the tray 14. Lower portions of the plate 610 extend downwardly from the base of the tray to engage (typically reside in) a thermal cycler heater block 30 while the openings of wells 611 in the plate 610 are accessible from inside of the sealed container 12. The PCR plate 610 can be sealed to the isolation container tray 14 so that the downwardly extending portions of wells 611 can be in direct contact with the thermal cycler or temperature control device.

[0150] In some embodiments, a compliant gasket, O-ring or other sealing mechanism may be used to attach the PCR plate 610 to the isolation container tray 14. The compliant gasket may be attached with a heat-swaged clamping feature. In some embodiments, an over-molded thermoplastic elastomer (TPE) seal 1030 is used for attaching and sealing the PCR plate 610 to the isolation container tray 14 as shown in **Figure 10**. In other embodiments, PCR plate features may be formed, such as molded and/or machined, into the isolation container tray substrate. In other embodiments, a glue, tape and/or adhesive may be used to attach the PCR plate 610 to the tray 14.

[0151] A lid, such as a heated thermal cycler lid 1010 may be used to reduce the loss of reaction fluid via evaporation. The lid 1010 may be lined, for example, with a flexible seal 430 to inhibit evaporated fluid escaping from some or each PCR well 611 and/or for maintaining isolation of the interior of the container 12. The lid 1010 can be heated to inhibit vapor condensing on the lid or any surface other than the reaction mixture. To provide access to all of the PCR wells, the thermal cycler lid 1010 may be lifted vertically to release the sealing pressure, then retracted substantially horizontally taking with it the flexible lid seal 430.

[0152] A drive system 310 for controlling the automatic movement of the lid 1010 may be mounted to the work surface 200 of the processing system 10, as shown in **Figure 3**. In other embodiments, the lid drive system 310 may be mounted at other locations above or below the work surface 200. Referring now to **Figure 11**, an exemplary lid drive system 310 is shown with the lid 1010 in the retracted position. The arm 1122 is connected to the lid 1010 and communicates with motor 1150; this provides for movement of the lid 1010 into and out of container 12, *e.g.*, through a side-ingress/egress aperture 14a in the wall of tray 14 where a lid seal (which can be described as a sleeve) is disposed between lid 1010 and the interior of the container as shown in **Figure 12**. Robotic tools or manual input may also be via the seal 430.

[0153] **Figure 13A** illustrates an exemplary configuration of the lid 1010 in the container 12 and inside the chamber 430c of the lid seal 430 when extended. **Figure 13B** illustrates the lid 1010 outside the container 12 in a retracted configuration.

[0154] The arm 1122 can be configured to direct the lid 1010 vertically as well as horizontally. In the embodiment shown in **Figure 11** and **12**, the drive system 310 includes a vertical movement mechanism 1124 that provides for vertical movement of the lid 1010, *e.g.*, when lid 1010 is positioned over the PCR plate 610 within the container 12. The vertical movement mechanism 1124 may provide a downward force

sufficient to seal the lid 1010 with the plate 610 and/or the block 30 (**Figure 10**), for example, using one or more biasing members 1152. One or more motors 1150, actuators, gears, linkages or other electro-mechanical devices may be used to drive horizontal and/or vertical movement. As shown in **Figure 12**, the drive system 310 includes an upper plate 1123 with a slot 1123s. The arm 1122 includes a keel 1122k that slides in the slot 1123s. The drive system 310 also includes a lower plate 1126 that is attached to the upper plate 1123 via pivots 1127 and biasing members 1152. The vertical drive 1124 is attached to the upper and lower plates 1123, 1126 and is configured to pull the upper plate 1123 down to force the lid 1010 down once the lid 1010 is in the extended configuration inside the container.

[0155] A portion of the drive system 310 can be physically attached to the interior surface of the sleeve or lid seal 430 to facilitate the seal 430 moving appropriately with the lid 1010. As shown, in **Figure 11**, in some embodiments vacuum cups 1140 may be incorporated onto the lid 1010 to engage the flexible lid seal 430 and to cause the seal 430 to remain in position during vertical and horizontal movement of the thermal cycler lid 1010. In other embodiments, the lid seal 430 may be attached in other ways or may be sufficiently flexible to conform to the lid 1010 and move in concert therewith.

[0156] In some embodiments, to facilitate a reliable seal between the isolation container 12 and the flexible lid seal 430, a clamp plate or other clamping member may be used to compress against an edge portion of the seal 430, such as via one or more sealing ribs (not shown) on the lid seal against the outside wall of the tray 14. In other embodiments, the lid seal 430 may be over-molded to the tray 14 using, for example, TPE as discussed above with respect to the PCR plate 610. O-rings, gaskets, adhesives, tapes, and mounting or sealing members may be used to provide the sealed connection of the lid seal 430 and the tray 14. **Figure 13A** shows the lid mechanism 310 with the lid 1010 and the seal 430 extended into the interior region of the tray 18 in an engaged position while **Figure 13B** shows the lid 1010 and retracted out through a wall of container 14. **Figure 13A** illustrates the lid 1010 in position over a thermal cycler and 96-well plate. **Figure 13C** illustrates a partial side perspective cutaway view of the lid mechanism 310 with the lid 1010 extended into the interior region of the container 18.

Exemplary Waste and Elution Systems

[0157] Various purification means can be used to process samples, such as nucleic acids, proteins, cells, tissues, and the like. Such purification devices include, but are not limited to, magnetic beads, size exclusion membranes, binding plates, filters, and binding columns. Such devices are known to those of skill in the art.

[0158] In one embodiment, the processing system 10 uses a technique of eluting from binding columns for tumor total RNA isolation, cDNA purification and IVT RNA purification. The binding column 1410 (Figure 14) can contain a silica membrane. A vacuum elution protocol can be integrated into the isolation container design. In other embodiments, a magnetic elution protocol can be integrated into the container.

[0159] One or more types/sizes of binding columns may be used. For example, in some embodiments, binding columns (e.g., Qiagen RNeasyTM columns) are used as they have a binding capacity suitable for the quantities of RNA, cDNA and IVT RNA that are processed. An additional, smaller Qiagen "Mini" column can be included to provide the ability to concentrate the RNA.

[0160] To inhibit the waste fluid from contaminating the elution vessels, the waste and elution stations 632, 630, respectively, can be separate as shown for example in Figure 6. In some embodiments, a manifold 50 is used to hold the binding columns (see Figures 14 and 15). The manifold 50 can be configured to hold one or more binding columns of various sizes/types, e.g., Qiagen maxi-, midi- and/or mini-binding columns 1410. The manifold 50 may include wells 50w for each binding column, lifting members or arms forming lift members 50h for the pipette head 220 to lift it, and one or more slidably movable lids 1430 that can be used to close off the unused binding columns. The lids 1430 can include a handle 1430h that can allow the head 220 to slide the lid 1430 in a desired direction. In other embodiments, a manifold 50 may be configured to hold other types of substrates or devices to be used during a desired process. The lift members 50h can be configured as any suitable lift, including one or more handles (as illustrated), wings, flanges, or other features to facilitate movement of the manifold 50 between stations.

[0161] Figure 15 shows an example of a mechanism and method for moving a manifold 50 between two or more stations or area of the container 12, e.g., between the waste and elution stations 632, 630, respectively. The pipette head 220 and robot 20 may be used to move the binding column manifold 50 and the columns 1410 to and from, i.e., between the two stations. In the embodiment shown, the manifold 50 may include handles 50h, wings or other features that interface with corresponding features

520 on the pipette head 220, and are used to simplify the engagement between the robot 20 and the binding manifold 50.

[0162] Each isolation and purification process can use a different set of columns; the pipette head robot may be used to reposition the lids 1430 to close the appropriate set of unused columns. This reduces or minimizes the airflow through the manifold 50, allowing the pump to generate a sufficiently high vacuum during the isolation and/or purification processing steps. To reduce operator handling of the binding columns 1410 after sterilization, the columns 1410 may be loaded into the manifold 50, and the assembly sealed into suitable packaging and gamma-sterilized in the manifold 50. At the time of loading the isolation container at a use and/or assembly facility (such as in a suitable clean room), an operator can remove the packaging from the manifold 50 and place it into the waste station 632, without ever needing to directly handle the binding columns.

[0163] The waste and elution station configurations can be flexible and/or scalable. The manifold 50 design can be large enough to allow modification or use to suit a 96-well format, or any other type of plate, well or columns, or changes in the combination of maxi-, midi- and mini- columns 1410.

[0164] Referring now to **Figures 16 and 17**, the elution station 630 can include an elution tray 1610 configured to capture the final output of the binding columns (*e.g.*, fluid containing DNA, RNA, etc.). To inhibit and/or prevent possible cross contamination between DNA and RNA, each binding column 1410 can have its own receptacle 1612 below it in the elution tray 1610. In some embodiments, the elution process employs a high vacuum, which may generate a significant airflow through the binding column(s) 1410. The elution receptacles 1612 may be shaped to allow splashed fluids, if any, to run off and pool in a collection vessel while deflecting the air stream away from the pooled fluid. Additional features may reduce or minimize the airflow that passes from one receptacle over another. Further discussion of the tray 1610 will be provided with respect to **Figures 29A-29C**.

[0165] Waste station 632 may include a waste tray 1630 and waste tray cover 1640. A waste tray cover 1640 may be incorporated into waste tray 1630 to minimize the evaporation of the waste fluid contained in the waste station 632. The waste tray cover 1640 may be shaped to direct all waste fluid to flow down into one or more (shown as a central) drain hole 1641 where it is protected from the main airflow below the cover 1640 inside the waste station 632. **Figures 30A and 30B** illustrate another embodiment

of the waste tray cover **1640** which employs a plurality of waste drain holes **1641** using a tray cover that is shaped substantially similar to the elution tray **1610**. In the shielded environment below the waste tray cover **1640**, the air directly above the waste fluid can maintain a high humidity, thus reducing further evaporation. Further discussion of the tray cover **1640** is provided with respect to **Figures 30A and 30B**.

[0166] In some embodiments, a vacuum system **1600** circulates air through container **12**. In some embodiments, the isolation container vacuum system **1600** is configured to eliminate the need for filters. The vacuum system can comprise tubing **1650**, typically flexible tubing, connected from a pump head **1602**, such as via a pinch valve **330** (**Figure 17**), to the waste **632** and elution **630** stations. The outlet of the pump head returns the aspirated air back into the isolation container **12**.

[0167] **Figure 17** shows a circulation path according to one embodiment of the vacuum system **1600**. In this embodiment, the tubing **1650** and disposable pump head **1602** may be attached to the isolation container tray **14** during manufacture. These can be sterilized and shipped as part of the assembly associated with the isolation container tray **14**. Once an isolation container **12** is loaded and sealed, the vacuum system **1600** can remain closed throughout the rest of the processing. During installation of an isolation container into the processing system **10**, the vacuum tubing **1650** can be inserted into the pinch valve **330** and the disposable pump head **1602** is connected to the vacuum pump **320**. In some embodiments, the pump **320** only operates when vacuum is required. The pinch valves **330** may be used to direct the vacuum to the appropriate station. When processing is completed, the tubing **1650** may be extracted from the valve **330** and the pump head **1602** is disconnected from the pump **320**. The tubing **1650** and pump head **1602** can be single-use disposable, along with the rest of the isolation container **12**.

[0168] **Figure 18** shows a cutaway view of a tray **14** in place on the work surface **200** of a processing system **10**, showing exemplary locations of the pinch valve **330** and disposable pump head **1602**. Peltier plates **370** and **372** may provide cooling for a segment of the rear wall **14p** of the tray **14** and for the waste station catchment in the base of the tray **14**, respectively. The wall segment **14p** may be substantially planar (typically substantially vertical, but may be angled) and project inward to define a receiving space for the plate **372**. The wall **14p** may be configured to cooperate with the plate **372** to define a condensation wall. It is noted that in **Figure 18**, the thermal cyclor lid drive system **310** is shown with the lid extended into container, without the seal **430**

in place and the disposable pump head 1602 is shown, without the flexible vacuum pump tubing 1650, in place.

Exemplary Process Control and/or Yield Measurement Systems

[0169] In some embodiments, disposable cuvettes 660, 2060 can be used, for example, as shown in **Figure 19A** and **Figure 20F**. One or more cuvettes 660, 2060 may be fixedly or releasably mounted to isolation container tray 14, *e.g.*, such that cuvettes 660, 2060 extend vertically down from the bottom of tray 14.

[0170] In some embodiments, the concentration and/or purity of samples, *e.g.* nucleic acids or proteins, can be measured using a spectrophotometer 1900s (**Figures 3, 19B**) and cuvettes 660 (**Figures 19A, 20F**) or alternative optical methods for concentration measurements, *e.g.*, fluorometer, can be similarly incorporated in the system.

[0171] In some embodiments, as shown in **Figure 19A**, one or more disposable concentration cuvettes 660 are sealably mounted to the tray 14 via a flexible sealing member 1918, such as a gasket or O-ring. The tray 14 includes mounting members 14m that engage a clamp 1920 to hold the cuvette 660 tightly against the sealing member 1918, thus sealing the cuvette 660 to the tray 14 and maintaining the sealed processing environment inside the isolation container. As shown, the cuvette 660 can include an outer edge that is formed as a rigid upper lip 661. The clamp 1920 includes an inner upstanding arm 1921 that resides against the lip 1901 and an outer arm 1922 that engages the mounting member 14m to force the cuvette 660 against the tray 14. The cuvette 660 includes a cuvette measurement window 660w, typically at a lower portion thereof.

[0172] Alternatively, the cuvettes 660 (or cuvettes 2060) can be molded into the tray, overmolded, mechanically clamped, solvent bonded, adhesively affixed, or the like. The spectrophotometer 1900s (**Figure 3**) can be mounted on the processing system 10, *e.g.*, beneath the isolation container 12. The spectrophotometer 1900s can be configured to make absorbance measurements through cuvettes 660 (**Figure 20F**) while remaining outside the isolation container.

[0173] In some embodiments, there is a cuvette 660, 2060 for each measurement, such that no cuvette need be reused. The processing system 10 can be configured to move a spectrophotometer cuvette holder 360 (*see, e.g.*, **Figure 3, 19B**)

from cuvette 660 to 660 for each measurement as required. In some embodiments, cuvettes 660 and/or 2060 may be removed from the tray 14, washed and reused in subsequent trays 14. In other embodiments, removable cuvettes 660, 2060 are single-use only (*i.e.*, single-use disposable).

[0174] Various types of spectrophotometers are known and may be utilized for nucleic acid concentration and purity measurements. The spectrophotometer 1900s may be able to communicate with and be controlled by a controller associated with the processing system 10. For example, the processing system 10 can command the spectrophotometer 1900s to take a measurement and the spectrophotometer 1900s can be able to return the absorbance measurements, typically at ultraviolet wavelengths, such as for example, at about 260 and/or 280 nm, or at any other wavelength of interest. Additionally, the geometry of the spectrophotometer 1900s and particularly that of a cuvette holder 360 can be integrated with other components of the overall system.

[0175] Figure 19B illustrates a spectrophotometer head mechanism that is used to move a single detector head between a number of cuvettes 660, shown as (4) cuvettes 660 in Figure 20F. A robotic operational platform may be used to position the spectrophotometer cuvette holder 360, *e.g.*, to raise, lower and traverse between cuvettes 660. The spectrophotometer 1900s and light source may be mounted in an electrical cabinet of the system, *e.g.*, on a left or right side of the system. Optical fibers may be used to allow the cuvette holder 360 to move while the spectrophotometer 1900s and light source remain stationary. That is, as shown in Figure 19B, a spectrophotometer drive mechanism can be used to move a single detector head 1900h to serially hold each of the different cuvettes 660. The detector in the detector head 1900h can be coupled to the spectrophotometer 1900s via a plurality (typically two) optical fibers. In other embodiments, each cuvette 660 could be located in an individual cuvette holder 360 and the light source switched between the optical fibers connecting the light source to the multiple cuvette holders (not shown) to communicate with the spectrometer for measurements.

[0176] Volume measurement(s) of a sample may be used in combination with the concentration measurement(s) to determine yields. In some embodiments, a volume measurement unit 2000 utilizes the pipetting system and a fluid sensor in a dedicated vessel, *e.g.*, as shown in Figures 20A-20E. For example:

- **Figure 20A** shows an empty cuvette **2060** in a detector head **2002**, wherein light from two IR emitters **2010** does not pass through the cuvette **2060**, and is received by two IR receivers **2020** for reflected light.
- When a fluid **2040** to be measured is pooled in the volumetric cuvette **2060**, *e.g.*, as shown in **Figure 20B**, light from the two IR emitters **2010** is transmitted through the cuvette **2060** and the fluid **2040** and is not received by the two IR receivers **2020** for reflected light.
- While a control system monitors the presence of the fluid detected by the system **2000** at the bottom of the measurement vessel **2060**, the pipette head **220** is used to aspirate the sample **2040** into a pipette tip **651** as shown in **Figure 20C**.
- As shown in **Figure 20D**, when the sensor system **2000** reports fluid absent, the syringe pump **350** (**Figure 3**) can be stopped and the volume aspirated can be electronically determined and recorded. Thus, the cuvette **2060** has a prism design in the bottom. Using a light source with detectors the instrument can determine the presence or absence of liquid in the cuvette **2060** based on the reflection. This, in combination with the pipetting device determines the volume by measuring the liquid it is removing until receiving the signal that no liquid is present. **Figure 20E** illustrates that the system **2000** can employ a plurality of spaced apart detector blocks **2002**, each having its own pair of transmitters **2010**. Each block **2002** can be configured to hold and cooperate with a respective cuvette **2060** for obtaining a volume measurement using the volume measurement system **2000**.

[0177] As shown in **Figure 20F**, the tray **14** can include a plurality of both the volume cuvettes **2060** (*e.g.*, volume measurement cuvette) and a plurality of spectrophotometer cuvettes **660** (the cuvettes **660** can be used for concentration measurements). The spectrophotometer cuvette **660** can be a standard UV visible plastic disposable such as BioRad "trUVView cuvettes". The device **10** can include spectrophotometer components for measurements. Suitable spectrophotometer components can be obtained from Ocean Optics, having a place of business at Dunedin, Florida.

Exemplary Process Constituent Storage Systems

[0178] In some embodiments, reagent vessels are used to contain the reagents, the sample and mixing volumes of fluid combinations within the isolation container 12. Reagent vessels with various different capacities may be used to accommodate the range of fluid volumes used during the process.

[0179] To reduce the risk of reagent contamination, evaporation or spillage, each vessel that contains reagent can be sealed, typically over a top surface, such as with polypropylene-lined foil, prior to loading into the tray 14. The seal can be configured to be pierced by a pipette tip 651. The seal allows reagents to be loaded and sealed into the appropriate reagent vessel and stored without the risk of contamination, spillage or evaporation.

[0180] An example of a reagent rack 620 is shown in Figure 21A. Rack 620 may have any desired layout, can accommodate any reagent vessel size, and can be adapted for any process. In the example shown, the reagent tray or rack 620 includes a base 2100 for housing a number of vessels 2110, 2112, 2114, typically tubes, of different sizes that may contain for example sample and reagents, as well as mixing vessels. Each of the vessels can be supported within the base 2100, and a cover 2120 may be clipped or otherwise attached onto the rack 620 to ensure the vessels are kept securely in place. The cover 2120 includes apertures to allow the pipette tip to access the vessels held thereunder.

[0181] In some embodiments, reagents, samples, or other fluids can be loaded into the rack 620 as a sub-assembly, and the rack 620 is then loaded into the tray 14. In some embodiments, the design of the reagent rack 620 is such that it can only be placed into the isolation container tray in one orientation. Alternatively, the reagent rack 620 may be molded or otherwise made an integral part of the isolation container tray 14. Reagents may be loaded directly into an integral reagent tray or tubes or other vessels containing a reagent may be placed in the reagent tray. The placement of the vessels 2110, 2112, 2114 at a defined rack location (address) allows the robotic interface to automatically engage the correct vessel (reagent) at the correct time in the process.

[0182] In some embodiments, the tray layout allows access to all the vessels without the pipette tip having to pass over other dissimilar reagents, and thus reduces the chance of reagent cross contamination. Of course, other configurations may be used, for example, depending upon the desired processes to be performed.

[0183] Figure 21B illustrates that a multi-point (shown as a three-point) piercing sequence can be used to open the seal on a vessel 2110, 2112, 2114,

respectively, before withdrawing the (reagent) liquid. That is, the pipette 651 can be directed to pierce a seal covering at two outer locations before moving to the actual withdraw piercing (typically at a center location) to facilitate pipetting accuracy.

Exemplary Aliquot Removal Systems

[0184] During automated processing in system 10, one or more aliquots of a sample and/or products may be used for process evaluation, control, quality testing and/or storage for further processing (e.g., see aliquots tubes 440 in Figures 4 and 5).

[0185] In some embodiments, the isolation container 12 and processing system 10 allow aliquot removal during processing without compromising the sealed nature of the isolation container 12. A plurality of flexible tubes can be in fluid communication with an interior sample capture region of the container 12 and extend from the system 10 to be externally accessible by an operator. Each flexible tube is presealed or has a closed end portion. Each aliquot may be aspirated into an individually labeled container 440, for example a tube, while the container 12 remains closed. An operator or an automated sealer may seal the aliquot into the tube 440, e.g., upstream of the captured aliquot of fluid, such as by using an RF tube sealer, or other seal closure mechanism. Once sealed, an aliquot tube can be detached from the isolation container and taken away for storage, testing, or further processing.

[0186] In some embodiments, an aliquot assembly 40 is used for aspirating the aliquot fluid into the tube 440 and utilizes a clamping member and the elasticity of aliquot tubing 440 to draw the fluid from inside the container 12 into the tube. This mechanism can be automated to facilitate the tubing being clamped for a short time, thus reducing the likelihood of any change in the elasticity of the tubing caused by clamping deformation.

[0187] Figure 22 illustrates an exemplary method 2200 of using an aliquot assembly 40, and shows a series of steps (from left to right and top to bottom) that can be used to load the aliquot tubes 440 with an aliquot fluid 445. As shown, an aliquot tube 440 with a closed end 441 is sealably attached to the tray 14 under a well 14w. In this example, a clamping member (tube expressor) 2210 is pressed against one or more aliquot tubes 440 to expel air from the tubes (as shown by the second and third figures). After or while air is discharged in response to the tube being completely compressed by clamp 2210 (with upper clamping member 2211 forced down against the tube and other

clamp surface), the aliquot substance 445 is placed or dispensed in the well 14w in communication with the tube 440. Upon subsequent release of the clamping force, an aliquot of fluid 445 is drawn into the tube 440 by a negative pressure within the elastic tube. A tube sealer 2220 (such as an RF welder) may be used to seal (at 442) and optionally cut the aliquot tube upstream of the seal to isolate the sample 445 within the tube. Other sealant mechanisms may also be used.

Exemplary Methods of Assembling a Container

[0188] **Figure 23A** is an exploded representation of a kit 2500 that can be provided to allow an operator to prepare a closed system for processing. The kit 2500 can include the tray 14, the binding manifold 50, the pipette tip rack 650 (and pipette tips 651), and cuvettes 2060, 660. The tray 14 can be packaged and shipped to a use site with the aliquot tubes 440 attached and/or the vacuum head and associated tubing attached. The components can be sterilized and packaged (or packaged, then sterilized) in a sterile package for shipment and handling. The components may be surface sterilized at a point of use and the assembly of the components may be in a Class 10,000, 1000, or even 100 clean room. The components may also be provided separately or preloaded in other combinations.

[0189] **Figure 23B** is a partially assembled view of the kit shown in **Figure 23A**. **Figure 23C** is a bottom view of the partially assembled kit shown in **Figure 23B**. **Figure 23D** is a top view of the container 14 shown in **Figure 23A** prior to assembly of the discrete components shipped with or separate from the container or tray 14.

[0190] **Figure 24** illustrates an exemplary method of sealing, respectively, an isolation container 12 according to embodiments of the invention (for example, for aseptic processing nucleic acids from one or more biological samples). For such aseptic processing, the barrier 16 and tray 14 sections of the isolation container assembly 12 may be individually pre-packaged and sterilized. When the isolation container 12 is needed for processing, the tray 14 and barrier 16 may be transferred to a biological safety cabinet or equivalent clean, controlled area for loading.

[0191] As shown in **Figure 23A**, the tray 14 of an isolation container 12 may be loaded with one or more reagent trays 620 comprising samples and reagents to be used in the desired process. The assembly and/or loading of the tray 14 can take place with the tray 14 on the trolley 399 (**Figure 27**) as discussed above. One or more pipette

tip racks **650** and binding column manifolds **50** may also be loaded into the working area **18** of the tray **14**. In some embodiments, one or more cuvettes **660**, **2060** are attached to the base of tray, for example, as shown in **Figure 20F**. Depending upon the desired assay or process to be performed, other samples, analytes, reagents, vessels, other consumables, devices, tools and/or other items may be loaded into tray **14**.

[0192] In some embodiments, after all of the desired items are placed within or attached to the tray **14**, the barrier **16** can be attached to the tray **14** to seal the assembled isolation container **12**, for example as shown in **Figure 24**. In some embodiments, an O-ring **2400** may be used to seal the flexible barrier **16** to the tray **14**. The O-ring can be forced snugly over the barrier **16** and into the perimeter slot on the tray **14**. In other embodiments, one or more gaskets, clips, clamps, fasteners, adhesives, and/or other attachment means may be used.

[0193] As shown in **Figure 27**, the tray **14** can be locked to a holding surface on a trolley during transport. After the tray **14** is loaded and sealed with the barrier **16**, the isolation container **12** may then be transferred to the work surface **200** of the processing system **10**. Alternatively, the isolation container can be assembled and sterilized. Then, reagents and samples can be introduced into a sealed isolation container using standard aseptic transfer methods or by other closed means. The trolley can also be used to hold the tray **14** during assembly. Alternatively, a separate barrier isolator trolley-assembly cart may be used when assembling the isolation container **12** (not shown). Such a barrier isolator trolley may be integrated into the barrier isolator itself and can mate with the transport trolley as discussed above.

[0194] The isolation container assembly **12** may be installed into the system **10** and connected to each piece of equipment used for processing the samples. To ensure correct alignment, the rigid tray **14** may be clamped onto the work surface **200**. The flexible barrier **16** and pipette head **220** may connect to the robotic pipette head adapter **210** (*see e.g.*, **Figure 2**). As shown for example, in **Figure 12**, thermal cycler evaporative seal **430** may connect to the thermal cycler lid **1010**, *e.g.*, using vacuum cups **1140** or other fasteners or attachment means, and vacuum tubing and the disposable pump head for the waste and elution stations are fitted to the corresponding valves and pump. To remove an isolation container, the reverse procedure may be used.

[0195] **Figure 25** is a flow chart of operations that can be carried out at a manufacturing site according to embodiments of the invention. As shown, an input sample **3000** is provided (typically from a patient collection site or a subject's specimen

storage site). When time-sensitive, the specimen can be shipped for receipt at the manufacturing site within 12-48 hours (such as overnight). At the manufacturing site, the isolation container 12 is prepared in a barrier isolator (block 3010) and sample may also be prepared (block 3000p) prior to placement in the container (*e.g.*, homogenized, mixed and/or centrifuged). The outer packaging of the isolation container components, *e.g.*, the tray 14, the barrier 16 and the container contents can be sterilized (block 3002). The assembled and sealed isolation container can be assembled (block 3004) and integrity-tested (block 3006) to confirm a sealed state.

[0196] The closed assembled isolation container can be moved to the instrument for processing (block 3020). As shown, the RNA from the patient sample can be isolated (block 3022) using silica membrane columns and appropriate RNA binding and elution reagents. Concentration and volume determinations are performed out to calculate yields and the concentration is normalized (block 3024). The cDNA is synthesized by a reverse transcription (RT) reaction, amplified through PCR, and purified (block 3026) using silica membrane columns and appropriate cDNA binding and elution reagents. Concentration and volume determinations are performed to calculate yield and the concentration is normalized (block 3028). IVT RNA is produced from the resulting cDNA, treated with DNase and purified (block 3030) using silica membrane columns and appropriate RNA binding and elution reagents. Concentration and volume determinations are performed to calculate yield and the concentration is normalized (block 3032) resulting in the final amplified RNA (block 3034). The RNA disposable can be integrity-checked (block 3036) to confirm that the system is still sealed and isolated from the environment to thereby ensure that there was no contamination during the process. Intermediate and/or final products can be output as one or more aliquot amounts (block 3050).

[0197] Figures 29A-29C show an exemplary elution tray 1610. As shown, the receptacles 1612 are spaced apart and angled to inhibit splash-over during use of a respective receptacle 1612. Two or more receptacles 1612 reside on each side of an upwardly extending barrier 1614 and the primary tubular receiving portion 1615 merges into a shallow channel 1616 that tapers downwardly and becomes deeper and narrower as it moves toward the tubular body portion 1615. The forward portion of the channel 1616 is also tapered inwardly and downwardly to capture splash and to direct the liquid to flow to the primary tubular portion 1615.

[0198] Figures 30A-30B illustrate a similar configuration for the waste tray cover 1640 but the tips 1632 of the receptacles are open or have apertures for draining the waste to the waste station 632 (Figure 16).

[0199] Figure 31 is a schematic illustration of a control circuit 4000 that is in communication with sensors 4010, 4020, 4030 that can be used to monitor the status of the inside of the container or provide desired feedback to allow the automatic control of components (heaters, coolers, robotic arm movement and the like). As shown, the control circuit 4000 can be in communication with the user interface 61 (Figure 1). The sensors can include a load sensor 4010, a temperature sensor 4020, and a pressure sensor 4030. The load sensor 4010 can be in communication with the new pipette rack to provide loading force data used to control the engagement force applied by the robotic arm to engage a new pipette. The temperature sensor 4020 can provide temperature data regarding the internal environment or a particular location within the closed container environment (e.g., one or more of the workstations). The pressure sensor 4030 can be used to monitor the sealed integrity status of the closed environment and/or vacuum during isolation or purification procedures. Multiple sensors of each or some of the sensors can be used and other sensors may also be used. The control circuit 4000 may reside wholly or partially in the system 10 or wholly or partially with or on the container 12.

[0200] As will be appreciated by one of skill in the art, embodiments of the invention may be embodied as a method, system, data processing system, or computer program product. Accordingly, the present invention may take the form of an entirely software embodiment or an embodiment combining software and hardware aspects, all generally referred to herein as a "circuit" or "module." Furthermore, the present invention may take the form of or use a computer program product on a computer-usable storage medium having computer-usable program code embodied in the medium. Any suitable computer readable medium may be utilized including hard disks, CD-ROMs, optical storage devices, a transmission media such as those supporting the Internet or an intranet, or magnetic or other electronic storage devices.

[0201] Computer program code for carrying out operations of the present invention may be written in PLC code such as Graph, Ladder or SCL. However, the computer code can be alternatively or additionally written in an object oriented programming language such as Java, Smalltalk or C++ and/or conventional procedural

programming languages, such as the "C" programming language or in a visually oriented programming environment, such as VisualBasic.

[0202] Certain portions (or all) of the program code may execute entirely on one or more of the system's computer(s), partly on the system computer(s), as a stand-alone software package, partly on the system computer(s) and partly on a remote computer or entirely on the remote computer. In the latter scenario, the remote computer may be connected to the system computer through a local area network (LAN) or a wide area network (WAN), or the connection may be made to an external computer (for example, through the Internet using an Internet Service Provider). In some embodiments, some program code may execute on local computers and some program code may execute on one or more local and/or remote server. The communication can be done in real time or near real time or off-line using a volume data set provided from the imaging modality.

[0203] The invention is described in part with reference to flowchart illustrations and/or block diagrams of methods, systems, computer program products and data and/or system architecture structures according to embodiments of the invention. It will be understood that each block of the illustrations, and/or combinations of blocks, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general-purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions/acts specified in the block or blocks.

[0204] These computer program instructions may also be stored in a computer-readable memory or storage that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable memory or storage produce an article of manufacture including instruction means which implement the function/act specified in the block or blocks.

[0205] The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer implemented process such that the instructions which execute on the

computer or other programmable apparatus provide steps for implementing the functions/acts specified in the block or blocks.

[0206] As illustrated in **Figure 32**, embodiments of the invention may be configured as a data processing system **4116**, which can be used to carry out or direct operations of the rendering, and can include a processor circuit **4100**, a memory **4136** and input/output circuits **4146**. The data processing system may be incorporated in, for example, one or more of a programmable logic controller (PLC), personal computer, workstation, server, router or the like. The system **4116** can reside on one machine or between a plurality of machines. The processor **4100** communicates with the memory **4136** via an address/data bus **4148** and communicates with the input/output circuits **4146** via an address/data bus **4149**. The input/output circuits **4146** can be used to transfer information between the memory (memory and/or storage media) **4136** and another computer system or a network using, for example, an Internet protocol (IP) connection. These components may be conventional components such as those used in many conventional data processing systems, which may be configured to operate as described herein.

[0207] In particular, the processor **4100** can be commercially available or custom microprocessor, microcontroller, digital signal processor or the like. The memory **4136** may include any memory devices and/or storage media containing the software and data used to implement the functionality circuits or modules used in accordance with embodiments of the present invention. The memory **4136** can include, but is not limited to, the following types of devices: ROM, PROM, EPROM, EEPROM, flash memory, SRAM, DRAM and magnetic disk. In some embodiments of the present invention, the memory **4136** may be a content addressable memory (CAM).

[0208] As further illustrated in **Figure 32**, the memory (and/or storage media) **4136** may include several categories of software and data used in the data processing system: an operating system **4152**; application programs **4154**; input/output device drivers **4158**; and data **1456**. As will be appreciated by those of skill in the art, the operating system **4152** may be any operating system suitable for use with a data processing system, such as IBM®, OS/2®, AIX® or zOS® operating systems or Microsoft® Windows®95, Windows98, Windows2000, WindowsXP or WindowsCE operating systems, Unix or Linux™. IBM, OS/2, AIX and zOS are trademarks of International Business Machines Corporation in the United States, other countries, or both while Linux is a trademark of Linus Torvalds in the United States, other countries,

or both. Microsoft and Windows are trademarks of Microsoft Corporation in the United States, other countries, or both. The input/output device drivers **4158** typically include software routines accessed through the operating system **4152** by the application programs **4154** to communicate with devices such as the input/output circuits **4146** and certain memory **4136** components. The application programs **4154** are illustrative of the programs that implement the various features of the circuits and modules according to some embodiments of the present invention. Finally, the data **4156** represents the static and dynamic data used by the application programs **4154** the operating system **4152** the input/output device drivers **4158** and other software programs that may reside in the memory **4136**.

[0209] The data **4156** may include (substantially real-time, archived or stored) Process Sequence data sets **4126** and/or closed environment sensor feedback data **4127**. As further illustrated in **Figure 32**, according to some embodiments of the present invention application programs **4154** include an Automated Process Sequence and Monitoring Module **4125**. The application program **4154** may be located in a local server (or processor) and/or database or a remote server (or processor) and/or database, or combinations of local and remote databases and/or servers.

[0210] While the present invention is illustrated with reference to the application programs **4154** in **Figure 32**, as will be appreciated by those of skill in the art, other configurations fall within the scope of the present invention. For example, rather than being application programs **4154**, these circuits and modules may also be incorporated into the operating system **4152** or other such logical division of the data processing system. Furthermore, while the application program **4154** is illustrated in a single data processing system, as will be appreciated by those of skill in the art, such functionality may be distributed across one or more data processing systems in, for example, the type of client/server arrangement described above. Thus, the present invention should not be construed as limited to the configurations illustrated in **Figure 32**, as it may be provided by other arrangements and/or divisions of functions between data processing systems. For example, although **Figure 32** is illustrated as having various circuits and modules, one or more of these circuits or modules may be combined or separated without departing from the scope of the present invention.

Other Embodiments

[0211] The foregoing exemplary system 10 was provided to illustrate various aspects and features of the present invention, and is not intended to limit the scope of the present invention to systems, devices and methods for nucleic acid processing. Rather, one skilled in the art will appreciate that various other applications fall within the scope of the present invention, including, for example, systems and methods for fabricating, assembling, processing or otherwise manipulating any items, typically in a closed container. The following sections provide additional examples of applications in which the apparatus and methods of the present invention may be employed.

Examples of Other Biological and/or Pharmaceutical Applications

[0212] In other aspects, the present invention provides methods of transferring a material, for example, a fluid, from a source to a target in a closed environment, wherein the closed environment is defined as the interior region or chamber in the container of an apparatus as described in the present application. A fluid to be transferred can contain, for example, a biologic; drug; toxin; isolate; radioisotope; virus; bacteria; eukaryotic cell; extract; analyte; biological specimen such as, for example, blood, plasma, saliva, etc.; vaccine; nucleic acid; protein; foodstuff; and the like, including suspensions, mixtures, and so on, thereof.

[0213] Applications for the instant systems and methods can be found, for example, where contamination of the material to be transferred inside the closed environment is to be avoided by substances potentially in the environment outside of container. In certain embodiments, the systems and methods can be directed to preparation of materials for, or for processing materials in, diagnostic assays, such as, by way of non-limiting examples, sterility assays, forensic analyses, or quality control assays, for example, to test purity of biologics to be used in clinical applications. In other embodiments, the instant methods can be for the preparation or manufacture of drugs and biologics, such as vaccines, and nucleic acids for experimental and/or clinical use. Various assays and methodologies that may be suitable for use in the systems and methods of the present invention are known to those of skill in the art as described, for example, in United States Pharmacopeia, *United States Pharmacopeia and National Formulary (USP 29-NF 24)* (2006), U.S. Department of Health and Human Services, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current*

Good Manufacturing Practice (September 2004), each of which is incorporated by reference herein in its entirety.

[0214] It will be understood by those skilled in the art that a target to which a fluid is transferred can be any receptacle, such as, for example, a tube, vial, vessel, and the like, that is intended to hold the transferred fluid. In some embodiments, the target is a substrate, such as a binding column, size exclusion column, chromatography media, or filter, or the like. However, depending upon the particular application in the methods provided, any flow-through device, that is, any device intended to capture and/or separate and/or concentrate one or more components of the transferred fluid from another component of the fluid, can be used.

[0215] **Figure 14** provides an example of a configuration of an exemplary apparatus wherein binding columns **1410** situated in the closed environment are a target for transferred fluid containing, for example, nucleic acids. In other embodiments, the manifold described in **Figure 14** can be adapted to fit filters or other devices discussed above.

[0216] In some embodiments, systems and methods provided by the invention can allow for aseptic preparation of an amplified nucleic acid product, comprising the steps of isolating RNA from a cell extract and amplifying a nucleic acid product from at least one RNA molecule from the isolated RNA, wherein the isolating and amplifying steps are performed in a closed environment as defined as the interior region or chamber in the container of an apparatus as described in the present application, thereby aseptically preparing the amplified nucleic acid product.

[0217] In certain embodiments for the aseptic preparation of an amplified nucleic acid product, the amplified nucleic acid product is derived from a pathogen, such as from a viral pathogen. In certain embodiments, the amplified nucleic acid product is derived from human tumor RNA. An amplified nucleic acid product from a human tumor RNA can be used, for example, in the preparation of a vaccine or immunotherapy.

[0218] The instant methods can be used for the sterilization of a material, for example, a biologic as defined under Title 21 of the United States Code of Federal Regulations, nucleic acid, and/or protein, and so forth, under aseptic conditions. Guidelines regarding the preparation of such materials for clinical applications are described in, *e.g.*, U.S. Department of Health and Human Services, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (September 2004).

[0219] Thus, in certain embodiments, methods are provided for the sterilization of a material comprising transferring a fluid comprising the material from a source to a filter and collecting the material after passage through the filter into a receptacle, wherein the source, filter and receptacle are contained in a closed environment as defined as the interior chamber or region in the container of an apparatus as described in the present application. Filters for sterilization are commercially available, for example, from Whatman Inc. (Florham Park, NJ).

[0220] It will also be recognized that transferring material, for example, dispensing the material into a vial, can be hazardous if the material comprises a pathogen, such as is the HIV virus, or other certain microorganisms, or comprises a biological toxin or a radioactive substance. Transferring such materials into receptacles in a closed environment such as defined in embodiments of the present invention can be used to reduce the potential exposure of the hazardous material to the individuals undertaking the transfer. Thus, in certain embodiments, methods are provided wherein a hazardous material is transferred from a source to a target in a closed environment as in the container of an apparatus as described in the present application. These methods can be applied to a variety of procedures and assays where hazardous materials are transferred between a source and a target, as will be known to those of skill in the art.

[0221] The apparatus of the present invention can be used for other applications typical of protein purification, nucleic acid purification, and other molecular biology processes. Such applications include, but are not limited to, cell lysing (*e.g.*, mechanical, chaotropic, thermal, or enzymatic lysing of cells), macromolecule purification (*e.g.*, ion exchange, bead, molecular weight cutoff), and recovery (silica elution, bead elution, membrane elution).

Exemplary Lithography, Microfabrication and Related Applications

[0222] Embodiments of the present invention can be used in any situation where clean room conditions are used or isolation is desired, such as, for example, lithography and assembly processes. In some embodiments, the apparatus of the present invention satisfy the conditions of a class 1, class 10, class 100, class 1000, class 10,000, or class 100,000 clean room as set forth by the U.S. Federal Standard 209b for clean room classification. See, Federal Standard No. 209B 1992, "Clean Room and Work Station Requirements, Controlled Environment," dated April 24, 1973, which is hereby

incorporated by reference in its entirety. As such, embodiments of the present invention can be used for a broad spectrum of processes that use a clean room environment. Such processes include lithography processes such as, but not limited to, wafer patterning (also known as photomasking, masking, photolithography, microlithography), doping (e.g., thermal diffusion, ion implantation), heat treatment (e.g., thermal, radiation). Specific patterning processes that can be conducted in the apparatus of the present invention include, but are not limited to (i) resist application (positive or negative); (ii) exposure (e.g. by contact, proximity, scanning projection, and stepper) to high pressure mercury, X-rays, or E-beams; (iii) imaging (e.g., single layer resist, multilayer resist, application of antireflector layers, off-axis illumination, planarization, contrast enhancement; and (iv) etch (e.g., wet chemistry-liquid/vapor, dry, plasma, lift-off, ion milling, reactive ion etching. Specific heat treatment processes include, but are not limited to, hot plate, convection, rapid thermal processing (RTP), and infrared. More description of these lithography processes are described in Van Zant, *Microchip Fabrication*, Fourth Edition, Chapter 4, 2000, McGraw-Hill, New York, which is hereby incorporated by reference in its entirety.

[0223] In addition to conventional lithographic techniques, the apparatus of the present invention can be used to house next-generation lithographies such as extreme ultraviolet lithography, X-ray lithography (e.g., LIGA), charged-particle-beam lithography (e.g., electron-beam, ion-beam), scanning probe lithography (e.g., scanning tunneling microscope lithography, atomic force microscope lithography, scanning electrochemical microscope lithography), soft lithography (e.g., replica mold, micro-contact printing, micro-molding in capillaries, micro-transfer molding, solvent-assisted micromolding, near-field conformal photolithography using an elastomeric phase-shifting mask) and three-dimensional lithography (e.g., holographic lithography, lithography on non-planar substrates). Such techniques are described in Madou, *Fundamentals of Microfabrication*, Second Edition, 2002, CRC Press LLC Boca Raton, Florida, pp. 48-68, which is hereby incorporated herein by reference in its entirety.

[0224] Embodiments of the present invention can be used for protein patterning microlithographic techniques that address, for example, the problem of non-specific protein absorption competing for detection sites in immunosensors. See, for example, Clementi *et al.*, *Structure and Motion: Membranes, Nucleic Acids, and Proteins*, Adenine Press, Schenectady, New York, 1985, which is hereby incorporated herein by reference in its entirety.

[0225] Devices, systems, apparatus and methods of the present invention can be used to perform dry etching techniques such as physical etching (*e.g.*, ion etching, sputtering, ion-beam milling), plasma etching (*e.g.*, radical etching), physical/chemical etching, deep reactive ion etching, vapor-phase etching without plasma, dry etching, and single-crystal reactive etching metallization (SCREAM) as disclosed in Chapter 2 of Madou *Fundamentals of Microfabrication*, Second Edition, 2002, CRC Press LLC Boca Raton, Florida, which is hereby incorporated herein by reference in its entirety.

[0226] The apparatus of the present invention can be used to perform pattern transfer with additive techniques such as silicon growth, doping of silicon, oxidation of silicon, physical vapor diffusion (*e.g.*, thermal evaporation, sputtering, molecular beam epitaxy, laser sputter deposition, ablation deposition, ion plating, cluster beam technology), chemical vapor deposition, silk-screening (screen printing), sol-gel deposition, plasma spraying, spray pyrolysis, and plasma-beam deposition as disclosed in Chapter 3 of Madou *Fundamentals of Microfabrication*, Second Edition, 2002, CRC Press LLC Boca Raton, Florida, which is hereby incorporated herein by reference in its entirety.

[0227] Embodiments of the present invention may be particularly useful in deposition and arraying methods used in the BIOMEMS field, which encompasses techniques for depositing organic materials for chemical and biological sensors, often arranged in some type of array configuration. Such techniques can be used, for example, to make organic gas permeable membranes, ion selective membranes, hydrogels, organic monolayers needed for room-temperature gas sensors, ion selective electrodes, enzyme sensors, immunosensors, and DNA and protein arrays. Specific techniques in the BIOMEMS field that can be implemented on the apparatus of the present invention are spin coating, dip coating, plastic spraying, casting, type casting, glow discharge (plasma) polymerization, Langmuir-Blogett processes, ink-jetting, microspotting, and mechanical microspotting, as disclosed in Madou *Fundamentals of Microfabrication*, Second Edition, pp. 159-167, 2002, CRC Press LLC Boca Raton, Florida, which is hereby incorporated herein by reference in its entirety.

[0228] Embodiments of the present invention can be used for other clean room applications, such as packaging of small devices (*e.g.*, integrated circuits). Specific packaging techniques that can be performed using the apparatus of the present invention include, but are not limited to, packaging of integrated circuits, dicing, cavity sealing and bonding, multi-chip packaging, and partitioning as disclosed in Madou *Fundamentals of*

Microfabrication, Second Edition, pp. 478-508, 2002, CRC Press LLC Boca Raton, Florida, which is hereby incorporated herein by reference in its entirety.

[0229] Embodiments of the present invention can be used for application of photoresists in lithographic processes. For instance, the apparatus of the present invention can be used to apply either positive or negative photoresist to a substrate in a clean room environment. As such, steps such as resist spin coating, softbake, hardbake, development, post-exposure bake, and multi-layer resists processes can be performed in the apparatus of the present invention as described in Levinson, *Principles of Lithography*, SPIE Press, Bellingham, Washington, 2001, Chapter 3, which is hereby incorporated herein by reference in its entirety. The apparatus of the present invention can be used for lithographic processes such as optical lithography, electron beam lithography, x-ray lithography, deep-UV resist application, photomask fabrication, as well as metrology methods in photolithography as described in *Microlithography, Micromachining, and Microfabrication*, ed. Rai-Choudhury, SPIE Press, Bellingham, Washington, 2001, Chapters 1-6, which is hereby incorporated herein by reference in its entirety. The systems, devices, apparatus and methods of the present invention can further be used to implement methods used to fabricate photovoltaic cells, including but not limited to phosphorous diffusion, edge isolation, ARC deposition, front-contact printing, back-contact printing, co-firing, testing and sorting, as disclosed in *Handbook of Photovoltaic Science and Engineering*, Luque and Gegedu eds., John Wiley & Sons, West Sussex, England, 2003, pp. 271-279, which is hereby incorporated herein by reference in its entirety.

[0230] All references cited herein are incorporated herein by reference in their entirety to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. However, the incorporated by reference documents are not to be used to narrow an interpretation of a claim element of the pending application or any patent issuing thereon.

[0231] While the foregoing description and drawings represent embodiments of the present invention, it will be understood that various additions, modifications and substitutions may be made therein without departing from the spirit and scope of the present invention as defined in the accompanying claims. In particular, it will be clear to those skilled in the art that the present invention may be embodied in other specific forms, structures, arrangements, proportions, and with other elements, materials, and

components, without departing from the spirit or essential characteristics thereof. The presently disclosed embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims, and not limited to the foregoing description.

THAT WHICH IS CLAIMED:

1. An apparatus for manipulating items in a closed container, comprising:
a container having an interior region configured to hold a plurality of items to be manipulated;
a flexible barrier configured to sealably attach to the container; and
a tool integrated with or within the flexible barrier, the tool having a first interface and a second interface, wherein the first interface is configured to attach to a robotic device on a first side of the barrier outside of the interior region of the container and the second interface is disposed within the interior region of the container under the flexible barrier and configured to manipulate the items in the interior region when the flexible barrier is sealably attached to the container.
2. The apparatus of claim 1, wherein the plurality of items comprise nucleic acid samples.
3. The apparatus of claim 1, wherein the tool comprises a component of a pipetting device.
4. The apparatus of claim 2, wherein the container further comprises a plurality of stations for processing the nucleic acid samples.
5. The apparatus of claim 4, further comprising a manifold configured to hold at least one nucleic acid binding column, the manifold configured to move between at least two of said plurality of stations.
6. The apparatus of claim 5, wherein the manifold comprises a handle, and wherein the second interface is configured to engage the handle to move the manifold to and from at least two stations.
7. The apparatus of claim 6, wherein the at least two stations comprise an elution station and a waste station.

8. The apparatus of claim 4, wherein at least one of the plurality of stations comprises a reagent station.

9. The apparatus of claim 8, further comprising a reagent rack disposed within the reagent station, the reagent rack holding a plurality of reagents for processing the nucleic acid samples.

10. The apparatus of claim 1, further comprising a single-well or multi-well vessel sealed to a base of said container and designed to fit into a thermal block, wherein the vessel is accessible from the interior region of the container.

11. The apparatus of claim 10, wherein the container further comprises a flexible seal sealably coupled to a sidewall of the container and extending over an aperture in the sidewall defining closed flexible side entry channel, the flexible side entry channel dimensioned to allow a lid to reciprocate in and out of the aperture in the sidewall inside the flexible seal and to travel vertically to close over and cover the vessel, whereby the flexible seal allows the lid to travel in and out of the interior region of the container while maintaining a closed environment within the container.

12. The apparatus of claim 11, further comprising a drive member with an automated drive system for automatically moving the lid in and out of the sidewall aperture of the container while held in the flexible seal.

13. The apparatus of claim 1, further comprising a plurality of aliquot tubes extending outwardly from the container and being in fluid communication with the interior region of the container, the plurality of aliquot tubes configured to receive processed fluid samples.

14. The apparatus of claim 13, further comprising an aliquot tube expressor for drawing the plurality of processed samples into the plurality of aliquot tubes.

15. The apparatus of claim 14, wherein the aliquot tube expressor comprises a tube sealer to seal one or more of the plurality of aliquot tubes.

16. The apparatus of claim 3, wherein the pipetting device comprises:
a pipette tip adapter for releasably engaging pipette tips stored within the container;
a working fluid chamber for communicating with a fluid pump outside of the container; and
a diaphragm or a filter for isolating the working fluid chamber from the pipette tip adapter and for transmitting pressure from the fluid pump to the pipette tip adapter.

17. The apparatus of claim 1, further comprising a spectrophotometer for quantifying a sample, wherein the container comprises a connector for sealing a cuvette to the base of the container, said cuvette configured to hold the sample to be quantified by the spectrophotometer.

18. The apparatus of claim 1, further comprising a recirculating vacuum system configured to circulate air sealed within the interior region of the container in a closed loop when the flexible barrier is sealed to the container.

19. The apparatus of claim 1, wherein the vacuum system comprises a single-use disposable vacuum head and flexible tubing.

20. The apparatus of claim 19, further comprising at least one heat exchange device for controlling humidity and/or vapor concentration within the sealed container.

21. The apparatus of claim 1, wherein the container and the barrier are single-use disposable.

22. The apparatus of claim 13, wherein the processed fluid is discharged from the container while the container remains sealed without impacting the closed status of the closed system, and wherein the container and barrier remain sealed during and after use to define a closed-system disposable.

23. The apparatus of claim 1, further comprising a pressure sensor in communication with the closed container and a control circuit in communication with the

pressure sensor configured to monitor pressure in the closed container to verify seal integrity.

24. The apparatus of claim 1, further comprising a housing with a work surface having a container position guide, the apparatus further comprising a trolley configured to hold a container with the flexible barrier, then allow an operator to align the trolley with the housing to slidably transfer the closed container to proper operative position on the work surface using the container position guide.

25. The apparatus of claim 24, wherein the work surface container position guide comprises spaced apart slots, and wherein the trolley comprises corresponding slots that align with the slots on the work surface, whereby the closed container can be slidably transferred from the trolley to the work surface into proper operative position.

26. The apparatus of claim 24, further comprising a spring-biased member that pushes against the closed container on the work surface to force the closed container to a desired operative position under a robotic arm.

27. A method of processing samples, comprising:
providing a single-use disposable container having an interior comprising a plurality of processing stations;
loading at least one reagent and at least one sample into the container;
sealing the container with a flexible barrier, the flexible barrier comprising a pipette head integrated with or within the flexible barrier, and the pipette head having a pipette tip adapter extending from one side of the barrier for engaging pipette tips within the interior of the container and a receptacle on an opposite side of the barrier for receiving a pipette head adapter of a robotic arm;
attaching the pipette head adapter of the robotic arm to the pipette head, such that the robotic arm resides outside of the sealed container;
manipulating the pipette head using the robotic arm from outside of the container to transfer the sample and the reagent between one or more of the processing stations in the container; and
processing at least one sample at one or more of the processing stations.

28. The method of claim 27, wherein the plurality of processing stations comprise a PCR plate, an elution station and a waste station.

29. The method of claim 28, further comprising loading at least one manifold holding a binding column into the container before sealing the container, the manifold configured to fit within the elution station and the waste station.

30. The method of claim 29, wherein the processing step comprises moving the manifold between the elution station and waste station positions.

31. The method of claim 27, further comprising maintaining a closed volume within the container during the processing.

32. The method of claim 31, wherein maintaining the closed volume comprises recirculating air within the container.

33. The method of claim 32, wherein maintaining the closed volume further comprises controlling the humidity and/or vapor concentration(s) within the container.

34. An apparatus for the transfer of fluid, comprising:
a pump for pumping a working fluid;
a diaphragm in communication with the pump through the working fluid, the diaphragm configured to isolate the working fluid and working fluid pump from a fluid sample; and
a tube in communication with the diaphragm and the sample, the tube having a lumen in communication with the diaphragm;
wherein the diaphragm is configured to transmit a change in pressure in the working fluid to the lumen of the tube such that the change in pressure draws a fluid into or expels fluid from the lumen.

35. The apparatus of claim 34, wherein the tube comprises a releasable pipette tip.

36. An apparatus for measuring volume of a fluid, comprising:
at least one emitter configured to project a signal toward a predetermined position of a sample container;
at least one receiver configured to receive the signal after the signal interacts with the sample container, wherein a change in the signal received by the receiver indicates when the fluid has dropped below said predetermined position; and
a fluid transfer device in communication with the receiver and sample container, wherein the fluid transfer device determines the volume of fluid that it has removed from the sample container when the receiver detects that the fluid has dropped below said predetermined position.

37. The apparatus of claim 36, wherein the emitter is a light emitter and the signal comprises light.

38. The apparatus of claim 36, wherein the fluid transfer device comprises at least a portion of a pipette.

39. The apparatus of claim 36, wherein the sample container comprises a cuvette.

40. The apparatus of claim 39, further comprising a plurality of sample containers that are serially in communication with the emitter.

41. An apparatus for measuring volume of a fluid, comprising:
at least one light source for emitting light;
at least one receiver for receiving light from the light source;
a cuvette through which a change in the light path dependent upon whether the cuvette contains fluid or is empty can be detected; and
a fluid transfer device in communication with the receiver to determine the volume of fluid that has been removed from the cuvette when the receiver detects that the cuvette is empty.

42. The apparatus of claim 41, wherein the fluid transfer device comprises at least a portion of a pipette.

43. A processing container, comprising:

a first member having a substantially rigid body with a plurality of regions defining spaced apart workstations; and

a flexible barrier member sealably attached to the first member to define a closed chamber over the plurality of workstations, wherein the flexible barrier is substantially impermeable, and wherein the flexible barrier member comprises a manipulation tool that is sealably attached to the barrier, the tool having a first internal interface that resides in the closed chamber under the flexible barrier and a second external interface that resides outside the closed chamber.

44. The container of claim 43, wherein the barrier and first member are single-use disposable.

45. The container of claim 43, wherein the first member has a wall segment configured to snugly receive an external cooling element, wherein, in operation, the wall segment cooperates with the cooling element to define a condensation wall inside the container.

46. The container of claim 43, wherein the first member comprises a sidewall with a side entry receiving aperture, and wherein the side entry receiving aperture is sealably covered by a substantially laterally extending sleeve that is configured to allow at least one item to enter into and exit from an interior region of the container.

47. The container of claim 43, wherein one of the workstation regions is configured to hold a PCR plate, another of the workstation regions is configured to hold a pipette rack with pipette tips, and another of the workstation regions is configured to hold a tray of sealed reagent vessels.

48. A biological sample processing container, comprising:

a single-use disposable sterile tray having a substantially rigid body with a first workstation configured to hold a PCR plate, a second workstation configured to hold reagents, and a third workstation configured to hold sterile pipettes.

49. A flexible barrier having an outer edge portion configured to seal to a tray to define a sealed closed interior chamber, wherein the flexible barrier comprises an elastomer and is sealably attached to a robotic arm interface at a medial portion of the barrier.

50. The barrier of claim 49, wherein the flexible barrier is substantially impermeable.

51. The barrier of claim 49, wherein the flexible barrier comprises a plurality of radial pleats.

52. The barrier of claim 49, wherein the medial portion of the flexible barrier comprises a plurality of substantially vertically oriented stepped portions.

53. An automated pipette tip disengagement system, comprising:
a tray having a sidewall; and
a robotic arm merging into a manipulation tool having an outwardly extending lever configured to contact the tray sidewall, whereby contact with the sidewall forces the lever to pivot and release a respective used pipette tip held by the manipulation tool.

54. The system of claim 53, wherein the tray sidewall angles down to a base of the tray that holds a pipette tip rack substantially horizontally below and adjacent the angled sidewall.

55. The system of claim 53, further comprising a load sensor in communication with a pipette tip rack, wherein the manipulation tool is configured to advance to exert between about a 5N-50N load against a target pipette tip to engage a respective pipette tip held by the pipette tip rack.

56. A system for processing liquids:
a robotic arm; and
a manipulation tool that cooperates with the robotic arm, the tool configured to releasably engage a pipette tip and automatically translate to pierce a cover on a vessel a

plurality of times in different spaced apart locations before withdrawing fluid from the vessel through one of the pierced openings in the cover.

57. An elution tray, comprising:

a sterile biocompatible elution tray having a plurality of spaced apart receptacles, some of the receptacles located on a first side of an upwardly extending barrier and other of the receptacles located on an opposing side of the barrier, wherein each of the receptacles has a channel that extends on each side of and tapers downwardly in the direction of a primary tubular portion.

58. A kit for use with an automated processing system, comprising:

a single-use disposable container comprising a tray and a flexible barrier configured to sealably attach thereto;

a single-use disposable reagent rack configured to reside in the container at a first workstation;

a single-use disposable binding column manifold configured to reside in the container; and

a single-use disposable pipette rack configured to reside in the container.

59. The kit of claim 58, further comprising a second pipette rack configured to reside in the container to hold used pipettes.

60. The kit of claim 58, further comprising a single-use disposable vacuum pump head with tubing attached to the tray and configured to recirculate air in the container during operation.

61. The kit of claim 58, further comprising a manifold with a handle configured to reside in the container and move between workstations.

62. A method of releasing liquids from pipettes, comprising:

programmatically directing a robotic arm to move an interface tool releasably holding a pipette to orient the pipette in a downwardly extending angled orientation with the tip proximate to a receiving surface in a closed container;

then automatically moving the downwardly oriented angled pipette in a substantially straight line along a plane, while releasing a flowable substance from the pipette.

63. A method of processing a sample in a closed system, comprising:
providing a sample in a sealably closed container having a flexible barrier; and
programmatically directing a robotic arm to cooperate with the flexible barrier to move an interface tool inside the closed container through a series of operations while the closed container remains sealed to process the sample.

64. The method of claim 63, further comprising electronically automatically measuring volume and concentration of the sample at a plurality of times during the amplification; and

65. The method of claim 63, further comprising capturing at least one processed sample in an aliquot vessel without disrupting the sealed status of the closed system.

66. The method of claim 63, further comprising electronically automatically monitoring seal integrity of the closed container.

67. An apparatus for manipulating items in a closed container, comprising:
a container having an interior region configured to hold a plurality of items to be manipulated; and
a recirculating vacuum system configured to circulate air sealed within the interior region of the container in a closed loop.

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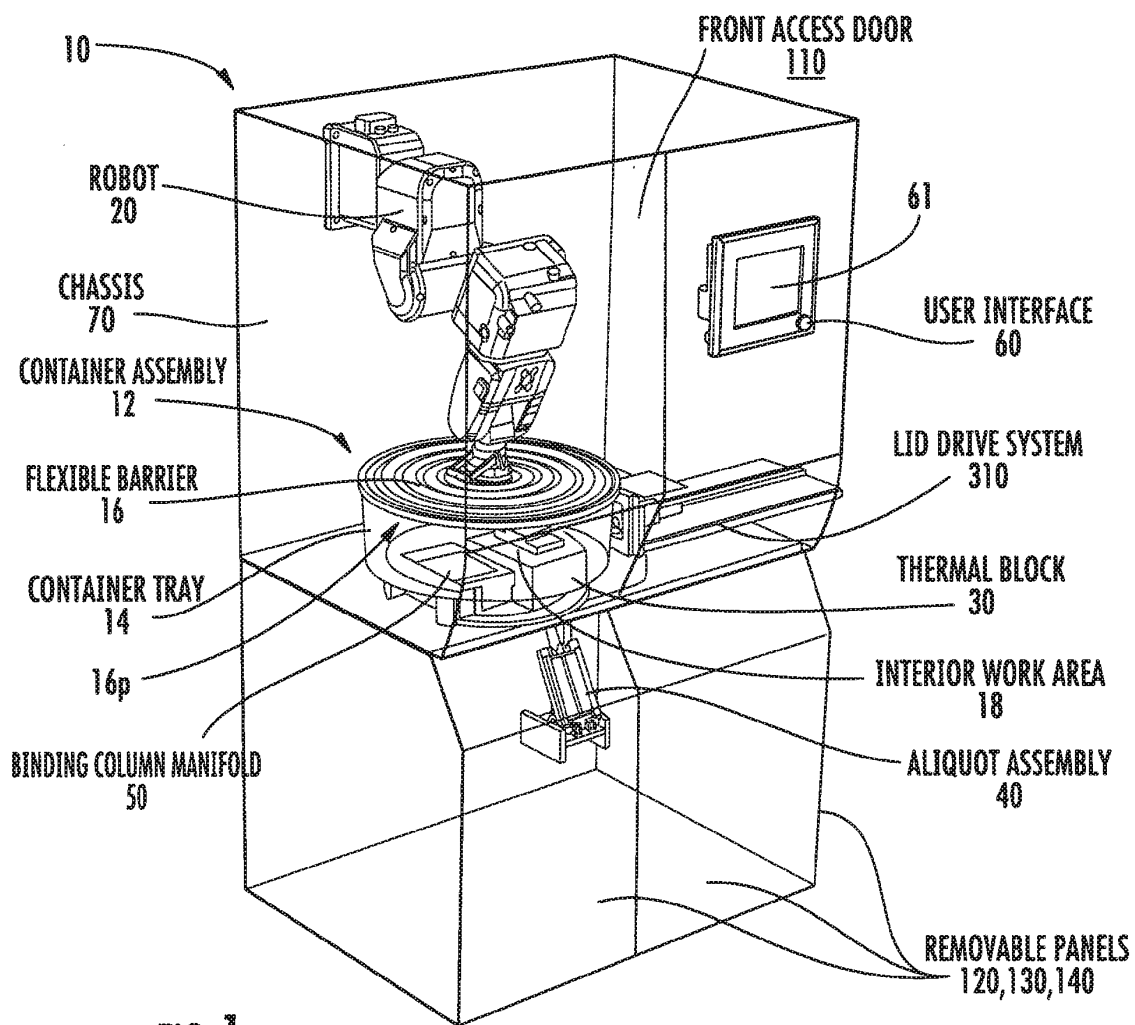


FIG. 1

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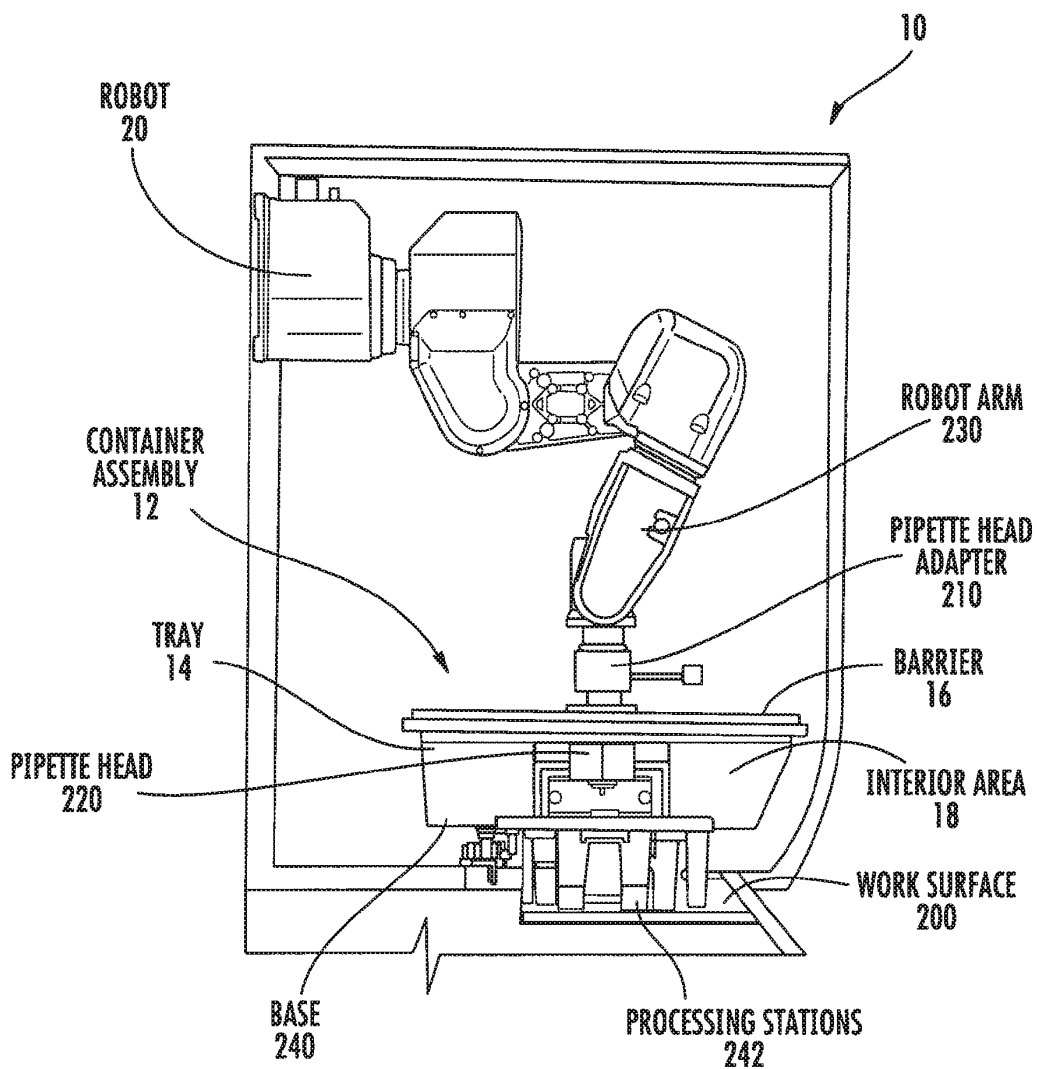


FIG. 2

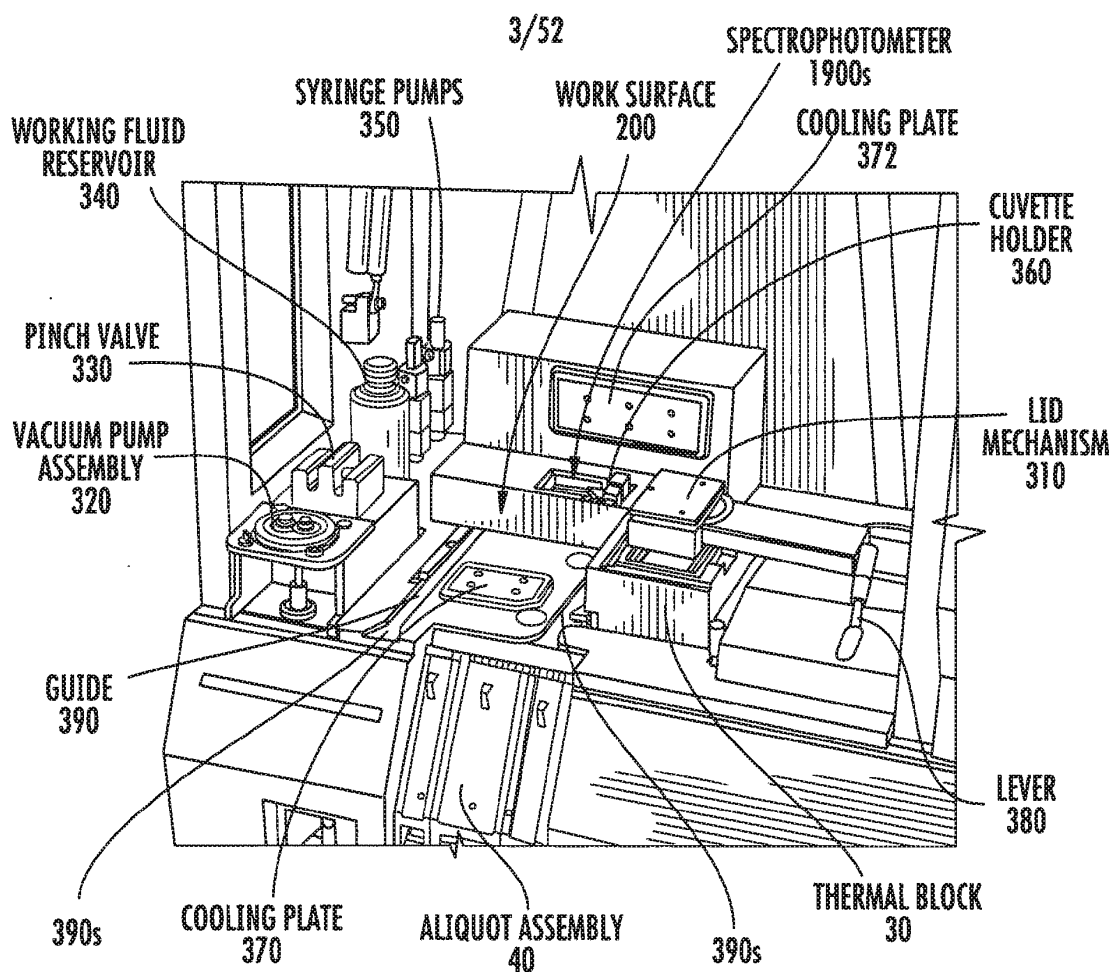
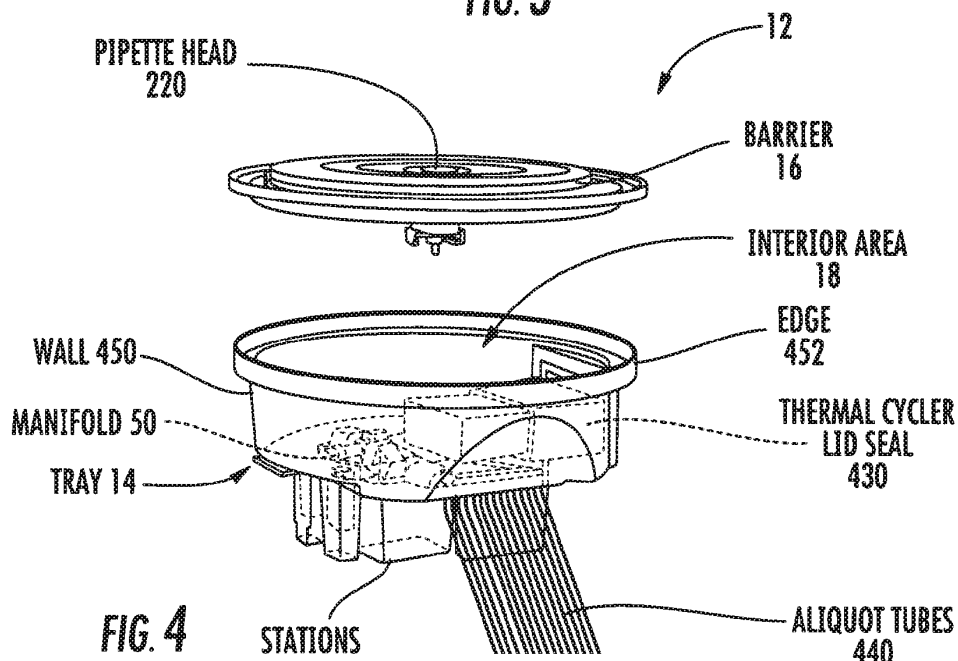
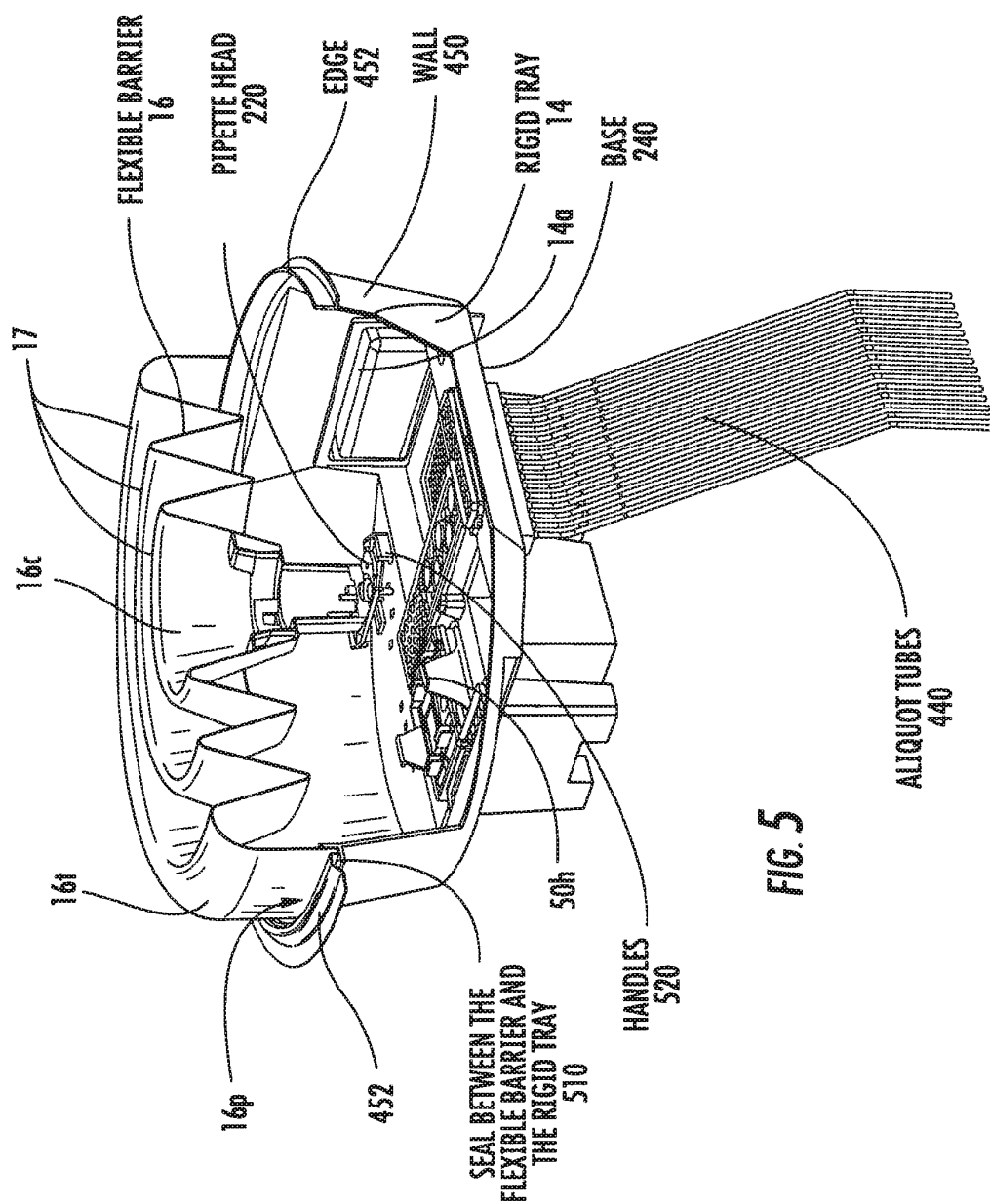


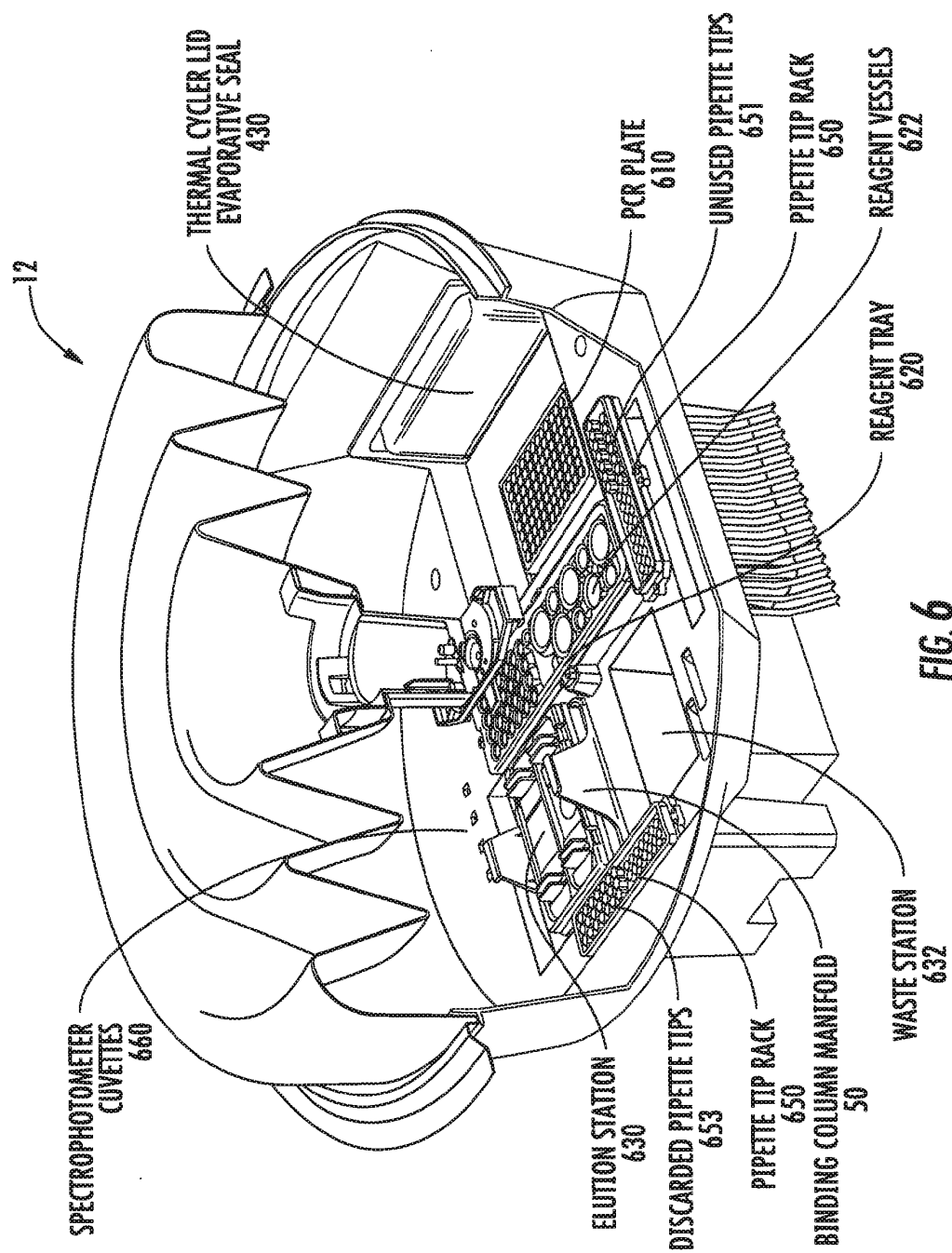
FIG. 3



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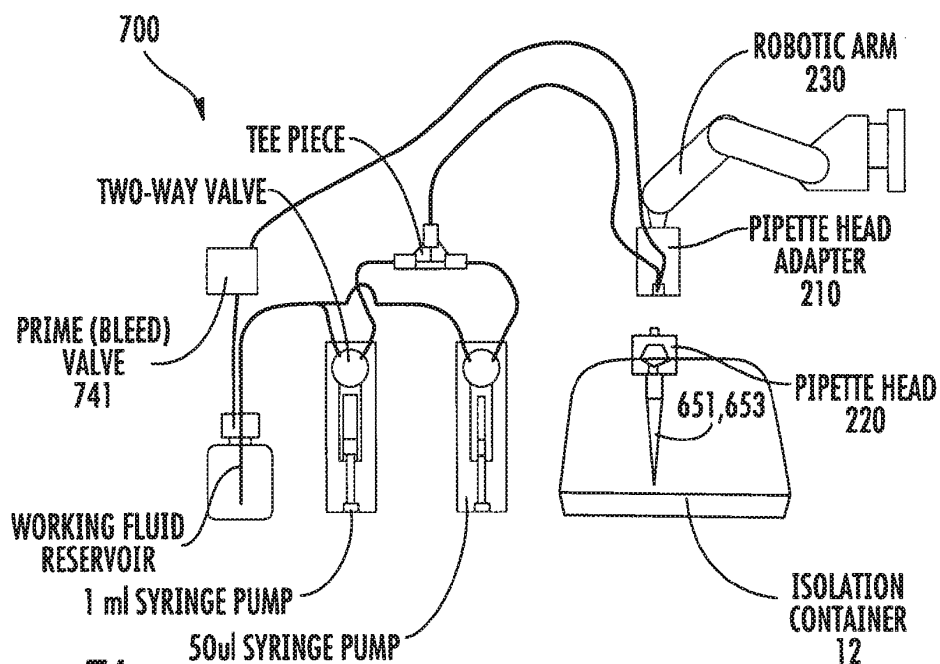


FIG. 7A

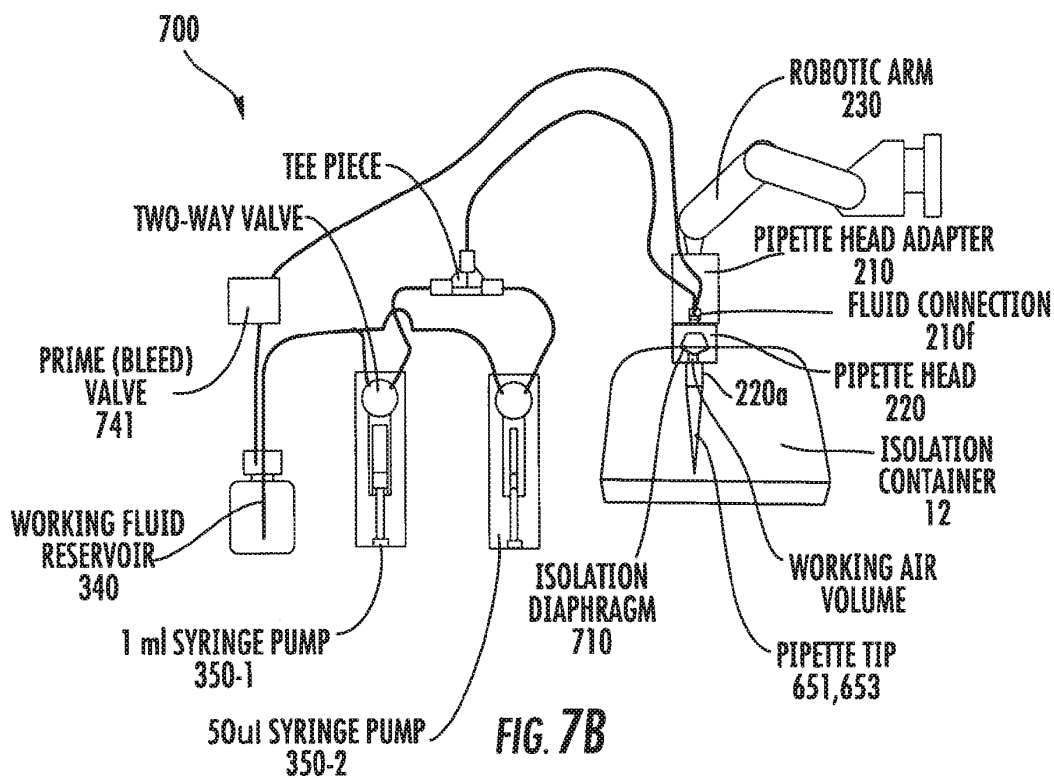
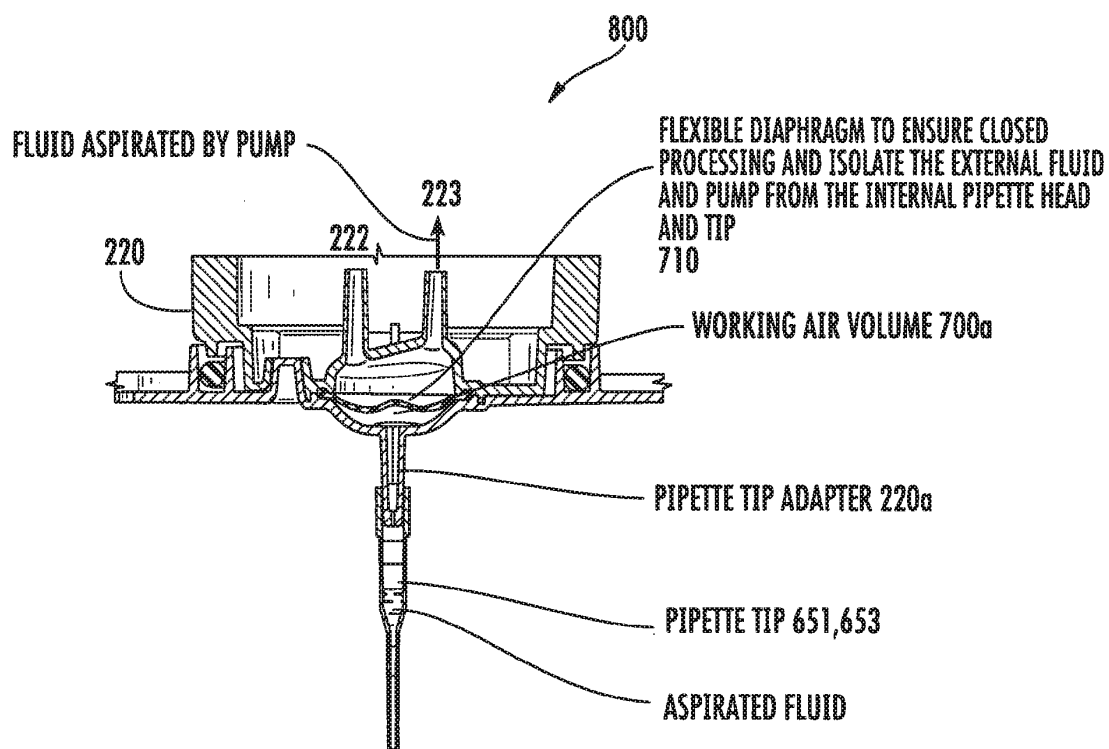
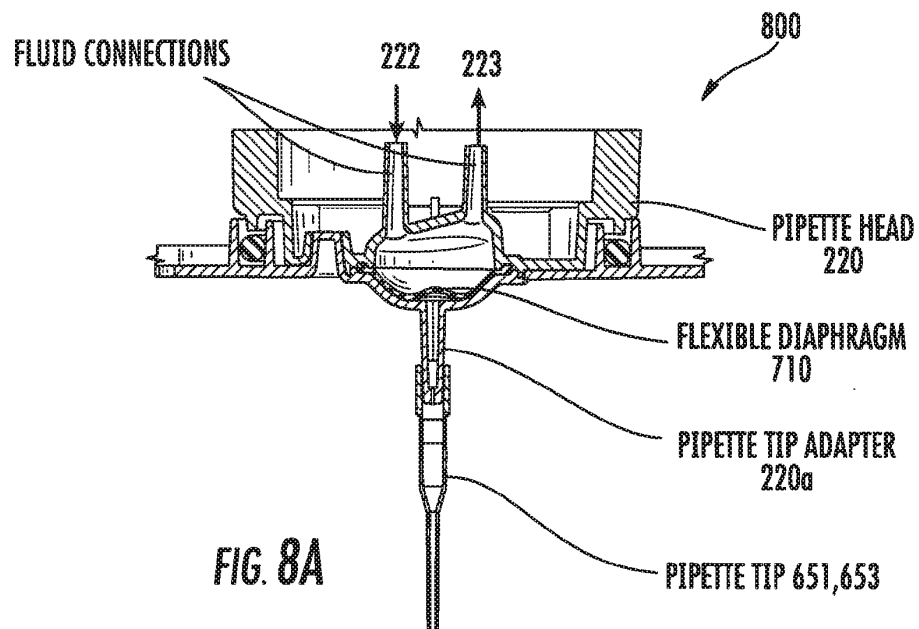


FIG. 7B

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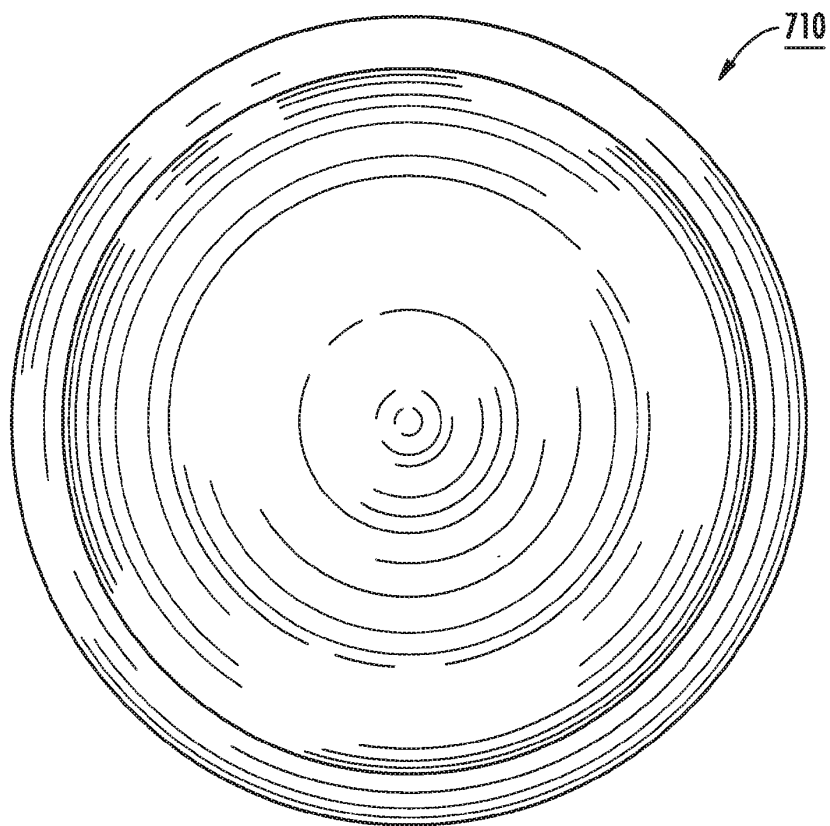


FIG. 8C

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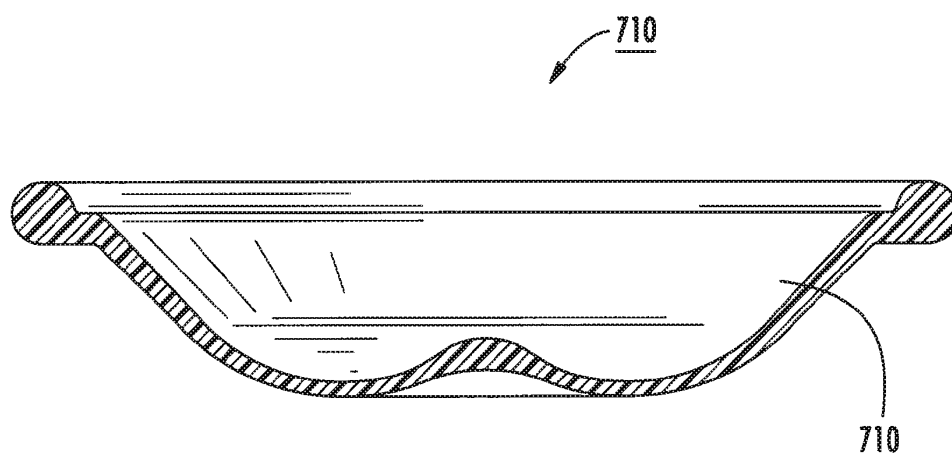


FIG. 8D

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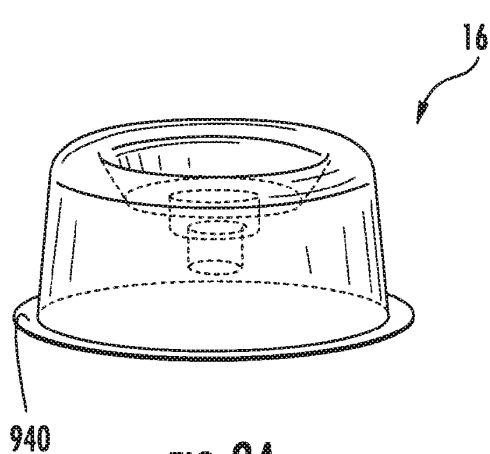


FIG. 9A

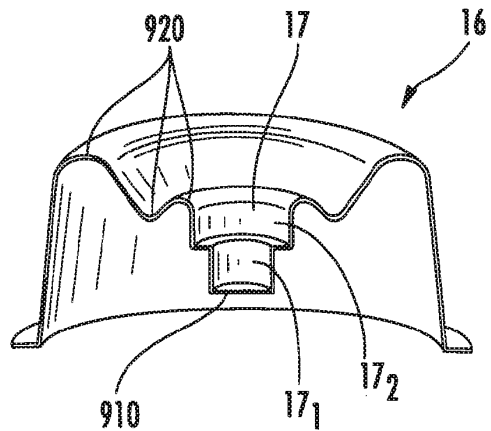


FIG. 9B

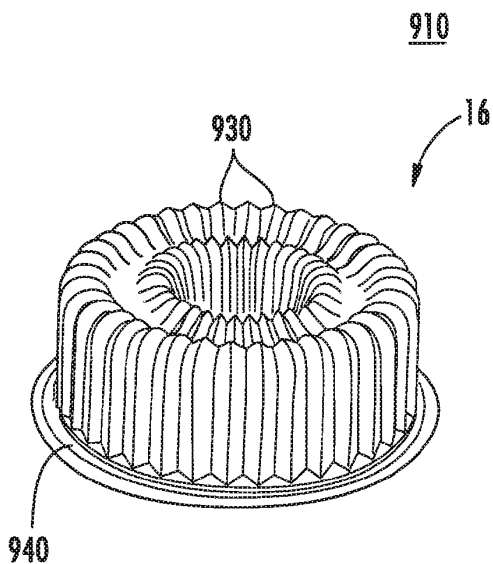


FIG. 9C

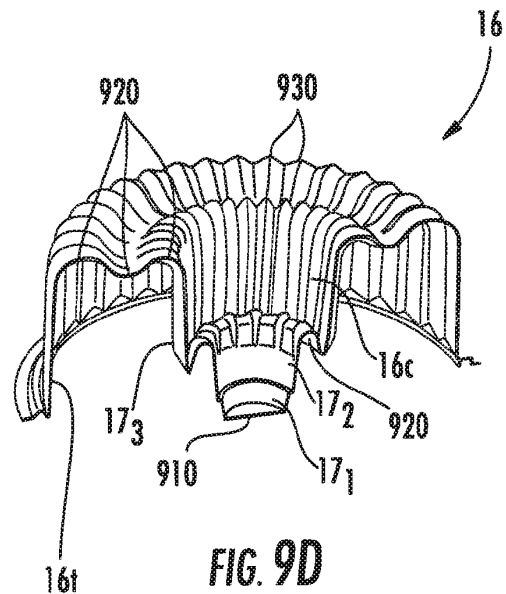


FIG. 9D

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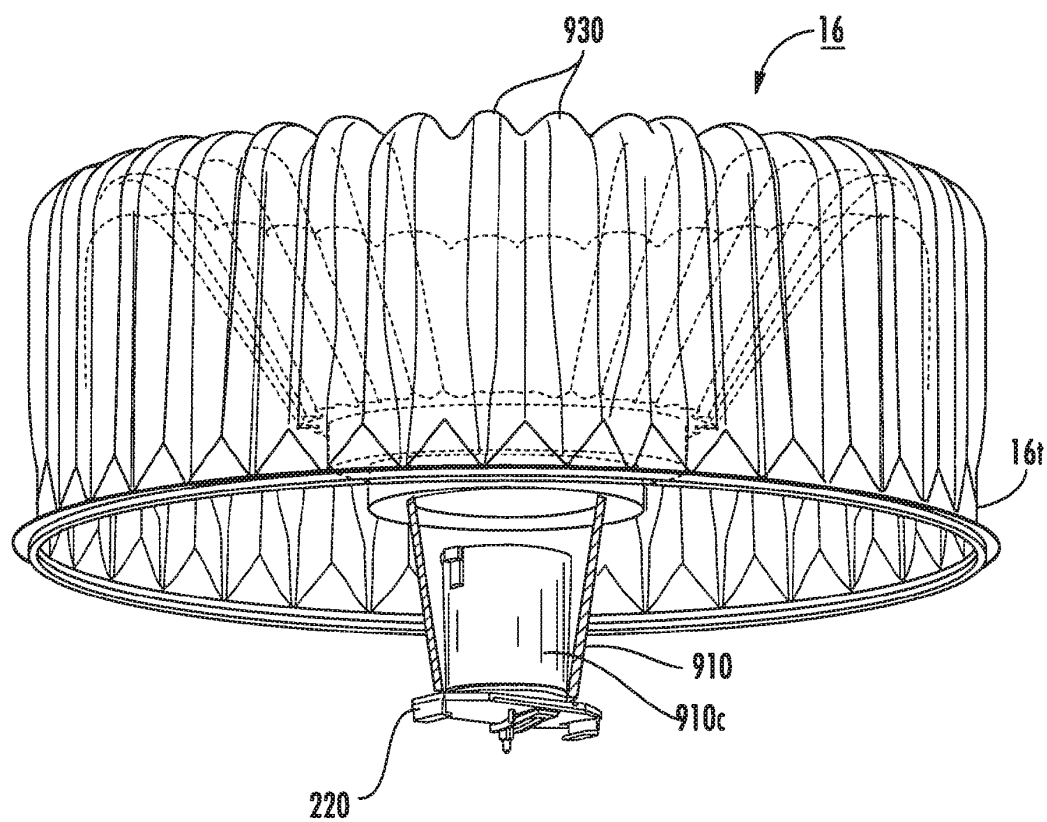


FIG. 9E

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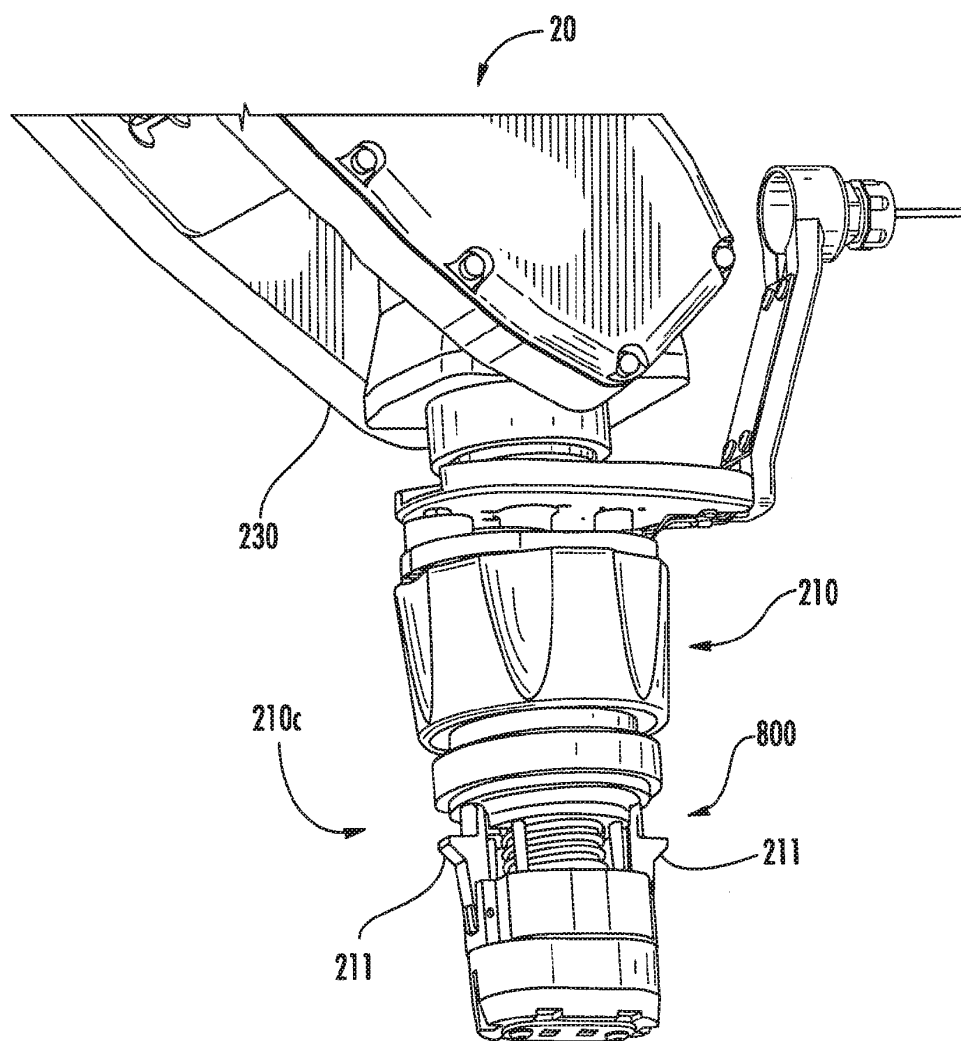


FIG. 9F

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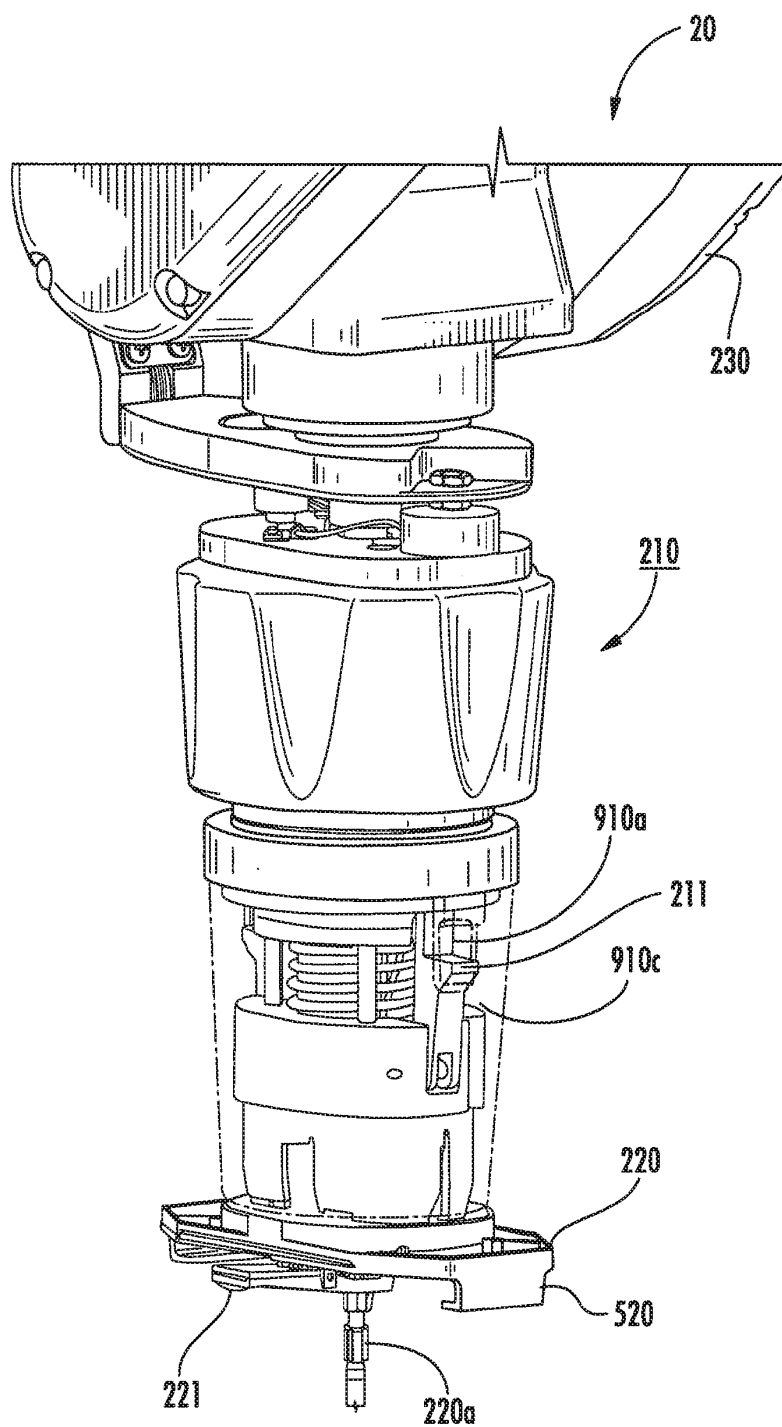
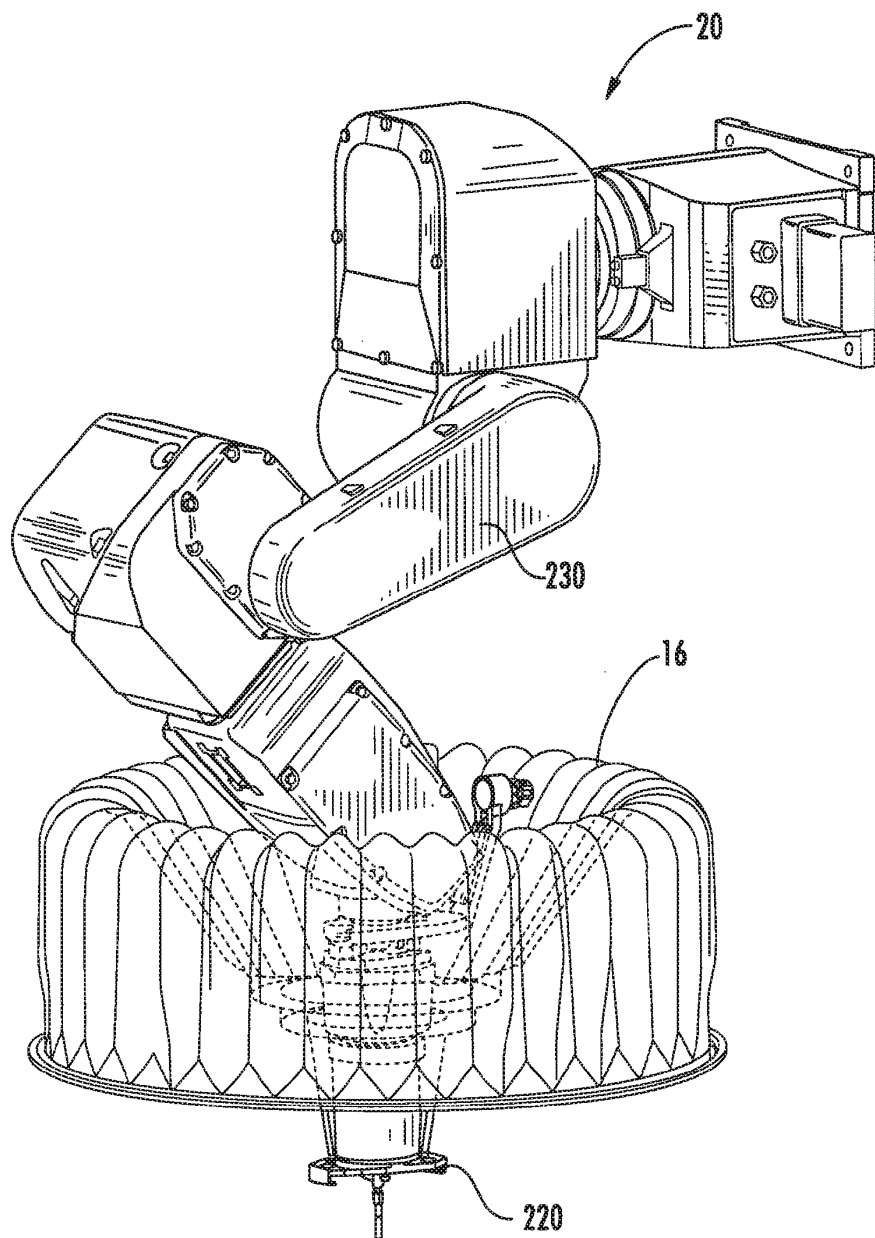
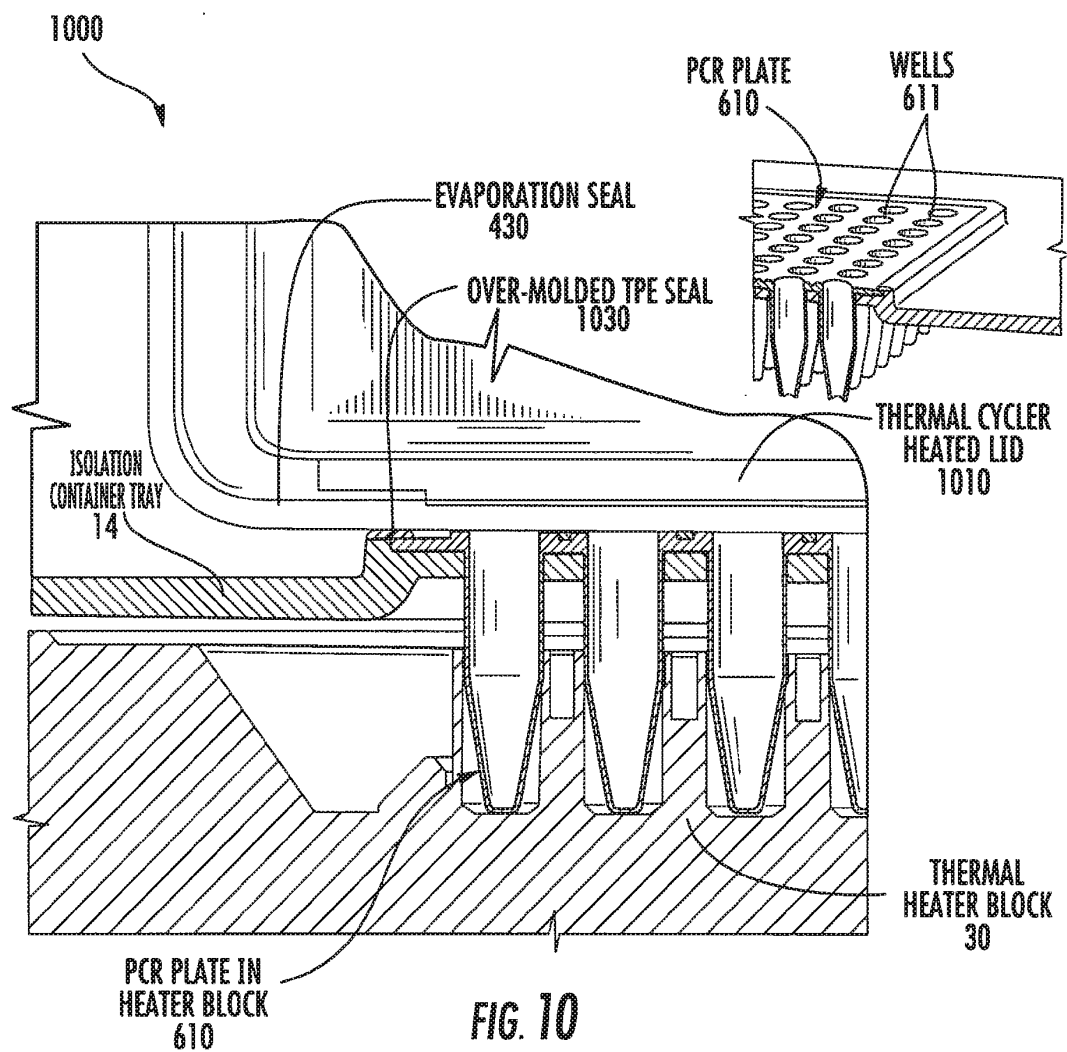


FIG. 9G

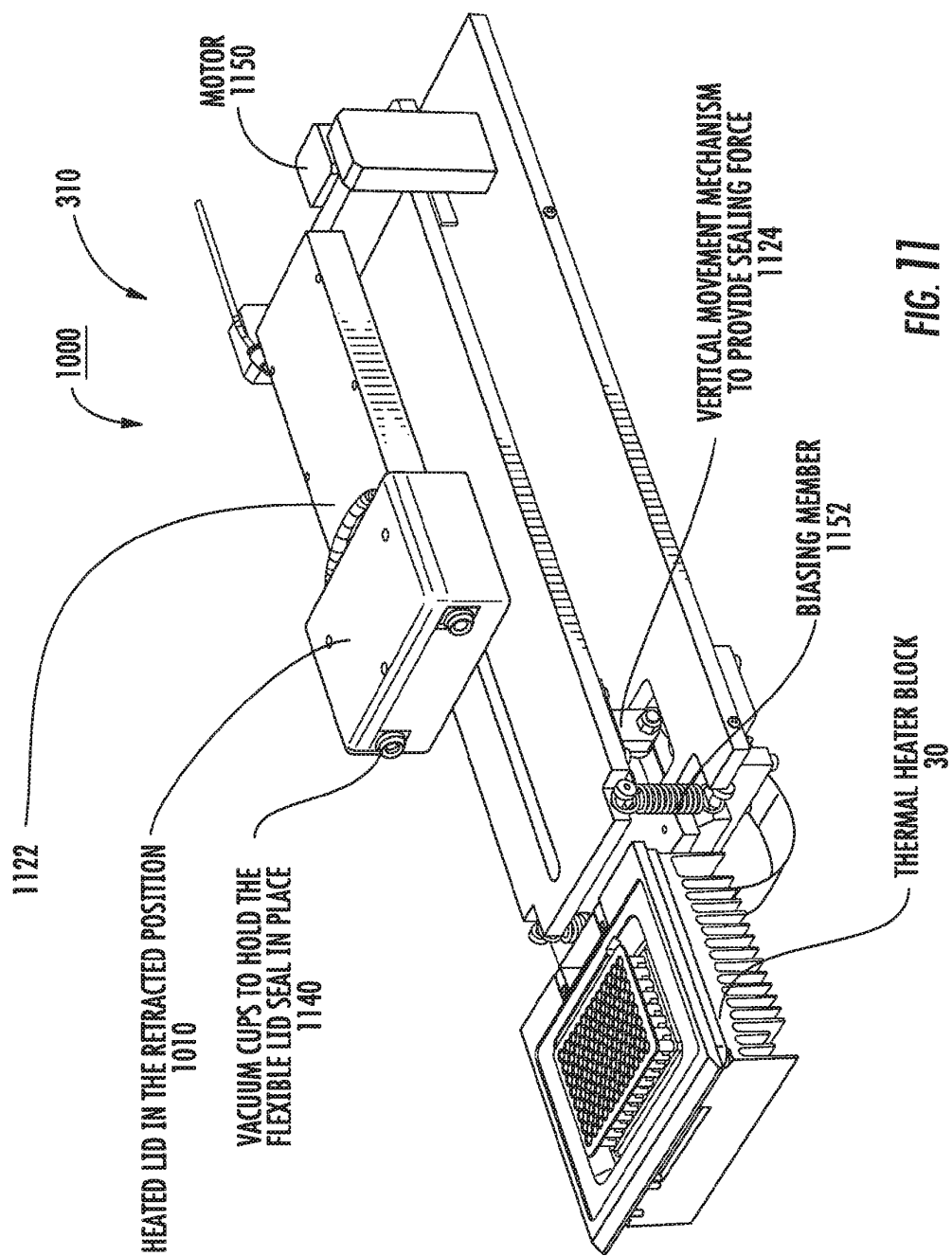
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**FIG. 9H**

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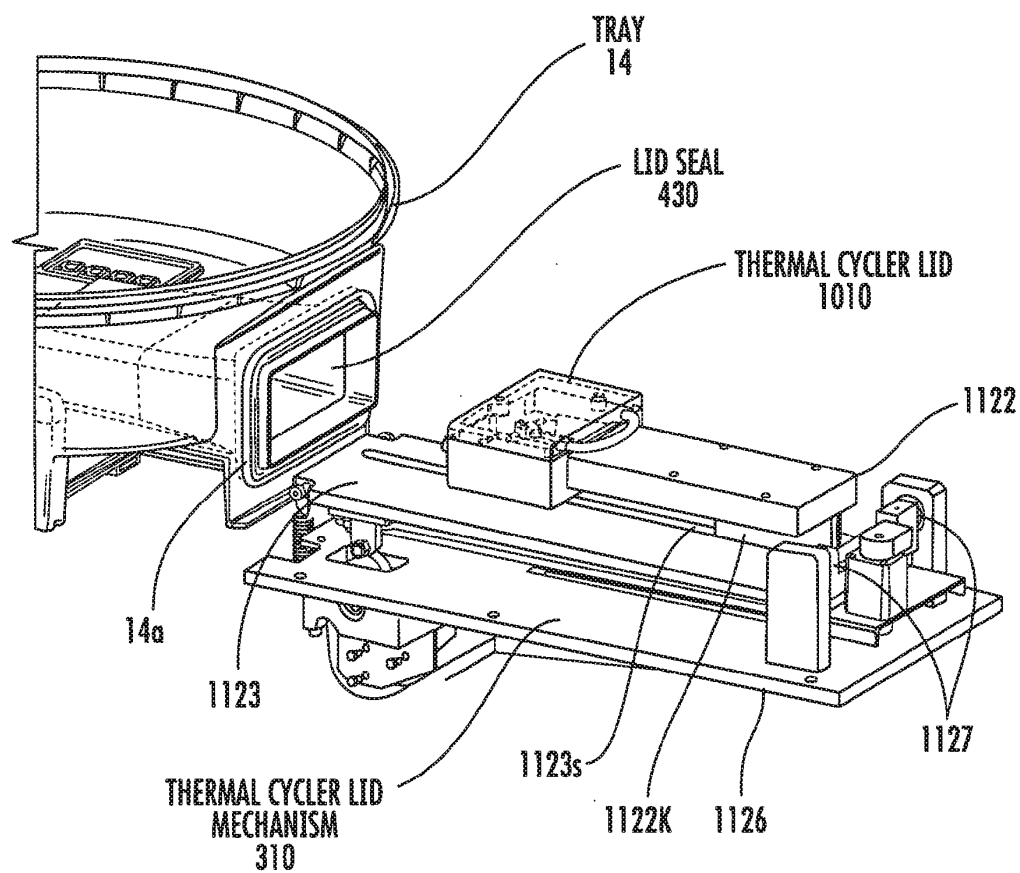


FIG. 12

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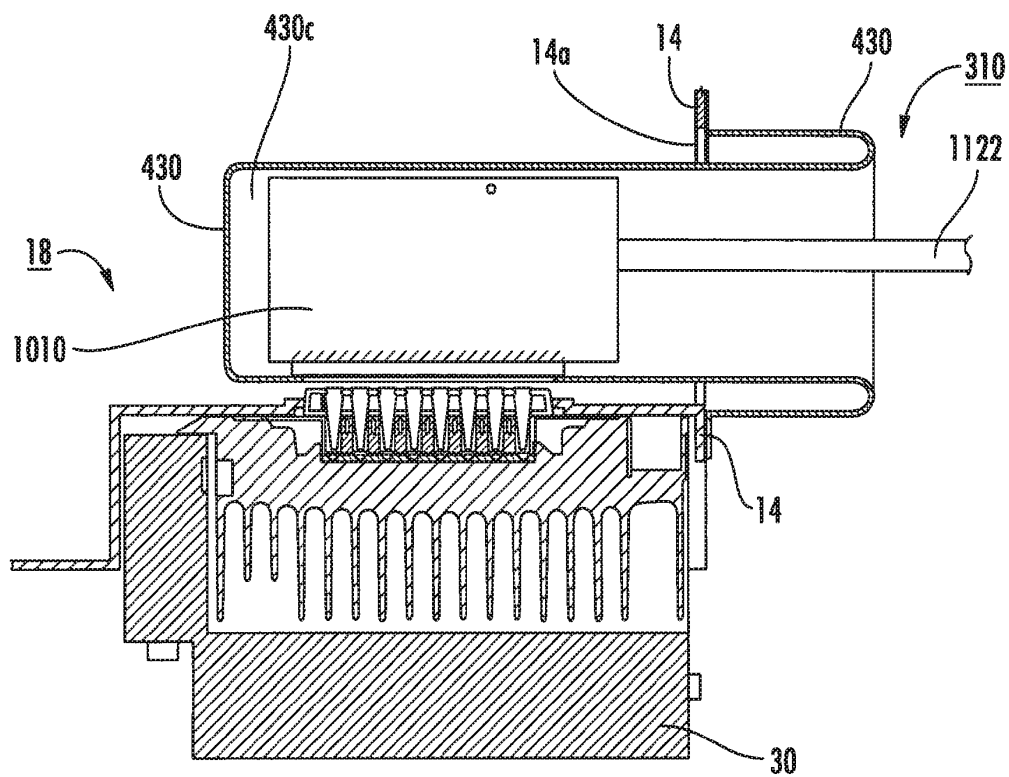


FIG. 13A

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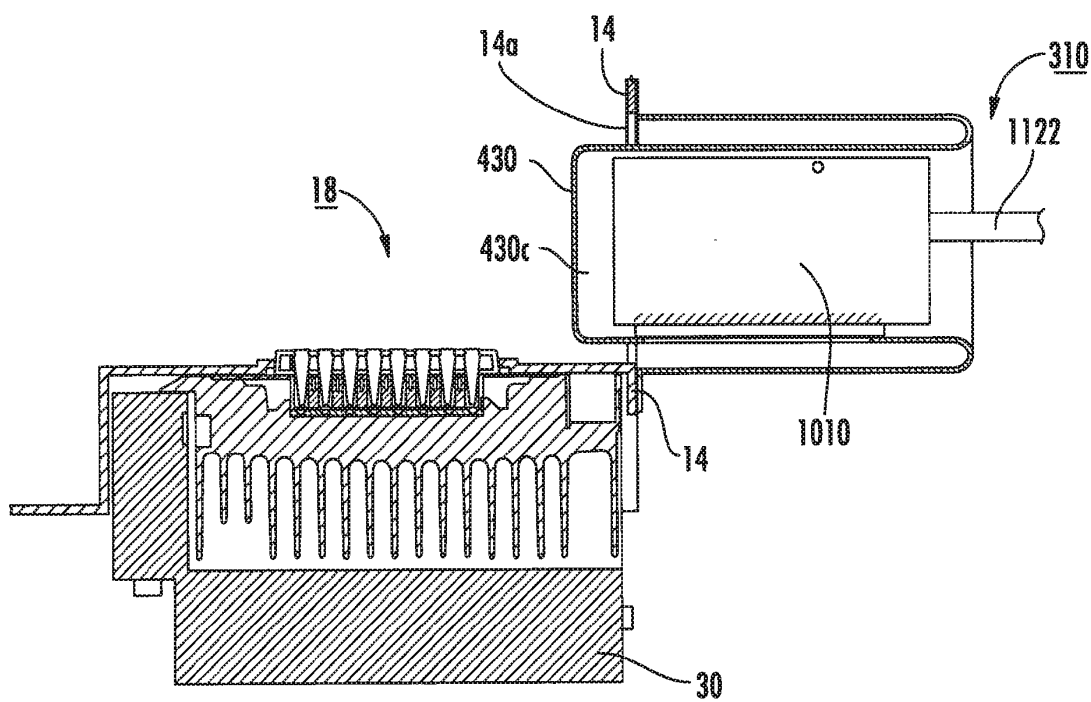
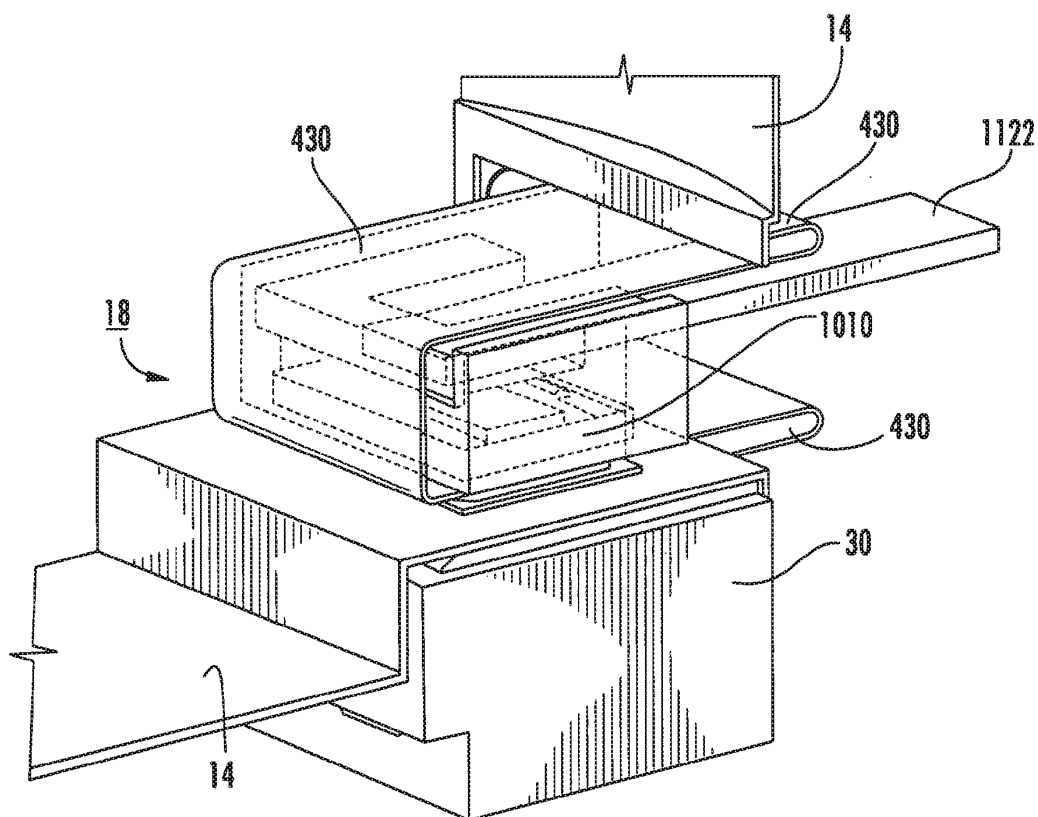


FIG. 13B

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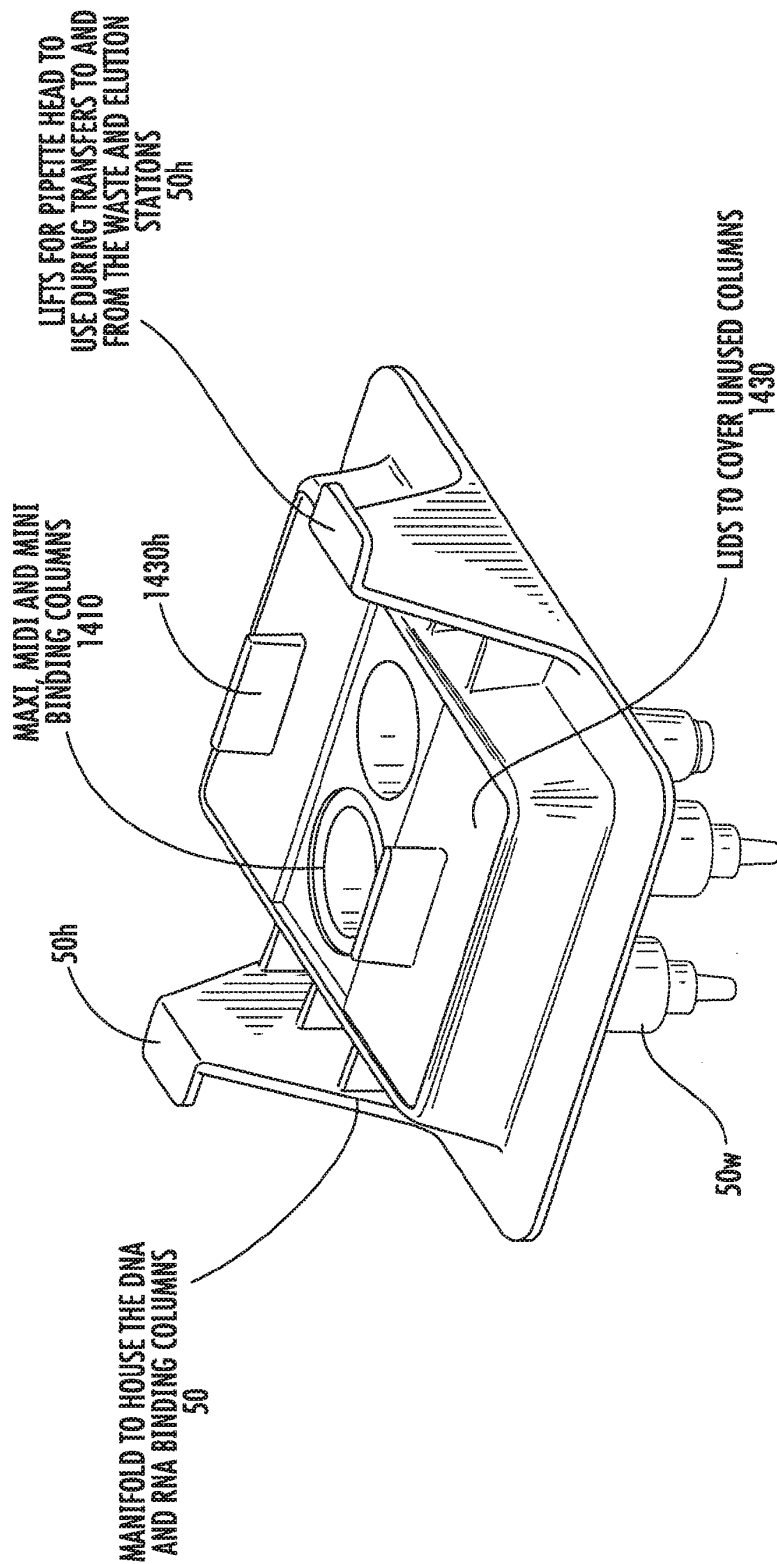
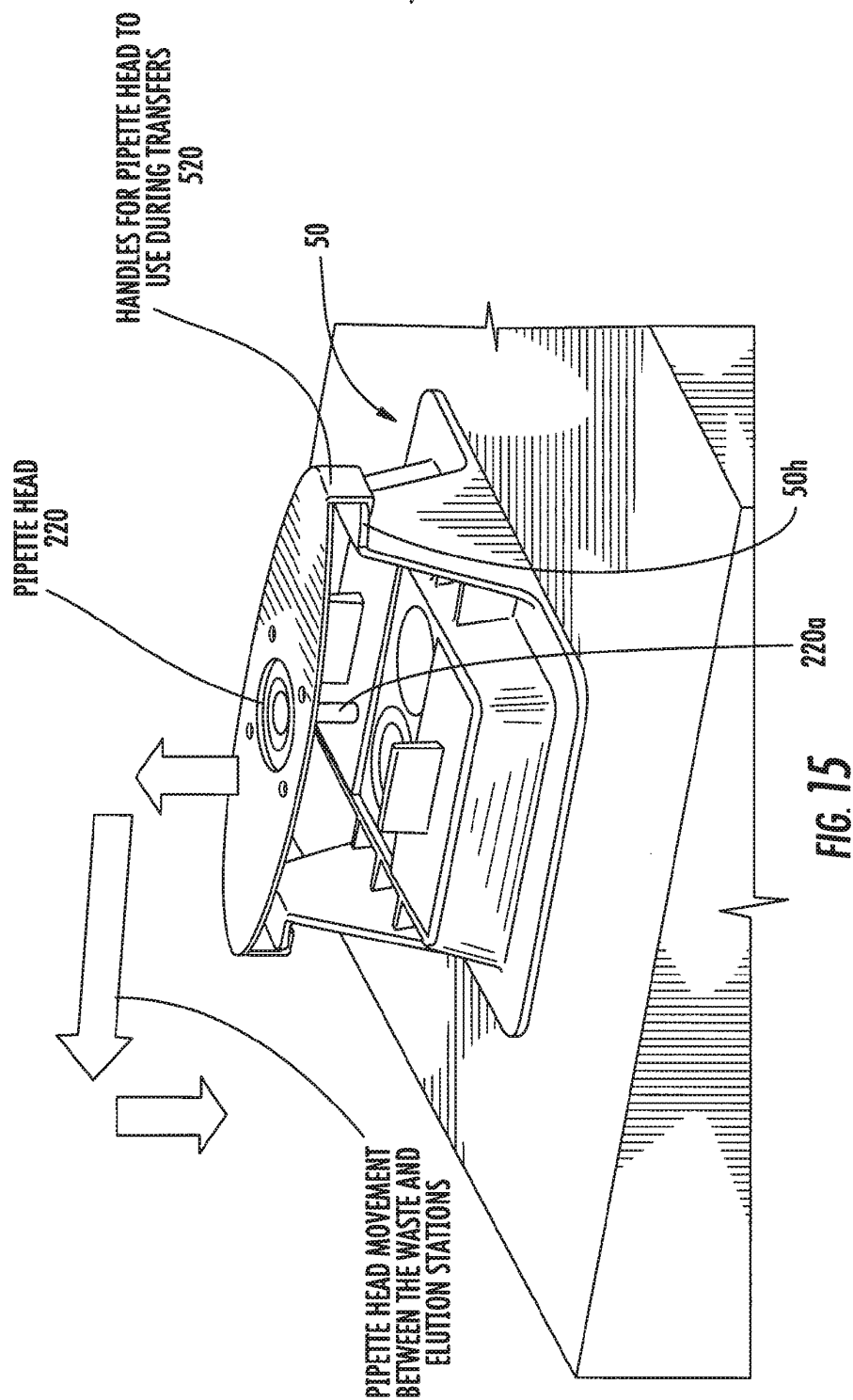
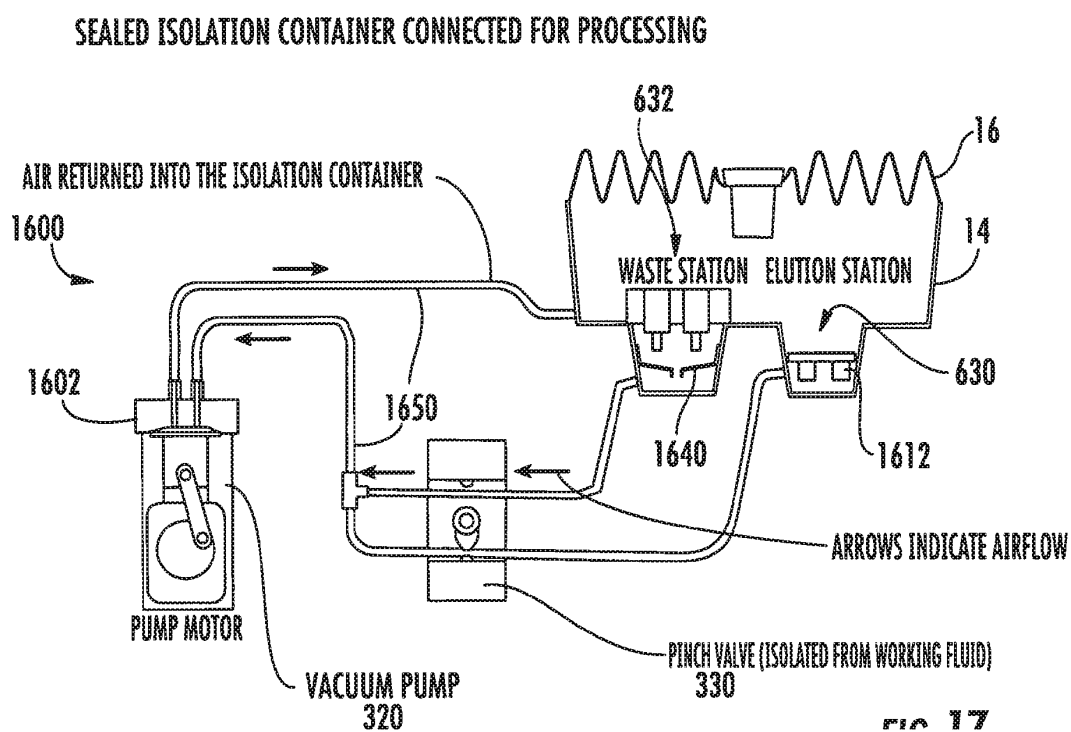
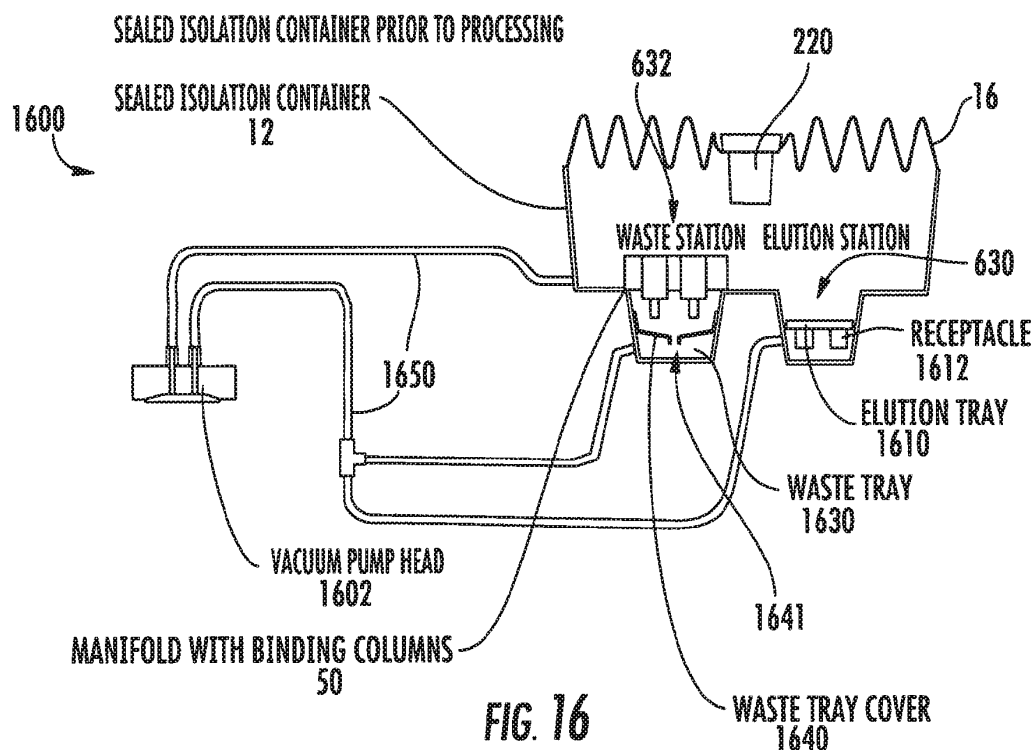


FIG. 14

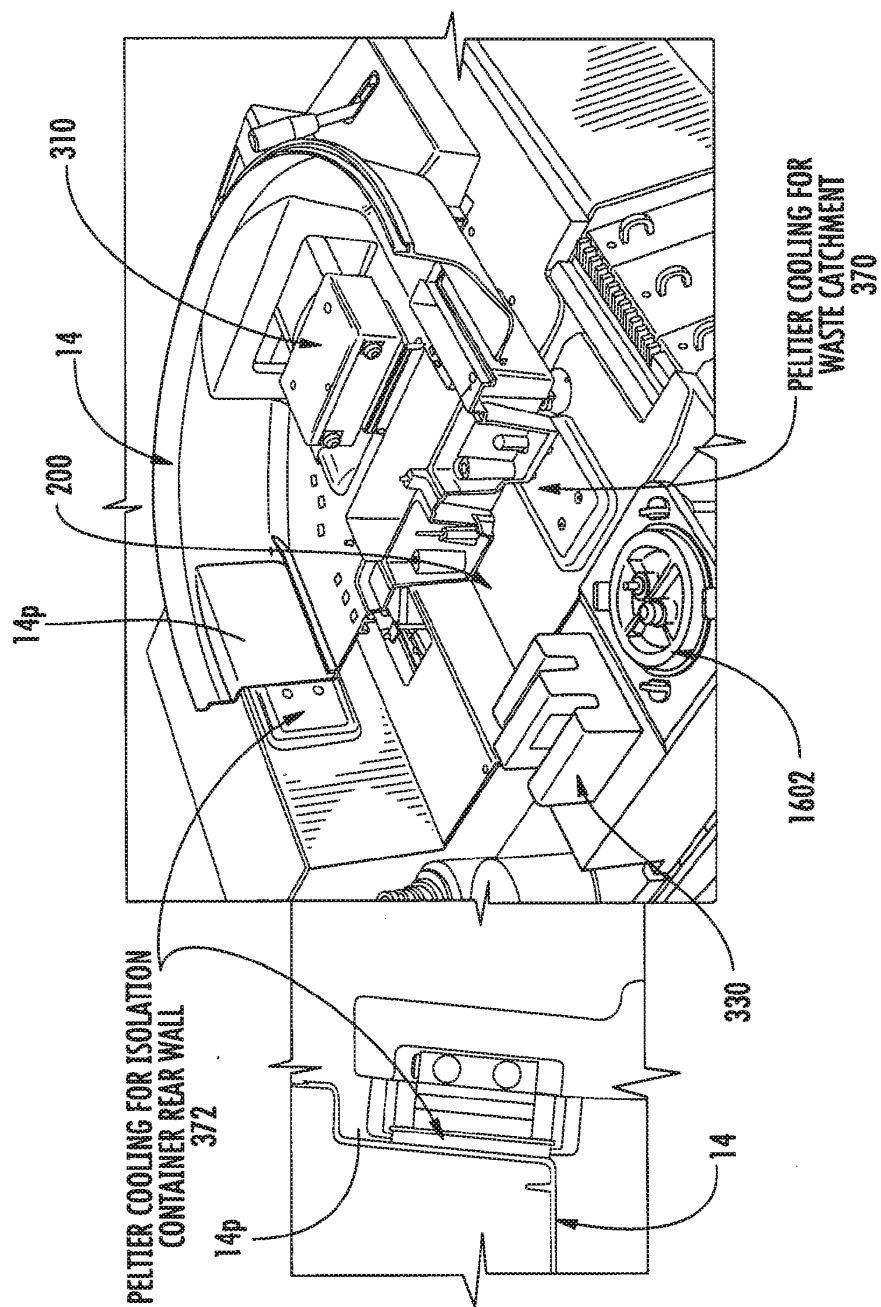
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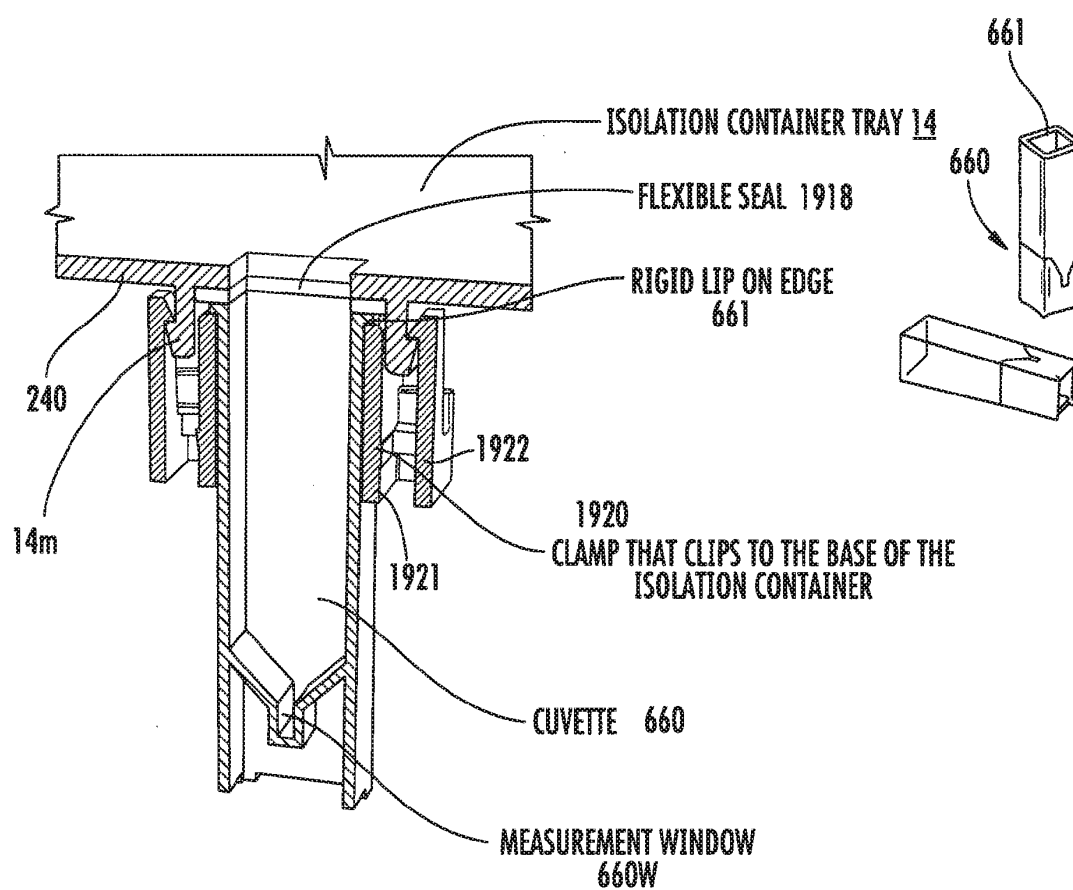
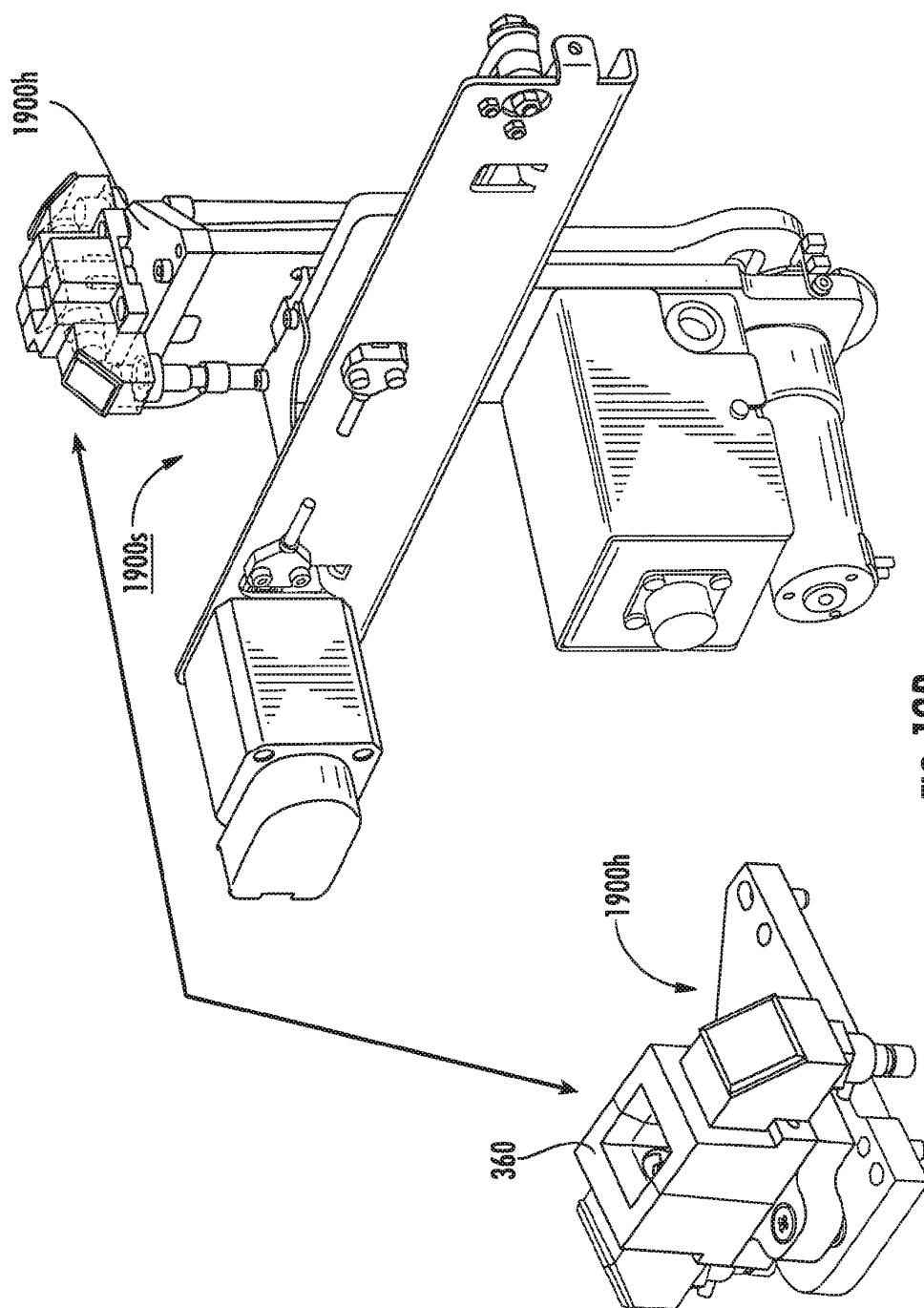
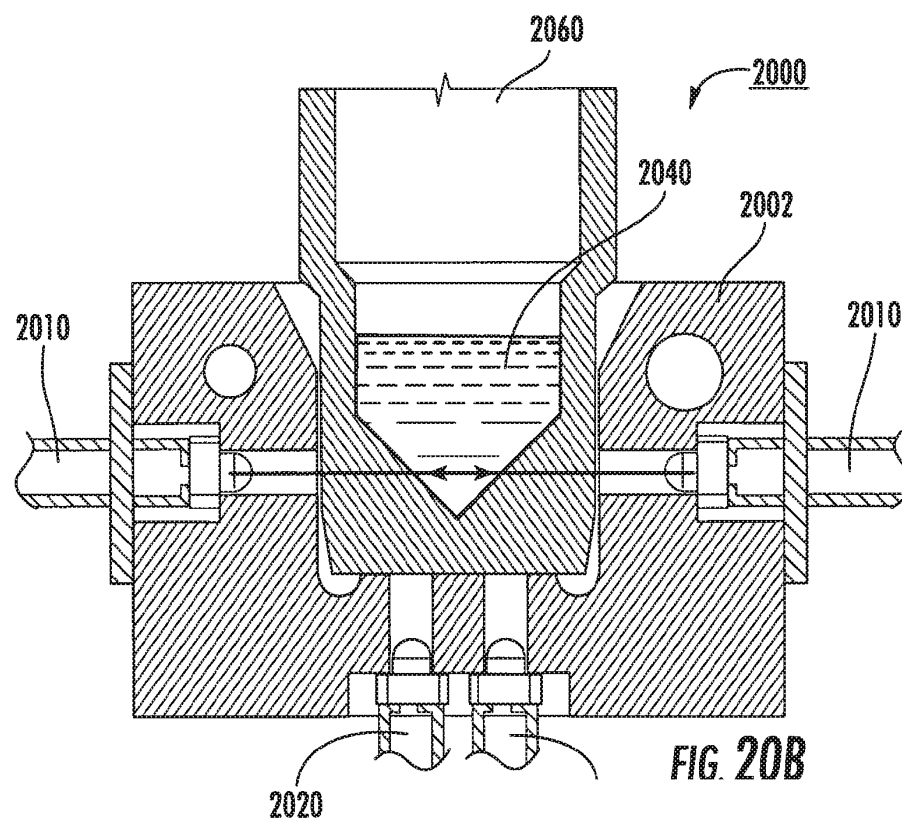
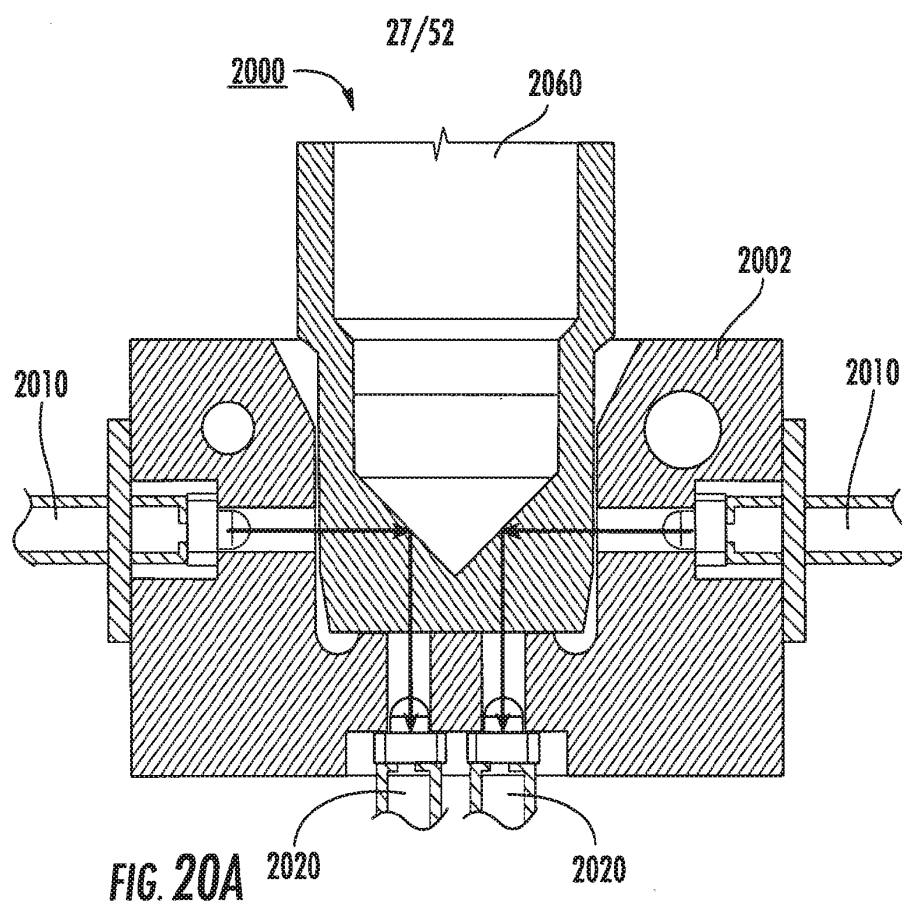


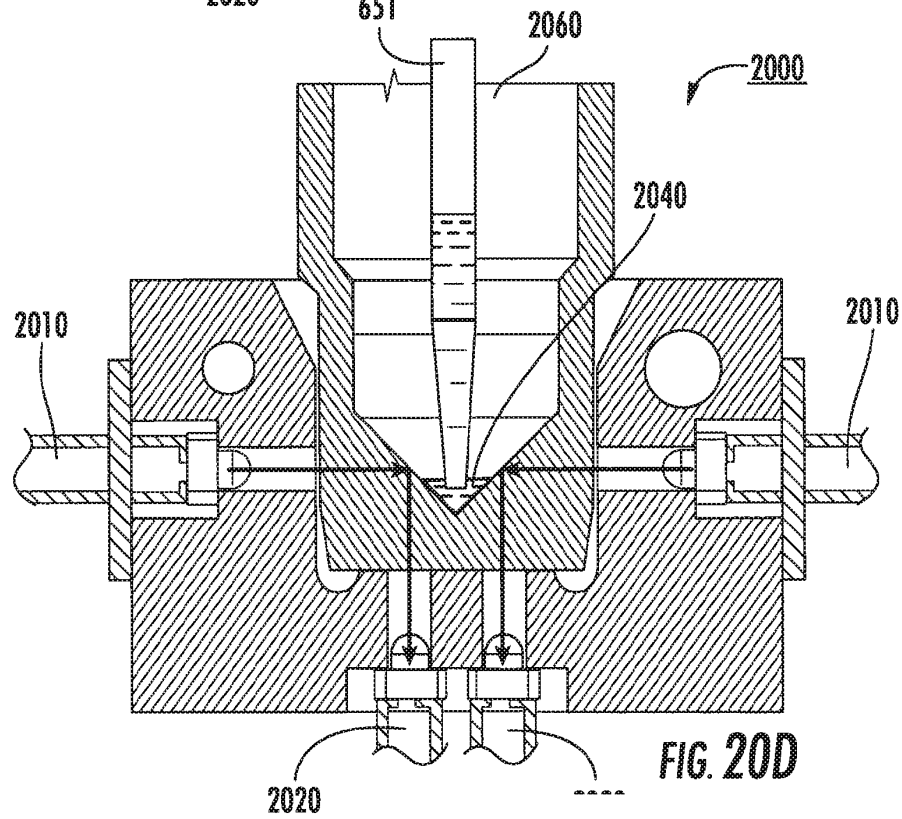
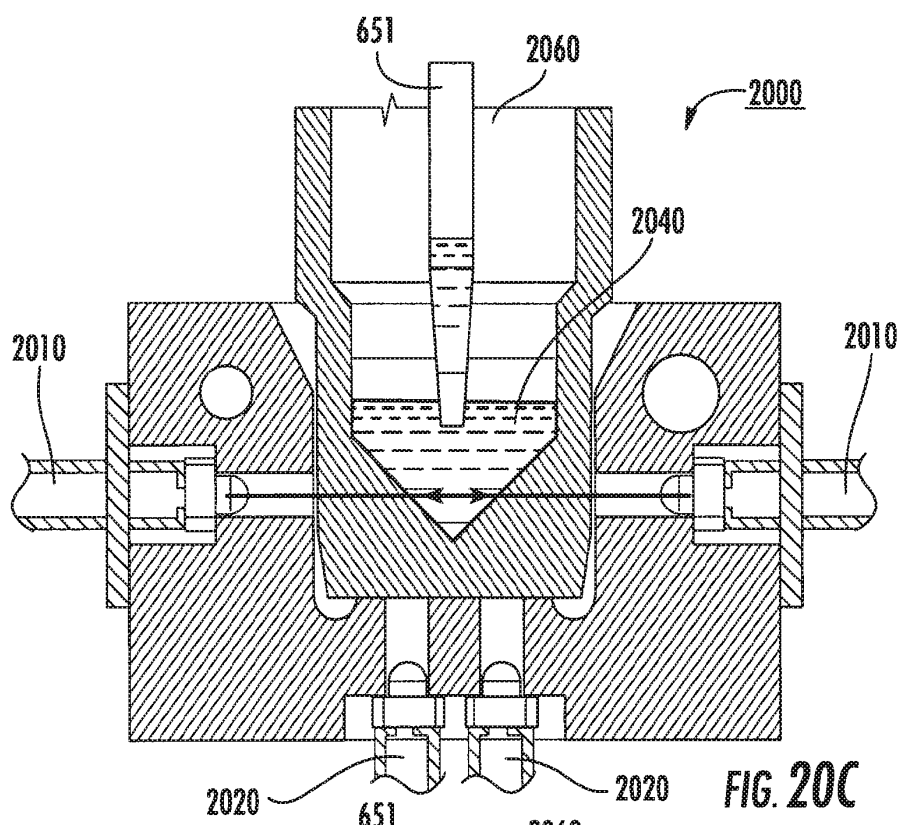
FIG. 19A

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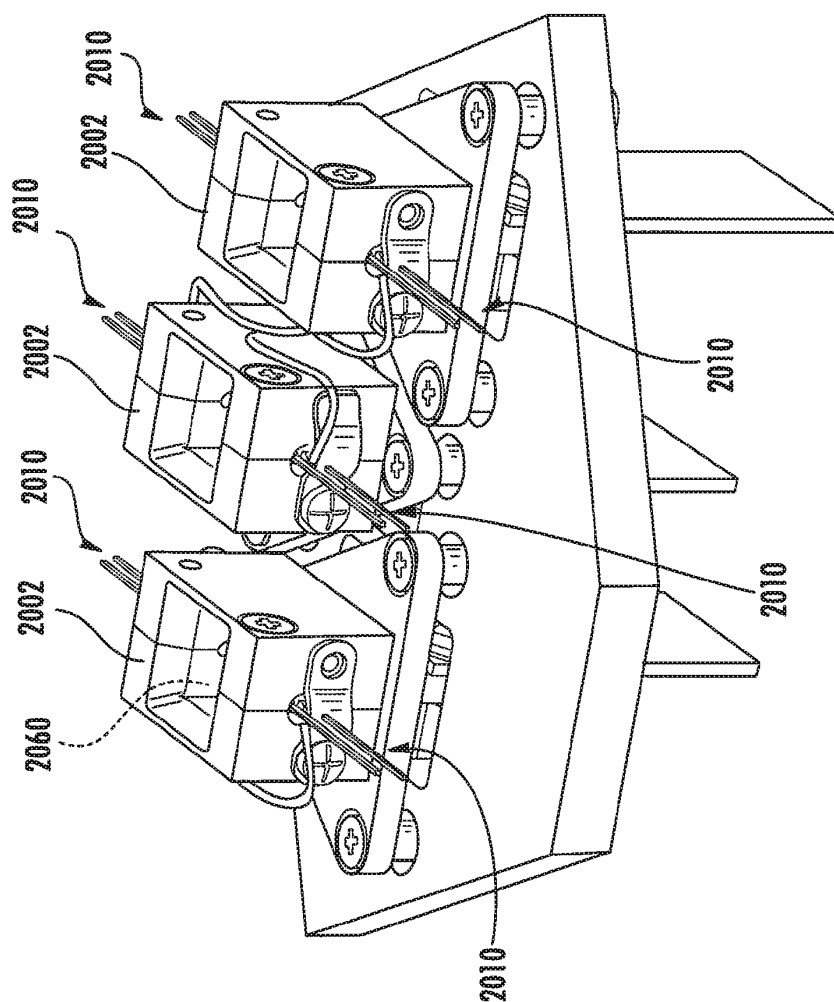


FIG. 20E

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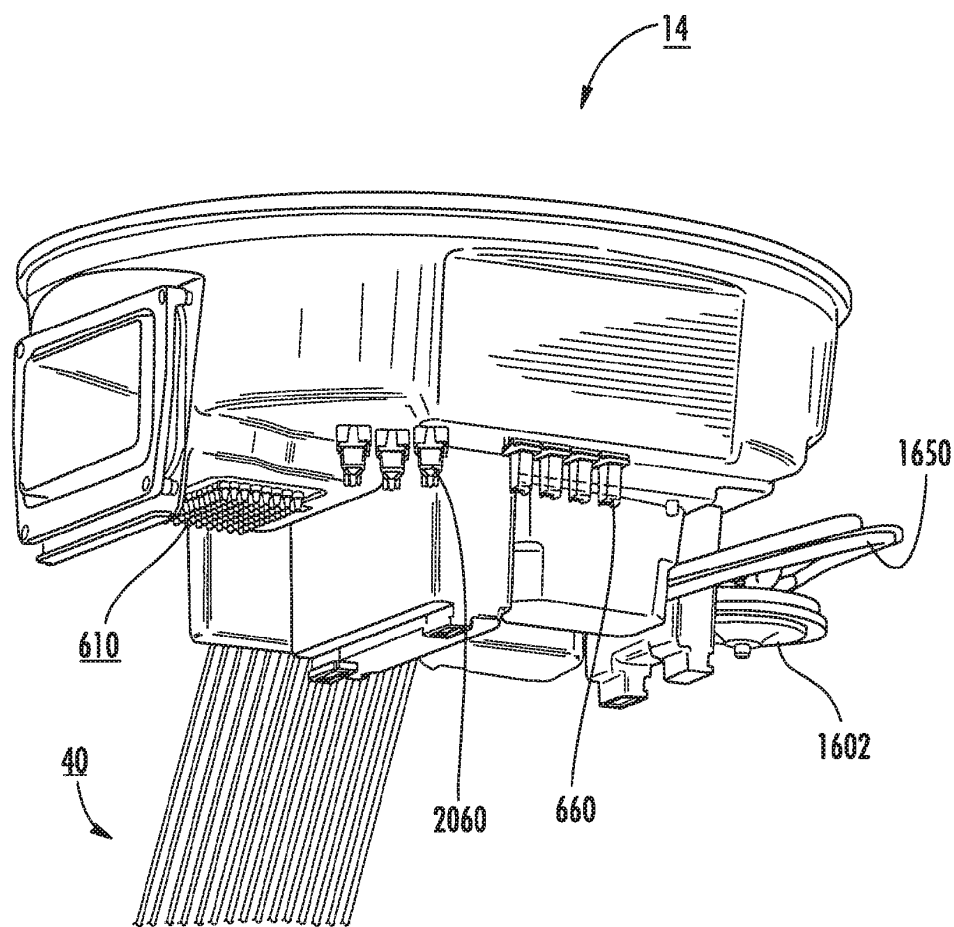
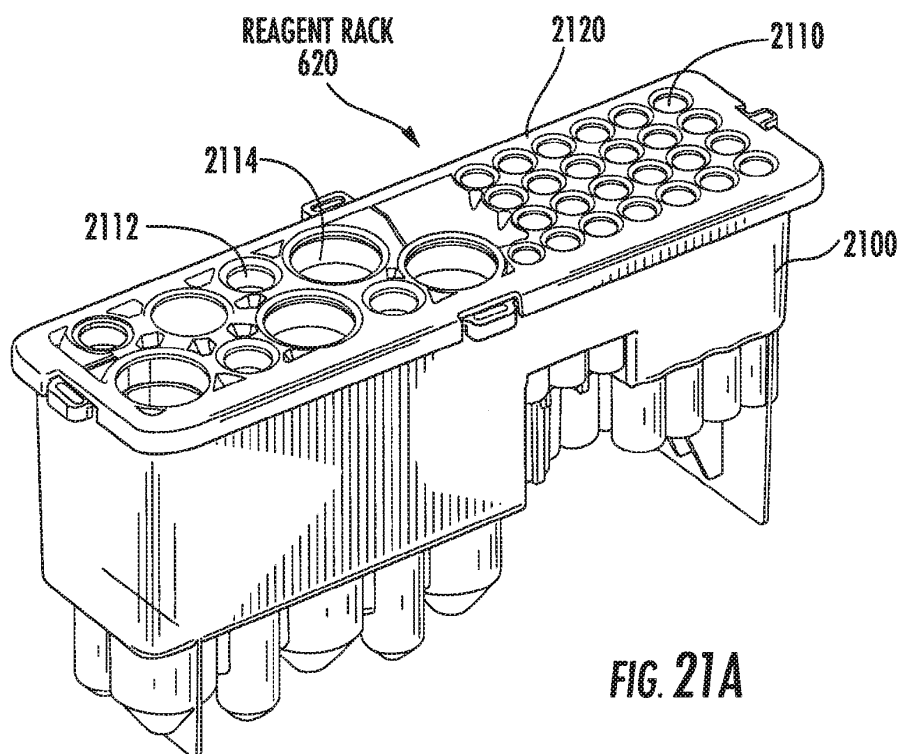
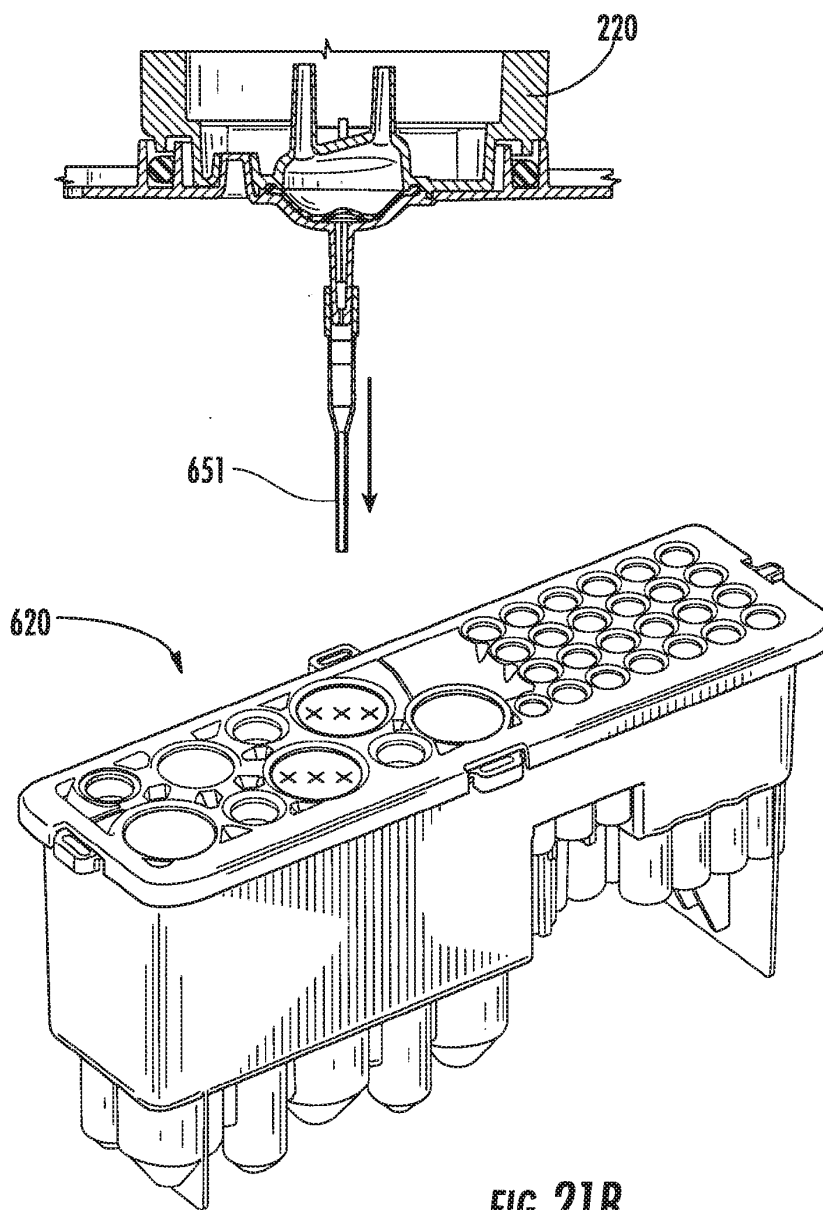


FIG. 20F

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**FIG. 21B**

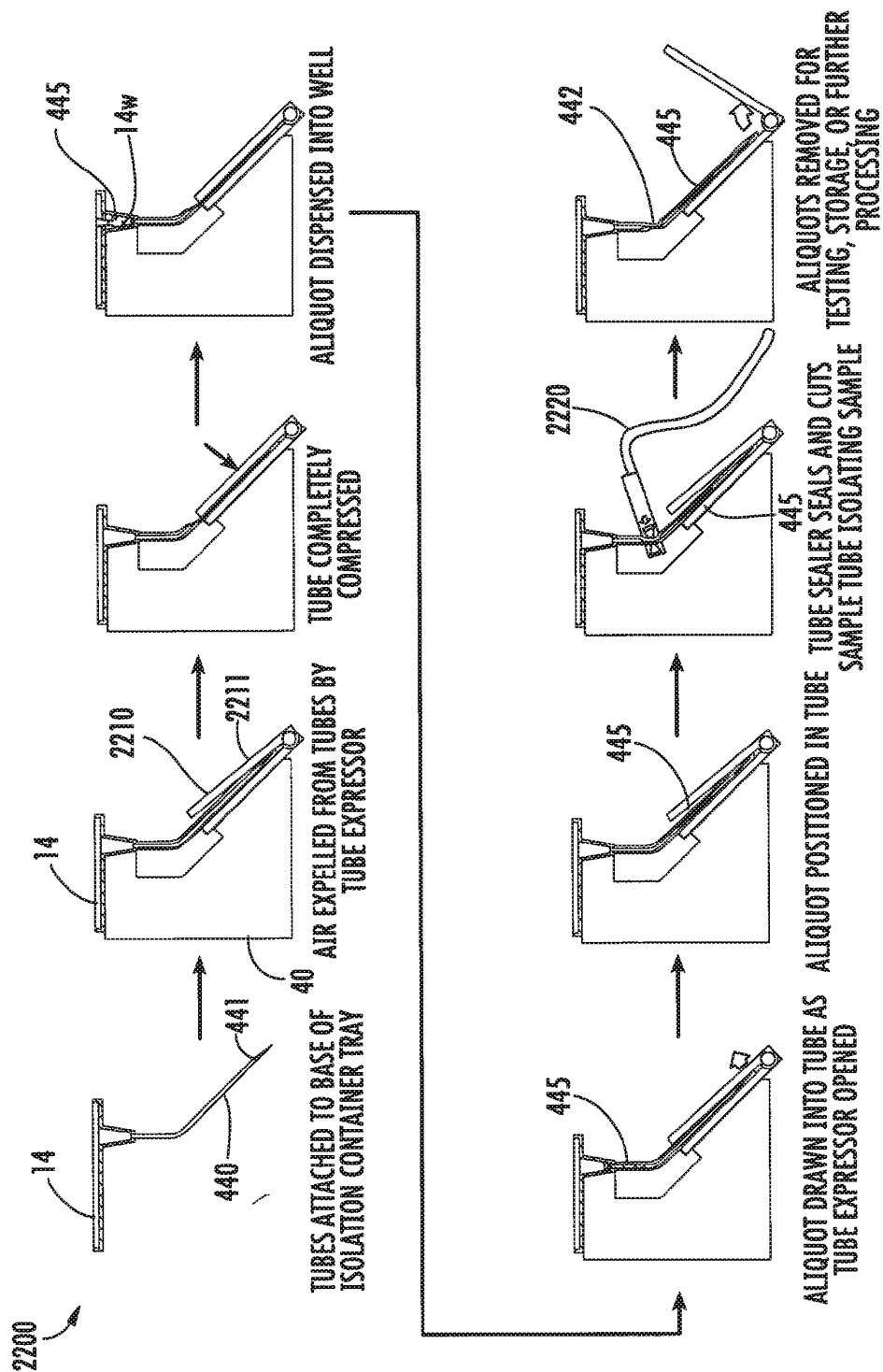
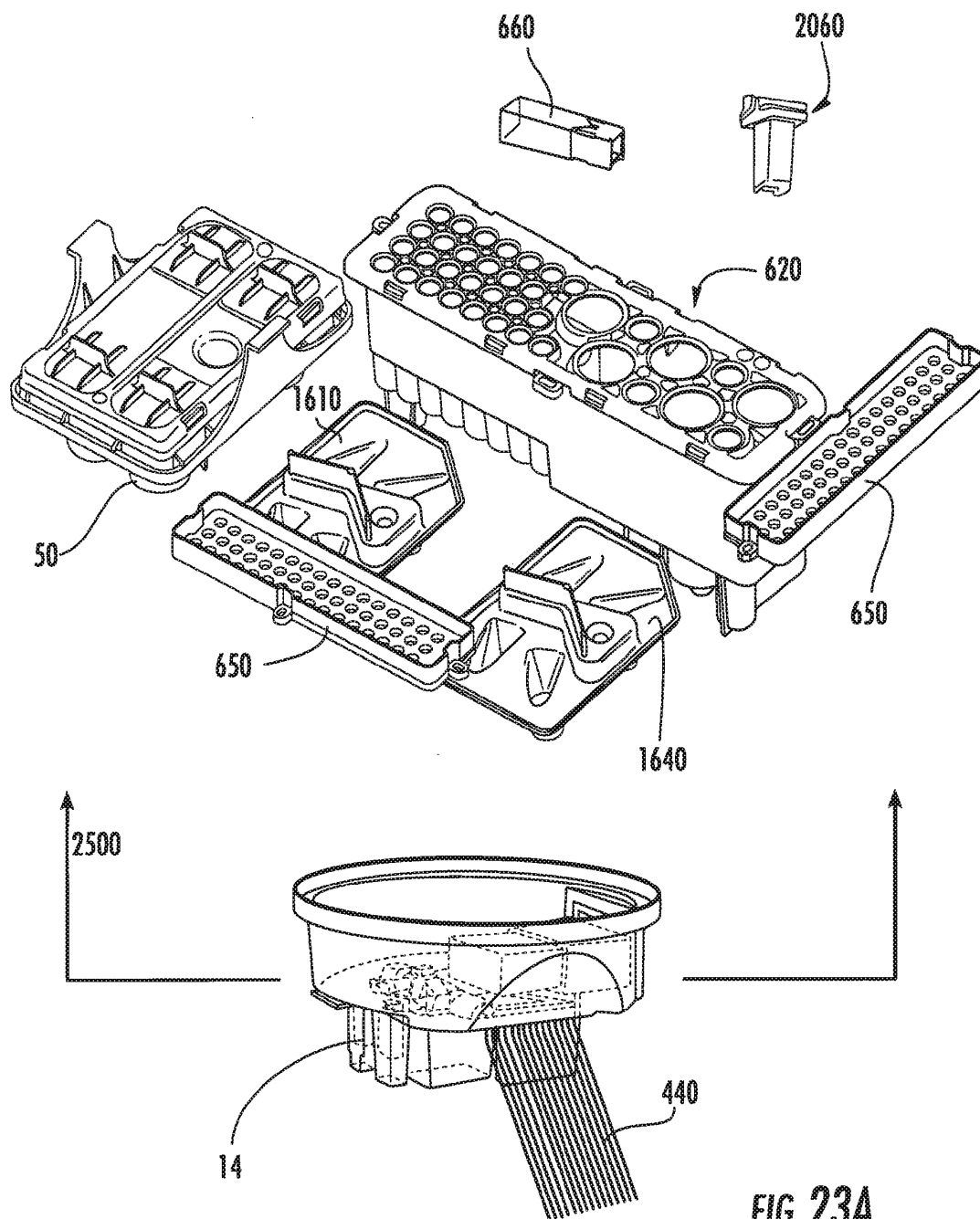


FIG. 22

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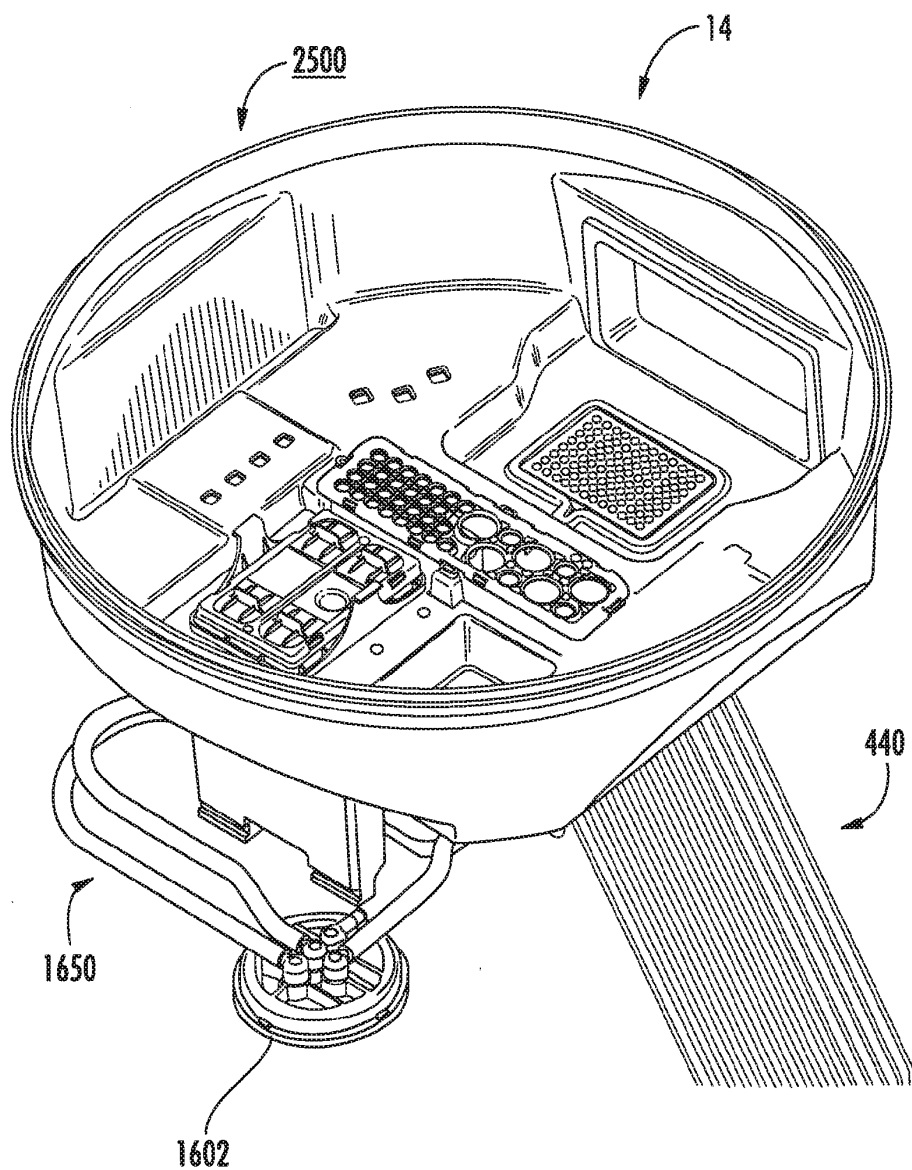
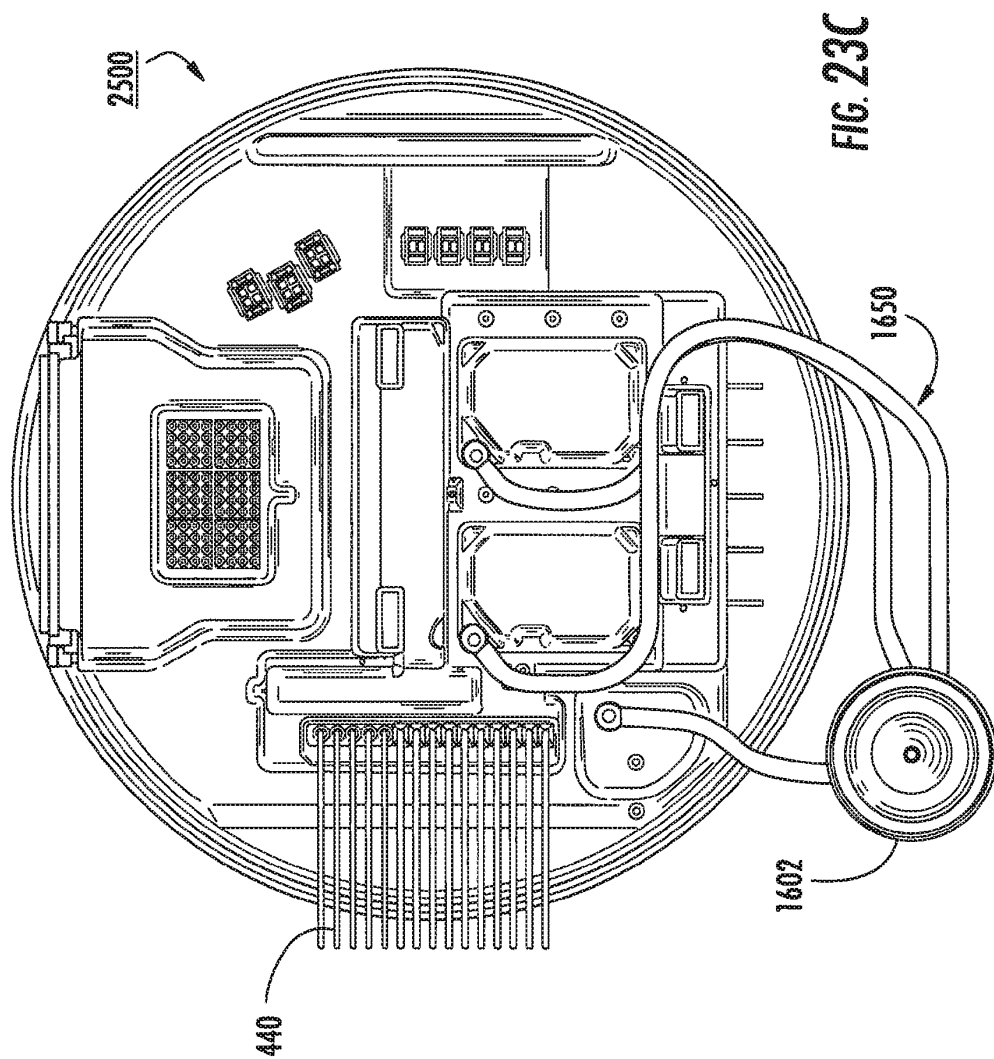
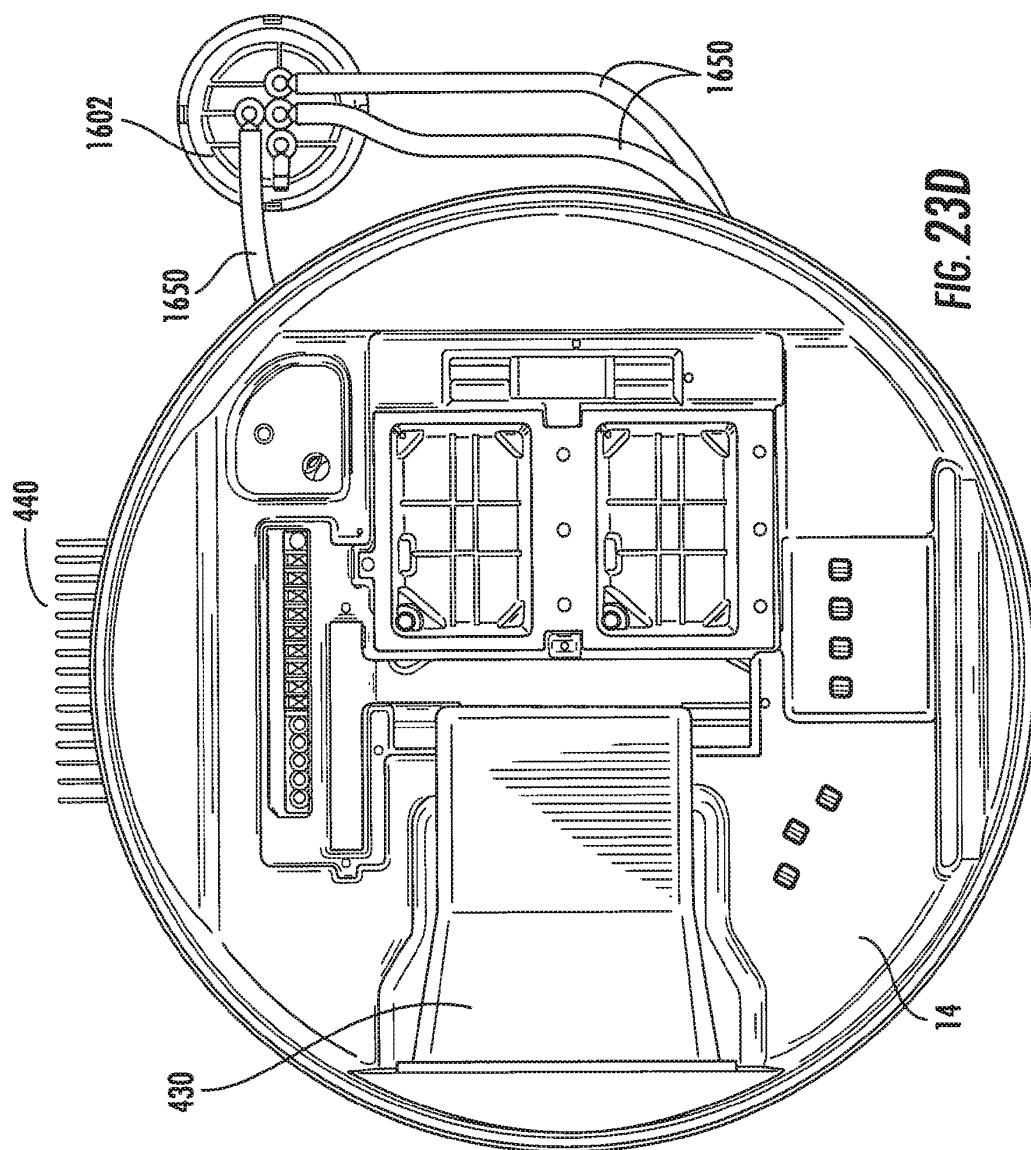


FIG. 23B

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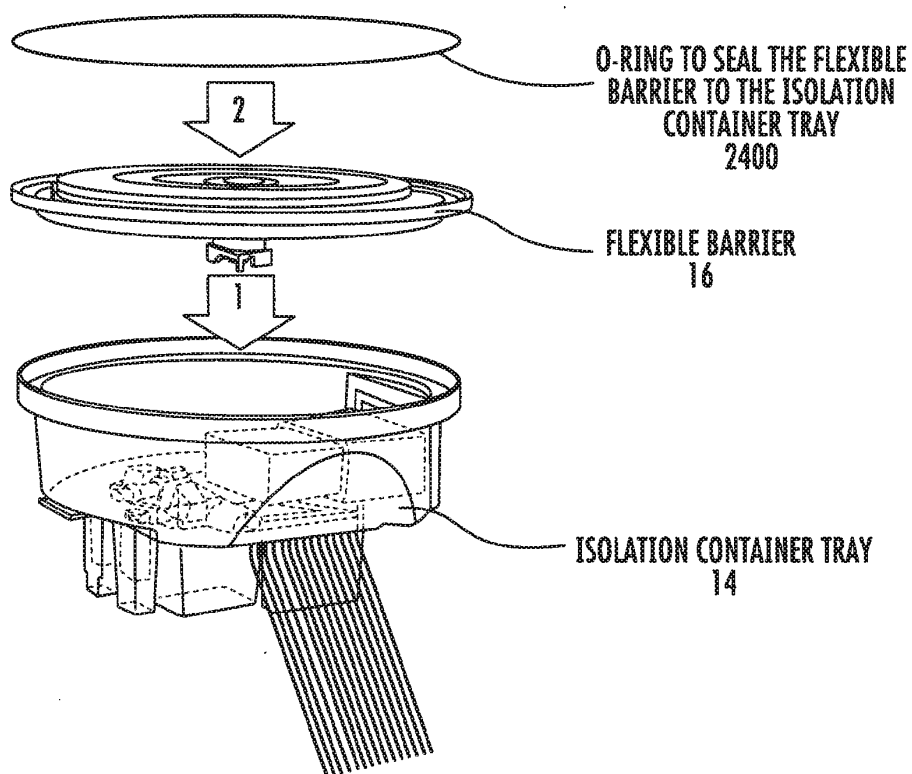


FIG. 24

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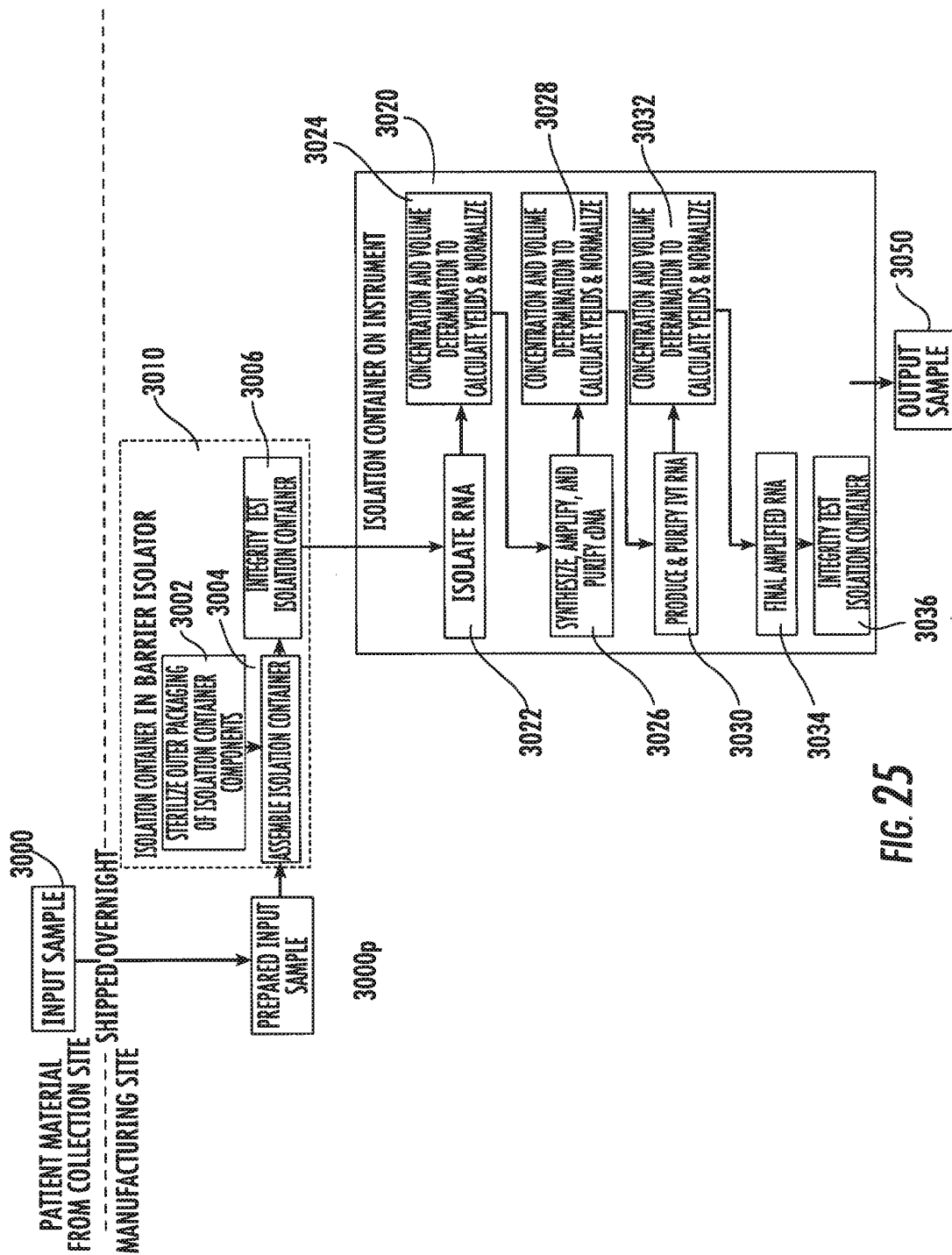


FIG. 25

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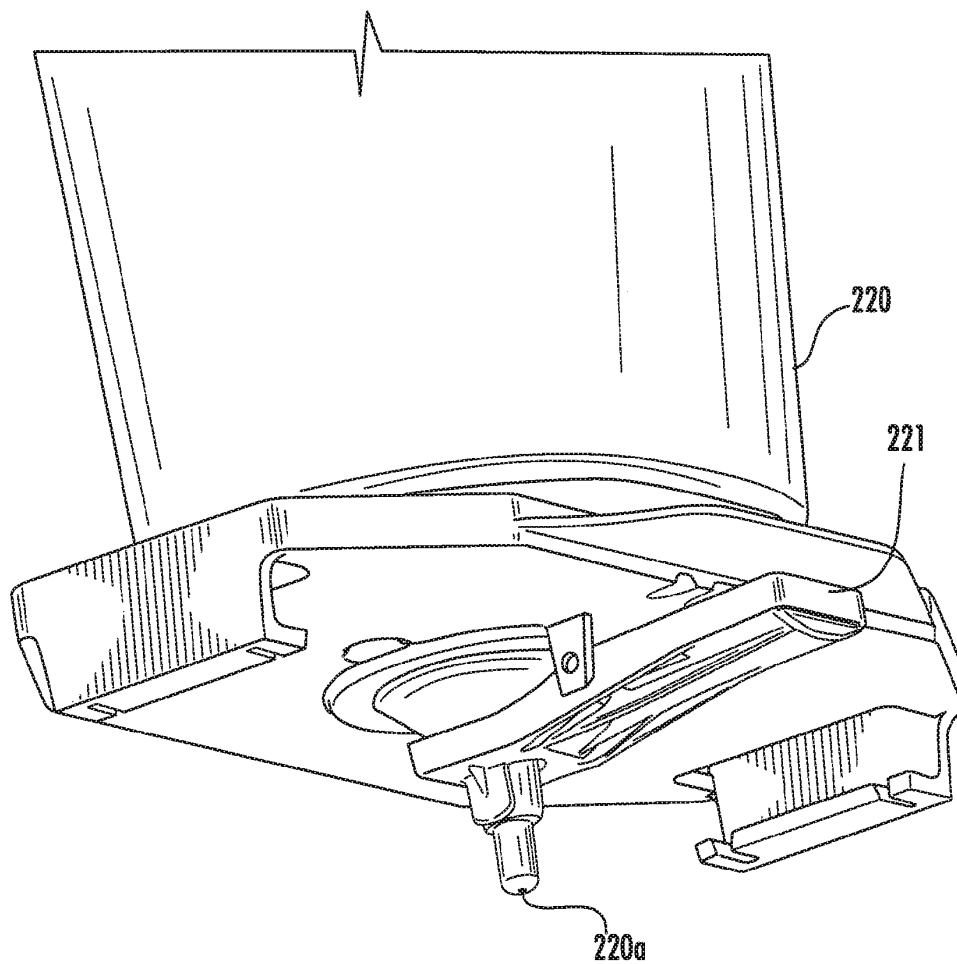
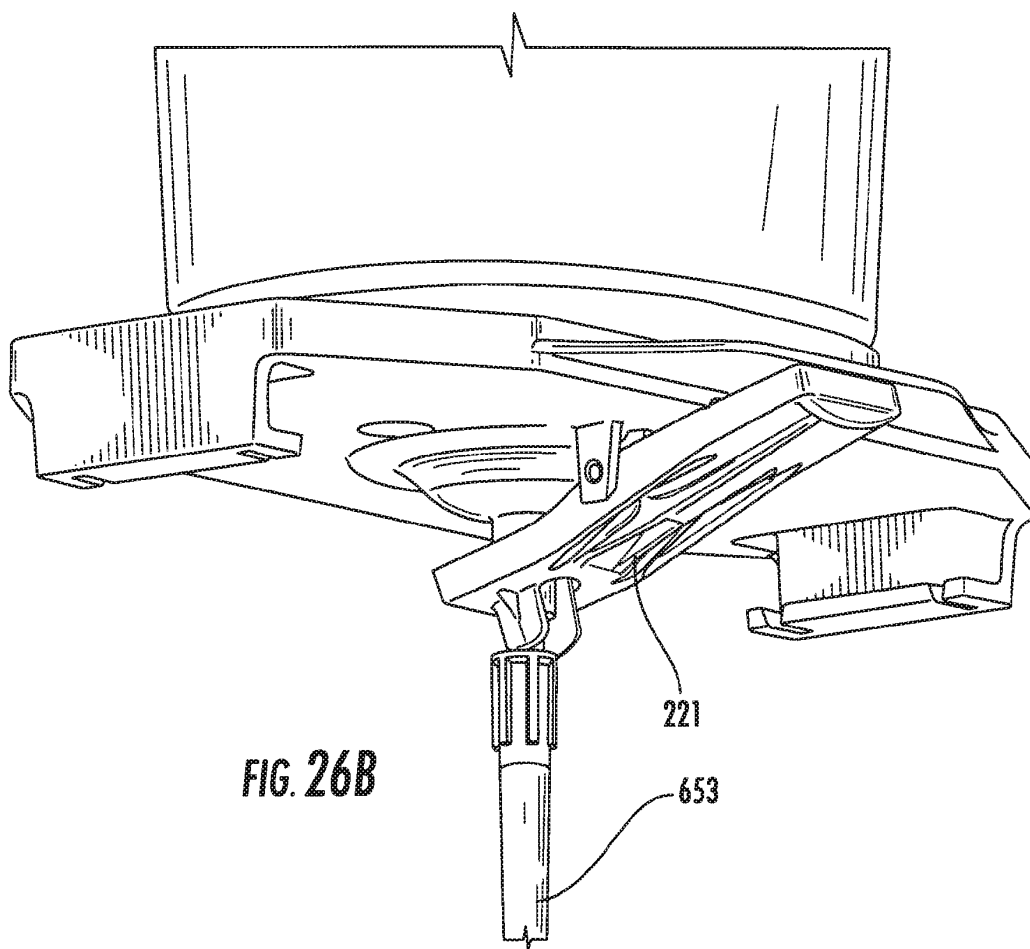


FIG. 26A

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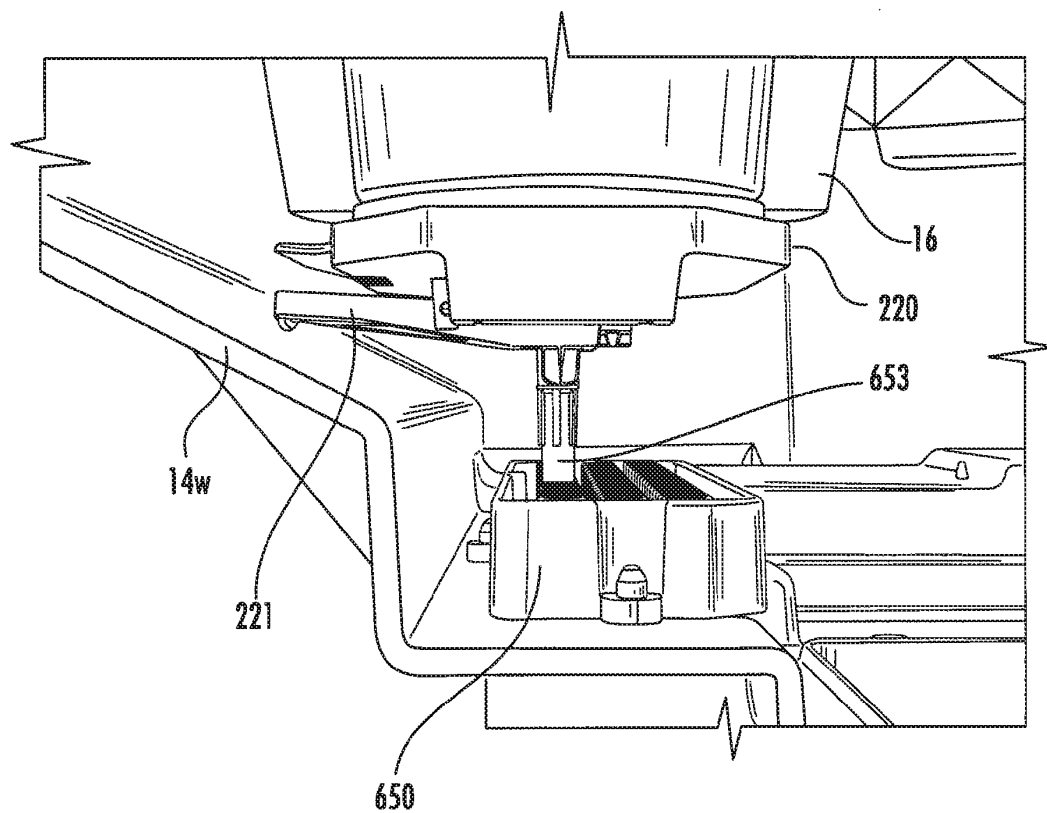
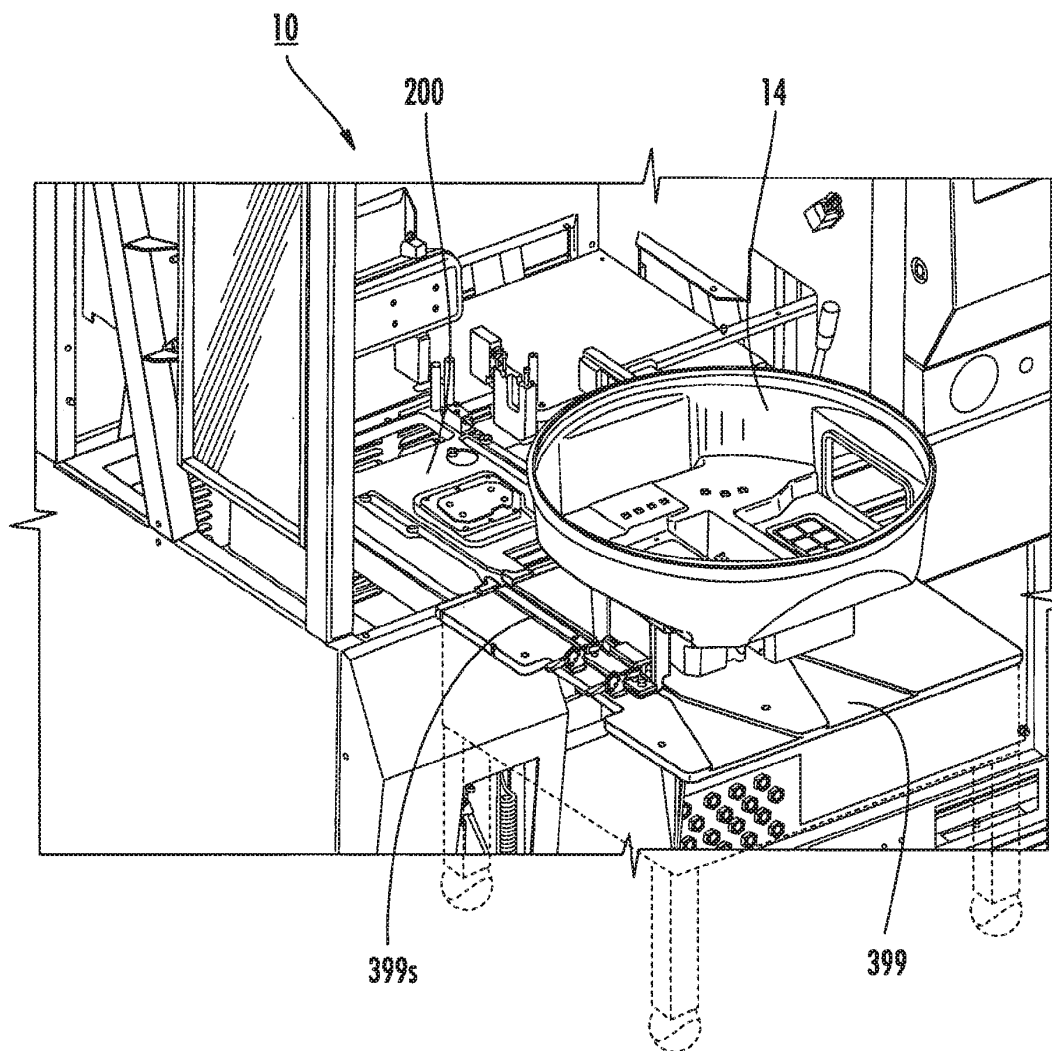


FIG. 26C

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**FIG. 27**

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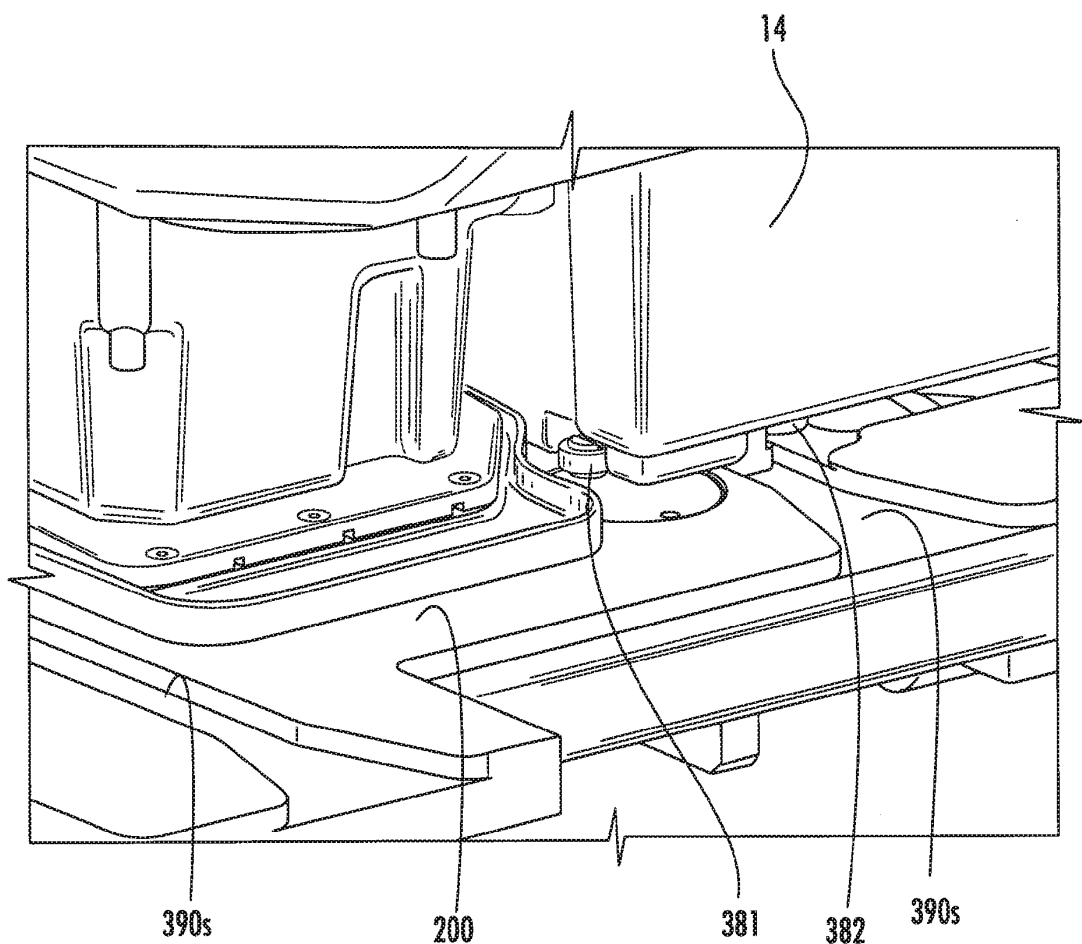


FIG. 28A

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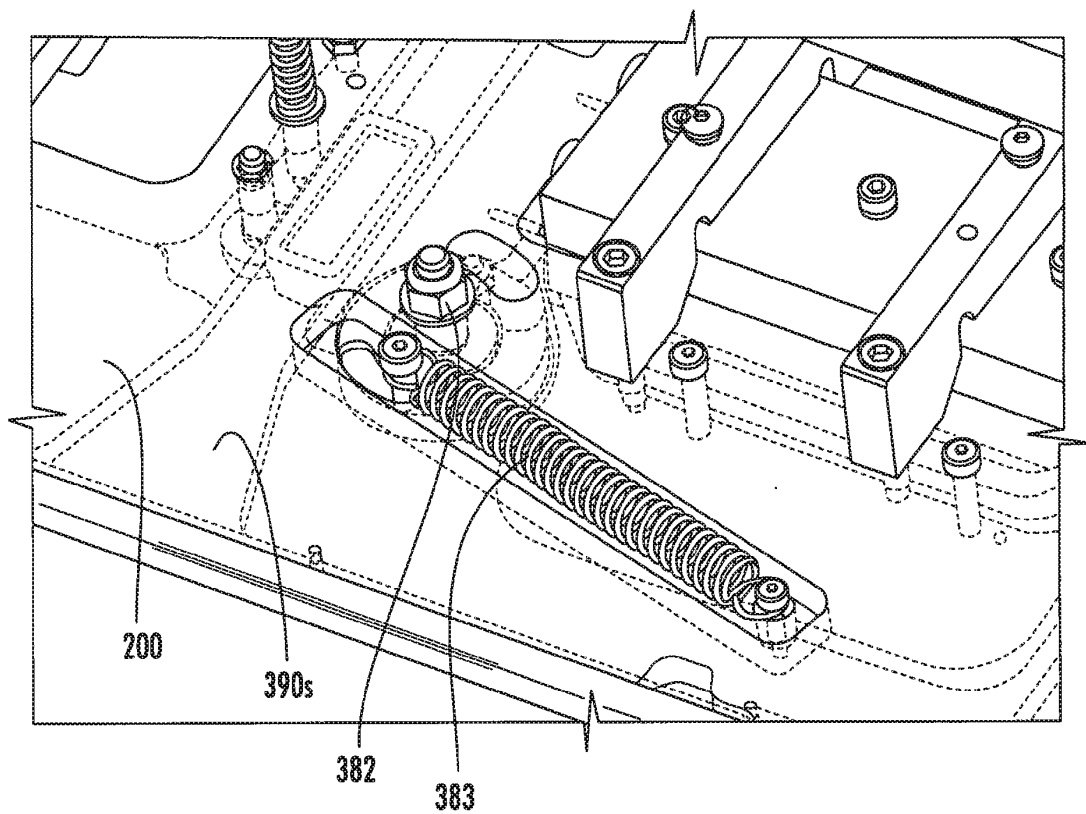


FIG. 28B

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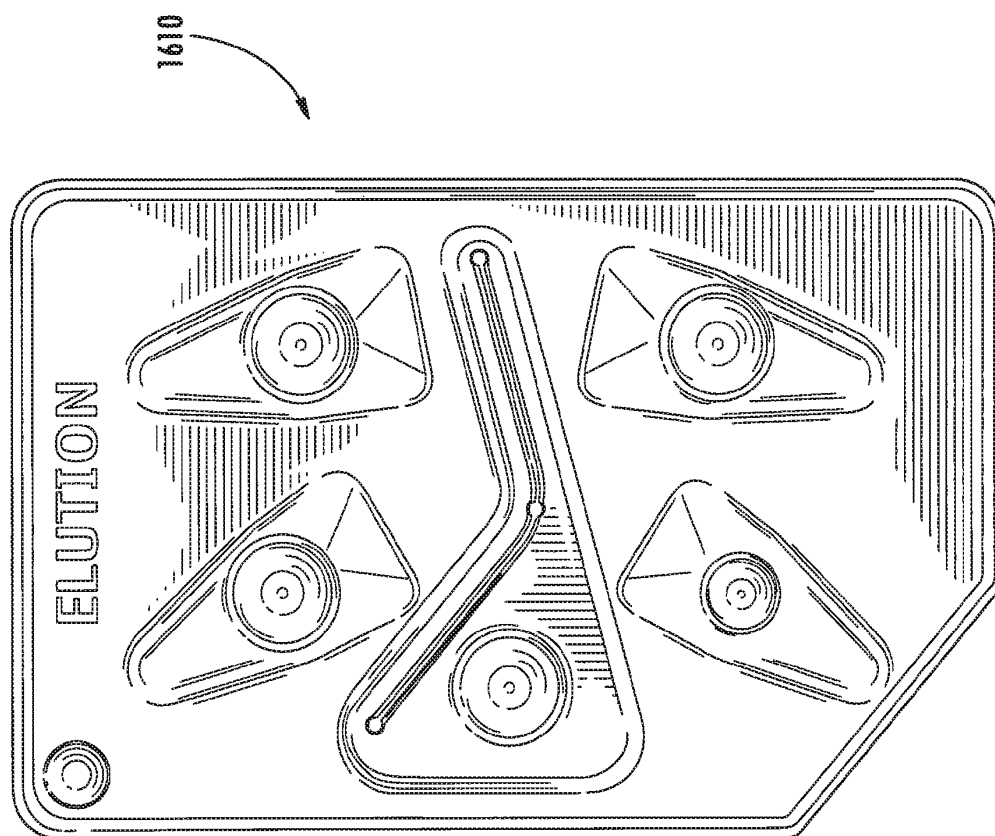


FIG. 29A

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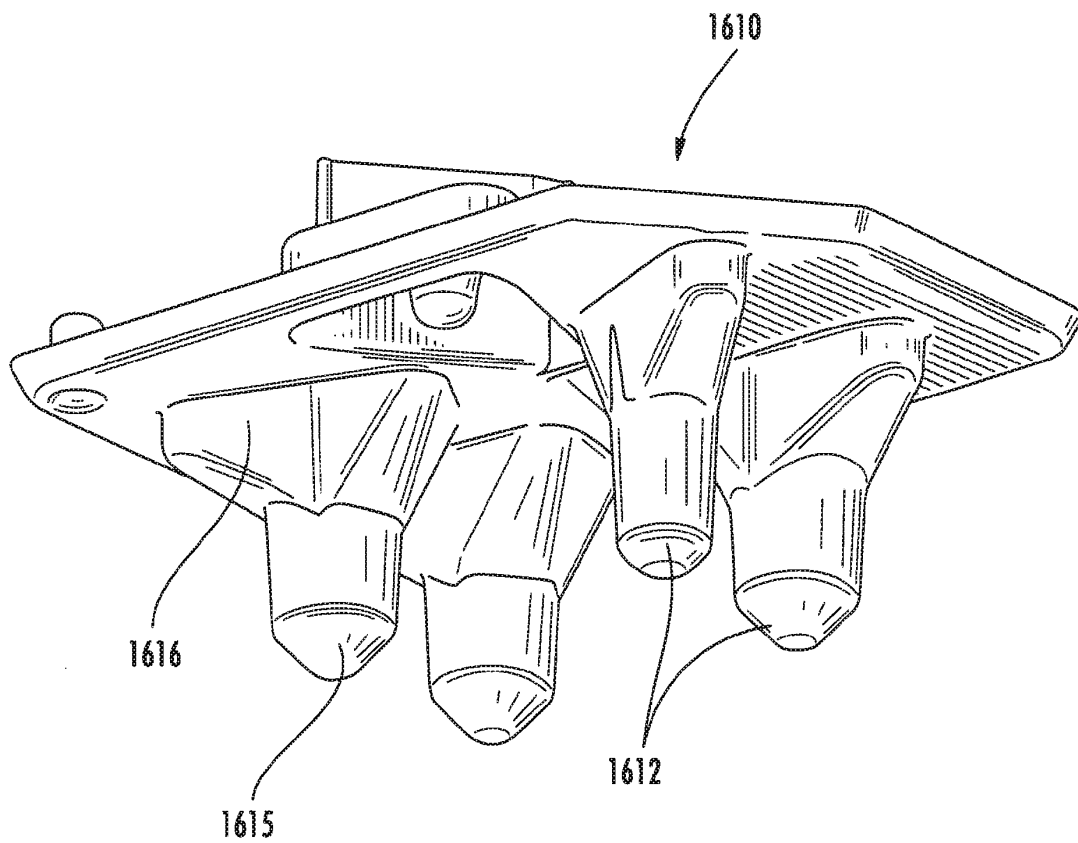


FIG. 29B

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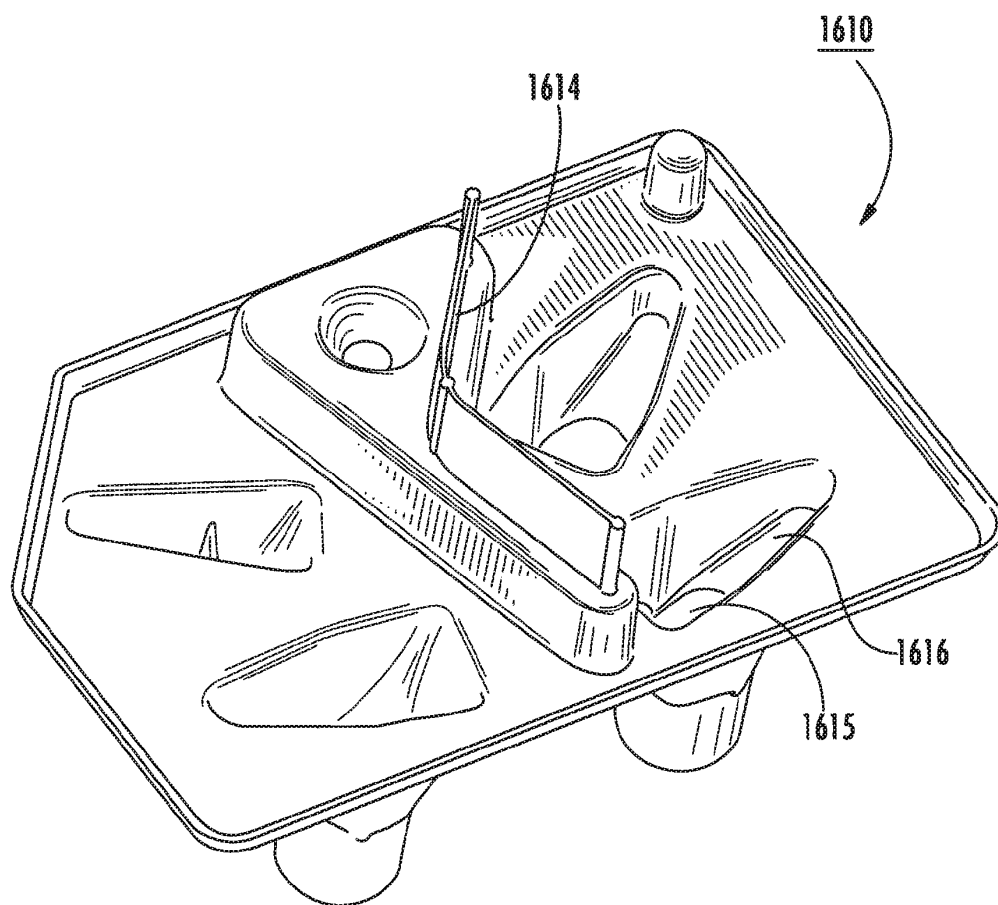
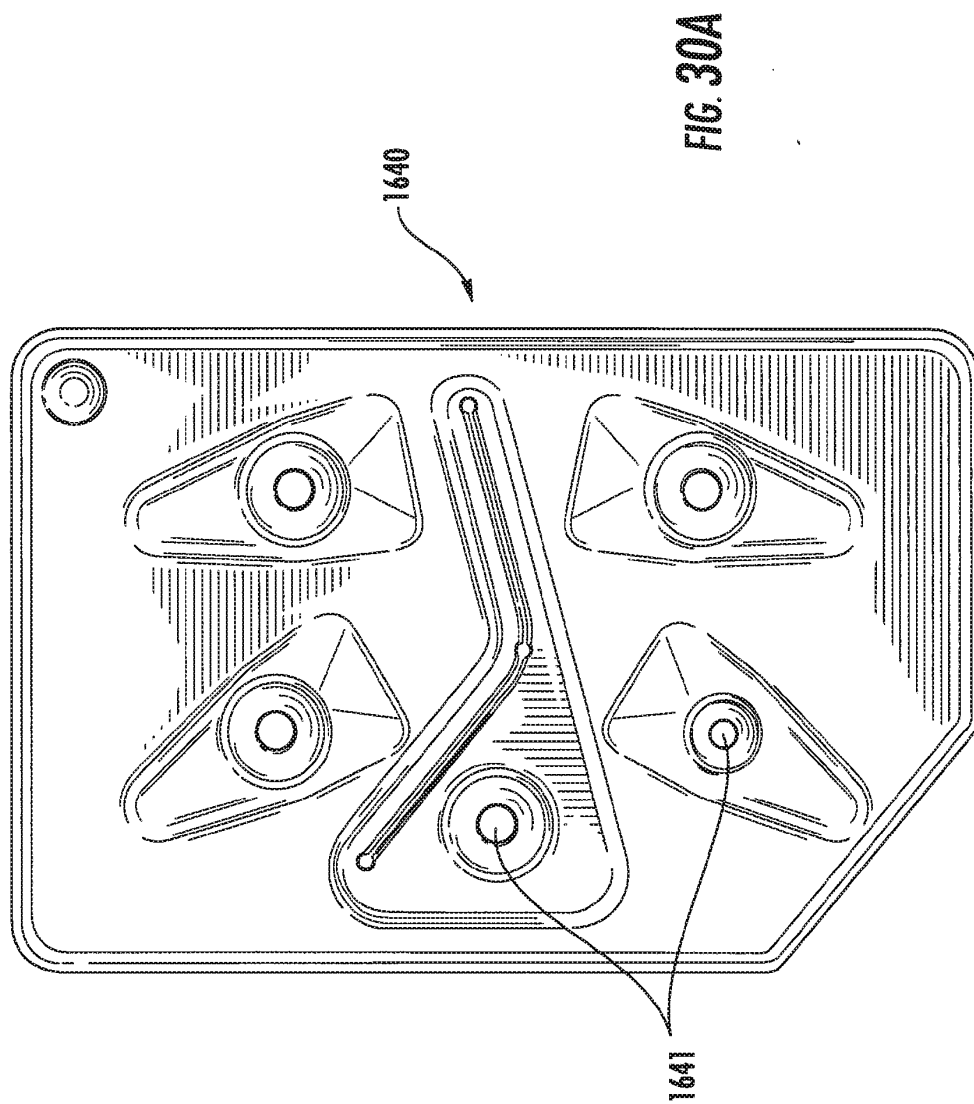
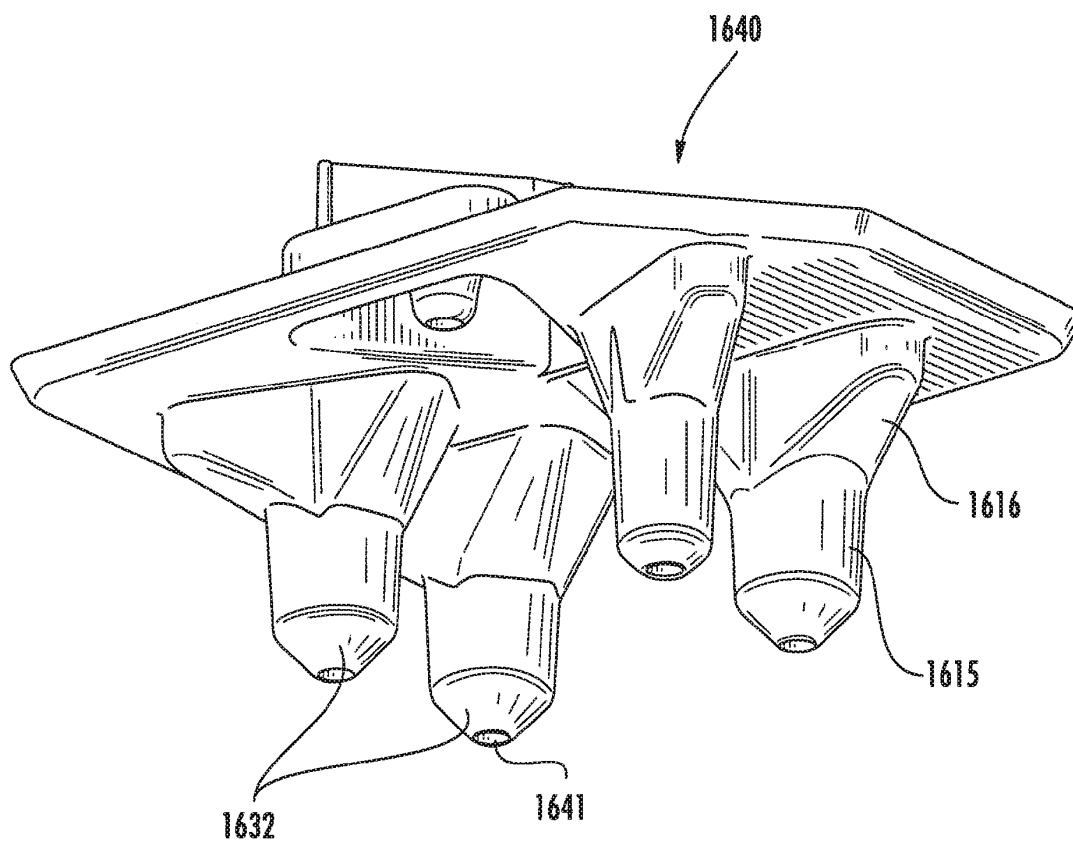


FIG. 29C

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**FIG. 30B**

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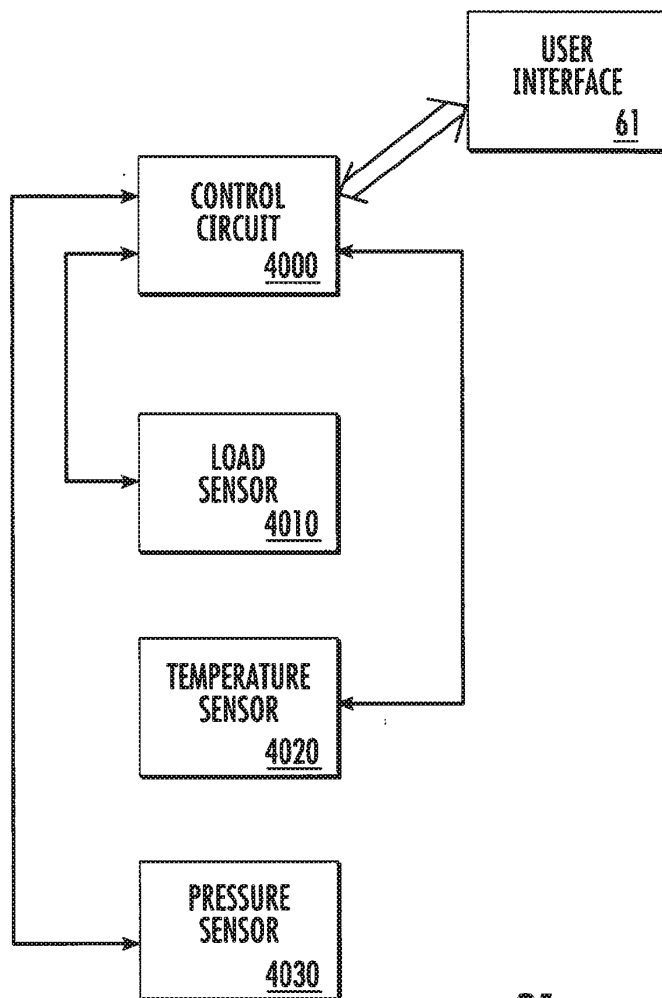


FIG. 31

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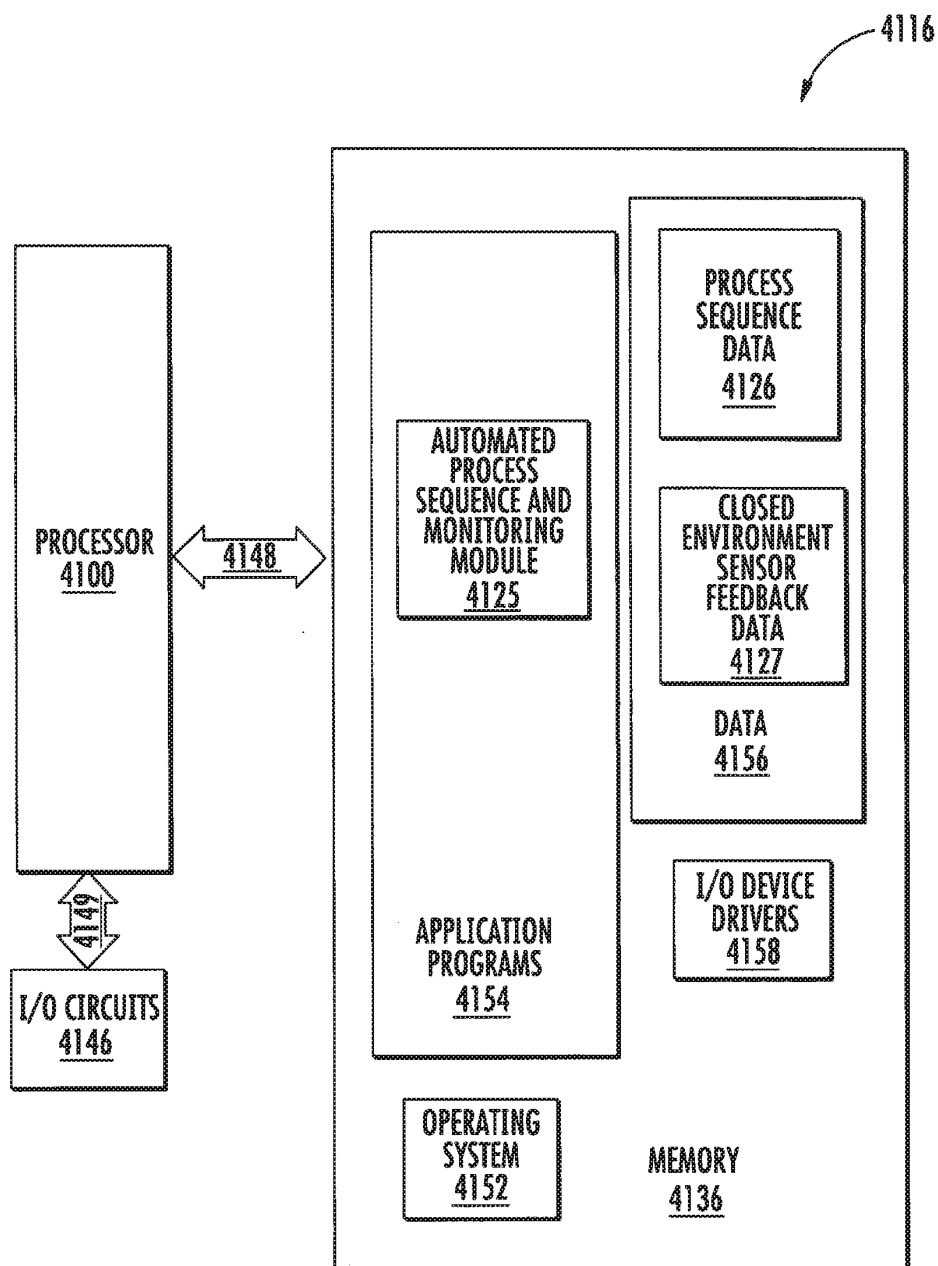


FIG. 32

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: March 21, 2016

Electronic Signature for Kathleen Libby: /Kathleen Libby/

Docket No.: 739712000201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: J. Wecker

AMENDMENT UNDER 37 C.F.R. 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the non-final Office Action dated September 22, 2015, please amend this application as follows.

Amendments to the Claims begin on page 2.

Remarks begin on page 9.

va-470208

AMENDMENTS

In the Claims:

1-39. (Canceled).

40. (New) An automated isothermal titration micro calorimetry (ITC) system, comprising:
a controller configured to control automated operation of the ITC system,
a micro calorimeter comprising a sample cell and a reference cell, the sample cell being accessible via a sample cell stem and the reference cell being accessible via a reference cell stem,
a pipette assembly comprising a syringe, a titration needle configured to be inserted into the sample cell and supply titrant to the sample cell, and an activator configured to drive a plunger in a cavity of the syringe,
a rotatable pipette translation unit configured to support the pipette assembly and place the pipette assembly in a titration position and in a washing position,
a rotatable cell preparation unit configured to wash the sample cell and replace sample liquid in the sample cell,
the controller being configured to control operation of the ITC system to wash the syringe and titration needle of the pipette assembly, fill the syringe with new titrant, wash the sample cell, and fill the sample cell with new sample liquid.

41. (New) The system of claim 40 comprising a titrant transfer unit configured to supply titrant to the syringe.

42. (New) The system of claim 40 wherein the rotatable cell preparation unit comprises a rotatably supported arm and a cell cannula that enables dispensing of liquid to at least one of the sample cell and the reference cell and withdrawal of liquid from at least one of the sample cell and the reference cell.

43. (New) The system of any of claims 40, 41 and 42 wherein the pipette translation unit comprises a rotatably supported arm configured to support the pipette assembly and enable vertical movement of the pipette assembly.

44. (New) The system of any of claims 40 and 41 comprising a hollow structure configured to enable at least one of withdrawal of liquid from the sample cell, introduction of wash liquid into the sample cell, and introduction of sample into the sample cell.

45. (New) The system of claim 44 wherein the hollow structure comprises a cell cannula.

46. (New) The system of any of claims 40, 41 and 42 comprising a hollow structure configured to enable at least one of introduction of wash liquid into the syringe and introduction of titrant into the syringe.

47. (New) The system of claim 46 wherein the hollow structure comprises a fill port.

48. (New) The system of claim 41 wherein the titrant transfer unit is rotatable.

49. (New) The system of any of claims 40, 41 and 42 wherein the controller is configured to control operation of the ITC system to wash the syringe and titration needle of the pipette assembly and fill the syringe with new titrant while the sample cell is washed and filled with new sample liquid.

50. (New) The system of any of claims 40, 41 and 42 wherein the controller is configured to enable performance of multiple unattended titration experiments in series.

51. (New) The system of any of claims 40, 41 and 42 wherein the rotatable cell preparation unit is configured to wash and replace sample in the reference cell and wash and replace sample in the sample cell.

52. (New) The system of any of claims 40, 41 and 42 comprising a syringe fluidics system configured to supply multiple cleaning agents to a wash station.

53. (New) The system of any of claims 40, 41 and 42, comprising:
a syringe fluidics system configured to enable at least one of pulling and pushing fluid through the syringe,
a syringe fill port, and
a fill port connection unit configured to enable fluidic contact between the syringe cavity and the syringe fluidics system.

54. (New) The system of claim 53 wherein the fluid comprises at least one of a liquid and a gas.

55. (New) An automated isothermal titration micro calorimetry (ITC) system, comprising:
a micro calorimeter comprising a sample cell and a reference cell, the sample cell being accessible via a sample cell stem and the reference cell being accessible via a reference cell stem,
a pipette assembly comprising a syringe, a titration needle configured to be inserted into the sample cell to supply titrant, and an activator configured to drive a plunger in a cavity of the syringe,
a rotational pipette translation unit configured to support the pipette assembly and place the pipette assembly in positions for titration and washing operations,
a wash station for the titration needle,
a cell fluidics system configured to dispense and withdraw liquid in the sample cell, and
a cell preparation unit configured to perform operations for replacing the sample liquid in the sample cell when the pipette assembly is placed in another position than the position for titration, the cell preparation unit comprising a cell arm that is supported for rotation about an axis, supporting a cell cannula connected to the cell fluidics system.

56. (New) The system of claim 55, comprising a waste fluidics system, wherein the wash station comprises a wash cavity configured to receive at least the section of the titration needle that is immersed in the sample during titration, wherein the wash station comprises a waste outlet port at the wash cavity connected to the waste fluidics system.

57. (New) The system of claim 56 wherein the waste fluidics system comprises a waste pump configured to selectively withdraw fluid from the wash station.

58. (New) The system of claim 55, comprising:
a syringe fluidics system configured to selectively pull or push liquid or gas through the syringe,
a syringe fill port, and
a fill port connection unit configured to enable fluidic contact between the syringe cavity and the syringe fluidics system.

59. (New) The system of claim 58 wherein the syringe is rotatable, wherein the fill port connection unit comprises a connection member and a port alignment mechanism, and wherein the port alignment mechanism is configured to prevent rotation of the syringe when the connection member is aligned with the syringe fill port.

60. (New) The system of claim 58 wherein the fill port connection unit enables connection between the syringe cavity and the syringe fluidics system when the pipette assembly is positioned at the wash station.

61. (New) The system of claim 58 wherein the syringe fluidics system comprises a syringe fill valve arrangement configured to:

connect the syringe fill port to a syringe fill pump and a source of purge gas, and
connect the syringe fill pump to at least one wash liquid reservoir and a waste outlet.

62. (New) The system of claim 61 wherein the syringe fluidics system is configured to push at least one wash liquid through the syringe and the titration needle via the syringe fill port when the titration needle is arranged in the wash cavity and to optionally purge gas through the syringe and the titration needle via the syringe fill port.

63. (New) The system of any of claims 58-61 wherein the syringe defines a first volume, wherein the syringe fluidics system is configured to push or pull a second volume of titrant into the syringe from a titrant source, the second volume being larger than the first volume, and wherein the activator is configured to move the plunger to a position which closes the fill port.

64. (New) The system of claim 63 wherein the titrant source comprises a well in a sample tray.

65. (New) The system of claim 63 comprising a titrant transfer unit configured to transfer titrant to the syringe.

66. (New) The system of claim 65 wherein the titrant transfer unit is rotatable.

67. (New) The system of claim 65 wherein the titrant transfer unit comprises a cannula configured to draw titrant from a titrant source and transfer titrant to the syringe.

68. (New) The system of claim 55 comprising a titrant transfer unit, the titrant transfer unit comprising a titrant transfer arm supporting a transfer cannula connected to a syringe fluidics system.

69. (New) The system of any of claims 63 to 67, wherein the syringe fluidics system is configured to control aspiration and dispensing of fluids during titrant transfer operations and during washing operations of the transfer cannula.

70. (New) The system of any of claims 63 to 67, wherein the syringe fluidics system is configured to selectively pull or push liquid or gas through the syringe.

71. (New) The system of any of claims 63 to 67, wherein the syringe comprises a fill port configured to enable fluidic contact with the syringe cavity.

72. (New) The system according to any of claims 63 to 67, wherein the syringe fluidics system comprises a fill pump configured to selectively pull or push liquid in the syringe fluidics system.

73. (New) The system of claim 72, wherein the fill pump comprises a pump common to both the syringe fluidics system and the cell fluidics system.

74. (New) The system of claim 72, wherein:
the syringe comprises a fill port configured to enable fluidic contact with the syringe cavity, and comprising
a syringe control configured to enable connection and disconnection between the fill pump and at least one of: the fill port of the syringe, the transfer cannula, multiple reservoirs, a waste outlet and a vent port.

75. (New) An automated isothermal titration micro calorimetry (ITC) system, comprising:
a controller configured to control automated operation of the ITC system,
a micro calorimeter comprising a sample cell and a reference cell,
a pipette assembly comprising a syringe, a titration needle configured to be inserted into the sample cell to supply titrant, and an activator configured to drive a plunger in a cavity of the syringe,
a pipette translation unit configured to support the pipette assembly and rotatably place the pipette assembly in at least a titration position and a washing position, and
a cell fluidics system configured to enable introduction of fluid to and withdrawal of fluid from the sample cell,

the controller being configured to control operation of the ITC system to wash the syringe and titration needle of the pipette assembly, fill the syringe with new titrant, wash the sample cell and fill the sample cell with new sample liquid.

76. (New) An automated isothermal titration micro calorimetry (ITC) system, comprising:
a controller configured to control automated operation of the ITC system,
a micro calorimeter comprising a sample cell and a reference cell,
a pipette assembly comprising a syringe, a titration needle configured to be inserted into the sample cell to supply titrant, and an activator configured to drive a plunger in a cavity of the syringe,

a pipette translation unit configured to support the pipette assembly and rotatably place the pipette assembly in at least a titration position and a washing position,

a cell fluidics system configured to enable introduction of fluid to and withdrawal of fluid from the sample cell, and

a syringe fluidics system configured to enable at least one of pulling and pushing fluid through the syringe,

the controller being configured to control operation of the ITC system to wash the syringe and titration needle of the pipette assembly, fill the syringe with new titrant, wash the sample cell and fill the sample cell with new sample liquid.

77. (New) The system of any of claims 75 and 76 comprising
a cell preparation unit configured to enable replacement of sample fluid in the sample cell,
the cell preparation unit comprising an arm supported for rotation about an axis.

78. (New) The system of any of claims 75 and 76 wherein
the controller is configured to control operation of the ITC system to wash the syringe and titration needle of the pipette assembly and fill the syringe with new titrant while the sample cell is washed and filled with new sample liquid.

REMARKS

Claims 1-39 have been cancelled. New claims 40 - 78 have been added. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Applicants wish to thank Examiners Wecker and Alexander for the courtesy extended to the undersigned attorney during the telephone interview that took place on October 7, 2015. The issues discussed during the interview are summarized in the remarks below.

The rejection of claim 1 as anticipated by Plotnikov (US 2010/0238968) is made moot by the cancellation of claim 1. The rejection of claim 1 on the ground of non-statutory double patenting as being unpatentable over claim 1 of U.S. Patent 9,103,782 is made moot by the cancellation of claim 1.

In accordance with the conversation that took place during the interview, new claims 40 - 78 recite combinations that include both functional and structural features including, for example, functional and structural aspects of a pipette translation unit, a cell preparation unit, a titration unit and a controller. Similar combinations are not disclosed or suggested in the prior art, and in particular are not disclosed or suggested in the cited prior art reference of Plotnikov.

Additionally, Plotnikov is not available as prior art under 35 USC 103. The critical reference date of Plotnikov under 35 USC 103/102(a) is its April 29, 2010 PCT publication date, which does not antedate the December 2, 2008 priority date of the present application. The October 31, 2008 international filing date of Plotnikov is not a critical reference date under 35 USC 103/102(e) because Plotnikov is commonly owned with the present application and, therefore, under 35 USC 103(c)(1) is not available as prior art under 35 USC 102(e). Accordingly, Plotnikov is not available as prior art under 35 USC 103.

It is respectfully submitted that new claims 40 - 78 are in condition for allowance.

Application No.: 14/736,905

Docket No.: 739712000201

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **739712000201**.

Dated: March 21, 2016

Respectfully submitted,

Electronic signature: /Alex Chartove/
Alex Chartove

Registration No.: 31,942
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Electronic Patent Application Fee Transmittal				
Application Number:		14736905		
Filing Date:		11-Jun-2015		
Title of Invention:		AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
First Named Inventor/Applicant Name:		Martin BROGA		
Filer:		Alex Chartove/Kathleen Libby		
Attorney Docket Number:		739712000201		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	18	80	1440
Multiple Dependent Claims	1203	1	780	780
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with \$0 paid	1253	1	1400	1400
Miscellaneous:				
Total in USD (\$)				3620

Electronic Acknowledgement Receipt

EFS ID:	25252359
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Alex Chartove/Kathleen Libby
Filer Authorized By:	Alex Chartove
Attorney Docket Number:	739712000201
Receipt Date:	21-MAR-2016
Filing Date:	11-JUN-2015
Time Stamp:	12:20:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 3620
RAM confirmation Number	11170
Deposit Account	031952
Authorized User	CHARTOVE, ALEX
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		739712000201.pdf	310950 26afb0283c2645777b775b10e02828a3c941c00	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	8	
	Applicant Arguments/Remarks Made in an Amendment		9	10	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	34315 ef7e315bde26c29f3d77664f89511cb8f69fd218	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			345265		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 14/736,905		Filing Date 06/11/2015		<input type="checkbox"/> To be Mailed					
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO													
APPLICATION AS FILED – PART I													
(Column 1)		(Column 2)											
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)					
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A							
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A							
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =		*		X \$		=					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$		=					
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).											
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))													
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL							
APPLICATION AS AMENDED – PART II													
(Column 1)		(Column 2)		(Column 3)									
AMENDMENT	03/21/2016		CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))		* 39		Minus	** 21	= 18		x \$80 =		1440		
	Independent (37 CFR 1.16(h))		* 2		Minus	*** 7	= 0		x \$420 =		0		
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))												
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE		1440	
(Column 1)		(Column 2)		(Column 3)									
AMENDMENT			CLAIMS REMAINING AFTER AMENDMENT			HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))		*		Minus	**	=		X \$		=		
	Independent (37 CFR 1.16(h))		*		Minus	***	=		X \$		=		
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))												
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE			
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>										LIE /DORRETTA BROOKS/			

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	Jennifer Wecker
Sheet	1	of	2	Attorney Docket Number	739712000201

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number-Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶

Examiner Signature		Date Considered	
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*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	1.	MicroCal, LLC, "Experimental Guide for AutoITC User's Manual," <i>Ultrasensitive Calorimetry for the Life Science</i> , MAU230010 Rev. C-2; 29 pages.	
	2.	MicroCal, LLC, "AutoITC User's Manual," <i>Ultrasensitive Calorimetry for the Life Science</i> , MAU230020 Rev. D; 109 pages.	

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal				
Application Number:		14736905		
Filing Date:		11-Jun-2015		
Title of Invention:		AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
First Named Inventor/Applicant Name:		Martin BROGA		
Filer:		Jonathan Bockman/Kathleen Libby		
Attorney Docket Number:		739712000201		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Total in USD (\$)				180

Electronic Acknowledgement Receipt

EFS ID:	24283712
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Jonathan Bockman/Kathleen Libby
Filer Authorized By:	Jonathan Bockman
Attorney Docket Number:	739712000201
Receipt Date:	07-DEC-2015
Filing Date:	11-JUN-2015
Time Stamp:	16:22:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 180
RAM confirmation Number	3230
Deposit Account	031952
Authorized User	AMII, LISA
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		739712000201.pdf	91148	yes	3
			2443e44470f79bb4dbb27086ec4a267740686889		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
2	Non Patent Literature	MAU230010RevC2.pdf	3949683	no	30
			e487db446673b161e904b172545cc0de050e65ec		
Warnings:					
Information:					
3	Non Patent Literature	MAU230020RevD.pdf	10577205	no	110
			80448d80bdced98659708c1c1db089e0ccff221fd		
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30774	no	2
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Warnings:					
Information:					
Total Files Size (in bytes):			14648810		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: December 7, 2015

Electronic Signature for Kathleen Libby: /Kathleen Libby/

Patent
Docket No. 739712000201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: Jennifer Wecker

**INFORMATION DISCLOSURE
STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicants submit for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of the non-patent literature are submitted herewith. The Examiner is requested to make these documents of record.

This Information Disclosure Statement is submitted after receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance. The required fee is submitted herewith.

va-463503

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

If the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **739712000201**.

Dated: December 7, 2015

Respectfully submitted,

Electronic signature: /Alex Chartove/

Alex Chartove

Registration No.: 31,942

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1650 Tysons Blvd, Suite 400

McLean, Virginia 22102

(703) 760-7744

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	Jennifer Wecker
Sheet	1	of	2	Attorney Docket Number	739712000201

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	1.	US-4,604,363	08-05-1986	Newhouse et al.	
	2.	US-5,340,541	08-23-1994	Jackson et al.	
	3.	US-5,813,763	09-29-1998	Plotnikov et al.	
	4.	US-6,387,277	05-14-2002	North, Jr.	
	5.	US-2002/0176803	11-28-2002	Hamel et al.	
	6.	US-2003/0226857	12-11-2003	Bibbo et al.	
	7.	US-2004/0024542	02-05-2004	Plotnikov et al.	
	8.	US-2004/0063208	04-01-2004	Chandler, Jr.	
	9.	US-7,488,106	02-10-2009	Brushwyler	
	10.	US-2009/0186374	07-23-2009	Okun et al.	
	11.	US-2010/0238968	09-23-2010	Plotnikov et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	12.	WO-81/01045	04-16-1981	CROMEMCO Inc. (Marvin L. KAUSCH)		
	13.	WO-87/00086	01-15-1987	American Hospital Supply Corporation (Richard W. HANAWAY)		
	14.	WO-2009/059110	05-07-2009	GE Healthcare Bio-Sciences Corp.; MicroCal LLC (Valerian V. PLOTNIKOV et al.)		

Examiner Signature		Date Considered	
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*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	Jennifer Wecker
Sheet	2	of	2	Attorney Docket Number	739712000201

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	15.	Cooper, A. et al. (1994). "Isothermal Titration Microcalorimetry," located at <http://www.chem.gla.ac.uk/staff/alanc/MMB-ITC-1994.pdf> retrieved on January 15, 2010. (14 pages).	
	16.	Doyle, M. L. (1999). "Titration Microcalorimetry in Current Protocols in Protein Science, Supplement 18," located at <http://www.nshvtn.org/ebook/molbio/Current%20Protocols/CPPS/ps2004.pdf> retrieved on January 15, 2010.	
	17.	International Search Report and Written Opinion mailed February 9, 2009, directed to International Application No. PCT/US2008/081961; 6 pages.	
	18.	MicroCal, LLC, "Autosampler for AutoITC User's Manual," <i>Ultrasensitive Calorimetry for the Life Science</i> , MAU190040; 44 pages.	
	19.	Broga et al., Office Action dated November 15, 2010, directed to U.S. Application No. 12/326,300; 18 pages.	
	20.	Broga et al., Office Action dated June 21, 2011, directed to U.S. Application No. 12/326,300; 20 pages.	
	21.	Broga et al., Office Action dated July 15, 2013, directed to U.S. Application No. 12/326,300; 19 pages.	
	22.	Broga et al., Office Action dated December 16, 2013, directed to U.S. Application No. 12/326,300; 22 pages.	
	23.	Broga et al., Office Action dated November 10, 2014, directed to U.S. Application No. 12/326,300; 22 pages.	

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹Applicant's unique citation designation number (optional). ²Applicant is to place a check mark here if English language Translation is attached.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: November 17, 2015

Electronic Signature for Monica Freeman: /Monica J. Freeman/

Patent
Docket No. 739712000201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: J. Wecker

**REQUEST TO CORRECT PREVIOUSLY FILED INFORMATION
DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

On September 17, 2015, Applicants filed an Information Disclosure Statement which contained an error on Form PTO/SB/08a/b. Specifically, Applicants erroneously listed cite no. 18 on Form PTO/SB/08a/b as “MicroCal, LLC, (1995). ‘Autosampler for AutoITC User’s Manual,’ *Ultrasensitive Calorimetry for the Life Science*, MAU190040; 74 pages.” The correct listing should be “MicroCal, LLC, ‘Autosampler for AutoITC User’s Manual,’ *Ultrasensitive Calorimetry for the Life Science*, MAU190040; 44 pages.” Applicants submit herewith a revised Form PTO/SB/08a/b to correct this error. The referenced “Autosampler for AutoITC User’s Manual” is believed to depict and describe a device believed to have been marketed in the US prior to 2008. Although Applicants are unable to provide the month and year of publication for cite no. 18 listed on the

va-462347

attached Form PTO/SB/08a/b, the publication date is sufficiently prior to the effective filing date and any foreign priority date such that the publication date is not an issue. Applicants respectfully request the Examiner to strike the previous Form PTO/SB/08a/b from the record and replace it with the attached Form PTO/SB/08a/b.

The Information Disclosure Statement filed on September 17, 2015 was submitted within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements were required.

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing (739712000201). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: November 17, 2015

Respectfully submitted,

Electronic signature: /Alex Chartove/
Alex Chartove
Registration No.: 31,942
MORRISON & FOERSTER LLP
1650 Tysons Blvd, Suite 400
McLean, Virginia 22102
(703) 760-7744

va-462347

Electronic Acknowledgement Receipt

EFS ID:	24104776
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Alex Chartove/Monica Freeman
Filer Authorized By:	Alex Chartove
Attorney Docket Number:	739712000201
Receipt Date:	17-NOV-2015
Filing Date:	11-JUN-2015
Time Stamp:	13:43:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	739712000201_CorrSB08.pdf	37009	no	2
			403cbf769a0f73dc2f1587c8d7f717ea6bff95a7		
Warnings:					
Information:					

This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	739712000201_ReqforCorrIDS.pdf	29512 2941aa721247b71058052d7faa68f5e8567da26e	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			66521		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/736,905	06/11/2015	Martin BROGA	739712000201	4808

25227	7590	10/14/2015
MORRISON & FOERSTER LLP		
1650 TYSONS BOULEVARD		
SUITE 400		
MCLEAN, VA 22102		

EXAMINER	
WECKER, JENNIFER	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
10/14/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficeVA@mofo.com
PatentDocket@mofo.com

<i>Applicant-Initiated Interview Summary</i>	Application No. 14/736,905	Applicant(s) BROGA ET AL.	
	Examiner JENNIFER WECKER	Art Unit 1797	

All participants (applicant, applicant's representative, PTO personnel):

(1) JENNIFER WECKER. (3) Lyle Alexander.

(2) Alex Chartove. (4) _____.

Date of Interview: 07 October 2015.

Type: ☒ Telephonic ☐ Video Conference
 ☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
 If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☒ Others
 (For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 19-39.

Identification of prior art discussed: Plotnikov et al.

Substance of Interview
 (For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Discussed potential amendments to clarify claims 19-39. No formal agreement was reached.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JENNIFER WECKER/ Examiner, Art Unit 1797	/LYLE ALEXANDER/ Supervisory Patent Examiner, Art Unit 1797
--	--

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	J. Wecker
Sheet	1	of	1	Attorney Docket Number	739712000201

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number-Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶

Examiner Signature		Date Considered	
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*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	1.	Extended European Search Report dated September 22, 2015, directed to EP Application No. 09830940.4; 5 pages	

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	23778333
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Alex Chartove/Monica Freeman
Filer Authorized By:	Alex Chartove
Attorney Docket Number:	739712000201
Receipt Date:	14-OCT-2015
Filing Date:	11-JUN-2015
Time Stamp:	15:29:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	739712000201_IDS.pdf	25630	no	2
			045db698970828d92c18cd124e5b0f97b2232cf0		
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	739712000201_SB08.pdf	26238 bb3cd9c02c74db095644dd86cf9d7646bdf c58bc	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	NPL_EESR_2015Sep22.pdf	155226 4d1701b7e6b766eb73724dc42c382958f21 6e2e3	no	5
Warnings:					
Information:					
Total Files Size (in bytes):			207094		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: October 14, 2015

Electronic Signature for Monica Freeman: /Monica J. Freeman/

Patent
Docket No. 739712000201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: J. Wecker

**INFORMATION DISCLOSURE
STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicants submit for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. A copy of the non-patent literature is submitted herewith. The Examiner is requested to make this document of record.

The document listed on the attached Form PTO/SB/08a/b is an Extended European Search Report dated September 22, 2015, directed to a counterpart foreign application and has not been previously cited. A certification under 37 C.F.R. § 1.97(e)(1) follows:

va-459959

I hereby certify that each item of information contained in the Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Information Disclosure Statement.

This Information Disclosure Statement is submitted after receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance. A Certification under 37 C.F.R. § 1.97(e) is provided above; accordingly, no fee is believed to be due.

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing (739712000201). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 14, 2015

Respectfully submitted,

Electronic signature: /Alex Chartove/
Alex Chartove

Registration No.: 31,942
MORRISON & FOERSTER LLP
1650 Tysons Blvd, Suite 400
McLean, Virginia 22102
(703) 760-7744

va-459959



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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/736,905	06/11/2015	Martin BROGA	739712000201

CONFIRMATION NO. 4808

PUBLICATION NOTICE



25227
MORRISON & FOERSTER LLP
1650 TYSONS BOULEVARD
SUITE 400
MCLEAN, VA 22102

Title:AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE

Publication No.US-2015-0276634-A1

Publication Date:10/01/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <http://pair.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/736,905	06/11/2015	Martin BROGA	739712000201	4808

25227	7590	09/22/2015
MORRISON & FOERSTER LLP		
1650 TYSONS BOULEVARD		
SUITE 400		
MCLEAN, VA 22102		

EXAMINER	
WECKER, JENNIFER	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
09/22/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficeVA@mofo.com
PatentDocket@mofo.com

Office Action Summary	Application No. 14/736,905	Applicant(s) BROGA ET AL.	
	Examiner JENNIFER WECKER	Art Unit 1797	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6/11/2015.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1 is/are pending in the application.
5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☒ The drawing(s) filed on 6/11/2015 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 3) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____. | 4) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(I)(1) - 706.02(I)(3) for

applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 9,103,782. Although the claims at issue are not identical, they are not patentably distinct from each other because while claim 1 of US 9,103,782 is not verbatim the only difference in claim language is that US 9,103,782 recites “a pipette translation unit supporting the pipette assembly that places a pipette in position for titration with the titration needle in the sample cell and in position for washing and filling operations with the titration needle in the wash station and the sample fill station” while claim 1 of the instant application recites “a pipette translation unit supporting the pipette assembly that places a pipette in position for titration with the titration needle in the sample cell and in position for washing operations with the titration needle in the wash station.”

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 1 is rejected under pre-AIA 35 U.S.C. 102(e) as being anticipated by Plotnikov et al (US PGPub 2010/0238968).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under pre-AIA 35 U.S.C. 102(e). This rejection under pre-AIA 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131(a).

Regarding Claim 1, Regarding Claim 1, Plotnikov et al teaches an automated isothermal titration microcalormetry (ITC) system 200 arranged to perform unattended titration experiments, the system comprising:

a system controller (referred to as the ITC control system) for controlling the automated operation of the ITC system (see [0032]), wherein stir and titration controllers 450, 460 (wherein stir controller 450 controls the stirring motor 400, which drives titration needle 360, see [0028]-[0031]) may be arranged in the pipette assembly 220, and in turn connected to the ITC control system or they may be an integrated part of the ITC control system;

a micro calorimeter 210 with a sample cell 250 and a reference cell 240, the sample cell is accessible via a sample cell stem 330 and the reference cell is accessible via a reference cell stem 320 (see [0023] and [0027]);

an automatic pipette assembly 220 (see [0023]) comprising a syringe 350 with a titration needle 360 arranged to be inserted into the sample cell for supplying titrant, the pipette assembly comprises a linear activator 370 for driving a plunger 380 in the syringe cavity (see [0028]);

a wash station (referred to as washing apparatus 600, which is disposed at washing position 580, see [0040]-[0041] and Figures 5a-c);

a sample fill station (referred to as titrant source 590, which is disposed at filling position 570, see [0040]-[0041] and Figures 5a-c);

a pipette translation unit (referred to as pipette guiding mechanism 510) supporting the pipette assembly and being arranged to place pipette in position for titration (referred to as titration position 560) with the titration needle in the sample cell, and in position for washing operations (referred to as washing position 580, which is connected to washing apparatus 600) with the titration needle in the wash station (see Figures 5a-c, [0041] and [0044]); and

a cell preparation unit (referred to as an auxiliary syringe) arranged to perform operations for replacing the sample liquid in the sample cell when the pipette is placed in another position than the position for titration (see [0046]);

In addition, Plotnikov et al teaches that the pipette assembly further comprises position sensors 500a, 500b for detecting two predetermined positions of the threaded

plunger 380. This design allows syringe to be rotated independently of the main body 340 of the pipette assembly 220; at the same time, the linear activator 370 can drive the threaded plunger 380. In the ITC system the titration 460 controller is arranged to control the linear activator of the pipette assembly 220. According to one embodiment, titration controller 460 uses the position sensors 500a, 500b for detecting two predetermined positions of the threaded plunger, and the titration controller 460 is arranged to register the two predetermined positions of the threaded plunger 380 and to determine the pitch of the threads of the plunger 380 from the number of steps performed by the stepper motor 470 to move the threaded plunger 380 between said positions (see [0033]-[0034]). In addition, Plotnikov et al also teaches non-manual (i.e. automated) alignment of the syringe for filling titrant, washing the pipette and delivering the titrant to the syringe (see [0045]), wherein the guiding mechanism 510 is used to position the pipette for filling the syringe with titrant and the movements of the pipette are performed using a program (such as that provided by the ITC control system) according to the experiment which is to be performed (see [0046]).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER WECKER whose telephone number is (571)270-1109. The examiner can normally be reached on Monday - Thursday, 9 AM - 6PM and Fridays 9 AM - 1 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lyle Alexander can be reached on (571) 272- 1254. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER WECKER/
Examiner, Art Unit 1797

Notice of References Cited	Application/Control No. 14/736,905		Applicant(s)/Patent Under Reexamination BROGA ET AL.	
	Examiner JENNIFER WECKER		Art Unit 1797	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2010/0238968 A1	09-2010	Plotnikov; Valerian V.	G01N25/20	374/33
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.




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BIB DATA SHEET

CONFIRMATION NO. 4808

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
14/736,905	06/11/2015	422	1797	739712000201		
APPLICANTS Malvern Instruments Incorporated, Westborough, MA; INVENTORS Martin BROGA, Amherst, MA; Phillip PRICE, North Granby, CT; Stephen SMITH, Northampton, MA; ** CONTINUING DATA ***** This application is a CON of 12/326,300 12/02/2008 PAT 9103782 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 06/22/2015						
Foreign Priority claimed <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No 35 USC 119(a-d) conditions met <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Verified and Acknowledged <u>/JENNIFER WECKER/</u> Examiner's Signature		<input type="checkbox"/> Met after Allowance Initials	STATE OR COUNTRY MA	SHEETS DRAWINGS 13	TOTAL CLAIMS 1	INDEPENDENT CLAIMS 1
ADDRESS MORRISON & FOERSTER LLP 1650 TYSONS BOULEVARD SUITE 400 MCLEAN, VA 22102 UNITED STATES						
TITLE AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE						
FILING FEE RECEIVED 1740	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			<input type="checkbox"/> All Fees <input type="checkbox"/> 1.16 Fees (Filing) <input type="checkbox"/> 1.17 Fees (Processing Ext. of time) <input type="checkbox"/> 1.18 Fees (Issue) <input type="checkbox"/> Other _____ <input type="checkbox"/> Credit		

<i>Index of Claims</i> 	Application/Control No. 14736905	Applicant(s)/Patent Under Reexamination BROGA ET AL.
	Examiner JENNIFER WECKER	Art Unit 1797

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

<input type="checkbox"/> Claims renumbered in the same order as presented by applicant <input type="checkbox"/> CPA <input type="checkbox"/> T.D. <input type="checkbox"/> R.1.47									
CLAIM		DATE							
Final	Original	09/15/2015							
	1	✓							

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	2	"12326300" and controll\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 18:06
L4	8	(calorimet\$4) and (sample and reference)(cell) and (pipett\$3 and titration needle) and (control unit or controller) and (G01K17/006 OR G01N1/14 OR G01N25/20 OR G01N25/48 OR G01N25/4813 OR G01N25/4866).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 18:07
L5	8	(calorimet\$4) and (sample and reference)(cell) and (pipett\$3 and titration needle) and (control unit or controller)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 18:07
L6	8	(calorimet\$4) and (sample and reference)(cell) and (pipett\$3 and titrat\$3 needle) and (control unit or controller)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 18:07
L7	34	(calorimet\$4) and (sample and reference)(cell) and (pipett\$3 and titrat\$3) and (control unit or controller)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 18:07
L8	3	((Martin) near2 (BROGA)).INV.	US-PGPUB; USPAT	ADJ	ON	2015/09/15 18:11
L9	7	((Phillip) near2 (PRICE)).INV.	US-PGPUB; USPAT	ADJ	ON	2015/09/15 18:11
L10	1445	((Stephen) near2 (SMITH)).INV.	US-PGPUB; USPAT	ADJ	ON	2015/09/15 18:11
L11	2	((Stephen) near2 (SMITH)).INV. and (titrat\$4 same calorimet\$4)	US-PGPUB; USPAT	ADJ	ON	2015/09/15 18:12
L12	0	("Malvern Instruments Incorporated").AANM.	US-PGPUB; USPAT	ADJ	ON	2015/09/15 18:14
S1	8	("20020176803" "20040063208" "4604363" "5340541").PN.	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2010/10/08 14:58

			EPO; JPO; DERWENT; IBM_TDB			
S8	0	(micro calorimet\$4) and (pipete with titration needle) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:40
S9	0	(micro calorimet\$4) and (pipette) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:40
S10	363	(calorimet\$4) and (pipette) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:40
S11	40	(calorimet\$4) and (pipette with needle) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:40
S12	0	(calorimeter) and (pipette with needle) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:42
S13	30	(calorimeter) and (pipette with needle)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:42
S14	98	(calorimeter) with (isothermal titrat\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:48
S15	1	(calorimeter) with (isothermal titrat\$3) and wash\$4 and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:52
S16	216	422/51.ccls.	US-PGPUB; USPAT;	ADJ	ON	2010/11/02 11:53

			USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S17	41	422/51.ccls. and isothermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 11:57
S18	12	422/75,81.ccls. and calorimeter	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:00
S19	0	422/75,81.ccls. and calorimeter and isothermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:01
S20	18	422/75,81.ccls. and isothermal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:01
S21	2	(isothermal with calorimet\$4) and wash (station or unit or apparatus)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:02
S22	104	(calorimet\$4) and wash (station or unit or apparatus)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:03
S23	1300	(calorimet\$4) and cell preparation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:04
S24	32	(calorimeter) and cell preparation	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:04

S25	2	(calorimeter) and pipette translat\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:05
S26	2	calorimeter and waste pump	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:12
S27	5	calorimeter and waste outlet	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:13
S28	1	calorimeter and waste fluidics	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:13
S29	1	calorimeter and wash cavity	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:14
S30	133	calorimeter and (sample and reference) cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:14
S31	12	calorimeter and (sample and reference) cell and pipette	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:14
S32	80	isothermal and calorimeter and (sample and reference) cell	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:15
S33	7	calorimeter and (syringe with fill port)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	ADJ	ON	2010/11/02 12:16

			DERWENT IBM_TDB			
S34	53	calorimeter and (syringe with rotat\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:16
S35	1	calorimeter and (syringe with fill valve)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:17
S36	93	calorimeter and (syringe with valve)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:17
S37	1	calorimeter and (titrant and sample tray)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:18
S38	46	calorimeter and (sample tray)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:19
S39	1	calorimeter and (titrant transfer\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:19
S40	6	calorimeter and (fill station)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 12:20
S41	13	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$).did.	US-PGPUB; USPAT	ADJ	ON	2010/11/02 15:19
S42	10	S41 and (wash\$4 or clean\$4)	US-PGPUB; USPAT;	ADJ	ON	2010/11/02 15:19

			USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S43	13	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$).did.	US-PGPUB; USPAT	ADJ	ON	2010/11/02 17:31
S44	6	S43 and replac\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 17:31
S45	17	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$).did.	US-PGPUB; USPAT	ADJ	ON	2010/11/02 17:37
S46	0	S45 and (cell or sample) prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 17:37
S47	1	S45 and (cell or sample)with prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 17:38
S48	0	S45 and cell arm	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2010/11/02 17:38
S49	2	(titration) with (calorimetr\$4) and (pipette with (translat\$4 or moving) with (wash\$4 or fill\$4 or titrat\$4))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/06 13:43
S50	5	(titration) with (calorimetr\$4) and (pipette with (translat\$4 or moving or rotat\$4))	US-PGPUB; USPAT; USOCR;	ADJ	ON	2011/06/06 13:44

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S51	1	"12326300"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:42
S52	3	calorimeter and (pipette with (translat\$4 or guid\$4)) same (titration and wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:50
S53	2	"0881961"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:51
S54	3	(pipette with (translat\$4 or guid\$4)) same (titration and wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:52
S55	5	(pipette with (translat\$4 or guid\$4 or rotat\$4)) same (titration and wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:53
S56	5	(pipette with (translat\$4 or guid\$4 or rotat\$4)) same (titrat\$4 and wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/13 16:53
S57	6	calorimeter and (cell with preparat\$4 with unit)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/14 17:45
S58	7664	(cell with preparation) and (calorimetr\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 09:15
S59	2	(cell with preparation) same (sample	US-PGPUB;	ADJ	ON	2011/06/15

		with (replac\$4)) same (calorimetr\$4)	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			09:15
S60	25	(sample with (replac\$4)) same (calorimetr\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 09:18
S61	52	(cell with preparat\$4) with arm	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 09:23
S62	389	((replac\$4 or supply\$4) with sample and (422/51,75,81.ccls.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:03
S63	20	((replac\$4 or supply\$4) with sample) same (arm or cannula) and (422/51,75,81.ccls.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:04
S64	78	((replac\$4 or supply\$4) with sample) same (calorimetr\$4 or titration) and "422".clas.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:06
S65	15	((cannula or arm) with sample) same (calorimetr\$4 or titration) and "422".clas.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:09
S66	40	(automat\$4) with (calorimeter) and "422".clas.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:16
S67	2	((automat\$4) with (calorimeter)) and (wash\$4 with station) and (fill\$4 with station)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT;	ADJ	ON	2011/06/15 10:55

			IBM_TDB			
S68	51	((automat\$4) with (calorimeter)) and (wash\$4) and (fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/06/15 10:55
S69	0	(micro calorimeter and (sample and reference) cell) and (pipete with titration needle) and wash and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:19
S70	0	(calorimet\$4 and (sample and reference) cell) and (pipete with titration needle) and wash and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:19
S71	0	(calorimet\$4) and (pipete with titration needle) and wash and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:19
S72	0	(calorimet\$4) and (pipete with titrat\$4) and wash and cell prepar\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:19
S73	34	"422".clas. and calorimetr\$4 and cell prepar\$5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:20
S74	246	"422".clas. and calorimetr\$4 and titrat\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:22
S75	88	"422".clas. and calorimetr\$4 and titrat\$4 and controller	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:22
S76	50	"422".clas. and calorimetr\$4 with isothermal	US-PGPUB; USPAT; USOCR; FPRS;	ADJ	ON	2012/04/10 13:34

			EPO; JPO; DERWENT; IBM_TDB			
S77	2	"5813763".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/04/10 13:37
S78	39	("3022664" "3319456" "3858433" "4255961" "4333332" "4530608" "4812051" "4892707" "5248199" "5439291" "5547282" "5599104").PN. OR ("5813763").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2012/04/10 13:37
S79	336	(automat\$4 or controller) and (isothermal with calorimet\$4) and (pipette or syringe or cannula)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/04/10 14:07
S80	35	(automat\$4 or controller) and (isothermal with calorimet\$4) and (pipette or syringe or cannula) with (translat\$4 or rotat\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/04/10 14:07
S81	28	(US-20040063208-\$ or US- 20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542- \$ or US-20020034210-\$ or US- 20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994- \$ or US-20080003140-\$ or US- 20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043- \$ or US-20070104245-\$).did. or (US- 5340541-\$ or US-4604363-\$ or US- 7488106-\$ or US-7288229-\$ or US- 6513969-\$ or US-6485173-\$ or US- 5967659-\$ or US-5813763-\$ or US- 6846455-\$ or US-7712956-\$ or US- 4072050-\$ or US-7371006-\$).did.	US-PGPUB; USPAT	ADJ	ON	2012/12/04 14:04
S82	0	S81 and (pipette with translation)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/04 14:04
S83	0	S81 and (pipette with translat\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/04 14:04
S84	2	S81 and (pipette or syringe) same (robot\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/04 14:04
S85	4	S81 and (pipette or syringe) same (rotat\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/04 14:05
S86	232	422/51.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/12/04 14:17
S87	13	(calorimeter\$4) and ((syringe or pipette or needle) with (rotat\$4 or translat\$4 or moving) with (position))	US-PGPUB; USPAT; USOCR;	AND	ON	2012/12/07 10:59

			FPRS; EPO; JPO; DERWENT; IBM_TDB			
S88	15	(calorimeter\$4) and ((syringe or pipette or needle) with (rotat\$4 or translat\$4 or moving or guid\$4) with (position))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2012/12/07 11:05
S89	39	(calorimeter\$4) and (syringe or pipette or needle) and (replac\$4 or refill\$4) with (sample cell)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2012/12/07 11:17
S90	0	"123256300"	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/10 16:16
S91	1	"12326300"	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/10 16:16
S92	2	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) same (titrat\$4 with position)	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/12 20:45
S93	3	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) same (titrat\$4 and (wash\$4 or fill\$4))	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/12 20:46
S94	788	(automat\$4 with calorimet\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/12/14 10:18
S95	112	(automat\$4 with calorimet\$4) and titrat\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2012/12/14 10:18
S96	1	"12326300"	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/14 11:12
S97	26	microcalorimet\$4 and (waste with (container or receptacle or vial or tube or vessel))	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/14 14:00
S98	27	microcalorimet\$4 and (waste with (container or receptacle or vial or tube or vessel or cavity))	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/14 14:01
S99	86230	(container or receptacle or vial or tube or vessel or cavity) with (bottom) with (outlet or port or hole or aperture)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/14 14:02
S100	1	S99 and S98	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/14 14:02

S101	28	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$).did.	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:26
S102	3	S101 and (purg\$4 with gas)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2012/12/17 19:26
S103	20	S101 and (air or gas)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:27
S104	10	S101 and (pressure source)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:28
S105	17	S101 and (valve)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:29
S106	5	S101 and (wash\$4 same fill\$4)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:36
S107	0	calorimeter\$4 annd (wash\$4 same fill\$4)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:38
S108	696	calorimeter\$4 and (wash\$4 same fill\$4)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:38
S109	6	calorimeter\$4 and (wash\$4 same fill\$4) with (combin\$3 or together)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:39
S110	9	calorimeter\$4 and (wash\$4 same fill\$4) with (reservoir or chamber or station)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:39
S111	7	S101 and (wash\$4 and fill\$4)	US-PGPUB; USPAT	ADJ	ON	2012/12/17 19:40
S112	1	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) same (titrat\$4 with position) and 422/500-501.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 13:43
S113	2	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) and(wash\$4 or fill\$4 or titrat\$4) and 422/500-501.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 13:44
S114	0	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) and(wash\$4 or fill\$4 or titrat\$4) and 422/500-50, "5091".ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 13:45
S115	2	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4) and(wash\$4 or fill\$4 or titrat\$4) and 422/500-501,509.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 13:45
S116	2	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4 or guid\$4) and(wash\$4 or fill\$4 or titrat\$4) and 422/500-501,509.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 13:45
S117	1	((calorimetr\$4).clm. and ((pipette or	US-PGPUB;	ADJ	ON	2012/12/18

		syringe) with (translat\$4 or guid\$4 or rotat\$4)).clm. and (wash\$4 with (container or station or receptacle or chamber) same (outlet) same waste)).clm.	USPAT; EPO; JPO			13:47
S122	0	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4 or guid\$4) and(wash\$4 or fill\$4 or titrat\$4) and 436/163.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 14:47
S123	0	(calorimetr\$3) and (syringe or pipette) with (translat\$4 or rotat\$4 or guid\$4) and(wash\$4 or fill\$4 or titrat\$4) and 436/163,267.ccls.	US-PGPUB; USPAT; EPO; JPO	AND	ON	2012/12/18 14:48
S124	1	"12326300"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/02/05 12:10
S125	1	S124 and (controller or computer or control\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/02/05 12:30
S126	1	"12326300"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/03/12 13:40
S127	1	S126 and (supervis\$4 or monitor\$4 or attend\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/03/12 13:40
S128	1	422/51.ccls. and calorimet\$5 and wash\$3 same waste	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 12:48
S129	4	422/51.ccls. and calorimet\$5 and wash\$3 and waste	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 12:48
S130	11693	("422" or "435").clas. and (wash\$3) same (outlet or waste or exit)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 12:49
S131	452	("422" or "435").clas. and calorimet\$5 and (wash\$3) same (outlet or waste or	US-PGPUB; USPAT;	ADJ	ON	2013/06/27 12:49

		exit)	USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S132	437	("422" or "435").clas. and calorimet\$5 and (wash\$3) same (outlet or waste)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 12:50
S133	85	("422" or "435").clas. and calorimet\$5 and titrat\$3 and (wash\$3) same (outlet or waste)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 12:50
S134	28	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$).did.	US-PGPUB; USPAT	ADJ	ON	2013/06/27 12:50
S135	5	S134 and waste	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 12:51
S136	1	S134 and (waste or outlet) same (wash\$3 with (reservoir or chamber or cavity))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 13:01
S137	2	S134 and (waste or outlet) same (wash\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 13:01
S138	1	S137 not S136	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 13:01
S139	130	("422" or "435").clas. and calorimet\$5 and ((wash\$3) with (cavity or chamber	US-PGPUB; USPAT;	ADJ	ON	2013/06/27 13:02

		or reservoir)) same (outlet or waste)	USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S140	3	S134 and (drain or waste) with (pump\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:07
S141	1	"422".clas. and (calorimet\$3 or titrat\$3) (drain or waste) with (pump\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:10
S142	232	"422".clas. and (calorimet\$3 or titrat\$3) and (drain or waste) with (pump\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:11
S143	26	"422".clas. and (calorimeter) and (drain or waste) with (pump\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:16
S144	3	S134 and (drain or waste) with (pump\$3)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:18
S145	9	S134 and (syringe)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:19
S146	1	"12326300"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:20
S147	3	S134 and (syringe or cannula or needle) same (port) same fill\$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:29

S148	139	calorimet\$5 and (syringe or cannula or needle) same (port) same fill\$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:31
S149	58	calorimet\$5 and (syringe or cannula or needle) same (port) same fill\$3 and ("422" or "435").clas.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:31
S150	89	calorimet\$5 and (syringe or cannula or needle) same (connect\$3) same fill\$3 and ("422" or "435").clas.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:34
S151	1	S134 and (syringe or needle or cannula or pipette) same (rotat\$3) same (align\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:39
S152	5	S134 and (syringe or needle or cannula or pipette) same (valve)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:40
S153	17	S134 and valve	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:41
S154	1	S134 and (fill station)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:45
S155	2	S134 and (titrant with source)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:46
S156	0	calorimetr\$5 and (titrant with source) with (first and second)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	ADJ	ON	2013/06/27 14:48

			DERWENT IBM_TDB			
S157	0	calorimet\$5 and (titrant with source) with (first and second)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:49
S158	2	calorimet\$5 and (titrat\$3 with source) with (first and second)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:49
S159	0	calorimet\$5 and (titrat\$3 with source) SAME TRAY	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2013/06/27 14:50
S160	41	(US-20040063208-\$ or US- 20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542- \$ or US-20020034210-\$ or US- 20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994- \$ or US-20080003140-\$ or US- 20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043- \$ or US-20070104245-\$ or US- 20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340- \$ or US-20090162942-\$ or US- 20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729- \$).did. or (US-5340541-\$ or US- 4604363-\$ or US-7488106-\$ or US- 7288229-\$ or US-6513969-\$ or US- 6485173-\$ or US-5967659-\$ or US- 5813763-\$ or US-6846455-\$ or US- 7712956-\$ or US-4072050-\$ or US- 7371006-\$ or US-5817954-\$ or US- 6653124-\$ or US-6387277-\$ or US- 4610845-\$).did.	US-PGPUB; USPAT	ADJ	ON	2013/06/27 14:52
S161	0	S160 AND (TRAY) SAME (TITRANT)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:52
S162	0	S160 AND (TRAY) SAME (TITRA\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:52
S163	1	S160 AND (TRAY OR RACK) SAME (TITRA\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:52
S164	76	(CALORI MET\$5) AND (TRAY OR RACK) SAME (TITRA\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:53
S165	5	(CALORI MET\$5) AND (PI PETTE OR CANNULA) SAME (FILL\$3) SAME	US-PGPUB; USPAT;	ADJ	ON	2013/06/27 14:55

		(SAMPLE CELL)	EPO; JPO			
S166	692	(CALORIMET\$5) AND (PIPETTE OR CANNULA) SAME (FILL\$3 OR REFILL\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:59
S167	112	S166 AND "422".CLAS.	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 14:59
S168	51	(CALORIMET\$5) AND (PIPETTE OR CANNULA) SAME (FILL\$3 OR REFILL\$3) WITH SAMPLE AND ("422" OR "435" OR "436").clas.	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:01
S169	8	(needle or PI PETTE OR CANNULA) SAME (FILL\$3 OR REFILL\$3) and S160	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:05
S170	3	S160 and (purg\$3 WITH GAS)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:07
S171	8	S160 and (purg\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:07
S172	0	S160 and (gas) same (sample cell)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:08
S173	23	S160 and (gas)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:08
S174	15	S160 and (purg\$3 or pressure) with (source)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:11
S175	5	S160 and (purg\$3 or pressure) with (source) same (sample cell)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:12
S176	9	S160 and (fill or refill\$3) with (sample)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:13
S177	11	S160 and (fill or refill\$3) same (sample)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:14
S178	9	S160 and (fill\$3 or refill\$3) same (sample cell)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:15
S179	21	S160 and (fill\$3 or refill\$3) same (sample) and calorimet\$5	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:16
S180	16	S160 and (fill\$3 or refill\$3) with (sample) and calorimet\$5	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:17
S181	2	S160 and (fill\$3 or refill\$3) with (sample) same (needle or cannula or pipette) and calorimet\$5	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:19
S182	6	S160 and (fill\$3 or refill\$3) same (needle or cannula or pipette) and calorimet\$5	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 15:19
S183	41	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-	US-PGPUB; USPAT	ADJ	ON	2013/06/27 17:50

		20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$ or US-20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340-\$ or US-20090162942-\$ or US-20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$ or US-5817954-\$ or US-6653124-\$ or US-6387277-\$ or US-4610845-\$).did.				
S184	4	S183 and (wash\$3) same (outlet) same (waste or drain\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 17:50
S185	10	S183 and (wash\$3) same (waste or drain\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 17:55
S186	6	S185 not S184	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 17:56
S187	6	S183 and (wash\$3) same (outlet)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:01
S188	7	S183 and (waste) with (pump\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:05
S189	12	S183 and (waste) same (pump\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:06
S190	5	S183 and (fill\$3) same (port) same (connect\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:12
S191	2	S183 and (fill port) same connect\$4	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:20
S192	0	S183 and (waste pump\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:23
S193	2	S183 and (port) same (align\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:30
S194	17	S183 and (align\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:30
S195	2	S183 and (fill\$3 port) with connect\$3	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:39
S196	2	S183 and (syringe or pipette or cannula) same fill\$3 same pump\$3	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:42

S197	29	S183 and (pressure source or purg\$3 or gas)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:44
S198	1	S183 and (pressure source or purg\$3 or gas) same (after) same (wash\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:50
S199	1	S183 and (pressure source or purg\$3 or gas) (wash\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:50
S200	6	S183 and (pressure source or purg\$3 or gas) same (wash\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:50
S201	0	S183 and (overfill\$3 or overflow\$3) same (syringe)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:52
S202	0	S183 and (overfill\$3 or overflow\$3) same (syringe or pipette or cannula)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:52
S203	1	S183 and (titrat\$3) and (rack or tray)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:55
S204	1	S183 and (cannula or pipette or conduit) same (fill\$3 with sample) same (mov\$3 or moveable)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:58
S205	1	S183 and (cannula or pipette or conduit) same (fill\$3) same (mov\$3 or moveable)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 18:59
S206	7	S183 and (cannula or pipette or conduit or pipe\$4) same (mov\$3 or moveable)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/27 19:00
S207	41	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$ or US-20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340-\$ or US-20090162942-\$ or US-20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$ or US-5817954-\$ or US-6653124-\$ or US-6387277-\$ or US-4610845-\$).did.	US-PGPUB; USPAT	ADJ	ON	2013/06/28 11:09
S208	10	S207 and (waste or drain) with (pump\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:09
S209	3	S207 and (fill port)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:39

S210	448	("422" or "435" or "436").clas. and calorimet\$5 and (syringe or needle or pipette) with (fill\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:47
S211	4	("422" or "435" or "436").clas. and calorimet\$5 and (syringe or pipette) with (fill\$3) same ((push\$3 or pull\$3) with (liquid or gas))	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:53
S212	29	("422" or "435" or "436").clas. and calorimet\$5 and (syringe or pipette) same ((push\$3 or pull\$3) with (liquid or gas))	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:55
S213	25	S212 not S211	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:55
S214	7	("422" or "435" or "436").clas. and calorimet\$5 and titrat\$4 and (syringe or pipette or tube) with fill\$3 with connect\$3	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 11:58
S215	18	("422" or "435" or "436").clas. and calorimet\$5 and titrat\$4 and (syringe or pipette or tube) with fill\$3 same (contact\$3 OR CONNECT\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 12:00
S216	18	S207 AND SYRINGE	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 12:06
S217	17	"422".clas. and (fill\$3 port) with connection	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/06/28 12:36
S218	6	S207 and (cannula or syringe or pipette or tube or conduit) with (moving or moveable)	US-PGPUB; USPAT	ADJ	ON	2013/06/28 13:38
S219	66	(titrat\$3 or calorimeter) and (cannula or syringe or pipette or tube or conduit) with (moving or moveable) and sample cell	US-PGPUB; USPAT	ADJ	ON	2013/06/28 13:46
S220	42	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$ or US-20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340-\$ or US-20090162942-\$ or US-20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729-\$ or US-20050265978-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$ or US-5817954-\$ or US-6653124-\$ or US-6387277-\$ or US-4610845-\$).did.	US-PGPUB; USPAT	ADJ	ON	2013/06/28 14:46
S221	3	S220 and fill port	US-PGPUB;	ADJ	ON	2013/06/28

			USPAT; EPO; JPO			14:46
S222	808	(titration) with (calorimetr\$3) and (automat\$3 or ITC control\$3 or system control\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/12/05 10:47
S223	43	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$ or US-20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340-\$ or US-20090162942-\$ or US-20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729-\$ or US-20050265978-\$).did. or (US-20030226857-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$ or US-5817954-\$ or US-6653124-\$ or US-6387277-\$ or US-4610845-\$).did.	US-PGPUB; USPAT	ADJ	ON	2013/12/05 10:47
S224	36	S223 and (ITC or system) with (control\$3 or automat\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/12/05 10:47
S225	737	(titration) near2 (calorimetr\$3) and (automat\$3 or ITC control\$3 or system control\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/12/05 11:34
S226	27	(titration) near2 (calorimetr\$3) same (automat\$3 or ITC control\$3 or system control\$3)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2013/12/05 11:34
S227	0	"12326300" and system control\$4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2014/10/28 17:41
S229	44	(US-20040063208-\$ or US-20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542-\$ or US-20020034210-\$ or US-20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994-\$ or US-20080003140-\$ or US-20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043-\$ or US-20070104245-\$ or US-20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340-\$ or US-20090162942-\$ or US-20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729-\$ or US-20050265978-\$).did. or (US-	US-PGPUB; USPAT	ADJ	ON	2014/10/30 16:39


		20030226857-\$ or US-20090275144-\$).did. or (US-5340541-\$ or US-4604363-\$ or US-7488106-\$ or US-7288229-\$ or US-6513969-\$ or US-6485173-\$ or US-5967659-\$ or US-5813763-\$ or US-6846455-\$ or US-7712956-\$ or US-4072050-\$ or US-7371006-\$ or US-5817954-\$ or US-6653124-\$ or US-6387277-\$ or US-4610845-\$).did.				
S230	2	S229 and (titrant) with (transmit\$4 or transfer\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2014/10/30 16:40
S231	4	S229 and (titrant)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2014/10/30 16:40
S232	1	"14033365"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2014/10/31 11:34
S233	1	((isothermal with calorimet\$4) and (sample and reference) cell) and ((syringe or pipette) with titrat\$4 needle) and cell prepar\$5 and (titrant with (well or tray or plate)) and (controller or control unit or computer or processor) and ((syringe or pipette) with (translat\$4 or mov\$4 or transfer\$4) with (fill\$3 and wash\$3 and titrat\$4))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/30 09:30
S234	1	((isothermal with calorimet\$4) and (sample and reference) cell) and ((syringe or pipette) with titrat\$4 with needle) and (replac\$3 with (liquid or fluid or titrant) with (sample cell)) and (titrant with (well or tray or plate)) and (controller or control unit or computer or processor) and ((syringe or pipette) with (translat\$4 or mov\$4 or transfer\$4) with (fill\$3 and wash\$3 and titrat\$4))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/30 09:32
S235	1	((calorimet\$4 same titrat\$4) and (sample and reference) cell) and ((syringe or pipette) with titrat\$4 with needle) and (replac\$3 with (liquid or fluid or titrant) with (sample cell)) and (titrant with (well or tray or plate)) and (controller or control unit or computer or processor) and ((syringe or pipette) with (translat\$4 or mov\$4 or transfer\$4) with (fill\$3 and wash\$3 and titrat\$4))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/30 09:32
S236	1	((calorimet\$4 same titrat\$4) and (sample and reference) cell) and ((syringe or pipette) with titrat\$4 with needle) and (replac\$3 with (liquid or fluid or titrant) with (sample cell)) and (titrant with (well or tray or plate)) and (controller or control unit or computer or processor) with (AUTOMAT\$3) and ((syringe or pipette) with (translat\$4 or mov\$4 or transfer\$4) with (fill\$3 and wash\$3 and	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/30 09:33

		titrat\$4))				
S237	1	((calorimet\$4 same titrat\$4) and (sample and reference) cell) and ((syringe or pipette) with titrat\$4 with needle) and (titrant with (well or tray or plate OR SOURCE)) and (controller or control unit or computer or processor) and ((syringe or pipette) with (translat\$4 or mov\$4 or transfer\$4) SAME (fill\$3 and wash\$3 and titrat\$4))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/01/30 09:34
S243	0	(micro calorimeter and (sample and reference) cell) and (pipete with titration needle) and (plunger) and (wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:44
S244	0	(micro calorimeter) and (sample and reference) near2 cell and (pipete with titration needle) and (plunger) and (wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:44
S245	0	(micro calorimet\$4) and (pipete with titration needle) and (plunger) and (wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:45
S246	0	(calorimet\$4) and (sample and reference)(cell) and (pipete with titration needle) and (plunger) and (wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:45
S247	0	(calorimet\$4) and (sample and reference)(cell) and (pipete with titration needle) and (plung\$4) and (wash\$4 and fill\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:45
S248	0	(calorimet\$4) and (sample and reference)(cell) and (pipete with titration needle) and (plung\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:45
S249	12	(calorimet\$4) and (sample and reference)(cell) and (pipette with titration needle) and (plung\$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2015/09/15 15:45
S250	12	(calorimet\$4) and (sample and reference)(cell) and (pipette and	US-PGPUB; USPAT;	ADJ	ON	2015/09/15 15:46

		titration needle) and (plung\$4)	USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB			
S251	9	("20030032171" "4259843" "4643879" "4681741" "5000921" "5096670" "5813763" "6395231" "6573088").PN. OR ("8449175").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/15 15:48
S252	10	("20020176803" "20030226857" "20040024542" "20040063208" "20090186374" "20100238968" "4604363" "5340541" "6387277" "7488106").PN. OR ("9103782").URPN.	US-PGPUB; USPAT; USOCR	ADJ	ON	2015/09/15 15:51
S253	44	(US-20040063208-\$ or US- 20020176803-\$ or US-20100238968-\$ or US-20070189920-\$ or US-20040024542- \$ or US-20020034210-\$ or US- 20010030987-\$ or US-20040213700-\$ or US-20050276724-\$ or US-20080240994- \$ or US-20080003140-\$ or US- 20080274551-\$ or US-20030039579-\$ or US-20060251145-\$ or US-20080204043- \$ or US-20070104245-\$ or US- 20090061522-\$ or US-20090227041-\$ or US-20090186374-\$ or US-20020086340- \$ or US-20090162942-\$ or US- 20040219062-\$ or US-20100285521-\$ or US-20060133968-\$ or US-20080069729- \$ or US-20050265978-\$).did. or (US- 20030226857-\$ or US-20090275144- \$).did. or (US-5340541-\$ or US- 4604363-\$ or US-7488106-\$ or US- 7288229-\$ or US-6513969-\$ or US- 6485173-\$ or US-5967659-\$ or US- 5813763-\$ or US-6846455-\$ or US- 7712956-\$ or US-4072050-\$ or US- 7371006-\$ or US-5817954-\$ or US- 6653124-\$ or US-6387277-\$ or US- 4610845-\$).did.	US-PGPUB; USPAT	ADJ	ON	2015/09/15 15:52
S254	25	S253 and (wash\$4)	US-PGPUB; USPAT; EPO; JPO	ADJ	ON	2015/09/15 15:52

9/ 15/ 2015 6:20:56 PM

C:\Users\jwecker\Documents\EAST\Workspaces\12326300.wsp

Search Notes 	Application/Control No. 14736905	Applicant(s)/Patent Under Reexamination BROGA ET AL.
	Examiner JENNIFER WECKER	Art Unit 1797

CPC- SEARCHED		
Symbol	Date	Examiner
searched (G01K17/006 OR G01N1/14 OR G01N25/20 OR G01N25/48 OR G01N25/4813 OR G01N25/4866).CPC.	9/15/2015	/JW/

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
east text search in (G01K17/006 OR G01N1/14 OR G01N25/20 OR G01N25/48 OR G01N25/4813 OR G01N25/4866).CPC.	9/15/2015	/JW/
performed inventor and assignee name search	9/15/2015	/JW/
updated EAST text search for 12/326,3000	9/15/2015	/JW/

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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Dated: September 17, 2015

Electronic Signature for Monica Freeman: /Monica J. Freeman/

Docket No.: 739712000201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: J. Wecker

THIRD PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Prior to examination on the merits, Applicants respectfully request entry of this Preliminary Amendment for the above-captioned patent application.

Amendments to the Claims begin on page 2.

Remarks begin on page 6.

va-458351

AMENDMENTS TO THE CLAIMS

1-18. (Canceled)

19. (New) An automated system comprising:

an isothermal titration calorimetry (ITC) system, and

a controller configured to cause the ITC system to:

supply titrant from a titration needle to a first sample in a sample cell,

refill the titrant,

wash at least a portion of the titration needle,

replace the first sample in the sample cell with a second sample, and

supply titrant from the titration needle to the second sample in the sample cell.

20. (New) An automated isothermal titration calorimetry (ITC) method comprising:

supplying titrant from a titration needle to a first sample in a sample cell,

refilling the titrant,

washing at least a portion of the titration needle,

replacing the first sample in the sample cell with a second sample, and

supplying titrant from the titration needle to the second sample in the sample cell.

21. (New) An automated device comprising:

a calorimeter comprising a sample cell,

an automated pipette translation unit that places at least a portion of a titration needle in the sample cell for supplying titrant for titration and places at least a portion of the titration needle in a wash station for washing the titration needle or refilling the titrant, and

a cell preparation unit that replaces a sample in the sample cell.

22. (New) An automated isothermal titration micro calorimetry system comprising:

a micro calorimeter comprising a sample cell and a reference cell,

a pipette comprising a titration needle,

an automated pipette translation unit that places the pipette in a titration position at which the titration needle is inserted in the sample cell, that places the pipette in a washing position at which the titration needle is washed, and that places the pipette in a titrant filling position at which the titration needle is filled with titrant,

a cell preparation unit that enables replacement of liquid in the sample cell when the pipette is not in the titration position, and

a controller that controls automated operation of at least the automated pipette translation unit.

23. (New) An automated micro titration calorimetry system comprising:

an automated pipette assembly that supplies titrant to a sample cell, the automated pipette assembly comprising a titration needle configured to be inserted in the sample cell,

a pipette washing position wherein the titration needle is inserted in a washing apparatus, and

a titration position wherein the titration needle is inserted into the sample cell and calorimetric measurements are performed, and

a pipette guiding mechanism that guides the automated pipette assembly to the titration position and to the pipette washing position.

24. (New) An automated micro titration calorimetry system comprising:

an automated pipette assembly that supplies titrant to a sample cell, the automated pipette assembly comprising a titration needle configured to be inserted in the sample cell, and

a pipette guiding mechanism that moves the automated pipette assembly between multiple operation positions along safe paths that reduce a risk of damage to the titration needle during movement of the automated pipette assembly.

25. (New) The automated system of claim 19 wherein the first sample in the sample cell is replaced with a second sample and at least a portion of the titration needle is washed or the titrant is refilled at the same time.

26. (New) The automated system of claim 20 wherein the first sample in the sample cell is replaced with a second sample and at least a portion of the titration needle is washed or the titrant is refilled at the same time.

27. (New) The automated device of claim 21 wherein the cell preparation unit replaces the sample in the sample cell while the automated pipette translation unit concurrently places at least a portion of the titration needle in the wash station.

28. (New) The automated system of claim 22 wherein the washing position and the titrant filling position at least partially coincide.

29. (New) The automated device of claim 21 wherein the automated pipette translation unit comprises a pipette arm configured to rotate and enable movement of the titration needle to the sample cell and to the wash station.

30. (New) The automated device of claim 22 wherein the automated pipette translation unit comprises a pipette arm configured to rotate and enable movement of the titration needle to the titration position and to the washing position.

31. (New) The automated device of claim 21 comprising a well in a sample tray from which the titrant is supplied.

32. (New) The automated device of claim 21 comprising a titrant transfer unit comprising a cannula arranged to deliver titrant from a well in a sample tray.

33. (New) The automated device of claim 21 comprising a syringe and a source of material used to purge at least one of the syringe and the titration needle.

34. (New) The automated device of claim 21 comprising a syringe, wherein the wash station is configured to purge at least one of the syringe and the titration needle with a purge gas.

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35. (New) The automated device of claim 21, wherein the cell preparation unit comprises a moveable cannula configured for insertion into the sample cell.

36. (New) An automated isothermal titration micro calorimetry system comprising:

a micro calorimeter comprising a sample cell and a reference cell,

a pipette comprising a titration needle,

an automated pipette translation unit that places the pipette in a titration position at which the titration needle is inserted in the sample cell, and that places the pipette in a washing position at which the titration needle is washed,

a titrant transfer unit that enables titrant to be transferred from a titrant source to a position from which the pipette is supplied with titrant,

a cell preparation unit that enables replacement of liquid in the sample cell when the pipette is not in the titration position, and

a controller that controls automated operation of at least the automated pipette translation unit.

37. (New) The automated system of claim 36 comprising a fill position, where the position from which the pipette is supplied with titrant comprises at least one of the washing position and the fill position.

38. (New) The automated device of claim 36, wherein the cell preparation unit comprises a moveable cannula configured for insertion into the sample cell.

39. (New) The automated system of claim 33, wherein the syringe comprises a fill port and the automated system comprises a fill port connection unit arranged to selectively connect to the fill port and selectively pull or push liquid or gas through the syringe.

REMARKS

Applicants have canceled claims 1-18 and added new claims 19-39. No new matter has been added.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no.

739712000201. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 17, 2015

Respectfully submitted,

Electronic signature: /Alex Chartove/
Alex Chartove

Registration No.: 31,942
MORRISON & FOERSTER LLP
1650 Tysons Blvd, Suite 400
McLean, Virginia 22102
(703) 760-7744

va-458351

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	Jennifer Wecker
Sheet	1	of	2	Attorney Docket Number	739712000201

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	1.	US-4,604,363	08-05-1986	Newhouse et al.	
	2.	US-5,340,541	08-23-1994	Jackson et al.	
	3.	US-5,813,763	09-29-1998	Plotnikov et al.	
	4.	US-6,387,277	05-14-2002	North, Jr.	
	5.	US-2002/0176803	11-28-2002	Hamel et al.	
	6.	US-2003/0226857	12-11-2003	Bibbo et al.	
	7.	US-2004/0024542	02-05-2004	Plotnikov et al.	
	8.	US-2004/0063208	04-01-2004	Chandler, Jr.	
	9.	US-7,488,106	02-10-2009	Brushwyler	
	10.	US-2009/0186374	07-23-2009	Okun et al.	
	11.	US-2010/0238968	09-23-2010	Plotnikov et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
	12.	WO-81/01045	04-16-1981	CROMEMCO Inc. (Marvin L. KAUSCH)		
	13.	WO-87/00086	01-15-1987	American Hospital Supply Corporation (Richard W. HANAWAY)		
	14.	WO-2009/059110	05-07-2009	GE Healthcare Bio-Sciences Corp.; MicroCal LLC (Valerian V. PLOTNIKOV et al.)		

Examiner Signature		Date Considered	
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*EXAMINER: Initial if information considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	14/736,905
				Filing Date	June 11, 2015
				First Named Inventor	Martin BROGA
				Art Unit	1797
				Examiner Name	Jennifer Wecker
Sheet	2	of	2	Attorney Docket Number	739712000201

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²	
	15.	Cooper, A. et al. (1994). "Isothermal Titration Microcalorimetry," located at <http://www.chem.gla.ac.uk/staff/alanc/MMB-ITC-1994.pdf> retrieved on January 15, 2010. (14 pages).		
	16.	Doyle, M. L. (1999). "Titration Microcalorimetry in Current Protocols in Protein Science, Supplement 18," located at <http://www.nshvtn.org/ebook/molbio/Current%20Protocols/CPPS/ps2004.pdf> retrieved on January 15, 2010.		
	17.	International Search Report and Written Opinion mailed February 9, 2009, directed to International Application No. PCT/US2008/081961; 6 pages.		
	18.	MicroCal, LLC. (1995). "Autosampler for AutoITC User's Manual," <i>Ultrasensitive Calorimetry for the Life Science</i> , MAU190040; 74 pages.		
	19.	Broga et al., Office Action dated November 15, 2010, directed to U.S. Application No. 12/326,300; 18 pages.		
	20.	Broga et al., Office Action dated June 21, 2011, directed to U.S. Application No. 12/326,300; 20 pages.		
	21.	Broga et al., Office Action dated July 15, 2013, directed to U.S. Application No. 12/326,300; 19 pages.		
	22.	Broga et al., Office Action dated December 16, 2013, directed to U.S. Application No. 12/326,300; 22 pages.		
	23.	Broga et al., Office Action dated November 10, 2014, directed to U.S. Application No. 12/326,300; 22 pages.		

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Dated: September 17, 2015

Electronic Signature for Monica Freeman: /Monica J. Freeman/

Patent
Docket No. 739712000201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1797

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: Jennifer Wecker

**INFORMATION DISCLOSURE
STATEMENT UNDER 37 C.F.R. § 1.97 & § 1.98**

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.97 and § 1.98, Applicants submit for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a/b. Copies of foreign documents and non-patent literature (cite nos. 12, 13, 14, and 17) are submitted herewith. However, copies of the remaining documents were previously submitted in an Information Disclosure Statement and/or Office Action, directed to the related U.S. Patent Application Number 12/326,300, filed December 2, 2008, and, accordingly, copies are not included herewith. This protocol conforms with 37 C.F.R. § 1.98(d) and M.P.E.P. 609.02(A)(2). The Examiner is requested to make these documents of record in the application.

va-454851

This Information Disclosure Statement is submitted within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required.

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

The information contained in this Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal form is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing (739712000201). However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 17, 2015

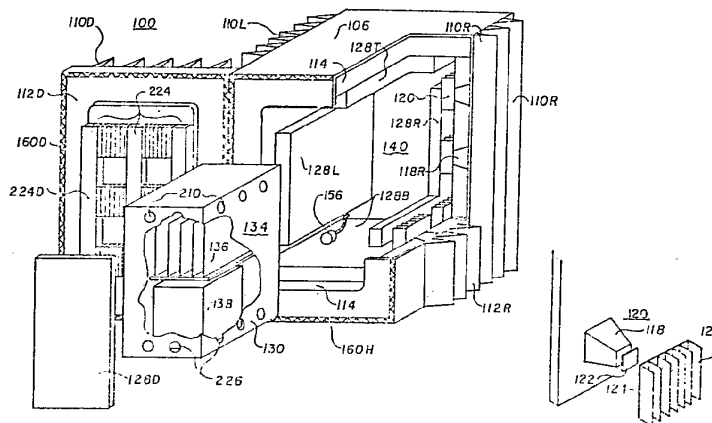
Respectfully submitted,

Electronic signature: /Alex Chartove/
Alex Chartove
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McLean, Virginia 22102
(703) 760-7744



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ³: F25B 27/00	A1	(11) International Publication Number: WO 81/01045 (43) International Publication Date: 16 April 1981 (16.04.81)
(21) International Application Number: PCT/US80/01322 (22) International Filing Date: 9 October 1980 (09.10.80) (31) Priority Application Number: 082,965 (32) Priority Date: 9 October 1979 (09.10.79) (33) Priority Country: US (71) Applicant: CROMEMCO INC. [US/US]; 280 Bernardo Avenue, Mountain View, CA 94043 (US). (72) Inventor: KAUSCH, Marvin, L.; 2970 Wexford Drive, San Jose, CA 94132 (US). (74) Agent: HENTZEL, Paul, M.; 441 Nevada Avenue, Palo Alto, CA 94301 (US).		(81) Designated States: AU, DE, GB, JP, NO, RO. Published <i>With international search report Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments</i>

(54) Title: AN ISOLATION CHAMBER FOR ELECTRONIC DEVICES**(57) Abstract**

The isolation chamber (100) has an aluminum outer housing (106) with heat transfer fins (110L, 110D, 110R) extending therefrom on the outside vertical surfaces, and insulation material (114) mounted along each inside surface thereof forming a thermally insulative shell. Large aluminum studs (118L, 118R, 118D) extend inwardly from the side surfaces of the housing through the insulative shell for supporting a solid state heat pump (122). Each pump has a set of inwardly directed heat exchange fins (126). Each stud and associated pump and inwardly directed set of fins forms a heat conductive path between the surrounding ambient air and the interior of the isolation chamber for controlling the heat flow therebetween. The combined configuration of the inner heat exchange fins defines a central cavity (140) which is temperature controlled to within a desired operating temperature range. A card cage (130) containing the electronic devices is installed in the temperature regulated central region. The atmosphere within the central region is isolated from the surrounding ambient air, and supports internal convective heat transfer between the electronic devices and the inner fins by recirculating throughout the card cage and between the inner heat transfer fins. The operating level of the heat pumps are adjustable to provide the most efficient pumping as the external temperature varies. The outer housing and card cage form a double walled electrically conductive structure which twice encloses the electronic devices for providing double shielding from electrical interference. The card cage is cushioned from external vibration by the absorption effect of the insulative shell material.

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-1-

1 AN ISOLATION CHAMBER FOR ELECTRONIC DEVICES
 TECHNICAL FIELD

 This invention relates to isolation chambers which
 provide an operating environment for electronic devices,
5 and more particularly to such isolation chambers which
 regulate internal temperature without external convective
 heat transfer.

BACKGROUND ART

 Heretofore, convection cooled isolation chambers and
10 the like employed a cooling flow of external ambient air
 across the heat generating components within the chamber.
 The external air frequently contained foreign matter such
 as dust and other undesirable substances which were
 distributed throughout the chamber by the air flow, causing
15 malfunctions of precision devices therein such as read-
 write heads.

 The conventional isolation chamber systems which did
 not employ air flow cooling required an alternative
 form of cooling such as mechanical refrigeration. The
20 compressor motors in these units generated undesirable
 electrical and acoustical noise. Further, the failure of
 a single element of the refrigerator system caused the
 entire system to fail. Standby refrigeration could not be
 provided by operational redundancy in the system design
25 without creating an entire parallel cooling system.



-2-

1 DISCLOSURE OF THE INVENTION

It is therefore an object of this invention to provide an isolation chamber which does not require a convective flow of external air to supply heat to or
5 remove heat from an electrical device therein.

It is a further object of this invention to provide an isolation chamber which maintains internal "clean" standards during the installation period.

It is another object of this invention to provide
10 an isolation chamber having heat pumps arranged in a functionally redundant design for standby operation.

It is an additional object of this invention to provide an isolation chamber with heat pumps having a variable level of operation.

15 It is yet another object of this invention to provide an isolation chamber with improved electrical shielding for operating sensitive electrical equipment therein.

It is still another object of this invention to
20 provide an isolation chamber which absorbs external vibrations for preventing the displacement of delicate electrical equipment therein.

It is yet a further object of this invention to provide an isolation chamber which does not generate
25 internal electrical or acoustical noise.

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1 BASIC DESCRIPTION OF THE DRAWING

Further objects and advantages of the isolation chamber will become apparent to those skilled in the art from the following detailed description taken in conjunction with the drawing, in which:

Figure 1A is an isometric, broken away view of the isolation chamber showing the card cage partially inserted;

Figure 1B is a fragmentary, exploded view of a heat transfer module showing the Peltier heat pump;

Figure 2A is a sectional side view of an isolation chamber showing the internal convection currents during cooling;

Figure 2B is a sectional side view of an isolation chamber showing the internal convection currents during heating;

Figure 2C is a sectional top view of a dual mode isolation chamber showing a heat responsive switch for reversing the energizing voltage applied to the heat pumps;

Figure 3 is an isometric view of the back of an isolation chamber showing the interface and power supply housing; and

Figure 4 is a fragmentary isometric view showing a modified card cage central region.

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1 DETAILED DESCRIPTION

General Structure

Isolation chamber 100, shown in Figures 1 and 2, is formed by outer shell or housing 106 having outer heat transfer fins 110L, 110R, and 110D extending from left side 112L, right side 112R, and access door 112D respectively. A thermally insulative layer 114 is mounted immediately inside outer shell 106 along each surface thereof for preventing uncontrolled heat transfer between isolation chamber 100 and the surrounding external environment. An array of six thermally conductive stand-offs or studs 118L, 118R, and 118D extend inwardly from each of sides 112L, 112R, and 112D respectively through insulative layer 114 for supporting a bank of six heat transfer modules 120L, 120R, and 120D. Each heat exchange module 120 (see Figure 1B) is formed by a heat pump 122 in thermal contact with the end of the stud, a backplate 124 in thermal contact with the heat pump 122, and a vertical array of spaced inner heat transfer fins 126 in thermal contact with the backplate 124 and the atmosphere within the interior of isolation chamber 100. The six modules 120 within each bank are coplanarly positioned. A set of inner insulative sheets 128L, 128R, and 128D cover the fin side of each bank of modules 120 forming a series of adjacent vertical ducts each bounded by a backplate 124 on one side, two spaced fins 126 on opposed sides adjacent to backplate 124, and inner insulative sheet 128 on the remaining side.

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1 Additional inner insulative sheets 128T and 128B may be
provided along the top and bottom of isolation chamber
100. An inner housing or card cage 130 contains a com-
puter 134 including circuit boards 136 and disc drives 138
5 is inserted into a central cavity 140 defined by insulative
sheets 128. Heat pumps 122 are serially mounted in the
heat path between studs 118 and backplates 124 for moving
heat between inner fins 126 and outer fins 110. Insulative
shell 114 and insulative sheets 128 minimize heat leakage
10 outside the heat conductive paths. Heat modules are as-
sembled and secured to the end of studs 118 by a suitable
thermally conductive bonding agent. Alternatively, small
bolts extending from backplate 124 to stud 118 may be em-
ployed to secure heat pump 122 in place. Heat leakage
15 around heat pump 122 may be minimized by used small dia-
meter bolts with insulative washers, or bolts formed of an
insulative material.

A separate rear housing 150 (see Figure 3) is provided
to contain the computer interface circuitry and the power
20 supply for computer 134 and heat pumps 122. Rear housing
is not temperature regulated, and is environmentally iso-
lated from chamber 100 by back wall 112B of housing 106 and
insulative shell 114. Power-data cable 156 passes through
back wall 112B via a sealed port 158.

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1 Cooling Cycle

5 The preferred operating temperature of conventional integrated circuit component 136 and disc drive 138 is from about 10 degrees C to about 51 degrees C. In external environments having an ambient temperature varying from warm to cool, heat generated within card cage 130 by computer 134 must be removed as shown in Figure 2A. The atmosphere within card cage 130 absorbs heat from computer 134 and expands causing an upward convection flow layer.

10 The warm atmosphere spreads laterally and flows out through upper ports 210 into distribution passage 214 and enters the upper portion 218 of inner fins 126, which absorb heat from the atmosphere causing a slight contraction thereof. The cooling atmosphere develops a downward convection

15 flow through the heat transfer ducts of modules 120, causing the cooling atmosphere to descend into lower distribution passage 220. The vertical space between adjacent columns of modules is filled by insulative columns 224L, 224R, and 224D. The cool atmosphere returns to card

20 cage 130 through lower ports 226 and is reheated by computer 134. The heat sensitive disc drive 138 is mounted in the lower portion of card cage 130 in order to receive the maximum benefit of the cool atmosphere flow from lower ports 226. Circuit boards 136 are less sensitive to the

25 temperature within card cage 130, and are therefore mounted in the upper portion and receive the flow of cool atmosphere after disc drive 138. Heat pumps 122 move the heat from

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1 backplate 124 to studs 118, where the heat conducts to
outer fins 110 and is dissipated into the surrounding
external environment which may have an ambient temper-
ature greater than the operating temperature within
5 card cage 130.

Warming Cycle

In colder external environments, heat must be added
to card cage 130 in order to maintain the preferred
operating temperature for disc drive 138 and circuit boards
10 136, as shown in Figure 2B. Heat from the external en-
vironment is absorbed by outer fins 110 and transferred
to inner fins 126 via heat pump 122. The atmosphere
within the ducts of heat transfer modules 120 absorb the
heat and move upwards due to expansion. The upwards con-
15 vention causes the warm atmosphere to enter upper distri-
bution passage 214 and pass into card cage 130 via upper
ports 210. Heat from the warm atmosphere is transferred
to disc drive 138 and circuit boards 136, causing the
atmosphere to contract and move downward into lower dis-
20 tribution passage 220 via lower ports 226. In cold climate
applications, disc drive 138 is mounted in the upper por-
tion of card cage 130 in order to receive the immediate
benefit of the warm atmosphere flow. Circuits 136 occupies
a secondary position in the lower portion of card cage 130.
25 The Figure 2 embodiments employ a warming upward
convection flow and a cooling downward convection flow for
circulating the atmosphere within cavity 140 of isolation

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1 chamber 100. The thermal transfer efficiency of the
cooling and heating cycles may be increased by forcing
the internal atmosphere to flow with a suitable circula-
tion device such as fan 230C. A reserve fan 230R may be
5 employed to provide circulation in the event of fan 230C
malfunction. The copper losses of the windings of fans
230 add to the heat load generated within card cage 130,
and must be removed by heat pumps 122 along with the heat
generated by computer 134. This copper loss heat load may
10 be minimized by employing a forced circulation flow in a
cooperating direction with the natural convection flow
described in connection with Figures 2A and 2B. The heat
loss may be further minimized by staggering the duty cycles
of fans 230C and 230R. The copper losses thus generated
15 are the same as if a single fan were employed, yet two
fans are present to provide functional redundancy. Pre-
ferably the fans have a minimum blade - maximum port arco-
dynamic profile for minimizing "feather drag" while off.

The thermal transfer efficiency within cavity 140
20 may be further increased by employing an atmosphere having
a higher specific heat and a larger coefficient of thermal
expansion.

Heat Pump 122

The heat pump may be any suitable thermo-electric
25 valve such as a Peltier device. Peltier heat pump 122 is
a thin ceramic solid state unit, which when activated by
a dc voltage, permits heat to flow unilaterally thereacross
in the direction of the electric field. When deactivated,
Peltier heat pump 122 assumes a partial insulative state
30 which inhibits the return flow of heat back through the
pump. The direction of the unilateral heat flow may be

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1 reversed by reversing the polarity of the applied voltage.
Consequently, the cooling cycle employed during warm per-
iods such as late morning and early afternoon to remove
heat card cage 130, may be reversed during cold periods
5 such as late evening and early morning to supply heat to
card cage 130. Figure 2C shows a thermally responsive
controller 240 mounted proximate card cage 130 for control-
ling the duty cycle of heat pumps 122 in response to var-
iations in the heat generation rate of computer 134 and to
10 variations in the temperature of the surrounding environ-
ment. Thermal controller 240 may also reverse the polarity
of the voltage leads 242A and 242B from dc source 246 as
applied to Peltier heat pumps 122 in response to daily or
seasonal cold-warm patterns. If desired, thermal controller
15 240 may be mounted within card cage 130 or form an element
of computer 134.

The operation of Peltier heat pump 122 requires a
current flow therethrough which generates resistive heat
losses. This resistive heat must be removed from isolation
20 chamber 100 along with the load heat generated within card
cage 130. The resistive heat losses within each heat pump
122 are a function of the square of the current therethrough,
and may be minimized by operating the pumps almost continu-
ously at the lowest current level permitted by the heat
25 load. The long on-short off duty cycle also minimizes the
off period during which heat may leak back through the
moderately conductive ceramic material of the heat pump.

In warm climate applications requiring cooling of

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1 card cage 130, the resistive heat may be more readily
dissipated by outer fins 110, if heat pump 122 is mounted
on the outer end of stud 118 as shown in Figure 2A. In
cold climate applications requiring heating of card cage
5 130, the resistive heat may be pumped into card cage 130
along with the heat taken from the surrounding air via
outer fins 110. The resistive heat will be more effective
as a heat source for card cage 130 if heat pump 122 is
mounted on the inner end of stud 118 as shown in Figure 2B.
10 Additional internal heat sources such as heating elements
250 may be employed within cavity 140 as shown in Figure
2C. Placement of heat pumps 122 in the middle of stud 118
is suitable for cooling-heating applications.

Interface and Power Supply

15 Rear housing 150, shown in Figure 3, contains ferro-
resonant power supply 310 for providing power to computer
134, heat pumps 122, and fans 230. Rear housing 150 also
contains I/O modules 316 and relays 318 for interfacing
with conventional I/O devices and process control appar-
20 atus. Terminal strip 320 provides connection for cable 156
which extends through back side wall 112B between rear
housing 150 and the isolation chamber housing 106 for
power distribution and data flow therebetween (see Figure 1).
Rear housing 150 is environmentally separate from isolation
25 chamber 100, and does not require temperature regulation.
The heat generated by power supply 310 is independently
dissipated through rear housing hatch 330, and does not
contribute to the heat load which must be removed from

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1 isolation chamber 100. Foreign matter entering rear
housing 150 during interface procedures can not enter
isolation chamber 100 to contaminate disc drive 138.

Functionally Redundant Design

5 Heat pumps 122 are arranged in three banks of six
modules each to provide functional redundancy. Each
bank may be failure isolated from the other banks by a
suitable fuse device. If a module 120 in any of the
banks fails in short or open mode, the other two banks
10 continue to provide temperature regulation at two-thirds
capacity. The modules may be arranged in six banks of
three, or nine banks of two, or individually isolated by
fuse 260 as shown in Figure 2C, in accordance with the
redundancy factor required. Each module 120 is a separ-
15 ate and complete heat transfer unit which may be operated
or deactivated independently of the other modules, in
contrast with prior art mechanical type refrigeration
system which is not functionally redundant and must be
controlled as a single unit.

20 Modules 120 may be arranged in progressively acti-
vated mixed banks in which each bank has modules on more
than one side. At low heat transfer requirements, only
one bank of modules is required to be activated. The
current to the activated bank may be optimized to provide
25 the most efficient heat transfer. At higher heat transfer
requirements, additional banks of modules may be activated
as required to maintain temperature regulation at the
optimum current through heat pumps 122.

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1 Double Shielding

Computer 134 is surrounded by two electrically conductive enclosures, an outer enclosure housing 106, and an inner enclosure card cage 130; which form a double electrostatic shield against radio-frequency interference and high frequency transients. In addition, the periphery of housing door 112D is provided with conductive rfi gasket tape 160D and the door frame on housing 106 is provided with a cooperating conductive rfi gasket tape 160H which engages tape 160D to create an electrostatic seal around the door 112D-housing 106 interface.

The above shielding provisions isolate chamber 100 from nearby data transmissions, motor and generator noise, jamming etc. associated with industrial applications. Computer 134 is also protected against electrical disturbances generated by electrical storms, the electrolytic bath affect of salt water waves in an electrically active environment, and other static discharges and transient voltage spikes inherent in field conditions.

20 Vibration Isolation

Disc drive 138 within card cage 130 is mechanically isolated from machine vibration, wind motion, and other physical disturbances, by a cushion nest completely surrounding card cage 130. The cushion on the left, right, and door sides of card cage 130 is formed by inner insulative sheets 128L, 128R and 128D. The cushion on the back side of card cage 130 is formed by the back portion of insulative shell 114. A double cushion is formed along

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1 the top and bottom surfaces of card cage 130 by the
top and bottom portions of insulative shell 114 in com-
bination with upper and lower insulative sheets 128T
and 128B. The insulative material is resilient and
5 absorbs vibration energy to create the cushion effect.
The cushion reduces read and write errors generated by
spurious acceleration of read-write head in disc drive
138. Without the cushion nest, external vibrations
would be transmitted through the structure of isolation
10 chamber 100 to the read-write head.

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1 150 WATT EMBODIMENT

The dimensions and circuit parameters for an isolation chamber having a 150 watt heat generation load (computer plus disc drive) and an operating range of between 10

5 degrees C and 51 degrees C are:

outer shell 106: 24.5" (62.23cm) high, 16.75" (42.54cm) wide, 30" (76.2cm) deep; with 82 heat transfer fins 1.25" (3.175cm) deep spaced along the left, right, and door sides .56" (1.42cm) apart.

10 insulative shell 114: 2" (5.08cm) of closed polyurethane foam.

Peltier heat pumps 122: three parallel connected banks of six parallel connected heat pumps mounted on left, right, and door sides, each heat pump having a heat
15 transfer area of 2.89 square inches (18.6 cm²) on each side, and a power consumption of 8.88 amps at 2.52 volts per heat pump.

• backplate 124: 3" (7.62cm) high, 4" (10.16cm) wide with 40 vertical fins 1" (2.54cm) deep.

20 insulation sheets 128: .5" (1.27cm) thick of closed cell polyurethane foam.

card cage 130: 11.5" (44.45cm) high, 6 3/8" (16.2cm) wide, and 9.75" (24.76cm) deep.

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1 CONCLUSION

It will be apparent to those skilled in the art that the objects of this invention have been achieved by providing a series of independent solid state heat pumps
5 around a central cavity for regulating the temperature therein. The heat pumps are connected in banks to provide for standby cooling capability in the event of a malfunction of an individual heat pump in one of the banks. The electronic device within the isolation chamber is
10 doubly enclosed in electrical conductive and thermal insulative material to reduce external electrical interference and to minimize heat leakage transfer.

Additional changes and modifications may be made in the disclosed embodiments without departing from the
15 scope of the invention. For example, as shown in Figure 4, the fans 410C and 410R may be mounted above and below the housing 430, without forming part of the housing itself. Spacer pads 428F and 428R in front of and behind fans 410 are formed of resilient, insulative material for supporting the cushioning effect of outer insulative
20 shell 114. The inner insulative sheets 128F, 128R, and 128D have been eliminated to provide a direct heat transfer path between the outer surface of housing 430 and the internal atmosphere and the inner heat exchange fins 426. Housing
25 430 has a separate upper compartment 430U for the circuit boards., and another separate compartment 430L for the disc drives. These compartments 430U and 430L may be removed and inserted independently. Therefore, the scope of the invention is to be determined by the terminology
30 of the following claims and the legal equivalents thereof.

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I claim as my invention:

1. An isolation chamber for providing a controlled environment for an electronic device, comprising:

a rigid outer support shell formed of thermally conductive material with outer heat exchange means exposed to the external environment;

a plurality of inner heat exchange means positioned inside the isolation chamber defining a temperature controlled central region for receiving the electronic device;

thermal insulation means positioned inside the isolation chamber between the outer support shell and the inner heat exchange means;

a plurality of thermally conductive standoff means extending from the outer shell through the insulation means to the plurality of inner heat exchange means forming a plurality of heat conductive paths therebetween;

a plurality of heat pump means, one positioned in each of the plurality of heat paths for controlling the temperature of the central region by supporting heat flow along the conductive paths when energized and inhibiting heat flow along the conductive paths when not energized;

an internal atmosphere within the central region for supporting convection heat currents which transfer heat between the electronic device and the inner heat exchange means;

circulation means within the central region for moving the internal atmosphere therein; and

power means for providing electric power to the electronic device and to the heat pumps.



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2. The isolation chamber of claim 1, wherein the heat pumps are solid state devices.

3. The isolation chamber of claim 2, further comprising a thermal controller responsive to the temperature within the isolation chamber for controlling the operation of the solid state heat pumps.

4. The isolation chamber of claim 3, wherein the thermal controller controls the duty cycle of the solid state heat pumps to regulate the temperature within the central region.

5. The isolation chamber of claim 3, wherein the pumping level of the solid state heat pumps is variable as a function of the power applied thereto.

6. The isolation chamber of claim 5, wherein the thermal controller controls the power applied to the solid state heat pumps to determine the pumping level thereof and regulate the temperature within the central region.

7. The isolation chamber of claim 6, wherein the thermal controller minimizes the power applied to the heat pumps in response to the temperature within the isolation chamber to operate the solid state heat pumps at the lowest pumping level and longest on time permitted by the thermal requirements of the isolation chamber.

8. The isolation chamber of claim 1, wherein the heat pumps are connected to the power means in banks of at least one.

9. The isolation chamber of claim 8, wherein each bank of pumps is separately fused to the power means.



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10. The isolation chamber of claim 1, further comprising an inner housing shell enclosing the central region for housing the electronic device.

11. The isolation chamber of claim 10, wherein the inner housing shell is removable from the central region for housing the electronic device when the electronic device is removed from the isolation chamber.

12. The isolation chamber of claim 10, further comprising a layer of resilient material positioned between the inner heat exchange means and the inner housing shell.

13. The isolation chamber of claim 12, wherein the resilient material is compressed outwardly by the insertion of the inner housing shell into the central region for securely retaining the inner housing shell and the electronic device therein,

14. The isolation chamber of claim 10, wherein the outer support shell is made of an electrically conductive material and is connected to a reference potential means for shielding the interior of the isolation chamber from external electro-magnetic radiations.

15. The isolation chamber of claim 14, wherein the inner housing shell is made of an electrically conductive material and is connected to a reference potential means for shielding the interior of the central region from electro-magnetic radiations.

16. The isolation chamber of claim 15, wherein the outer support shell and the inner housing shell are connected to a common reference potential.



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17. The isolation chamber of claim 16, wherein the common reference potential is the ground potential of the surrounding environment.

18. The isolation chamber of claim 1, wherein;
the circulation means is the expansion and upwards motion of the internal atmosphere as it absorbs heat from that portion of the surrounding structure which is warmer than the internal atmosphere, and the contraction and downwards motion of the internal atmosphere as it releases heat to that portion of the surrounding structure which is cooler than the internal atmosphere; and

the circulation means causes the internal atmosphere to move vertically through the electronic device in one direction and then vertically through the inner heat exchange means in the other direction and then return to the electronic device.

19. The isolation chamber of claim 18, wherein the the circulation means additionally comprises a fan means for supporting the motion of the internal atmosphere vertically through the electronic device in the one direction and vertically through the inner heat exchange means in the other direction.

20. The isolation chamber of claim 1, wherein the circulation means is a rotary fan means for causing the internal atmosphere to circulate between the electronic device and the inner heat exchange means.

21. The isolation chamber of claim 20, wherein the fan means is a first and second fan having staggered duty cycles for alternately causing the internal atmosphere to circulate.



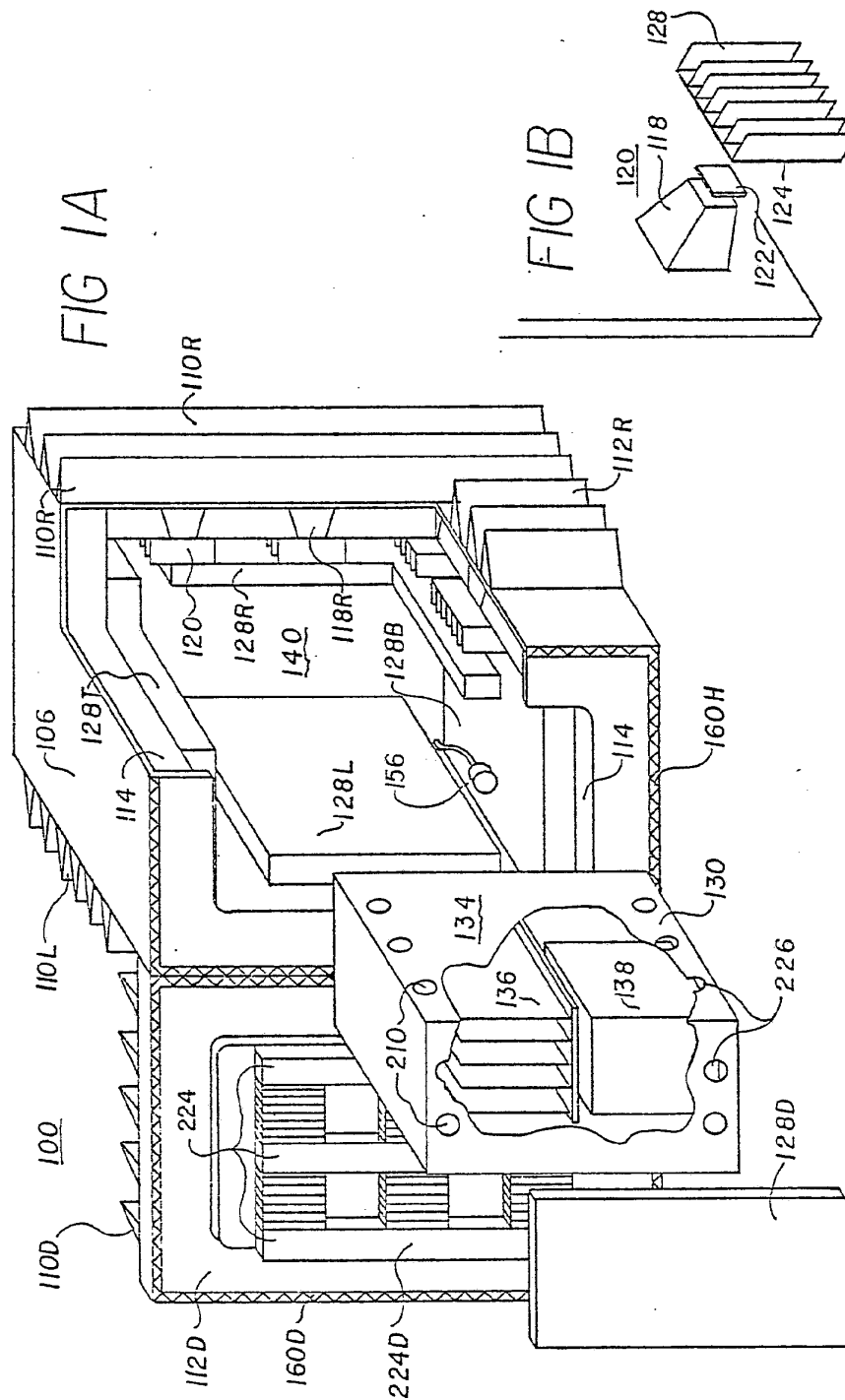


FIG 2B

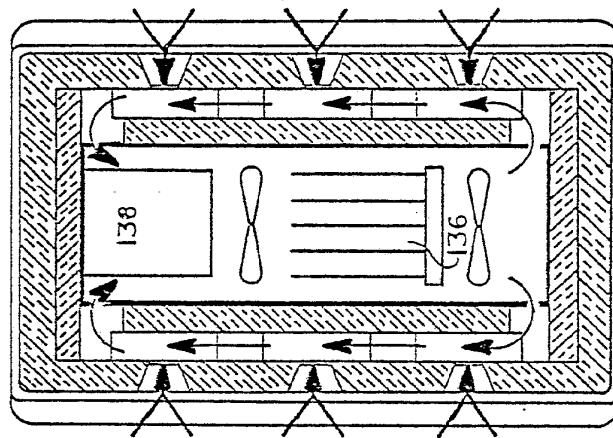


FIG 2A

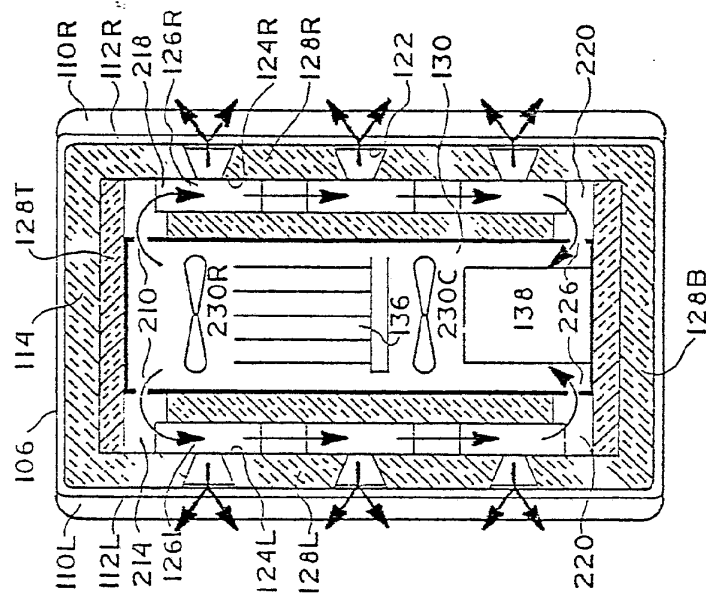


FIG 3

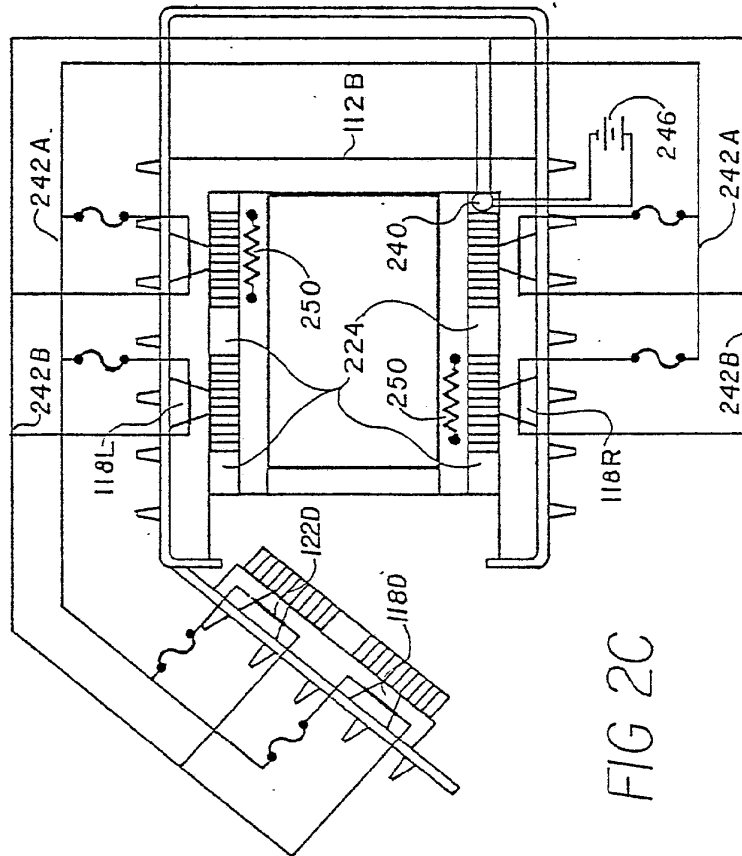
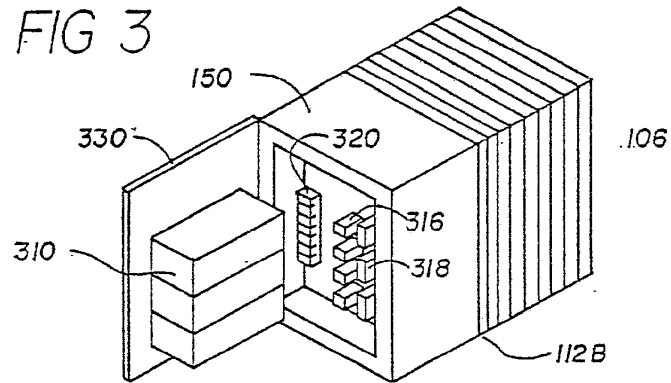
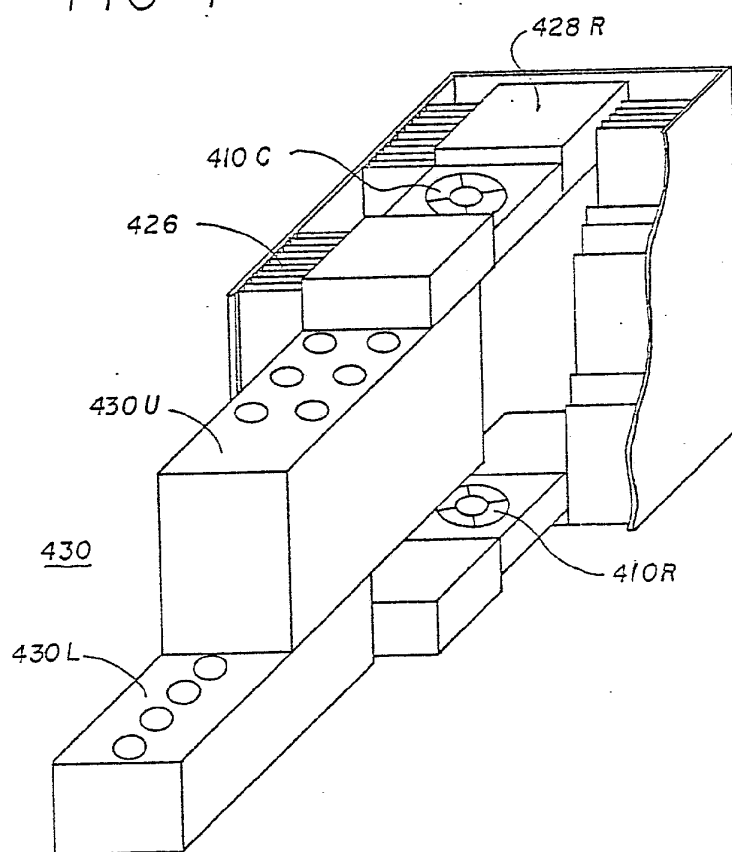


FIG 2C

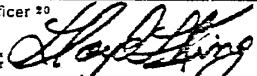


FIG 4



INTERNATIONAL SEARCH REPORT

International Application No PCT/US80/01322

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
INTL C. 3 F25B 27/00 U.S. CL. 62/3		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	62/3	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 14		
Category *	Citation of Document, 15 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No. 18
X	US,A, 3,168,816 Published 9 February 1965 PETRIE	1-21
X	US,A, 3,234,595 Published 15 February 1966 WEICHSELBAUM ET AL	1-21
X	US,A, 3,733,836 Published 22 May 1973 CORINI	1-21
A	US,A, 3,018,631 Published 30 January 1962 BURY ET AL	1-21
A	US,A, 3,194,023 Published 13 July 1965 SUDMEIER	1-21
A	US,A, 3,307,365 Published 7 March 1967 TOWNSEND	1-21
A	US,A, 3,464,218 Published 2 September 1969 BUCK	1-21
A	US,A, 3,823,570 Published 16 July 1974 WALLACE	1-21
<p>* Special categories of cited documents: 15</p> <p>"A" document defining the general state of the art</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or 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</p> <p>"X" document of particular relevance</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search *	Date of Mailing of this International Search Report *	
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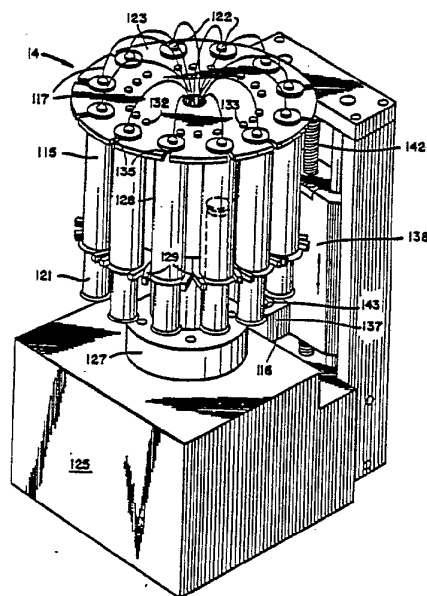
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(21) International Application Number: PCT/US86/01055 (22) International Filing Date: 15 May 1986 (15.05.86) (31) Priority Application Number: 750,791 (32) Priority Date: 1 July 1985 (01.07.85) (33) Priority Country: US (71) Applicant: AMERICAN HOSPITAL SUPPLY CORPORATION [US/US]; One American Plaza, Evanston, IL 60201 (US). (72) Inventor: HANAWAY, Richard, W. ; 906 Carol Ann Court, Roseville, CA 95678 (US). (74) Agent: GREEN, Clarence, A.; Perman & Green, 425 Post Road, Fairfield, CT 06430 (US).		(81) Designated States: CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, NL (European patent). Published <i>With international search report.</i> <i>With amended claims.</i>

(54) Title: REAGENT DISPENSER FOR ANALYZING SYSTEM**(57) Abstract**

A reagent dispensing assembly (14) for use in an automated specimen analysis system (10). The assembly (14) comprises a dispensing station (116), a plurality of reagent supply containers (115) and a carousel (123) for releasably mounting the containers (115). Assembly (14) includes a system (124, 125, 126) for positioning a desired one of the reagent containers (115) at the dispensing station (116). A device (119, 137-142) acts on the containers (115) at the dispensing station (116) for dispensing the desired amount of reagent. A control system (16) coordinates the movement of the respective reagent containers (115) to the dispensing station (116) and the amount of reagent dispensed within a specimen in a specimen tray (18).

DIAGRAMATIC
VIEW



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FI	Finland	ML	Mali		
FR	France				

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REAGENT DISPENSER FOR ANALYZING SYSTEM

BACKGROUND OF THE INVENTION

This invention relates to a reagent dispenser apparatus for an automatic specimen analyzing system. Cross
5 reference is made to three other related copending applications assigned to the same assignee: patent application of William P. Armes, Andrew M. Cherniski, Richard W. Hanaway and James C. Hathaway entitled "Automatic Specimen Analyzing System" (attorney's
10 docket 018-840301-NA); and my two patent applications entitled "Tower for Analyzing System" (attorney's docket 018-840428-NA) and entitled "Tray for Analyzing System" (attorney's docket 018-840429-NA).

15 This invention relates to an automatic specimen analyzing system which substantially reduces operator involvement over presently available systems. After the operator loads the specimen trays into the system

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of this invention, various operations including incubation after inoculation, adding reagents and analysis of the specimen following incubation are all handled automatically without further operator involvement. A computer-type processor controls the system so that the various operations are carried out in appropriate sequence and the results of the analysis are recorded with specific reference to the sample analyzed.

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Automation in microbiology has lagged far behind chemistry and hematology in the clinical laboratory. However, there is presently an intensive effort by industry to develop this field. The best publicized devices for performing automated antimicrobial susceptibility testing use optical detection methods. A continuous flow device for detecting particles 0.5 micron or less has been commercially available since 1970; however, probably due to its great expense, it has not been widely used in the laboratory. Other devices using laser light sources have been suggested but have not proven commercially practicable. Recently, the most attention has been directed to three

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devices discussed below.

The Pfizer Autobac 1 system (U.S. Patent No. Re 28,801) measures relative bacterial growth by light scatter at a fixed 35 degree angle. It includes twelve test chambers and one control chamber in a plastic device that forms multiple contiguous cuvettes. Antibiotics are introduced to the chambers via impregnated paper discs. The antimicrobial sensitivity reader comes with an incubator, shaker, and disc dispenser. Results are expressed as a light scattering index (LSI), and these numbers are related to the Kirby-Bauer "sensitive, intermediate and resistant." MIC measurements which are not available routinely with this instrument. In a comparison with susceptibilities of clinical isolates measured by the Kirby-Bauer method, there was 91% agreement. However, with this system some bacteria strain-drug combinations have been found to produce a resistant Kirby-Bauer zone diameter and at the same time a sensitive LSI.

The Auto Microbic System has been developed by McDonnell-Douglas to perform identification,

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enumeration and susceptibility studies on nine urinary tract pathogens using a plastic plate containing a 4 x 5 array of wells. (See Gibson et al, U.S. Patent No. 3,957,583; Charles et al, U.S. Patent No. 4,118,280, and Charles et al, U.S. Patent No. 4,116,775.) The specimen is drawn into the small wells by negative pressure and the instrument monitors the change in optical absorbance and scatter with light-emitting diodes and an array of optical sensors. A mechanical device moves each plate into a sensing slot in a continuous succession so that each plate is scanned at the rate of one an hour, and an onboard digital computer stores the optical data. The system will process either 120 or 240 specimens at a time. One can query the status of each test via a CRT-keyboard console, and hard copy can be made from any display. When the system detects sufficient bacterial growth to permit a valid result, it automatically triggers a print-out. Following identification in four to thirteen hours, a technologist transfers positive cultures to another system which tests for antimicrobial susceptibility. The results are expressed as "R" (resistant) and "S" (susceptible); however, no

-5-

quantitative MIC data are provided.

It should be noted that Gibson et al, U.S. Patent No. 3,957,583 do not include automation techniques, but use
5 naked-eye inspection or a manually-operated colorimeter. Scanning is therefore a hand or a mechanical operation. Charles et al, Patents Nos. 4,116,775 and 4,118,280 also require mechanical movement of their cassette for reading different rows.

10

The Abbot MS-2 system consists of chambers composed of eleven contiguous cuvettes. Similar to the Pfizer Autobac 1, the antimicrobial compounds are introduced
by way of impregnated paper discs. An inoculum
15 consisting of a suspension of organisms from several colonies is introduced into the culture medium, and the cuvette cartridge is filled with this suspension. The operator inserts the cuvette cartridge into an analysis module which will handle eight cartridges (additional
20 modules can be added to the system). Following agitation of the cartridge, the instrument monitors the growth rate by turbidimetry. When the log growth phase occurs, the system automatically transfers the broth

-6-

solution to the eleven cuvette chambers; ten of these chambers contain antimicrobial discs while the eleventh is a growth control.

5 The device performs readings at five minute intervals, and stores the data in a microprocessor. Following a pre-set increase of turbidity of the growth control, the processor establishes a growth rate constant for each chamber. A comparison of the antimicrobial growth
10 rate constant and control growth rate constant forms the basis of susceptibility calculations. The printout presents results as either resistant or susceptible and if intermediate, susceptibility information is expressed as an MIC.

15 Non-optical methods have also been used or suggested for measuring antimicrobial sensitivity in susceptibility testing. These have included radio-respirometry, electrical impedance, bioluminescence and
20 microcalorimetry. Radiorespirometry, based on the principle that bacteria metabolized carbohydrate and the carbohydrate carbon may be detected following its release as CO₂ involves the incorporation of the

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isotope C14 into carbohydrates. Released C¹⁴O₂ gas is trapped and beta counting techniques are used to detect the isotope.

- 5 The major difficulty in applying the isotope detection system to susceptibility testing, however, is that an antimicrobial agent may be able to stop growth of a species of bacteria, yet metabolism of carbohydrate may continue. Less likely, a given drug may turn off the
- 10 metabolic machinery that metabolizes certain carbohydrates, but growth may continue. This dissociation between metabolism and cell growth emphasizes the fact that measurements for detecting antimicrobial susceptibility should depend upon a
- 15 determination of cell mass or cell number rather than metabolism.

- The electrical impedance system is based on the fact that bacterial cells have a low net charge and higher
- 20 electrical impedance than the surrounding electrolytic bacterial growth media. A pulse impedance cell-counting device can be used to count the cells; however, available counting devices are not designed to

-8-

handle batches of samples automatically, and generally do not have the capacity to distinguish between live and dead bacterial cells.

5 Another approach with electrical impedance has been to monitor the change in the conductivity of the media during the growth phase of bacteria. As bacteria utilize the nutrients, they produce metabolites which have a greater degree of electrical conductance than
10 the native broth so that as metabolism occurs, impedance decreases. However, since this technique measures cell metabolism rather than cell mass, its applicability to antimicrobial susceptibility detection suffers from the same drawback as radiorespirometry.

15
• Bioluminescence has also been suggested for the detection of microorganisms. It is based on the principle that a nearly universal property of living organisms is the storage of energy in the form of high
20 energy phosphates (adenosine triphosphate, ATP), which can be detected through reaction with firefly luciferase. The reaction results in the emission of light energy which can be detected with great

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sensitivity by electronic light transducers. Although a clinical laboratory may obtain a bioluminescence system to detect the presence of bacteria in urine, the technique is expensive due to the limited availability
5 of firefly luciferase, and problems have been encountered in standardizing the system.

Microcalorimetry is the measurement of minute amounts of heat generated by bacterial metabolism. The
10 principle exhibits certain advantages, but laboratories have not adopted such a system, one serious drawback being that the system measures metabolic activity rather than bacterial mass or number.

15 In U.S. Application Serial No. 082,228, filed on October 5, 1979, by Wertz, Hathaway and Cook, now U.S. Patent No. 4,448,534, granted May 15, 1984, assigned to the assignee of the present invention, an automatic scanning apparatus for performing optical density tests
20 on liquid samples as well as methods for testing for antibiotic susceptibility and identifying microorganisms is disclosed. The apparatus of the prior application includes a system for automatically

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scanning electronically each well of a multi-well tray containing many liquid samples. A light source, preferably a single source, is passed through the wells to an array of photosensitive cells, one for each well.

5 There is also a calibrating or comparison cell receiving the light. Electronic apparatus read each cell in sequence quickly completing the scan without physical movement of any parts. The resultant signals are compared with the signals from a comparison cell

10 and with other signals or stored data, and determinations are made and displayed or printed out.

A system of the type described in this prior application is sold under the trademarks "MicroScan"

15 and "autoSCAN-3" by the American Scientific Products Division of American Hospital Supply Corporation, McGraw Park, Illinois.

A description of the MicroScan System appears in a

20 brochure covering it which was published in 1981.

While the MicroScan System represents a substantial advancement in the automation of microbiological

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analysis, it still requires operator involvement to handle operations such as incubation, addition of reagents and insertion for the autoscan analysis operation. In other words, for the MicroScan System, presently in use, an operator must perform the operations of placing the tray in a suitable system for incubation for the desired period and after incubation, adding reagents and inserting the tray in the analyzer. In accordance with the present invention, all of these operations after insertion of the tray in the system are carried out fully and automatically.

SUMMARY OF THE INVENTION

In accordance with this invention, a reagent dispenser assembly is provided for use in an automated analysis system. The reagent delivery system in accordance with this invention utilizes a plurality of remote reagent supply containers and a system for selectively dispensing the desired amount of reagent from the corresponding supply container. The system preferably includes a remote dispensing head arranged at a work station for administering the reagents to specimen

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trays holding a plurality of specimen.

The reagent dispenser assembly of this invention comprises a dispensing station having a plurality of
5 reagent supply containers associated therewith. Means are provided for positioning a desired one of the reagent containers at the dispensing station for dispensing a desired amount of reagent therefrom and means are provided for acting on the desired one of the
10 containers for dispensing the desired amount of reagent. Preferably, the positioning means comprises a reagent container support carousel arranged to rotate the containers past the dispensing station which is arranged tangentially of the carousel. Preferably, a
15 means is provided for releasably securing the containers to the carousel.

Preferably, the reagent containers comprise syringes and the means acting on the containers to dispense the
20 desired amount of reagent comprises an anvil for engaging a plunger of the desired one of the syringes. The anvil is arranged for movement longitudinally of the desired one of the syringes. Means are provided

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for driving the anvil to move it selectively between a first home position where it does not engage the syringe, a second dispense start position where it first engages the plunger and a third finish position
5 where it pushes the plunger in order to dispense the desired amount of reagent.

Preferably, a control system is provided for coordinating the movement of the dispense carousel to
10 position the desired one of the syringes at the dispensing station and coordinate the movement of the anvil between its respective position to dispense the desired amount of reagent. Preferably, the control means includes means for sensing the first engagement
15 between the anvil and the plunger and responsive thereto means for closing the anvil to move to its third position.

Preferably, a dispense head is arranged remotely from
20 the dispenser assembly. The dispense head is arranged to administer the reagent to a desired specimen in the specimen tray. A suitable conduit is used to connect the dispense head to the dispenser assembly.

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It is an aim of this invention to provide a reagent dispenser assembly for use with an automated specimen analysis system wherein the dispenser assembly is adapted to selectively administer one of a plurality of reagents contained therein.

It is a further aim of this invention to provide a dispenser assembly as above wherein a control system coordinates a movement of respective reagent containers to a dispensing station and the amount of reagent dispensed by a remote dispense head.

These and other aims will become more apparent from the following description and drawings.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic representation of an automatic specimen analyzing system in accordance with this invention.

20

Figure 2 is a schematic representation of a tray tower

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of the type used in the apparatus of Figure 1.

Figure 3 is a schematic perspective view of a specimen container tray which can be employed in the apparatus
5 of Figure 1.

Figure 4 is a perspective view of a cover member for use with the specimen container tray of Figure 3.

10 Figure 5 is a cross-section of a specimen tray in accordance with this invention comprising a tray container as in Figure 3 and a cover member as in Figure 5.

15 Figure 6 is a cross-section of a cover member of Figure 5 taken normal to the direction of the cross-section in Figure 5.

Figure 7 is a schematic perspective view of the
20 carousel and scanning assembly in accordance with this invention.

Figure 8 is an exploded view of the carousel and

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scanning assembly of this invention.

Figure 9 is a more detailed exploded view of the scanning system in accordance with this invention.

5

Figure 10 is a partial perspective view illustrating operation of the tray moving system of this invention.

Figure 11 is a partial side view in partial cross-section, illustrating the operation of the tray moving system of this invention.

10

Figure 12 is a partial side view as in Figure 11 at a later stage in the tray moving operation.

15

Figure 13 is a partial side view as in Figure 11 at a still later stage in the tray moving operation.

Figure 14 is a partial side view as in Figure 11 at a still later stage of the tray moving operation.

20

Figure 15 is a perspective view of the dispenser systems.

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Figure 16 is an exploded view of the dispenser system of this invention.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to Figure 1, an automatic specimen analyzing system 10 is shown schematically. The system
10 10 is adapted to analyze biologic specimens which have been selectively treated as desired. The specimens are arranged in specimen trays wherein each tray contains a plurality of the specimens. The system 10 is adapted to automatically carry out, after the operator loads
15 the specimen trays into the system 10, operations such as addition of reagents, incubation and the analysis.

The specimen trays are loaded by the operator into a plurality of specimen tray supporting towers 11. The
20 exact number of towers utilized in the system may be set as desired. However, the system is particularly adapted for use with a plurality of such towers 11. A

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work station 12 is arranged in association with the tray towers 11 for selectively treating or analyzing the specimens in the trays supported by the towers 11. A selectively operable tray moving means 13 is supported at the work station and serves to remove a specimen tray from the tray support tower and move it to the work station 12. The tray moving means 13 also serves to reinsert the tray into the tray supporting tower 11. A reagent delivery system 14 includes a remote dispensing head 15 connected thereto and supported by the work station 12. The reagent delivery system 14 is selectively operable to administer a desired amount of at least one reagent to desired ones of the specimens in the tray through the remote dispensing head 15.

A housing H preferably surrounds and encloses the environmentally sensitive elements of the automatic scanning analyzing system 10. Those elements include the tray support towers 11, the work station, the tray moving means 13, the reagent delivery means 14 and the remote dispensing means 15. Although these components can be used in a controlled environmental room without

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a housing, it is intended that the automatic specimen analyzing 10 of this invention includes such a housing for controlling temperature and humidity to provide proper incubation of the specimen.

5

The environmental control system E is connected to the housing H for controlling the temperature and humidity within the housing. The environmental control system comprises conventional means for controlling the humidity and temperature of the atmosphere within the housing H. While it is preferred for the housing H to enclose both the work stations and tray tower area and the remote dispensing area, if desired, the housing may enclose only the work station and tray tower area.

15

The housing is provided with one or more access doors (not shown) to enable the operator to remove tray tower 11 from the analyzing system 10. For maintenance purposes, the housing may be made removable from the system entirely. If desired, the control system 16 may be built into the housing and the housing H may include an indicator panel such as LED panel D. If desired, various other gages and indicators can be

-20-

mounted to the housing H.

The work station 12 also includes an analyzing means for determining at least one optical property of
5 desired ones of the specimens in the tray. A control means 16 is adapted to sequentially actuate the tray moving means 13 so that each of the trays are at least sequentially moved to the work station 12 for administration of the reagent by the reagent delivery
10 system 14, then return to the tray support tower 11 and held there for a desired incubation time. Thereafter, the control means again causes the tray to be removed from the tray tower 11 and returned to the work station for analysis. The control means then causes the tray
15 moving means to return the tray to the tray support tower 11 from which it can be removed by the operator for storage or disposal.

While the specimen tray itself has not been shown in
20 Figure 1, it will now be described in detail by reference to Figures 2-5. The specimen tray assembly 17 comprises an assembly which is adapted for use in the automatic system 10 for analyzing the specimens.

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Each tray assembly 17 is adapted to contain a plurality of separate specimens. The tray assembly 17 is comprised of a container tray 18 having a plurality of microcuvettes 19 arranged in a spaced apart grid-like pattern. The container tray 18 is best shown in Figure 3 and corresponds to the MicroScan specimen panels as described in the background of this application. A cover member 20 is adapted to seat over a top surface 21 of the container tray 18. The cover member 20 is clearly illustrated by reference to the aforementioned Figures 2, 4 and 5. The cover member 20 includes tab portions 22 and 23 which extend outwardly in the plane of the cover members 20 from first and opposing edges 24 and 25 of the member. The tab portions 22 and 23 are adapted, when the tray assembly 17 is inserted in the tray tower 11, to control the movement of the cover member 20 so that the container tray 18 can be readily removed from the tray tower 11 without the cover member. The cover member is left in the tray tower so that the aforementioned operations of reagent additions or analysis can be readily carried out on the specimens in the container tray 18.

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The cover member also includes means for automatically centering the container tray relative to the cover member 20 to provide proper seating of the cover member on the container tray. With reference to Figure 5, the centering means preferably comprises a recess 26 in a bottom face 27 of the cover member 20 having a first peripheral wall 28. The first peripheral wall 28 is adapted to seat about a second peripheral wall 29 of the container tray 18. The centering action is provided by inclining the first peripheral wall 28 in the cover member inwardly of its periphery so that when the cover member 20 is urged against a misaligned container tray 18, the inclined first peripheral wall 28 acts on the second peripheral wall 29 of the container tray 18 to center and align the container tray with respect to the cover member. This centering feature of the tray assembly of the present invention plays an important role with respect to the proper removal and reinsertion of the container tray 18 into the tray tower 11. This function will be described in greater detail hereinafter. Proper seating of the cover member 20 over the container tray 18 is important in order to insure that there is no undue evaporation

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of the contents of the cuvettes 19 in the container tray 18.

The cover member 20 preferably includes stiffening ribs 30 arranged as shown generally parallel to one another along a top face 31 of the cover member 20 and extending longitudinally between the respective tab portions 22 and 23. A plurality of such stiffening ribs 30 are utilized in order to strengthen the cover member so that it can be resiliently urged against the container tray 18 to provide effective sealing against evaporation as will be described in greater detail hereinafter. The stiffening ribs 30 therefore prevent bowing of the cover member 20. It is preferred to avoid such bowing of the cover member 20 in order to reduce evaporation and prevent interference with the container tray 18 as it is removed from the tray tower 11.

In accordance with a preferred embodiment of the present invention, each container tray 18 includes ninety-six cuvettes or wells 19. Further, each container tray 18, as shown in Figure 3, can be

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recognized and identified by a bar code 32 which is provided on a side wall 33 of the container tray which will face the remote dispensing head 15. The bar code is added to the container tray 18 at the time of
5 placing particular samples or specimens in the tray into the control system 16, and have the information associated with each tray represented thereon. The control system preferably comprises a programmable computer which can print out the desired bar code at
19 the time the information is in the system.

Referring again to Figure 2, it is apparent that the tray support tower 11 is adapted to support a plurality of tray assemblies 17. The exact number of tray
15 assemblies 17 may be set as desired. Each tray tower 11 is readily removable from the automatic specimen analyzing system 10 by loosening tie down bolts 34. This allows the tray tower 11 to be releasably connected to the automatic specimen analyzing system.

20

Each tray assembly 17 rests upon a shelf 35 which is slidably supported so that it is removable in a first slot 36 in each of a first sidewall 37 and a second

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side wall 38 of the tray tower. The slots 36 extend in a spaced apart, generally parallel, manner from a first open face 39 in the plane of the drawing to a second open face (not shown) behind the first open face 39.

5 The slots are closed at an end adjacent one of the open faces as will be described in greater detail hereinafter. Each of the shelves 35 is removably supported in the first slots in each of the first and second side walls 37 and 38 to provide a spaced apart

10 parallel and overlapping array of shelves 35 with the spaces between the shelves being adapted to receive the specimen tray assemblies 17.

A corresponding plurality of second slots 40 in each of

15 the first and second side walls 37 and 38 extend in a spaced apart, generally parallel, manner from the first open face 39 to the second face (not shown). The second slots are closed at an end adjacent one of the open faces which is selected to be the same face as for

20 the first slots 36. The second slots 40 are adapted to receive the cover members 20 and to provide support for movement of the cover member 20 upwardly or downwardly within the width of the slot W. The width W is

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selected to permit the cover member 20 to move widthwise of the slot as will be described in greater detail hereinafter.

5 Preferably, selectively operable means 41 are provided at one of the open faces 39 of at least one side wall 37 for partially blocking the open face to prevent the tray assemblies 17 loaded in the tray tower from being pushed out of the opening in that face. The
10 selectively operable means 41 preferably comprises a multi-tabbed member 42 which is slidably mounted on an edge of the side wall 37 by any suitable means (not shown). The tab member may be moved up and down so that the tray assembly 17 can be inserted or removed
15 from the tower 11 or locked in place. The tabs 43 of the member 42 serve to interfere with the cover member 20 when it is desired to lock the tray assembly 17 in place or to allow free passage of the cover member when the member 42 is moved upwardly out of blocking
20 position. This movement may be accomplished manually by operator intervention or automatically through the use of a suitable solenoid 44 which is controlled by the programmable control system 16.

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The tie-down bolts 34 are supported by the respective side walls 37 and 38 of the tower 11 and these, with a top portion 45 and bottom portion 46, comprise a tray tower frame. The tie-down bolts 34 are adapted to screw into a tray tower moving carousel 47 as illustrated in Figure 1.

If it is desired to sterilize the tray tower, the specimen tray assemblies 17 are removed from the tower. The shelves 35 can also be removed from the tower and sterilized if desired. The tower itself which comprises essentially the frame comprising top and bottom portions 45 and 46 and side walls 37 and 38, can then be sterilized also.

Referring now to Figures 7-9, further details of the automatic specimen analyzing system 10 will be provided. In particular, these figures show the various apparatus for moving the tray towers 11 selectively into operative position with respect to the work station, the various elements of the tray assembly moving system and the work station itself. It is

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desirable to employ a plurality of tray towers 11 which are arranged on a tray tower moving system or carousel 47. The carousel 47 comprises a donut-shaped plate which surrounds the work station 12. Holes 48 are provided in the top surface of the carousel 47. These holes are tapped so that the tie down bolts 34 of a respective tray tower 11 can be screwed therein in order to mount the tray tower to the carousel 47. The tray towers are not shown in Figures 8 and 9 in order to better illustrate the other aspects of the automatic specimen analyzing system 10.

A carousel drive pulley 49 is driven by means of a cogged belt 50 arranged about the drive pulley 49 and a cogged pulley 51. A stepping motor 52 drives the cogged pulley 51 via a stepped-down cogged pulley and belt arrangement 53. The actuation of the stepping motor is controlled by the control system 16 and serves to rotate the carousel 47 to position a desired tray tower in operative association with the work station 12. The carousel 47 is rotatably supported on a base frame 54 by means of V-track bearings 55. If desired, however, any appropriate means for rotatably supporting

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the carousel 47 could be employed. Similarly, any desired drive arrangement could be employed which is adapted to selectively position a desired one of the tray towers in operative association with the work station 12.

A pair of vertical shafts 56 support the work station 12 for vertical movement up and down along the shaft 56 axes. The shafts 56 are supported in the frame 54 and at their opposing ends by a shaft mount 57. A work station carrier frame 58 includes holes 59 with suitable bushings or bearings to provide for sliding movement of the carrier frame 58 along the shafts 56. A vertical axis drive screw 60 is provided to drive the carrier frame 58, supporting the work station 12, up and down vertically along the shafts 56. The drive screw 60 is journaled for rotation in the shaft mount 57 by means of ball bearings 61 and is also journaled for rotation in the frame 54 by means of bearings 62. The portions of the drive screw 60 which are journaled through rotation do not include threads. In addition, the lower portion which is journaled in the base frame 54 includes a drive cogged pulley 63 which is driven by

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means of a cogged belt 64 and pulley 65 mounted to the shaft of a stepping motor 66. The drive cogged pulley 63 is of a larger diameter than the pulley 65 to provide a step-down drive arrangement. The stepper
5 motor 66 is controlled by the control system 16 to advance the work station 12 up and down as required to carry out the operations of the automatic specimen analyzing system which will be described hereinafter.

10 Referring now, more particularly, to Figure 9, the details of the work station itself will be described. The work station carrier frame 58 as previously described is arranged for movement along the shafts 56
by means of linear bearings 67. The remote dispensing
15 head 15 is arranged for movement in a plane normal to the plane of movement provided by the shafts 56 and drive screw 60. This is accomplished by means of a guide rod 68 and dispensing head drive screw 69. The dispensing head 15 is arranged for sliding movement on
20 the rod 68 by means of oilless bearings 70. The drive screw 69 is threaded through a hole 71 so as to provide the desired movement of the dispensing head 15 from side-to-side relative to the carrier frame 58.

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Preferably, anti-backlash nuts 72 and 73 are employed with respect to drive screws 60 and 69.

5 The drive screw 69 is journaled for rotation in end support blocks 74 and 75 which, in turn, are mounted to the carrier frame 58. The drive screw is journaled for rotation in the end blocks 74 and 75 by means of bearings 76 and 77. A cogged drive pulley 78 is secured to one end of the drive screw 69. A stepper
10 motor 79 mounted to the carrier frame 58 drives the drive screw 69 by means of a cogged pulley 80 and belt 81. The cogged pulley 80 is relatively larger in diameter than the drive pulley 78, thereby providing a step-up in the drive arrangement.

15

A photodiode reader card assembly 82 is supported on the underside of the carrier frame 58. This reader card assembly 82 serves in the analysis function of the work station to determine an optical property of the
20 specimens in the tray assembly 17.

An important element of the present automatic specimen analyzing system 10 is a selectively operable tray

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moving system 13 which serves to remove a tray container 18 from the tray tower and move it into the work station for dispensing reagents into the specimens or their analysis, and for moving the tray container 18
5 back into the tray tower 11 as required. The tray moving system 13 is supported by the carrier frame 58 and comprises a tray drive mount 83 which is secured to the carrier frame 58. The mount 83 supports therein two parallel spaced-apart helical drive screws 84 which
10 are journaled for rotation in the mount by means of bearings 85. The tray drive mount 83 is located at one end of drive screws 84.

A moving carriage or tray pick-up body 86 is drivingly
15 supported about the drive screws 84 by means of anti-backlash nut assemblies 87. The carriage 86 supports two parallel spaced apart tray pick-up tines 88 and 89. At the opposing ends of the drive screws, drive pulleys 90 are mounted which are driven by means of a cogged
20 belt 91 through cogged pulley 92 which, in turn, is driven by stepper motor 93. The stepper motor 93 is controlled by the control system 16 so as to advance or retract the tines 88 and 89 to respectively move a

-33-

container tray 18 to and fro in a plane normal to the plane of movement of the carrier frame 58 and in a direction normal to the direction of movement of the remote dispensing head 15.

5

Supported above and below the tray moving means is the specimen analyzing system or scanning system 94 and 82 comprising a tray block 95, an aperture plate 96, fiber bundle block 97 and photodiode reader card 82. The specimen analyzing system 94 and 82 is essentially the same as that employed commercially in the MicroScan system described in the background of this application. The tray block 95, the aperture plate 96 and the fiber bundle block 97 are arranged for movement vertically to and fro in the same direction as the carrier frame 58, however, in respect to the carrier frame 58. The aforementioned elements are mounted to an optics block frame 98 via optics mounts 99.

20 The tray block 95, the fiber bundle block 97 and the aperture 96 are arranged for vertical movement on the optics block frame 98 by means of gear racks 100 which are spring-loaded against mounts 99. Mounts 99 are

-34-

located by two tooling balls and one locating button through three position posts. The three position posts are bolted to frame 98. Gear racks 100 are slidably supported in holes 101 in the optics block frame 98.

5 Shafts 102 are journaled for rotation in the frame 98 by means of bearings 103. Drive gears 104, in respective alignment with the gear racks 100, are supported on shafts 102 whose axes are arranged normal to the direction of movement of the gear rack 100.

10 Cogged pulleys 105 are supported at one end of the shafts 102 to provide drive to the shafts. The pulleys 105 are driven by means of a stepper motor 106 and a cogged belt 107. The stepper motor 106 is controlled by the control system 16 to provide clockwise or

15 counterclockwise rotation of the shafts 102 in order to advance the gear racks 100 up or down and thereby advance the specimen analyzing system 94 up and down into and out of engagement with the bottom of a respective container tray 18 arranged at the work

20 station 12.

While a carousel-type arrangement is shown for moving the respective tray tower 11 into operative association

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with the work station 12, any desired moving means could be employed including various belt-type arrangements. As previously described, the tray towers 11 comprise generally rectangular frames having a plurality of tray support shelves 35 removably supported therein.

Referring to the Figures 10 - 14, tower 11, preferably, also includes means 108 for biasing the cover member 20 against the container tray 18 when they are positioned in the tower. The biasing means 108 and the operation of the tray moving system 13 and work station 12 will now be illustrated by considering Figures 10-14.

As shown in Figure 10, the tray tower 11 includes side wall 37 having respective slots 36 and 40 as previously described. A tray shelf 35 is supported in the slot 36 whereas the cover member 20 is held captive by the tray tower second slot 40. It is held captive because the second slot 40 is closed at its end at open space 109. Similarly, the tray shelf 35 is captured by the closed end of the slot 36 at the open space 109. The tray tines 88 and 89 include at their leading edges an

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inclined surface 110 which serves to engage the tab portions 22 or 23 to raise the cover member 20 off of the container tray 18 as the tines proceed into the tray tower by means of the drive imparted by stepper motor 93. A resilient biasing means, as shown in Figure 11, comprises a compression spring 108 which is supported by the bottom of the next above shelf 35. The purpose of the biasing means or spring 108 is to ensure engagement sealingly as possible between the cover member 20 and the container tray 18. As the tines move into the tray tower 11 in the direction of arrow 111, the tray cover lifts slightly as shown in Figure 12 and the spring 108 is compressed.

Referring now to Figure 13, after the tines 88 and 89 are fully advanced into the tray tower, the vertical drive stepping motor 66 is actuated to slightly raise the tines 88 and 89. This causes the tray cover 20 to be fully lifted off the container tray 18 and held in that position by the tray tine 88 and the opposing tray tine 89 not shown. This also serves to capture the container tray 18 in a recess 112 in the lower edge of the tines 88 and 89. The spring 108 is now fully

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compressed. The slight vertical jog in the direction of arrow 113 is all that is necessary in order to capture the container tray 18 in the recess or pocket 112. The container tray is then withdrawn from the tray tower 11 by movement of the tines 88 and 89 in the direction of arrow 114 as shown in Figure 14. Upon withdrawal of the container tray 18 from the tray tower 11, the biasing spring 108 returns the tray cover 20 to its normal position at the bottom of the second slot 40. The tray cover member 20 does not follow the tines 88 and 89 out of the tray tower because of the closed end 109 of the second slot 40 which captures the tab portion of the tray cover member 20.

To return the container tray 18 to the tray tower 11, the operation is reversed. As the tines 88 and 89 advance into the tray tower 11, the tray cover member 20 is raised up to permit the tray container 18 to enter. After the tines are fully inserted into the tray tower 11, the stepper motor 66 is jogged to move the tines vertically, downwardly, to release the tray container. The tines are then withdrawn from the tray tower. The work station can then be advanced up or

-38-

down to remove another tray from the tray tower.

In operation of the system thus far described, the specimen tray assembly 17 is inserted in the tray tower 11 by the operator. The computer controller 16 controls the actuation of the respective stepper motors previously described to withdraw desired tray assemblies 17 one at a time from a tray tower and transport them to the work station 12. At an appropriate time a tray assembly 17 is withdrawn from the tray tower, it is intended to dispense suitable reagents into the specimens in the tray container. This reagent dispensing process is accomplished by utilizing the respective X axis and Y axis movements achievable through the use of the tray moving system and the remote dispense head moving system. For example, X movement can be achieved by appropriately controlling stepper motor 93 to stepwise advance the tray container supported in the tines 88 and 89 under the dispensing head 15. Y movement is achieved by stepwise advancing the dispensing head from side-to-side of the carrier frame 58 under the actuation of stepper motor 79. The computer controller 16 controls

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the respective actuations of the stepper motors to move the dispensing head to the desired cuvette 19 in the tray container 18 wherein a desired reagent is then metered therein.

5

The dispensing head 15 also includes a reader means R for reading the bar code 32 on the side 29 of the container tray 18. This is achieved by scanning the dispensing head 15 laterally across the bar reading means R. The reading means R comprises a sensor on the remote dispensing head for reading the bar code and is appropriately connected to the control system 16 to identify the sample being analyzed.

15 After reagent dispensing is completed by the respective X and Y axis movements of the respective tray moving system 13 and movement of the dispensing head 15, the stepper motor 93 is energized to advance the tines in a direction to reinsert the container tray 18 back into
20 its respective slot in the tray tower 11 as described by reference to Figures 10-14. The computer controller 16 then allows the inoculated samples with added reagents to incubate a desired amount of time after

-40-

which the container tray 18 is again removed from the tower by repeating the sequence described by reference to Figures 10-14 and withdrawn to the work station 12.

5 At this time, the analysis is carried out in a manner similar to that described for the MicroScan system in the background of this application. When the container tray is in the work station 12, the respective tray block, aperture plate and optics block frame are moved
10 into engagement with the bottom of the container tray 18 by means of actuating stepper motor 106. After the analysis has been completed in a conventional fashion and the results recorded in the computer controller 16, the tray block, is lowered by actuation of stepper
15 motor 106 and the tray tines again return the tray container to the tray tower. At this point, the tray container may be removed for storage or disposal as desired. In the alternative, it may be retained in the tray tower for an additional incubation period if so
20 desired and the analyzing operation just described repeated following the incubation period.

It has previously been described that the tray cover

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member 20 includes a recess 26 defining an inclined peripheral wall 28 which serves to center the container tray relative to the cover member. This action is achieved as shown by reference to Figures 10-14 under the influence of the biasing spring 108. If the tray container 18 should be reinserted in the tower 11 in slight misalignment from the cover member 20, then the cover member 20 can properly align it. This is possible since as the cover member 20 is engaged to the container tray 18 as the tines 88 and 89 are withdrawn, the inclined surface 28 serves to move the container tray relative to the cover member which is held from moving by the sidewalls in order to center the container tray and provide good sealing engagement between the cover member and the container tray.

The incubation in the apparatus of this invention is preferably carried out at about 37 degrees C, plus or minus 3 degrees. Since different tests require different incubation times, the computer controller 16 is set up so that each tray assembly 17 will be read based upon the tests which are desired for the specimens in that respective container tray 18. The

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apparatus 10 of this invention is designed to read trays which have differing tests as the analysis functions, reagent dispensing functions and incubation periods are software determined. It is possible with
5 the apparatus 10 of this invention to do kinetic readings as the various readings can be taken over a period of time thereby providing rate of growth studies in any particular cuvette 19.

10 The reader assembly for analysis includes a light source assembly comprising ninety-six fiber-optic lines from a light source. Each fiber-optic line is provided under each well in the tray. Over the tray, an aperture plate, or merely the light sensor, is used.
15 The light is provided by a light source which is separated from the end of the fiber-optic bundle by an appropriate color wheel which provides filtering of the light due to various tests. Preferably, the color wheel includes nine colors, although normally only
20 seven colors are read. The color wheel and light source assembly, as previously described, is essentially of the type previously employed with the autoSCAN system described in the background of this

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application. All seven readings are taken for each cuvette 19 and the associated software of the controller 16 throws out any unnecessary readings for each well. After a particular tray 18 has been read to completion, a light emitting diode D on the housing H will either be lighted or turned off to indicate that the tray has been analyzed and can be removed or replaced with another tray.

10 While the operation of the remote dispensing head 15 has been described in detail, reference will now be had to Figures 15 and 16 wherein the reagent delivery system 14 is shown in detail. The reagent delivery system 14 comprises a plurality of reagent supply
15 containers 115 arranged remotely from the work station 12 and means for selectively dispensing a desired amount of a reagent from a corresponding one of the reagent supply containers 115. A suitable conduit 117, as shown in Figure 1, connects each respective
20 container 115 to a respective dispensing hole 118 in the dispensing head 15 shown in Figure 9. Accordingly, there are as many conduits 117 and dispensing holes 118 employed as there are containers 115 mounted in the

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delivery system 14.

The selective dispensing means comprises a dispensing station 116 in which the reagent containers 115 are arranged for movement past the dispensing station. Metering means are provided at the dispensing station for controlling the amount of reagent dispensed from the reagent container 115 selected. Preferably, the reagent containers 115 comprise syringes comprising a container body 120 and plunger 121. A suitable syringe nozzle 122 is used to connect the syringe 115 to the conduit 117.

It is preferable, in accordance with this invention, to move the syringes past the dispensing station 116 by supporting the syringes in a carousel 123 arranged to rotate the syringes past the dispensing station 116. Means are provided for selectively moving the carousel 123 to position a desired one of the syringes 115 at the dispensing station 116. The carousel 123 is mounted to shaft 124 which is journaled for rotation in a support base 125 by means of bearings 126. A stepping motor (not shown) in the base 125 is drivingly

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connected to the shaft 124 and, under the influence of control system 16, stepwise advances the carousel 123 to position a desired one of the containers 115 at the dispensing station 116. The control system 16 not only
5 coordinates the movement of a desired one of the reagent containers to the dispensing station 116, but also controls the amount of reagent metered therefrom at the dispensing station in correspondence with the specimen arranged to receive the reagent.

10

The syringes 115 are releasably supported in carousel 123. This is achieved by providing a dispenser body housing support collar 127 about shaft 124 and a dispenser body housing 128 fitted over the collar 127.
15 The carousel 123 is then supported on the end of shaft 124. A movable syringe mounting block 129 is arranged to support the syringe by engaging a flange 130 of the syringe container body 120 from below. The mounting block 129 is mounted on two dowel pins 131 arranged
20 parallel to one another and arranged for sliding movement in holes 132 in the dispenser body housing 128. A syringe release shaft 133 is also slidingly mounted in housing 128 so as to be spring biased by a

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spring 134 in an upward direction. The lower end of the shaft 133 is secured to mounting block 129.

The carousel 123 includes a series of slots 135 about
5 its periphery through which the nozzle 122 of the syringe can pass, however, the shoulder 136 of the syringe abuts against the carousel plate from below. Therefore, in operation, to insert the syringe in the carousel assembly, the shaft 133 is depressed to lower
10 the mounting block 129. The syringe 115 is then inserted so that the nozzle 122 protrudes through a slot 135 and the shaft 133 is then released so that under spring biasing, the block 129 engages the flange 130 to securely mount the syringe in the carousel
15 assembly by spring biasing it between the mounting block 129 and the carousel plate 123.

The carousel plate 123, depending on its size, can include any desired number of syringes. A metering
20 means 119 is arranged at the dispensing station 116 which itself is positioned tangentially of the carousel 123. The metering means 119 comprises an anvil 137 arranged for movement longitudinally of the desired one

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of the syringes at the dispensing station 116. The anvil is supported on a movable carriage 138. The carriage is arranged for movement in a sliding fashion along vertical shafts 139 which are supported at one
5 end in the base 125 and at an opposing end in a frame secured to the base and comprising side bars 140 and top bar 141. Sleeve or linear bearings are used to mount the carriage 138 to the shafts 139.

10 A drive screw 142 is journaled for rotation in the top bar 141 and extends through the base 125 wherein it is also journaled for rotation. The drive screw is drivingly connected to a stepping motor (not shown) which serves, by virtue of the driving connection
15 between the drive screw and the carriage 138, to move the carriage 138 and the anvil 137 to and fro in a vertical direction; namely, vertically upwardly or downwardly as controlled by the control system. By moving the anvil longitudinally of the syringe 115, it
20 is possible to push the plunger 121 into the body 120 in order to dispense the desired amount of reagent.

The control system 16 controls the stepping motor

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connected to the drive screw 142, to drive the anvil 138 between respective positions. These comprise a first home position wherein it does not engage the syringe at all, a second dispense start position
5 wherein it first engages the plunger 121 and a third finish position wherein it pushes the plunger into the body 120 to dispense the desired amount of reagent. The control system 16 coordinates the movement of the carousel 123 to position the desired one of the
10 syringes at the dispensing station and also controls via the stepping motor (not shown), the movement of the anvil 138 between its respective positions to dispense the desired amount of reagent. The control system 16 includes a position sensor 143 for sensing the first
15 engagement between the anvil and the plunger 121 and for causing responsive thereto the anvil to move to its third position. In this embodiment, the carousel plate 123 is adapted to rotate just under 360 degrees in either direction in aligning the reagent containers
20 relative to the dispensing station. Each syringe position is coded as well as the home position. In searching for a particular syringe, the sensor is activated by the slots 135 and the computer can

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identify which syringe is at the dispensing station. If a particular syringe is not placed at the dispensing station before the sensor reaches the home slot the carousel is reversed in direction until it finds the particular syringe.

The apparatus in accordance with this invention is adapted to load and unload a tray container 18 from a tray tower 11 in approximately seven seconds, and a similar amount of time is required to analyze the specimens in the tray. The apparatus, in addition to the position sensor 143 can include a number of other sensing and encoding devices for enabling the control system to control the operation as previously described. For example, encoders are used on the X and Y axes drives during the dispensing operation. Various optical interrupter type sensors are employed for detecting the container tray edge, the time home position, the dispenser head home position, etc.

20

It is preferred, in accordance with this invention, as shown in Figure 8A, to employ roller bearings B supported by frame 98 against which the tines 88 and 89

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ride when extending to take the tray from the tray tower 11. This helps to improve the stability of the tray moving system.

- 5 The control system 16 has not been described in detail but preferably comprises a programmable computer controller as are well known in the art. It is believed to be well within the skill of the art to program such a device to perform the desired sequences
10 as described.

The patents, patent applications and publications referred to in the background of this application are intended to be incorporated by reference herein.

- 15 It should be understood that the above described embodiments of the invention are illustrative only and that modifications thereof may occur to those skilled in the art. Accordingly, this invention is not to be
20 regarded as limited to the embodiments disclosed herein but is to be limited only as defined by the appended claims.

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CLAIMS

1. A reagent dispenser assembly for use in an automated analysis system, said dispenser comprising:

a dispensing station;

a plurality of reagent supply containers associated with said dispensing station;

means for positioning a desired one of said reagent containers at said dispensing station for dispensing a desired amount of reagent therefrom; and

means acting on said desired one of said containers at said dispensing station for dispensing therefrom said desired amount of reagent.

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2. A dispenser as in Claim 1 wherein said positioning means comprises a reagent container support carousel arranged to rotate said containers past said dispensing station which is arranged tangentially of said carousel and means are provided for releasably securing said containers to said carousel.

3. A dispenser as in Claim 2 wherein said reagent containers comprise syringes and wherein said means acting on said container to dispense said desired amount of reagent comprises an anvil for engaging a plunger of said desired one of said syringes, said anvil being arranged for movement longitudinally of said desired one of said syringes, and means for driving said anvil to move it selectively between a first home position where it does not engage said syringe, a second dispense start position where it first engages said plunger and a third finish position where it pushes the plunger in order to dispense said desired amount of reagent.

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4. A dispenser as in Claim 3 wherein control means are provided for coordinating the movement of said carousel to position said desired one of said syringes at said dispensing station and the movement of said anvil between its respective positions to dispense said desired amount of said reagent.

5. A dispenser as in Claim 4 wherein said control means includes means for sensing the first engagement between said anvil and said plunger and responsive thereto said control means causes said anvil to move to its third position.

6. A dispenser as in Claim 5 further including a dispense head arranged remotely from said dispenser, said dispense head being arranged to administer said reagent to a desired specimen and conduit means connecting said dispense head to said dispenser.

AMENDED CLAIMS

[received by the International Bureau on 28 August 1986 (29.08.86)
original claims 1,3 and 4 cancelled; claims 5,2 and 6 amended and
renumbered 7,8 and 9 respectively; new claim 10 added (4 pages)]

7. A reagent dispenser assembly for use in an automated analysis system, said dispenser comprising:

a dispensing station;

a plurality of reagent supply containers associated with said dispensing station;

means for positioning a desired one of said reagent containers at said dispensing station for dispensing a desired amount of reagent therefrom;

means acting on said desired one of said containers at said dispensing station for dispensing therefrom a desired amount of reagent, said dispensing means comprising a plurality of plungers, with each respective reagent container, the position of each plunger relative to its associated container being determined by

the amount of reagent remaining in its container;

a means separate from said containers and plungers for moving said plunger associated with said one of said containers to dispense said desired amount of reagent irrespective of the position of the plunger of said one of said containers prior to said reagent being dispensed, said means for moving said plunger associated with said one of said containers comprises an anvil for engaging said plunger, said anvil being arranged for movement longitudinally of said desired one of said reagent container, a means for driving said anvil to move it selectively between a first home position where it does not engage said plunger, a second dispense start position where it first engages said plunger and a third finish position where it pushes the plunger in order to

dispense said desired amount of reagent;
and

control means for coordinating the movement of said anvil between its respective positions to dispense said desired amount of said reagent, said control means including means for sensing the first engagement between said anvil and said plunger and responsive thereto said control means causes said anvil to move to its third position whereby the amount of reagent dispensed is a function of the movement of said anvil between the second dispense start position, which is determined by said means for sensing the first engagement, and said third position.

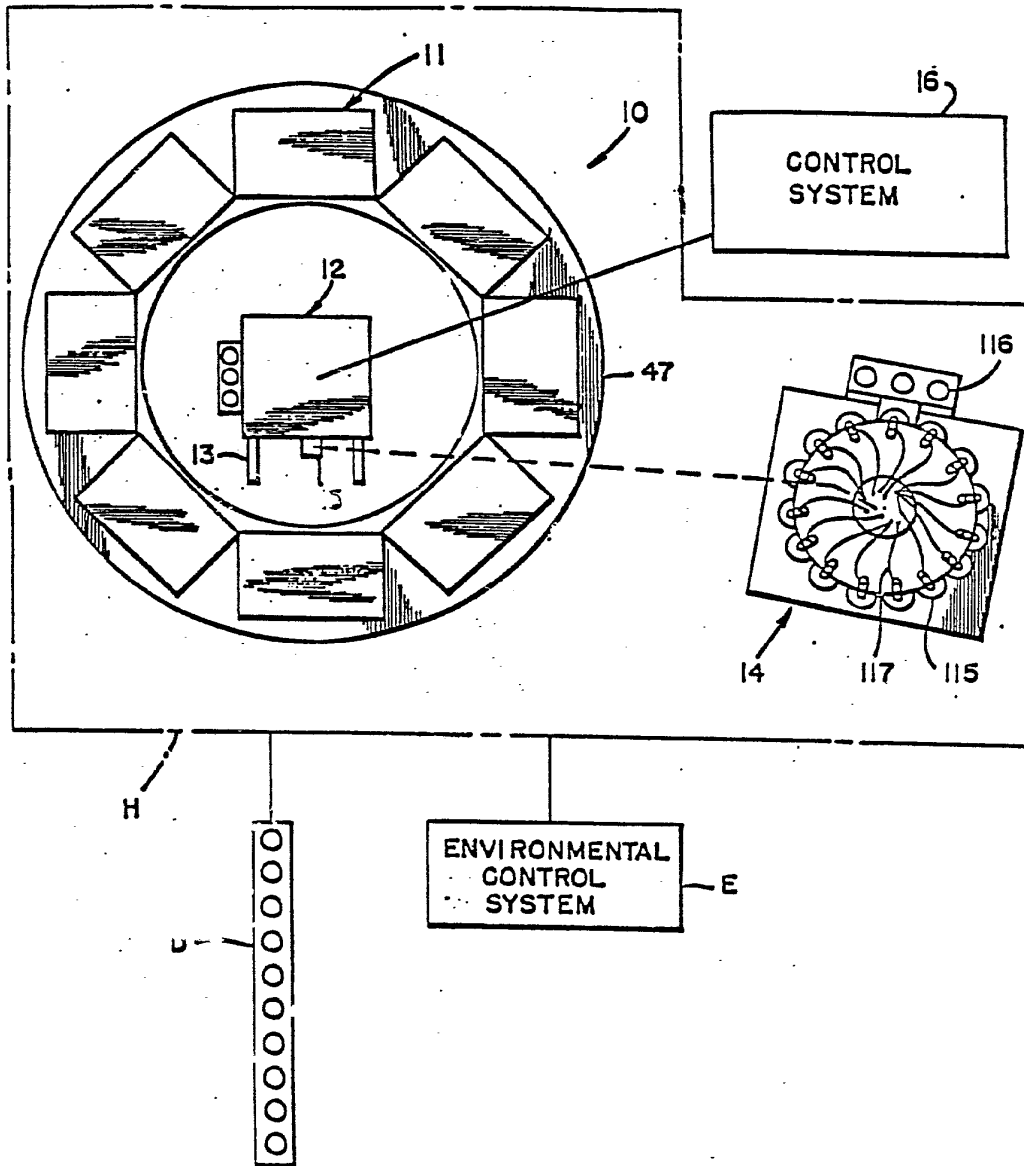
8. A dispenser as in Claim 7 wherein said positioning means comprises a reagent container support carousel arranged to rotate said containers past said

dispensing station which is arranged tangentially of said carousel and means are provided for releasably securing said containers to said carousel.

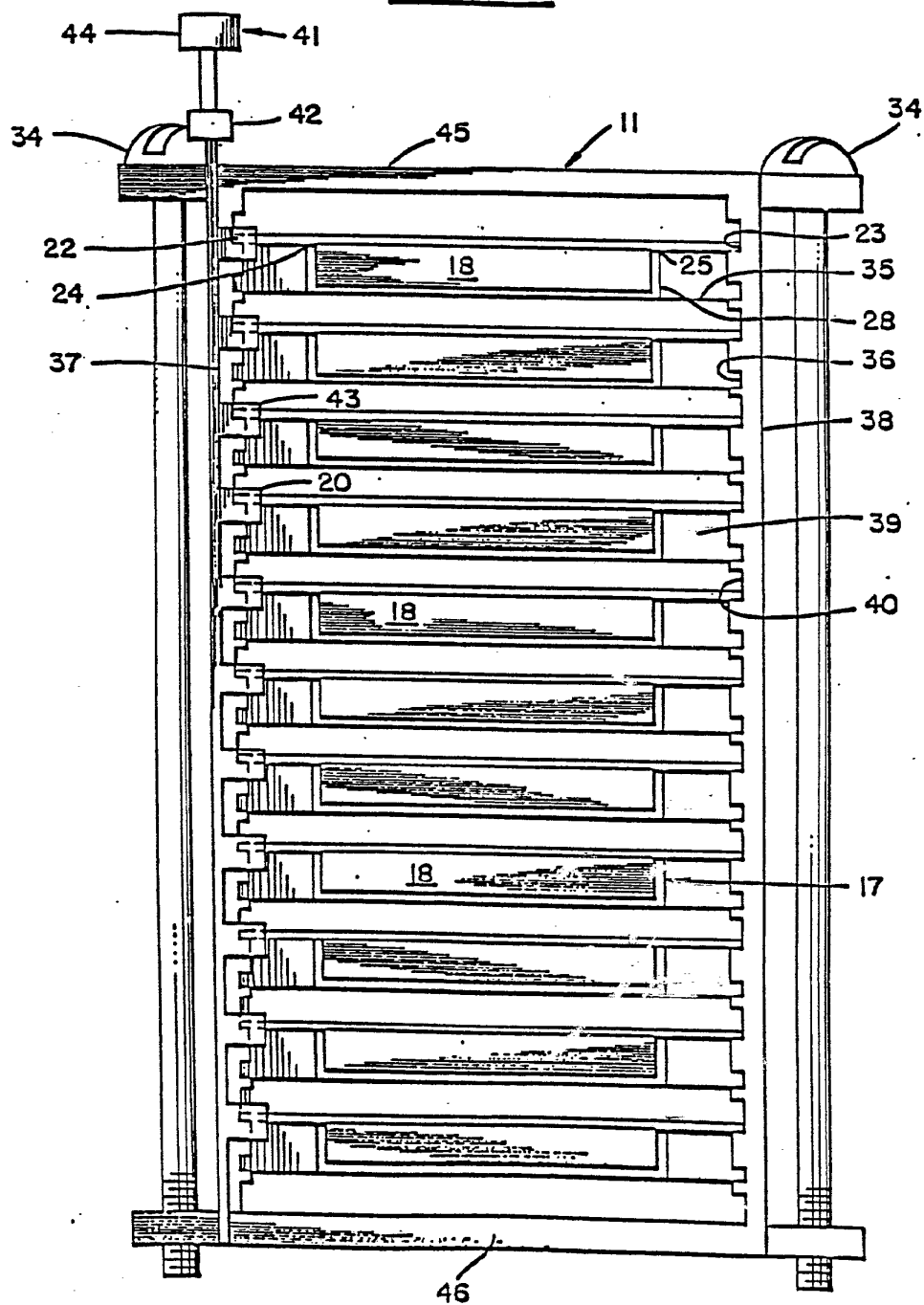
9. A dispenser as in Claim 8 further including a dispense head arranged remotely from said dispenser, said dispense head being arranged to administer said reagent to a desired specimen and conduit means connecting said dispense head to said dispenser.

10. A dispenser as in Claim 8 wherein said reagent containers comprise syringes and wherein said control means is provided for also coordinating the movement of said carousel to position said desired one of said syringes at said dispensing station.

FIG. 1.



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FIG. 2.

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FIG. 3.

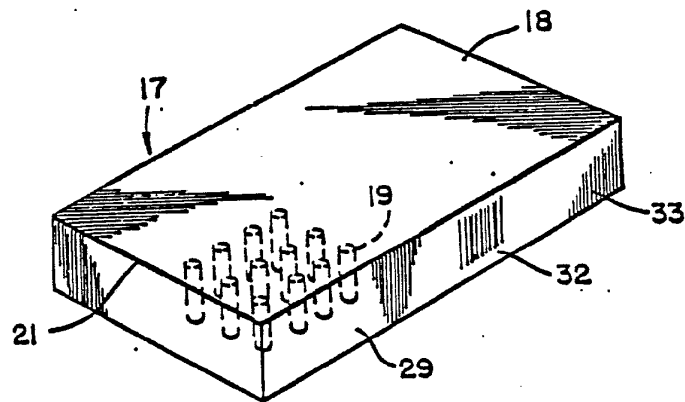
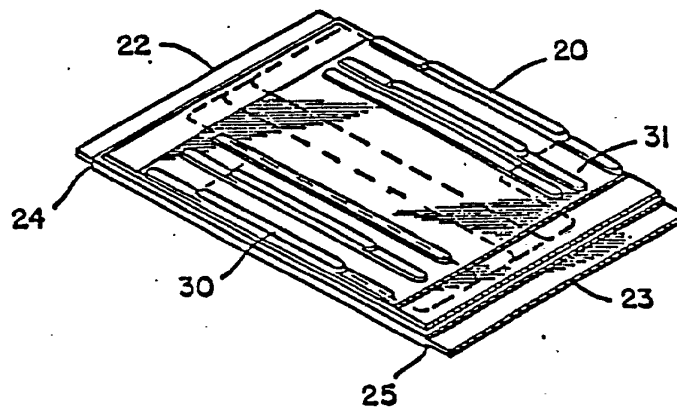


FIG. 4.



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FIG. 5.

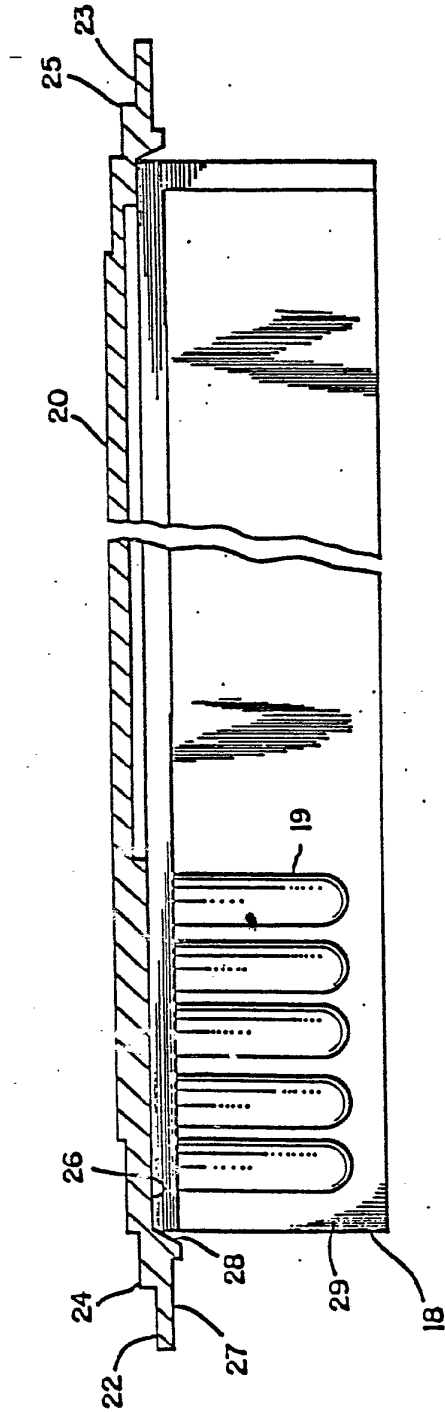
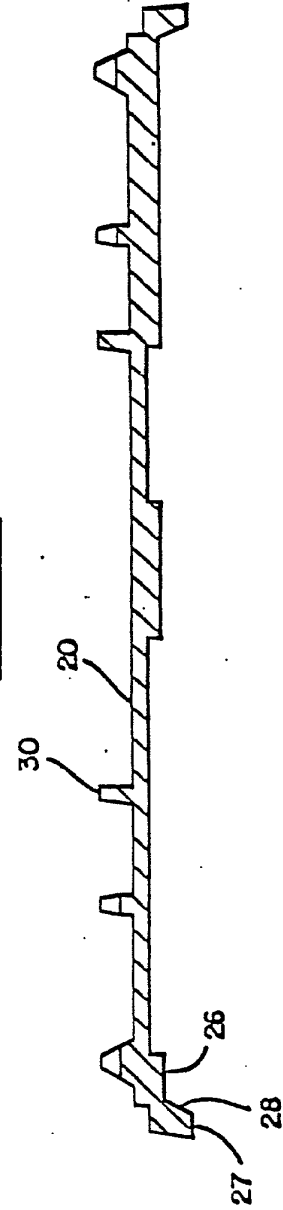


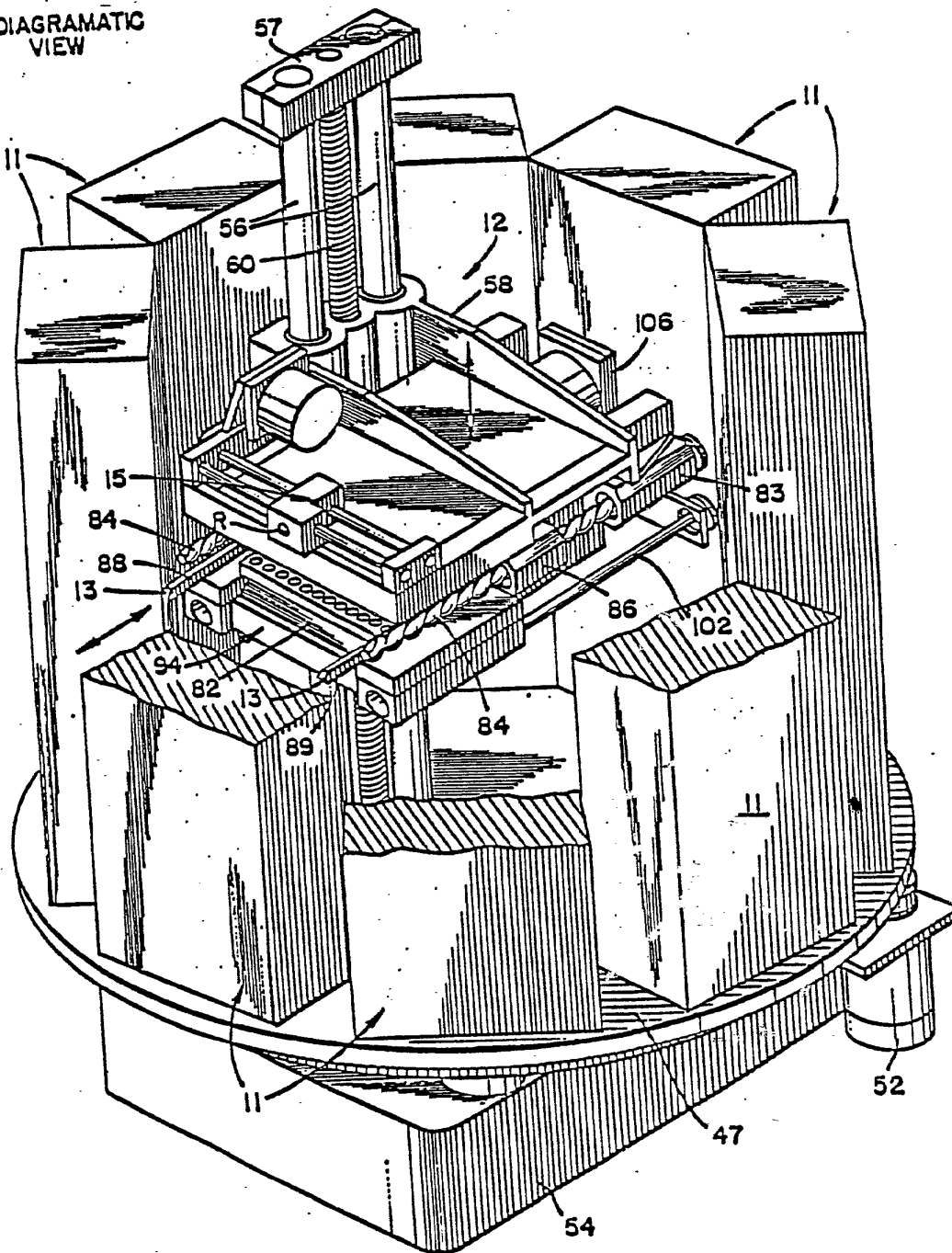
FIG. 6.



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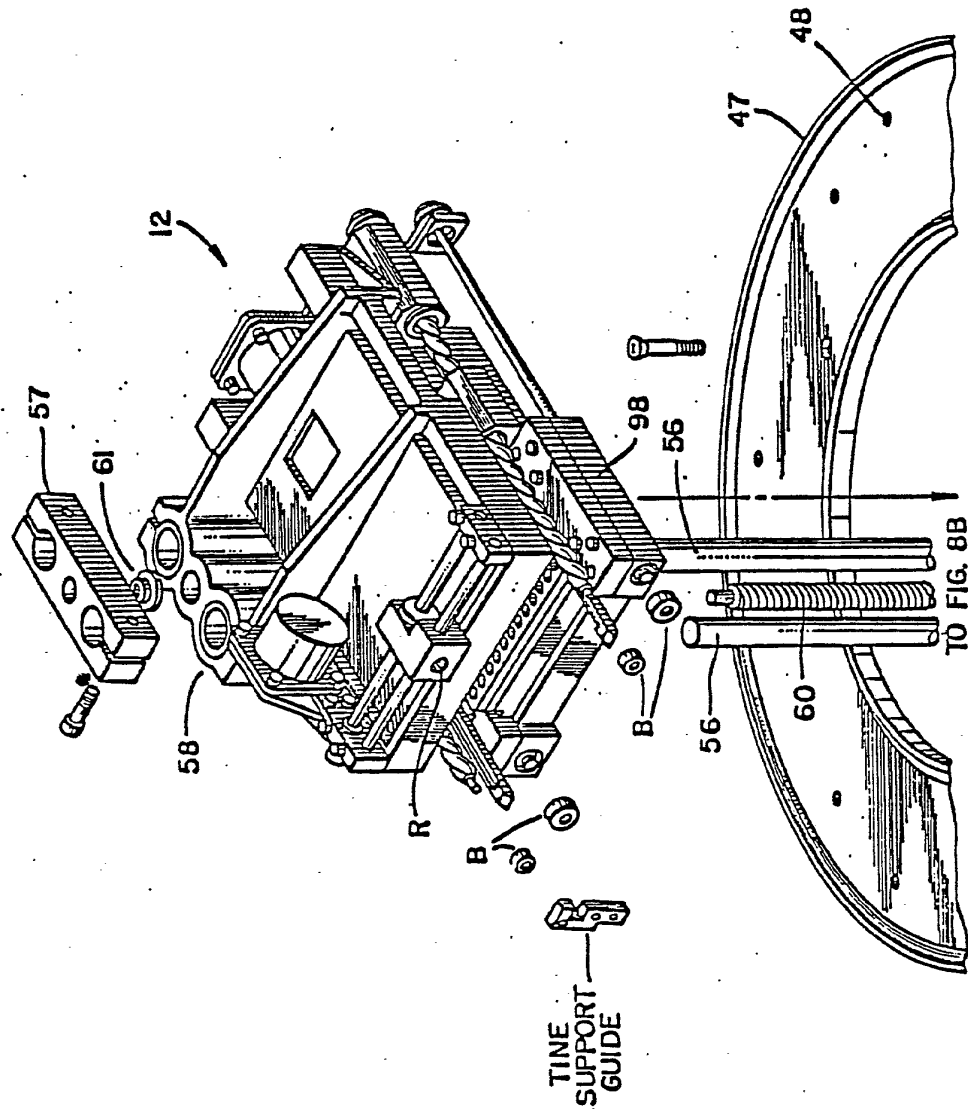
FIG. 7.

DIAGRAMATIC
VIEW



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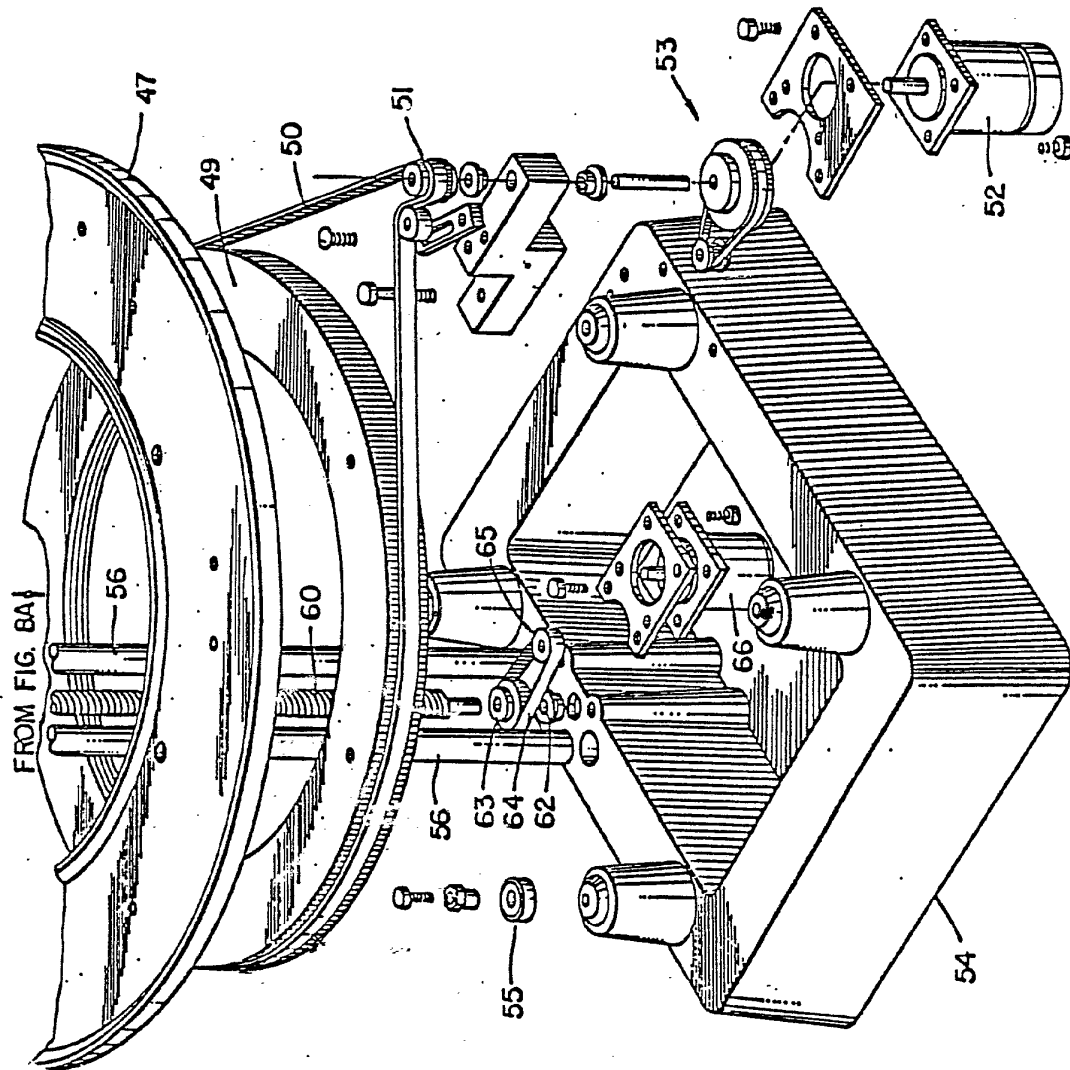
FIG. 8A.



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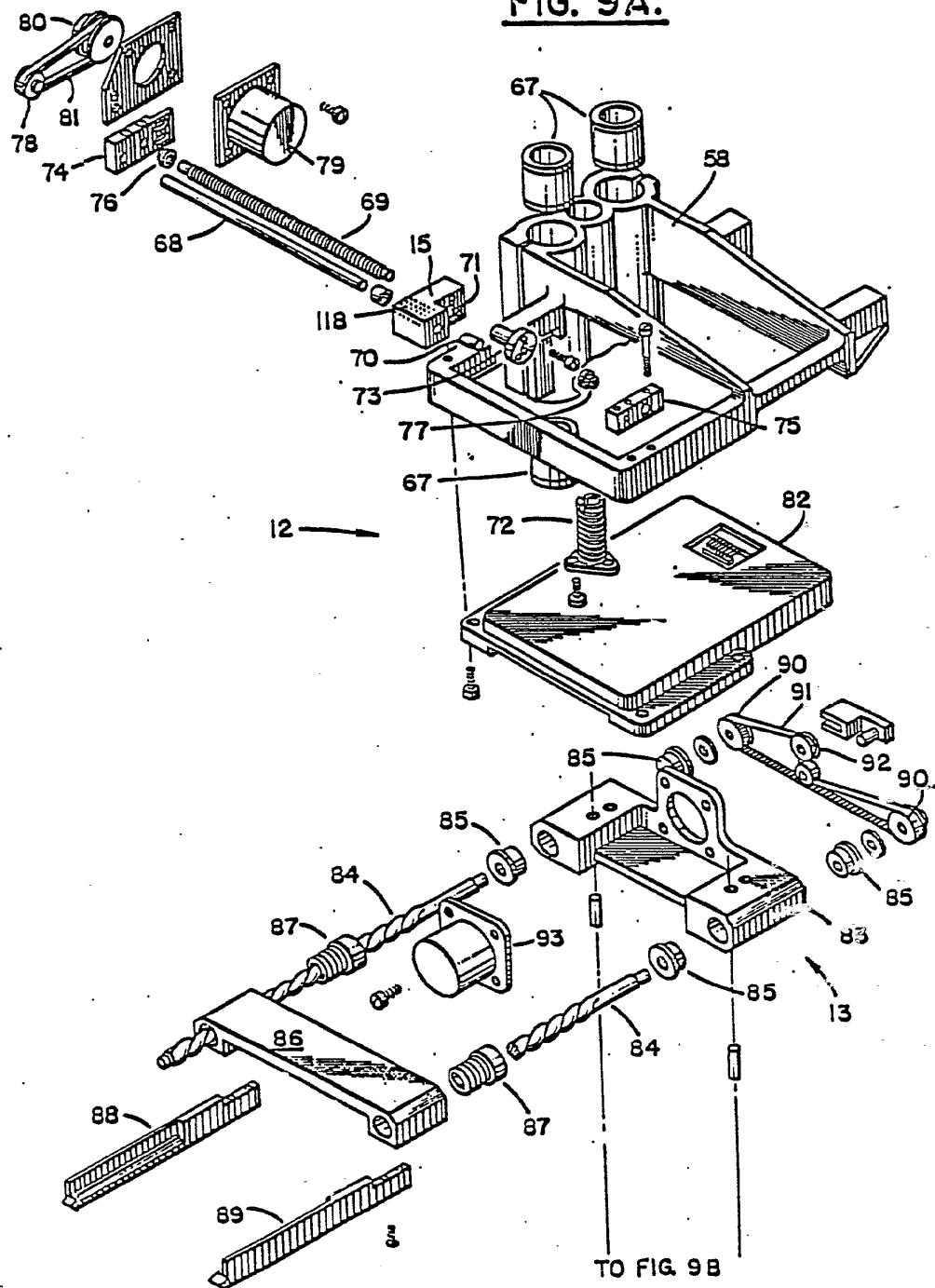
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FIG. 8B.



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FIG. 9A.



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FIG. 10.

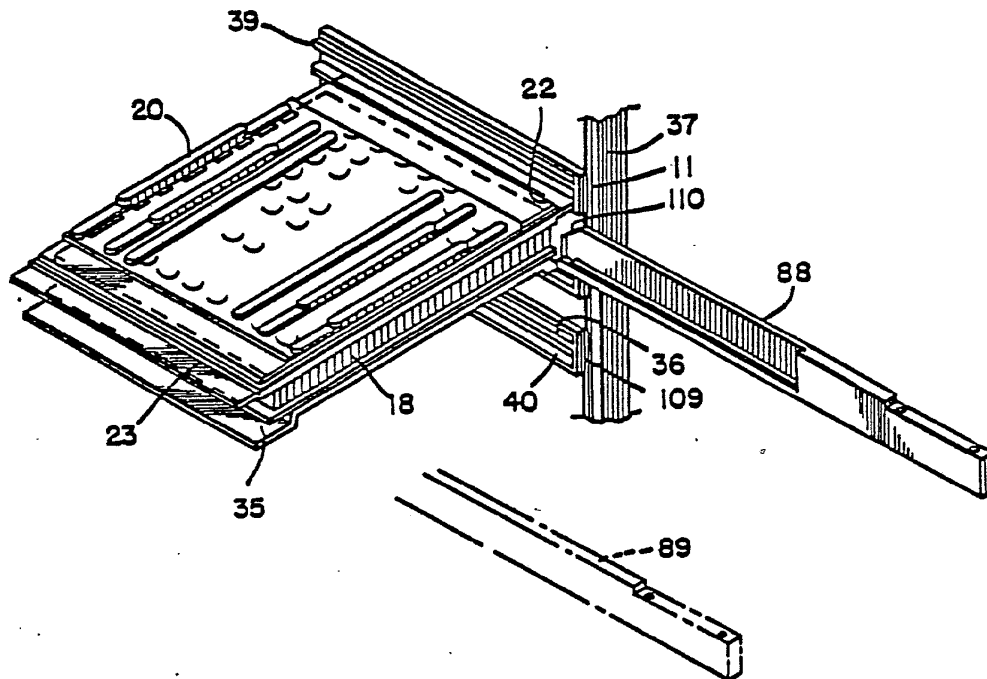
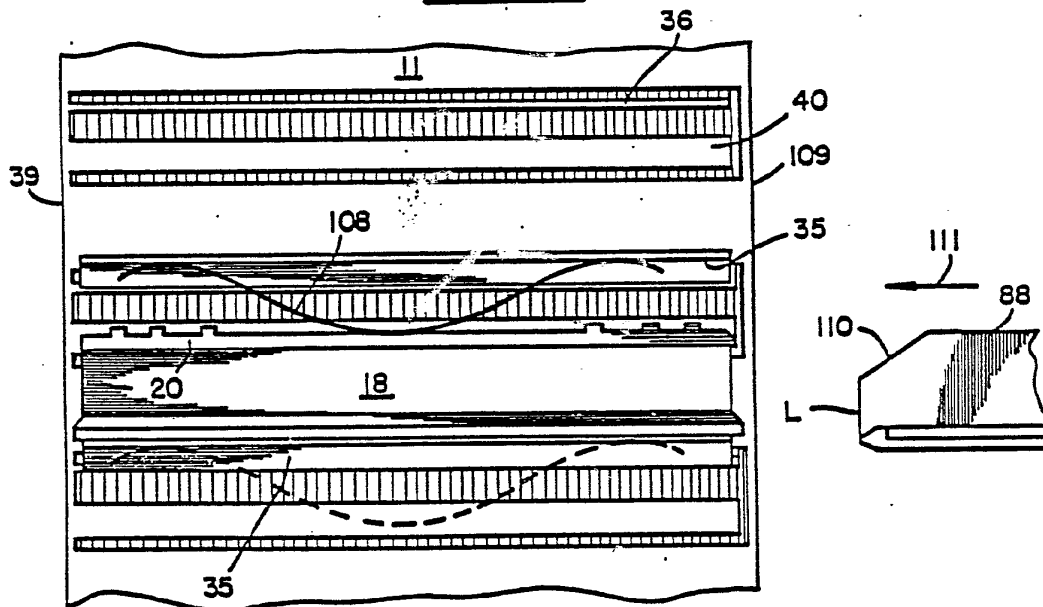


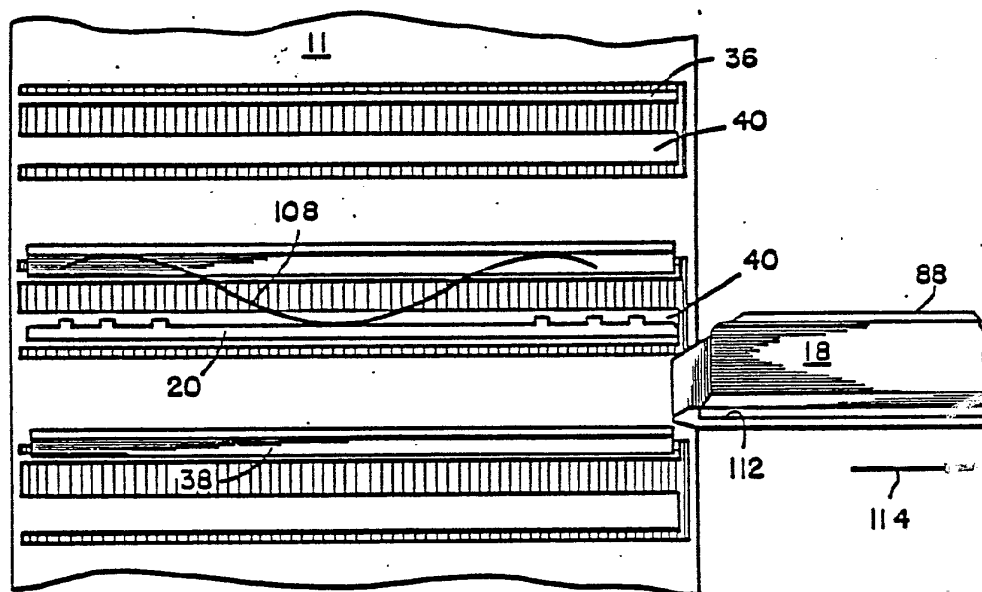
FIG. 11.



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FIG. 14.



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FIG. 12.

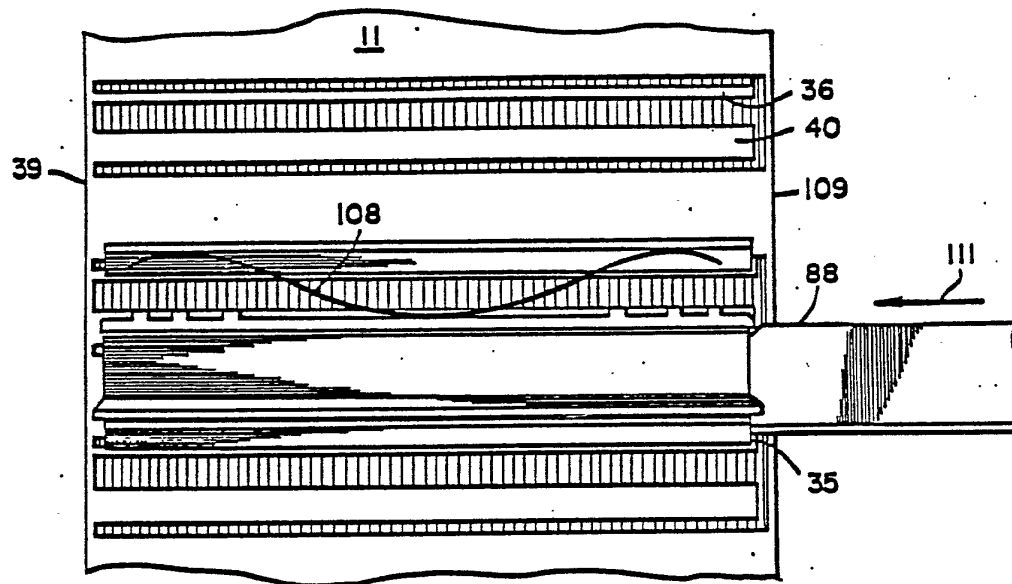
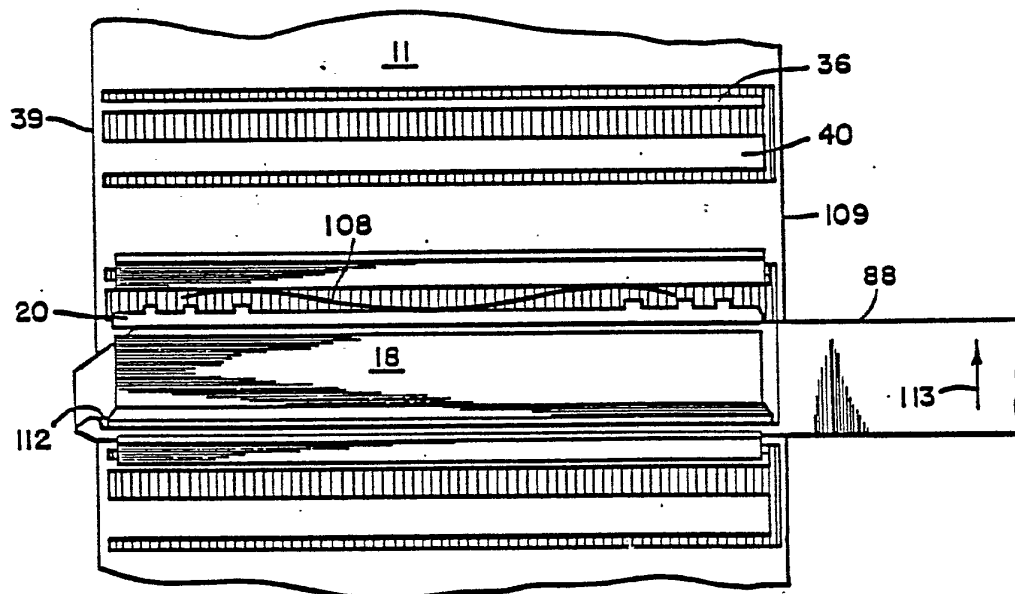
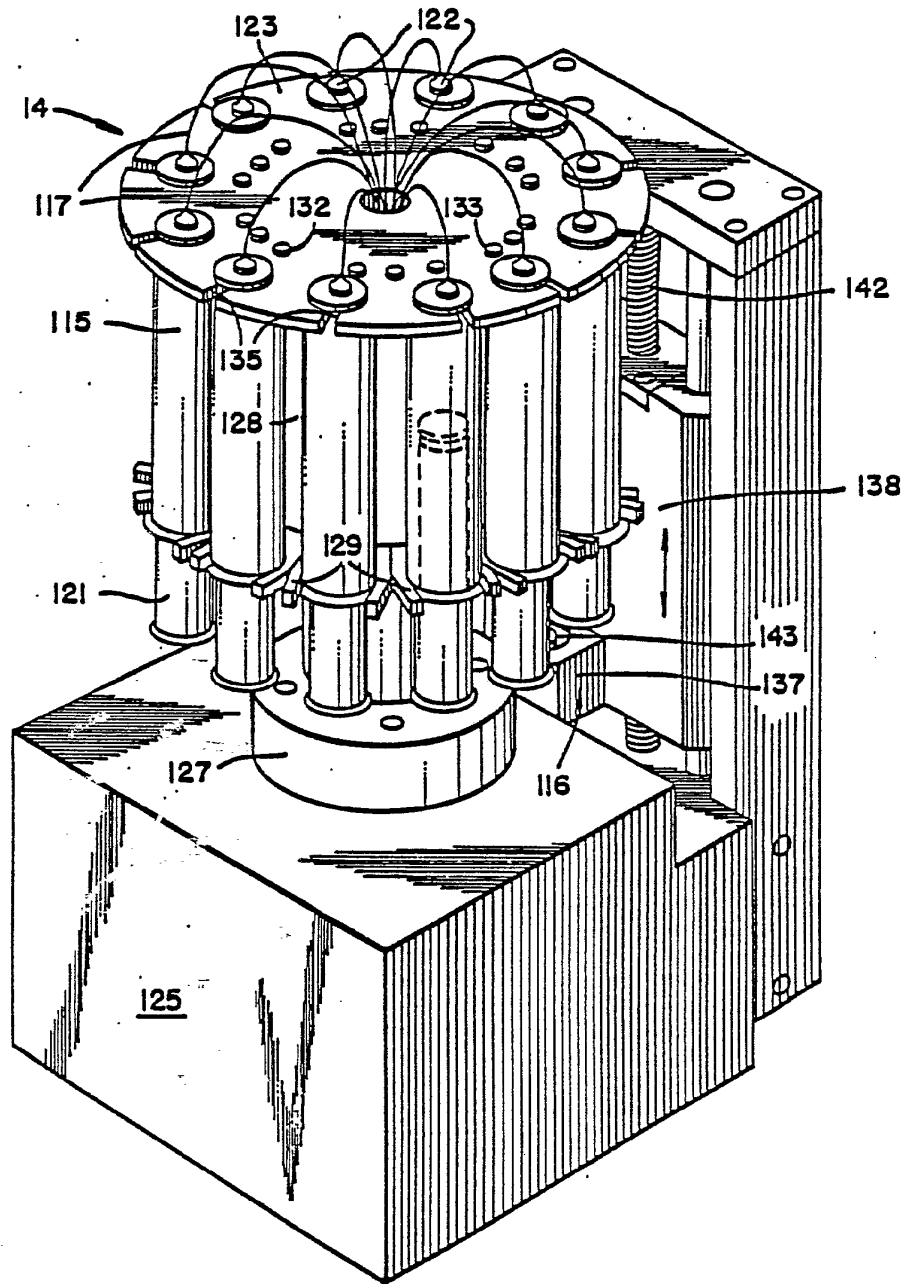


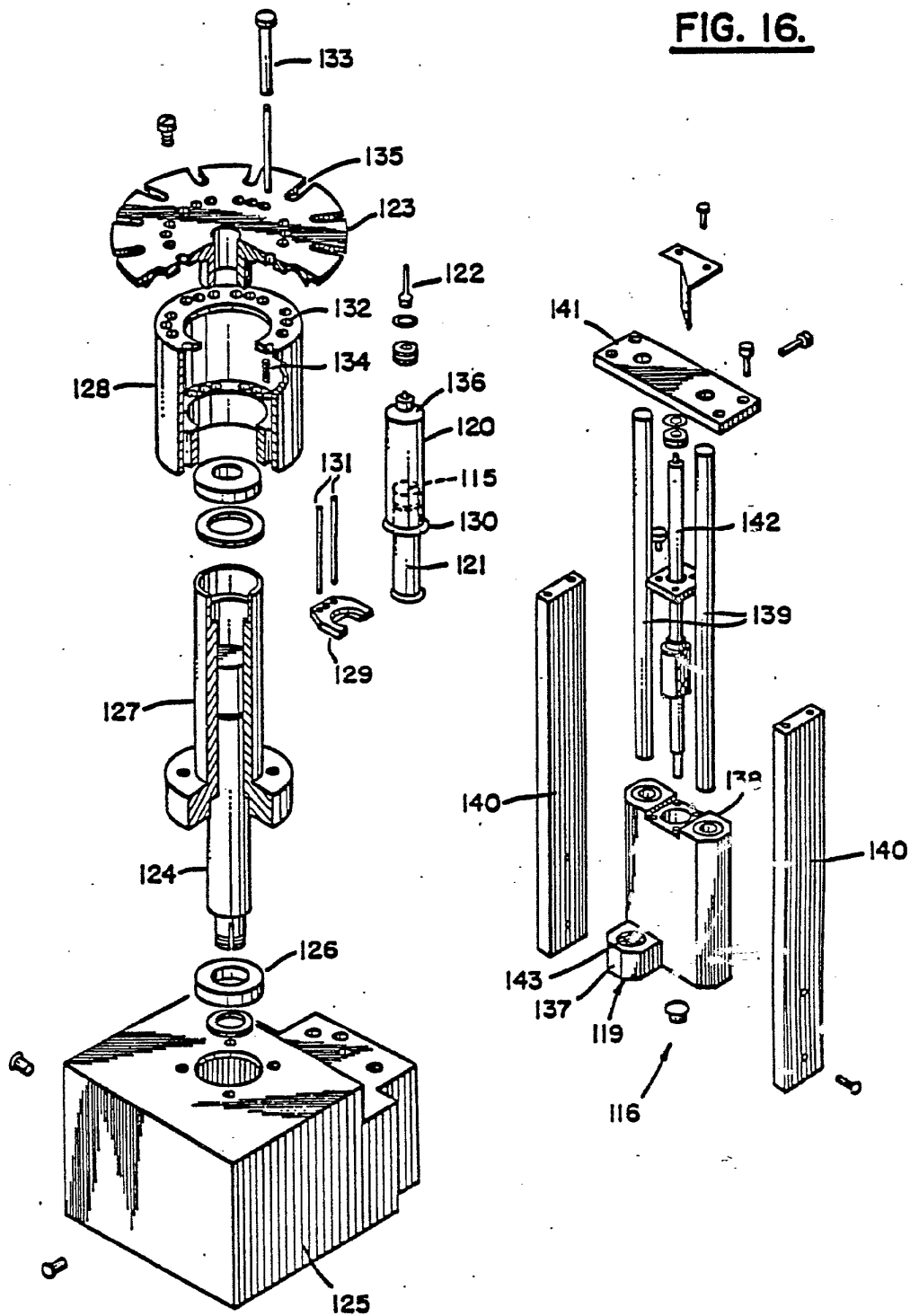
FIG. 13.



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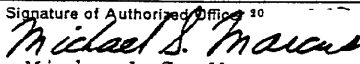
FIG. 15.DIAGRAMATIC
VIEW

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FIG. 16.**SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/01055

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC (4) B01L 3/02, G01N 35/06		
US 422/100 422/63 73/863.32, 864.17		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	73/863.21, 863.32, 864.17, 864.18 222/135, 137, 144, 144.5 422/63, 64, 65, 100	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category [*]	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US, A, 4,458,544 (Gyer) 10 July 1984 see column 4, lines 64-68, column 5, lines 21-53.	1-6
<u>X</u> <u>Y</u>	US, A, 4,096,972 (Bartels) 27 June 1978 see column 4, lines 44-68 column 5 lines 1-10, 51-68.	<u>1, 2</u> <u>3-6</u>
X	US, A, 4,116,067 (Pankratz) 26 September 1978, see entire document.	1,2
<p>[*] Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
23 July 1986	06 AUG 1986	
International Searching Authority ¹	Signature of Authorized Officer ¹⁰	
ISA/US	 Michael S. Marcus	

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[Continued on next page]

(54) Title: ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE

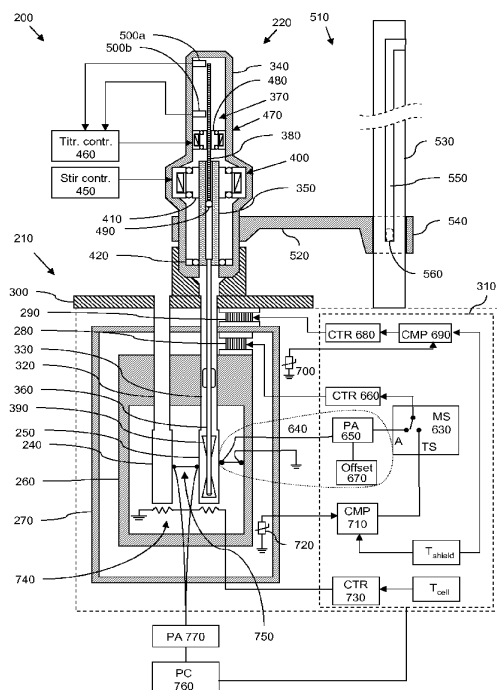


Fig. 2

(57) Abstract: An automatic pipette assembly for an isothermal titration micro calorimetry system, comprising a pipette housing, a syringe with a titration needle arranged to be inserted into a sample cell for supplying titrant, and a linear activator for driving a plunger in the syringe, the titration needle is rotatable with respect to the housing and is provided with a stirring paddle arranged to stir fluid in the sample cell, wherein the automatic pipette assembly comprises a stirring motor for driving the rotation of the titration needle. There is also provided an isothermal titration micro calorimetry system.

WO 2009/059110 A1



European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

ISOTHERMAL TITRATION MICROCALORIMETER
APPARATUS AND METHOD OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 This application claims priority to United States provisional patent application number 60/984,432 filed November 1, 2007; the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

10 1. Field of the Invention.

 The present invention relates generally to microcalorimeters and more specifically to features that improve the performance of microcalorimeters, especially isothermal titration calorimeters.

 2. Background.

- 15 Microcalorimeters are broadly utilized in fields of biochemistry, pharmacology, cell biology, and others. Calorimetry provides a direct method for measuring changes in thermodynamic properties of biological macromolecules. Microcalorimeters are typically two cell instruments in which properties of a dilute solution of test substance in an aqueous buffer in a sample cell are continuously compared to an equal quantity of
- 20 aqueous buffer in a reference cell. Measured differences between the properties of the two cells, such as temperature or heat flow, are attributed to the presence of the test substance in the sample cell.

- One type of microcalorimeter is an isothermal titration calorimeter. The isothermal titration calorimeter (ITC) is a differential device, but operates at a fixed
- 25 temperature and pressure while the liquid in the sample cell is continuously stirred. The most popular application for titration calorimetry is in the characterization of the

thermodynamics of molecular interactions. In this application, a dilute solution of a test substance (e.g., a protein) is placed in the sample cell and, at various times, small volumes of a second dilute solution containing a ligand, which binds to the test substance, are injected into the sample cell. The instrument measures the heat which is evolved or
5 absorbed as a result of the binding of the newly-introduced ligand to the test substance. From results of multiple-injection experiments, properties, such as, the Gibbs energy, the association constant, the enthalpy and entropy changes, and the stoichiometry of binding, may be determined for a particular pairing between the test substance and the ligand.

While currently utilized ITCs provide reliable binding data results, their
10 widespread utilization in the early stages of drug development have been limited by several factors: the relatively high amounts of protein required to perform a binding determination (e.g., about 0.1 milligram (mg) to about 1.0 mg of a protein), the time required to perform the measurement, and the complexity of using conventional ITCs. Due to the extremely high costs of biological substances used in research, there is a need
15 to reduce the amount of biological substance used for each experiment. A reduction in the amount of the biological substance used in a calorimeter experiment, will require a more accurate, sensitive, and reliable titration calorimeter than what is currently available.

Furthermore, gathering binding data utilizing prior art ITCs require extensive preparation and skill by the practitioner. For example, using prior art ITCs, the reference
20 and sample cells are first filled respectively with the reference substance and sample substance via a corresponding cell stem. Next, a syringe of the ITC is filled with a titrant. Then a needle of the ITC is placed in the sample cell via a cell stem leading to the sample cell while the syringe fits into a holder on the ITC enabling the syringe to rotate around its axis. Subsequently, the syringe is aligned with the sample cell so that the needle does
25 not touch either the cell stem or the sample cell. Then, the syringe is connected to a

stirring motor and a linear activator of the ITC, wherein the stirring motor and the linear activator must also be aligned with the sample cell.

As would be appreciated by a reading of the above-described prior art procedure, utilizing prior art ITCs, the quality of binding measurements performed with these prior art ITCs depends heavily of the operator's skills and experience, and involves a
5 considerable amount of preparation time.

More recently developed prior art ITCs have attempted to simplify the preparatory procedures described above. For example, in one such prior art ITC, which is partly shown in Figure 1 as ITC 100, a syringe 102, a syringe holder 104, and a linear actuator
10 106, which actuates syringe 102's plunger, are integrated into a single unit referred to as an automatic pipette. ITC 100 further comprises a stirring mechanism comprising a stirring motor 108, which is attached to calorimeter body 110. ITC 100 also comprises an inner magnet couple 112 located around syringe 102, and an outer magnet couple 114 located on calorimeter body 110 in close proximity to stirring motor 108. The rotation
15 from stirring motor 108 to syringe 102 is transferred via magnet couplings 112 and 114. Attached to syringe 102 is a needle 116 and a paddle 118. The needle 116 is arranged to be inserted into a sample cell 120 via a cell stem 122 for performing ITC experiments. For reference purposes, ITC 100, also comprises a reference cell, not shown, in communication with the ambient atmosphere via a reference cell stem.

20 The prior art design discussed above and depicted in Figure 1 has certain limitations. For example, since the magnet coupling is a soft/flexible transmission, it is prone to resonant vibration of the stirrer at certain rotation speeds and accelerations, which negatively affects the instrument's sensitivity. The resonant vibration can be reduced by either employing a less sensitive feedback mechanism controlling the rotation
25 speed (which leads to less stable rotation speed), or by lowering the rotation speed.

However, less stable rotation speed also reduces the ITC's sensitivity, while lower rotation speed impedes proper mixing of reagents which reduces the ITC's accuracy.

Another limitation of the prior art design is that the stirring motor and the magnet coupling are placed closely to the sensitive measuring unit of the instrument and
5 generates a substantial alternating magnetic field that produces electric noise which negatively affects the operation of the ITC's sensitive electronic circuitry. Since the ITC's sensors process signals of approximately 10^{-9} volts, and the noise generated by the motor and the magnetic coupling is a reciprocal of the distance between the sensor and the source of the noise, further improvements in the performance characteristics of this
10 ITC design become increasingly challenging. As stated earlier, one of the underlying factors affecting the design of new microcalorimeters is the need to reduce the amount of biological substance used for each experiment. This requires smaller sample cells and shorter cell stems which in turn leads to, smaller distances between the cell sensor and the motor and magnetic coupling (source of electric noise), which limits the instrument's
15 sensitivity.

The invention described herein is aimed to improve the aforementioned characteristics and use of prior art ITCs such that the sensitivity of the ITC is improved, the amount of biological substance necessary for testing is reduced, the reliability of the results generated by the ITC is improved, and use of the ITC is eased.

20

SUMMARY OF THE INVENTION

The object of the invention is to provide a new automatic pipette assembly for an isothermal titration micro calorimetry system and an ITC system, which pipette assembly and ITC system overcomes one or more drawbacks of the prior art. This is achieved by
25 the pipette assembly and the ITC system as defined in the independent claims.

One advantage with the present pipette assembly and the associated ITC system is that it makes it possible to reduce the cell compartment volume by about a factor of seven as compared to prior art ITCs, without a reduction in sensitivity, and with a significantly faster response time. Such an ITC system permits the performance of experiments with about 10 times less protein sample, and with only a total of about 2 to about 4 titrations per hour.

In addition to reducing the costs associated with running the ITC experiment, a smaller cell volume also extends the number of ITC applications. For example, the range of binding affinities that can be measured by ITC is dictated by a parameter called “c value,” which is equal to the product of the binding affinity (K_a) and the total concentration (M_{total}) of macromolecule ($c = [M_{total}]K_a$). For accurate affinity determination, the c value must be between 1 and 1,000. A decrease in the cell volume by a factor of ten results in a similar increase in c value if the same amount of protein is used, and, consequently, the ability to measure weak binders. This ability is especially important in the early stages of drug discovery, in which binding affinities are weak, especially in conjunction with a fully automated instrument.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic example of a prior art isothermal titration microcalorimeter highlighting the automatic pipette feature of the microcalorimeter;

Figure 2 shows, in cross-section, a schematic embodiment of an isothermal titration calorimeter system of the present invention with a guiding mechanism;

Figure 3 shows, in cross-section, a schematic embodiment of an automatic pipette assembly for an isothermal titration micro calorimetry system;

Figure 4 shows a section of the ITC system shown in fig. 2, wherein the pipette

assembly is retracted from the sample cell;

Figures 5a to 5c show a schematic embodiment of a guiding mechanism for an isothermal titration calorimeter system in perspective;

Figure 6 shows another schematic embodiment of a guiding mechanism for an isothermal titration calorimeter system in perspective.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 2 schematically shows one embodiment of an ITC system 200 according to the present invention. The ITC system 200 comprises a micro calorimeter 210 and an automatic pipette assembly 220. The micro calorimeter 210 comprises a reference cell 240 and a sample cell 250 which are designed to be essentially identical in heat capacity and volume. The cells 240 and 250 are comprised of a suitable chemically inert and heat conductive material, such as gold, Platinum, tantalum, hastelloy or the like. The cells 240 and 250 may be of essentially any suitable shape, but it is desirable that they are of the same shape, that they are possible to arrange in a fully symmetric arrangement, and that efficient mixing of the titrant with the sample may be achieved. In the disclosed embodiment, the cross-section of the cells 240 and 250 is rectangular, and the cross-section in the transverse horizontal direction may be circular, resulting in coin shaped cells with circular facing surfaces.

In order to reduce any external thermal influences to a minimum, the, reference cell 240 and the sample cell 250 are both enclosed by a first thermal shield 260 which in turn is enclosed by a second thermal shield 270. The thermal shields 260, 270 may be comprised of any suitable thermally conductive material such as silver, aluminum, copper or the like. The shields 260, 270 may further be comprised of one or more thermally interconnected sub shields (not shown, to provide even further stable temperature

conditions for the calorimetric cells 240, 250.

In order to control the temperature of the shields 260, 270, thermal control means may be arranged to control the temperature thereof. In an ITC system said thermal control means are mainly used to set the “isothermal” temperature of the calorimeter, ie. of the thermal shields 260, 270, before the titration experiments are initiated. But as will be disclosed in greater detail below, said thermal control means may also be used to improve the adiabatic behavior of the calorimeter. According to one embodiment, the thermal control means are comprised of one or more heat pump unit, such as a thermoelectric heat pump device based on the peltier effect or the like. Other types of thermal control means include thermostatically controlled liquid baths, mechanical heat pumps, chemical heating or cooling systems or the like.

In the disclosed embodiment a first heat pump unit 280 is arranged to transfer heat energy between the first 260 and second thermal shields 270, a second heat pump unit 290 is arranged to transfer heat energy between the second thermal shield 270 and a heat sink 300 in thermal contact with the ambient temperature. A temperature controller 310 is arranged to control the first and second heat pump units 280, 290 so that the desired temperature conditions are achieved. The temperature controller 310 and associated sensors will be disclosed in more detail below.

A reference cell stem 320 and a sample cell stem 330 provides access to the reference cell 240 and sample cell 250, respectively, for supplying reference and sample fluids, titration fluid, washing of the cells etc. In the disclosed embodiment, the cell stems 320 and 330 both extends essentially vertically through both thermal shields and the heat sink to provide direct communication with cells 240 and 250 and the cell stems 320 and 330 each support their respective cell 240 and 250 in the cavity of the first thermal shield 260.

The automatic pipette assembly 210 comprises a pipette housing 340, a syringe 350 with a titration needle 360 arranged to be inserted into the sample cell 250 for supplying titrant, and a linear activator 370 for driving a plunger 380 in the syringe 350. The titration needle 360 is rotatable with respect to the housing 340 and is provided with
5 a stirring paddle 390 arranged to stir sample fluid in the sample cell 250 in order to achieve efficient mixing of titrant and sample fluid. The automatic pipette assembly 210 further comprises a stirring motor 400 for driving the rotation of the titration needle 360.

In the embodiment disclosed in fig. 2 the stirring motor 400 is a direct drive motor with a hollow rotor 410 arranged concentric with the syringe 350 and the titration needle
10 360. The syringe 350 is at its upper end supported for rotation by the stirring motor 400 and at the lower end by a bearing 420. Both the stirring motor 400 and the bearing 420 are schematically disclosed as comprising ball bearings, but any other type of bearing, bushings or the like capable of providing smooth and low friction rotation of the titration needle 360 may be used.

In the embodiment disclosed in fig. 2, the syringe 350 is arranged to be rotatable with respect to the housing 340 and the titration needle 360 is non-rotatably attached to the syringe 350. In an alternative embodiment (not shown in figs.), the needle 360 is rotatable with respect to the syringe 350 and the syringe 350 static with respect to the pipette housing 340. Fig. 3 shows an alternative embodiment, wherein the syringe 350 is
15 detachably arranged in a rotation frame 430 within the pipette housing 340, the rotation frame 430 being rotably supported by the motor 400 and bearing 420. In the disclosed embodiment, the syringe 350 is retained in the rotation frame 430 by a cap 440 that is detachably attached to the rotation frame 430 by threads or the like. By removing the cap
20 440, the syringe 350 with the titration needle 360 can be replaced.

In an alternative embodiment, not shown in the figures, the stirring motor 400
25

drives the titration needle for rotation by a rotation transmission arrangement, such as a drive belt arrangement, a drive wheel arrangement or the like. In such an arrangement, the drive motor may be placed at an ever greater distance from the calorimetric cells.

The stirring motor is controlled by a stir controller 450 of the ITC system. The stir
5 controller be a conventional BLDC. The linear actuator is controlled by a titration controller 460 of the ITC system. The stir and titration controllers 450, 460 may be arranged in the pipette assembly 220, and in turn connected to the ITC control system (not shown in detail), or they may be an integrated part of the ITC control system.

In the disclosed embodiment, the linear activator 370 comprises a stepper motor
10 470 arranged to drive a threaded plunger 380 that extends coaxially through the hole of a hollow rotor 480 and into the syringe 350 wherein it is rotatably attached to a pipette tip 490 that seals against the inner wall of the syringe 350 to allow displacing a precise volume of titration liquid from syringe 350. The pipette assembly further comprises position sensors 500a, 500b for detecting two predetermined positions of the threaded
15 plunger 380. The linear activator 370 may be of any other type capable of perform controlled linear motion with sufficient precision. This design allows syringe to be rotated independently of the main body 340 of the pipette assembly 220; at the same time, the linear activator 370 can drive the threaded plunger 380.

In the ITC system the titration 460 controller is arranged to control the linear
20 activator of the pipette assembly 220. According to one embodiment, titration controller 460 uses the position sensors 500a, 500b for detecting two predetermined positions of the threaded plunger, and the titration controller 460 is arranged to register the two predetermined positions of the threaded plunger 380 and to determine the pitch of the threads of the plunger 380 from the number of steps performed by the stepper motor 470
25 to move the threaded plunger 380 between said positions. The so determined pitch of the

threaded plunger is thereafter used by the pipette controller to increase the accuracy of the titration pipette, when displacing small volumes of titrant.

In the disclosed embodiments, the pipette assembly housing 340 serves as mounting base for the stators of the stirring motor 400 and the linear activator 470. The
5 housing 340 may further comprise an attachment section for precise positioning of the pipette assembly with respect to the sample cell stem.

The automatic pipette assembly 220 with an integrated stirring motor 400 arranged at the upper end of, or above the syringe 350 not only increases the distance between the stirring motor 400 (i.e., the source of an alternating electro-magnetic field)
10 and the sensitive electronic circuitry, which is located at and/or nearby the thermal core of the calorimeter, but it also allows for the reduction in the amount of power needed to operate the stirring motor 400. That is, due to the placement of the stirring motor 400 on the pipette assembly 220, the size of the stirring motor 400 is not determined by the space between the sample cell and the reference cell as it is determined by prior art ITCs that
15 place the stirring motor on the calorimeter housing (fig. 2). In the prior art, then, the cell stems protrude through the center of rotation of the magnetically coupled stirrer. Therefore, the lower limit of size for the stirrer mechanism is determined by the spacing between the cell stems. Accordingly, the size of the stirring motor of the present invention can be significantly reduced, e.g., by a factor of about 5 times that of stirring
20 motors found in prior art ITCs, thereby resulting in a significant reduction in the amount of power needed to operate the ITC, e.g., about 2 watts versus the 100 watts used to power conventionally known ITCs.

The reduction in size of the stirring motor to a size of about five times less than stirring motors of prior art ITCs, and the placement of the stirring motor on the pipette
25 such that the stirring motor is at a distance of about 50 millimeters or more away from the

sensitive electronic circuitry of the calorimeter, and the removal of the magnetic coupling, closes the magnetic field that exists in conventionally used ITCs. Accordingly, the sensitivity of the inventive ITC is raised by the lower power, the lower heat, the lower electricity, and the lower noise and vibration caused by the placement of the stirring
 5 motor as disclosed herein. Furthermore, the disclosed embodiments also exclude magnetic coupling which is an additional source of alternating electro-magnetic field.

These improvements reduce the electrical noise induced in the sensitive electronic circuitry which, in turn, helps improve the calorimeter's sensitivity, whereby the volume of the sample and reference cells may be significantly reduced. Reducing the size of the
 10 sample cell and its corresponding cell stem, in turn, reduces the amount of biological substance used for each experiment.

The following Table 1 represents certain key dimensions of the cell stems and test and reference cells of both the prior art ITC and the ITC of the present invention. As shown in Table 1, the inventive ITC, which places the stirring motor directly on the
 15 pipette subassembly, rather than positioning it on the calorimeter body, allows a smaller volume of test substance to be used, thereby reducing the costs associated with conducting calorimeter experiments.

Table 1		
	Prior Art ITC	Inventive ITC
Stem Interior Diameter	2.6 millimeters	2.0 millimeters
Cell stem Length	72.0 millimeters	40.5 millimeters
Cell stem Volume	382.0 microliters	127.0 microliters
Cell Interior Diameter	22.0 millimeters	11.0 millimeters
Cell Thickness	3.7 millimeters	2.2 millimeters
Cell Volume	1,400 microliters	200 microliters

According to one embodiment, the micro titration calorimetry system 200 is

provided with a pipette guiding mechanism 510 arranged to guide the pipette assembly 220 between and into at least two positions of operation. The first position of operation is a pipette washing position 580 wherein the titration needle 360 is inserted in a washing apparatus (see figs 5a-5c), and the second position of operation is a titration position 560 wherein the syringe is inserted into the sample cell 250 for calorimetric measurements. In the embodiment of fig 2, the guiding mechanism 510 is comprised of a pipette arm 520 that supports the pipette assembly 220, and an essentially vertical guide rod 530. The pipette arm 520 is moveably attached by a sleeve 540 to the guide rod 530, but its motion about the guide rod is restricted by a guide groove 550 in the guide rod 530 and a guide pin 560 that protrudes from the inner surface of the sleeve 540 and which fits into the guide groove 550. The disclosed guiding mechanism 510 is of rotational type, and the positions of operation are arranged at equal distance about the centre of rotation of the guide assembly but at different angular positions, wherein movement of the pipette assembly 220 in the vertical direction is restricted to the angular positions of the positions of operation, and wherein rotational movement of the pipette assembly 220 between the angular positions only is permitted when the titration needle 260 is fully retracted from respective positions of operation. Fig. 4 shows the guide mechanism 510 in a position wherein the pipette assembly 220 is fully retracted from the titration position, i.e. from the sample cell 250. At this position the guiding mechanism 510 restricts the possible movement of the pipette arm 520 to a vertical movement down into the titration position, or a rotational movement to reach another position of operation. In a micro titration calorimetry system 200 with two positions of operation, the washing apparatus 600 may be arranged to allow filling of titrant to the pipette assembly 220 after washing of the pipette assembly is completed. Alternatively, filling of the pipette may be performed through other means, such as a specific filling port in the syringe or the like.

Figs. 5a to 5c show a schematic perspective view of one embodiment of a micro titration calorimetry system 200 with a pipette guiding mechanism 510, arranged to guide the pipette assembly 220 to and from three different positions of operation 560, 570, 580. According to one embodiment, the third position of operation is a titrant filling position 570, wherein the titration needle 360 is inserted in a titrant source 590. Fig. 5a shows the guiding mechanism 510 in a state wherein the pipette assembly 220 is in the titration position 560. Fig. 5b shows the guiding mechanism 510 in a state intermediate the titration position 560 and the filling position 570. Fig. 5c shows the guiding mechanism 510 in a state wherein the titration needle 360 of the pipette assembly 220 is in the filling position 570. As is disclosed in figs. 4a to 5c, the vertical guide grooves 550 associated with a specific position of operation 560, 570, 580 may be arranged to position the pipette assembly 220 at a predetermined height with respect to the operation to be performed.

Fig. 6 shows another embodiment of the guide mechanism 510, wherein the guide groove in the guide rod 530 is replaced by a coaxial external guide sleeve 610 with corresponding guide paths 620 for the guide arm 520.

According to one embodiment, the micro titration calorimetry system 200 comprises one or more position sensors, not shown, arranged to register when the pipette assembly 220 is positioned at one or more of the positions of operation 560, 570, 580, and wherein the associated operation is restricted by the state of the position sensor. A sensor may, e.g. be arranged to register when the pipette assembly 220 is in correct position for titration 560, and the calorimetry system 200 may be arranged to prevent start of a titration operation unless said sensor confirms that the pipette assembly 220 is in correct position.

Again referring to the figures, the guiding mechanism 510 ensures proper alignment and positioning of pipette assembly 220 in the sample cell 250 etc. All

elements of the pipette assembly 220 (syringe, needle, paddle, plunger, linear activator, hollow rotor) and the guiding mechanism 510 are preferably precisely aligned during the manufacturing process and do not require any additional alignment during the use of the instrument. The pre-set factory alignment significantly improves usability and reliability of the instrument, considerably reduces the amount of preparatory time for an experiment, and makes the quality of measurements independent of the user skills. The guiding mechanism 510 also enables proper positioning of the pipette assembly 220 in the washing apparatus 600 for cleaning and drying of the syringe and e.g. for filling the syringe with titrant.

10 An exemplary method for utilizing the ITC apparatus disclosed herein comprises the non-manual alignment, both in depth and in breadth, of the syringe for filling titrant, washing the pipette, and delivering the titrant to the syringe.

 An exemplary method for operating the inventive ITC apparatus comprises using the guiding mechanism 510 to position the pipette for filling the syringe with titrant (see Figure 5c). In this position, the end of the needle with the paddle is placed in the titrant. The plunger of the syringe is moved from its lower position to its upper position thereby filling the syringe with the titrant. The sample cell is filled with the sample solution via the cell stem using an auxiliary syringe. Using the guiding mechanism, the pipette is moved to a position for performing an experiment (see Figure 5a). The program for performing the experiment is activated. Consistent with the program used for the experiment, the rotor of the stirring motor rotates the syringe, needle, and paddle with the assigned speed enabling proper mixing of the reagents. Consistent with the program used for the experiment (e.g., when a certain temperature and/or equilibrium are reached), the linear activator moves the plunger and injects the titrant into the sample solution. The injection can be done discretely (step-by-step) or continuously, depending on the program

settings. The calorimeter continuously measures and records the heat release/absorption versus time associated with the interaction of reagents. The analysis of the results is done according to the established algorithm.

Referring again to fig. 2, the temperature controller 310 is arranged to control the first and second heat pump units 280, 290 in accordance with predetermined control-modes. The temperature controller 310 is schematically disclosed by functional blocks, and it may either be designed as an electronic circuit, as a software in a CPU based controller, or as a combination thereof. In the disclosed embodiment, the thermal controller 310 may be switched between two modes of operation:

- Isothermal mode
- Thermal set mode

by means of a mode select block 630.

In the isothermal mode the thermal controller 310 is arranged to control the first heat pump 280 to minimize the temperature difference between the sample cell 250 and the first thermal shield 260. The temperature difference between the sample cell 250 and the first thermal shield 260 is registered by a temperature sensor arrangement 640 in communication with the temperature controller 310. In the disclosed embodiment, the temperature sensor arrangement 640 is a differential thermocouple that gives a non-zero signal when there is a temperature difference between the two points of registration, and the output from the thermocouple is connected to a preamplifier block 650 in the temperature controller 310. The out-put from the preamplifier 650 is directed by the mode select block 630 to a first heat pump controller block 660 that controls the first heat pump 280 in response to the signal from the preamplifier 650. By this arrangement, the first heat pump controller 660 will strive to compensate for any thermal difference between the sample cell 250 and the first thermal shield 260, whereby a compensated adiabatic

state is achieved in the calorimeter 210. In order to compensate for minor systematic drifts in adiabatic behavior, an offset parameter 670 may be applied on the signal from the preamplifier 650. The offset parameter 670 may be set during calibration of the calorimeter 210. In the isothermal mode, the temperature controller 310 is arranged to

5 control the second heat pump 290 to keep the second thermal shield 270 at a predetermined temperature, as is defined by a parameter T_{shield} . The control of the second heat pump 290 is performed by a second heat pump controller block 680 that receives an output from a second comparator block 690 wherein T_{shield} is compared with the present temperature of the second shield registered by a second shield thermal sensor 700,.

10 In the temperature set mode the temperature controller 310 is arranged to control the first and second heat pump 280, 290 to bring the first and second thermal shields 260, 270 to a predetermined temperature, defined by the temperature T_{shield} . This mode is mainly used to bring the calorimeter 210 to the temperature at which the ITC experiments are to be run. In this mode, a first comparator block 710 compares T_{shield} with the present

15 temperature of the first shield registered by a first shield thermal sensor 720, and the output from the first comparator block 710 is directed by the mode select block 630 to the first heat pump controller 660. The second heat pump 290 is controlled in the same manner as in the isothermal mode. The thermal set mode may further be used as a stand by mode in order to keep a constant temperature in the calorimeter 210.

20 The temperature controller 310 may further comprise a cell temperature controller block 730 for controlling cell heating elements 740 arranged to heat the sample and the reference cells 240, 250 in accordance with a predetermined temperature set by a parameter T_{cell} . The cell heating elements 740, are mainly used for fine tuning of the temperature of the cells 240, 250.

25 The parameters T_{shield} , T_{cell} and offset may be set via a dedicated user interface of

the thermal controller, not shown, or e.g. via a calorimeter user interface run on a computer 760 or the like. Calorimetric sensors 750 for sensing the temperature difference between the sample cell 250 and reference cell 240 during the ITC experiments may be connected to the computer 760, e.g. via a preamplifier 770.

5 With respect to the above description, it is to be realized that the optimum dimensional relationships for the parts of the invention, to include variations in size, materials, shape, form, function and manner of operation, assembly and use, are deemed readily apparent and obvious to one skilled in the art, and all equivalent relationships to those illustrated in the drawings and described in the specification are intended to be
10 encompassed by the present invention. Therefore, the foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of
15 the invention.

WHAT IS CLAIMED IS:

1. An automatic pipette assembly for an isothermal titration micro calorimetry system, comprising a pipette housing, a syringe with a titration needle arranged to be inserted into a sample cell for supplying titrant, and a linear activator for driving a plunger in the syringe, the titration needle is rotatable with respect to the housing and is provided with a stirring paddle arranged to stir fluid in the sample cell, wherein the automatic pipette assembly comprises a stirring motor for driving the rotation of the titration needle.
2. An automatic pipette assembly according to claim 1, wherein the stirring motor is a direct drive motor with a hollow rotor arranged concentric with the titration needle.
3. An automatic pipette assembly according to claim 1, wherein the stirring motor drives the titration needle for rotation by a rotation transmission arrangement.
4. An automatic pipette assembly according to claim 1, wherein the syringe is rotatable with respect to the housing and the titration needle is non-rotatably attached to the syringe.
5. An automatic pipette assembly according to claim 4, wherein the syringe is detachably arranged in a rotation frame within the pipette housing.
6. An automatic pipette assembly according to claim 1, wherein the linear activator comprises a stepper motor arranged to drive a threaded plunger, the pipette

assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger.

7. Isothermal titration micro calorimetry system with an automatic pipette assembly according to claim 1.
8. Isothermal titration micro calorimetry system according to claim 7, comprising a pipette controller arranged to control the linear activator and the stirring motor of the pipette assembly, wherein the linear activator comprises a stepper motor arranged to drive a threaded plunger, the pipette assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger, and wherein the pipette controller is arranged to register the two predetermined positions of the threaded plunger and to determine the pitch of the threads of the plunger from the number of steps performed by the stepper motor to move the threaded plunger between said positions.
9. A micro titration calorimetry system comprising an automatic pipette assembly with a titration needle arranged to be inserted into a sample cell for supplying titrant, and a pipette guiding mechanism arranged to guide the pipette assembly between and into at least two positions of operation, wherein a first position of operation is a pipette washing position wherein the titration needle is inserted in a washing apparatus, and a second position of operation is a titration position wherein the syringe is inserted into the sample cell for calorimetric measurements.
10. A micro titration calorimetry system according to claim 9, wherein the washing

apparatus is arranged to allow filling of titrant to the pipette assembly after washing of the pipette assembly is completed.

11. A micro titration calorimetry system according to claim 9, comprising a third position of operation in the form of a titrant filling position, wherein the titration needle is inserted in a titrant source.
12. A micro titration calorimetry system according to claim 9, wherein the guiding mechanism is of rotational type, and the positions of operation are arranged at equal distance about the centre of rotation of the guide assembly but at different angular positions, wherein movement of the pipette assembly in the vertical direction is restricted to the angular positions of the positions of operation, and wherein rotational movement of the pipette assembly between the angular positions only is permitted when the needle is fully retracted from respective positions of operation.
13. A micro titration calorimetry system according to claim 9, comprising a position sensor arranged to register when the pipette assembly is positioned at one of the positions of operation, and wherein the associated operation is restricted by the state of the position sensor.
14. Isothermal titration micro calorimetry system comprising a sample cell and a reference cell, both enclosed by a first thermal shield which in turn is enclosed by a second thermal shield, a first heat pump unit is arranged to transfer heat energy between the first and second thermal shields, a second heat pump unit is arranged

to transfer heat energy between the second thermal shield and a heat sink, wherein the calorimetry system further comprises a controller arranged to control the first and second heat pump units, and a temperature sensor arrangement for sensing the temperature difference between the sample cell and the first thermal shield, and wherein the controller in an isothermal mode is arranged to control the first heat pump to minimize the temperature difference between the sample cell and the first thermal shield.

15. Isothermal titration micro calorimetry system according to claim 14, wherein the temperature sensor arrangement is a differential thermocouple.
16. Isothermal titration micro calorimetry system according to claim 14, wherein the controller in an isothermal mode is arranged to control the second heat pump to keep the second thermal shield at a predetermined temperature.
17. Isothermal titration micro calorimetry system according to claim 14, wherein the controller in a temperature set mode is arranged to control the first and second heat pump to bring the first and second thermal shield to a predetermined temperature.
18. Isothermal titration micro calorimetry system according to claim 14, comprising heating elements arranged to heating the sample and the reference cells
19. Isothermal titration micro calorimetry system according to claim 14, wherein one or both of the thermal shields is comprised of two or more sub shields

20. Isothermal titration micro calorimetry method using an isothermal titration micro calorimetry system according to claim 14, comprising the steps:
- filling sample and reference cell;
 - controlling the first heat pump to minimize the temperature difference between the sample cell and the first thermal shield; and
 - performing titration calorimetric measurements.
21. Method according to claim 20 comprising the step of:
- after filling sample, controlling the first and second heat pump to bring the first and second thermal shield to a predetermined titration temperature.

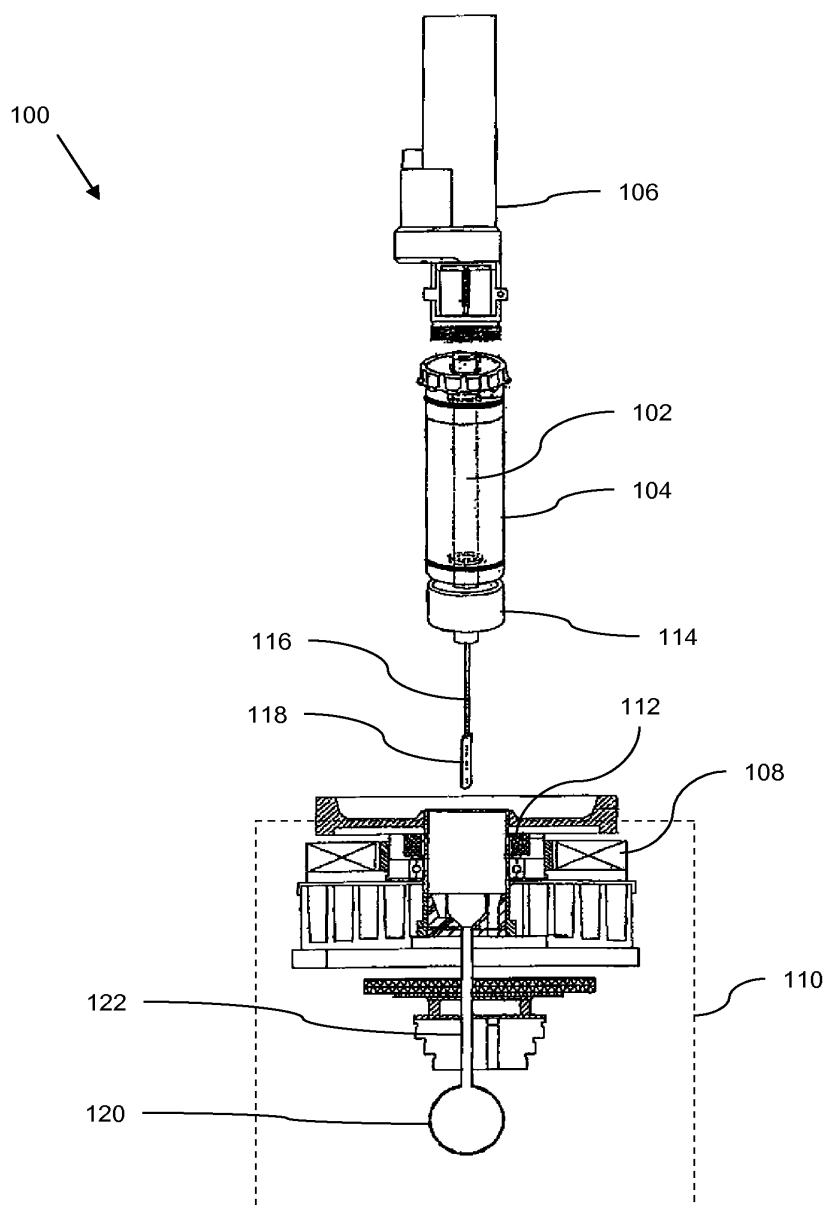


Fig. 1

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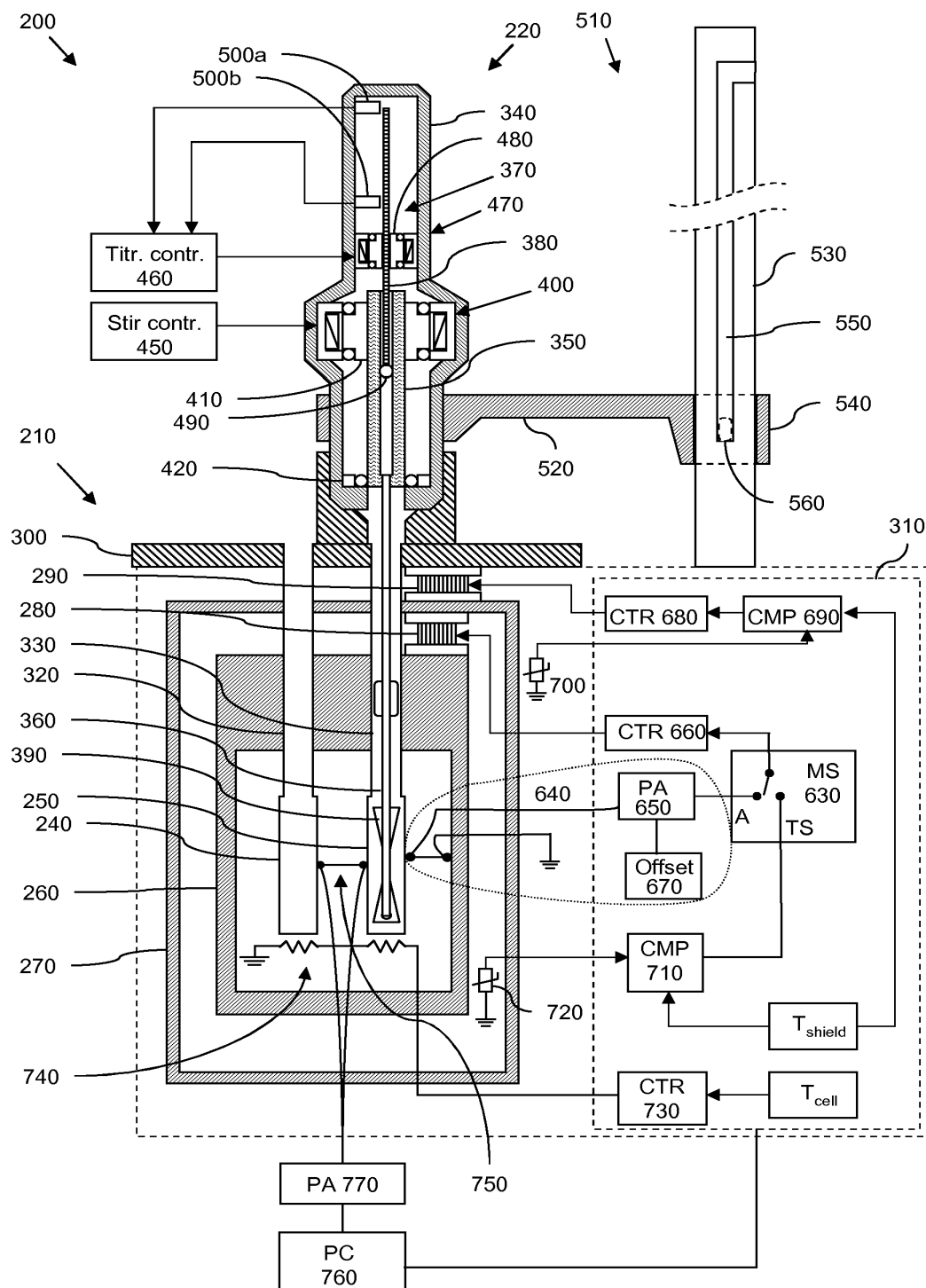


Fig. 2

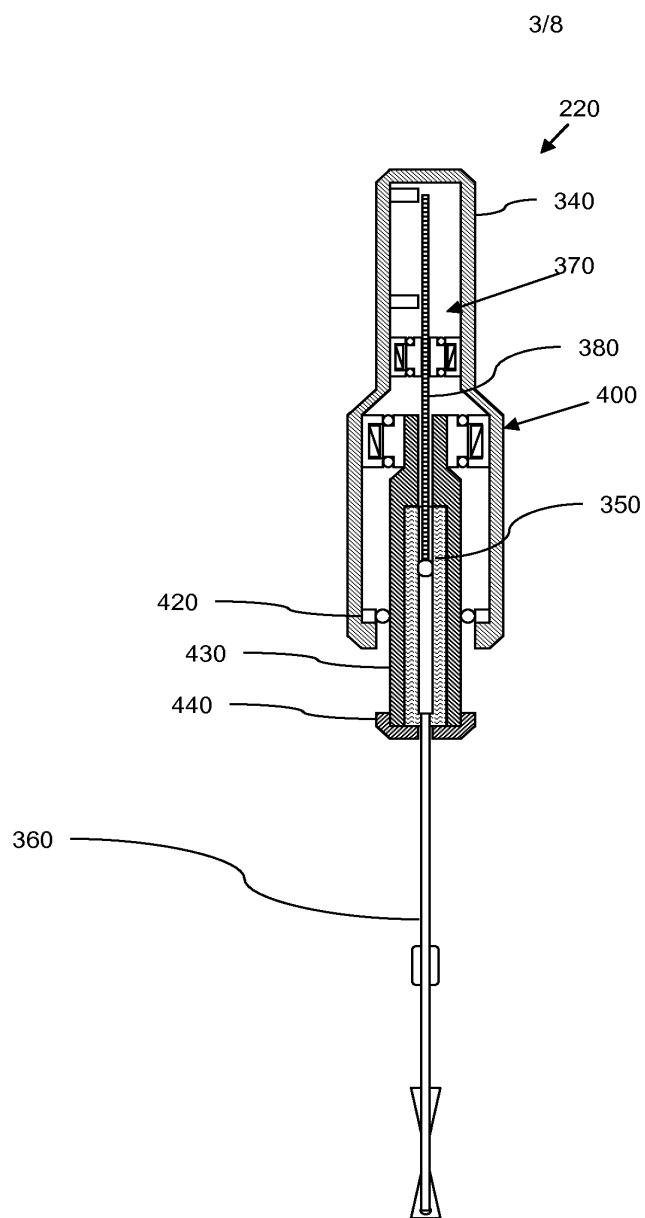


Fig. 3

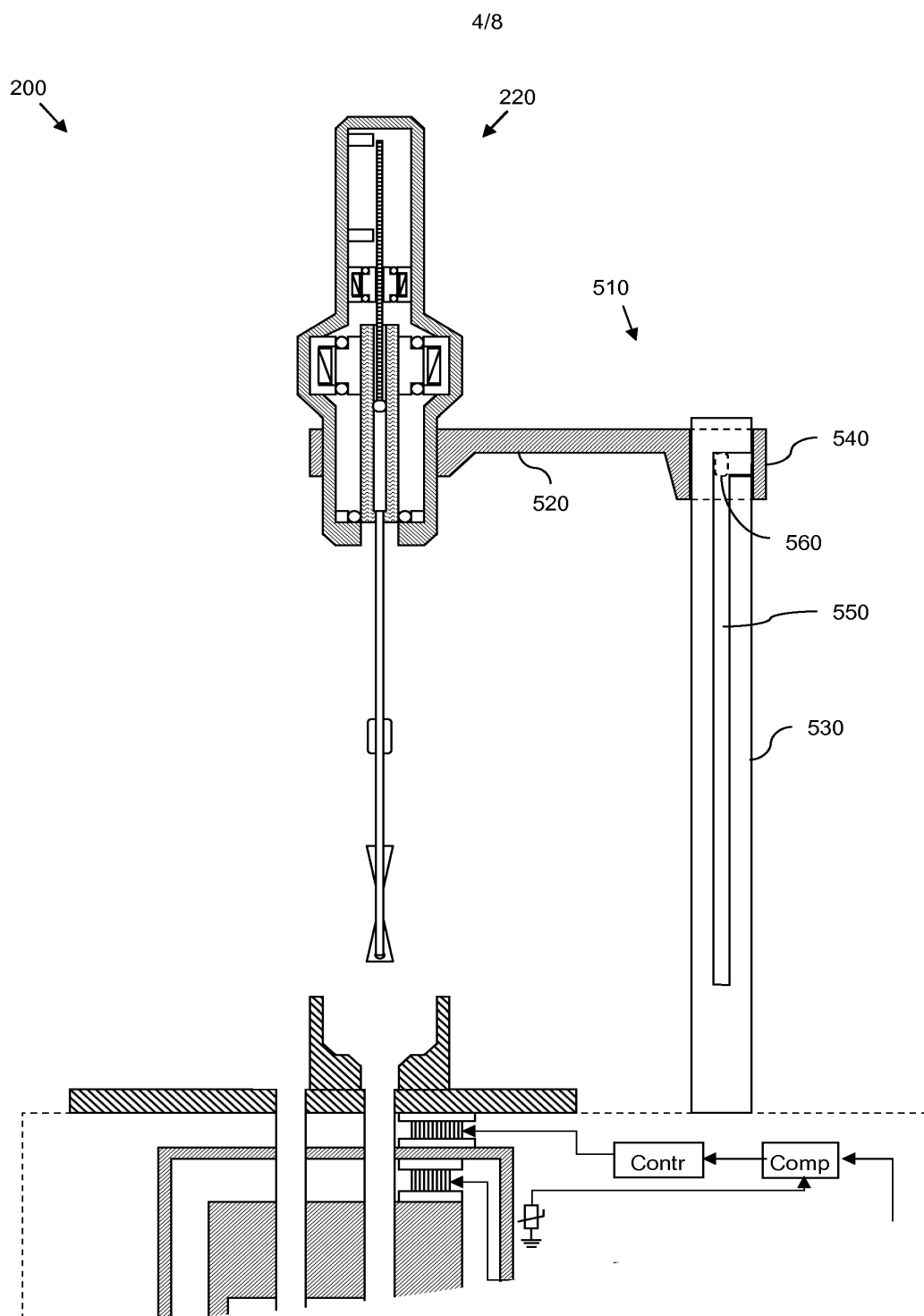


Fig. 4

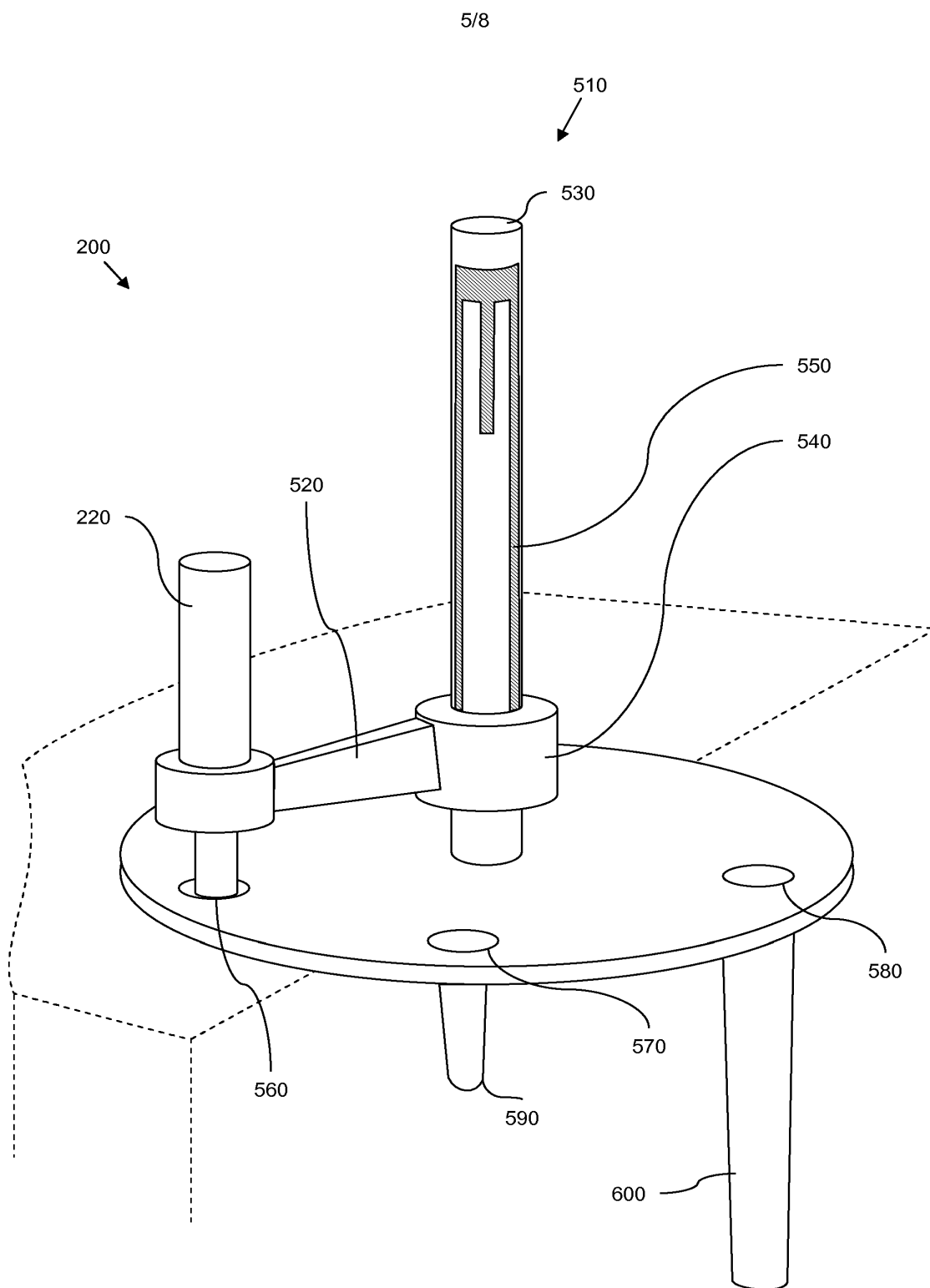


Fig. 5a

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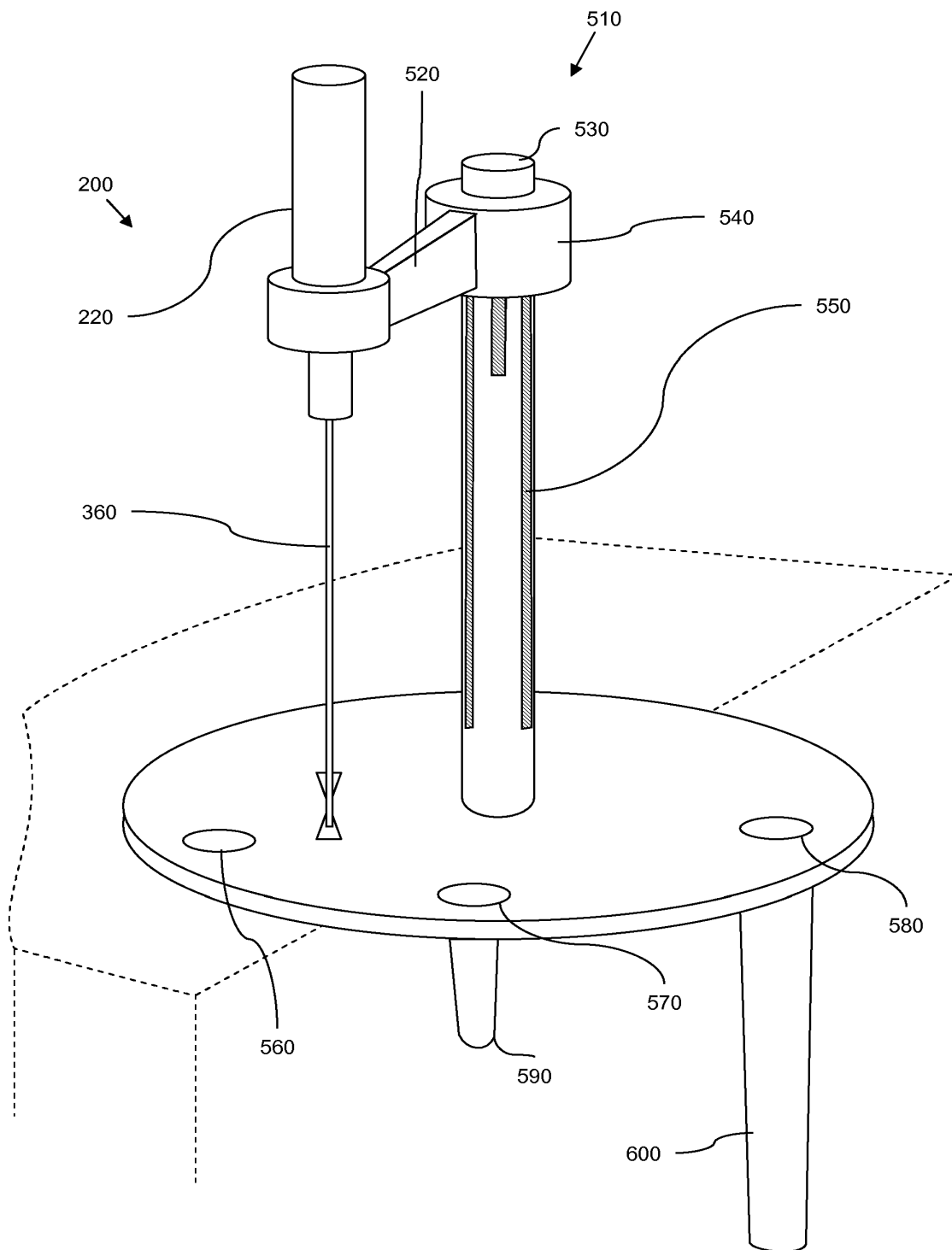


Fig. 5b

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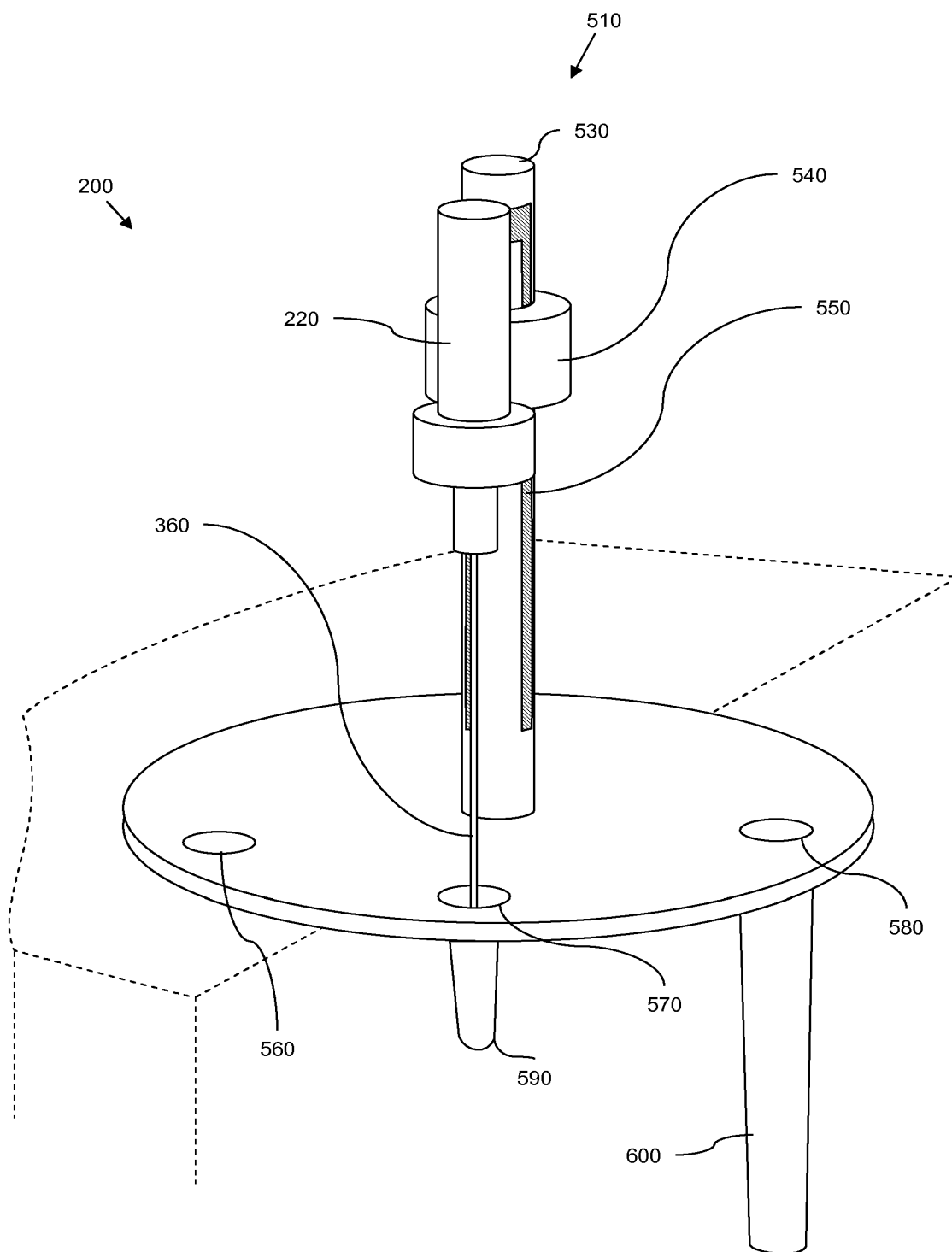


Fig. 5c

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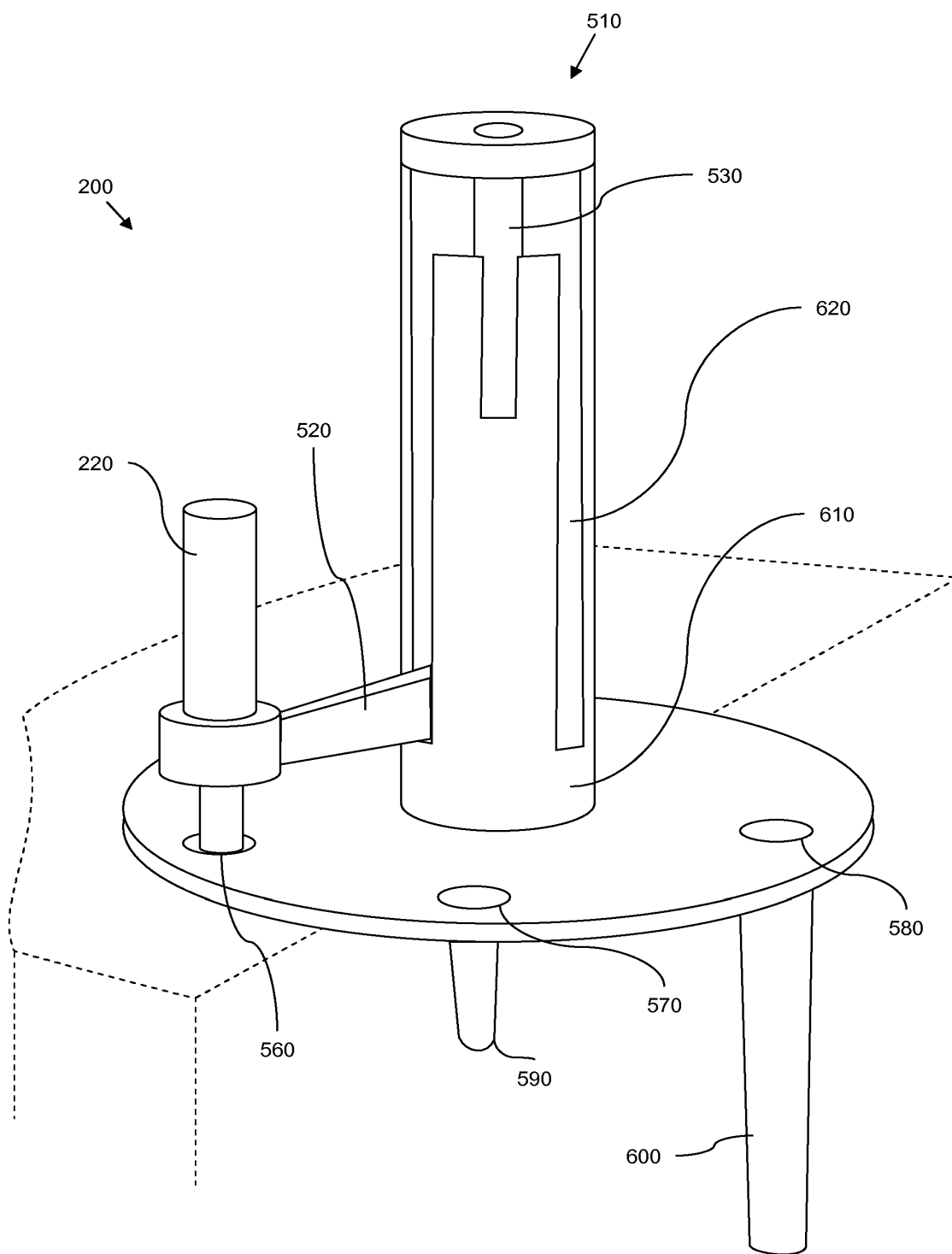


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/81961

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 25/20 (2009.01)

USPC - 374/10

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)

IPC(8)- G01N 25/20 (2009.01)

USPC 374/10

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

USPC - 374/10, 12, 31; 422/51; 436/147 (text search)

[01 November 2007 (01.11.2007)]

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

PubWEST(USPT,PGPB,EPAB,JPAB); Google Patent and Google Scholar. Search terms: needle, pipet, pipette, syringe, plunger, hypodermic, isothermal, titrate microcalorimetry, housing, chamber, container, cell, rotate, spin, swivel, twist, turn, revolve, moving, direct, linear and drive.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Cooper, Allan and Johnson Christopher, M, Isothermal Titration Microcalorimetry, Ch 11, Methods in Molecular Biology, Vol 22: Microscopy, Optical Spectroscopy, and Macroscopic Techniques Edited by C. Jones, B Mulloy and A.H. Thomas, Humana press Inc. 1994 [online] From the internet: [retrieved on 2009-01-12] <URL-http://www.chem.gla.ac.uk/staff/alanc/MMB-ITC-1994.pdf> Entire document, especially Fig. 3 and caption; pg 141 para 1 and page 142	1-5, 7
Y		6, 8-14
Y	WO 87/00086 A1 (Hanaway) 15 January 1987 (15.01.1987) Entire document, especially (Fig 15 and 16 and pg 13, ln 1-6; pg 47, ln 10- pg 48, ln 17)	6, 8-13
Y	Doyle, Michael L. Titration Microcalorimetry, Current protocols in Protein Science (1999) 20.1.1-20.4.24 online [Retrieved on 2009-01-13] retrieved from the internet URL:http://www.nshvtn.org/ebook/molbio/Current%20Protocols/CPPS/ps2004.pdf> pg. 4.8, para 12; pg 4.20, top section and pg 4.22 para 2.	9-13
Y	US 5,813,763 A (Plotnikov et al.) 29 September 1998 (29.09.1998) Entire document, especially Fig 1 and cl 1; col 2, ln 57-67; col 4, ln 56-66; col 5, ln 1-20; col 8, ln 22-40; col 11, ln 10-25.	14-21
Y	WO 81/01045 A (Kausch) 16 April 1981 (16.04.1981) Entire document, especially pg 4, ln 7-25	14-21

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

* 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

15 January 2009 (15.01.2009)

Date of mailing of the international search report

09 FEB 2009

Name and mailing address of the ISA/US

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Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-276-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/81961

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 25/20 (2009.01)

USPC - 374/10

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)

IPC(8)- G01N 25/20 (2009.01)

USPC 374/10

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

USPC - 374/10, 12, 31; 422/51; 436/147 (text search)

[01 November 2007 (01.11.2007)]

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

PubWEST(USPT,PGPB,EPAB,JPAB); Google Patent and Google Scholar. Search terms: needle, pipet, pipette, syringe, plunger, hypodermic, isothermal, titrate microcalorimetry, housing, chamber, container, cell, rotate, spin, swivel, twist, turn, revolve, moving, direct, linear and drive.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Cooper, Allan and Johnson Christopher, M, Isothermal Titration Microcalorimetry, Ch 11, Methods in Molecular Biology, Vol 22: Microscopy, Optical Spectroscopy, and Macroscopic Techniques Edited by C. Jones, B Mulloy and A.H. Thomas, Humana press Inc. 1994 [online] From the internet: [retrieved on 2009-01-12] <URL-http://www.chem.gla.ac.uk/staff/alanc/MMB-ITC-1994.pdf> Entire document, especially Fig. 3 and caption; pg 141 para 1 and page 142	1-5, 7
Y		6, 8-14
Y	WO 87/00086 A1 (Hanaway) 15 January 1987 (15.01.1987) Entire document, especially (Fig 15 and 16 and pg 13, ln 1-6; pg 47, ln 10- pg 48, ln 17)	6, 8-13
Y	Doyle, Michael L. Titration Microcalorimetry, Current protocols in Protein Science (1999) 20.1.1-20.4.24 online [Retrieved on 2009-01-13] retrieved from the internet URL:http://www.nshtvn.org/ebook/molbio/Current%20Protocols/CPPS/ps2004.pdf> pg. 4.8, para 12; pg 4.20, top section and pg 4.22 para 2.	9-13
Y	US 5,813,763 A (Plotnikov et al.) 29 September 1998 (29.09.1998) Entire document, especially Fig 1 and cl 1; col 2, ln 57-67; col 4, ln 56-66; col 5, ln 1-20; col 8, ln 22-40; col 11, ln 10-25.	14-21
Y	WO 81/01045 A (Kausch) 16 April 1981 (16.04.1981) Entire document, especially pg 4, ln 7-25	14-21

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

* Special categories of cited documents:

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"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

15 January 2009 (15.01.2009)

Date of mailing of the international search report

09 FEB 2009

Name and mailing address of the ISA/US

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Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-276-7774

Form PCT/ISA/210 (second sheet) (April 2007)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: DWAYNE L. BENTLEY
GE HEALTHCARE BIO-SCIENCES CORP.
800 CENTENNIAL AVENUE
PISCATAWAY, NJ 08855

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **09 FEB 2009**

Applicant's or agent's file reference
PB07143

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US 08/81961

International filing date (day/month/year)
31 October 2008 (31.10.2008)

Priority date (day/month/year)
01 November 2007 (01.11.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 25/20 (2009.01)
USPC - 374/10

Applicant **GE HEALTHCARE BIO-SCIENCES CORP.**

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion
15 January 2009 (15.01.2009)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/81961

Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:
 - a. type of material
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/81961

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6, 8-21	YES
	Claims	1-5, 7	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-21	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims	None	NO

2. Citations and explanations:

Claims: 1-5 and 7 lack novelty under PCT Article 33(2) as being anticipated by the article titled "Isothermal Titration Microcalorimetry" by Cooper et al. (hereinafter, Cooper.)

Regarding claim 1, Cooper discloses an automatic pipette assembly for an isothermal titration micro calorimetry system, comprising a pipette housing, a syringe with a titration needle arranged to be inserted into a sample cell for supplying titrant, and a linear activator for driving a plunger in the syringe, the titration needle is rotatable with respect to the housing and is provided with a stirring paddle arranged to stir fluid in the sample cell, wherein the automatic pipette assembly comprises a stirring motor for driving the rotation of the titration needle (Fig.3 and pg 141, para 1 to pg 6 top).

Regarding claim 2, Cooper discloses an automatic pipette assembly according to claim 1, wherein the stirring motor is a direct drive motor with a hollow rotor arranged concentric with the titration needle (Fig.3 and pg 141, para 1 to pg 6 top).

Regarding claim 3, Cooper discloses an automatic pipette assembly according to claim 1, wherein the stirring motor drives the titration needle for rotation by a rotation transmission arrangement (Fig.3 and pg 141, para 1 to pg 6 top).

Regarding claim 4, Cooper discloses an automatic pipette assembly according to claim 1, wherein the syringe is rotatable with respect to the housing and the titration needle is non-rotatably attached to the syringe (Fig 3 and caption).

Regarding claim 5, Cooper discloses an automatic pipette assembly according to claim 4, wherein the syringe is detachably arranged in a rotation frame within the pipette housing (Fig 3 and caption).

Regarding claim 7, Cooper disclose the isothermal titration micro calorimetry system with an automatic pipette assembly according to claim 1 (Fig.3 and pg 141, para 1 to pg 6 top).

Claims 6 and 8 lacks an inventive step under PCT Article 33(3) as being obvious over Cooper in view of WO 87/00086 A1 to Hanaway.

Regarding claim 6 Cooper discloses an automatic pipette assembly according to claim 1, wherein the linear activator comprises a stepper motor arranged to drive a plunger (Fig.3 and caption and pg 5, para 1 to pg 6 top). However, Cooper does not disclose wherein a stepper motor arranged to drive a threaded plunger, the pipette assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger.

Hanaway discloses wherein the linear activator comprises a stepper motor arranged to drive a threaded plunger, the pipette assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger (Fig 15 and 16 and pg 47, in 10- pg 48, in 17). In view of the fact that both Cooper and Hanaway disclose microcalorimetry systems, it would have been obvious to one skilled in the art to use the threaded plunger and position sensor of as shown in Hanaway with the automatic pipette of Cooper in order to automate the system of Cooper because this would provide a stand alone system which can collect titration data without the need for constant personal attention.

Regarding claim 8, Cooper discloses an isothermal titration micro calorimetry system according to claim 7, comprising a pipette controller arranged to control the linear activator and the stirring motor of the pipette assembly (Fig.3 and pg 5, para 1 to pg 6 top). However, Cooper does not disclose wherein the linear activator comprises a stepper motor arranged to drive a threaded plunger, the pipette assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger, and wherein the pipette controller is arranged to register the two predetermined positions of the threaded plunger and to determine the pitch of the threads of the plunger from the number of steps performed by the stepper motor to move the threaded plunger between said positions.

Continue on first supplemental page.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 08/1961

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V(2) Citation and explanation.

Hanaway discloses wherein the linear activator comprises a stepper motor arranged to drive a threaded plunger, the pipette assembly further comprises position sensors for detecting two predetermined positions of the threaded plunger, and wherein the pipette controller is arranged to register the two predetermined positions of the threaded plunger and to determine the pitch of the threads of the plunger from the number of steps performed by the stepper motor to move the threaded plunger between said positions (Fig 15 and 16 and pg 47, in 10- pg 48, in 17). In view of the fact that both Cooper and Hanaway disclose automated syringe dispensing systems, it would have been obvious to one skilled in the art to use the threaded plunger and position sensors for detecting two predetermined positions of the threaded plunger and to determine the pitch of the threads of the plunger from the number of steps performed by the stepper motor to move the threaded plunger as shown in Hanaway with Cooper. Further, it would be obvious to combine the teachings with the automatic pipette of Cooper in order to automate the system of Cooper, because this would provide a stand alone system which could collect titration data without the need for constant personal attention.

Claims 9-13 lack an inventive step under PCT Article 33(3) as being obvious over Cooper in view of Hanaway and further in view of the article entitled: "Titration Microcalorimetry" by Doyle (hereinafter 'Doyle').

Regarding claim 9, Cooper discloses a micro titration calorimetry system comprising an automatic pipette assembly with a titration needle arranged to be inserted into a sample cell for supplying titrant. However, Cooper does not disclose a pipette guiding mechanism arranged to guide the pipette assembly between and into at least two positions of operation, wherein a first position of operation is a pipette washing position wherein the titration needle is inserted in a washing apparatus, and a second position of operation is a titration position wherein the syringe is inserted into the sample cell for calorimetric measurements.

Hanaway discloses a pipette guiding mechanism arranged to guide the pipette assembly between and into at least two positions of operation, wherein a second position of operation is a titration position wherein the syringe is inserted into the sample cell for calorimetric measurements (Fig 15 and 16 and pg 13, in 1-6; pg 47, in 10- pg 48, in 17). In view of the fact that both Cooper and Hanaway disclose automated syringe dispensing systems, it would have been obvious to one skilled in the art to use a pipette guiding mechanism arranged to guide the pipette assembly between and into at least two positions of operation, to a second position of operation which is a titration position wherein the syringe is inserted into the sample cell for calorimetric measurements as shown in Hanaway with the automatic pipette of Cooper. The teachings of Hanaway and Cooper would be combined in order to automate the system of Cooper because this would provide a mechanized system which could perform titrations and obtain data without the need for constant personal attention.

Neither Cooper nor Hanaway disclose wherein a first position of operation is a pipette washing position wherein the titration needle is inserted in a washing apparatus. Doyle discloses a washing step (pg 4.8, para 12). In view of the fact that Cooper, Hanaway and Doyle disclose syringe-based analytical systems, it would have been obvious to one skilled in the art to use the wash/rinse step of Doyle with the automated system of Cooper and Hanaway to produce a system that automates the pipette-based analytical process normally performed by a laboratory technician, because this would provide consistent analysis of samples without the need for personal supervision.

Regarding claim 10, Cooper in combination with Hanaway and Doyle disclose a micro titration calorimetry system according to claim 9. While Cooper in combination with Hanaway and Doyle do not specify wherein the washing apparatus is arranged to allow filling of titrant to the pipette assembly after washing of the pipette assembly is completed, it would have been obvious to one of skill of the art to automate the procedure of filling of the pipette with titrant after washing in order to automate the pipette-based analytical process normally performed by a laboratory technician, because this would provide consistent analysis of samples without the need for operator being present.

Regarding claim 11 Cooper in combination with Hanaway and Doyle disclose a micro titration calorimetry system according to claim 9. Further, Cooper discloses filling of the syringe (pg 141, para 1). While Cooper in combination with Hanaway and Doyle do not specify, a third position of operation in the form of a titrant filling position, wherein the titration needle is inserted in a titrant source, it would be obvious to one of skill in the art to automate the process of filling the syringe by moving it to a position for filling with a titrant in order to automate the analytical process, because this would provide consistent analysis of sample without the need for supervision by a technician.

Regarding claim 12, Cooper in combination with Hanaway and Doyle disclose a micro titration calorimetry system according to claim 9. Further, Hanaway discloses wherein the guiding mechanism is of rotational type, and the positions of operation are arranged at equal distance about the centre of rotation of the guide assembly but at different angular positions wherein movement of the pipette assembly in the vertical direction is restricted to the angular positions of the positions of operation (Fig 15, pg 46, in 4-16). While Cooper in combination with Hanaway and Doyle do not specify wherein rotational movement of the pipette assembly between the angular positions only is permitted when the needle is fully retracted from respective positions of operation, it would have been obvious to one of ordinary skill in the art to limit rotation movement when the needle is fully retracted to avoid damage to the needle (as noted by Doyle pg 4.20, top section and pg 4.22 para 2) because a bent needle may cause damage to the device or result in bad test results.

Regarding claim 13, Cooper in combination with Hanaway and Doyle disclose a micro titration calorimetry system according to claim 9. Further Hanaway discloses a position sensor arranged to register when the pipette assembly is positioned at one of the positions of operation, and wherein the associated operation is restricted by the state of the position sensor (pg 48 in 13 to pg 49, in 19).

Continue on second supplemental page.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US 08/81961

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
First supplemental page.

Claims 14-21 lack an inventive step under PCT Article 33(3) as being obvious over US 5,813,763 to Plotnikov et al. (hereinafter Plotnikov.) in view of WO 81/01045 A to Kausch.

Regarding claim 14, Plotnikov discloses an isothermal titration micro calorimetry system comprising a sample cell and a reference cell (Fig 1 and cl 1), both enclosed by a first thermal shield which in turn is enclosed by a second thermal shield (col 11, ln 25), a second heat pump unit is arranged to transfer heat energy between the second thermal shield and a heat sink (Fig 1, col 2, ln 57-67), wherein the calorimetry system further comprises a controller arranged to control the second heat pump units (Fig 1 and col 5, ln 15-20) and a temperature sensor arrangement for sensing the temperature difference between the sample cell and the first thermal shield and wherein the controller in an isothermal mode (Fig 1, col 5, ln 15-20). However, Plotnikov does not disclose a first heat pump unit is arranged to transfer heat energy between the first and second thermal shields, wherein the calorimetry system further comprises a controller arranged to control the first heat pump and wherein the controller in an isothermal mode is arranged to control the first heat pump to minimize the temperature difference between the sample cell and the first a first heat pump unit is arranged to transfer heat energy between the first and second thermal shields thermal shield.

Kausch discloses a first heat pump unit arranged to transfer heat energy between the first and second thermal shields, and wherein the controller is arranged to control the first heat pump to minimize the temperature difference between the interior and the first a first heat pump unit is arranged to transfer heat energy between the first and second thermal shields thermal shield (pg 4, ln 7-25). In view of the fact that Plotnikov and Kausch disclose insulated systems for use with instrumentation, it would have been obvious to one skilled in the art to use the heat transfer elements as shown in Kausch with the temperature control system of Plotnikov to provide better temperature control and stability of the sample cell environment in order to generate better calorimetry data.

Regarding claim 15, Plotnikov in combination with Kausch disclose the Isothermal titration micro calorimetry system according to claim 14. Further, Plotnikov discloses wherein the temperature sensor arrangement is a differential thermocouple (col 5, ln 1-3).

Regarding claim 16, Plotnikov in combination with Kausch disclose the Isothermal titration micro calorimetry system according to claim 14. Further, Plotnikov discloses wherein the controller in an isothermal mode is arranged to control the second heat pump to keep the second thermal shield at a predetermined temperature (col 11, ln 10-17).

Regarding claim 17, Plotnikov in combination with Kausch disclose the isothermal titration microcalorimetry system according to claim 14. Further, Plotnikov discloses wherein the controller in a temperature set mode is arranged to control the second heat pump to bring the second thermal shield to a predetermined temperature (col 11, ln 10-17). Kausch discloses controller in a temperature set mode is arranged to control the first heat pump to bring the first thermal shield to a predetermined temperature (pg 4, ln 10-15). In view of the fact that Plotnikov and Kausch disclose insulated systems for use with instrumentation, it would have been obvious to one skilled in the art to use the heat transfer elements as shown in Kausch with the temperature control system of Plotnikov to provide better temperature control and stability of the sample cell environment in order to generate better calorimetry data.

Regarding claim 18 Plotnikov in combination with Kausch disclose the isothermal titration micro calorimetry system according to claim 14. Further, Plotnikov discloses heating elements arranged to heat the sample and the reference cells (Fig. 1 and col 4, ln 56-66).

Regarding claim 19, Plotnikov in combination with Kausch disclose the isothermal titration micro calorimetry system according to claim 14. Further, Plotnikov disclose wherein one or both of the thermal shields are comprised of two or more sub shields (col 11, ln 23-25).

Regarding claim 20, Plotnikov in combination with Kausch disclose the isothermal titration micro calorimetry method using an isothermal titration micro calorimetry system according to claim 14. Further, Plotnikov discloses the steps filling sample and reference cell; and performing titration calorimetric measurements (col 8, ln 22-40). While Plotnikov in combination with Kausch do not specify controlling the first heat pump to minimize the temperature difference between the sample cell and the first thermal shield, it would have been obvious to one of skill in the art to minimize the temperature difference between the sample cell and the first shield in order to obtain test data that can be used to identify other features of the sample.

Regarding claim 21, Plotnikov in combination with Kausch disclose the method according to claim 20. Further, Plotnikov discloses comprising the step of after filling sample, controlling the first heat pump to bring the first and second thermal shield to a predetermined titration temperature (col 8, ln 22-40). Plotnikov does not disclose temperature control with respect to two thermal shields. Kausch discloses two heat pumps to control the temperature between two heat shields. In view of the fact that Plotnikov and Kausch disclose insulated systems for use with instrumentation, it would have been obvious to one skilled in the art to use the heat transfer elements as shown in Kausch with the temperature control system of Plotnikov to provide better temperature control and stability of the sample cell environment in order to generate better calorimetry data.

Claims 1-21 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Electronic Patent Application Fee Transmittal				
Application Number:		14736905		
Filing Date:		11-Jun-2015		
Title of Invention:		AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
First Named Inventor/Applicant Name:		Martin BROGA		
Filer:		Alex Chartove/Monica Freeman		
Attorney Docket Number:		739712000201		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	1	80	80
Independent claims in excess of 3	1201	4	420	1680
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1760

Electronic Acknowledgement Receipt

EFS ID:	23526777
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Alex Chartove/Monica Freeman
Filer Authorized By:	Alex Chartove
Attorney Docket Number:	739712000201
Receipt Date:	17-SEP-2015
Filing Date:	11-JUN-2015
Time Stamp:	17:12:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 1760
RAM confirmation Number	4062
Deposit Account	031952
Authorized User	CHARTOVE, ALEX
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		739712000201_Prelim3.pdf	31108 a126d4413ae70bdb21988c2857dd6d3e213d513f	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		Start		End
	Preliminary Amendment		1		1
	Claims		2		5
	Applicant Arguments/Remarks Made in an Amendment		6		6
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	739712000201_SB08.pdf	36350 2cf645920736a99bc1f0da80d8bb93bdc753178f	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Transmittal Letter	739712000201_IDS.pdf	25059 cd31faadC23e9577e6be9f748253f3ae4c567996	no	2
Warnings:					
Information:					
4	Foreign Reference	WO8101045A1.pdf	1087117 ab27b8542fd4a54c42900aa111152616f83d0e11	no	26
Warnings:					
Information:					
5	Foreign Reference	WO8700086A1.pdf	2354683 2382e8b7dfa25800a80bb8a7e652fb50b26fd1c4	no	74
Warnings:					
Information:					

6	Foreign Reference	WO2009059110.pdf	1242635 d5be9e19ff93b4f3f4d4b1fd41c88ec0d7a bd41	no	33
Warnings:					
Information:					
7	Non Patent Literature	ISR_WO2009059110_2009Feb9.pdf	413563 2db97675735f77566ea797af7685994c61a8 e79a	no	6
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	32304 315a3f6b6607f0e7442aadaed347067918f8 9dcd	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			5222819		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 14/736,905		Filing Date 06/11/2015		<input type="checkbox"/> To be Mailed	
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR	NUMBER FILED	NUMBER EXTRA			RATE (\$)	FEE (\$)			
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A			N/A				
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A			N/A				
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A			N/A				
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*			X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*			X \$	=			
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL				
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	09/17/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	x \$80 =		80	
	Independent (37 CFR 1.16(h))	* 7	Minus	***3	= 4	x \$420 =		1680	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		1760	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$		=	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$		=	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE			
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>									

LIE
/DEANNA RORIE/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
-------------------------------	--

As the below named inventor, I hereby declare that:

This declaration ☐ The attached application, or
is directed to: ☒ United States application or PCT international application number 14/736,905
filed on 06/11/2015

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Phillip PRICE Date (Optional): 8/2/2015

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

va-452358

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
-------------------------------	--

As the below named inventor, I hereby declare that:

This declaration ☐ The attached application, or
is directed to: ☒ United States application or PCT international application number 14/736,905
filed on 06/11/2015

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Stephen SMITH Date (Optional): 28 JULY 2015

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

va-452358

Electronic Acknowledgement Receipt	
EFS ID:	23474825
Application Number:	14736905
International Application Number:	
Confirmation Number:	4808
Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
Filer:	Alex Chartove/Monica Freeman
Filer Authorized By:	Alex Chartove
Attorney Docket Number:	739712000201
Receipt Date:	11-SEP-2015
Filing Date:	11-JUN-2015
Time Stamp:	22:37:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no				
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	739712000201_Declaration.pdf	105739 3115fac6bb55d400978e0fa173c220df0e388a85	no	3
Warnings:					

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

Total Files Size (in bytes):

105739

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/736,905	06/11/2015	Martin BROGA	739712000201

CONFIRMATION NO. 4808

INFORMAL NOTICE



25227
MORRISON & FOERSTER LLP
1650 TYSONS BOULEVARD
SUITE 400
MCLEAN, VA 22102

Date Mailed: 06/23/2015

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Martin BROGA
Phillip PRICE
Stephen SMITH

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/eggolla/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 14/736,905				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	600			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720			
TOTAL CLAIMS (37 CFR 1.16(i))	1	minus 20 = *				x 80 =	0.00			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *				x 420 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600			
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
TOTAL ADD'L FEE									TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=		x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=		x	=
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
TOTAL ADD'L FEE									TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.										



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY DOCKET NO	TOT CLAIMS	IND CLAIMS
14/736,905	06/11/2015	1798	1740	739712000201	1	1

CONFIRMATION NO. 4808

FILING RECEIPT



000000073866919

25227
MORRISON & FOERSTER LLP
1650 TYSONS BOULEVARD
SUITE 400
MCLEAN, VA 22102

Date Mailed: 06/23/2015

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Martin BROGA, Amherst, MA;
Phillip PRICE, North Granby, CT;
Stephen SMITH, Northampton, MA;

Applicant(s)

Malvern Instruments Incorporated, Westborough, MA;

Assignment For Published Patent Application

Malvern Instruments Incorporated, Westborough, MA

Power of Attorney: The patent practitioners associated with Customer Number 25227

Domestic Priority data as claimed by applicant

This application is a CON of 12/326,300 12/02/2008

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 06/22/2015

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/736,905**

Projected Publication Date: 10/01/2015

Non-Publication Request: No

Early Publication Request: No

Title

AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE

Preliminary Class

422

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit <http://www.SelectUSA.gov> or call +1-202-482-6800.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 12, 2015

Electronic Signature for Vilavanh Ong: /Vilavanh Ong/

Docket No.: 739712000201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: 14/736,905

Confirmation No.: 4808

Filed: June 11, 2015

Art Unit: 1798

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: Not Yet Assigned

SECOND PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Prior to examination on the merits, Applicants respectfully request entry of this Preliminary Amendment for the above-captioned patent application.

Amendments to the Claims begin on page 2.

Remarks begin on page 3.

va-452232

AMENDMENTS TO THE CLAIMS

1-17. (Canceled)

18. (New) An automated isothermal titration micro calorimetry (ITC) system arranged to perform a plurality of unattended titration experiments in series, the system comprising:

a system controller for controlling the automated operation of the ITC system;

a micro calorimeter comprising a sample cell and a reference cell, the sample cell being accessible via a sample cell stem and the reference cell being accessible via a reference cell stem;

an automatic pipette assembly comprising a syringe with a titration needle arranged to be inserted into the sample cell for supplying titrant, the pipette assembly comprising an activator for driving a plunger in the syringe cavity;

a wash station;

a sample fill station;

a pipette translation unit supporting the pipette assembly that places a pipette in position for titration with the titration needle in the sample cell and in position for washing operations with the titration needle in the wash station;

a cell preparation unit that performs operations for replacing the sample liquid in the sample cell when the pipette is placed in another position than the position for titration.

REMARKS

Applicants have canceled claims 1-17 and added new claim 18. No new matter has been added. Amended specifications in marked and clean format are also provided with this application.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no.

739712000201. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 12, 2015

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	Preliminary Amendment		1	1	
	Claims		2	2	
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<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER
APPARATUS AND METHOD OF USE

5 CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 12/326,300, filed on December 2, 2008, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The present invention relates generally to microcalorimeters and more specifically to
10 features that improve the performance of microcalorimeters, especially an automated isothermal titration micro calorimetry system (ITC system).

Microcalorimeters are broadly utilized in fields of biochemistry, pharmacology, cell biology, and others. Calorimetry provides a direct method for measuring changes in thermodynamic properties of biological macromolecules. Microcalorimeters are typically two cell
15 instruments in which properties of a dilute solution of test substance in an aqueous buffer in a sample cell are continuously compared to an equal quantity of aqueous buffer in a reference cell. Measured differences between the properties of the two cells, such as temperature or heat flow, are attributed to the presence of the test substance in the sample cell.

One type of microcalorimeter is an isothermal titration calorimeter. The isothermal
20 titration calorimeter (ITC) is a differential device, but operates at a fixed temperature and pressure while the liquid in the sample cell is continuously stirred. The most popular application for titration calorimetry is in the characterization of the thermodynamics of molecular interactions. In this application, a dilute solution of a test substance (e.g., a protein) is placed in the sample cell and, at various times, small volumes of a second dilute solution containing a ligand, which binds
25 to the test substance, are injected into the sample cell. The instrument measures the heat, which is evolved or absorbed as a result of the binding of the newly introduced ligand to the test substance. From results of multiple-injection experiments, properties, such as, the Gibbs energy, the association constant, the enthalpy and entropy changes, and the stoichiometry of binding,

may be determined for a particular pairing between the test substance and the ligand.

While currently utilized ITCs provide reliable binding data results, their widespread utilization in the early stages of drug development have been limited by several factors: the relatively high amounts of protein required to perform a binding determination (e.g., about 0.1 milligram (mg) to about 1.0 mg of a protein), the limited throughput due to the time required to perform the measurement and the complexity of using conventional ITCs.

Today, gathering binding data utilizing prior art ITCs require extensive preparation and skill by the practitioner. For example, using prior art ITCs, the reference and sample cells are first filled respectively with the reference substance and sample substance via a corresponding cell stem. Next, a titration pipette of the ITC is filled with a titrant, which is a delicate operation as it is very important that the syringe in the pipette is accurately filled and that there is no air trapped therein. Then a needle of the titration pipette is manually placed in the sample cell via the cell stem, and the ITC experiments can be initiated. The ITC measurement procedure is controlled by a control unit in the form of a computer or the like running a program for performing the experiments. Consistent with the program used for the experiment, a stirring motor rotates the syringe, needle, and paddle at an assigned speed enabling proper mixing of the reagents. Consistent with the program used for the experiment (e.g., when a certain temperature and/or equilibrium are reached), a plunger in the syringe is activated to inject the titrant into the sample solution. The injection can be done discretely (step-by-step) or continuously, depending on the program settings. The calorimeter continuously measures and records the heat release/absorption versus time associated with the interaction of reagents. The analysis of the results is done according to the established algorithm.

As would be appreciated by a reading of the above-described prior art procedure,

utilizing prior art ITCs, the quality of binding measurements performed with these prior art ITCs depends heavily of the operator's skills and experience, and involves a considerable amount of preparation time.

For some time there has been at least one automated ITC system on the market,
5 MicroCal AutoITC, which is based on a commercially available micro calorimeter and a linear robot system and a fluidics system arranged to perform automatic sample handling.

SUMMARY OF THE INVENTION

The object of the invention is to provide a new automatic isothermal titration
10 micro calorimetry system (ITC system), which ITC system overcomes one or more drawbacks of the prior art. This is achieved by the ITC system as defined in the independent claims.

One advantage with the present ITC system is that each titration experiment requires less time compared to the prior art. This is e.g. due to the reduced cell volume
15 and that washing and refilling of the pipette assembly and the sample cell is performed essentially in parallel. Hence the system throughput is considerably higher compared to the prior art systems, making it possible to evaluate large number of samples to make screening type experiments.

Another advantage is that the ITC system may be arranged to perform a large
20 number of unattended titration experiments.

Embodiments of the invention are defined in the dependent claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic example of a prior art manual ITC system in cross-
25 section, the ITC system comprising an automatic pipette assembly.

Figure 2 shows a schematic view of one embodiment of an automated ITC system.

Figures 3a and 3b show schematic views of other embodiments of the automated ITC system.

Figures 4a and 4b show schematic views of two embodiments of a syringe fluidics system for an automated ITC system.

Figures 5a to 5c show schematic views of the function of a syringe fill port connector unit according to an embodiment.

Figure 6 shows a schematic view of a cell preparation fluidics system according to one embodiment.

Figure 7 schematically shows different states of operations for the ITC system of fig. 2

Figures 8a to 8d shows different states of operations for the ITC system of fig. 2 more in detail.

15 DETAILED DESCRIPTION OF THE INVENTION

In the PCT application PCT/US2008/081961, which is incorporated by reference, a manual ITC system 10 of the type disclosed in fig. 1 is presented. According to one embodiment, the manual ITC system 10 is utilized as micro-calorimeter in the present automatic ITC system, but in other embodiments, the micro-calorimeter is of other types, as will be discussed in greater detail below. In the disclosed manual ITC system 10, the cell compartment volume is reduced by about a factor of seven as compared to prior art ITCs, without a reduction in sensitivity, and with a significantly faster response time. Such an ITC system permits the performance of experiments with about 10 times less protein sample, and with only a total of about 2 to about 4 titrations per hour. In addition to reducing the costs associated with running the ITC experiment, a smaller cell volume

also extends the number of ITC applications. For example, the range of binding affinities that can be measured by ITC is dictated by a parameter called “c value,” which is equal to the product of the binding affinity (K_a) and the total concentration (M_{total}) of macromolecule ($c = [M_{total}]K_a$). For accurate affinity determination, the c value must be
5 between 1 and 1,000. A decrease in the cell volume by a factor of ten results in a similar increase in c value if the same amount of protein is used, and, consequently, the ability to measure weak binders. This ability is especially important in the early stages of drug discovery, in which binding affinities are weak, especially in conjunction with a fully automated instrument.

10 Fig. 1 schematically shows one embodiment of the manual ITC system 10 that may be automated in accordance with the present invention. The ITC system 10 comprises a micro calorimeter 20 and an automatic pipette assembly 30. The micro calorimeter 20 comprises a reference cell 40 and a sample cell 50 which are designed to be essentially identical in heat capacity and volume. The cells 40 and 50 are comprised of
15 a suitable chemically inert and heat conductive material, such as gold, Platinum, tantalum, hastelloy or the like. The cells 40 and 50 may be of essentially any suitable shape, but it is desirable that they are of the same shape, that they are possible to arrange in a fully symmetric arrangement, and that efficient mixing of the titrant with the sample may be achieved. In the disclosed embodiment, the cross-section of the cells 40 and 50 is
20 rectangular, and the cross-section in the transverse horizontal direction may be circular, resulting in coin shaped cells with circular facing surfaces.

In order to reduce any external thermal influences to a minimum, the, reference cell 40 and the sample cell 50 are both enclosed by a first thermal shield 60 which in turn is enclosed by a second thermal shield 70. The thermal shields 60, 70 may be comprised
25 of any suitable thermally conductive material such as silver, aluminum, copper or the like.

The shields 60, 70 may further be comprised of one or more thermally interconnected sub shields (not shown, to provide even further stable temperature conditions for the calorimetric cells 40, 50.

In order to control the temperature of the shields 60, 70, thermal control means
5 may be arranged to control the temperature thereof. In an ITC system said thermal control means are mainly used to set the “isothermal” temperature of the calorimeter, ie of the thermal shields 60, 70, before the titration experiments are initiated. But as will be disclosed in greater detail below, said thermal control means may also be used to improve the adiabatic behavior of the calorimeter. According to one embodiment, the thermal
10 control means are comprised of one or more heat pump units, such as a thermoelectric heat pump device based on the peltier effect or the like. Other types of thermal control means include thermostatically controlled liquid baths, mechanical heat pumps, chemical heating or cooling systems or the like.

In the disclosed embodiment a first heat pump unit 80 is arranged to transfer heat
15 energy between the first 60 and second thermal shields 70, a second heat pump unit 90 is arranged to transfer heat energy between the second thermal shield 70 and a heat sink 100 in thermal contact with the ambient temperature. A temperature controller 110 is arranged to control the first and second heat pump units 80, 90 so that the desired temperature conditions are achieved. The temperature controller 110 monitors the temperatures of the
20 first 60 and second thermal shield by associated temperature sensors 120 and 130 respectively. Furthermore, the thermal controller 110 is arranged to control the cell temperature by a cell heating arrangement 145. The thermal controller 110 is controlled via a calorimeter user interface run on a computer 150 or the like. Calorimetric sensors 140 for sensing the temperature difference between the sample cell 50 and reference cell
25 40 during the ITC experiments may be connected to the computer 150, e.g. via a

preamplifier 160.

A reference cell stem 170 and a sample cell stem 180 provides access to the reference cell 40 and sample cell 50, respectively, for supplying reference and sample fluids, titration fluid, washing of the cells etc. In the disclosed embodiment, the cell stems
5 170 and 180 both extends essentially vertically through both thermal shields and the heat sink to provide direct communication with cells 40 and 50 and the cell stems 170 and 180 each support their respective cell 40 and 50 in the cavity of the first thermal shield 60.

The automatic pipette assembly 30 comprises a pipette housing 190, a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying
10 titrant, and a linear activator 220 for driving a plunger 230 in the syringe 200. The titration needle 210 is rotatable with respect to the housing 190 and is provided with a stirring paddle 240 arranged to stir sample fluid in the sample cell 50 in order to achieve efficient mixing of titrant and sample fluid. The automatic pipette assembly 30 further comprises a stirring motor 250 for driving the rotation of the titration needle 210.

15 In the embodiment disclosed in fig. 1 the stirring motor 250 is a direct drive motor with a hollow rotor arranged concentric with the syringe 200 and the titration needle 210. The syringe 200 is at its upper end supported for rotation by the stirring motor 400 and at the lower end by a bearing 260.

In an alternative embodiment, not shown in the figures, the stirring motor 250
20 drives the titration needle for rotation by a rotation transmission arrangement, such as a drive belt arrangement, a drive wheel arrangement or the like. Moreover, the stirring motor may be arranged separated from the pipette assembly 30 and be arranged to drive the titration needle for rotation by a suitable transmission arrangement such as a magnetic coupling or the like.

25 The automatic pipette assembly 30 is controlled by a controller of the ITC system,

e.g. stirring of the sample and the titration.

In the disclosed embodiment, the linear activator 220 comprises a stepper motor 270 arranged to drive the threaded plunger 230 that extends coaxially through the hole of a hollow rotor and into the syringe 200 wherein it is rotatably attached to a pipette tip 280 that seals against the inner wall of the syringe 200 to allow displacing a precise volume of titration liquid from syringe 200. The linear activator 220 may be of any other type capable of perform controlled linear motion with sufficient precision. This design allows syringe to be rotated independently of the main body 190 of the pipette assembly 30; at the same time, the linear activator 220 can drive the threaded plunger 230.

In accordance with one embodiment, schematically disclosed in figs. 2 to 8d, there is provided an automated isothermal titration micro calorimetry (ITC) system 300 comprising:

- a micro calorimeter 20 with a sample cell 50 and a reference cell 40, the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170,
- an automatic pipette assembly 30 comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant, the pipette assembly 30 comprises a linear activator 220 for driving a plunger 230 in the syringe 200,
- a pipette translation unit 310 supporting the pipette assembly 30 and being arranged to place pipette in position for titration, washing and filling operations,
- a wash station 320 for the titrant needle 210, and
- a cell preparation unit 330 arranged to perform operations for replacing the sample liquid in the sample cell 50 when the pipette 30 is placed in another

position than the position for titration.

The micro calorimeter 20 may be of any type capable of performing ITC calorimetric measurements using sufficiently small volumes of sample such as the micro calorimeter 20 schematically shown in fig. 1. As disclosed above (fig. 1), but not specifically shown in figs 2 to 8d, a micro calorimeter generally comprises a sample cell 50 and a reference cell 40, wherein the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170 (shown as circular openings in fig. 2). The automatic pipette assembly 30 may be of the type disclosed above, but it may be of any suitable design comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant. Like above, the pipette assembly 30 may further comprise a linear activator 220 for driving a plunger 230 in the syringe 200. However, the syringe 200 may be of essentially any type, capable of providing well-defined volumes of titrant. The titration needle 210 may be rotatable and may be provided with a paddle 240 for stirring of the liquid in the sample cell 50 during the titration. The stirring may be accomplished as is discussed above or in any other suitable way.

The pipette translation unit 310 may be of any type capable of placing the pipette in the appropriate positions for titration, washing and filling. Figs 2 and 3 schematically show two different types of translation units, wherein fig. 2 shows a rotation translation unit 310 and fig. 3 shows a linear translation unit 310b. In order to place (insert) the titration needle 210 in position in the sample cell 50, and/or in other positions, the pipette translation unit 310 is capable of moving the pipette 30 in the vertical direction with respect to the micro calorimeter 20. The pipette translation unit 310 may be mechanically restricted with respect to its freedom of movement so that it only may move between mechanically predetermined positions, or it may be a general translation unit of robot type

that is restricted to movement between said predetermined positions by means of software parameters, or a combination thereof. For clarity reasons no such means for vertical movements have been included in the figures 2 to 8d.

5 The wash station 320 is arranged at a suitable position wherein the titration needle 210 of the pipette assembly 30 can be placed in position for washing. The wash station 320 may be of any suitable type capable of washing at least the section of the titration needle 210 that is immersed in the sample during titration when the pipette assembly 30 is placed in position for washing. According to one embodiment, the wash station 320 comprises a wash cavity 340 arranged to receive the titration needle. The wash station 10 320 is made of any suitable material that is inert with respect to the reagents used in the ITC experiments and the wash cycles. According to one embodiment, the wash station 320 comprises a waste outlet port 350 at the bottom end of the wash cavity connected to a waste removal unit 360. The waste outlet port 350 is used to remove waste liquids as well as wash liquids during the pipette washing cycle, as will be disclosed more in detail 15 below, and it is preferably arranged at the bottom end of the wash cavity 340 in order to enable complete drainage of the wash cavity. In one embodiment not disclosed in the figures, the pipette translation unit 310 is limited to movement in the vertical direction, and the wash station 320 instead is arranged to be moved to a position in alignment with the needle 240 for cleaning of the same.

20 In figs. 2 to 8d the cell preparation unit 330 is shown as a translation unit of the same type as the pipette translation unit 310, but arranged to be positioned in at least two positions related to washing and replacing sample liquid in the sample cell. By the provision of a cell preparation unit 330 for replacing the sample liquid in the sample cell 50 the total cycle time is reduced and thus the throughput of the ITC system 300 is 25 increased, as the sample cell 50 may be washed and filled with new sample liquid at the

same time as the pipette 30 is washed and filled with new titrant.

Fig. 2 schematically discloses an automated isothermal titration micro calorimetry (ITC) system 300 according to one embodiment of the present invention. As mentioned above, the translation units 310, 330, 370 in this embodiment are all of rotary type, and all
5 positions of operation are arranged along circular paths of the rotary translation units. In another embodiment, not shown, one or more of the rotary translation units are provided with additional linear translation means to extend work area and to increase the flexibility.

In fig. 2 the pipette translation unit 310 comprises a pipette arm 380 that is
10 rotatably supported for rotation about an axis A, and supporting the pipette assembly 30 at the other end thereof. The pipette arm 380 is further arranged to move the pipette vertically, either in that the arm 380 can be moved vertically along the axis A, or in that the arm 380 is limited for rotation in one plane and the pipette 30 is vertically moveable with respect to the arm 380. The pipette arm 380 is arranged to place pipette 30 in
15 position for:

- titration with the titration needle inserted into the sample cell 50,
- washing and filling with the titration needle inserted in a combined wash/fill station 320.

The combined wash/fill station 320 may be a wash station of the type discussed
20 above with an outlet port 350 at the bottom end of the wash cavity 340. The outlet port 350 is connected to a waste fluidics system 360 that will be discussed in more detail below.

The cell preparation unit 330 is in turn comprised of a corresponding cell arm 390 that is rotatably supported for rotation about an axis B, supporting a cell cannula 400
25 connected to a cell fluidics system 410 for dispensing and withdrawing liquid in the

sample cell 50 and potentially also in the reference cell 40. The cell fluidics system 410 will be disclosed in more detail below. The cell arm 390 is arranged to move the cell cannula 400 to a plurality of positions such as the cells, 40, 50 of the micro calorimeter, one or more sample sources, and a sample preparation station 420, or the like. In the

5 disclosed embodiment, four different sample source positions are included of which three positions represent large volume sample reservoirs of vial type 430a - 430c, e.g. for standard sample liquids, and the fourth position an autosampler position 440, e.g. for specific or sensitive sample liquids, wherein the cell cannula 400 is arranged to draw the sample liquid from a specific well in a sample tray 450 (e.g. micro plate or the like). In

10 the disclosed embodiment, the autosampler position 440 is a static position to which the cell cannula 400 can be moved by the cell arm 390 and be lowered into a specific well of a sample tray 450 that can be moved to position a selected well at the autosampler position 440 by a tray actuator (not shown). The tray actuator may be of any suitable type capable of selectively position a specific sample well of a sample tray 450 at a desired

15 position, such as a linear X-Y actuator or a rotary actuator with a carousel tray. The sample preparation station 430 may be used to prepare the sample before it is transferred into the cell 50 or 40, e.g. by bringing the sample to a temperature close to the experimental temperature, or by degassing through mixing.

The ITC system 300 disclosed in Fig. 2 further comprises a titrant transfer unit

20 370 arranged to transfer titrant from a primary titrant source, e.g. a sample tray 450, to the wash/fill station 320. In the disclosed embodiment, the transfer unit 370 comprises a titrant transfer arm 460, e.g. corresponding to the cell transfer arm 380, that is rotatably supported for rotation about an axis C, supporting a transfer cannula 470 connected to a syringe fluidics system 480. The titrant transfer arm 460 is arranged to position the titrant

25 cannula 470 in an autosampler position 440 for drawing a titrant sample from a titrant

well in a sample tray 450, and in position to dispense said titrant sample in the wash/fill station 320. The autosampler position 440 and the sample tray 450 may be a separate position and tray with respect to the cell cannula autosampler position 440 discussed above, but as is disclosed in fig 2, the cell cannula 470 and the titrant cannula 400 may be positioned at the same autosampler position 440 (not at the same time) and the tray actuator may be controlled to position appropriate wells for the respective cannula at the autosampler position 440. The syringe fluidics system 480 is further connected to a fill port connection unit 490 being arranged to selectively connect to a fill port 500 at an upper section of the syringe 200 in the pipette assembly. When connected to the fill port 500, the fill port connection unit 490 provides fluidic contact between the syringe cavity and the syringe fluidics system 480 to selectively pull or push liquid or gas through the syringe 200.

As previously mentioned, fig. 3a shows an ITC system corresponding to the system of fig. 2, but wherein the translation units 310b, 330b, 370b for the pipette 30, cell cannula 400 and transfer cannula 470 are of linear type, and the associated positions of operations are arranged accordingly. Moreover, the cell arm 390b and the transfer arm 460b are moveable in two dimensions (disregarding the vertical direction as mentioned above) whereby one or both may be controlled to position the associated cannula in a selected well in a static sample tray 450. Fig. 3b shows an embodiment of a linear ITC-system similar to fig. 3a, wherein the titrant transfer unit is omitted and the pipette translation unit 310c is arranged to place the pipette 30 in position for filling directly from a selected well in the sample tray 450. Moreover, the fill port connection unit 490 is arranged by the pipette 30 on the pipette arm 380c in order to connect to the fill port 500 both when the pipette 30 is placed in the wash station 320 and in a fill position in a well of the sample tray 450.

As mentioned above, the waste fluidics system 360 is connected to the outlet port 350 of the wash station 320 for withdrawing fluid from the wash station. According to one embodiment, the waste fluidics system 360 comprises a waste pump 510 for selective withdrawal of fluid from the wash station 320, optionally in combination with one or more controllable valves 520 to direct the flow of waste fluids. In other embodiments, the waste pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 510 may be any suitable pump capable of removing the fluids in the wash station, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a waste fluidics system 360 comprising a waste pump 510 of reservoir type, such as a syringe pump, and a waste control valve 520 for selective connection disconnection of the waste pump to the outlet port 350, a waste outlet 530 and a vent port 540.

As mentioned above, and shown more in detail in figs. 4a to 5c, the syringe 200 of the pipette may comprise a fill port 500 at an upper section thereof, providing fluidic contact with the syringe cavity when the plunger 230 is positioned above said fill port 500. Further the ITC system 300 may comprise a mating fill port connection unit 490 being arranged to selectively connect to the fill port 500, thereby providing fluidic contact between the syringe cavity and a syringe fluidics system 480 arranged to selectively pull or push liquid or gas through the syringe as part washing and filling operations, which will be disclosed more in detail below. As is schematically disclosed, the fill port 500 may be a bore through a wall of the syringe 200, and the bore may be of any suitable shape such as straight or conical. The connection unit 490 comprises a connection member 550 mating shape and/or of resilient material to achieve a reliable and fluid tight connection. The syringe fluidics system 480 may further be connected to the transfer

cannula 470, and arranged to control aspiration and dispensing of fluids during titrant transfer operations, as well as washing operations of the transfer cannula 470.

According to one embodiment, the syringe fluidics system 480 comprises a fill pump 560 to selectively pull or push liquid in the fluidics system, optionally in
5 combination with one or more controllable valves 570, 580, 590 to direct the flow of fluids and a purge gas source 600. In other embodiments, the fill pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 560 may be any suitable pump capable of push or pull the liquids in the syringe fluidic system with
10 relatively high accuracy, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a syringe fluidics system comprising a fill pump 560 of reservoir type, such as a syringe pump, a syringe control valve 570, syringe purge valve 580 and a transfer cannula purge valve 590. The syringe control valve 570 provides selective connection disconnection of the fill pump 560 to the fill port 500 of the
15 syringe 200, to the transfer cannula 470, to a plurality of reagent reservoirs 610a-d, to a waste outlet 620 and to a vent port 630. The reagent reservoirs 610a-d may comprise wash liquids for washing the syringe 210 and/or the transfer cannula 470 or the like. Fig. 4b shows a schematic view of another embodiment of the syringe fluidics system 480 and the waste fluidics system 360, wherein the transfer cannula 470 is not connected to the
20 syringe fluidics system 480, but instead connected to the waste fluidics system 360, whereby the titrant sample is transferred from the transfer cannula 470 to the wash station 320 via the waste fluidics system and the outlet port 350 of the wash station. Further, figs 4a and 4b schematically show the pipette assembly 30 in position for titration, with the titration needle 210 inserted into the sample cell 50.

25 In some embodiments, as is previously discussed, the syringe 200 is rotatable with

respect to the automatic pipette 30 and is driven for rotation by a stirring motor 250.

Then, in order to locate the position of the fill port 500, the fill port connection unit 490

may comprise a port alignment mechanism 640 arranged to prevent rotation of the

syringe at a predetermined angular position when a connection member 550 of the

5 connection unit is aligned with the fill port 500. Figs 5 a to 5c schematically shows an

example of an alignment mechanism 640, wherein the syringe 200, or any other part that

is arranged to rotate with the syringe 200, is provided with an alignment member 650, and

the fill port connection unit 490 is provided with a rotation stop unit 660 that may be

actuated to interfere with the rotation path of the alignment member 650, and when the

10 alignment member 650 abuts the rotation stop unit 660, then the connection member 550

is aligned with the fill port 500. The alignment procedure comprises the steps of:

- actuating the stop unit 660 (fig. 5a),
- rotating the syringe slowly in a predetermined direction until further
rotation is prevented by the stop unit 660 abutting the alignment member
15 650 (fig. 5b), and
- actuating the connection member 550 to connect to the fill port 500 (fig.
5c).

The stop unit 660 and the connection member 550 may be actuated by

electromagnetic drive actuators in the form of an electric motor arrangement, a solenoid

20 or the like, or they may be actuated by a hydraulic or pneumatic actuator or the like

capable of moving the stop unit 660 and the connection member 550. In order to achieve

a fluid tight connection between the syringe fill port 500 and the syringe fluidics system

480, the connection member 550 is pressed against the fill port 500 with a predetermined

force. In one embodiment (not shown) the connection member 550 is actuated by an

25 electromagnetic drive actuator, to move the connection member 550 into contact with the

fill port and the connection member 550 is spring loaded with respect to the actuator, whereby the scaling force is determined by the spring constant and the compression of said spring.

As is e.g. disclosed in fig. 2, the fill port connection unit 490 may be arranged at the wash station 320 to enable connection between the syringe cavity and the syringe fluidics system 480 when the pipette assembly 30 is arranged at the wash station 320. But, as is disclosed in fig. 3b, the fill port connection unit 490, may be arranged together with the pipette assembly 30 supported by the pipette translation unit 310, whereby fluidic connection between the syringe fill port 500 and the syringe fluidics system 480 may be established in any position of operation.

According to one embodiment, the ITC system 300 is arranged to utilize the syringe fill port 500 to wash the syringe 200 and the titration needle 210 by pushing one or more wash liquids through the syringe 200 and the titration needle 210 via the syringe fill port 500 when the titration needle 210 of the pipette 30 is arranged in the wash cavity 340 of the wash station 320. Thereafter the system may dry the syringe 200, needle 210 and the wash station 320 by purging gas through the syringe 200 and the titration needle 210 via the syringe fill port 500 after washing the same.

In many situations it is important to fill the syringe 200 of the pipette assembly 30 with titrant without having any trapped air in the syringe 200. In one embodiment, this is achieved by pulling a predetermined volume of titrant into the syringe from a titrant source, e.g. the wash station 320, in which the titration needle 210 is inserted, wherein the predetermined volume is selected to be larger than the syringe volume, whereby the syringe is overfilled and the titrant start to exit the syringe through the fill port 500. Then the linear activator 220 is activated to close the fill port 500 by moving the plunger 230 below to the fill port 500.

Fig. 6 schematically shows an example of a cell fluidics system 410 connected to the cell cannula 400 for dispensing and withdrawing liquid in the sample cell 50 and potentially also in the reference cell 40. As is previously discussed, the cell cannula 400 may be arranged to be positioned in the sample cell 50, in a well of a sample tray 450, in one or more large volume sample reservoirs 430a-c and a sample preparation station 420. According to one embodiment, the cell fluidics system 410 comprises a cell pump 670 for selective dispensing and withdrawing of fluid through the cell cannula 400, optionally in combination with one or more controllable valves 680, 690 to direct the flow of cell wash fluids or the like. In other embodiments, the cell pump 670 may be a common pump for one or more fluidics systems 360, 380, 410 in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The cell pump 670 may be any suitable pump capable of dispensing and withdrawing the fluids in e.g. the sample cell 50, such as a peristaltic pump, a syringe pump or the like. Fig. 6 shows a schematic view of an embodiment of a cell fluidics system 410 comprising a cell pump 670 of reservoir type, such as a syringe pump, a cell preparation control valve 680 for selective connection/disconnection of the waste pump to the cannula 400, four cell wash liquid reservoirs 700a-c, a waste outlet 710 and a vent port 720, and a purge select valve 690 for connection of the cannula 400 to the cell preparation valve 680 or a source of purge gas 600 for drying the cannula 400.

Fig 7 schematically shows the ITC system of fig. 2 wherein positions of operation for each translation arm is shown by broken lines.

Figs. 8a to 8D schematically show examples of states wherein operations for preparation of the pipette and the sample cell may be performed in parallel in the ITC system of fig. 2.

In fig. 8a the pipette assembly 30 is placed at the wash position with the titration

needle 210 in the wash station 320 for a syringe wash cycle. During a wash cycle, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to push and pull one or more washing liquids through the syringe 200 optionally followed by purging a gas, e.g. nitrogen, through the syringe to dry the syringe 200. To push a wash liquid through the syringe, firstly the syringe control valve 570 is arranged in position A to connect the fill pump to the appropriate reagent reservoir 610a-d and the fill pump 560 is actuated to draw wash liquid into its pump reservoir, secondly the syringe control valve 570 is arranged in position B to connect the fill pump 560 to the fill port 500 of the syringe 200 and the fill pump 560 is actuated to push wash liquid through the syringe 200, whereby the wash liquid is dispensed from the titration needle 210 into the wash station 320. A full syringe cleaning cycle might comprise pushing the same or a different wash liquid (syringe valve positions C-E) two or more times through the syringe 200, and it may further involve pulling liquid from the wash station 320 through the syringe 200 and into the pump reservoir whereby it can be pushed through the syringe 200 one more time, or be discarded through the waste outlet 620 of the syringe fluidics system 480. When the fill pump 570 is arranged to consecutively push two or more different wash liquids through the syringe 200, the fill pump 570 may be rinsed to avoid contamination between washing liquids, by filling the pump reservoir with a rinse liquid, e.g. water. Liquid that is dispensed into the wash station 320 may be selectively withdrawn through the outlet port 350 by the waste pump 510 into the pump reservoir by setting the waste valve 520 in position A, and may thereafter be discarded through the waste outlet 530 by setting the waste valve 520 in position B.

In fig. 8a, while the syringe wash cycle is performed at the wash station 320, the titrant transfer unit 370 is arranged to draw titrant sample from a well in the sample tray

450 by setting the syringe valve 570 in position F and pulling titrant from the well using the fill pump 560. The operation of drawing titrant from the well may e.g. be performed when the syringe 200 is purged with dry gas, whereby the fill pump 560 and the syringe valve 570 are not involved in the wash cycle, but after the fill pump 560 and the syringe
5 valve 570 has been thoroughly rinsed and washed to avoid contamination.

In fig. 8a, also while the syringe wash cycle is performed at the wash station 320, the cell preparation unit 330 is arranged to remove the previous sample from the sample cell 50 and to wash the sample cell 50. As the pipette assembly 30 is removed from the sample cell 50, the cell cannula 400 may be inserted into the sample cell 50, and by
10 arranging the cell preparation control valve 680 in position A the cell pump 670 may be activated to withdraw the previous sample into the pump reservoir, and the previous sample may thereafter be discarded through the waste outlet 710 by setting the cell preparation control valve 680 valve in position B. Cleaning of the cell is thereafter performed by dispensing and withdrawing one or more cell wash liquids in the sample
15 cell 50 optionally followed by purging a gas, e.g. nitrogen, through the cell cannula to dry the sample cell 50. To dispense a wash liquid in the sample cell, firstly the cell preparation control valve 680 is arranged in position C, D, E or F to connect the cell pump 670 to the appropriate wash liquid reservoir 700a-d and the cell pump 670 is actuated to draw wash liquid into its pump reservoir, secondly the cell preparation control
20 valve 680 is arranged in position A to connect the cell pump 670 to the cannula 400 and the cell pump 670 is actuated to dispense wash liquid in the sample cell 50 through the cell cannula 200. The cleaning liquid(s) are thereafter withdrawn and discarded through the waste port 710 of the cell preparation control valve 680. According to the disclosed embodiment, the cell cannula 400 stays in the sample cell during the cell wash procedure,
25 thereby the cell cannula 400 is washed at the same time as the cell 50 and is ready for

transfer of fresh sample liquid to the sample cell 50.

In fig. 8b the pipette assembly 30 is placed at an intermediate position between the sample cell 50 and the wash station 320, in order to grant the titrant transfer cannula 470 of the titrant transfer unit 370 access to the wash station 320 to dispense a new titrant sample therein, and to grant the cell cannula 400 cell preparation unit 300 access to the sample cell 50 to fill the sample cell with fresh sample in the next step. The titrant transfer unit 370 is arranged to dispense the titrant sample from the cannula 470 into the wash station by setting the syringe valve 570 in position F and dispensing titrant using the fill pump 560.

In fig. 8b the cell preparation unit is arranged to draw fresh sample from a well in the sample tray 450 by inserting the cell cannula 400 in a selected well containing the desired fresh sample, setting the cell preparation control valve 680 in position A and pulling fresh sample from the well into the pump reservoir of the cell pump 670. Alternatively, the cell cannula 400 may be inserted into one of the sample reservoirs 430a-c.

In fig. 8c the pipette assembly 30 again is placed at the wash position with the titration needle 210 in the wash station 320 to fill the syringe 200 with titrant. As is discussed in detail with reference to figs. 5a-c, during filling of the syringe 200, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to pull the titrant through titrant needle 210 into the syringe 200 until a small volume has passed the fill port 500, whereby the plunger 230 is lowered to close the fill port 500. By drawing the titrant into the syringe in this way, trapped air in the titrant is effectively avoided. During the state disclosed in fig 8b, the titrant transfer unit 370 is essentially inactive, but the cell preparation unit 330 is positioned with the cell cannula 400 in the sample cell 50 to fill

the later with an exact amount of fresh sample by arranging the cell preparation control valve 680 in position A and activating the cell pump 670 to dispense the fresh sample contained in the pump reservoir into the sample cell 50.

In fig. 8a the pipette assembly 30 is placed at the titration position with the titration needle 210 in the sample cell 50 to perform an ITC experiment. The Titration transfer unit 370 is now positioned with the titrant cannula in the wash station 320 to wash it before the next titrant transfer operation. The washing cycle may be essentially the same as for the syringe 200. During the state disclosed in fig 8b, the cell preparation unit 330 is essentially inactive, and shown with the cell cannula 400 in the sample preparation station 420.

Examples of Liquid handling sequences includes:

Cell wash:

- a. The cell cannula 400 is inserted into the cell 40, 50, resting on the bottom.
- b. The cell content is drawn through the cell cannula 400, into the cell pump 680, and dispensed out to the waste port 710.
- c. Water is drawn from one of the wash liquid reservoirs 700a-d into the pump reservoir of the cell pump 680 and dispensed out to the waste port 710 to rinse the syringe.
- d. A wash liquid is drawn into the pump reservoir of the cell pump 680 from one of the wash liquid reservoirs 700a-d and dispensed through the cell cannula 400 into the cell 40, 50 in the exact amount needed to fill the cell,
- e. The wash liquid is cycled back and forth from the pump reservoir of the cell pump 680 to the cell 40, 50 to wash the later.
- f. The steps beginning at step b are repeated a predetermined number of times until the cell 40, 50.

- g. The cell is emptied to waste as in step b.
 - h. The cell cannula 400 is moved to the sample preparation station 420 and dried with by purging gas, e.g. Nitrogen. If degassing is included in the cell load procedure, the sample preparation 420 station is cleaned before drying.
- 5

Pipette wash:

- a. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- 10 b. The pipette plunger 230 is raised above the fill port 500 allowing liquid to flow through the syringe 200 of the pipette 30.
- c. First water then air is dispensed from the syringe pump 560 into the fill port 500, through the syringe 200 and titration needle 210 into the wash/fill station 320. Simultaneously, this water is drawn in great excess from the bottom of the wash/fill station 320 through the waste outlet 350 into the waste pump 510.
- 15 d. The waste pump 510 is stopped and a precise amount of water is dispensed through the pipette 30 to fill the wash/fill station 320 to the top of the outside of the titration needle 210. The water is cycled back and forth to wash the entire syringe 200 and the titration, inside and outside.
- 20 e. Step c is repeated.
- f. Step d is repeated with methanol.
- g. Step c is repeated.
- h. Nitrogen is purged through the fill port 500 to dry the system.
- 25 i. The pipette 30 is removed from the wash/fill station 320 to allow the

titrant transfer unit 370 to load the station 320 with titrant sample.

- j. The syringe pump 560 is rinsed with water to clear any methanol from the system.

5 Cell Load:

- a. Titrant sample is drawn into the cell cannula 400 from a sample tray 450 or a sample reservoir 430a-c. It is then slowly dispensed into the cell to prevent air bubbles. Optionally, the sample is dispensed into the sample preparation station 420 to be warmed and mixed (degassed) before being
10 transferred into the cell 50.

Pipette load:

- a. Titrant is drawn into the titrant transfer cannula 470 from a sample tray 450 and dispensed into the wash/fill station 320.
- 15 b. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- c. The plunger 230 is raised above the fill port 500 allowing liquid to flow through the pipette.
- d. A precise volume of titrant is drawn up through the titration needle 210 by
20 the syringe pump 560, over-filling the syringe 200 such that a small amount of titrant exits the fill port 500.
- e. The plunger 230 is lowered below the fill port 500 leaving the titrant needle 210 and pipette syringe 200 completely filled.

Titrant Transfer Clean:

- a. The titrant transfer cannula 470 is placed in the wash/fill station 320 and is rinsed with water, then rinsed with methanol and dried in much the same way that the syringe 200 of the pipette is washed and dried.

5

It is to be understood that any feature described in relation to any one embodiment may be used alone, or in combination with other features described, and may also be used in combination with one or more features of any other of the embodiments, or any combination of any other of the embodiments. Furthermore, equivalents and
10 modifications not described above may also be employed without departing from the scope of the invention, which is defined in the accompanying claims.

AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER
APPARATUS AND METHOD OF USE

5 CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 12/326,300, filed on December 2, 2008, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The present invention relates generally to microcalorimeters and more specifically to
10 features that improve the performance of microcalorimeters, especially an automated isothermal titration micro calorimetry system (ITC system).

Microcalorimeters are broadly utilized in fields of biochemistry, pharmacology, cell biology, and others. Calorimetry provides a direct method for measuring changes in thermodynamic properties of biological macromolecules. Microcalorimeters are typically two cell
15 instruments in which properties of a dilute solution of test substance in an aqueous buffer in a sample cell are continuously compared to an equal quantity of aqueous buffer in a reference cell. Measured differences between the properties of the two cells, such as temperature or heat flow, are attributed to the presence of the test substance in the sample cell.

One type of microcalorimeter is an isothermal titration calorimeter. The isothermal
20 titration calorimeter (ITC) is a differential device, but operates at a fixed temperature and pressure while the liquid in the sample cell is continuously stirred. The most popular application for titration calorimetry is in the characterization of the thermodynamics of molecular interactions. In this application, a dilute solution of a test substance (e.g., a protein) is placed in the sample cell and, at various times, small volumes of a second dilute solution containing a ligand, which binds
25 to the test substance, are injected into the sample cell. The instrument measures the heat, which is evolved or absorbed as a result of the binding of the newly introduced ligand to the test substance. From results of multiple-injection experiments, properties, such as, the Gibbs energy, the association constant, the enthalpy and entropy changes, and the stoichiometry of binding,

may be determined for a particular pairing between the test substance and the ligand.

While currently utilized ITCs provide reliable binding data results, their widespread utilization in the early stages of drug development have been limited by several factors: the relatively high amounts of protein required to perform a binding determination (e.g., about 0.1 milligram (mg) to about 1.0 mg of a protein), the limited throughput due to the time required to perform the measurement and the complexity of using conventional ITCs.

Today, gathering binding data utilizing prior art ITCs require extensive preparation and skill by the practitioner. For example, using prior art ITCs, the reference and sample cells are first filled respectively with the reference substance and sample substance via a corresponding cell stem. Next, a titration pipette of the ITC is filled with a titrant, which is a delicate operation as it is very important that the syringe in the pipette is accurately filled and that there is no air trapped therein. Then a needle of the titration pipette is manually placed in the sample cell via the cell stem, and the ITC experiments can be initiated. The ITC measurement procedure is controlled by a control unit in the form of a computer or the like running a program for performing the experiments. Consistent with the program used for the experiment, a stirring motor rotates the syringe, needle, and paddle at an assigned speed enabling proper mixing of the reagents. Consistent with the program used for the experiment (e.g., when a certain temperature and/or equilibrium are reached), a plunger in the syringe is activated to inject the titrant into the sample solution. The injection can be done discretely (step-by-step) or continuously, depending on the program settings. The calorimeter continuously measures and records the heat release/absorption versus time associated with the interaction of reagents. The analysis of the results is done according to the established algorithm.

As would be appreciated by a reading of the above-described prior art procedure,

utilizing prior art ITCs, the quality of binding measurements performed with these prior art ITCs depends heavily of the operator's skills and experience, and involves a considerable amount of preparation time.

For some time there has been at least one automated ITC system on the market, MicroCal AutoITC, which is based on a commercially available micro calorimeter and a linear robot system and a fluidics system arranged to perform automatic sample handling.

SUMMARY OF THE INVENTION

The object of the invention is to provide a new automatic isothermal titration micro calorimetry system (ITC system), which ITC system overcomes one or more drawbacks of the prior art. This is achieved by the ITC system as defined in the independent claims.

One advantage with the present ITC system is that each titration experiment requires less time compared to the prior art. This is e.g. due to the reduced cell volume and that washing and refilling of the pipette assembly and the sample cell is performed essentially in parallel. Hence the system throughput is considerably higher compared to the prior art systems, making it possible to evaluate large number of samples to make screening type experiments.

Another advantage is that the ITC system may be arranged to perform a large number of unattended titration experiments.

Embodiments of the invention are defined in the dependent claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic example of a prior art manual ITC system in cross-section, the ITC system comprising an automatic pipette assembly.

Figure 2 shows a schematic view of one embodiment of an automated ITC system.

Figures 3a and 3b show schematic views of other embodiments of the automated ITC system.

Figures 4a and 4b show schematic views of two embodiments of a syringe fluidics system for an automated ITC system.

Figures 5a to 5c show schematic views of the function of a syringe fill port connector unit according to an embodiment.

Figure 6 shows a schematic view of a cell preparation fluidics system according to one embodiment.

Figure 7 schematically shows different states of operations for the ITC system of fig. 2

Figures 8a to 8d shows different states of operations for the ITC system of fig. 2 more in detail.

15 DETAILED DESCRIPTION OF THE INVENTION

In the PCT application PCT/US2008/081961, which is incorporated by reference, a manual ITC system 10 of the type disclosed in fig. 1 is presented. According to one embodiment, the manual ITC system 10 is utilized as micro-calorimeter in the present automatic ITC system, but in other embodiments, the micro-calorimeter is of other types, as will be discussed in greater detail below. In the disclosed manual ITC system 10, the cell compartment volume is reduced by about a factor of seven as compared to prior art ITCs, without a reduction in sensitivity, and with a significantly faster response time. Such an ITC system permits the performance of experiments with about 10 times less protein sample, and with only a total of about 2 to about 4 titrations per hour. In addition to reducing the costs associated with running the ITC experiment, a smaller cell volume

also extends the number of ITC applications. For example, the range of binding affinities that can be measured by ITC is dictated by a parameter called "c value," which is equal to the product of the binding affinity (K_a) and the total concentration (M_{total}) of macromolecule ($c = [M_{total}]K_a$). For accurate affinity determination, the c value must be
5 between 1 and 1,000. A decrease in the cell volume by a factor of ten results in a similar increase in c value if the same amount of protein is used, and, consequently, the ability to measure weak binders. This ability is especially important in the early stages of drug discovery, in which binding affinities are weak, especially in conjunction with a fully automated instrument.

10 Fig. 1 schematically shows one embodiment of the manual ITC system 10 that may be automated in accordance with the present invention. The ITC system 10 comprises a micro calorimeter 20 and an automatic pipette assembly 30. The micro calorimeter 20 comprises a reference cell 40 and a sample cell 50 which are designed to be essentially identical in heat capacity and volume. The cells 40 and 50 are comprised of
15 a suitable chemically inert and heat conductive material, such as gold, Platinum, tantalum, hastelloy or the like. The cells 40 and 50 may be of essentially any suitable shape, but it is desirable that they are of the same shape, that they are possible to arrange in a fully symmetric arrangement, and that efficient mixing of the titrant with the sample may be achieved. In the disclosed embodiment, the cross-section of the cells 40 and 50 is
20 rectangular, and the cross-section in the transverse horizontal direction may be circular, resulting in coin shaped cells with circular facing surfaces.

In order to reduce any external thermal influences to a minimum, the, reference cell 40 and the sample cell 50 are both enclosed by a first thermal shield 60 which in turn is enclosed by a second thermal shield 70. The thermal shields 60, 70 may be comprised
25 of any suitable thermally conductive material such as silver, aluminum, copper or the like.

The shields 60, 70 may further be comprised of one or more thermally interconnected sub shields (not shown, to provide even further stable temperature conditions for the calorimetric cells 40, 50.

In order to control the temperature of the shields 60, 70, thermal control means
5 may be arranged to control the temperature thereof. In an ITC system said thermal control means are mainly used to set the “isothermal” temperature of the calorimeter, ie of the thermal shields 60, 70, before the titration experiments are initiated. But as will be disclosed in greater detail below, said thermal control means may also be used to improve the adiabatic behavior of the calorimeter. According to one embodiment, the thermal
10 control means are comprised of one or more heat pump units, such as a thermoelectric heat pump device based on the peltier effect or the like. Other types of thermal control means include thermostatically controlled liquid baths, mechanical heat pumps, chemical heating or cooling systems or the like.

In the disclosed embodiment a first heat pump unit 80 is arranged to transfer heat
15 energy between the first 60 and second thermal shields 70, a second heat pump unit 90 is arranged to transfer heat energy between the second thermal shield 70 and a heat sink 100 in thermal contact with the ambient temperature. A temperature controller 110 is arranged to control the first and second heat pump units 80, 90 so that the desired temperature conditions are achieved. The temperature controller 110 monitors the temperatures of the
20 first 60 and second thermal shield by associated temperature sensors 120 and 130 respectively. Furthermore, the thermal controller 110 is arranged to control the cell temperature by a cell heating arrangement 145. The thermal controller 110 is controlled via a calorimeter user interface run on a computer 150 or the like. Calorimetric sensors 140 for sensing the temperature difference between the sample cell 50 and reference cell
25 40 during the ITC experiments may be connected to the computer 150, e.g. via a

preamplifier 160.

A reference cell stem 170 and a sample cell stem 180 provides access to the reference cell 40 and sample cell 50, respectively, for supplying reference and sample fluids, titration fluid, washing of the cells etc. In the disclosed embodiment, the cell stems
5 170 and 180 both extends essentially vertically through both thermal shields and the heat sink to provide direct communication with cells 40 and 50 and the cell stems 170 and 180 each support their respective cell 40 and 50 in the cavity of the first thermal shield 60.

The automatic pipette assembly 30 comprises a pipette housing 190, a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying
10 titrant, and a linear activator 220 for driving a plunger 230 in the syringe 200. The titration needle 210 is rotatable with respect to the housing 190 and is provided with a stirring paddle 240 arranged to stir sample fluid in the sample cell 50 in order to achieve efficient mixing of titrant and sample fluid. The automatic pipette assembly 30 further comprises a stirring motor 250 for driving the rotation of the titration needle 210.

15 In the embodiment disclosed in fig. 1 the stirring motor 250 is a direct drive motor with a hollow rotor arranged concentric with the syringe 200 and the titration needle 210. The syringe 200 is at its upper end supported for rotation by the stirring motor 400 and at the lower end by a bearing 260.

In an alternative embodiment, not shown in the figures, the stirring motor 250
20 drives the titration needle for rotation by a rotation transmission arrangement, such as a drive belt arrangement, a drive wheel arrangement or the like. Moreover, the stirring motor may be arranged separated from the pipette assembly 30 and be arranged to drive the titration needle for rotation by a suitable transmission arrangement such as a magnetic coupling or the like.

25 The automatic pipette assembly 30 is controlled by a controller of the ITC system,

e.g. stirring of the sample and the titration.

In the disclosed embodiment, the linear activator 220 comprises a stepper motor 270 arranged to drive the threaded plunger 230 that extends coaxially through the hole of a hollow rotor and into the syringe 200 wherein it is rotatably attached to a pipette tip 280 that seals against the inner wall of the syringe 200 to allow displacing a precise volume of titration liquid from syringe 200. The linear activator 220 may be of any other type capable of perform controlled linear motion with sufficient precision. This design allows syringe to be rotated independently of the main body 190 of the pipette assembly 30; at the same time, the linear activator 220 can drive the threaded plunger 230.

In accordance with one embodiment, schematically disclosed in figs. 2 to 8d, there is provided an automated isothermal titration micro calorimetry (ITC) system 300 comprising:

- a micro calorimeter 20 with a sample cell 50 and a reference cell 40, the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170,
- an automatic pipette assembly 30 comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant, the pipette assembly 30 comprises a linear activator 220 for driving a plunger 230 in the syringe 200,
- a pipette translation unit 310 supporting the pipette assembly 30 and being arranged to place pipette in position for titration, washing and filling operations,
- a wash station 320 for the titrant needle 210, and
- a cell preparation unit 330 arranged to perform operations for replacing the sample liquid in the sample cell 50 when the pipette 30 is placed in another

position than the position for titration.

The micro calorimeter 20 may be of any type capable of performing ITC calorimetric measurements using sufficiently small volumes of sample such as the micro calorimeter 20 schematically shown in fig. 1. As disclosed above (fig. 1), but not specifically shown in figs 2 to 8d, a micro calorimeter generally comprises a sample cell 50 and a reference cell 40, wherein the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170 (shown as circular openings in fig. 2). The automatic pipette assembly 30 may be of the type disclosed above, but it may be of any suitable design comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant. Like above, the pipette assembly 30 may further comprise a linear activator 220 for driving a plunger 230 in the syringe 200. However, the syringe 200 may be of essentially any type, capable of providing well-defined volumes of titrant. The titration needle 210 may be rotatable and may be provided with a paddle 240 for stirring of the liquid in the sample cell 50 during the titration. The stirring may be accomplished as is discussed above or in any other suitable way.

The pipette translation unit 310 may be of any type capable of placing the pipette in the appropriate positions for titration, washing and filling. Figs 2 and 3 schematically show two different types of translation units, wherein fig. 2 shows a rotation translation unit 310 and fig. 3 shows a linear translation unit 310b. In order to place (insert) the titration needle 210 in position in the sample cell 50, and/or in other positions, the pipette translation unit 310 is capable of moving the pipette 30 in the vertical direction with respect to the micro calorimeter 20. The pipette translation unit 310 may be mechanically restricted with respect to its freedom of movement so that it only may move between mechanically predetermined positions, or it may be a general translation unit of robot type

that is restricted to movement between said predetermined positions by means of software parameters, or a combination thereof. For clarity reasons no such means for vertical movements have been included in the figures 2 to 8d.

5 The wash station 320 is arranged at a suitable position wherein the titration needle 210 of the pipette assembly 30 can be placed in position for washing. The wash station 320 may be of any suitable type capable of washing at least the section of the titration needle 210 that is immersed in the sample during titration when the pipette assembly 30 is placed in position for washing. According to one embodiment, the wash station 320 comprises a wash cavity 340 arranged to receive the titration needle. The wash station 10 320 is made of any suitable material that is inert with respect to the reagents used in the ITC experiments and the wash cycles. According to one embodiment, the wash station 320 comprises a waste outlet port 350 at the bottom end of the wash cavity connected to a waste removal unit 360. The waste outlet port 350 is used to remove waste liquids as well as wash liquids during the pipette washing cycle, as will be disclosed more in detail 15 below, and it is preferably arranged at the bottom end of the wash cavity 340 in order to enable complete drainage of the wash cavity. In one embodiment not disclosed in the figures, the pipette translation unit 310 is limited to movement in the vertical direction, and the wash station 320 instead is arranged to be moved to a position in alignment with the needle 240 for cleaning of the same.

20 In figs. 2 to 8d the cell preparation unit 330 is shown as a translation unit of the same type as the pipette translation unit 310, but arranged to be positioned in at least two positions related to washing and replacing sample liquid in the sample cell. By the provision of a cell preparation unit 330 for replacing the sample liquid in the sample cell 50 the total cycle time is reduced and thus the throughput of the ITC system 300 is 25 increased, as the sample cell 50 may be washed and filled with new sample liquid at the

same time as the pipette 30 is washed and filled with new titrant.

Fig. 2 schematically discloses an automated isothermal titration micro calorimetry (ITC) system 300 according to one embodiment of the present invention. As mentioned above, the translation units 310, 330, 370 in this embodiment are all of rotary type, and all
5 positions of operation are arranged along circular paths of the rotary translation units. In another embodiment, not shown, one or more of the rotary translation units are provided with additional linear translation means to extend work area and to increase the flexibility.

In fig. 2 the pipette translation unit 310 comprises a pipette arm 380 that is
10 rotatably supported for rotation about an axis A, and supporting the pipette assembly 30 at the other end thereof. The pipette arm 380 is further arranged to move the pipette vertically, either in that the arm 380 can be moved vertically along the axis A, or in that the arm 380 is limited for rotation in one plane and the pipette 30 is vertically moveable with respect to the arm 380. The pipette arm 380 is arranged to place pipette 30 in
15 position for:

- titration with the titration needle inserted into the sample cell 50,
- washing and filling with the titration needle inserted in a combined wash/fill station 320.

The combined wash/fill station 320 may be a wash station of the type discussed
20 above with an outlet port 350 at the bottom end of the wash cavity 340. The outlet port 350 is connected to a waste fluidics system 360 that will be discussed in more detail below.

The cell preparation unit 330 is in turn comprised of a corresponding cell arm 390 that is rotatably supported for rotation about an axis B, supporting a cell cannula 400
25 connected to a cell fluidics system 410 for dispensing and withdrawing liquid in the

sample cell 50 and potentially also in the reference cell 40. The cell fluidics system 410 will be disclosed in more detail below. The cell arm 390 is arranged to move the cell cannula 400 to a plurality of positions such as the cells, 40, 50 of the micro calorimeter, one or more sample sources, and a sample preparation station 420, or the like. In the

5 disclosed embodiment, four different sample source positions are included of which three positions represent large volume sample reservoirs of vial type 430a - 430c, e.g. for standard sample liquids, and the fourth position an autosampler position 440, e.g. for specific or sensitive sample liquids, wherein the cell cannula 400 is arranged to draw the sample liquid from a specific well in a sample tray 450 (e.g. micro plate or the like). In

10 the disclosed embodiment, the autosampler position 440 is a static position to which the cell cannula 400 can be moved by the cell arm 390 and be lowered into a specific well of a sample tray 450 that can be moved to position a selected well at the autosampler position 440 by a tray actuator (not shown). The tray actuator may be of any suitable type capable of selectively position a specific sample well of a sample tray 450 at a desired

15 position, such as a linear X-Y actuator or a rotary actuator with a carousel tray. The sample preparation station 430 may be used to prepare the sample before it is transferred into the cell 50 or 40, e.g. by bringing the sample to a temperature close to the experimental temperature, or by degassing through mixing.

The ITC system 300 disclosed in Fig. 2 further comprises a titrant transfer unit

20 370 arranged to transfer titrant from a primary titrant source, e.g. a sample tray 450, to the wash/fill station 320. In the disclosed embodiment, the transfer unit 370 comprises a titrant transfer arm 460, e.g. corresponding to the cell transfer arm 380, that is rotatably supported for rotation about an axis C, supporting a transfer cannula 470 connected to a syringe fluidics system 480. The titrant transfer arm 460 is arranged to position the titrant

25 cannula 470 in an autosampler position 440 for drawing a titrant sample from a titrant

well in a sample tray 450, and in position to dispense said titrant sample in the wash/fill station 320. The autosampler position 440 and the sample tray 450 may be a separate position and tray with respect to the cell cannula autosampler position 440 discussed above, but as is disclosed in fig 2, the cell cannula 470 and the titrant cannula 400 may be positioned at the same autosampler position 440 (not at the same time) and the tray actuator may be controlled to position appropriate wells for the respective cannula at the autosampler position 440. The syringe fluidics system 480 is further connected to a fill port connection unit 490 being arranged to selectively connect to a fill port 500 at an upper section of the syringe 200 in the pipette assembly. When connected to the fill port 500, the fill port connection unit 490 provides fluidic contact between the syringe cavity and the syringe fluidics system 480 to selectively pull or push liquid or gas through the syringe 200.

As previously mentioned, fig. 3a shows an ITC system corresponding to the system of fig. 2, but wherein the translation units 310b, 330b, 370b for the pipette 30, cell cannula 400 and transfer cannula 470 are of linear type, and the associated positions of operations are arranged accordingly. Moreover, the cell arm 390b and the transfer arm 460b are moveable in two dimensions (disregarding the vertical direction as mentioned above) whereby one or both may be controlled to position the associated cannula in a selected well in a static sample tray 450. Fig. 3b shows an embodiment of a linear ITC-system similar to fig. 3a, wherein the titrant transfer unit is omitted and the pipette translation unit 310c is arranged to place the pipette 30 in position for filling directly from a selected well in the sample tray 450. Moreover, the fill port connection unit 490 is arranged by the pipette 30 on the pipette arm 380c in order to connect to the fill port 500 both when the pipette 30 is placed in the wash station 320 and in a fill position in a well of the sample tray 450.

As mentioned above, the waste fluidics system 360 is connected to the outlet port 350 of the wash station 320 for withdrawing fluid from the wash station. According to one embodiment, the waste fluidics system 360 comprises a waste pump 510 for selective withdrawal of fluid from the wash station 320, optionally in combination with one or more controllable valves 520 to direct the flow of waste fluids. In other embodiments, the waste pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 510 may be any suitable pump capable of removing the fluids in the wash station, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a waste fluidics system 360 comprising a waste pump 510 of reservoir type, such as a syringe pump, and a waste control valve 520 for selective connection disconnection of the waste pump to the outlet port 350, a waste outlet 530 and a vent port 540.

As mentioned above, and shown more in detail in figs. 4a to 5c, the syringe 200 of the pipette may comprise a fill port 500 at an upper section thereof, providing fluidic contact with the syringe cavity when the plunger 230 is positioned above said fill port 500. Further the ITC system 300 may comprise a mating fill port connection unit 490 being arranged to selectively connect to the fill port 500, thereby providing fluidic contact between the syringe cavity and a syringe fluidics system 480 arranged to selectively pull or push liquid or gas through the syringe as part washing and filling operations, which will be disclosed more in detail below. As is schematically disclosed, the fill port 500 may be a bore through a wall of the syringe 200, and the bore may be of any suitable shape such as straight or conical. The connection unit 490 comprises a connection member 550 mating shape and/or of resilient material to achieve a reliable and fluid tight connection. The syringe fluidics system 480 may further be connected to the transfer

cannula 470, and arranged to control aspiration and dispensing of fluids during titrant transfer operations, as well as washing operations of the transfer cannula 470.

According to one embodiment, the syringe fluidics system 480 comprises a fill pump 560 to selectively pull or push liquid in the fluidics system, optionally in
5 combination with one or more controllable valves 570, 580, 590 to direct the flow of fluids and a purge gas source 600. In other embodiments, the fill pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 560 may be any suitable pump capable of push or pull the liquids in the syringe fluidic system with
10 relatively high accuracy, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a syringe fluidics system comprising a fill pump 560 of reservoir type, such as a syringe pump, a syringe control valve 570, syringe purge valve 580 and a transfer cannula purge valve 590. The syringe control valve 570 provides selective connection disconnection of the fill pump 560 to the fill port 500 of the
15 syringe 200, to the transfer cannula 470, to a plurality of reagent reservoirs 610a-d, to a waste outlet 620 and to a vent port 630. The reagent reservoirs 610a-d may comprise wash liquids for washing the syringe 210 and/or the transfer cannula 470 or the like. Fig. 4b shows a schematic view of another embodiment of the syringe fluidics system 480 and the waste fluidics system 360, wherein the transfer cannula 470 is not connected to the
20 syringe fluidics system 480, but instead connected to the waste fluidics system 360, whereby the titrant sample is transferred from the transfer cannula 470 to the wash station 320 via the waste fluidics system and the outlet port 350 of the wash station. Further, figs 4a and 4b schematically show the pipette assembly 30 in position for titration, with the titration needle 210 inserted into the sample cell 50.

25 In some embodiments, as is previously discussed, the syringe 200 is rotatable with

respect to the automatic pipette 30 and is driven for rotation by a stirring motor 250.

Then, in order to locate the position of the fill port 500, the fill port connection unit 490 may comprise a port alignment mechanism 640 arranged to prevent rotation of the syringe at a predetermined angular position when a connection member 550 of the

5 connection unit is aligned with the fill port 500. Figs 5 a to 5c schematically shows an example of an alignment mechanism 640, wherein the syringe 200, or any other part that is arranged to rotate with the syringe 200, is provided with an alignment member 650, and the fill port connection unit 490 is provided with a rotation stop unit 660 that may be actuated to interfere with the rotation path of the alignment member 650, and when the
10 alignment member 650 abuts the rotation stop unit 660, then the connection member 550 is aligned with the fill port 500. The alignment procedure comprises the steps of:

- actuating the stop unit 660 (fig. 5a),
- rotating the syringe slowly in a predetermined direction until further rotation is prevented by the stop unit 660 abutting the alignment member
15 650 (fig. 5b), and
- actuating the connection member 550 to connect to the fill port 500 (fig. 5c).

The stop unit 660 and the connection member 550 may be actuated by electromagnetic drive actuators in the form of an electric motor arrangement, a solenoid
20 or the like, or they may be actuated by a hydraulic or pneumatic actuator or the like capable of moving the stop unit 660 and the connection member 550. In order to achieve a fluid tight connection between the syringe fill port 500 and the syringe fluidics system 480, the connection member 550 is pressed against the fill port 500 with a predetermined force. In one embodiment (not shown) the connection member 550 is actuated by an
25 electromagnetic drive actuator, to move the connection member 550 into contact with the

fill port and the connection member 550 is spring loaded with respect to the actuator, whereby the scaling force is determined by the spring constant and the compression of said spring.

As is e.g. disclosed in fig. 2, the fill port connection unit 490 may be arranged at the wash station 320 to enable connection between the syringe cavity and the syringe fluidics system 480 when the pipette assembly 30 is arranged at the wash station 320. But, as is disclosed in fig. 3b, the fill port connection unit 490, may be arranged together with the pipette assembly 30 supported by the pipette translation unit 310, whereby fluidic connection between the syringe fill port 500 and the syringe fluidics system 480 may be established in any position of operation.

According to one embodiment, the ITC system 300 is arranged to utilize the syringe fill port 500 to wash the syringe 200 and the titration needle 210 by pushing one or more wash liquids through the syringe 200 and the titration needle 210 via the syringe fill port 500 when the titration needle 210 of the pipette 30 is arranged in the wash cavity 340 of the wash station 320. Thereafter the system may dry the syringe 200, needle 210 and the wash station 320 by purging gas through the syringe 200 and the titration needle 210 via the syringe fill port 500 after washing the same.

In many situations it is important to fill the syringe 200 of the pipette assembly 30 with titrant without having any trapped air in the syringe 200. In one embodiment, this is achieved by pulling a predetermined volume of titrant into the syringe from a titrant source, e.g. the wash station 320, in which the titration needle 210 is inserted, wherein the predetermined volume is selected to be larger than the syringe volume, whereby the syringe is overfilled and the titrant start to exit the syringe through the fill port 500. Then the linear activator 220 is activated to close the fill port 500 by moving the plunger 230 below to the fill port 500.

Fig. 6 schematically shows an example of a cell fluidics system 410 connected to the cell cannula 400 for dispensing and withdrawing liquid in the sample cell 50 and potentially also in the reference cell 40. As is previously discussed, the cell cannula 400 may be arranged to be positioned in the sample cell 50, in a well of a sample tray 450, in one or more large volume sample reservoirs 430a-c and a sample preparation station 420. According to one embodiment, the cell fluidics system 410 comprises a cell pump 670 for selective dispensing and withdrawing of fluid through the cell cannula 400, optionally in combination with one or more controllable valves 680, 690 to direct the flow of cell wash fluids or the like. In other embodiments, the cell pump 670 may be a common pump for one or more fluidics systems 360, 380, 410 in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The cell pump 670 may be any suitable pump capable of dispensing and withdrawing the fluids in e.g. the sample cell 50, such as a peristaltic pump, a syringe pump or the like. Fig. 6 shows a schematic view of an embodiment of a cell fluidics system 410 comprising a cell pump 670 of reservoir type, such as a syringe pump, a cell preparation control valve 680 for selective connection/disconnection of the waste pump to the cannula 400, four cell wash liquid reservoirs 700a-c, a waste outlet 710 and a vent port 720, and a purge select valve 690 for connection of the cannula 400 to the cell preparation valve 680 or a source of purge gas 600 for drying the cannula 400.

Fig 7 schematically shows the ITC system of fig. 2 wherein positions of operation for each translation arm is shown by broken lines.

Figs. 8a to 8D schematically show examples of states wherein operations for preparation of the pipette and the sample cell may be performed in parallel in the ITC system of fig. 2.

In fig. 8a the pipette assembly 30 is placed at the wash position with the titration

needle 210 in the wash station 320 for a syringe wash cycle. During a wash cycle, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to push and pull one or more washing liquids through the syringe 200 optionally followed by purging a gas, e.g. nitrogen, through the syringe to dry the syringe 200. To push a wash liquid through the syringe, firstly the syringe control valve 570 is arranged in position A to connect the fill pump to the appropriate reagent reservoir 610a-d and the fill pump 560 is actuated to draw wash liquid into its pump reservoir, secondly the syringe control valve 570 is arranged in position B to connect the fill pump 560 to the fill port 500 of the syringe 200 and the fill pump 560 is actuated to push wash liquid through the syringe 200, whereby the wash liquid is dispensed from the titration needle 210 into the wash station 320. A full syringe cleaning cycle might comprise pushing the same or a different wash liquid (syringe valve positions C-E) two or more times through the syringe 200, and it may further involve pulling liquid from the wash station 320 through the syringe 200 and into the pump reservoir whereby it can be pushed through the syringe 200 one more time, or be discarded through the waste outlet 620 of the syringe fluidics system 480. When the fill pump 570 is arranged to consecutively push two or more different wash liquids through the syringe 200, the fill pump 570 may be rinsed to avoid contamination between washing liquids, by filling the pump reservoir with a rinse liquid, e.g. water. Liquid that is dispensed into the wash station 320 may be selectively withdrawn through the outlet port 350 by the waste pump 510 into the pump reservoir by setting the waste valve 520 in position A, and may thereafter be discarded through the waste outlet 530 by setting the waste valve 520 in position B.

In fig. 8a, while the syringe wash cycle is performed at the wash station 320, the titrant transfer unit 370 is arranged to draw titrant sample from a well in the sample tray

450 by setting the syringe valve 570 in position F and pulling titrant from the well using the fill pump 560. The operation of drawing titrant from the well may e.g. be performed when the syringe 200 is purged with dry gas, whereby the fill pump 560 and the syringe valve 570 are not involved in the wash cycle, but after the fill pump 560 and the syringe
5 valve 570 has been thoroughly rinsed and washed to avoid contamination.

In fig. 8a, also while the syringe wash cycle is performed at the wash station 320, the cell preparation unit 330 is arranged to remove the previous sample from the sample cell 50 and to wash the sample cell 50. As the pipette assembly 30 is removed from the sample cell 50, the cell cannula 400 may be inserted into the sample cell 50, and by
10 arranging the cell preparation control valve 680 in position A the cell pump 670 may be activated to withdraw the previous sample into the pump reservoir, and the previous sample may thereafter be discarded through the waste outlet 710 by setting the cell preparation control valve 680 valve in position B. Cleaning of the cell is thereafter performed by dispensing and withdrawing one or more cell wash liquids in the sample
15 cell 50 optionally followed by purging a gas, e.g. nitrogen, through the cell cannula to dry the sample cell 50. To dispense a wash liquid in the sample cell, firstly the cell preparation control valve 680 is arranged in position C, D, E or F to connect the cell pump 670 to the appropriate wash liquid reservoir 700a-d and the cell pump 670 is actuated to draw wash liquid into its pump reservoir, secondly the cell preparation control
20 valve 680 is arranged in position A to connect the cell pump 670 to the cannula 400 and the cell pump 670 is actuated to dispense wash liquid in the sample cell 50 through the cell cannula 200. The cleaning liquid(s) are thereafter withdrawn and discarded through the waste port 710 of the cell preparation control valve 680. According to the disclosed embodiment, the cell cannula 400 stays in the sample cell during the cell wash procedure,
25 thereby the cell cannula 400 is washed at the same time as the cell 50 and is ready for

transfer of fresh sample liquid to the sample cell 50.

In fig. 8b the pipette assembly 30 is placed at an intermediate position between the sample cell 50 and the wash station 320, in order to grant the titrant transfer cannula 470 of the titrant transfer unit 370 access to the wash station 320 to dispense a new titrant sample therein, and to grant the cell cannula 400 cell preparation unit 300 access to the sample cell 50 to fill the sample cell with fresh sample in the next step. The titrant transfer unit 370 is arranged to dispense the titrant sample from the cannula 470 into the wash station by setting the syringe valve 570 in position F and dispensing titrant using the fill pump 560.

In fig. 8b the cell preparation unit is arranged to draw fresh sample from a well in the sample tray 450 by inserting the cell cannula 400 in a selected well containing the desired fresh sample, setting the cell preparation control valve 680 in position A and pulling fresh sample from the well into the pump reservoir of the cell pump 670. Alternatively, the cell cannula 400 may be inserted into one of the sample reservoirs 430a-c.

In fig. 8c the pipette assembly 30 again is placed at the wash position with the titration needle 210 in the wash station 320 to fill the syringe 200 with titrant. As is discussed in detail with reference to figs. 5a-c, during filling of the syringe 200, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to pull the titrant through titrant needle 210 into the syringe 200 until a small volume has passed the fill port 500, whereby the plunger 230 is lowered to close the fill port 500. By drawing the titrant into the syringe in this way, trapped air in the titrant is effectively avoided. During the state disclosed in fig 8b, the titrant transfer unit 370 is essentially inactive, but the cell preparation unit 330 is positioned with the cell cannula 400 in the sample cell 50 to fill

the later with an exact amount of fresh sample by arranging the cell preparation control valve 680 in position A and activating the cell pump 670 to dispense the fresh sample contained in the pump reservoir into the sample cell 50.

In fig. 8a the pipette assembly 30 is placed at the titration position with the titration needle 210 in the sample cell 50 to perform an ITC experiment. The Titration transfer unit 370 is now positioned with the titrant cannula in the wash station 320 to wash it before the next titrant transfer operation. The washing cycle may be essentially the same as for the syringe 200. During the state disclosed in fig 8b, the cell preparation unit 330 is essentially inactive, and shown with the cell cannula 400 in the sample preparation station 420.

Examples of Liquid handling sequences includes:

Cell wash:

- a. The cell cannula 400 is inserted into the cell 40, 50, resting on the bottom.
- b. The cell content is drawn through the cell cannula 400, into the cell pump 680, and dispensed out to the waste port 710.
- c. Water is drawn from one of the wash liquid reservoirs 700a-d into the pump reservoir of the cell pump 680 and dispensed out to the waste port 710 to rinse the syringe.
- d. A wash liquid is drawn into the pump reservoir of the cell pump 680 from one of the wash liquid reservoirs 700a-d and dispensed through the cell cannula 400 into the cell 40, 50 in the exact amount needed to fill the cell,
- e. The wash liquid is cycled back and forth from the pump reservoir of the cell pump 680 to the cell 40, 50 to wash the later.
- f. The steps beginning at step b are repeated a predetermined number of times until the cell 40, 50.

- g. The cell is emptied to waste as in step b.
 - h. The cell cannula 400 is moved to the sample preparation station 420 and dried with by purging gas, e.g. Nitrogen. If degassing is included in the cell load procedure, the sample preparation 420 station is cleaned before drying.
- 5

Pipette wash:

- a. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- 10 b. The pipette plunger 230 is raised above the fill port 500 allowing liquid to flow through the syringe 200 of the pipette 30.
- c. First water then air is dispensed from the syringe pump 560 into the fill port 500, through the syringe 200 and titration needle 210 into the wash/fill station 320. Simultaneously, this water is drawn in great excess from the bottom of the wash/fill station 320 through the waste outlet 350 into the waste pump 510.
- 15 d. The waste pump 510 is stopped and a precise amount of water is dispensed through the pipette 30 to fill the wash/fill station 320 to the top of the outside of the titration needle 210. The water is cycled back and forth to wash the entire syringe 200 and the titration, inside and outside.
- 20 e. Step c is repeated.
- f. Step d is repeated with methanol.
- g. Step c is repeated.
- h. Nitrogen is purged through the fill port 500 to dry the system.
- 25 i. The pipette 30 is removed from the wash/fill station 320 to allow the

titrant transfer unit 370 to load the station 320 with titrant sample.

- j. The syringe pump 560 is rinsed with water to clear any methanol from the system.

5 Cell Load:

- a. Titrant sample is drawn into the cell cannula 400 from a sample tray 450 or a sample reservoir 430a-c. It is then slowly dispensed into the cell to prevent air bubbles. Optionally, the sample is dispensed into the sample preparation station 420 to be warmed and mixed (degassed) before being
10 transferred into the cell 50.

Pipette load:

- a. Titrant is drawn into the titrant transfer cannula 470 from a sample tray 450 and dispensed into the wash/fill station 320.
- 15 b. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- c. The plunger 230 is raised above the fill port 500 allowing liquid to flow through the pipette.
- d. A precise volume of titrant is drawn up through the titration needle 210 by
20 the syringe pump 560, over-filling the syringe 200 such that a small amount of titrant exits the fill port 500.
- e. The plunger 230 is lowered below the fill port 500 leaving the titrant needle 210 and pipette syringe 200 completely filled.

Titrant Transfer Clean:

- a. The titrant transfer cannula 470 is placed in the wash/fill station 320 and is rinsed with water, then rinsed with methanol and dried in much the same way that the syringe 200 of the pipette is washed and dried.

5

It is to be understood that any feature described in relation to any one embodiment may be used alone, or in combination with other features described, and may also be used in combination with one or more features of any other of the embodiments, or any combination of any other of the embodiments. Furthermore, equivalents and
10 modifications not described above may also be employed without departing from the scope of the invention, which is defined in the accompanying claims.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

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☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

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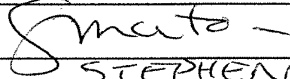
I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Malvern Instruments Incorporated

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
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- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	STEPHEN MANTON		
Title	IP MANAGER		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ Total of 1 forms are submitted.

va-438496

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:		AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
First Named Inventor/Applicant Name:		Martin BROGA		
Filer:		Takamitsu Fujiiu/Vilavanh Ong		
Attorney Docket Number:		739712000201		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1740

Electronic Acknowledgement Receipt

EFS ID:	22603282
Application Number:	14736905
International Application Number:	
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Title of Invention:	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE
First Named Inventor/Applicant Name:	Martin BROGA
Customer Number:	25227
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RAM confirmation Number	14995
Deposit Account	031952
Authorized User	CHARTOVE, ALEX
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	739712000201_ApplicationTransmittal.pdf	34351	no	1
			be88481312347ed9ecbcab08ec7fc280dbe65816		
Warnings:					
Information:					
2	Application Data Sheet	739712000201_ADS.pdf	110370	no	7
			6f859ff224f26cce525099cba439346bead177de		
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Drawings-only black and white line drawings	739712000201_Drawings.pdf	283254	no	13
			cb0387d920f647c0096082ae0a3aee63655cae34		
Warnings:					
Information:					
4		739712000201_Specification.pdf	1196527	yes	30
			f2d3730994c4c9b7ee917a700b46593515ea7084		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	25	
	Claims		26	29	
	Abstract		30	30	
Warnings:					
Information:					
5		739712000201_PreliminaryAmendment.pdf	28699	yes	3
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	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	

	Preliminary Amendment		1	1
	Specification		2	2
	Applicant Arguments/Remarks Made in an Amendment		3	3
Warnings:				
Information:				
6	Power of Attorney	739712000201_PowerofAttorney.pdf	103621 4f0df18b4293778b011d93f4e892e0acf191b1ad	no 1
Warnings:				
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing				
Information:				
7	Fee Worksheet (SB06)	fee-info.pdf	37092 4e88bf4973a9a358430f772e8ef6e9440c536b45	no 2
Warnings:				
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UTILITY PATENT APPLICATION TRANSMITTAL <small>(ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))</small>		Attorney Docket No. 739712000201	
		First Named Inventor Martin BROGA	
		Title AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE	
		Express Mail Label No. _____	
APPLICATION ELEMENTS <small>See MPEP chapter 600 concerning utility patent application contents.</small>		ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	
1. <input checked="" type="checkbox"/> Fee Transmittal Form <small>(PTO/SB/17 or equivalent)</small> 2. <input type="checkbox"/> Applicant asserts small entity status. <small>See 37 CFR 1.27</small> 3. <input type="checkbox"/> Applicant certifies micro entity status. See 37 CFR 1.29. <small>Applicant must attach form PTO/SB/15A or B or equivalent.</small> 4. <input checked="" type="checkbox"/> Specification [Total Pages 30] <small>Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement)</small> 5. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets 13] 6. Inventor's Oath or Declaration [Total Pages _____] <small>(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))</small> a. <input type="checkbox"/> Newly executed (original or copy) b. <input type="checkbox"/> A copy from a prior application (37 CFR 1.63(d)) 7. <input checked="" type="checkbox"/> Application Data Sheet * See note below. <small>See 37 CFR 1.76 (PTO/AIA/14 or equivalent)</small> 8. CD-ROM or CD-R <small>in duplicate, large table, or Computer Program (Appendix)</small> <input type="checkbox"/> Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission <small>(if applicable, items a. – c. are required)</small> a. <input type="checkbox"/> Computer Readable Form (CRF) b. <input type="checkbox"/> Specification Sequence Listing on: i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> Statements verifying identity of above copies		ACCOMPANYING APPLICATION PAPERS 10. <input type="checkbox"/> Assignment Papers <small>(cover sheet & document(s))</small> Name of Assignee <div style="border: 1px solid black; padding: 5px; text-align: center;">MALVERN INSTRUMENTS INCORPORATED</div> 11. <input type="checkbox"/> 37 CFR 3.73(c) Statement <input checked="" type="checkbox"/> Power of Attorney <small>(when there is an assignee)</small> 12. <input type="checkbox"/> English Translation Document (if applicable) 13. <input type="checkbox"/> Information Disclosure Statement <small>(PTO/SB/08 or PTO-1449)</small> <input type="checkbox"/> Copies of citations attached 14. <input checked="" type="checkbox"/> Preliminary Amendment 15. <input type="checkbox"/> Return Receipt Postcard <small>(MPEP § 503) (Should be specifically itemized)</small> 16. <input type="checkbox"/> Certified Copy of Priority Document(s) <small>(if foreign priority is claimed)</small> 17. <input type="checkbox"/> Nonpublication Request <small>Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.</small> 18. <input type="checkbox"/> Other: <div style="border: 1px solid black; height: 40px; width: 100%;"></div>	
<p>*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS). (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).</p>			
19. CORRESPONDENCE ADDRESS			
<input checked="" type="checkbox"/> The address associated with Customer Number: 25227 OR <input type="checkbox"/> Correspondence address below			
Name _____			
Address _____			
City _____		State _____	Zip Code _____
Country _____		Telephone _____	Email _____
Signature /Alex Chartove/		Date June 11, 2015	
Name (Print/Type) Alex Chartove		Registration No. (Attorney/Agent) 31,942	

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 11, 2015

Electronic Signature for Vilavanh Ong: /Vilavanh Ong/

va-452233

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
Mr.	Martin		BROGA		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	Amherst	State/Province	MA	Country of Residence	US
Mailing Address of Inventor:					
Address 1		24 Dennis Drive			
Address 2					
City	Amherst	State/Province	MA		
Postal Code	01002	Country i	US		
Inventor 2					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
Mr.	Phillip		PRICE		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					
City	North Granby	State/Province	CT	Country of Residence	US
Mailing Address of Inventor:					
Address 1		166 Loomis Street			
Address 2					
City	North Granby	State/Province	CT		
Postal Code	06060	Country i	US		
Inventor 3					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
Mr.	Stephen		SMITH		
Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service					

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		

City	Northampton	State/Province	MA	Country of Residence	US
------	-------------	----------------	----	----------------------	----

Mailing Address of Inventor:

Address 1	40 Maynard Road				
Address 2					
City	Northampton	State/Province	MA		
Postal Code	01060	Country	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add					

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).			
<input type="checkbox"/> An Address is being provided for the correspondence information of this application.			
Customer Number	25227		
Email Address	PatentDocket@mofo.com	Add Email	Remove Email

Application Information:

Title of the Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		
Attorney Docket Number	739712000201	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	13	Suggested Figure for Publication (if any)	

Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

<input type="checkbox"/> Request Early Publication (Fee required at time of Request 37 CFR 1.219)
<input type="checkbox"/> Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		

Representative Information:

<p>Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.</p>			
<p>Please Select One:</p>			
<input checked="" type="radio"/>	Customer Number	<input type="radio"/>	US Patent Practitioner
<input type="radio"/>	Limited Recognition (37 CFR 11.9)		
Customer Number	25227		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the application number blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	12326300	2008-12-02
<p>Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.</p>			

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove			
Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)
<p>Additional Foreign Priority Data may be generated within this form by selecting the Add button.</p>			

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

<p>This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.</p> <p><input type="checkbox"/> NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.</p>
--

Authorization to Permit Access:

<p><input type="checkbox"/> Authorization to Permit Access to the Instant Application by the Participating Offices</p> <p>If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.</p> <p>In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.</p> <p>In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.</p>

Applicant Information:

<p>Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.</p>
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		

Applicant 1			
<p>If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.</p> <p style="text-align: right;"><input type="button" value="Clear"/></p>			
<input checked="" type="radio"/> Assignee		<input type="radio"/> Legal Representative under 35 U.S.C. 117	
<input type="radio"/> Person to whom the inventor is obligated to assign.		<input type="radio"/> Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor : <input type="text"/>			
If the Applicant is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	Malvern Instruments Incorporated		
Mailing Address Information For Applicant:			
Address 1	117 Flanders Road		
Address 2			
City	Westborough	State/Province	MA
Country	US	Postal Code	01581
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

Assignee Information including Non-Applicant Assignee Information:

<p>Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.</p>	
Assignee 1	
<p>Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.</p>	
<p>If the Assignee or Non-Applicant Assignee is an Organization check here. <input checked="" type="checkbox"/></p>	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	739712000201
		Application Number	
Title of Invention	AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER APPARATUS AND METHOD OF USE		

Organization Name	Malvern Instruments Incorporated
-------------------	----------------------------------

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1		117 Flanders Road	
Address 2			
City	Westborough	State/Province	MA
Country ⁱ	US	Postal Code	01581
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.					
Signature	/Alex Chartove/			Date (YYYY-MM-DD)	2015-06-11
First Name	Alex	Last Name	Chartove	Registration Number	31942
Additional Signature may be generated within this form by selecting the Add button.					

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

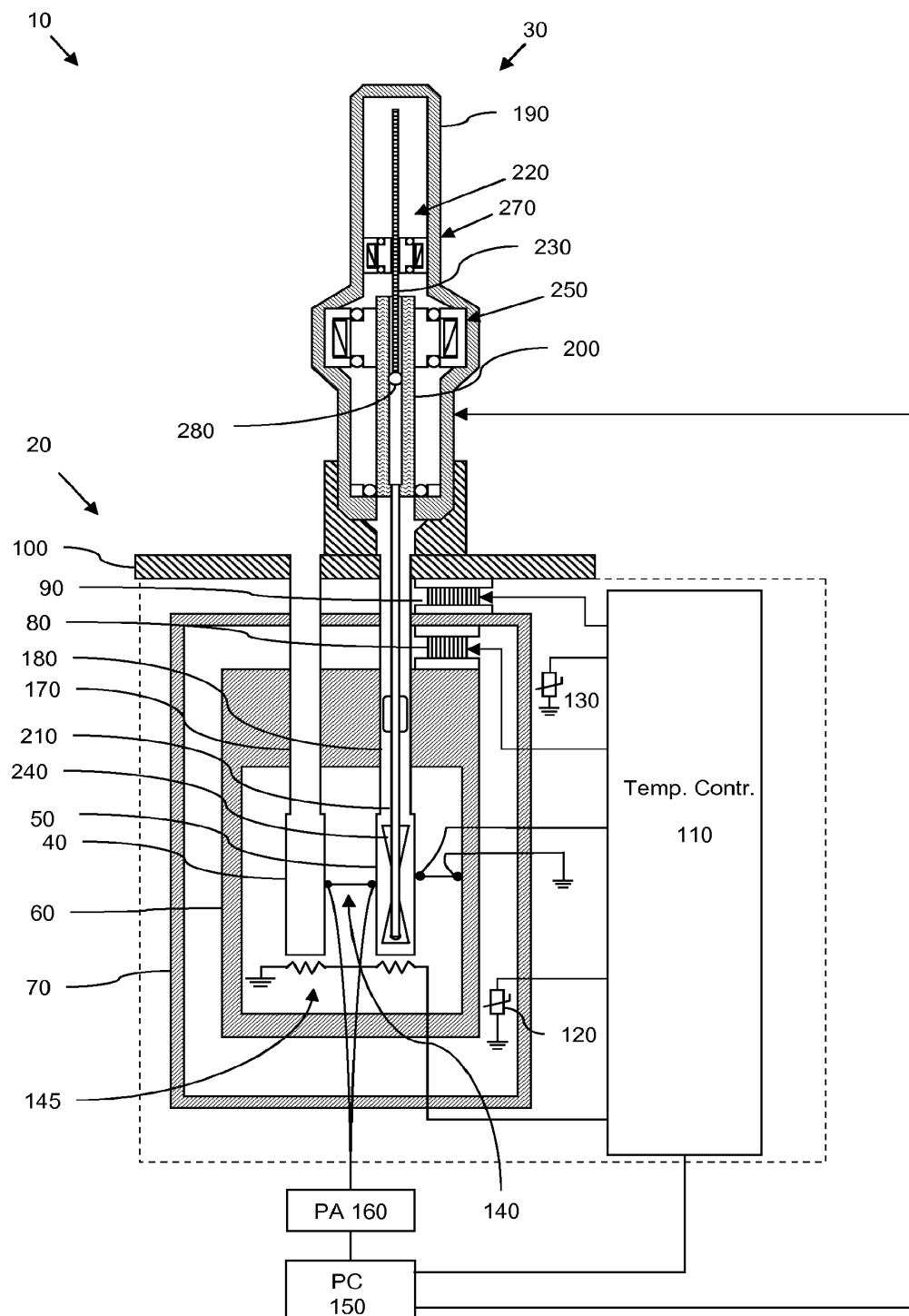


Fig. 1

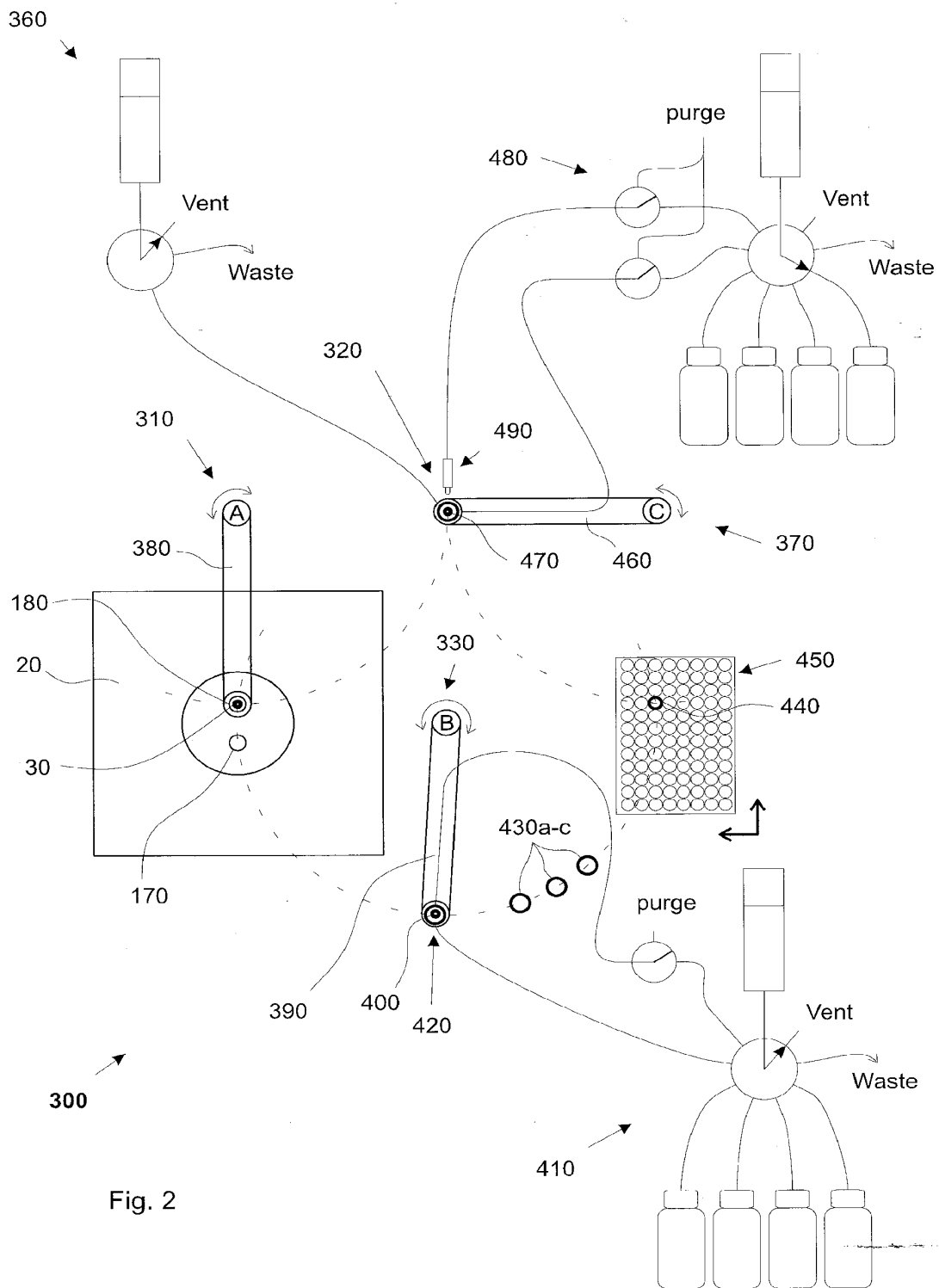


Fig. 2

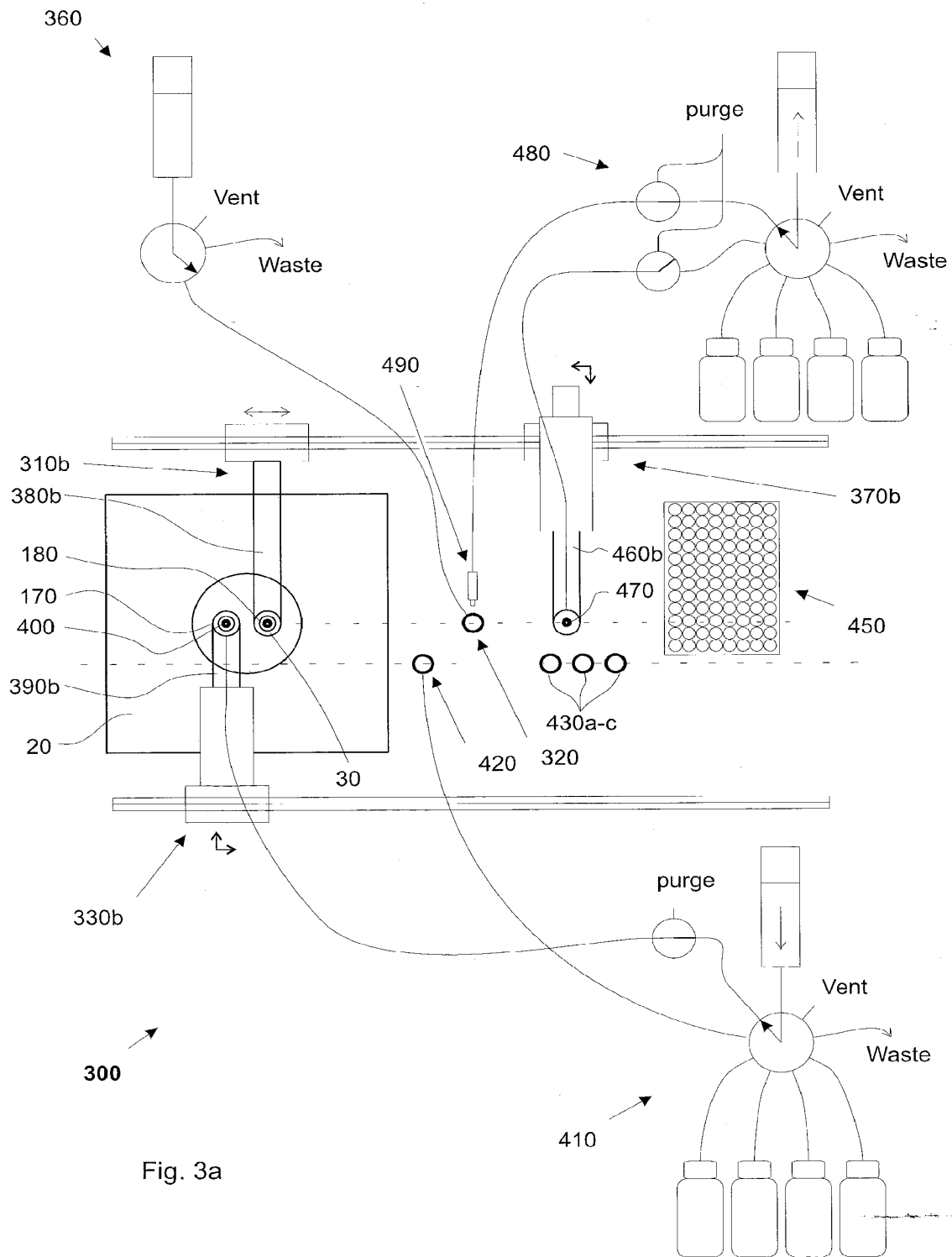
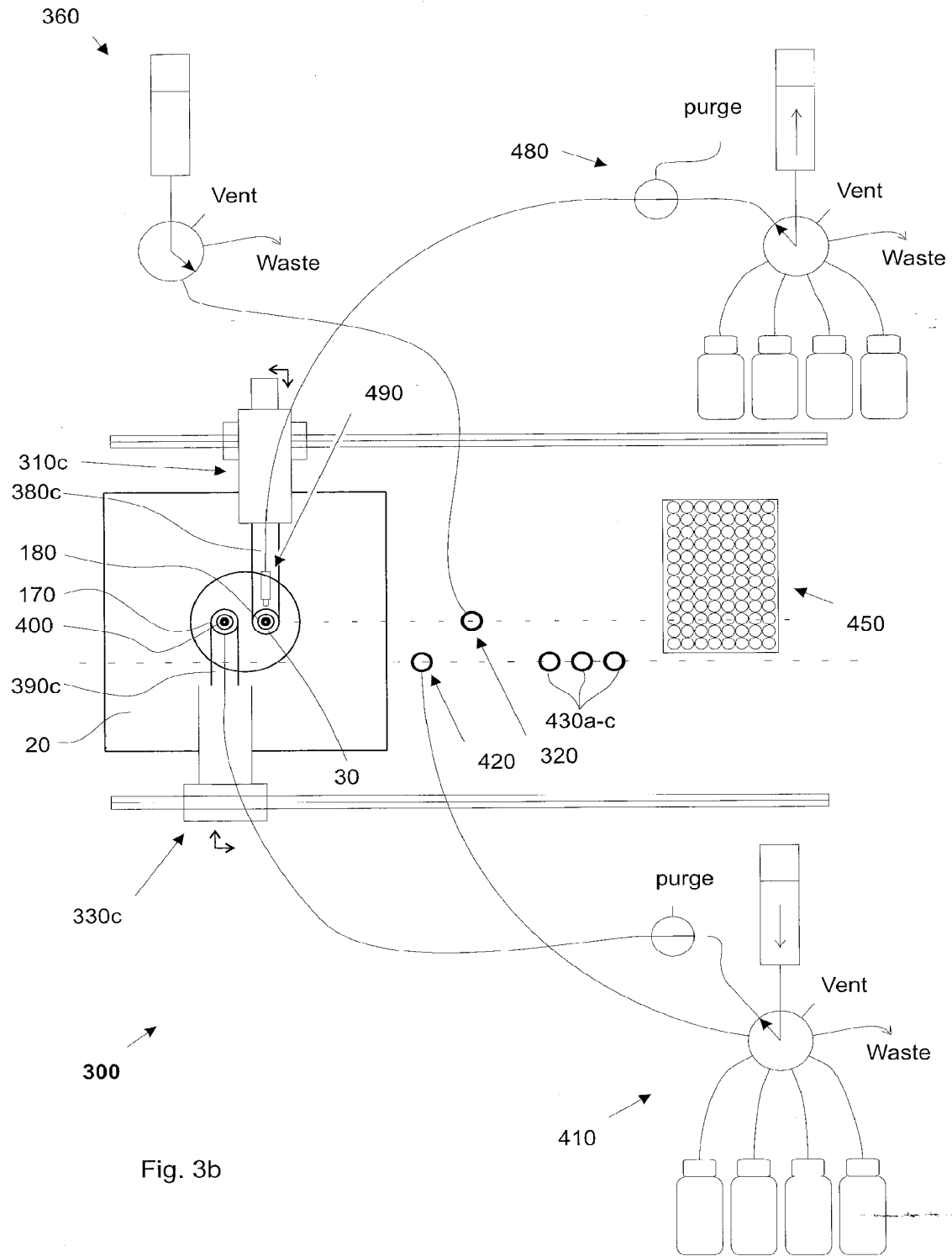


Fig. 3a



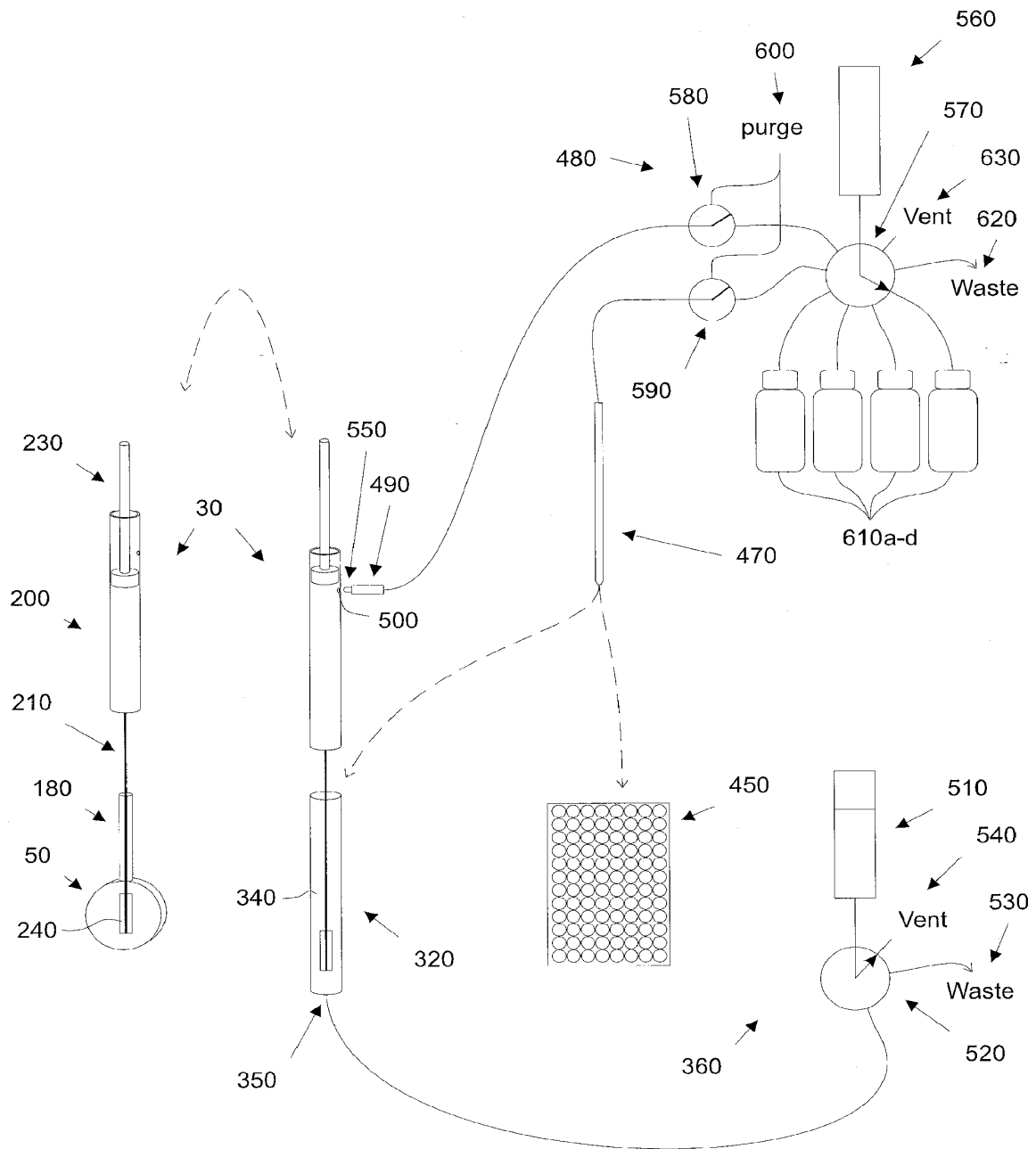


Fig. 4a

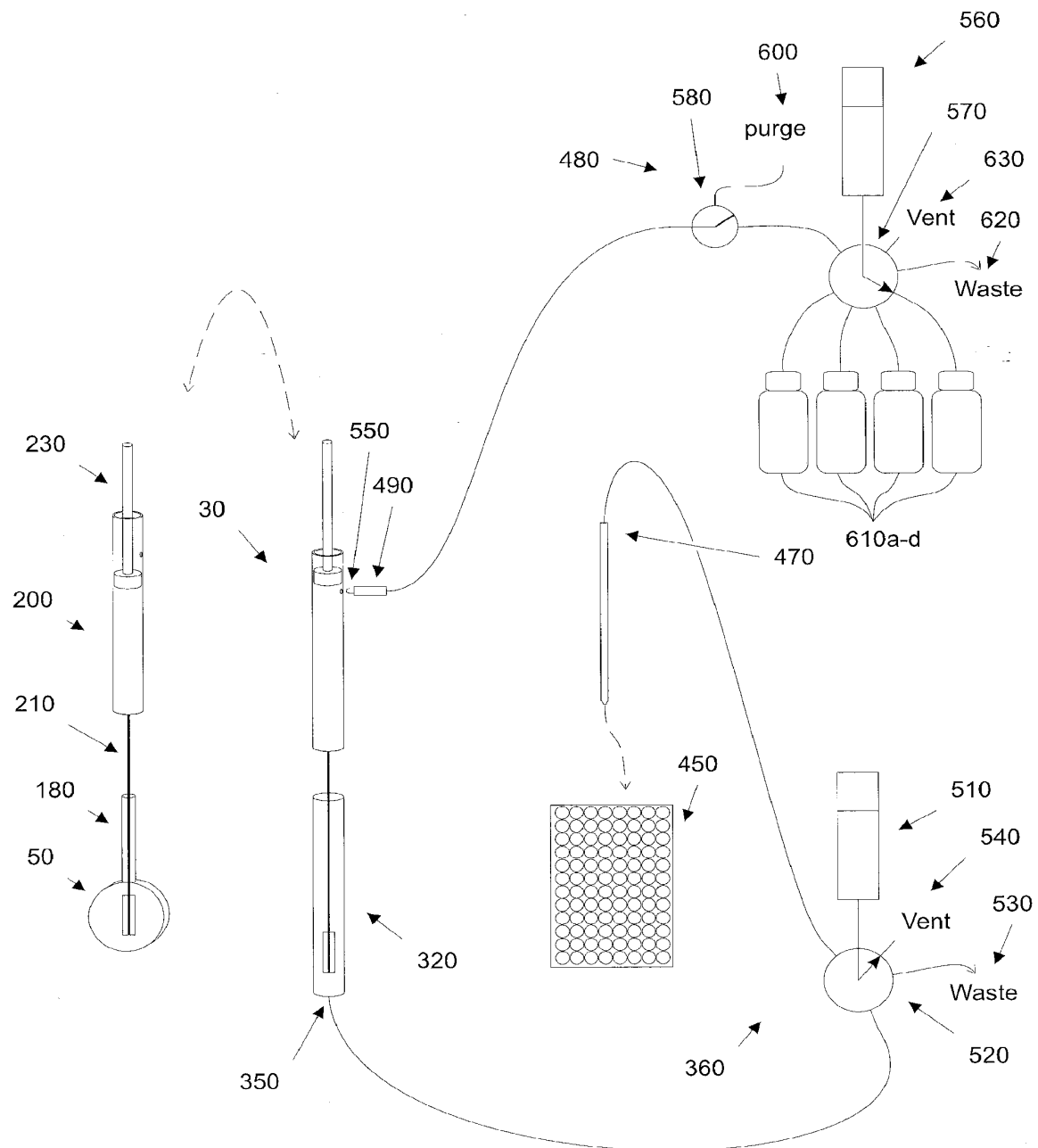


Fig. 4b

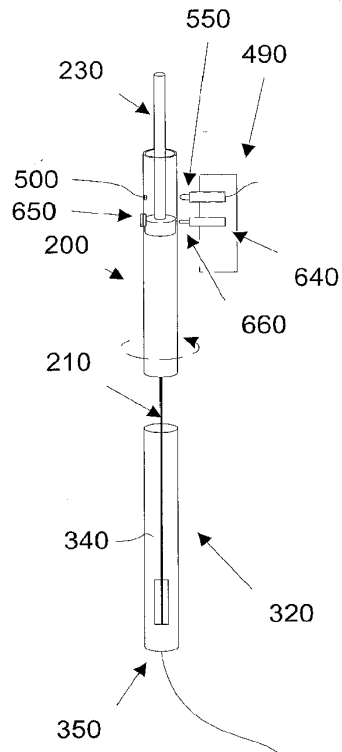


Fig. 5a

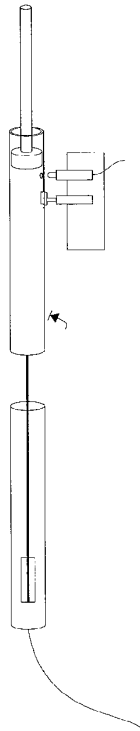


Fig. 5b

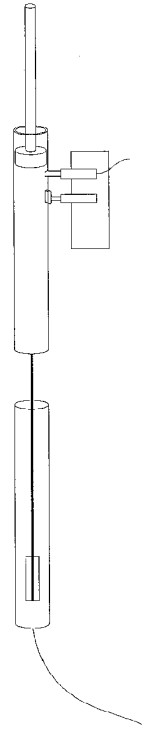


Fig. 5c

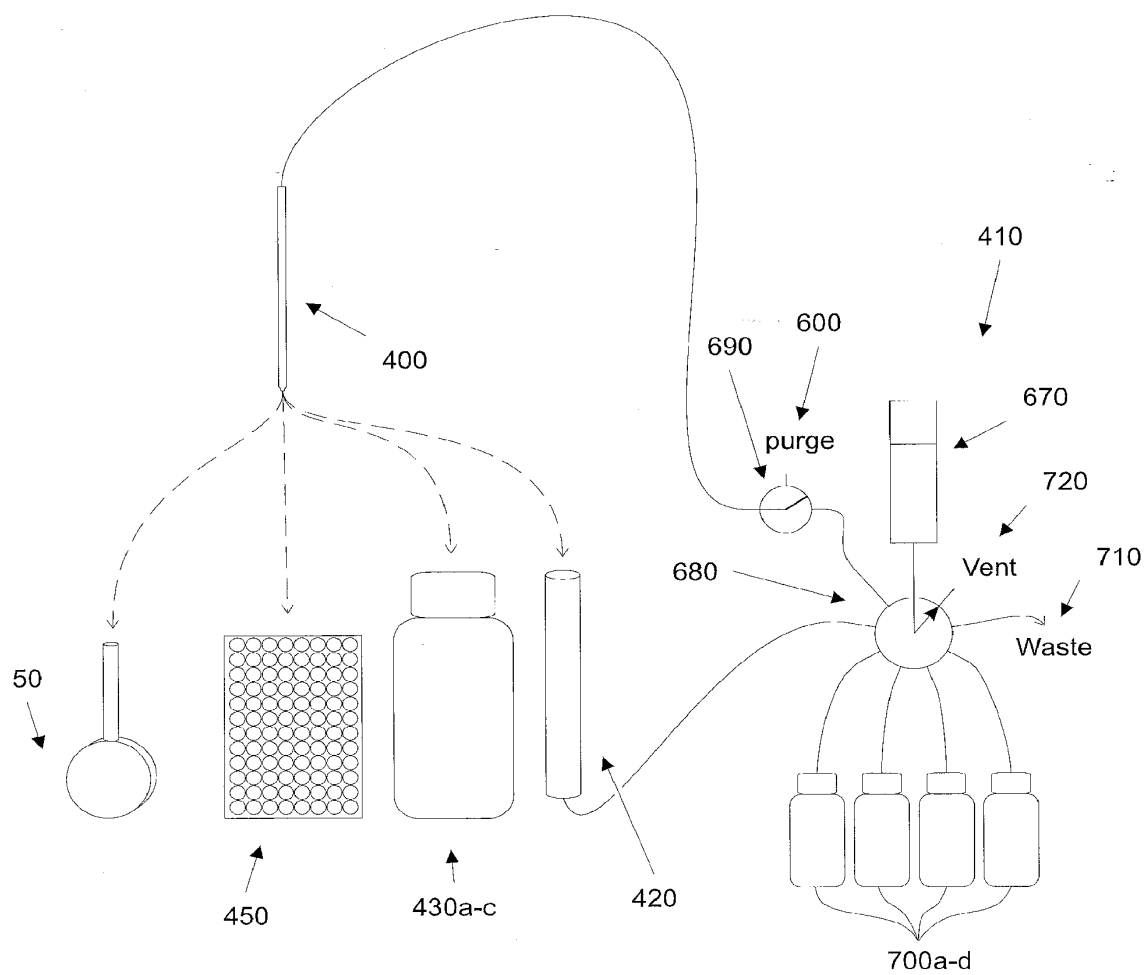


Fig. 6

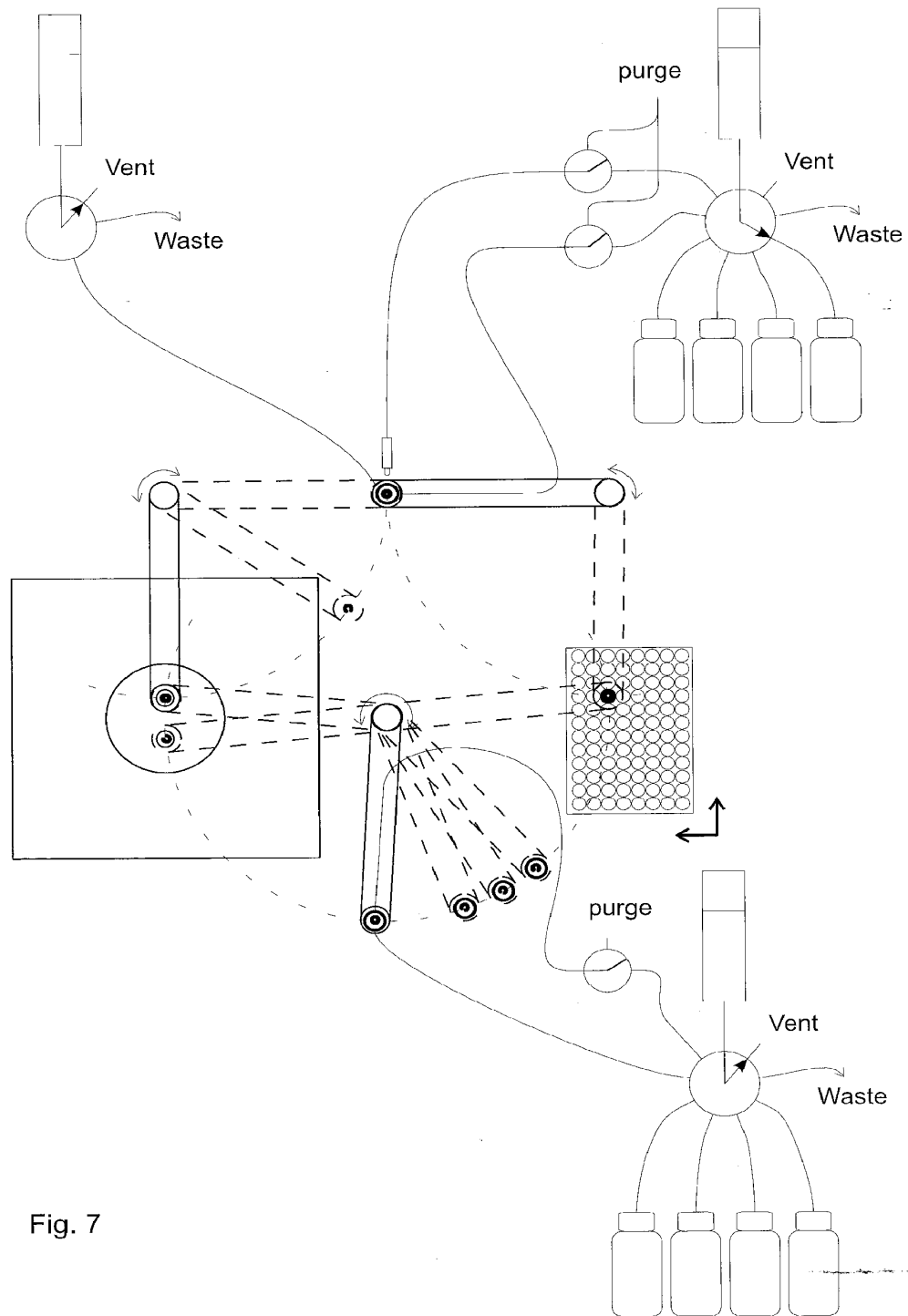
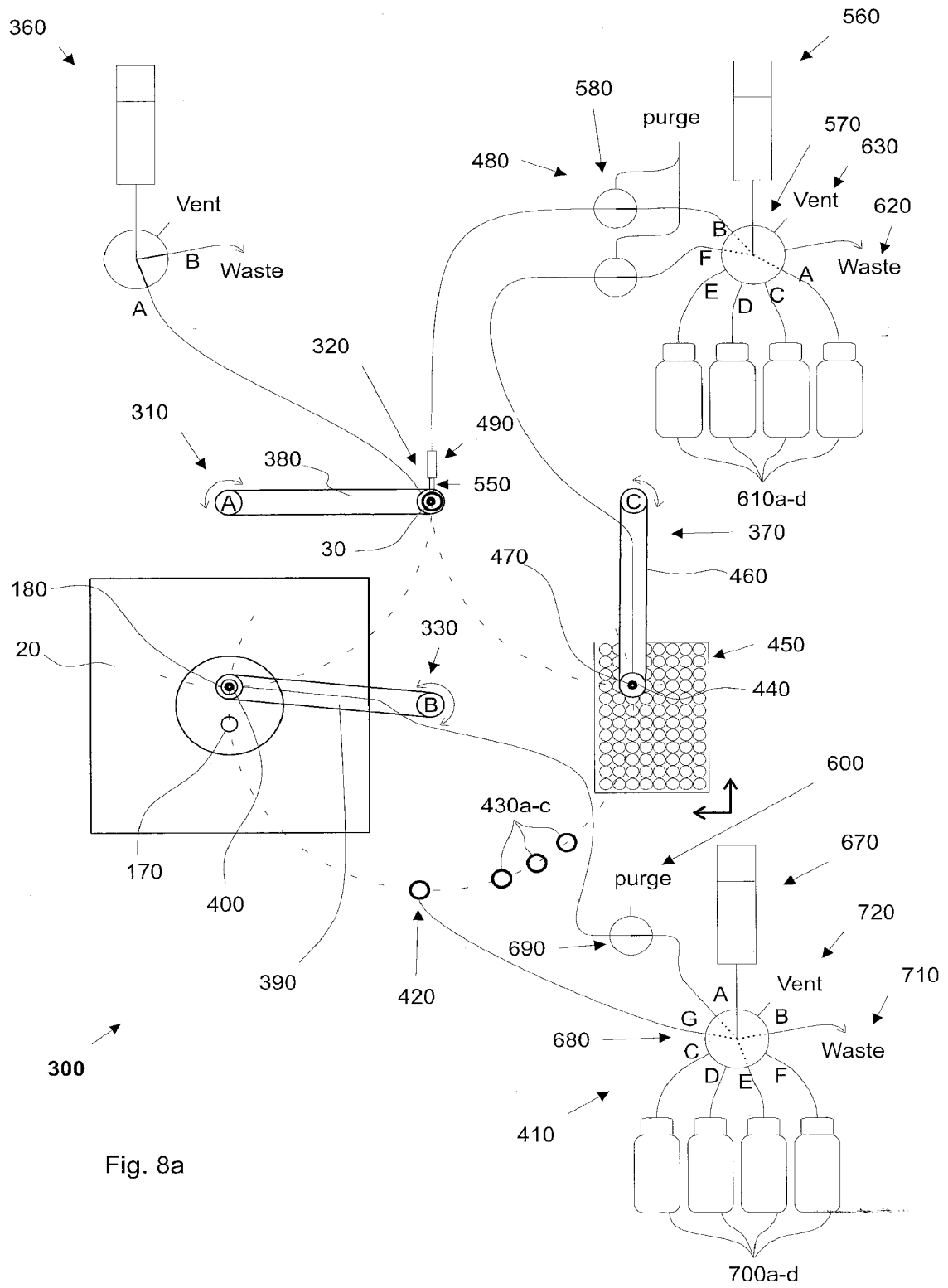


Fig. 7



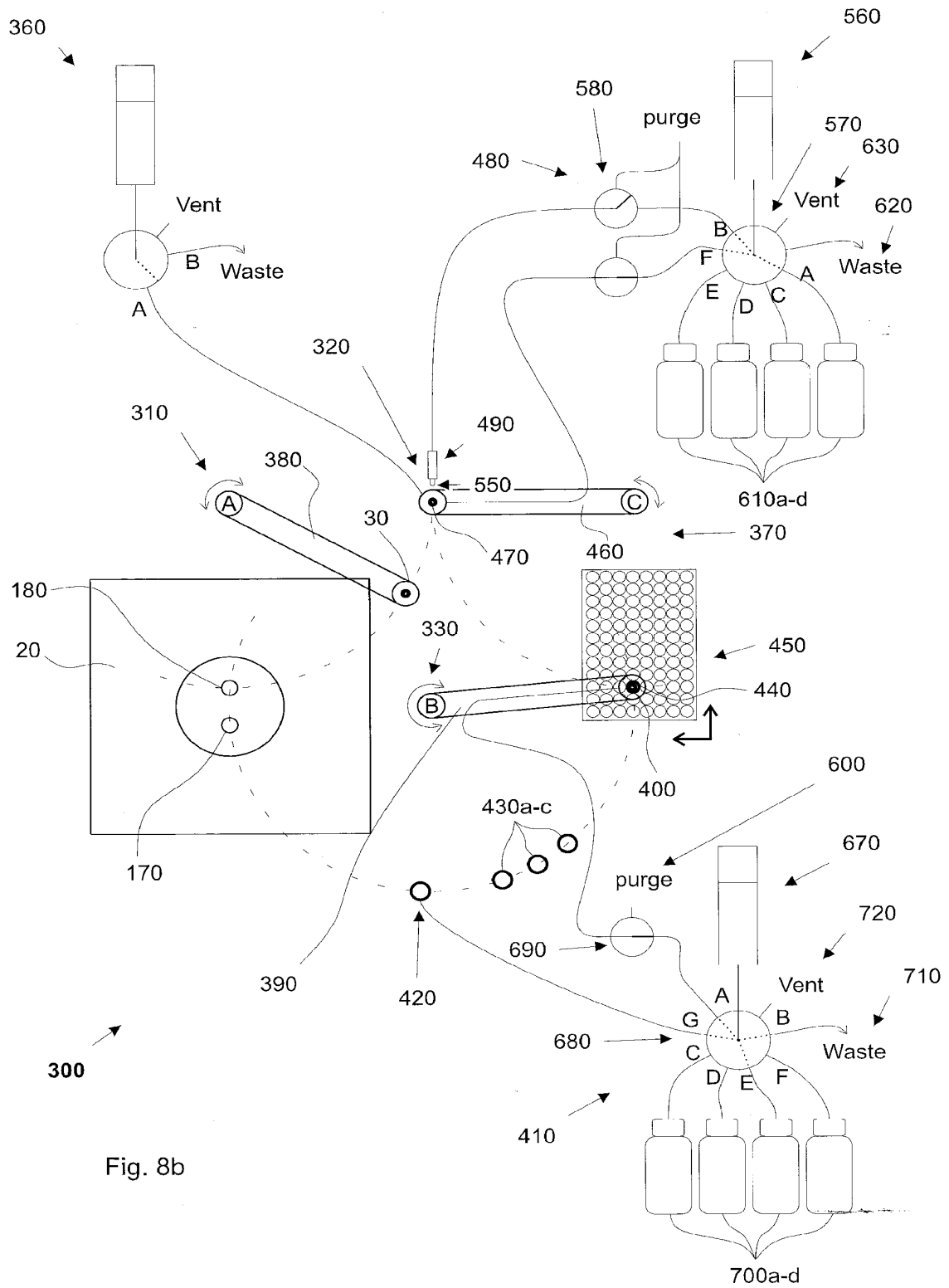


Fig. 8b

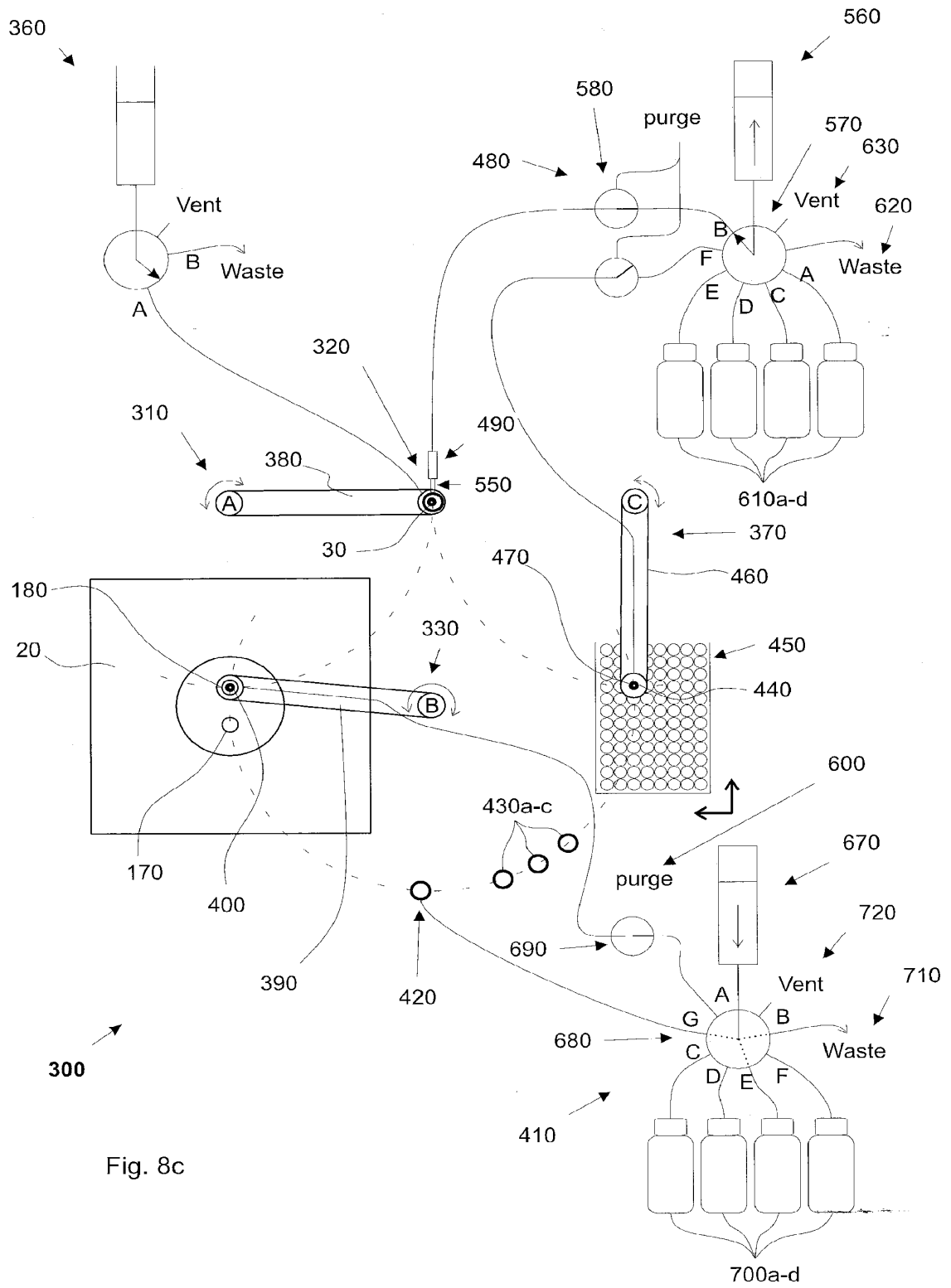


Fig. 8c

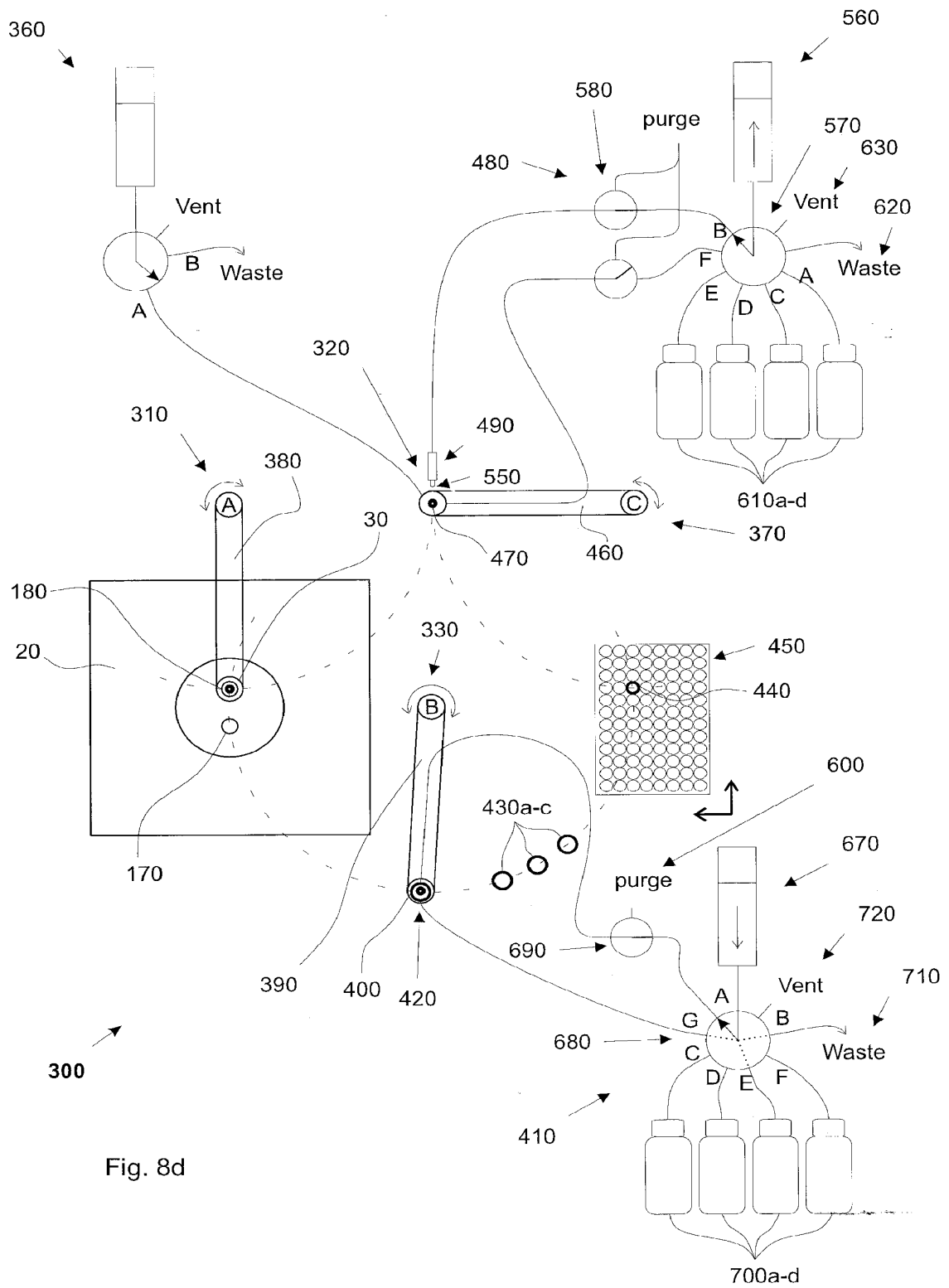


Fig. 8d

AUTOMATIC ISOTHERMAL TITRATION MICROCALORIMETER

APPARATUS AND METHOD OF USE

BACKGROUND OF THE INVENTION

5 The present invention relates generally to microcalorimeters and more specifically to features that improve the performance of microcalorimeters, especially an automated isothermal titration micro calorimetry system (ITC system).

 Microcalorimeters are broadly utilized in fields of biochemistry, pharmacology, cell biology, and others. Calorimetry provides a direct method for measuring changes in
10 thermodynamic properties of biological macromolecules. Microcalorimeters are typically two cell instruments in which properties of a dilute solution of test substance in an aqueous buffer in a sample cell are continuously compared to an equal quantity of aqueous buffer in a reference cell. Measured differences between the properties of the two cells, such as temperature or heat flow, are attributed to the presence of the test
15 substance in the sample cell.

 One type of microcalorimeter is an isothermal titration calorimeter. The isothermal titration calorimeter (ITC) is a differential device, but operates at a fixed temperature and pressure while the liquid in the sample cell is continuously stirred. The most popular application for titration calorimetry is in the characterization of the
20 thermodynamics of molecular interactions. In this application, a dilute solution of a test substance (e.g., a protein) is placed in the sample cell and, at various times, small volumes of a second dilute solution containing a ligand, which binds to the test substance, are injected into the sample cell. The instrument measures the heat, which is evolved or absorbed as a result of the binding of the newly introduced ligand to the test substance.
25 From results of multiple-injection experiments, properties, such as, the Gibbs energy, the association constant, the enthalpy and entropy changes, and the stoichiometry of binding,

may be determined for a particular pairing between the test substance and the ligand.

While currently utilized ITCs provide reliable binding data results, their widespread utilization in the early stages of drug development have been limited by several factors: the relatively high amounts of protein required to perform a binding determination (e.g., about 0.1 milligram (mg) to about 1.0 mg of a protein), the limited throughput due to the time required to perform the measurement and the complexity of using conventional ITCs.

Today, gathering binding data utilizing prior art ITCs require extensive preparation and skill by the practitioner. For example, using prior art ITCs, the reference and sample cells are first filled respectively with the reference substance and sample substance via a corresponding cell stem. Next, a titration pipette of the ITC is filled with a titrant, which is a delicate operation as it is very important that the syringe in the pipette is accurately filled and that there is no air trapped therein. Then a needle of the titration pipette is manually placed in the sample cell via the cell stem, and the ITC experiments can be initiated. The ITC measurement procedure is controlled by a control unit in the form of a computer or the like running a program for performing the experiments. Consistent with the program used for the experiment, a stirring motor rotates the syringe, needle, and paddle at an assigned speed enabling proper mixing of the reagents. Consistent with the program used for the experiment (e.g., when a certain temperature and/or equilibrium are reached), a plunger in the syringe is activated to inject the titrant into the sample solution. The injection can be done discretely (step-by-step) or continuously, depending on the program settings. The calorimeter continuously measures and records the heat release/absorption versus time associated with the interaction of reagents. The analysis of the results is done according to the established algorithm.

As would be appreciated by a reading of the above-described prior art procedure,

utilizing prior art ITCs, the quality of binding measurements performed with these prior art ITCs depends heavily of the operator's skills and experience, and involves a considerable amount of preparation time.

For some time there has been at least one automated ITC system on the market,
5 MicroCal AutoITC, which is based on a commercially available micro calorimeter and a linear robot system and a fluidics system arranged to perform automatic sample handling.

SUMMARY OF THE INVENTION

The object of the invention is to provide a new automatic isothermal titration
10 micro calorimetry system (ITC system), which ITC system overcomes one or more drawbacks of the prior art. This is achieved by the ITC system as defined in the independent claims.

One advantage with the present ITC system is that each titration experiment requires less time compared to the prior art. This is e.g. due to the reduced cell volume
15 and that washing and refilling of the pipette assembly and the sample cell is performed essentially in parallel. Hence the system throughput is considerably higher compared to the prior art systems, making it possible to evaluate large number of samples to make screening type experiments.

Another advantage is that the ITC system may be arranged to perform a large
20 number of unattended titration experiments.

Embodiments of the invention are defined in the dependent claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic example of a prior art manual ITC system in cross-
25 section, the ITC system comprising an automatic pipette assembly.

Figure 2 shows a schematic view of one embodiment of an automated ITC system.

Figures 3a and 3b show schematic views of other embodiments of the automated ITC system.

Figures 4a and 4b show schematic views of two embodiments of a syringe fluidics system for an automated ITC system.

Figures 5a to 5c show schematic views of the function of a syringe fill port connector unit according to an embodiment.

Figure 6 shows a schematic view of a cell preparation fluidics system according to one embodiment.

Figure 7 schematically shows different states of operations for the ITC system of fig. 2

Figures 8a to 8d shows different states of operations for the ITC system of fig. 2 more in detail.

15 DETAILED DESCRIPTION OF THE INVENTION

In the PCT application PCT/US2008/081961, which is incorporated by reference, a manual ITC system 10 of the type disclosed in fig. 1 is presented. According to one embodiment, the manual ITC system 10 is utilized as micro-calorimeter in the present automatic ITC system, but in other embodiments, the micro-calorimeter is of other types, as will be discussed in greater detail below. In the disclosed manual ITC system 10, the cell compartment volume is reduced by about a factor of seven as compared to prior art ITCs, without a reduction in sensitivity, and with a significantly faster response time. Such an ITC system permits the performance of experiments with about 10 times less protein sample, and with only a total of about 2 to about 4 titrations per hour. In addition to reducing the costs associated with running the ITC experiment, a smaller cell volume

also extends the number of ITC applications. For example, the range of binding affinities that can be measured by ITC is dictated by a parameter called “c value,” which is equal to the product of the binding affinity (K_a) and the total concentration (M_{total}) of macromolecule ($c = [M_{total}]K_a$). For accurate affinity determination, the c value must be
5 between 1 and 1,000. A decrease in the cell volume by a factor of ten results in a similar increase in c value if the same amount of protein is used, and, consequently, the ability to measure weak binders. This ability is especially important in the early stages of drug discovery, in which binding affinities are weak, especially in conjunction with a fully automated instrument.

10 Fig. 1 schematically shows one embodiment of the manual ITC system 10 that may be automated in accordance with the present invention. The ITC system 10 comprises a micro calorimeter 20 and an automatic pipette assembly 30. The micro calorimeter 20 comprises a reference cell 40 and a sample cell 50 which are designed to be essentially identical in heat capacity and volume. The cells 40 and 50 are comprised of
15 a suitable chemically inert and heat conductive material, such as gold, Platinum, tantalum, hastelloy or the like. The cells 40 and 50 may be of essentially any suitable shape, but it is desirable that they are of the same shape, that they are possible to arrange in a fully symmetric arrangement, and that efficient mixing of the titrant with the sample may be achieved. In the disclosed embodiment, the cross-section of the cells 40 and 50 is
20 rectangular, and the cross-section in the transverse horizontal direction may be circular, resulting in coin shaped cells with circular facing surfaces.

In order to reduce any external thermal influences to a minimum, the, reference cell 40 and the sample cell 50 are both enclosed by a first thermal shield 60 which in turn is enclosed by a second thermal shield 70. The thermal shields 60, 70 may be comprised
25 of any suitable thermally conductive material such as silver, aluminum, copper or the like.

The shields 60, 70 may further be comprised of one or more thermally interconnected sub shields (not shown, to provide even further stable temperature conditions for the calorimetric cells 40, 50.

In order to control the temperature of the shields 60, 70, thermal control means
5 may be arranged to control the temperature thereof. In an ITC system said thermal control means are mainly used to set the “isothermal” temperature of the calorimeter, ie of the thermal shields 60, 70, before the titration experiments are initiated. But as will be disclosed in greater detail below, said thermal control means may also be used to improve the adiabatic behavior of the calorimeter. According to one embodiment, the thermal
10 control means are comprised of one or more heat pump units, such as a thermoelectric heat pump device based on the peltier effect or the like. Other types of thermal control means include thermostatically controlled liquid baths, mechanical heat pumps, chemical heating or cooling systems or the like.

In the disclosed embodiment a first heat pump unit 80 is arranged to transfer heat
15 energy between the first 60 and second thermal shields 70, a second heat pump unit 90 is arranged to transfer heat energy between the second thermal shield 70 and a heat sink 100 in thermal contact with the ambient temperature. A temperature controller 110 is arranged to control the first and second heat pump units 80, 90 so that the desired temperature conditions are achieved. The temperature controller 110 monitors the temperatures of the
20 first 60 and second thermal shield by associated temperature sensors 120 and 130 respectively. Furthermore, the thermal controller 110 is arranged to control the cell temperature by a cell heating arrangement 145. The thermal controller 110 is controlled via a calorimeter user interface run on a computer 150 or the like. Calorimetric sensors 140 for sensing the temperature difference between the sample cell 50 and reference cell
25 40 during the ITC experiments may be connected to the computer 150, e.g. via a

preamplifier 160.

A reference cell stem 170 and a sample cell stem 180 provides access to the reference cell 40 and sample cell 50, respectively, for supplying reference and sample fluids, titration fluid, washing of the cells etc. In the disclosed embodiment, the cell stems
5 170 and 180 both extends essentially vertically through both thermal shields and the heat sink to provide direct communication with cells 40 and 50 and the cell stems 170 and 180 each support their respective cell 40 and 50 in the cavity of the first thermal shield 60.

The automatic pipette assembly 30 comprises a pipette housing 190, a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying
10 titrant, and a linear activator 220 for driving a plunger 230 in the syringe 200. The titration needle 210 is rotatable with respect to the housing 190 and is provided with a stirring paddle 240 arranged to stir sample fluid in the sample cell 50 in order to achieve efficient mixing of titrant and sample fluid. The automatic pipette assembly 30 further comprises a stirring motor 250 for driving the rotation of the titration needle 210.

15 In the embodiment disclosed in fig. 1 the stirring motor 250 is a direct drive motor with a hollow rotor arranged concentric with the syringe 200 and the titration needle 210. The syringe 200 is at its upper end supported for rotation by the stirring motor 400 and at the lower end by a bearing 260.

In an alternative embodiment, not shown in the figures, the stirring motor 250
20 drives the titration needle for rotation by a rotation transmission arrangement, such as a drive belt arrangement, a drive wheel arrangement or the like. Moreover, the stirring motor may be arranged separated from the pipette assembly 30 and be arranged to drive the titration needle for rotation by a suitable transmission arrangement such as a magnetic coupling or the like.

25 The automatic pipette assembly 30 is controlled by a controller of the ITC system,

e.g. stirring of the sample and the titration.

In the disclosed embodiment, the linear activator 220 comprises a stepper motor 270 arranged to drive the threaded plunger 230 that extends coaxially through the hole of a hollow rotor and into the syringe 200 wherein it is rotatably attached to a pipette tip 280 that seals against the inner wall of the syringe 200 to allow displacing a precise volume of titration liquid from syringe 200. The linear activator 220 may be of any other type capable of perform controlled linear motion with sufficient precision. This design allows syringe to be rotated independently of the main body 190 of the pipette assembly 30; at the same time, the linear activator 220 can drive the threaded plunger 230.

In accordance with one embodiment, schematically disclosed in figs. 2 to 8d, there is provided an automated isothermal titration micro calorimetry (ITC) system 300 comprising:

- a micro calorimeter 20 with a sample cell 50 and a reference cell 40, the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170,
- an automatic pipette assembly 30 comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant, the pipette assembly 30 comprises a linear activator 220 for driving a plunger 230 in the syringe 200,
- a pipette translation unit 310 supporting the pipette assembly 30 and being arranged to place pipette in position for titration, washing and filling operations,
- a wash station 320 for the titrant needle 210, and
- a cell preparation unit 330 arranged to perform operations for replacing the sample liquid in the sample cell 50 when the pipette 30 is placed in another

position than the position for titration.

The micro calorimeter 20 may be of any type capable of performing ITC calorimetric measurements using sufficiently small volumes of sample such as the micro calorimeter 20 schematically shown in fig. 1. As disclosed above (fig. 1), but not specifically shown in figs 2 to 8d, a micro calorimeter generally comprises a sample cell 50 and a reference cell 40, wherein the sample cell 50 is accessible via a sample cell stem 180 and the reference cell 40 is accessible via a reference cell stem 170 (shown as circular openings in fig. 2). The automatic pipette assembly 30 may be of the type disclosed above, but it may be of any suitable design comprising a syringe 200 with a titration needle 210 arranged to be inserted into the sample cell 50 for supplying titrant. Like above, the pipette assembly 30 may further comprise a linear activator 220 for driving a plunger 230 in the syringe 200. However, the syringe 200 may be of essentially any type, capable of providing well-defined volumes of titrant. The titration needle 210 may be rotatable and may be provided with a paddle 240 for stirring of the liquid in the sample cell 50 during the titration. The stirring may be accomplished as is discussed above or in any other suitable way.

The pipette translation unit 310 may be of any type capable of placing the pipette in the appropriate positions for titration, washing and filling. Figs 2 and 3 schematically show two different types of translation units, wherein fig. 2 shows a rotation translation unit 310 and fig. 3 shows a linear translation unit 310b. In order to place (insert) the titration needle 210 in position in the sample cell 50, and/or in other positions, the pipette translation unit 310 is capable of moving the pipette 30 in the vertical direction with respect to the micro calorimeter 20. The pipette translation unit 310 may be mechanically restricted with respect to its freedom of movement so that it only may move between mechanically predetermined positions, or it may be a general translation unit of robot type

that is restricted to movement between said predetermined positions by means of software parameters, or a combination thereof. For clarity reasons no such means for vertical movements have been included in the figures 2 to 8d.

5 The wash station 320 is arranged at a suitable position wherein the titration needle 210 of the pipette assembly 30 can be placed in position for washing. The wash station 320 may be of any suitable type capable of washing at least the section of the titration needle 210 that is immersed in the sample during titration when the pipette assembly 30 is placed in position for washing. According to one embodiment, the wash station 320 comprises a wash cavity 340 arranged to receive the titration needle. The wash station 10 320 is made of any suitable material that is inert with respect to the reagents used in the ITC experiments and the wash cycles. According to one embodiment, the wash station 320 comprises a waste outlet port 350 at the bottom end of the wash cavity connected to a waste removal unit 360. The waste outlet port 350 is used to remove waste liquids as well as wash liquids during the pipette washing cycle, as will be disclosed more in detail 15 below, and it is preferably arranged at the bottom end of the wash cavity 340 in order to enable complete drainage of the wash cavity. In one embodiment not disclosed in the figures, the pipette translation unit 310 is limited to movement in the vertical direction, and the wash station 320 instead is arranged to be moved to a position in alignment with the needle 240 for cleaning of the same.

20 In figs. 2 to 8d the cell preparation unit 330 is shown as a translation unit of the same type as the pipette translation unit 310, but arranged to be positioned in at least two positions related to washing and replacing sample liquid in the sample cell. By the provision of a cell preparation unit 330 for replacing the sample liquid in the sample cell 50 the total cycle time is reduced and thus the throughput of the ITC system 300 is 25 increased, as the sample cell 50 may be washed and filled with new sample liquid at the

same time as the pipette 30 is washed and filled with new titrant.

Fig. 2 schematically discloses an automated isothermal titration micro calorimetry (ITC) system 300 according to one embodiment of the present invention. As mentioned above, the translation units 310, 330, 370 in this embodiment are all of rotary type, and all
5 positions of operation are arranged along circular paths of the rotary translation units. In another embodiment, not shown, one or more of the rotary translation units are provided with additional linear translation means to extend work area and to increase the flexibility.

In fig. 2 the pipette translation unit 310 comprises a pipette arm 380 that is
10 rotatably supported for rotation about an axis A, and supporting the pipette assembly 30 at the other end thereof. The pipette arm 380 is further arranged to move the pipette vertically, either in that the arm 380 can be moved vertically along the axis A, or in that the arm 380 is limited for rotation in one plane and the pipette 30 is vertically moveable with respect to the arm 380. The pipette arm 380 is arranged to place pipette 30 in
15 position for:

- titration with the titration needle inserted into the sample cell 50,
- washing and filling with the titration needle inserted in a combined wash/fill station 320.

The combined wash/fill station 320 may be a wash station of the type discussed
20 above with an outlet port 350 at the bottom end of the wash cavity 340. The outlet port 350 is connected to a waste fluidics system 360 that will be discussed in more detail below.

The cell preparation unit 330 is in turn comprised of a corresponding cell arm 390 that is rotatably supported for rotation about an axis B, supporting a cell cannula 400
25 connected to a cell fluidics system 410 for dispensing and withdrawing liquid in the

sample cell 50 and potentially also in the reference cell 40. The cell fluidics system 410 will be disclosed in more detail below. The cell arm 390 is arranged to move the cell cannula 400 to a plurality of positions such as the cells, 40, 50 of the micro calorimeter, one or more sample sources, and a sample preparation station 420, or the like. In the
5 disclosed embodiment, four different sample source positions are included of which three positions represent large volume sample reservoirs of vial type 430a - 430c, e.g. for standard sample liquids, and the fourth position an autosampler position 440, e.g. for specific or sensitive sample liquids, wherein the cell cannula 400 is arranged to draw the sample liquid from a specific well in a sample tray 450 (e.g. micro plate or the like). In
10 the disclosed embodiment, the autosampler position 440 is a static position to which the cell cannula 400 can be moved by the cell arm 390 and be lowered into a specific well of a sample tray 450 that can be moved to position a selected well at the autosampler position 440 by a tray actuator (not shown). The tray actuator may be of any suitable type capable of selectively position a specific sample well of a sample tray 450 at a desired
15 position, such as a linear X-Y actuator or a rotary actuator with a carousel tray. The sample preparation station 430 may be used to prepare the sample before it is transferred into the cell 50 or 40, e.g. by bringing the sample to a temperature close to the experimental temperature, or by degassing through mixing.

The ITC system 300 disclosed in Fig. 2 further comprises a titrant transfer unit
20 370 arranged to transfer titrant from a primary titrant source, e.g. a sample tray 450, to the wash/fill station 320. In the disclosed embodiment, the transfer unit 370 comprises a titrant transfer arm 460, e.g. corresponding to the cell transfer arm 380, that is rotatably supported for rotation about an axis C, supporting a transfer cannula 470 connected to a syringe fluidics system 480. The titrant transfer arm 460 is arranged to position the titrant
25 cannula 470 in an autosampler position 440 for drawing a titrant sample from a titrant

well in a sample tray 450, and in position to dispense said titrant sample in the wash/fill station 320. The autosampler position 440 and the sample tray 450 may be a separate position and tray with respect to the cell cannula autosampler position 440 discussed above, but as is disclosed in fig 2, the cell cannula 470 and the titrant cannula 400 may be positioned at the same autosampler position 440 (not at the same time) and the tray actuator may be controlled to position appropriate wells for the respective cannula at the autosampler position 440. The syringe fluidics system 480 is further connected to a fill port connection unit 490 being arranged to selectively connect to a fill port 500 at an upper section of the syringe 200 in the pipette assembly. When connected to the fill port 500, the fill port connection unit 490 provides fluidic contact between the syringe cavity and the syringe fluidics system 480 to selectively pull or push liquid or gas through the syringe 200.

As previously mentioned, fig. 3a shows an ITC system corresponding to the system of fig. 2, but wherein the translation units 310b, 330b, 370b for the pipette 30, cell cannula 400 and transfer cannula 470 are of linear type, and the associated positions of operations are arranged accordingly. Moreover, the cell arm 390b and the transfer arm 460b are moveable in two dimensions (disregarding the vertical direction as mentioned above) whereby one or both may be controlled to position the associated cannula in a selected well in a static sample tray 450. Fig. 3b shows an embodiment of a linear ITC-system similar to fig. 3a, wherein the titrant transfer unit is omitted and the pipette translation unit 310c is arranged to place the pipette 30 in position for filling directly from a selected well in the sample tray 450. Moreover, the fill port connection unit 490 is arranged by the pipette 30 on the pipette arm 380c in order to connect to the fill port 500 both when the pipette 30 is placed in the wash station 320 and in a fill position in a well of the sample tray 450.

As mentioned above, the waste fluidics system 360 is connected to the outlet port 350 of the wash station 320 for withdrawing fluid from the wash station. According to one embodiment, the waste fluidics system 360 comprises a waste pump 510 for selective withdrawal of fluid from the wash station 320, optionally in combination with one or more controllable valves 520 to direct the flow of waste fluids. In other embodiments, the waste pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 510 may be any suitable pump capable of removing the fluids in the wash station, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a waste fluidics system 360 comprising a waste pump 510 of reservoir type, such as a syringe pump, and a waste control valve 520 for selective connection disconnection of the waste pump to the outlet port 350, a waste outlet 530 and a vent port 540.

As mentioned above, and shown more in detail in figs. 4a to 5c, the syringe 200 of the pipette may comprise a fill port 500 at an upper section thereof, providing fluidic contact with the syringe cavity when the plunger 230 is positioned above said fill port 500. Further the ITC system 300 may comprise a mating fill port connection unit 490 being arranged to selectively connect to the fill port 500, thereby providing fluidic contact between the syringe cavity and a syringe fluidics system 480 arranged to selectively pull or push liquid or gas through the syringe as part washing and filling operations, which will be disclosed more in detail below. As is schematically disclosed, the fill port 500 may be a bore through a wall of the syringe 200, and the bore may be of any suitable shape such as straight or conical. The connection unit 490 comprises a connection member 550 mating shape and/or of resilient material to achieve a reliable and fluid tight connection. The syringe fluidics system 480 may further be connected to the transfer

cannula 470, and arranged to control aspiration and dispensing of fluids during titrant transfer operations, as well as washing operations of the transfer cannula 470.

According to one embodiment, the syringe fluidics system 480 comprises a fill pump 560 to selectively pull or push liquid in the fluidics system, optionally in
5 combination with one or more controllable valves 570, 580, 590 to direct the flow of fluids and a purge gas source 600. In other embodiments, the fill pump may be a common pump for one or more fluidics systems in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The waste pump 560 may be any suitable pump capable of push or pull the liquids in the syringe fluidic system with
10 relatively high accuracy, such as a peristaltic pump, a syringe pump or the like. Fig. 4a shows a schematic view of an embodiment of a syringe fluidics system comprising a fill pump 560 of reservoir type, such as a syringe pump, a syringe control valve 570, syringe purge valve 580 and a transfer cannula purge valve 590. The syringe control valve 570 provides selective connection disconnection of the fill pump 560 to the fill port 500 of the
15 syringe 200, to the transfer cannula 470, to a plurality of reagent reservoirs 610a-d, to a waste outlet 620 and to a vent port 630. The reagent reservoirs 610a-d may comprise wash liquids for washing the syringe 210 and/or the transfer cannula 470 or the like. Fig. 4b shows a schematic view of another embodiment of the syringe fluidics system 480 and the waste fluidics system 360, wherein the transfer cannula 470 is not connected to the
20 syringe fluidics system 480, but instead connected to the waste fluidics system 360, whereby the titrant sample is transferred from the transfer cannula 470 to the wash station 320 via the waste fluidics system and the outlet port 350 of the wash station. Further, figs 4a and 4b schematically show the pipette assembly 30 in position for titration, with the titration needle 210 inserted into the sample cell 50.

25 In some embodiments, as is previously discussed, the syringe 200 is rotatable with

respect to the automatic pipette 30 and is driven for rotation by a stirring motor 250.

Then, in order to locate the position of the fill port 500, the fill port connection unit 490

may comprise a port alignment mechanism 640 arranged to prevent rotation of the

syringe at a predetermined angular position when a connection member 550 of the

5 connection unit is aligned with the fill port 500. Figs 5 a to 5c schematically shows an

example of an alignment mechanism 640, wherein the syringe 200, or any other part that

is arranged to rotate with the syringe 200, is provided with an alignment member 650, and

the fill port connection unit 490 is provided with a rotation stop unit 660 that may be

actuated to interfere with the rotation path of the alignment member 650, and when the

10 alignment member 650 abuts the rotation stop unit 660, then the connection member 550

is aligned with the fill port 500. The alignment procedure comprises the steps of:

- actuating the stop unit 660 (fig. 5a),
- rotating the syringe slowly in a predetermined direction until further
rotation is prevented by the stop unit 660 abutting the alignment member
15 650 (fig. 5b), and
- actuating the connection member 550 to connect to the fill port 500 (fig.
5c).

The stop unit 660 and the connection member 550 may be actuated by

electromagnetic drive actuators in the form of an electric motor arrangement, a solenoid

20 or the like, or they may be actuated by a hydraulic or pneumatic actuator or the like

capable of moving the stop unit 660 and the connection member 550. In order to achieve

a fluid tight connection between the syringe fill port 500 and the syringe fluidics system

480, the connection member 550 is pressed against the fill port 500 with a predetermined

force. In one embodiment (not shown) the connection member 550 is actuated by an

25 electromagnetic drive actuator, to move the connection member 550 into contact with the

fill port and the connection member 550 is spring loaded with respect to the actuator, whereby the scaling force is determined by the spring constant and the compression of said spring.

As is e.g. disclosed in fig. 2, the fill port connection unit 490 may be arranged at the wash station 320 to enable connection between the syringe cavity and the syringe fluidics system 480 when the pipette assembly 30 is arranged at the wash station 320. But, as is disclosed in fig. 3b, the fill port connection unit 490, may be arranged together with the pipette assembly 30 supported by the pipette translation unit 310, whereby fluidic connection between the syringe fill port 500 and the syringe fluidics system 480 may be established in any position of operation.

According to one embodiment, the ITC system 300 is arranged to utilize the syringe fill port 500 to wash the syringe 200 and the titration needle 210 by pushing one or more wash liquids through the syringe 200 and the titration needle 210 via the syringe fill port 500 when the titration needle 210 of the pipette 30 is arranged in the wash cavity 340 of the wash station 320. Thereafter the system may dry the syringe 200, needle 210 and the wash station 320 by purging gas through the syringe 200 and the titration needle 210 via the syringe fill port 500 after washing the same.

In many situations it is important to fill the syringe 200 of the pipette assembly 30 with titrant without having any trapped air in the syringe 200. In one embodiment, this is achieved by pulling a predetermined volume of titrant into the syringe from a titrant source, e.g. the wash station 320, in which the titration needle 210 is inserted, wherein the predetermined volume is selected to be larger than the syringe volume, whereby the syringe is overfilled and the titrant start to exit the syringe through the fill port 500. Then the linear activator 220 is activated to close the fill port 500 by moving the plunger 230 below to the fill port 500.

Fig. 6 schematically shows an example of a cell fluidics system 410 connected to the cell cannula 400 for dispensing and withdrawing liquid in the sample cell 50 and potentially also in the reference cell 40. As is previously discussed, the cell cannula 400 may be arranged to be positioned in the sample cell 50, in a well of a sample tray 450, in one or more large volume sample reservoirs 430a-c and a sample preparation station 420. According to one embodiment, the cell fluidics system 410 comprises a cell pump 670 for selective dispensing and withdrawing of fluid through the cell cannula 400, optionally in combination with one or more controllable valves 680, 690 to direct the flow of cell wash fluids or the like. In other embodiments, the cell pump 670 may be a common pump for one or more fluidics systems 360, 380, 410 in the ITC system 300, and one or more valves may control the flow in the systems, respectively. The cell pump 670 may be any suitable pump capable of dispensing and withdrawing the fluids in e.g. the sample cell 50, such as a peristaltic pump, a syringe pump or the like. Fig. 6 shows a schematic view of an embodiment of a cell fluidics system 410 comprising a cell pump 670 of reservoir type, such as a syringe pump, a cell preparation control valve 680 for selective connection/disconnection of the waste pump to the cannula 400, four cell wash liquid reservoirs 700a-c, a waste outlet 710 and a vent port 720, and a purge select valve 690 for connection of the cannula 400 to the cell preparation valve 680 or a source of purge gas 600 for drying the cannula 400.

Fig 7 schematically shows the ITC system of fig. 2 wherein positions of operation for each translation arm is shown by broken lines.

Figs. 8a to 8D schematically show examples of states wherein operations for preparation of the pipette and the sample cell may be performed in parallel in the ITC system of fig. 2.

In fig. 8a the pipette assembly 30 is placed at the wash position with the titration

needle 210 in the wash station 320 for a syringe wash cycle. During a wash cycle, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to push and pull one or more washing liquids through the syringe 200 optionally followed by purging a gas, e.g. nitrogen, through the syringe to dry the syringe 200. To push a wash liquid through the syringe, firstly the syringe control valve 570 is arranged in position A to connect the fill pump to the appropriate reagent reservoir 610a-d and the fill pump 560 is actuated to draw wash liquid into its pump reservoir, secondly the syringe control valve 570 is arranged in position B to connect the fill pump 560 to the fill port 500 of the syringe 200 and the fill pump 560 is actuated to push wash liquid through the syringe 200, whereby the wash liquid is dispensed from the titration needle 210 into the wash station 320. A full syringe cleaning cycle might comprise pushing the same or a different wash liquid (syringe valve positions C-E) two or more times through the syringe 200, and it may further involve pulling liquid from the wash station 320 through the syringe 200 and into the pump reservoir whereby it can be pushed through the syringe 200 one more time, or be discarded through the waste outlet 620 of the syringe fluidics system 480. When the fill pump 570 is arranged to consecutively push two or more different wash liquids through the syringe 200, the fill pump 570 may be rinsed to avoid contamination between washing liquids, by filling the pump reservoir with a rinse liquid, e.g. water. Liquid that is dispensed into the wash station 320 may be selectively withdrawn through the outlet port 350 by the waste pump 510 into the pump reservoir by setting the waste valve 520 in position A, and may thereafter be discarded through the waste outlet 530 by setting the waste valve 520 in position B.

In fig. 8a, while the syringe wash cycle is performed at the wash station 320, the titrant transfer unit 370 is arranged to draw titrant sample from a well in the sample tray

450 by setting the syringe valve 570 in position F and pulling titrant from the well using the fill pump 560. The operation of drawing titrant from the well may e.g. be performed when the syringe 200 is purged with dry gas, whereby the fill pump 560 and the syringe valve 570 are not involved in the wash cycle, but after the fill pump 560 and the syringe
5 valve 570 has been thoroughly rinsed and washed to avoid contamination.

In fig. 8a, also while the syringe wash cycle is performed at the wash station 320, the cell preparation unit 330 is arranged to remove the previous sample from the sample cell 50 and to wash the sample cell 50. As the pipette assembly 30 is removed from the sample cell 50, the cell cannula 400 may be inserted into the sample cell 50, and by
10 arranging the cell preparation control valve 680 in position A the cell pump 670 may be activated to withdraw the previous sample into the pump reservoir, and the previous sample may thereafter be discarded through the waste outlet 710 by setting the cell preparation control valve 680 valve in position B. Cleaning of the cell is thereafter performed by dispensing and withdrawing one or more cell wash liquids in the sample
15 cell 50 optionally followed by purging a gas, e.g. nitrogen, through the cell cannula to dry the sample cell 50. To dispense a wash liquid in the sample cell, firstly the cell preparation control valve 680 is arranged in position C, D, E or F to connect the cell pump 670 to the appropriate wash liquid reservoir 700a-d and the cell pump 670 is actuated to draw wash liquid into its pump reservoir, secondly the cell preparation control
20 valve 680 is arranged in position A to connect the cell pump 670 to the cannula 400 and the cell pump 670 is actuated to dispense wash liquid in the sample cell 50 through the cell cannula 200. The cleaning liquid(s) are thereafter withdrawn and discarded through the waste port 710 of the cell preparation control valve 680. According to the disclosed embodiment, the cell cannula 400 stays in the sample cell during the cell wash procedure,
25 thereby the cell cannula 400 is washed at the same time as the cell 50 and is ready for

transfer of fresh sample liquid to the sample cell 50.

In fig. 8b the pipette assembly 30 is placed at an intermediate position between the sample cell 50 and the wash station 320, in order to grant the titrant transfer cannula 470 of the titrant transfer unit 370 access to the wash station 320 to dispense a new titrant sample therein, and to grant the cell cannula 400 cell preparation unit 300 access to the sample cell 50 to fill the sample cell with fresh sample in the next step. The titrant transfer unit 370 is arranged to dispense the titrant sample from the cannula 470 into the wash station by setting the syringe valve 570 in position F and dispensing titrant using the fill pump 560.

In fig. 8b the cell preparation unit is arranged to draw fresh sample from a well in the sample tray 450 by inserting the cell cannula 400 in a selected well containing the desired fresh sample, setting the cell preparation control valve 680 in position A and pulling fresh sample from the well into the pump reservoir of the cell pump 670. Alternatively, the cell cannula 400 may be inserted into one of the sample reservoirs 430a-c.

In fig. 8c the pipette assembly 30 again is placed at the wash position with the titration needle 210 in the wash station 320 to fill the syringe 200 with titrant. As is discussed in detail with reference to figs. 5a-c, during filling of the syringe 200, the connection member 550 of the fill port connection unit 490 is connected to the fill port 500 of the syringe 200, and the syringe fluidics system 480 is arranged to pull the titrant through titrant needle 210 into the syringe 200 until a small volume has passed the fill port 500, whereby the plunger 230 is lowered to close the fill port 500. By drawing the titrant into the syringe in this way, trapped air in the titrant is effectively avoided. During the state disclosed in fig 8b, the titrant transfer unit 370 is essentially inactive, but the cell preparation unit 330 is positioned with the cell cannula 400 in the sample cell 50 to fill

the later with an exact amount of fresh sample by arranging the cell preparation control valve 680 in position A and activating the cell pump 670 to dispense the fresh sample contained in the pump reservoir into the sample cell 50.

In fig. 8a the pipette assembly 30 is placed at the titration position with the titration needle 210 in the sample cell 50 to perform an ITC experiment. The Titration transfer unit 370 is now positioned with the titrant cannula in the wash station 320 to wash it before the next titrant transfer operation. The washing cycle may be essentially the same as for the syringe 200. During the state disclosed in fig 8b, the cell preparation unit 330 is essentially inactive, and shown with the cell cannula 400 in the sample preparation station 420.

Examples of Liquid handling sequences includes:

Cell wash:

- a. The cell cannula 400 is inserted into the cell 40, 50, resting on the bottom.
- b. The cell content is drawn through the cell cannula 400, into the cell pump 680, and dispensed out to the waste port 710.
- c. Water is drawn from one of the wash liquid reservoirs 700a-d into the pump reservoir of the cell pump 680 and dispensed out to the waste port 710 to rinse the syringe.
- d. A wash liquid is drawn into the pump reservoir of the cell pump 680 from one of the wash liquid reservoirs 700a-d and dispensed through the cell cannula 400 into the cell 40, 50 in the exact amount needed to fill the cell,
- e. The wash liquid is cycled back and forth from the pump reservoir of the cell pump 680 to the cell 40, 50 to wash the later.
- f. The steps beginning at step b are repeated a predetermined number of times until the cell 40, 50.

- g. The cell is emptied to waste as in step b.
 - h. The cell cannula 400 is moved to the sample preparation station 420 and dried with by purging gas, e.g. Nitrogen. If degassing is included in the cell load procedure, the sample preparation 420 station is cleaned before drying.
- 5

Pipette wash:

- a. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- 10 b. The pipette plunger 230 is raised above the fill port 500 allowing liquid to flow through the syringe 200 of the pipette 30.
- c. First water then air is dispensed from the syringe pump 560 into the fill port 500, through the syringe 200 and titration needle 210 into the wash/fill station 320. Simultaneously, this water is drawn in great excess from the bottom of the wash/fill station 320 through the waste outlet 350 into the waste pump 510.
- 15 d. The waste pump 510 is stopped and a precise amount of water is dispensed through the pipette 30 to fill the wash/fill station 320 to the top of the outside of the titration needle 210. The water is cycled back and forth to wash the entire syringe 200 and the titration, inside and outside.
- 20 e. Step c is repeated.
- f. Step d is repeated with methanol.
- g. Step c is repeated.
- h. Nitrogen is purged through the fill port 500 to dry the system.
- 25 i. The pipette 30 is removed from the wash/fill station 320 to allow the

titrant transfer unit 370 to load the station 320 with titrant sample.

- j. The syringe pump 560 is rinsed with water to clear any methanol from the system.

5 Cell Load:

- a. Titrant sample is drawn into the cell cannula 400 from a sample tray 450 or a sample reservoir 430a-c. It is then slowly dispensed into the cell to prevent air bubbles. Optionally, the sample is dispensed into the sample preparation station 420 to be warmed and mixed (degassed) before being
10 transferred into the cell 50.

Pipette load:

- a. Titrant is drawn into the titrant transfer cannula 470 from a sample tray 450 and dispensed into the wash/fill station 320.
- 15 b. The pipette 30 is placed in the wash/fill station 320 and the fill port 500 is connected.
- c. The plunger 230 is raised above the fill port 500 allowing liquid to flow through the pipette.
- d. A precise volume of titrant is drawn up through the titration needle 210 by
20 the syringe pump 560, over-filling the syringe 200 such that a small amount of titrant exits the fill port 500.
- e. The plunger 230 is lowered below the fill port 500 leaving the titrant needle 210 and pipette syringe 200 completely filled.

Titrant Transfer Clean:

- a. The titrant transfer cannula 470 is placed in the wash/fill station 320 and is rinsed with water, then rinsed with methanol and dried in much the same way that the syringe 200 of the pipette is washed and dried.

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It is to be understood that any feature described in relation to any one embodiment may be used alone, or in combination with other features described, and may also be used in combination with one or more features of any other of the embodiments, or any combination of any other of the embodiments. Furthermore, equivalents and
10 modifications not described above may also be employed without departing from the scope of the invention, which is defined in the accompanying claims.

WHAT IS CLAIMED IS:

1. An automated isothermal titration micro calorimetry (ITC) system comprising:
 - a micro calorimeter with a sample cell and a reference cell, the sample cell is
5 accessible via a sample cell stem and the reference cell is accessible via a
reference cell stem;
 - an automatic pipette assembly comprising a syringe with a titration needle
arranged to be inserted into the sample cell for supplying titrant, the pipette
assembly comprises an activator for driving a plunger in the syringe;
 - 10 • a pipette translation unit supporting the pipette assembly and being arranged to
place pipette in position for titration, washing and filling operations;
 - a wash station for the titrant needle; and
 - a cell preparation unit arranged to perform operations for replacing the sample
liquid in the sample cell when the pipette is placed in another position than the
15 position for titration.
2. The automated ITC system of claim 1, wherein the wash station comprises a wash
cavity arranged to receive at least the section of the titration needle that is
immersed in the sample during titration when the pipette assembly is placed in
20 position for washing, wherein the wash station comprises a waste outlet port at the
bottom end of the wash cavity connected to a waste fluidics system.
3. The automated ITC system of claim 2, wherein the waste fluidics system
comprises a waste pump for selective withdrawal of fluid from the wash station.

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4. The automated ITC system of claim 1, wherein
- the syringe comprises a fill port at an upper section thereof, providing fluidic contact with the syringe cavity when the plunger is positioned above said fill port, and
- 5
- the automated ITC system comprises a fill port connection unit being arranged to selectively connect to the fill port, thereby providing fluidic contact between the syringe cavity and a syringe fluidics system to selectively pull or push liquid or gas through the syringe.
- 10 5. The automated ITC system of claim 4, wherein the syringe is rotatable with respect to the automatic pipette and is driven for rotation by a stirring motor, the fill port connection unit comprises a port alignment mechanism arranged to prevent rotation of the syringe at a predetermined angular position when a connection member is aligned with the fill port.
- 15
6. The automated ITC system of claim 4, wherein the fill port connection unit is arranged at the wash station to enable connection between the syringe cavity and the syringe fluidics system when the pipette is arranged at the wash station.
- 20 7. The automated ITC system of claim 4, wherein the syringe fluidics system comprises a syringe fill valve arrangement capable of:
- connecting the fill port of the syringe to a source of purge gas, and to a syringe fill pump, and
 - connecting the syringe fill pump to one or more wash liquid reservoirs, and to
- 25 a waste outlet.

8. The automated ITC system of claim 7, wherein the syringe fluidics system is arranged to wash the syringe and the titration needle by pushing one or more wash liquids through the syringe and the titration needle via the syringe fill port when the titration needle of the pipette is arranged in the wash cavity.
9. The automated ITC system of claim 8, wherein the syringe fluidics system is arranged to purge gas through the syringe and the titration needle via the syringe fill port after washing the same.
10. The automated ITC system of claim 4, wherein the syringe fluidics system is arranged to fill the syringe with titrant by pulling a predetermined volume of titrant into the syringe from a titrant source in which the titration needle is inserted, wherein the predetermined volume is selected to be larger than the syringe volume to overfill the same, and the linear activator is arranged to thereafter position the plunger below the fill port to close the same.
11. The automated ITC system of claim 10, wherein the titrant source is a well in a sample tray, and wherein the pipette translation unit is arranged to place the pipette in position for filling from said well.
12. The automated ITC system of claim 10, comprising a titrant transfer unit arranged to transfer titrant from a primary titrant source to a secondary titrant source in the form of a fill station, and wherein the pipette translation unit is arranged to place the pipette in position for filling at said fill station.

13. The automated ITC system of claim 12, wherein the primary titrant source is a well in a sample tray.
- 5 14. The automated ITC system of claim 12, wherein the titrant transfer unit comprises a cannula arranged to draw titrant from the primary titrant source, and a fluidic system connected to a port in the fill station for transfer of the titrant volume from the cannula to the fill station.
- 10 15. The automated ITC system of claim 12, wherein the titrant transfer unit comprises a cannula arranged to draw titrant from the primary titrant source, and is arranged to move the cannula to the fill station to dispense the titrant therein.
16. The automated ITC system of claim 12, wherein the fill station and the wash
15 station are combined as one combined station.
17. The automated ITC system of claim 1, wherein the cell preparation unit comprises a cannula that is moveable to be inserted into the sample cell.

ABSTRACT

ISOTHERMAL TITRATION MICROCALORIMETER

APPARATUS AND METHOD OF USE

5 Automated isothermal titration micro calorimetry (ITC) system comprising a
micro calorimeter with a sample cell and a reference cell, the sample cell is accessible via
a sample cell stem and the reference cell is accessible via a reference cell stem. The
system further comprises an automatic pipette assembly comprising a syringe with a
titration needle arranged to be inserted into the sample cell for supplying titrant, the
10 pipette assembly comprises an activator for driving a plunger in the syringe, a pipette
translation unit supporting the pipette assembly and being arranged to place pipette in
position for titration, washing and filling operations, a wash station for the titrant needle,
and a cell preparation unit arranged to perform operations for replacing the sample liquid
in the sample cell when the pipette is placed in another position than the position for
15 titration.

I hereby certify that this paper is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: June 11, 2015

Electronic Signature for Vilavanh Ong: /Vilavanh Ong/

Docket No.: 739712000201
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Martin BROGA et al.

Application No.: Not Yet Assigned

Confirmation No.: Not Yet Assigned

Filed: Concurrently Herewith

Art Unit: Not Yet Assigned

For: AUTOMATIC ISOTHERMAL TITRATION
MICROCALORIMETER APPARATUS AND
METHOD OF USE

Examiner: Not Yet Assigned

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Prior to examination on the merits, Applicants respectfully request entry of this Preliminary Amendment for the above-captioned patent application.

Amendments to the Specification begin on page 2.

Remarks begin on page 3.

va-452231

AMENDMENTS TO THE SPECIFICATION

Please add the following new header and paragraph after the title as follows:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 12/326,300, filed on December 2, 2008, the contents of which are hereby incorporated by reference.

REMARKS

Applicants have amended the specification to reflect the priority application. No new matter has been added.

If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no.

739712000201. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 11, 2015

Respectfully submitted,

Electronic signature: /Alex Chartove/
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 14/736,905		Filing Date 06/11/2015		<input type="checkbox"/> To be Mailed	
ENTITY: <input checked="" type="checkbox"/> LARGE <input type="checkbox"/> SMALL <input type="checkbox"/> MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR	NUMBER FILED	NUMBER EXTRA			RATE (\$)	FEE (\$)			
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A			N/A				
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A			N/A				
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A			N/A				
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*			X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*			X \$	=			
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))									
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL				
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	06/12/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 1	Minus	** 20	= 0	x \$80 =		0	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	x \$420 =		0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		0	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	06/11/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 1	Minus	** 20	= 0	x \$80 =		0	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	x \$420 =		0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))								
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		0	
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>									

LIE
/JULIET MCMILLAN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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