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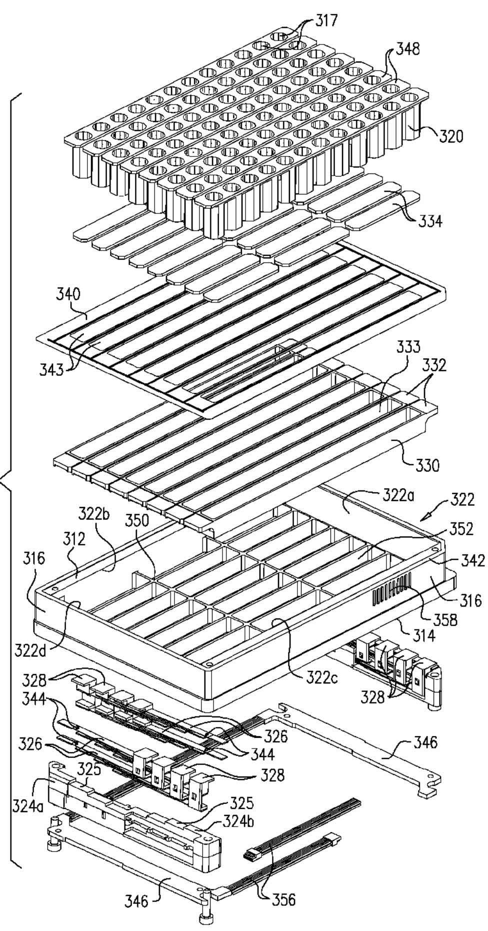

FIG. 3C

(57) Abstract: There is provided plate equipped with a mechanism to facilitate determination of the amount of a fluid added to or removed from a well in the plate. Other embodiments are also described.

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MULTI-WELL PLATES AND METHODS OF USE THEREOF

RELATED APPLICATIONS

This application claims Paris Convention priority from, and the benefit under 35 U.S.C. §120, of the following US provisional applications: no. 61/905865, filed November 19, 2013; no. 61/929086, filed January 19, 2014; and no. 61/949272, filed March 7, 2014. The contents of the aforesaid provisional applications are incorporated herein by reference.

BACKGROUND

Plates containing a multiplicity of wells for holding samples of chemicals, cells or other biological materials for observation, are known in the art. Commonly, such plates have a 3:2 aspect ratio and thus contain 24 (4 x 6), 96 (8 x12), 384 (16 x 24), or 1536 (32 x 48) wells; a typical 96-well plate is 128 mm long and 86 mm wide, and standards for the footprint and bottom outside flange of 96-well plates are described in ANSI/SBS 1-2004 and ANSI/SBS 3-2004, respectively.

Such multi-well plates, also sometimes referred to as microwell plates or microtiter plates depending on the volume of the wells, are generally constructed of plastic, e.g. polystyrene, polypropylene or polycarbonate, or a combination of such materials, in some cases also incorporating glass in the bottom portion of the plate. In many applications, the bottom of the well is transparent to a frequency of light that will be used to observe the sample. The size of wells in terms of depth, height, and total volume, as well the shape of the wells and the shape of the bottoms of the wells, varies in accordance with the particular use to which the plate is to be put.

Examples of commercial suppliers of such plates are:

Perkin-Elmer (see http://www.perkinelmer.com/CMSResources/Images/44-73879SPC_MicroplateDimensionsSummaryChart.pdf);

Sigma-Aldrich (see http://www.sigmaaldrich.com/labware/labware-products.html?TablePage=9576216); and

Thermo-Scientific (see http://www.thermoscientific.com/ecomm/servlet/productscatalog_11152__81996_-1_4).

One area in which widespread use of such plates is made is high-throughput screening for the testing of compounds in drug development, binding assays for antigens and the like.

Often, in high-throughput screening and other applications, automated machinery is used to dispense a volume of liquid into some or all of the wells simultaneously, for example, by dispensing fluid simultaneously into the wells of an 8-well row in a 96-well plate or into all the wells of a 384-well plate. However, if the amount of liquid added to a specific well is incorrect, such fact may not become known until the entire experiment is completed; and if the specific well to which the incorrect amount of fluid was added is not identified, it may be necessary to disregard the results for the entire plate.

BRIEF DESCRIPTION

There is provided in accordance with an embodiment of the invention a plate, comprising a first substantially planar surface having at least one first aperture defined therein; a second substantially planar surface substantially parallel to the first substantially planar surface, the second substantially planar surface being spaced from the first substantially planar surface; at least one well defined within the plate, the at least one well having a second aperture corresponding to and in alignment with one of the at least one first aperture, the at least one well having a sidewall and a bottom and the at least one well extending from the first substantially planar surface toward the second substantially planar surface, the at least one well being displaceable away from the first substantially planar surface; and at least one signal provider, functionally associated with the at least one well, capable of producing a signal in response to displacement of the at least one well away from the first surface.

In some embodiments, the first surface has a plurality of first apertures defined therewithin, and a plurality of wells are defined within the plate, each well having a second aperture corresponding to and in alignment with a first aperture of the plurality of first apertures defined in the first surface, and each of the wells having a sidewall and a bottom and each well extending from the first substantially planar surface toward the second substantially planar surface. In some embodiments, each of the plurality of wells is displaceable away from the first substantially planar surface.

There is also provided in accordance with an embodiment of the invention a multiwell plate, comprising a first substantially planar surface having a plurality of first apertures defined therein; a second substantially planar surface substantially parallel to the first substantially planar surface, the second substantially planar surface being spaced from the first substantially planar surface; a plurality of wells defined within the plate, each well having a second aperture corresponding to and in alignment with one of the first apertures defined in the first surface, each of the wells having a sidewall and a bottom and each well extending from the first substantially planar surface toward the second substantially planar surface, each of the wells being displaceable away from the first substantially planar surface; and at least one signal provider, functionally associated with the plurality of wells, capable of producing a signal in response to displacement of at least one the well away from the first surface.

In some embodiments, the first and second surfaces are spaced apart by a plurality of sidewalls extending between the first and second surfaces.

In some embodiments, movement of all the wells is coupled, so that the signal provider is capable of providing a single signal in response to displacement of any one or more of the wells. In some embodiments, movement of some of the wells is coupled into two or more groups, and the at least one signal provider comprises multiple signal providers, each capable of providing a signal in response to displacement of one of the groups. In some embodiments, movement of some of the wells is coupled into two or more groups, and the signal provider is capable of providing a separate signal in response to displacement of each one of the groups.

In some embodiments, the at least one signal provider comprises a plurality of signal providers, each associated with one well of the plurality of wells, each of the plurality of wells is independently displaceable away from the first surface, and each of the plurality of signal providers is capable of providing a signal in response to displacement of one of the plurality of wells associated therewith.

In some embodiments, the at least one signal provider is capable of providing a signal in response to placement in a the well of 300 milligrams of material, 250 milligrams of material, 200 milligrams of material, 150 milligrams of material, 100 milligrams of material, 75 milligrams of material, 50 milligrams of material, 45 milligrams of material, 40 milligrams of material, 35 milligrams of material, 30 milligrams of material, 25 milligrams of material, 20 milligrams of material, 15 milligrams of material, 10 milligrams of material, 5 milligrams of material, 4 milligrams of material, 3 milligrams of material, 2 milligrams of material, or 1 milligram of material, 500 micrograms (μg) of material, 300 μg of material, 200 μg of material, or 100 μg of material.

In some embodiments, the at least one signal provider is capable of providing a signal in response to placement in a the well of 300 microliters (μl) of fluid, 250 μl of fluid, 200 μl of fluid, 150 μl of fluid, 100 μl of fluid, 75 μl of fluid, 50 μl of fluid, 45 μl of fluid, 40 μl of fluid, 35 μl of fluid, 30 μl of fluid, 25 μl of fluid, 20 μl of fluid, 15 μl of fluid, 10 μl of fluid, 5 μl of fluid, 4 μl of fluid, 3 μl of fluid, 2 μl of fluid, 1 μl of fluid, 0.5 μl of fluid, 0.3 μl of fluid, 0.5 μl of fluid, or 0.1 μl of fluid.

In some embodiments, the signal provider is capable of providing a signal in response to displacement of at least one the well toward the first surface.

In some embodiments, the at least one signal provider is capable of providing a signal in response to removal from a the well of 300 milligrams of material, 250 milligrams of material, 200 milligrams of material, 150 milligrams of material, 100 milligrams of material, 75 milligrams of material, 50 milligrams of material, 45 milligrams of material, 40 milligrams of material, 35 milligrams of material, 30 milligrams of material, 25 milligrams of material, 20 milligrams of material, 15 milligrams of material, 10 milligrams of material, 5 milligrams of material, 4 milligrams of material, 3 milligrams of material, 2 milligrams of material, or 1 milligram of material, 500 micrograms (μg) of material, 300 μg of material, 200 μg of material, or 100 μg of material.

In some embodiments, the at least one signal provider is capable of providing a signal in response to removal from a the well of 300 microliters (μl) of fluid, 250 μl of fluid, 200 μl of fluid, 150 μl of fluid, 100 μl of fluid, 75 μl of fluid, 50 μl of fluid, 45 μl of fluid, 40 μl of fluid, 35 μl of fluid, 30 μl of fluid, 25 μl of fluid, 20 μl of fluid, 15 μl of fluid, 10 μl of fluid, 5 μl of fluid, 4 μl of fluid, 3 μl of fluid, 2 μl of fluid, 1 μl of fluid, 0.5 μl of fluid, 0.3 μl of fluid, 0.2 μl of fluid, or 0.1 μl of fluid.

In some embodiments, at least one well in the plate is removable therefrom.

In some embodiments, the plate comprises at least one temperature sensor associated with at least one of the wells. In some embodiments, the temperature sensor is located in or on one of the wells. In some embodiments, the at least one temperature sensor is configured to provide a signal representing a temperature in the at least one well or in a vicinity thereof. In some such embodiments, the at least one temperature sensor is configured to continuously detect the temperature in the at least one well, and to periodically provide the signal representing the temperature.

In some embodiments, the plate further comprises an electronic storage element for storage of at least one signal provided by at least one of the at least one signal provider and the at least one temperature sensor.

In some embodiments, the at least one temperature sensor is configured to detect the temperature in a group of wells from the plurality of the wells.

In some embodiments, the at least one temperature sensor comprises a single temperature sensor configured to detect the temperature in all the wells.

In some embodiments, the at least one temperature sensor comprises a plurality of temperature sensors, each associated with one of the plurality of wells for detecting the temperature in the one of the plurality of wells associated therewith.

In some embodiments, the plate further comprises at least one heating component associated with the at least one well, the at least one heating component being located in sufficient proximity to the at least one well to heat the at least one well or its interior. In some embodiments, the at least one heating component comprises a plurality of heating components, each associated with one well of the plurality of wells and located in sufficient proximity to the one well associated therewith to heat the one well or its interior, without substantially heating others of the plurality of wells. In some embodiments, the at least one heating component comprises a heating coil. In some embodiments, the at least one heating component is also capable of cooling the at least one well. In some embodiments, the heating component comprises a Peltier device.

In some embodiments, at least one well in the plate is removable therefrom, in a manner that does not remove from the plate a heating component associated with the at least one removable well. In some embodiments, at least one well in the plate is removable therefrom, and the heating component associated with the at least one removable well is attached to or formed integrally with the at least one well and is removable therewith.

In some embodiments, the plate further comprises an electrical port functionally associated with at least one of the at least one signal provider and the at least one temperature sensor. In some embodiments, the plate further comprises a rechargeable power supply, functionally associated with at least one of the at least one signal provider and the at least one temperature sensor, and configured to be recharged by connection thereof to a power source. In some embodiments, the rechargeable power supply is configured to be recharged when the electrical port is electrically connected to a power source.

There is also provided in accordance with an embodiment of the invention a data reader configured to receive therein a plate according embodiments of the present invention, the data reader comprising a base for placement of the plate thereon; an electrical port corresponding to the electrical port of the plate for electrical engagement therewith; and a processor functionally associated with the electrical port, for processing signals obtained from at least one of the signal provider and the temperature sensor via the electrical port. In some embodiments, the processor is configured to obtain the signals directly from at least one of the signal provider and the temperature sensor via the electrical port. In some embodiments, the processor is configured to obtain the signals from an electronic storage component storing at least one signal provided by at least one of the signal provider and the temperature sensor.

In some embodiments the data reader further comprises a display functionally associated with the processor, the display configured to provide to a user information obtained from the processed signals. In some embodiments, the information comprises an indication of at least one of: (i) an amount of fluid in the plate at a specific time; (ii) an amount of fluid in at least one the well at a specific time; (iii) a change in an amount of fluid in the plate over a period of time; (iv) a change in an amount of fluid in at least one the well over a period of time; (v) a temperature of at least one the well at a specific time; and (vi) a change in temperature of at least one the well over a period of time. In some embodiments, the processor is configured to process the signals in real time and the display is configured to provide to the user the information in real-time.

There is also provided in accordance with an embodiment of the invention a plate comprising a first substantially planar surface having at least one first aperture defined therein; a second substantially planar surface substantially parallel to the first substantially planar surface, the second substantially planar surface being spaced from the first substantially planar surface; at least one well defined within the plate, the at least one well having a second aperture corresponding to and in alignment with one of the at least one first apertures defined in the first surface, the at least one well having a sidewall and a bottom and the at least one well extending from the first substantially planar surface toward the second substantially planar surface; and at least one heating component associated with the at least one well, which is located in sufficient proximity to the at least one well to heat the at least one well or its interior. In some embodiments, the first surface has a plurality of first apertures defined therewithin; the at least one well comprises a plurality of wells defined within the plate, each well having a second aperture corresponding to and in alignment with one first aperture from the plurality of first apertures defined in the first surface, each of the wells having a sidewall and a bottom and each well extending from the first substantially planar surface toward the second substantially planar surface; and the at least one heating component comprising a plurality of heating components such that each of the wells has one of the plurality of heating components associated therewith, each of the heating components being located in sufficient proximity to the well with which the heating component is associated to heat the well or its interior without substantially heating other wells. In some embodiments, the heating component comprises a heating coil. In some embodiments, the heating component is also capable of cooling the well. In some embodiments, the heating component comprises a Peltier device. In some embodiments, at least one well in the plate is removable therefrom, without removing from the plate a heating component associated with the at least one removable well. In some embodiments, at least one well in the plate is removable therefrom, and the heating component associated with the at least one removable well is attached to or formed integrally with the at least one well and is removable therewith.

There is also provided in accordance with an embodiment of the invention a method for measuring the amount of fluid added to a plate according to any one of the embodiments of the present invention, the method comprising recording an initial signal provided by the signal provider, and after a fluid has been added to at least one well in the plate, obtaining a second signal generated by the signal provider in response to the addition of the fluid, wherein, on the basis of a difference between the initial signal and the second signal, the amount of the fluid added to the at least one well can be calculated. In some embodiments, the method further comprises adding fluid to the plate after the recording an initial signal and before the obtaining a second signal. In some embodiments, the method further comprises on the basis of the difference between the initial signal and the second signal, calculating an amount of the fluid added to the at least one well. In some embodiments, the calculating an amount comprises calculating a volume of the fluid added to the at least one well. In some embodiments, the calculating an amount comprises calculating a mass of the fluid added to the at least one well. In some embodiments, the calculating an amount comprises calculating a volume and a mass of the fluid added to the at least one well.

There is also provided in accordance with an embodiment of the invention a method for measuring the amount of fluid lost from a plate according to any one of the embodiments of the present invention, the plate having an initial amount of fluid disposed in at least one well of the plate, the method comprising recording an initial signal provided by the signal provider at a first time; obtaining from the signal provider a second signal at a second time after the first time; and on the basis of the difference between the initial signal and the second signal, calculating an amount of the fluid lost from the at least one well of the plate. In some embodiments, the calculating an amount comprises calculating a volume of the fluid lost from the at least one well. In some embodiments, the calculating an amount comprises calculating a mass of the fluid lost from the at least one well. In some embodiments, the calculating an amount comprises calculating a volume and a mass of the fluid lost from the at least one well. In some embodiments, the method further comprises periodically repeating the step of obtaining a signal, and on the basis of the difference between signals obtained at two different times, calculating an amount of fluid lost from the at least one well in a duration between the two different times.

There is also provided in accordance with an embodiment of the invention a method comprising obtaining a baseline measurement of displacement of at least one well in a multi-well plate having disposed therein a displacement measuring assembly for measuring the displacement of at least one well in the plate in response a change in an amount of fluid in the at least one well, the baseline measurement being obtained via the displacement measuring assembly; at a time after the obtaining of the baseline measurement, obtaining a second measurement of displacement of the at least one well; and on the basis of the second measurement of displacement, calculating the change in the amount of fluid in the at least one well.

There is also provide in accordance with an embodiment of the invention a method comprising at a first time, obtaining a baseline measurement of displacement of at least one well in a multi-well plate having disposed therein a displacement measuring assembly for measuring the displacement of at least one well in the plate in response a change in an amount of fluid in the at least one well, the baseline measurement being obtained via the displacement measuring assembly; at a second time after the first time, measuring the displacement of the at least one well; and on the basis of a change in displacement between the first and second times, calculating a change in the amount of fluid in the at least one well, wherein at at least one of the first and second times, a detectable amount of fluid is present in the well. In some embodiments, the method further comprises periodically repeating the step of measuring the displacement of the at least one well at a second time, and on the basis of a change in displacement between two the measurements of displacement, calculating a change in the amount of fluid in the at least one well during a period between the two the measurements of displacement. In some embodiments, the change in the amount of fluid is due to addition of fluid to the at least one well. In some embodiments, the change in the amount of fluid is due to loss of fluid from the at least one well.

In some embodiments of the aforemention methods, the plate is a plate according to any one of the embodiments of the present invention.

In some embodiments of the aforemention methods, the signal provider is sufficiently sensitive to detect a change of 300 microliters (µl), 250 µl, 200 µl, 150 µl, 100 µl, 75 µl, 50 µl, 45 µl, 40 µl, 35 µl, 30 µl, 25 µl, 20 µl, 15 µl, 10 µl, 5 µl, 4 µl, 3 µl, 2 µl, 1 µl, 0.5 µl of fluid, 0.3 µl of fluid, 0.2 µl of fluid, or 0.1 µl of fluid, in the volume of fluid in the at least one well.

In some embodiments of the aforemention methods, the signal provider is sufficiently sensitive to detect a change of 300 milligrams (mg), 250 mg, 200 mg, 150 mg, 100 mg, 75 mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, 5 mg, 4 mg, 3 mg, 2 mg, 1 mg, 500 micrograms (µg), 300 µg, 200 µg, or 100 µg in the mass of fluid in the at least one well.

In some embodiments of the aforemention methods, the method further comprises detecting a temperature in at least one well. In some embodiments, the method further comprises detecting the temperature in the at least one well at at least two different points in time. In some embodiments, the method further comprises adjusting the temperature of an individual well in response to the detecting the temperature.

In some embodiments of the aforemention methods, at least one well in the multi-well plate is removable therefrom.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. In case of conflict, the specification, including definitions, will take precedence.

As used herein, the terms “comprising”, “including”, "having" and grammatical variants thereof are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers, steps, components or groups thereof. These terms encompass the terms "consisting of" and "consisting essentially of".

As used herein, the indefinite articles "a" and "an" mean "at least one" or "one or more" unless the context clearly dictates otherwise.

Embodiments of methods and/or devices of the invention may involve performing or completing selected tasks manually, automatically, or a combination thereof. Some embodiments of the invention are implemented with the use of components that comprise hardware, software, firmware or combinations thereof. In some embodiments, some components are general-purpose components such as general purpose computers or monitors. In some embodiments, some components are dedicated or custom components such as circuits, integrated circuits or software.

For example, in some embodiments, some of an embodiment is implemented as a plurality of software instructions executed by a data processor, for example which is part of a general-purpose or custom computer. In some embodiments, the data processor or computer comprises volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. In some embodiments, implementation includes a network connection. In some embodiments, implementation includes a user interface, generally comprising one or more of input devices (e.g., allowing input of commands and/or parameters) and output devices (e.g., allowing reporting parameters of operation and results.

BRIEF DESCRIPTION OF THE FIGURES

Some embodiments of the invention are described herein with reference to the accompanying figures. The description, together with the figures, makes apparent to a person having ordinary skill in the art how some embodiments of the invention may be practiced. The figures are for the purpose of illustrative discussion and no attempt is made to show structural details of an embodiment in more detail than is necessary for a fundamental understanding of the invention. For the sake of clarity, some objects depicted in the figures may not be to scale.

In the Figures:

Fig. 1 is a perspective view of a multi-well plate of the prior art;

Fig. 2A is a perspective view of a multi-well plate constructed and operative in accordance with an embodiment of the invention;

Fig. 2B is an exploded view of the multi-well plate of Fig. 2A;

Figs. 2C and 2D are perspective sectional views of the multi-well plate of Figs. 2A and 2B, taken along section lines IIC-IIC and IID-IID in Fig. 2A, respectively;

Figs. 3A and 3B are perspective views of a multi-well plate constructed and operative in accordance with another embodiment of the invention;

Fig. 3C is an exploded view of the multi-well plate of Figs. 3A and 3B;

Fig. 3D is an enlarged perspective view of supports, arms, and blocks forming part of the multi-well plate of Figs. 3A and 3B;

Figs. 3E, 3F, and 3G are sectional views of the multi-well plate of Figs. 3A to 3C, taken along section lines IIIE-IIIE, IIIF-IIIF, and IIIG-IIIG in Fig. 3A;

Fig. 4A is a perspective view of a multi-well plate constructed and operative in accordance with yet another embodiment of the invention;

Fig. 4B is an exploded view of the multi-well plate of Fig. 4A;

Fig. 4C is a sectional view of the multi-well plate of Figs. 4A and 4B, taken along section lines IVC-IVC in Fig. 4A;

Figs. 5A – 5D are screen shots illustrating a graphical user interface for on-line (real time) monitoring of addition of fluid to a multi-well plate in accordance with embodiments of the teachings herein;

Figs. 6A and 6B are screen shots illustrating a graphical user interface for off-line volume monitoring of fluid in a multi-well plate in accordance with embodiments of the teachings herein;

Fig. 7 is a screen shot illustrating a graphical user interface for off-line temperature monitoring of fluid in a multi-well plate in accordance with embodiments of the invention;

Fig. 8 is a perspective view of a plate base and data reader constructed and operative in accordance with an embodiment of the teachings herein, for receiving signals from a multi-well plate in accordance with the teachings herein; and

Figs. 9A and 9B are perspective views of a device for removing well-containing elements or well-defining elements from and/or for emplacing such elements in a multi-well plate, the device constructed and operative in accordance with an embodiment of the teachings herein.

DESCRIPTION OF SOME EMBODIMENTS OF THE INVENTION

The principles, uses and implementations of the teachings herein may be better understood with reference to the accompanying description and figures. Upon perusal of the description and figures present herein, one skilled in the art is able to implement the invention without undue effort or experimentation.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its applications to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or illustrated in the drawings and/or the Examples. The invention can be implemented with other embodiments and can be practiced or carried out in various ways. It is also understood that the phraseology and terminology employed herein is for descriptive purpose and should not be regarded as limiting.

Reference is now made to Fig. 1, which is a perspective view of a multi-well plate of the prior art. Figure 1 shows a typical 96-well plate **10** as is known in the art. Plate **10** has an upper surface **12**, a lower surface **14**, and a plurality of sides **16** between the upper and lower surfaces **12** and **14**. Extending between surfaces **12** and **14** are a plurality of wells **17**, ninety-six such wells in all, arranged in eight rows of twelve wells each. Each well has an aperture **18** formed in upper surface **12**, to facilitate the injection of sample fluid into the well. Plate

10 may be made of plastic, such as polystyrene or polycarbonate, or a combination of such materials; in some cases, it may have a glass bottom. Typically the lower surface **14** is transparent at at least some particular frequency or range of frequencies of light at which the sample placed in the well will be observed, although for some uses such transparency may not be necessary. Sides **20** of the wells **17** may or may not be transparent, depending on the nature of the sample and the type of observations to be made.

The wells are typically of circular cross-section in the x-y plane and of essentially cylindrical shape, but they may have cross-sections of other shapes, such as rectangular or square, and they may have different shapes along their lengths, for example the sides of the wells may taper from the upper opening to the bottom of the well along a portion thereof or along their entire length. The bottoms of the wells are typically flat but, depending upon the intended use of the plate, may be formed with other shapes, such as conical, frusto-conical, or spherical bottoms (i.e. V- or U-shaped bottom cross sections when viewed along the z-axis).

A plate such as plate **10** is typically of 85-86 mm width and 127-128 mm length, with an overall height that varies within the range of 10-20 mm, and with the centers of the wells being spaced 9 mm apart along the x and y axes. Standards for the footprint and bottom outside flange of 96-well microplates are described in ANSI/SBS 1-2004 and ANSI/SBS 3-2004, respectively. That said, the plate may have different length, width, and height dimensions, may have a different distance between the wells, and may have a different number of wells, as is suitable for the specific application or use of the plate. For example, the plate may be a 384-well plate including 384 wells, arranged in sixteen rows of twenty four wells each, such that the centers of the wells are 4.5 mm apart along the x and y axes. Standards for the footprint and bottom outside flange of 384-well microplates are described in ANSI/SBS 1-2004 and ANSI/SBS 3-2004, respectively.

Reference is now made to Fig. 2A, which is a perspective view of a multi-well plate **100** constructed and operative in accordance with an embodiment of the invention, to Fig. 2B, which is an exploded view of the multi-well plate **100** of Fig. 2A, and to Figs. 2C and 2D, which are perspective sectional views of the multi-well plate **100** of Figs. 2A and 2B, taken along section lines IIC-IIC and IID-IID in Fig. 2A, respectively.

As shown in Fig. 2A, plate **100** is designed for use with existing equipment and is therefore sized in accordance with standard plate sizes currently in use, with its wells similarly spaced, as defined in ANSI/SBS 1-2004 and in ANSI/SBS 3-2004. As such, when assembled, plate **100** looks similar to a typical 96-well plate, with an upper surface **112**, a lower surface **114**, and a plurality of sides **116** between surfaces **112** and **114**. A plurality of wells **117** are formed in plate **100** and extend between surfaces **112** and **114**. Each well has an aperture **118** formed in upper surface **112**, to facilitate the injection of sample fluid into the well.

Turning to Fig. 2B, which is an exploded view of plate **100**, it is seen that plate **100** is actually formed of several parts. Sides **116** form part of a frame **122**, which has formed on an inner portion thereof, at each lengthwise end of the frame, a pair of supports **124a** and **124b**, which supports will be explained in more detail in connection with Figs. 2C and 2D. Each of the supports **124a** and **124b** has attached thereto a pair of flexible arms **126**, consisting of an upper arm **126a** and a lower arm **126b**, wherein each arm is attached at the proximal end thereof to one of the supports, and is attached the distal end thereof to a block **128**. As seen in the enlarged portion of Fig. 2B, each block **128** includes an upper portion and a lower portion, with the arms **126a** and **126b** being attached to lower surfaces **128a** and **128b** of the upper and lower portions, respectively. The flexible arms **126** may be made of a material, generally metal or plastic, which is suitably flexible that it will be sensitive to the addition of a few micrograms weight to the wells, as will be explained in more detail below. The arms may be attached to blocks **128** by suitable means, such as adhesive or in some cases melting or welding.

Cylindrical side walls of wells **117** are formed in a well-containing element **130**, which may be formed of plastic, glass, or another suitable material. The well containing element **130** includes upper surface **112** and has flanges **132** at longitudinal ends thereof. When plate **100** is assembled, each flange **132** rests on, and optionally is attached to, upper surfaces of upper portions **128a** of two blocks **128**, one block at each end of the flange, and in some embodiments also on supports **124a** and **124b** (see Fig. 2D). A bottom piece **134**, which is a piece of plastic or glass approximately 170-1000 microns in thickness, is sealingly attached to the underside of well-containing element **130**, so as to form the bottom of each well **117** in a manner that seals each well at that end.

In the embodiment shown in Figs. 2A-2D, the circumference of the uppermost portion of well-containing element **130**, including the flanges **132**, is slightly less than the inner circumference of frame **122**. Consequently, when the flanges **132** of well-containing element **130** rest on blocks **128**, there is a small gap **138** between the well-containing element **130** and the frame **122** (see Fig. 2D). The presence of gap **138** allows for movement of the well-containing element **130** along the vertical axis and for concomitant deformation of arms **126**, as will be explained below. In order to seal the gap **138** without inhibiting such movement, a very thin (approximately 7 micron) film **140** of a flexible material, such as a suitable plastic, is attached to an upper edge **142** of the frame **122** and to an outer edge of upper surface **112** of well-containing element **130**. One way to accomplish such attachment to well-containing element **130** is by having a slightly raised rim **143** around the circumference of the upper edge of element **130**, so that film **140** engages the rim **143** and, when also attached to an outer edge of upper surface **112**, is disposed above gap **138**.

As shown in Figs. 2A and 2B, film **140** is hollow in the center, so that most of upper surface **112**, and particularly the area of surface **112** including wells **117**, is exposed and film **140** covers just the edge of well-containing element **130**, gap **138**, and upper edge **142** of the frame **122**. However, it will also be appreciated that in some embodiments, film **140** may be formed to cover the upper edge **142** of frame **122** as well as the entire upper surface **112** of element **130**, in which case film **140** will be formed with a plurality of circular openings which would be aligned with apertures **118** in well-containing element **130**, to allow user access to wells **117**. In such embodiments, well-containing element **130** may be formed with slightly raised portions, or rims, around apertures **118**, so as to provide additional surfaces to which film **140** may be affixed.

Film **140**, well-containing element **130**, bottom piece **134**, and frame **122**, are attached to each other using any suitable means, such as soldering, adhering, melting, bonding, or any other suitable attachment mechanism.

As noted, when plate **100** is assembled, well-containing element **130** rests on, and is optionally attached at each of its longitudinal ends to, a pair of blocks **128**. This restricts the motion of element **130** in the x- and y-directions, but allows for motion in the vertical (z) direction. Thus, when fluid is placed into wells **117** in element **130**, the weight of the fluid will result in downward displacement of element **130** and in deformation of arms **126**. It will be appreciated that typically not more than several hundred microliters of fluid, and in some applications only a few microliters of fluid, are added to a given well **117**. Consequently, the flexible arms **126** should be of suitable flexibility to deflect in response to the addition of micrograms of fluid to the wells.

Reference is additionally made to Figs. 2C and 2D show in greater detail the supports **124a** and **124b**, the arms **126** and blocks **128**, and the attachment of the arms **126** to the supports. Fig. 2C shows plate **100**, as in Fig. 2A, but with a perspective cross-sectional view showing the end of the plate, the cross-sectional view taken along section lines IIC-IIC in Fig. 2A. Fig. 2D shows the same plate, with an enlarged cross-sectional view taken from the same angle as Fig. 2C along section lines IID-IID in Figure 2A, which cross-sectional view shows the other end of plate. Fig. 2C shows the pair of arms **126** closest to the end of the plate, whereas Fig. 2D shows the pair of arms **126** disposed slightly inward from the end of the plate.

Support **124a** protrudes from both the inner wall **122a** which is located at one longitudinal end of frame **122**, as well as from the longitudinal wall **122b** adjacent thereto. Support **124b** protrudes from the opposite longitudinal wall **122c** and is spaced from the inner wall **122a** by the width of support **124a**. Supports **124a** and **124b** project in opposite directions from the longitudinal walls, each of supports **124a** and **124b** projecting about one third of the way between the longitudinal walls, with each support having a pair of tongues (shown in Fig. 2D for support **124b** as **124b'** and **124b"**) that project further until approximately midway between the two longitudinal walls. The distance between the upper faces of the tongues is equal to the distance between the arms **126a** and **126b**. One pair of arms is attached at its proximal end to support tongues **124a'** and **124a"** (not shown) of support **124a** and the other pair of arms is attached at its proximal end to tongues **124b'** and **124b"** of support **124b**. Each pair of arms is attached at its distal end to a block **128**. As noted, element **130** is placed so as to rest upon and be attached to blocks **128**. If this is position is considered the neutral or ground position, arms **126** are constructed so as to have sufficient flexibility in the z-axis to deform from this neutral position upon the addition of liquid to some of wells **117**.

Attached to the upper and lower surfaces of each arm **126**, in the free region of the arm but, in some embodiments, near the point at which the arm is attached to frame **122**, there is a thin, flat strain gauge **144**. Each of the strain gauges is electrically connected (e.g. by thin wires, not shown) to a thin, flat electronic card **146** located below the lower arms **126b**. Preferably, electronic cards **146** are positioned so as to minimize the length of the connections between the strain gauges **144** and the cards **146**. Cards **146** are electrically coupled to a processor (not shown). It will be appreciated that use of strain gauges **144** and cards **146** allows for correlation of the deflection of the arms **126** to the change in electrical resistance in a circuit, for example measured using a Wheatstone Bridge, which is also located on card **146**, allowing calculation of the mass of the fluid added to the wells. As such, arms **126** together with strain gauges **144** form a signal provider, for providing a signal indicative of a change in the amount of fluid in one or more of the wells. If the density of the fluid is known, this facilitates computation of the volume of fluid added. In some embodiments, plate **100** further includes a power supply (not shown) such as a rechargeable battery, for example connected to electronic card **146**, which power supply provides power to electronic components of plate **100** and may be recharged when plate **100** is connected to a power source or computation device via a suitable port (not shown).

For example, if rows A through L of plate **100** are filled sequentially using an 8-tip pipette, it is possible to iteratively calculate the amount of fluid added to each row, and therefore to identify in real time, on a row-by-row basis, when an incorrect amount of fluid has been added to the row. This allows that particular row to be discarded from the calculations at the end of the experiment, rather than discarding the results for the entire plate. Preferably, the apparatus used to add fluid to the wells will be equipped with control software to allow the affected row only to be excluded from further manipulations during the remainder of the experiment, such as the addition of reagents and reactants. It will also be appreciated that even if all the wells are filled simultaneously, the use of plate **100** in conjunction with appropriate software to identify in real time the addition of an incorrect amount of fluid to the plate enables the user to stop running experiments using that particular plate, thus avoiding waste of reagents, reactants and the like in downstream experiments.

In accordance with some embodiments of the invention, plate **100** includes means for heating and, optionally, cooling individual wells. Such heating means may take the form of, for example, (a) a heating coil disposed around at least a portion of the well, or (b) a Peltier device, sometimes called a Peltier heat pump or thermoelectric cooler. As will be appreciated, a Peltier device can be used to cool as well as to heat an individual well, as well as to sense or monitor the temperature in the well or in the vicinity thereof. In this way, the temperature in individual wells may be controlled, for example the temperature in each well may be maintained at 37°C ± 0.5°C.

In one embodiment, a single heating coil or Peltier device may be disposed on the well-containing element **130** for collectively heating two or more wells **117**. In another embodiment, heating coils or Peltier devices may be disposed on one or more individual wells **117** for heating thereof.

It will also be appreciated that if the temperature of the wells is periodically measured, and if the device used to measure the temperature is coupled to a controller that controls the heating means for each individual well, then the individual well heating means, used in conjunction with the periodic measuring of temperature in individual wells, can provide a way to improve control over the conditions in a given well. Thus, for example, plates **100** having such heating means may be stored in an incubator and the temperature of the wells monitored periodically and the temperature of individual wells adjusted, if necessary, by heating (or cooling) individual wells. Alternatively, the heating means may themselves be used to effect incubation, for example temperature monitoring and adjustment may be effected frequently, say for example every 15, 10 or 5 minutes, to maintain the temperature in particular wells at e.g. 37°C ± 0.5°C so as to effect incubation. Thus, by equipping the plate **100**, the well-containing element **130**, or the wells **117** with individual heating elements for each well, in cases in which it is found that the temperature is incorrect, the temperature may be adjusted and controlled.

It will be appreciated that since reagents and other fluids may be added into or removed from wells **117** in well-containing element **130** which may be removed from plate **100** and optionally disposed of, plate **100** may be used multiple times and/or for multiple experiments, provided that well-containing element **130** are replaced between each use of the plate **100**.

Reference is now made to Figs. 3A to 3G, which show a multi-well plate **300** and components thereof, constructed and operative in accordance with embodiments of the invention. Specifically, Figs. 3A and 3B are perspective views of multi-well plate **300**, Fig. 3C is an exploded view of the multi-well plate **300**, Fig. 3D is an enlarged perspective view of supports, arms, and blocks forming part of the multi-well plate **300**, and Figs. 3E, 3F, and 3G are sectional views of the multi-well plate **300** taken along section lines IIIE-IIIE, IIIF-IIIF, and IIIG-IIIG in Fig. 3A.

As shown in Figs. 3A and 3B, plate **300** is designed for use with existing equipment and is therefore sized in accordance with standard plate sizes currently in use, with its wells similarly spaced. Thus, when assembled, plate **300** looks similar to a typical 96-well plate, with an upper surface **312**, a lower surface **314**, a plurality of sides **316** between surfaces **312** and **314**, and having a plurality of wells **317** formed therein.

As shown in Fig. 3C, which is an exploded view of plate **300**, plate **300** is actually formed of several parts. Sides **316** are part of a frame **322**, which has formed on an inner portion thereof, at the lengthwise ends of the frame, a pair of supports **324a** and **324b** each including a plurality of “stairs” **325**, which supports will be explained in more detail in connection with Figs. 3D, 3F, and 3G. Frame **322** includes end walls **322a** and **322d** disposed at longitudinal ends of the frame, as well as longitudinal walls **322b** and **322c**.

Each of the supports **324a** and **324b** has attached thereto multiple flexible arms **326**, wherein each arm is attached at the proximal end thereof to one of the supports, and is attached the distal end thereof to a block **328**. The structure and functionality of flexible arms **326** and of blocks **328** will be described in further detail hereinbelow with reference to Figs. 3D, 3F, and 3G. The flexible arms **326** may be made of a suitable material, generally metal or plastic, which is suitably flexible as to be sensitive to the addition or removal of a small volume to or from the wells, as will be explained in more detail below. For example, flexible arms **326** would be sensitive to the addition to the wells of less than 300 microliters (μl), less than 250 μl, less than 200 μl, less than 150 μl, less than 100 μl, less than 75 μl, less than 50 μl, less than 45 μl, less than 40 μl, less than 35 μl, less than 30 μl, less than 25 μl, less than 20 μl, less than 15 μl, less than 10 μl, less than 5 μl, less than 4 μl, less than 3 μl, less than 2 μl, or less than 1 μl.

The arms **326** may be attached to blocks **328** by suitable means, such as adhesive or in some cases melting or welding.

Plate **300** further includes eight identical well-supporting elements **330**, each including a longitudinal aperture **333** suited to receive a well-containing element **348** therein. Each well-containing element **348** has twelve cylinders **320**, forming side walls of tubular wells **317**, formed therein. Each of elements **330** also has a pair of flanges **332**, one flange at each of the longitudinal ends thereof. Well-supporting elements **330** may be formed of plastic or another suitable material and may contain other materials such as glass. When assembled, each flange **332** rests on, and preferably is attached to, two blocks **328**, one block per flange; the manner in which blocks **328** are held in place relative to frame **322** will be discussed in more detail below.

A plurality of bottom pieces **334**, which are pieces of plastic or glass approximately 170-1000 microns in thickness, are sealingly attached to the undersides of well-containing elements **348**, so as to form the bottom of each well **317** in a manner that seals each well at that end of the well. In the illustrated embodiment, three pieces **334**, each sealing four wells **317**, are attached to each well containing element **348**. That said, any suitable arrangement or number of bottom pieces may be used, e.g. all the wells in a single well containing element **348** may be sealed with a single piece **334**, each well **317** may be sealed with an individual bottom piece **334**, or six bottom pieces **334** may be used to seal pairs of wells **317** in a single well containing element **348**. In some embodiments, frame **322** includes, adjacent a bottom portion thereof, partitions **350** which divide the frame into sections **352**, each section **352** being suitably sized to fit one of bottom pieces **334**, and the wells **317** attached thereto.

It will be appreciated that when assembled together, the circumference of the uppermost portion of the collection of well-supporting elements **330**, including the flanges **332**, is slightly less than the inner circumference of frame **322**, so that when the flanges **332** of well-supporting elements **330** rest on blocks **328**, there is a small gap **338** between the well-supporting elements **330** and the frame **322** (see Fig. 3E), as well as between elements

330 themselves (see Fig. 3E). The presence of gaps **338** allows for movement of the well-supporting elements **330** along the vertical axis and for concomitant deformation of arms **326**, as will be explained below. In order to seal the gaps **338** without inhibiting such movement, a very thin (for example, approximately 7 micron) film **340** of a flexible material, such as a suitable plastic, is attached to an upper edge **342** of the frame **322** and to at least a portion of the upper surface of well-supporting elements **330**. Film **340** includes eight rectangular openings **343** which are aligned with the apertures **333** in the assembled well-supporting elements **330**.

Film **340**, well supporting elements **330**, bottom pieces **334**, and frame **322**, are attached to each other using any suitable means, such as soldering, adhering, melting, bonding, or any other suitable attachment mechanism. It will be appreciated that in the embodiment shown, well-containing elements **348** may be easily removed from well supporting elements **330**, without damaging the sensitive structure and functionality of arms **326**, which is described in further detail hereinbelow.

As noted, when plate **300** is assembled, well-supporting elements **330** rest on, and are attached at each of their longitudinal ends to, a pair of blocks **328**. This restricts the motion of elements **330** in the lateral and longitudinal (x- and y-) directions, but allows for motion in the vertical (z-) direction. Thus, when fluid is placed into (or removed from) a well in a well containing element **348** located in any of well supporting elements **330**, the increase (or decrease) in the weight of the fluid will result in the deformation of arms **326** attached to that well supporting element **330**. It will be appreciated that typically not more than several hundred microliters, and in some applications only a few microliters or less, are added to a given well **317**. Consequently, the flexible arms **326** should be of suitable flexibility to deflect in response to the addition (or removal) of such quantities of fluid (or the equivalent masses) to (or from) the wells. For example, less than 300 microliters (μl), less than 250 μl, less than 200 μl, less than 15 μl, less than 100 μl, less than 75 μl, less than 50 μl, less than 45 μl, less than 40 μl, less than 35 μl, less than 30 μl, less than 25 μl, less than 20 μl, less than 15 μl, less than 10 μl, less than 5 μl, less than 4 μl, less than 3 μl, less than 2 μl, or less than 1 μl of fluid may be added to a well **317** at any given time.

Attached to the upper and lower face of each arm **326** near the point at which the arm is attached to one of "stairs" **325** (which will themselves be described in more detail below) is a thin, flat strain gauge **344**. It will be appreciated that alternatively, rather than place a strain gauge on the upper face and one on the lower face an arm, two strain gauges may be placed on the upper face of an arm, one near where the arm is attached to frame **322** and the other near where the arm is attached to block **328**, or two strain gauges may be placed on the lower face of an arm only, one near where the arm is attached to frame **322** and the other near where the arm is attached to block **328**.

Each strain gauge **344** is electrically coupled (e.g. by thin wires, not shown) to a thin, flat electronic card **346** located below lower arms **326**. Preferably, electronic cards **346** are positioned so as to minimize the length of the connections between the strain gauges **344** and the cards. Cards **346** are electrically coupled, via a plurality of wires **356**, to a port **358** located on frame **322**, which port is configured for connection to an electrical port of a suitably equipped plate base and data reader, as described hereinbelow with reference to Figs. 8 to 9B. In some embodiments, the data reader may run a graphical user interface as described hereinbelow with reference to Figures 5A to 7. Preferably, port **358** does not extend beyond, and preferably is flush with, the outer surface of frame **322**, and does not affect the overall dimensions of plate **300**, thus allowing use of standard equipment. In some embodiments, plate **300** further includes a power supply (not shown) such as a rechargeable battery, for example connected to electronic card **346**, which power supply provides power to electronic components of plate **300** and may be recharged when plate **300** is connected to a power source or computation device via port **358** or a USB port.

Electronic cards **346** may have located thereon an element for measuring electrical resistance in a circuit, such as a Wheatstone Bridge. The deflection of the arms **326** caused by a change of the volume, or weight, contained in one or more of wells **317**, leads to a change in the length of the resistors in corresponding strain gauges **344**. This change in strain gauges **344** is correlated to the change in electrical resistance in a circuit, which change is measured by the elements on electronic cards **346**, using e.g. a Wheatstone Bridge. The change in the electrical resistance in the circuit allows for calculation of the mass of the fluid added to (or removed from) the wells **317**. Specifically, a greater mass of fluid added to (or removed from) the wells, results in a greater change in the deflection of arms **326**, which in turn leads to a greater change in the electrical resistance in the circuit. Thus, measurement of changes in the electrical resistance in the circuit, is indicative of, and allows for calculation of the change in the mass of fluid in the wells. If the density of the fluid is known, this facilitates computation of the volume of fluid added (or removed). As such, arms **326** together with strain gauges **344** form signal providers, for providing signals indicative of a change in the amount of fluid in one or more of the wells.

For example, if columns A through L of plate **300** are filled sequentially using an 8-tip dispenser, it is possible to iteratively calculate the amount of fluid added to each well in each column, and thereby to identify in real time, on a well-by-well basis, when an incorrect amount of fluid, either too much or too little, has been added to a particular well. Preferably, the apparatus used to add fluid to the wells will be equipped with control software that will allow the apparatus used to correct for the error. In the case in which too little fluid has been added, additional fluid may be dispensed to the affected well so as to reach the correct amount of fluid in the well, and/or the software may be able to adjust for the error by adding proportionately less reagent or reactant liquid to the affected well in later manipulations. Similarly, if too much fluid has been added to a particular well, the addition of reagents or reactants in further manipulations may be scaled up appropriately.

Alternately, the affected well, or well-containing element, may be included in further manipulations during the remainder of the experiment, and the results of the particular well may be used in the calculations at the end of the experiment by adjusting the calculations to account for the incorrect volume used while conducting the experiment.

As a further alternative, identification of a particular well as having had an incorrect amount of fluid added thereto allows that particular well to be discarded from the calculations at the end of the experiment, rather than discarding the results for the entire row or column in which the well is located, or for the entire plate.

It will also be appreciated that even if all the wells are filled simultaneously, the use of plate **300** in conjunction with appropriate software to identify in real time the addition of an incorrect amount of fluid to a specific well supporting element **330**, enables the user to stop running experiments using wells in that particular element **330** or in the plate **300**, thus avoiding waste of reagents, reactants and the like in downstream experiments.

Additionally, electronics cards **346** may have electrically coupled thereto components for manipulating data collected by the various sensor elements coupled to the cards, such as an analog-to-digital converting component for converting the analog signals of the Wheatstone Bridge to digital signals, and normalizing components for normalizing the collected signals.

In some embodiments, plate **300** also includes one or more temperature sensors (not shown), electrically coupled to electronics cards **346**, and configured to provide an indication of the temperature, or of a temperature change, in the vicinity of one or more of wells **317**. It is appreciated that a temperature change in the system may affect the strain gauges **344**, and therefore knowledge of and computational consideration of changes to the temperature can allow for more accurate identification of the weight in a well and for ensuring a stable temperature of the sample in the well, which may be sensitive to temperature changes.

In accordance with some embodiments of the invention, plate **300** includes means for heating and, optionally, cooling individual wells. Such heating means may take the form of, for example, (a) a heating coil disposed around at least a portion of the well, or (b) a Peltier device, sometimes called a Peltier heat pump or thermoelectric cooler. As will be appreciated, a Peltier device can be used to cool as well as to heat an individual well, as well as to sense or monitor the temperature in the well or in the vicinity thereof. In this way, the temperature in individual wells may be controlled, for example the temperature in each well may be maintained at 37°C ± 0.5°C.

In some embodiments, a heating coil or Peltier device may be disposed on some or all of the well-supporting elements **330**, for collectively heating two or more the wells supported by that well-supporting element. In other embodiments, heating coils or Peltier devices may be disposed on some or all of the individual wells **317**, for example on cylinders **320** thereof, such that each heating coil or Peltier device heats a specific well **317** on or in which it is disposed.

It will also be appreciated that if the temperature of the wells is periodically measured, and if the device used to measure the temperature is coupled to a controller that controls the heating means for each individual well, then the individual well heating means, used in conjunction with the periodic measuring of temperature in individual wells, can provide a way to improve control over the conditions in a given well. Thus, for example, plates **300** having such heating means may be stored in an incubator and the temperature of the wells monitored periodically and the temperature of individual wells adjusted, if necessary, by heating (or cooling) individual wells. Alternatively, the heating means may themselves be used to effect incubation, for example temperature monitoring and adjustment may be effected frequently, say for example every 15, 10 or 5 minutes, to maintain the temperature in particular wells at e.g. 37°C ± 0.5°C so as to effect incubation. Thus, by equipping the plate **300**, the well-supporting elements **330**, or the wells **317** with individual heating elements for each well, in cases in which it is found that the temperature is incorrect, the temperature may be adjusted and controlled.

Reference is now made to Fig. 3D, which is an enlarged perspective view of the supports **324a** and **324b**, including arms **326** and blocks **328**, and to Figures 3F and 3G, which are sectional illustrations taken along section lines IIIF-IIIF and IIIG-IIIG respectively in Fig. 3A. Figs. 3D, 3F, and 3G show in greater detail the supports **324a** and **324b**, the arms **326**, the blocks **328**, and the attachment of the arms **326** to the supports.

As seen, eight blocks **328** are located near each longitudinal end of frame **322**, so that each well supporting element **330** rests on and is attached to two blocks **328**, one at each longitudinal end of element **330**. In order to accommodate eight blocks at each end of the frame **322**, the supports **324a** and **324b** and the blocks **328** are designed in a step-stair fashion, as described hereinbelow. A first support **324a** protrudes from the inner wall **322d** of one longitudinal end of frame **322** as well as from the longitudinal wall **322b** adjacent thereto. At the other longitudinal end of frame **322**, a second support **324a** protrudes from longitudinal wall **322b** but is spaced slightly from the inner wall **322a**. In both cases, in order to accommodate four pairs of arms **326** and to facilitate appropriate positioning of the blocks **328**, support **324a** is constructed in stair-step fashion, having two sets of “stairs”, an upper set **360a** and a lower set **360b**, formed in parallel. All of the “stairs” of support **324a** protrude from inner wall **322b** of frame **322**, but whereas all of the “stairs” have the same width along the longitudinal axis of frame **322**, the uppermost “stairs” of each set, **325a** and **325a’**, protrude the least from inner wall **322b**, “stairs” **325b** and **325b’** protrude slightly more, “stairs” **325c** and **325c’** protrude more, and “stairs” **325d** and **325d’** protrude to about halfway between wall **322b** and wall **322c**.

The distance between the upper surfaces of each pair of corresponding “stairs” (i.e. between **325a** and **325a’**, between **325b** and **325b’**, between **325c** and **325c’**, and between **325d** and **325d’**) is the same as the distance between the lower surfaces of each pair of arms. A first pair of arms **326a** and **326a’** is thus attached at the proximal ends thereof to “stairs” **325a** and **325a’**, a second pair of arms **326b** and **326b’** is attached at the proximal ends thereof to “stairs” **325b** and **325b’**, a third pair of arms **326c** and **326c’** is attached at the proximal ends thereof to “stairs” **325c** and **325c’** and a fourth pair of arms **326d** and **326d’** is attached at the proximal ends thereof to “stairs” **325d** and **325d’**. The “stairs” are spaced from each other such that the arms in each pair of arms are parallel to one another, and so that in the course of normal use, each pair of arms may move without contacting another pair of arms.

As seen in Figs. 3D and 3F, at their distal ends, the arms **326** are attached to blocks **328**, such that each pair of arms is attached in parallel to a single block **328**. In order to facilitate a compact arrangement of the arms, each block **328** comprises an upper inner surface for attachment of a first arm thereto, a lower inner surface for attachment of a second arm thereto, and a recess allowing the additional arms to pass therethrough. Thus, arm **326a** attached to stair **325a** is attached to an upper inner face **328a’** of block **328a** which is closest to the center of the frame, and block **328a** is constructed with a recess **328a”** in order to allow arms **326b**, **326c** and **326d** to pass therethrough without touching each other and without touching block **328a**. Similarly, arm **326a'** attached to stair **325a'** is attached at its distal end to the bottommost surface **328a'''** of block **328a**, with arms **326b'**, **326c'** and **326d'** passing thereunder in parallel to one another. Block **328b** is similarly constructed, to allow for attachment of arms **326b** and **326b'** at surfaces **328b'** and **328b'''** respectively and to allow passage therethrough of arms **326c** and **326d** and passage of arms **326c'** and **326d'** thereunder. Block **328c** is constructed to allow for attachment of arms **326c** and **326c'** at surfaces **328c'** and **328c'''** and to allow passage therethrough of arm **326d** and passage of arm **326d'** thereunder. Block **328d**, which of the four blocks **328a**, **328b**, **328c** and **328d** is closest to wall **322c**, is constructed to allow attachment of arms **326d** and **326d'** at surfaces **328d'** and **328d'''** respectively.

It will be appreciated that as a result of this construction, the sizes of the upper portion of blocks **328a**, **328b**, **328c** and **328d** differ from one another. It will also be appreciated that each of blocks **328a**, **328b**, **328c** and **328d** are of different overall height, and while it is preferable that the location of the uppermost surface of each block, relative to the top of the frame **322**, be the same, there can be slight differences in the location of the uppermost surface of each block, as the software used to calculate the displacement and thus the mass of fluid added to the wells can be programmed to account for such differences. For the same reason, it is not necessary that all the blocks **328** have the same mass.

As seen clearly in Figure 3G, support **324b** is arranged in an analogous manner to that of support **324a**, in the opposite direction. At one longitudinal end of the frame **322**, a first support **324b** protrudes from the inner wall **322a** of one longitudinal end of frame **322** as well as from the longitudinal wall **322c** adjacent thereto. At the other longitudinal end of frame **322**, a second support **324b** protrudes from longitudinal wall **322c** but is spaced slightly from inner wall **322d**. Near wall **322d**, support **324b** is spaced therefrom so as to accommodate arms **326a**, **326a'**, **326b**, **326b'**, **326c**, **326c'**, **326d** and **326d'**. In order to accommodate four pairs of arms **326** and to facilitate appropriate positioning of the blocks **328**, support **324b** is constructed in stair-step fashion, having two sets of "stairs", an upper set **362a** and a lower set **362b**, formed in parallel. All of the "stairs" of support **324b** protrude from inner walls **322a** (or **322d**) and **322c** of frame **322**, but whereas all of the "stairs" have the same width and thus project the same distance from wall **322a** (or **322d**), the uppermost "stairs" of each set, **325e** and **325e'**, protrude the least from inner wall **322c**, "stairs" **325f** and **325f'** protrude slightly more, "stairs" **325g** and **325g'** protrude more, and "stairs" **325h** and **325h'** protrude to about halfway between wall **322c** and wall **322b**.

The distance between the upper surfaces of each pair of corresponding "stairs" (i.e. between **325e** and **325e'**, between **325f** and **325f'**, between **325g** and **325g'**, and between **325h** and **325h'**) is the same as the distance between the lower surfaces of each pair of arms. A first pair of arms **326e** and **326e'** is thus attached at the proximal ends thereof to "stairs" **325e** and **325e'**, a second pair of arms **326f** and **326f'** is attached at the proximal ends thereof to "stairs" **325f** and **325f'**, a third pair of arms **326g** and **326g'** is attached at the proximal ends thereof to "stairs" **325g** and **325g'** and a fourth pair of arms **326h** and **326h'** is attached at the proximal ends thereof to "stairs" **325h** and **325h'**. The "stairs" are spaced from each other such that the arms in each pair of arms are parallel to one another, and so that in the course of normal use, each pair of arms may move without contacting another pair of arms.

As seen in Figures 3D and 3G, at their distal ends, the arms **326** are attached to blocks **328**, each pair of arms being attached in parallel to a single block **328**. In order to facilitate a compact arrangement of the arms, each block **328** comprises an upper inner surface for attachment of a first arm thereto, a lower inner surface for attachment of a second arm thereto, and a recess allowing the additional arms to pass therethrough. Thus, arm **326e** attached to stair **325e** is attached to an upper inner face **328e'** of block **328e** which is closest to the center of the frame, and block **328e** is constructed with a recess **328e"** in order to allow arms **326f**, **326g** and **326h** to pass therethrough without touching each other and without touching block **328e**. Similarly, arm **326e'** attached to stair **325e'** is attached at its distal end to the bottommost surface **328e'''** of block **328e**, with arms **326f'**, **326g'** and **326h'** passing thereunder in parallel to one another. Block **328f** is similarly constructed, to allow for attachment of arms **326f** and **326f'** at surfaces **328f'** and **328f'''** respectively and to allow passage therethrough of arms **326g** and **326h** and passage of arms **326g'** and **326h'** thereunder. Block **328g** is constructed to allow for attachment of arms **326g** and **326g'** at surfaces **328g'** and **328g'''** and to allow passage therethrough of arm **326h** and passage of arm **326h'** thereunder. Block **328h**, which of the four blocks **328e**, **328f**, **328g** and **328h** is closest to wall **322b,** is constructed to allow attachment of arms **326h** and **326h'** at surfaces **328h'** and **328h'''** respectively.

It will be appreciated that as a result of this construction, the sizes of the upper portion of blocks **328e**, **328f**, **328g** and **328h** differ from one another. It will also be appreciated that each of blocks **328e**, **328f**, **328g** and **328h** are of different overall height, and while it is preferable that the location of the uppermost surface of each block, relative to the top of the frame **322**, be the same, there can be slight differences in the location of the uppermost surface of each block, as the software used to calculate the displacement and thus the mass of fluid added to the wells can be programmed to account for such differences. For the same reason, it is not necessary that all the blocks **328** have the same mass.

It will be appreciated that since reagents and other fluids are added into or removed from wells **317** in well-containing elements **348**, which are removable from plate **300**, plate **300** may in principle be used multiple times and/or for multiple experiments, provided that well-containing elements **348** are replaced between each use of the plate **300**.

Reference is now made to Figs. 4A – 4C, which show a multi-well plate **400** and components thereof, constructed and operative in accordance with embodiments of the teachings herein. Specifically, Fig. 4A is a perspective view of the multi-well plate **400**, Fig. 4B is an exploded view of the multi-well plate **400**, and Fig. 4C is a sectional view of the multi-well plate **400**, taken along section lines IVC-IVC in Fig. 4A.

As seen in Fig. 4A, when assembled, plate **400** looks generally similar to plate **300** of Figs. 3A-3G. However, it will also be apparent from Fig. 4B and from the description herein that although the purposes and uses of plates **300** and **400** are similar, the construction of plate **400** is somewhat different from that of plate **300**.

Plate **400** is designed for use with existing equipment and is therefore sized in accordance with standard plate sizes currently in use, with its wells similarly spaced; thus when assembled, plate **400** looks similar to a typical 96-well plate, with an upper surface **412**, a lower surface **414**, a plurality of sides **416** between surfaces **412** and **414**, and having a plurality of wells **417** formed therein.

As shown in Fig. 4B, which is an exploded view of plate **400**, plate **400** is actually formed of several parts. Sides **416** are part of a frame **422**, which also includes a well-defining skeleton **450**, which defines 96 bores **452** in frame **422**, each bore having a generally circular cross section along the horizontal plane, and a generally rectangular cross section along the vertical plane.

Plate **400** further includes 96 individual identical cylindrical well supporting elements **430**, each including an aperture **433**, each sized to fit in one of bores **452** and suited to receive a single well-defining element **419**, which may be easily removed from a well supporting element **430** in which it is accommodated. Each individual well **417** is defined in by well-defining element **419** which is formed of a cylindrical portion **466** and is sealed at its bottom with a generally circular bottom piece **434**.

Each well-supporting element **430** is adhered to, or otherwise attached to, two arms **426** and **426’** located in plates **474** and **476**, respectively. Arms **426** and **426’** may be, but are not necessarily, formed integrally in plates **474** and **476**. For ease of reference, henceforth arms **426** and **426'** will be referred to as **426**, unless specifically noted otherwise. The flexible arms **426** may be made of a suitable material, generally metal or plastic, which is suitably flexible as to be sensitive to the addition or removal of a small volume to or from the wells, as will be explained in more detail below.

Arm **426** is generally flat and, as shown in the inset in Fig. 4B, each arm **426** and **426'** has a generally rectangular portion **426a** from which extend, at two adjacent corners thereof, protrusions, which form a partial annulus **426b** that extends more than half-way but not completely around cylindrical well supporting element **430**, and is sized to have an inner circumference slightly larger than the outer circumference of cylindrical well supporting element **430**. Within partial annulus **426b** is formed a ring **426c**, which is sized to have the same inner circumference as cylindrical well supporting element **430**. Cylindrical well supporting element **430** is thus affixed to ring **426c** (the upper surface of cylindrical well supporting element **430** being attached to the lower surface of the ring **426c** of arm **426** and the lower surface of cylindrical well supporting element **430** being attached to the upper surface of the ring **426c** of arm **426'**), for example by an adhesive. This construction enables a pair of arms **426** and **426'** to hold well supporting element **430** in place in the x- and y-axes but allows movement of the element and the well contained therein along the z-axis, with concomitant bending of arms **426**.

In order to maximize and localize the strain felt by the arms at rectangular portions **426a** and partial annuluses **426b**, the partial annuluses **426b** and rectangular portions **426a** are formed of a suitably thin and flexible material, such as metal or plastic. In some embodiments, to facilitate bending, arms **426** and **426'** are made thinner than the rest of plates **474** and **476**, respectively. In some embodiments, portions of plates **474** and **476** exterior to arms **426** and **426'** are adhered, or otherwise attached, to frame **422** and/or to an electronic card **446** (described in more detail hereinbelow), so as to strengthen portions of the plates **474** and **476** which need not bend, thereby localizing the strain felt by the arms **426**.

It will be appreciated that typically not more than several hundred microliters, and in some applications only a few microliters or less of fluid are added to a given well. For example, less than 300 microliters (μl), less than 250 μl, less than 200 μl, less than 150 μl, less than 100 μl, less than 75 μl, less than 50 μl, less than 45 μl, less than 40 μl, less than 35 μl, less than 30 μl, less than 25 μl, less than 20 μl, less than 15 μl, less than 10 μl, less than 5 μl, less than 4 μl, less than 3 μl, less than 2 μl, or less than 1 μl may be added to a given well. Consequently, the flexible arms **426** should be of suitable flexibility to deflect in response to the addition (or removal) of such quantities of fluid (or the equivalent masses) to (or from) the wells.

When assembled together, the outer circumference of cylindrical well supporting elements **430** is slightly smaller than the inner circumference of bores **452**, thereby forming small gaps **438** between the well-defining skeleton **450** and the cylindrical well supporting elements **430** (see Fig. 4C). The presence of these gaps allows for independent movement of each well-supporting element **430** along the vertical (z-) axis and concomitant deformation of arms **426**, as will be explained below.

In order to seal the gaps **438** without inhibiting such vertical movement, a very thin (e.g. approximately 7 micron) film **440** of a flexible material, such as a suitable plastic, is attached to the upper edge **442** of the frame **422**, and in some embodiments also to an upper card **446** (described in more detail hereinbelow). Film **440** includes 96 circular openings **443** which are aligned with the apertures **447** in cards **446** (described hereinbelow), with rings **426d** discussed in more detail below, and with apertures **433** in the assembled well-supporting elements **430**.

Film **440** is attached to frame **422** using any suitable means, such as soldering, adhering, melting, bonding, or any other suitable attachment mechanism. It will be appreciated that in the embodiment shown, each well-defining element **419** may be easily removed from the well-supporting element **430** in which it is positioned, without damaging the sensitive structure and functionality of arms **426**.

Each arm **426** has a pair of flat strain gauges **444** attached alongside one another on the upper face thereof at the rectangular portion **426a**. Alternately, the strain gauges may be attached to upper and lower faces of rectangular portion **426a**. Each strain gauge is electrically coupled, for example via wires (not shown), to an electronic card **446**. In some embodiments, arms **426** may be formed with holes **445** to facilitate the passage of such wires therethrough. Electronic cards **446** are positioned so as to minimize the length of the connections between the strain gauges **444** and the cards.

In some embodiments, such as that shown in an enlarged portion of Figure 4B, which in order to shown certain details is rotated 90 degrees about a longitudinal axis of the well-supporting element relative to the rest of the Figure 4B, well-supporting elements **430** may include protecting protrusions **431a** at top and bottom rims thereof, which protecting protrusions are designed to protect strain gauges **444**. Additionally, in some embodiments, well-supporting elements **431** may include top and bottom protrusions **431b**, rotationally offset from protrusions **431a** by 180 degrees, which protrusions **431b** engage plates **474** and **476** and limit the range of deflection of arms **426**.

In some embodiments, cards **446** (each of which may actually be a plurality of cards) are electrically coupled, via a plurality of wires (not shown) to a port **458** located on frame **422**, which port is configured for connection to an electrical port of a suitably equipped plate base and data reader, as described hereinbelow with reference to Figures 8 to 9A. In some embodiments, cards **446** (each of which may actually be a plurality of cards) are electrically coupled, via a plurality of wires (not shown) to a USB port (not shown), or to a similar input/output port such as is presently known or as may be developed in the future, located on frame **422**, which port is configured for connection of plate **400** to a power source and/or to a computation device. The data reader and/or the computation device to which plate **400** may be connected may run a Graphical User Interface as described hereinbelow with reference to Figures 5A to 7. Preferably, port **458** and/or the USB port (not shown) does not extend beyond, and preferably is flush with, the outer surface of frame **422** and does not affect the overall dimensions of plate **400**, thus allowing use of standard equipment.

In some embodiments, plate **400** further includes a power supply (not shown) such as a rechargeable battery, for example connected to electronic card **446**, which power supply provides power to electronic components of plate **400** and may be recharged when plate **400** is connected to a power source or computation device via port **458** or a USB port.

Each electronic card **446** includes 96 apertures **447** having a circular cross-section, such that when plate **400** is assembled, apertures **447** are aligned with rings **426d**, with sections **452**, and with well supporting elements **430**. Arranged near apertures **447** are an additional ninety-six smaller apertures **448**. Apertures **448** allow for the passage of wires (not shown) connecting the strain gauges **444** to cards **446**.

Electronic cards **446** may have located thereon an element for measuring electrical resistance in a circuit, such as a Wheatstone Bridge. The deflection of the arms **426** leads to a change in the length of the resistors in corresponding strain gauges **444**, which is correlated to the change in electrical resistance in a circuit, which change is measured by the elements on electronic cards **446**, using e.g. a Wheatstone Bridge. The change in the electrical resistance in the circuit allows for calculation of the mass of the fluid added to (or removed from) each well. Specifically, a greater mass of fluid added to (or removed from) the well, results in a greater change in the deflection of arms **426**, which in turn leads to a greater change in the electrical resistance in the circuit. Thus, measurement of changes in the electrical resistance in the circuit is indicative of a change in the mass of fluid in the well, and allows for calculation of this change. If the density of the fluid is known, this facilitates computation of the volume of fluid added (or removed). As such, arms **426** together with strain gauges **444** form a signal provider, for providing a signal indicative of a change in the amount of fluid in a well associated therewith. In some embodiments, the electronic cards **446** include a storage component, for storing signals generated by the signal provider, for example when the plate **400** is not connected to a data reader such as the data reader of Figure 8. Such stored signals may then be retrieved from the cards **446** by a data reader when the plate **400** is connected thereto.

For example, if rows A through L of plate **400** are filled sequentially using an 8-tip dispenser, or if individual wells are filled sequentially, or even if all the wells are filled simultaneously, it is possible to calculate the amount of fluid added to each well, and thereby to identify in real time, on a well-by-well basis, when an incorrect amount of fluid, either too much or too little, has been added to a particular well.

Preferably, the apparatus used to add fluid to the wells will be equipped with control software that will allow the apparatus used to correct for the error. In the case in which too little fluid has been added, additional fluid may be dispensed to the affected well so as to reach the correct amount of fluid in the well, and/or the software may be able to adjust for the error by adding proportionately less reagent or reactant liquid to the affected well in later manipulations. Similarly, if too much fluid has been added to a particular well, the addition of reagents or reactants in further manipulations may be scaled up appropriately.

Alternately, the affected well, or well containing element, may be included in further manipulations during the remainder of the experiment, and the results of the particular well may be used in the calculations at the end of the experiment by adjusting the calculations to account for the incorrect volume used while conducting the experiment. As a further alternative, identification of a particular well as having had an incorrect amount of fluid added thereto allows that particular well to be discarded from the calculations at the end of the experiment, rather than discarding the results for the entire row or column in which the well is located, or for the entire plate.

It will also be appreciated that even if all the wells are filled simultaneously, the use of plate **400** in conjunction with appropriate software to identify in real time the addition of an incorrect amount of fluid to a specific well supporting element **430**, enables the user to stop running experiments using the well in that particular element or in the plate **400**, thus avoiding waste of reagents, reactants and the like in downstream experiments.

It will further be appreciated that the plate **400** may also operate without being continuously monitored. In such cases, a baseline measurement of a well or of the plate is obtained from the signal provider. Subsequently, the plate may be disconnected from the power source and/or the data reader or processor to which the signals are provided, and fluid added to or removed from the plate. The plate may then be reconnected to the power source and/or the data reader or processor, and a second signal obtained from the signal provider. Comparison of the initial and second signals enables identification of specific wells where an incorrect amount of fluid is present, allowing for those wells to be discarded from further experiments and computations.

In some embodiments, plate **400** also includes one or more temperature sensors (not shown), electrically coupled to electronics cards **446**, and configured to provide an indication of the temperature, or of a temperature change, in the vicinity of one or more of wells **417**. It is appreciated that a temperature change in the system may affect the strain gauges **444**, and therefore knowledge of, and computational consideration of changes to the temperature can allow for more accurate identification of the weight in a well and for ensuring a stable temperature of the sample in the well, which may be sensitive to temperature changes.

Additionally, electronics cards **446** may have electrically coupled thereto components for manipulating data collected by the various sensors elements coupled to the cards, such as an analog-to-digital converting component for converting the analog signals of the Wheatstone Bridge to digital signals, and normalizing components for normalizing the collected signals.

Because the deflection of each arm can be calculated, and thus the amount of material or volume of liquid added to each individual well can be calculated in real time, the use of plate **400** facilitates the correcting of the amount of material to be added to each well, or the ignoring of an individual well, rather than a row of wells or the whole plate, in further experimental manipulations. Also, with this configuration it is possible to observe loss of material from a given well over time, as will be described hereinbelow with reference to Figures 5A-7.

In accordance with some embodiments of the invention, plate **400** includes means for heating and, optionally, cooling individual wells. Such heating means may take the form of, for example, (a) a heating coil disposed around at least a portion of the well, or (b) a Peltier device, sometimes called a Peltier heat pump or thermoelectric cooler. As will be appreciated, a Peltier device can be used to cool as well as to heat an individual well, as well as to sense or monitor the temperature in the well or in the vicinity thereof. In this way, the temperature in individual wells may be controlled, for example the temperature in each well may be maintained at 37°C ± 0.5°C.

In one embodiment, a Peltier device for each well may be built into one or both electronics cards **446** shown in Fig. 4B, for example adjacent each aperture **447** for heating of a specific well-supporting element **430** or well-defining element **419** disposed in the aperture. Alternatively, a heating coil or Peltier device may be disposed on some of or on each of the well-supporting elements **430** or the well-defining elements **419**, for heating the well associated therewith or the interior thereof. As a further alternative, a heating coil or a Peltier device may be disposed adjacent a group of well-supporting elements **430** or well-defining elements **419**, for example on electronic card **446**, for heating the wells in the group or the interiors thereof. Although reference is made to Fig. 4B, it will be appreciated that the provision of such well heating means is not limited to plates in which the wells are displaceable along the z-axis, and that such heating means may be provided in plates in which the wells are not displaceable.

It will also be appreciated that if the temperature of the wells is periodically measured, and if the device used to measure the temperature is coupled to a controller that controls the heating means for each individual well, then the individual well heating means, used in conjunction with the periodic measuring of temperature in individual wells, can provide a way to improve control over the conditions in a given well. Thus, for example, plates **400** having such heating means may be stored in an incubator and the temperature of the wells monitored periodically and the temperature of individual wells adjusted, if necessary, by heating (or cooling) individual wells. Alternatively, the heating means may themselves be used to effect incubation, for example temperature monitoring and adjustment may be effected frequently, say for example every 15, 10 or 5 minutes, to maintain the temperature in particular wells at e.g. 37°C ± 0.5°C so as to effect incubation. Thus, by equipping the plate **400**, the well-supporting elements **430**, or the well-defining elements **419** with individual heating elements for each well, in cases in which it is found that the temperature is incorrect, the temperature may be adjusted and controlled.

It will be appreciated that since reagents and other fluids may be added into or removed from well-defining elements **419**, which may be removed from plate **400** and optionally disposed of, plate **400** may be used multiple times and/or for multiple experiments, provided that well-defining elements **419** are replaced between each use of the plate **400**.

Reference is now made to Figures 5A to 5D, which are screen shots illustrating a graphical user interface for on-line (real-time) monitoring of addition of fluid to a multi-well plate in accordance with embodiments of the teachings herein.

As described hereinabove, multi-well plates in accordance with embodiments of the present invention, such as multi-well plate **300** of Figures 3A to 3G and multi-well plate **400** of Figures 4A to 4C, may be electrically coupled to a processor, for example via a suitably equipped plate data reader, as described hereinbelow with reference to Figures 8 to 9B, or via a USB or other cable connected to a computation device such as a computer. The graphical user interface of Figures 5A to 5D runs on such a processor coupled to the plate, using data provided to the processor from the electronics cards of the plates (such as electronics cards **546** and **646**). The processor may be configured to provide only graphical user information, or it may also be configured to control the amount fluid dispensed into the wells.

It will be appreciated that the data for providing online monitoring depends on measurement of a baseline electrical resistance measured by the strain gauges on the plate (such as strain gauges **344** and **444**), which baseline measurement when monitoring the filling of a well generally corresponds to an empty well. Once fluid is dispensed into the well, the electronics cards provide to the processor an indication of the volume of fluid added into each well, thereby facilitating the function of the graphical user interface as described hereinbelow. In some embodiments, the analog data representing the baseline electrical resistance is normalized and converted to digital data by suitable elements located on the electronics cards of the plate, such that the processor receives data suitable for use in the graphical user interface.

As seen, a graphical user interface **500** is associated with experiment planning software (not shown), such that the specific details of the experiment being conducted, such as the experiment name, the material used, the volume(s) of liquid(s) to be dispensed, the volume upper and lower limits, the required accuracy (i.e. the experimental sensitivity), and any other suitable experimental parameters are displayed in an information box **502** of the graphical user interface. The details included in information box **502** provide an indication to the user of the criteria that will be used to alert the user of incorrect addition of material to any one or more wells, as described hereinbelow. It will be appreciated that in some embodiments, the software running the apparatus dispensing the fluid is able to calibrate quantities to be dispensed and the degree of sensitivity to be used based on these experimental parameters.

Graphical user interface **500** further includes a graphic representation **504** of a multi-well plate in which the experiment is currently being conducted, based on information provided from the electronics card of the plate. Graphic representation **504** of the plate includes a plurality of circles **506**, each corresponding to a well in the plate (here shown as a 96 well plate), as well as indications of the rows and columns of the plate, indicated by reference numerals **508** and **510**, respectively.

The purpose of online monitoring of addition of fluid to the plate is to facilitate real time control of the volume of fluid added to the plate. The graphic user interface **500** allows a user to monitor the situation in real time and, in cases in which control of the process is not completely automated after the initial inputting of parameters, to instruct the system as necessary to correct the fluid volume or take other steps to compensate for an incorrect volume in a given well. Typically, the graphic user interface additionally provides a graphic indication whether the target volume of fluid has been reached, or whether additional fluid should be added to the plate. In some embodiments, such as that shown in Figures 5A to 5D, the graphic indication comprises a fill pattern or color indication, such that a first fill pattern or color represents an empty well, a second fill pattern or color represents a well in which the volume of fluid is less than the target volume of fluid, and a third fill pattern or color represents a well in which the volume of fluid is correct and is equal to the target volume of fluid, within the specified tolerance. In some embodiments, a fourth fill pattern or color is used to represent a well in which the target volume of fluid has been exceeded.

Figure 5A illustrates the graphical user interface **500** prior to the beginning of the experiment. As such, all the circles **506** have no fill pattern (or are in a first color), which is indicative of an empty well.

Figure 5B illustrates the graphical user interface **500** when dispensation of fluid into column 1 of the plate has begun. As seen, in graphic representation **504**, the circles **512** corresponding to the wells of column 1 (wells A1, B1, C1, D1, E1, F1, G1, and H1) have a second fill pattern (or are in a second color), here shown as diagonal lines sloping from right to left, indicative of a volume of fluid, which is less than the target volume, being in the wells, while the remaining circles **506**, corresponding to wells in columns 2-12, remain in the pattern or color indicating empty wells.

In some embodiments (not shown), graphic representation **504** indicates the volume of fluid that must be added to a well in order to reach the fluid target volume in that well. For example, this may be achieved by scrolling a pointer, such as is controlled by a computer mouse, over one of circles **506** resulting in a pop-up box indicating the volume that should be added to the corresponding well.

In Figure 5C it is seen that as dispensation of fluid into the wells of column 1 continues, most of the circles **512**, corresponding to wells in which the target volume of fluid has been reached, are represented in a third fill pattern (or are in a third color), here shown as dense diagonal lines sloping rom left to right, indicative of reaching the target volume. The graphic representation **504** additionally indicates that in well C1 the target volume of fluid has not yet been reached, by maintaining circle **514**, corresponding to well C1, in the second fill pattern of diagonal lines sloping from right to left (or in the same color).

Alternately, in embodiments in which the amount of fluid in the wells is determined only after completion of dispensation of fluid into a well (as opposed to making continuous or multiple determinations as the well is filled, for example if liquid is dispensed continuously but slowly or is dispensed drop-wise), graphic representation **504** does not provide information such as that shown in Figure 5B. Rather, once the fluid has been dispensed, graphic representation **504** indicates in which wells the volume of fluid falls short of (or exceeds) the required volume, in a manner similar to that shown in Figure 5C.

Figure 5D is identical to Figure 5C, but illustrates the graphical user interface following the dispensation of additional volume fluid into well C1 so as to correct the initial shortfall, such that the volume of fluid in well C1 is equal to the target volume for the experiment. As all the wells of column 1 are now correctly filled with the target volume of fluid, the corresponding circles **512** are represented with the third fill pattern of dense diagonal lines sloping from left to right (or in the third color), indicating that the target volume has been reached.

As fluid is dispensed into wells in additional columns of the plate, the graphic representation **504** changes, such that the color of each circle **506** is indicative of the volume of fluid in the corresponding well, thereby providing a real-time indication of the volume of fluid in each well, and assisting in preventing errors in the volume of fluid added to the wells.

In some embodiments, fluid is dispensed into all the wells **506** of the plate simultaneously, whether incrementally, continuously slowly or continuously quickly. In such embodiments, graphic representation **504** provides indications, similar to those shown in Figures 5B, 5C, and 5D, for all the wells at once, rather than row by row as described hereinabove.

Reference is now made to Figures 6A and 6B, which are screen shots illustrating a graphical user interface for off-line volume monitoring of fluid in a multi-well plate in accordance with embodiments of the teachings herein.

Graphical user interface **600** of Figures 6A and 6B is similar to graphical user interface **500** of Figures 5A to 5D, in that it runs on the processor coupled to the plate, using data provided to the processor from electronics cards of the plates (such as electronics cards **346** and **446**) via a plate data reader or a USB or other connector as is presently known or may be developed in the future. Similarly, graphical user interface **600** includes a graphic representation **604** of a multi-well plate in which the experiment is currently being conducted, based on information provided from the electronics card of the plate. Graphic representation **604** of the plate includes a plurality of circles **606**, each corresponding to a well in the plate (here shown as a 96 well plate), as well as indications of the rows and columns of the plate, indicated by reference numerals **608** and **610**, respectively.

However, during off-line monitoring, the purpose is not to indicate to the user whether or not an appropriate volume of fluid has been dispensed into a well, but rather to provide an alarm if, for some reason, the volume of fluid in a well has dropped below the target volume, or below a predetermined threshold value. As such, graphical user interface **600** is not associated with experiment planning software, but rather has inputted thereto values at which the user should receive an indication that the volume in a well is inappropriate, such as an alarm or an audible or text notification to take corrective action. In some embodiments, the values are predetermined absolute volume values, such that when the volume of fluid in a well drops below the predetermined volume, the graphical user interface **600** provides an indication of a specific well in which the volume is low. In some embodiments, such as the illustrated embodiment, the values are volume change values, such that the graphical user interface **600** provides an indication when the volume of fluid in a well changes by more than a predetermined value. In a variation on this (not shown), an indication may be given when the volume falls by more than certain percentage below a predetermined baseline value. The values used for providing an indication to the user may be default values, or may be set by the user based on the sensitivity of the experiment, or based on other considerations as suitable.

As seen in Figures 6A and 6B, volume changes of different magnitudes are indicated by different fill patterns or colors, and a legend **612** is provided so that the user can identify, based on the fill pattern or color of a circle **606**, how much fluid is missing from the corresponding well. In the illustrated embodiment a fill pattern of diagonals indicates that the volume of fluid in the corresponding well is unchanged, and is equal to the initial volume, a dotted fill pattern indicates a change of less than one microliter in the volume of fluid in the corresponding well, and a checkered fill pattern indicates a change of at least 1 microliter but less than three microliters in the volume of fluid in the corresponding well.

Graphical user interface **600** further includes one or more graphs **614**, in which the volume of fluid in one or more specific wells may be plotted as a function of time. In some embodiments, the specific well for which information is displayed in graph **614** may be selected by the user, for example by pointing the cursor of the mouse to a specific well or by typing the well identification in a suitable text box (not shown). In some embodiments, information corresponding to each of the wells may be displayed sequentially and/or repeatedly in graph **614**.

Typically, the data reader or USB or other connector associated with the electronics cards of the plate reports the measured volume in each well to the processor at a fixed rate, for example once every day, once every hour, once every minute, once every half a minute, or even once every second. The exact rate may be factory coded in the electronics card, or may be set by the user in accordance with the demands of the experiment being conducted.

Turning to Figure 6A, it is seen that at a first time point T1, there is no change in the volume of fluid in any of the wells, and thus all of circles **606** are filled in the fill pattern corresponding to the nominal volume, diagonal lines. Since there is no change in the volume of fluid in any of the wells, no plot is presented on graph **614**.

In Figure 6B, which illustrates the graphical user interface at a second time point T2 later than T1, it is seen that circles **616** corresponding to wells C1, D1, and E1 are filled in the fill pattern indicating a change of less than 1 microliter in the volume of fluid in the wells (dots), and circles **618** corresponding to wells A4, B1, F1, and G1 are filled in the fill pattern indicating a change of at least 1 microliter but less than 3 microliters in the volume of the fluid in the wells (checkered). In the illustrated example, graph **614** depicts a plot **620** of the change in volume in well A4 as a function of time, based on multiple readings of the volume of fluid in well A4.

Reference is now made to Figure 7, which is a screen shot illustrating a graphical user interface for off-line temperature monitoring of fluid in a multi-well plate in accordance with embodiments of the teachings herein.

Graphical user interface **700** of Figure 7 is analogous to graphical user interface **600** of Figures 6A and 6B, but differs from graphical user interface **700** in that the fill patterns (or colors) of circles **706** represent a temperature of a corresponding well in the plate, as measured by one or more temperature sensors forming part of the plate, and in that one or more graphs **714** may include a plot of the temperature in one or more specific wells as a function of time.

In some embodiments (such as shown in Fig. 7) there is a temperature sensor associated with each well, whereas in other embodiments there may be fewer temperature sensors than wells but still multiplicity of temperature sensors.

As seen in Figure 7, different temperatures are indicated by different fill patterns (or colors), and a legend **712** is provided so that the user can identify, based on the fill pattern (or color) of a circle **706**, what the temperature is in, or in the vicinity of, the well.

In Figure 7 it is seen that at a time point T1, each well has a specific temperature as indicated by the fill patterns of the corresponding circle **706**. For example, the fill pattern of circle **706** corresponding to well E1 indicates that the temperature of well E1 is 39°C.

In the illustrated example graph **714** includes a plot **720** showing the change in temperature at well A5 as a function of time.

Typically, the data reader or USB or other connector associated with the temperature sensor(s) of the plate reports the temperature in each well or in the vicinity of each sensor to the processor at a fixed rate, for example once every day, once every hour, once every minute, once every half a minute, or even once every second. The exact rate may be factory coded in the electronics card, or may be set by the user in accordance with the demands of the experiment being conducted. As such, the fill patterns (or colors) of circles **706** in graphical user interface **700** change when the data reader indicates a change in the temperature of the corresponding wells, as measured by the temperature sensor(s).

It will appreciated that since well-containing elements **348** and well-defining elements **419** are removable from their respective plates **300** and **400**, it is possible to obtain measurements using elements **348** or elements **419**, as described above, and then to remove elements **348** or elements **419** and insert them into other, simpler plates (not shown) which lack the detecting means detailed above, for storage, for example for storage in a refrigerator or incubator. At a later time, if another measurement is desired, elements **348** or elements **419** may re-inserted into plate **300** or **400**, respectively.

Reference is now made to Fig. 8, which is a perspective view of a plate base and data reader **800** constructed and operative in accordance with an embodiment of the teachings herein, for receiving signals from a multi-well plate in accordance with embodiments of the invention.

As seen in Figure 8, the base plate and data reader **800** includes a base **802** having formed thereon a frame **810**, suitably shaped and sized for receipt therein of a multiwell plate, such as plate **200**, **300**, or **400** described hereinabove. In some embodiments, the base plate and data reader 800 may form part of an optical instrument or imaging device, such as, for example, the Hermes system (http://www.idea-bio.com/page-87-__Hermes.aspx) commercially available from Idea Bio-Medical Ltd. of Rehovot, Israel. In some such embodiments, the base **802** may be transparent to at least some wavelengths of illumination, so as to allow for imaging of samples in the multi-well plate by the optical instrument or imaging device while a plate is disposed in the data reader **800**.

In some embodiments, frame **810** includes a retaining mechanism for retaining the plate stable and immobile within data reader **800**. In some embodiments, the retaining mechanism comprises protrusions **812** which engage the frame of the plate, which protrusions **812** may be retractable into frame **810**, for example under the force of a spring. As such, when a user inserts the plate into data reader **800**, the user pushes the plate against the protrusions **812**, causing the protrusions **812** to retract into frame **810**. Once the user stops pushing the plate, for example when the plate is in place, the springs push protrusions **812** outward such that protrusions **812** engage the plate and retain it within data reader **800**. In some embodiments, the retaining mechanism may comprise a mechanism for snap-fitting the plate into place on data reader **800**, a rim on which the plate may rest, and the like.

In some embodiments, frame **810** includes indentations **814** to assist the user in gripping the plate disposed within frame **810** when the user wishes to remove the plate. Other mechanisms for assisting in removal of the plate from frame **810**, such as an eject button, may also be used.

Frame **810** additionally includes an electrical port **820**, positioned and configured to electrically engage a corresponding port on the plate disposed within the data reader, for example such as port **358** of Fig. 3B or port **458** of Figure 4B. Electrical port **820** is also electrically connected to a processor (not shown) for provision of information from the plate to the processor, for example for use of dedicated software such as experiment planning software or Graphical User Interface software as described hereinabove with reference to Figs. 5A to 7.

Reference is now made to Figs. 9A and 9B, which are perspective views of a device for removing well-containing elements or well-defining elements from and/or for emplacing such elements in a multi-well plate, the device constructed and operative in accordance with an embodiment of the teachings herein.

As seen in Figs. 9A and 9B, a device **900** for manipulation of well containing elements such as elements **330** or of well defining elements such as elements **419** is functionally associated with a plate-bearing base **902** arranged to have a multi-well plate **904** disposed therein. The plate bearing-base **902** may be a data reader and base such as data reader and base **800** described hereinabove, or may be a simple base on which a multiwell plate rests, as illustrated in Figures 9A and 9B.

Arranged above plate-bearing base **902** is a well-engaging portion **906** which is movably mounted onto a vertical displacement mechanism **908**. Vertical displacement mechanism **908** is configured to enable vertical displacement of well-engaging portion **906** toward and away from a plate **904** disposed on plate-bearing base **902**. In some embodiments, vertical displacement mechanism **908** includes vertical mounts **910** and a displaceable portion **912** vertically displaceable along mount **910**, such that said well engaging portion **906** is mounted onto displaceable portion **912** and is displaceable therewith.

Disposed on a lower surface **914** of well engaging portion **906** are a plurality of well-engaging protrusions **916**, each configured to fit in one of the wells of a well-containing element or a well-defining element to be placed in plate **904** or being removed from plate **904** for attachment thereto. In some embodiments, well-engaging protrusions **916** engage the corresponding wells by snap fit mechanism, though other methods of engagement, such as by vacuum, are also considered.

For placement of well-defining elements or well-containing elements in plate **904**, well-engaging protrusions **916** engage the well-defining elements or well-containing elements, and subsequently well engaging portion **906** is vertically displaced toward plate **904** until the well defining elements or well-containing elements are fitted in their suitable locations within plate **904**, such as within sections **352** of plate **300** or within well-supporting elements **430** of plate **400**. The well engaging protrusions **916** then disengage from the well-defining elements or well-containing elements and well engaging portion **906** is vertically displaced away from plate **904**, leaving the elements properly placed within plate **904** and accessible for insertion of reagents thereinto.

For removal of well-defining elements or well-containing elements from plate **904**, well-engaging portion **906** is vertically displaced toward plate **904** until the well-defining elements or well-containing elements located within plate **904** engage to well-engaging protrusions **916**. Well-engaging portion **906** together with well-engaging protrusions **916** and the wells engaged therewith are vertically displaced away from plate **904**, resulting in removal of the well-defining elements or well containing elements from their locations within plate **904**. When the well-engaging portion is sufficiently displaced from plate **904**, the well-engaging protrusions **916** then disengage from the well-defining elements or well-containing elements.

It is appreciated that a similar device may be used for engaging pipette tips or the like, and for dispensing fluids such as reagents into the wells in plate **904**.

Described hereinbelow are variations in construction that may employed with multiwell plates such as those herein described with reference to Figures 2A to 4C, and in some cases with other multiwell plates, as well as variations in the methods of using those plates.

The plates described above utilize the physical displacement of wells along the z-axis to determine the volume of fluid dispensed into one or more wells. In the embodiments described above, such physical displacement is coupled to strain gauges, in order to induce a signal that is correlated to the amount of displacement and thus the volume of fluid dispensed into (or lost from) the well(s) under observation (given that a fluid of a known density and mass occupies a determinable volume). However, it will be appreciated that other methods may be employed instead of or in addition to the use of strain gauges to determine volume.

Thus, for example, if a multiwell plate having wells which are displaceable in the z-axis is used in conjunction with a reading device that has an auto-focus mechanism, this may be used to determine the amount of displacement of a well. An example of such an auto-focus mechanism is described in US Patent No. 7,109,459, entitled “Auto-focusing method and device for use with optical microscopy”, the contents of which are incorporated by reference.

To illustrate, a multiwell plate having displaceable wells may be introduced into a reading device having an auto-focus mechanism, such as the Wiscan™ scanner available from Idea Bio-Medical Ltd., Rehovot, Israel. By combining the auto-focus mechanism with appropriate feedback controls, the bottoms of the wells of interest may set to the same height prior to dispensing of fluid. Fluid may then be dispensed into the wells; it will be appreciated that in some cases, this may be done on-line, without moving the plate to another location, whereas in other cases, the plate may need to be moved to a dispensing station. After dispensing of the fluid, the auto-focus mechanism may again be employed (preceded if necessary by return of the plate to the auto-focus location), this time to determine the motion of the well in the z-axis; this information can in turn be used to determine the amount of fluid dispensed in to one or more wells, as described above. Moreover, periodic measurements may be obtained to determine if fluid has been lost from one or more wells, for example through evaporation. This method may be employed with individual wells or with groups of wells, as described above. As noted, this method may be employed in conjunction with or instead of strain gauges to determine the displacement of one or more wells.

As with the methods already described above, detection of an incorrect amount of fluid in a well or group of wells facilitates correction of the amount of fluid in the well(s), exclusion of the well(s) from further manipulations and/or calculations, or in some cases correction of calculations.

Another method for determining the amount of fluid lost from a well involves periodic monitoring of the temperature of the individual well. Often, multiwell plates which contain live cells are incubated at 37°C. However, the heat distribution in the incubator may be uneven, or other factors may cause uneven temperature distribution in the plate, which can lead to differential losses of fluid from different wells and can adversely affect the cells therein. By tracking the temperature of an individual well periodically, for example once an hour, and by taking into account the nature of the fluid in the well, it is possible to determine the amount of fluid lost from the well over time, as well as to correct the temperature in the well, for example using heating or cooling means as described hereinabove. Such monitoring may be facilitated by the placement of individual temperature sensors at each well, for example on the bottom or the side thereof. Such sensors may be electronically coupled to a card, such as **346** or **446** described above, to facilitate reading in a data reader. Alternatively, one or more thermal cameras may be employed to periodically detect the temperature of individual wells.

As with the methods already described above, detection of an incorrect amount of fluid in a well or group of wells facilitates correction of the amount of fluid in the well(s), exclusion of the well(s) from further manipulations and/or calculations, or in some cases correction of calculations. In cases in which the wells of the plate are displaceable along the z-axis, this method may be used in conjunction with or instead of strain gauges, and in conjunction with or instead of the method using an auto-focus mechanism as described above. However, it will be appreciated that unlike the methods using strain gauges or auto-focus, this method may be utilized with plates in which the wells are not displaceable.

It will be appreciated that the embodiments shown in the figures are for illustrative purposes only and that variations of these are contemplated within the scope of the invention. For example, the number of wells per plate, the shape of the wells, and the materials used may differ what is shown or specifically described herein, as may the means for detecting adding or removal of liquid from the plate. Additionally, each of the wells may include additional layers or inserts, such as well inserts in which cells are grown such that reagents can be added to the environment of the well for osmosis of the reagent into the well without directly engaging the cells grown in the insert.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the scope of the appended claims.

Citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the invention.

Section headings are used herein to ease understanding of the specification and should not be construed as necessarily limiting.

CLAIMS:

1. A plate, comprising:

a first substantially planar surface having at least one first aperture defined therein;

a second substantially planar surface substantially parallel to said first substantially planar surface, said second substantially planar surface being spaced from said first substantially planar surface;

at least one well defined within said plate, said at least one well having a second aperture corresponding to and in alignment with one of said at least one first aperture, said at least one well having a sidewall and a bottom and said at least one well extending from said first substantially planar surface toward said second substantially planar surface, said at least one well being displaceable away from said first substantially planar surface; and

at least one signal provider, functionally associated with said at least one well, capable of producing a signal in response to displacement of said at least one well away from said first surface.

2. The plate of claim 1, wherein:

said first surface has a plurality of first apertures defined therewithin; and

a plurality of wells are defined within said plate, each well having a second aperture corresponding to and in alignment with a first aperture of said plurality of first apertures defined in said first surface, each of said wells having a sidewall and a bottom and each well extending from said first substantially planar surface toward said second substantially planar surface.

3. The plate of claim 2, wherein each of said plurality of wells is displaceable away from said first substantially planar surface.

4. A multiwell plate, comprising:

a first substantially planar surface having a plurality of first apertures defined therein;

a second substantially planar surface substantially parallel to said first substantially planar surface, said second substantially planar surface being spaced from said first substantially planar surface;

a plurality of wells defined within said plate, each well having a second aperture corresponding to and in alignment with one of said first apertures defined in said first surface, each of said wells having a sidewall and a bottom and each well extending from said first substantially planar surface toward said second substantially planar surface, each of said wells being displaceable away from said first substantially planar surface; and

at least one signal provider, functionally associated with said plurality of wells, capable of producing a signal in response to displacement of at least one said well away from said first surface.

5. The plate of any one of claims 1 to 4, wherein said first and second surfaces are spaced apart by a plurality of sidewalls extending between said first and second surfaces.

6. The plate of any one of claims 2 to 5, wherein movement of all said wells is coupled, so that said signal provider is capable of providing a single signal in response to displacement of any one or more of said wells.

7. The plate of any one of claims 2 to 5, wherein movement of some of said wells is coupled into two or more groups, and said at least one signal provider comprises multiple signal providers, each capable of providing a signal in response to displacement of one of said groups.

8. The plate of any one of claims 2 to 5, wherein:

said at least one signal provider comprises a plurality of signal providers, each associated with one well of said plurality of wells;

each of said plurality of wells is independently displaceable away from said first surface; and

each of said plurality of signal providers is capable of providing a signal in response to displacement of one of said plurality of wells associated therewith.

9. The plate of any one of claims 1 to 8, wherein said at least one signal provider is capable of providing a signal in response to placement in a said well of 300 milligrams of material, 250 milligrams of material, 200 milligrams of material, 150 milligrams of material, 100 milligrams of material, 75 milligrams of material, 50 milligrams of material, 45 milligrams of material, 40 milligrams of material, 35 milligrams of material, 30 milligrams of material, 25 milligrams of material, 20 milligrams of material, 15 milligrams of material, 10 milligrams of material, 5 milligrams of material, 4 milligrams of material, 3 milligrams of

material, 2 milligrams of material, or 1 milligram of material, 500 micrograms (μg) of material, 300 μg of material, 200 μg of material, or 100 μg of material.

10. The plate of any one of claims 1 to 9, wherein said at least one signal provider is capable of providing a signal in response to placement in a said well of 300 microliters (μl) of fluid, 250 μl of fluid, 200 μl of fluid, 150 μl of fluid, 100 μl of fluid, 75 μl of fluid, 50 μl of fluid, 45 μl of fluid, 40 μl of fluid, 35 μl of fluid, 30 μl of fluid, 25 μl of fluid, 20 μl of fluid, 15 μl of fluid, 10 μl of fluid, 5 μl of fluid, 4 μl of fluid, 3 μl of fluid, 2 μl of fluid, 1 μl of fluid, 0.5 μl of fluid, 0.3 μl of fluid, 0.5 μl of fluid, or 0.1 μl of fluid.

11. The plate of any one of claims 1 to 10, wherein said signal provider is capable of providing a signal in response to displacement of at least one said well toward said first surface.

12. The plate of any one of claims 1 to 11, wherein said at least one signal provider is capable of providing a signal in response to removal from a said well of 300 milligrams of material, 250 milligrams of material, 200 milligrams of material, 150 milligrams of material, 100 milligrams of material, 75 milligrams of material, 50 milligrams of material, 45 milligrams of material, 40 milligrams of material, 35 milligrams of material, 30 milligrams of material, 25 milligrams of material, 20 milligrams of material, 15 milligrams of material, 10 milligrams of material, 5 milligrams of material, 4 milligrams of material, 3 milligrams of material, 2 milligrams of material, or 1 milligram of material, 500 micrograms (μg) of material, 300 μg of material, 200 μg of material, or 100 μg of material.

13. The plate of any one of claims 1 to 12, wherein said at least one signal provider is capable of providing a signal in response to removal from a said well of 300 microliters (μl) of fluid, 250 μl of fluid, 200 μl of fluid, 150 μl of fluid, 100 μl of fluid, 75 μl of fluid, 50 μl of fluid, 45 μl of fluid, 40 μl of fluid, 35 μl of fluid, 30 μl of fluid, 25 μl of fluid, 20 μl of fluid, 15 μl of fluid, 10 μl of fluid, 5 μl of fluid, 4 μl of fluid, 3 μl of fluid, 2 μl of fluid, 1 μl of fluid, 0.5 μl of fluid, 0.3 μl of fluid, 0.2 μl of fluid, or 0.1 μl of fluid.

14. The plate of any one of claims 1 to 13, wherein at least one well in said plate is removable therefrom.

15. The plate of any one of claims 1 to 14, wherein the plate comprises at least one temperature sensor associated with at least one of said wells.

16. The plate of claim 15, wherein said temperature sensor is located in or on one of said wells.

17. The plate of claim 15 or 16, wherein said at least one temperature sensor is configured to provide a signal representing a temperature in said at least one well or in a vicinity thereof.

18. The plate of claim 17, wherein said at least one temperature sensor is configured to continuously detect the temperature in said at least one well, and to periodically provide said signal representing said temperature.

19. The plate of any one of claims 1 to 18, further comprising an electronic storage element for storage of at least one signal provided by at least one of said at least one signal provider and said at least one temperature sensor.

20. The plate of any one of claims 15 to 19, wherein said at least one temperature sensor is configured to detect the temperature in a group of wells from said plurality of said wells.

21. The plate of any one of claims 15 to 19, wherein said at least one temperature sensor comprises a single temperature sensor configured to detect the temperature in all the wells.

22. The plate of any one of claims 15 to 19, wherein said at least one temperature sensor comprises a plurality of temperature sensors, each associated with one of said plurality of wells for detecting the temperature in said one of said plurality of wells associated therewith.

23. The plate of any one of claims 1 to 22, further comprising at least one heating component associated with said at least one well, said at least one heating component being located in sufficient proximity to said at least one well to heat said at least one well or its interior.

24. The plate of claim 23, wherein said at least one heating component comprises a plurality of heating components, each associated with one well of said plurality of wells and

located in sufficient proximity to said one well associated therewith to heat said one well or its interior, without substantially heating others of said plurality of wells.

25. The plate of claim 23 or 24, wherein said at least one heating component comprises a heating coil.

26. The plate of claim 23 or 24, wherein said at least one heating component is also capable of cooling said at least one well.

27. The plate of claim 26, wherein said heating component comprises a Peltier device.

28. The plate of any one of claims 23 to 27, wherein at least one well in said plate is removable therefrom, without removing from said plate a said heating component associated with said at least one removable well.

29. The plate of any one of claims 23 to 27, wherein at least one well in said plate is removable therefrom, and the heating component associated with said at least one removable well is attached to or formed integrally with said at least one well and is removable therewith.

30. The plate of any one of claims 1 to 29, further comprising an electrical port functionally associated with at least one of said at least one signal provider and said at least one temperature sensor.

31. The plate of any one of claims 1 to 30, further comprising a rechargeable power supply, functionally associated with at least one of said at least one signal provider and said at least one temperature sensor, and configured to be recharged by connection thereof to a power source.

32. The plate of claim 31, wherein said rechargeable power supply is configured to be recharged when said electrical port is electrically connected to a said power source.

33. A data reader configured to receive therein a plate according to any one of claims 30 to 32, said data reader comprising:

a base for placement of said plate thereon;

an electrical port corresponding to said electrical port of said plate for electrical engagement therewith; and

a processor functionally associated with said electrical port, for processing signals obtained from at least one of said signal provider and said temperature sensor via said electrical port.

34. The data reader of claim 33, wherein said processor is configured to obtain said signals directly from at least one of said signal provider and said temperature sensor via said electrical port.

35. The data reader of claim 33, wherein said processor is configured to obtain said signals from an electronic storage component storing at least one signal provided by at least one of said signal provider and said temperature sensor.

36. The data reader of any one of claims 33 to 35, further comprising a display functionally associated with said processor, the display configured to provide to a user information obtained from said processed signals.

37. The data reader of claim 36, wherein said information comprises an indication of at least one of:

an amount of fluid in said plate at a specific time;

an amount of fluid in at least one said well at a specific time;

a change in an amount of fluid in said plate over a period of time;

a change in an amount of fluid in at least one said well over a period of time;

a temperature of at least one said well at a specific time; and

a change in temperature of at least one said well over a period of time.

38. The data reader of claim 37, wherein said processor is configured to process said signals in real time and said display is configured to provide to the user said information in real-time.

39. The data reader of any one of claims 22 to 38, which has disposed therein a plate according to any one of claims 1 to 21 and 40 to 48.

40. A plate comprising:

a first substantially planar surface having at least one first aperture defined therein;

a second substantially planar surface substantially parallel to said first substantially planar surface, said second substantially planar surface being spaced from said first substantially planar surface;

at least one well defined within said plate, said at least one well having a second aperture corresponding to and in alignment with one of said at least one first apertures defined in said first surface, said at least one well having a sidewall and a bottom and said at least one well extending from said first substantially planar surface toward said second substantially planar surface; and

at least one heating component associated with said at least one well, which is located in sufficient proximity to said at least one well to heat said at least one well or its interior.

41. The plate of claim 40, wherein:

said first surface has a plurality of first apertures defined therewithin;

said at least one well comprises a plurality of wells defined within said plate, each well having a second aperture corresponding to and in alignment with one first aperture from the plurality of first apertures defined in said first surface, each of said wells having a sidewall and a bottom and each well extending from said first substantially planar surface toward said second substantially planar surface; and

said at least one heating component comprising a plurality of heating components such that each of said wells has one of said plurality of heating components associated therewith, each of said heating components being located in sufficient proximity to said well with which said heating component is associated to heat said well or its interior without substantially heating other wells.

42. The plate of claim 40 or 41, wherein said heating component comprises a heating coil.

43. The plate of claim 40 or 41, wherein said heating component is also capable of cooling said well.

44. The plate of claim 43, wherein said heating component comprises a Peltier device.

45. The plate of any one of claims 40 to 44, wherein at least one well in said plate is removable therefrom, without removing from said plate a said heating component associated with said at least one removable well.

46. The plate of any one of claims 40 to 44, wherein at least one well in said plate is removable therefrom, and the heating component associated with said at least one removable well is attached to or formed integrally with said at least one well and is removable therewith.

47. The plate of any one of claims 40 to 46, which is also a plate according to any one of claims 1 to 32.

48. The plate of any one of claims 40 to 46, which is not a plate according to any one of claims 1 to 32.

49. A method for measuring the amount of fluid added to a plate according to any one of claims 1 to 32 and 47, comprising:

recording an initial signal provided by said signal provider; and

after a fluid has been added to at least one well in said plate, obtaining a second signal generated by said signal provider in response to the addition of said fluid,

wherein, on the basis of a difference between said initial signal and said second signal, the amount of said fluid added to said at least one well can be calculated.

50. The method of claim 49, further comprising adding fluid to said plate after said recording an initial signal and before said obtaining a second signal.

51. The method of claim 49 or 50, further comprising on the basis of said difference between said initial signal and said second signal, calculating an amount of said fluid added to said at least one well.

52. The method of claim 51, wherein said calculating an amount comprises calculating at least one of (a) a volume of said fluid added to said at least one well; (b) a mass of said fluid added to said at least one well; and (c) a volume and a mass of said fluid added to said at least one well.

53. A method for measuring the amount of fluid lost from a well-containing plate according to any one of claims 1 to 22 and 47, said plate having an initial amount of fluid disposed in at least one well of said plate, the method comprising:

recording an initial signal provided by said signal provider at a first time;

obtaining from said signal provider a second signal at a second time after said first time; and

on the basis of the difference between said initial signal and said second signal, calculating an amount of said fluid lost from said at least one well of said plate.

54. The method of claim 53, wherein said calculating an amount comprises calculating at least one of (a) a volume of said fluid lost from said at least one well; (b) a mass of said fluid lost from said at least one well; and (c) a volume and a mass of said fluid lost from said at least one well.

55. The method of any one of claims 53 to 54, further comprising:

periodically repeating said step of obtaining a signal; and

on the basis of the difference between signals obtained at two different times, calculating an amount of fluid lost from said at least one well in a duration between said two different times.

56. A method comprising:

obtaining a baseline measurement of displacement of at least one well in a multi-well plate having disposed therein a displacement measuring assembly for measuring the displacement of at least one well in said plate in response a change in an amount of fluid in said at least one well, said baseline measurement being obtained via said displacement measuring assembly;

at a time after said obtaining of said baseline measurement, obtaining a second measurement of displacement of said at least one well; and

on the basis of said second measurement of displacement, calculating the change in the amount of fluid in said at least one well.

57. A method comprising:

at a first time, obtaining a baseline measurement of displacement of at least one well in a multi-well plate having disposed therein a displacement measuring assembly for measuring the displacement of at least one well in said plate in response a change in an amount of fluid in said at least one well, said baseline measurement being obtained via said displacement measuring assembly;

at a second time after said first time, measuring the displacement of said at least one well; and

on the basis of a change in displacement between said first and second times, calculating a change in the amount of fluid in said at least one well,

wherein at at least one of said first and second times, a detectable amount of fluid is present in said well.

58. The method of claim 57, further comprising:

periodically repeating said step of measuring the displacement of said at least one well at a second time; and

on the basis of a change in displacement between two said measurements of displacement, calculating a change in the amount of fluid in said at least one well during a period between said two said measurements of displacement.

59. The method of any one of claims 56 to 58 wherein said change in said amount of fluid is due to addition of fluid to said at least one well.

60. The method of any one of claims 56 to 58 wherein said change in the amount of fluid is due to loss of fluid from said at least one well.

61. The method of any one of claims 56 to 60 wherein the plate is a plate according to any one of claims 1 to 32 and 47.

62. The method of any one of claims 51 to 61, wherein the signal provider is sufficiently sensitive to detect a change of 300 microliters (μl), 250 μl, 200 μl, 150 μl, 100 μl, 75 μl, 50 μl, 45 μl, 40 μl, 35 μl, 30 μl, 25 μl, 20 μl, 15 μl, 10 μl, 5 μl, 4 μl, 3 μl, 2 μl, 1 μl, 0.5 μl of fluid, 0.3 μl of fluid, 0.2 μl of fluid, or 0.1 μl of fluid, in the volume of fluid in said at least one well.

63. The method of any one of claims 51 to 62, wherein the signal provider is sufficiently sensitive to detect a change of 300 milligrams (mg), 250 mg, 200 mg, 150 mg, 100 mg, 75

mg, 50 mg, 45 mg, 40 mg, 35 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, 5 mg, 4 mg, 3 mg, 2 mg, 1 mg, 500 micrograms (μg), 300 μg, 200 μg, or 100 μg in the mass of fluid in said at least one well.

64. The method of any one of claims 51 to 63, further comprising detecting a temperature in at least one well.

65. The method of claim 64, further comprising detecting said temperature in said at least one well at at least two different points in time.

66. The method of claim 64 or 65, further comprising adjusting the temperature of an individual well in response to said detecting said temperature.

67. The method of any one of claims 51 to 66, wherein at least one well in said multi-well plate is removable therefrom.

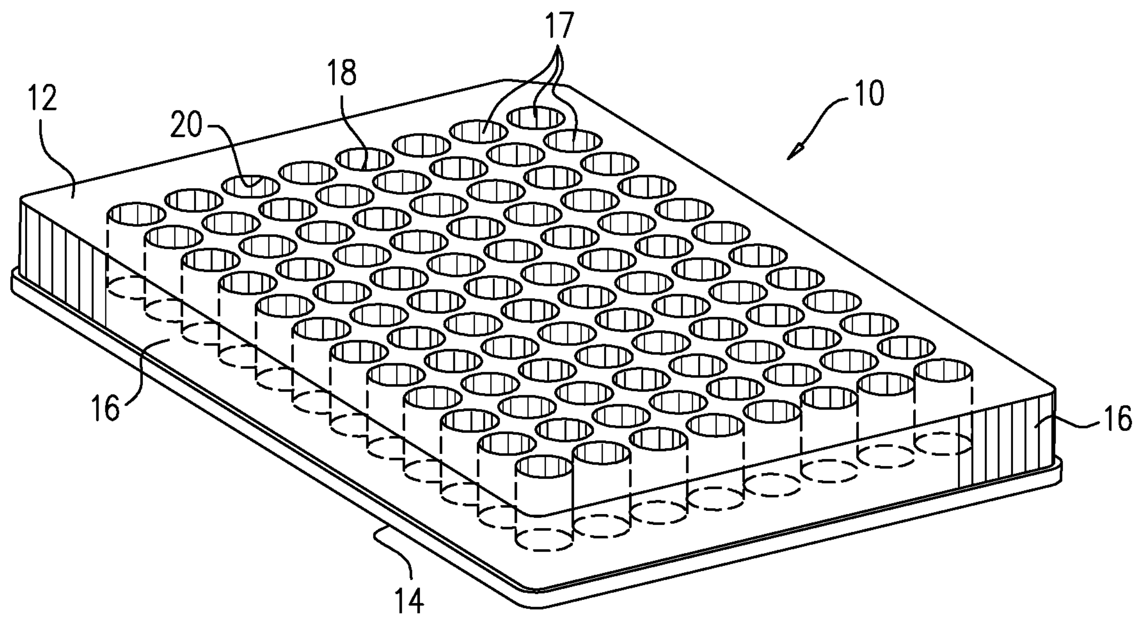
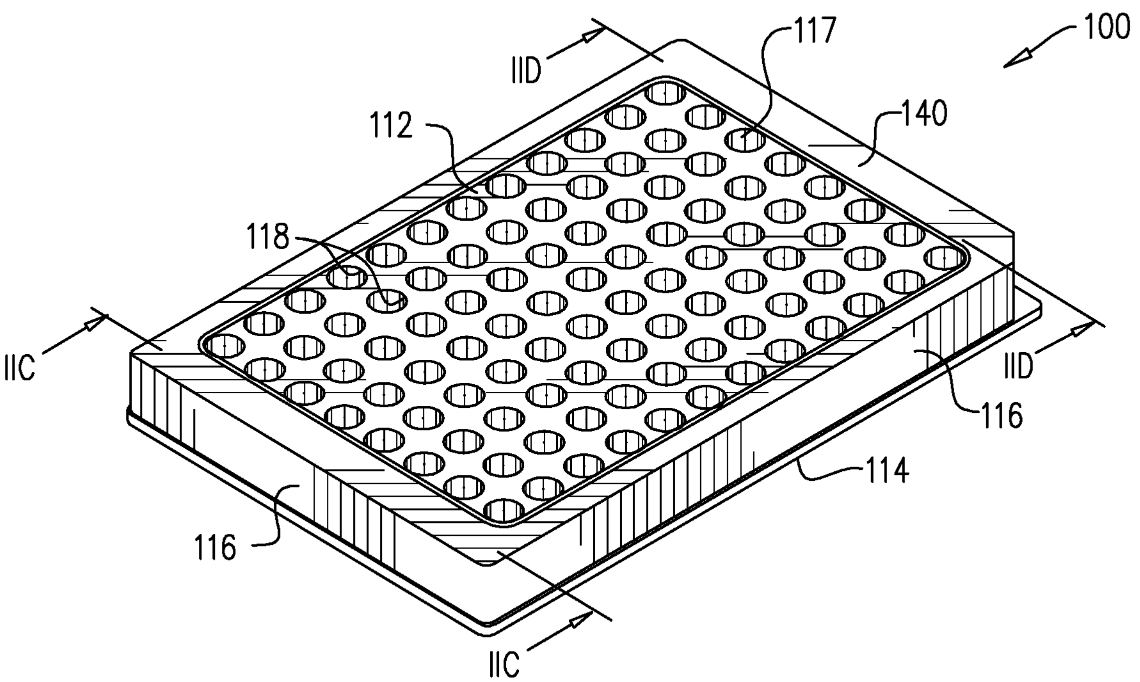

17
18
12
20
10
16
16
14

FIG. 1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100
IID
140
112
118
IIC
IID
116
114
116
IIC

FIG. 2A

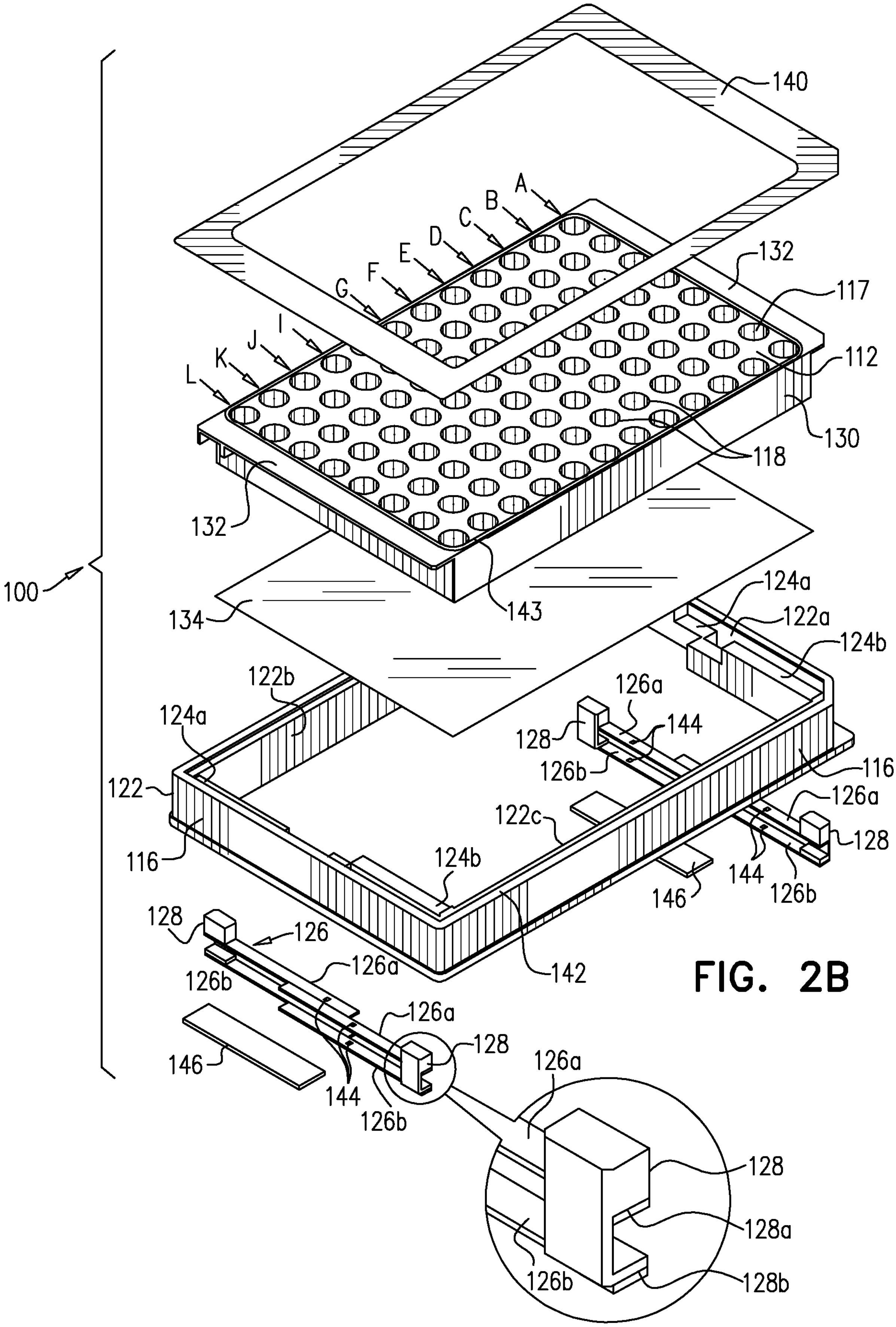

140
A
B
C
D
E
F
G
I
J
K
L
132
117
112
130
118
132
143
100
134
124a
122a
124b
122b
126a
124a
144
128
126b
116
122
126a
122c
128
116
124b
144
146
126b
128
126
126a
126b
126a
128
146
144
126b
126a
128
128a
126b
128b
142

FIG. 2B

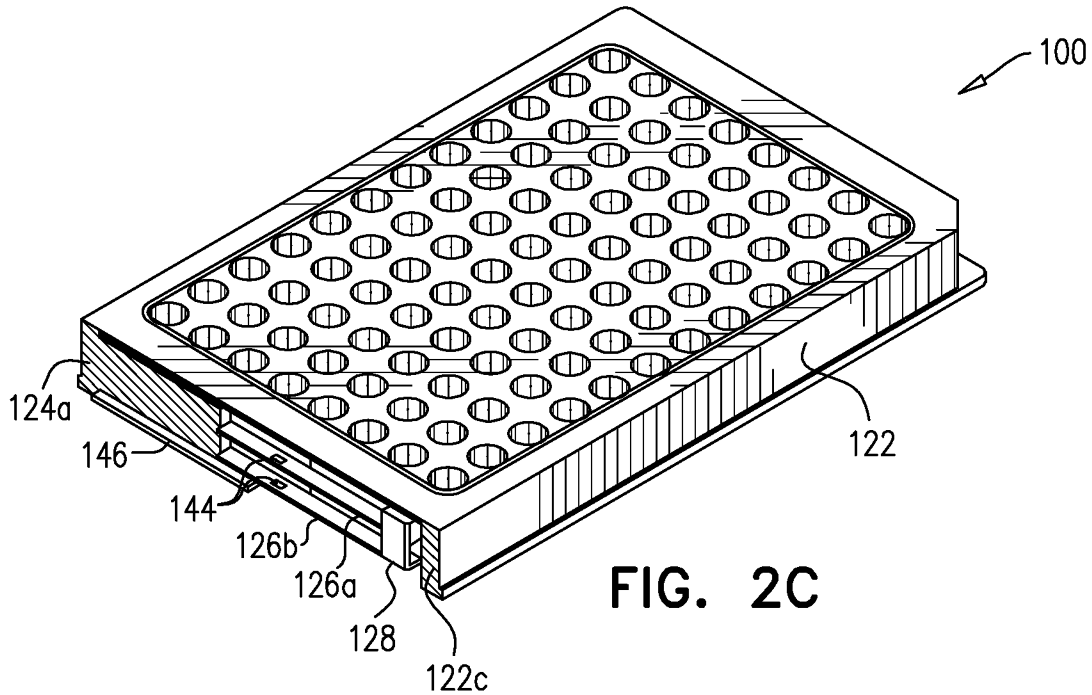

100
124a
146
144
126b
126a
128
122c
122

FIG. 2C

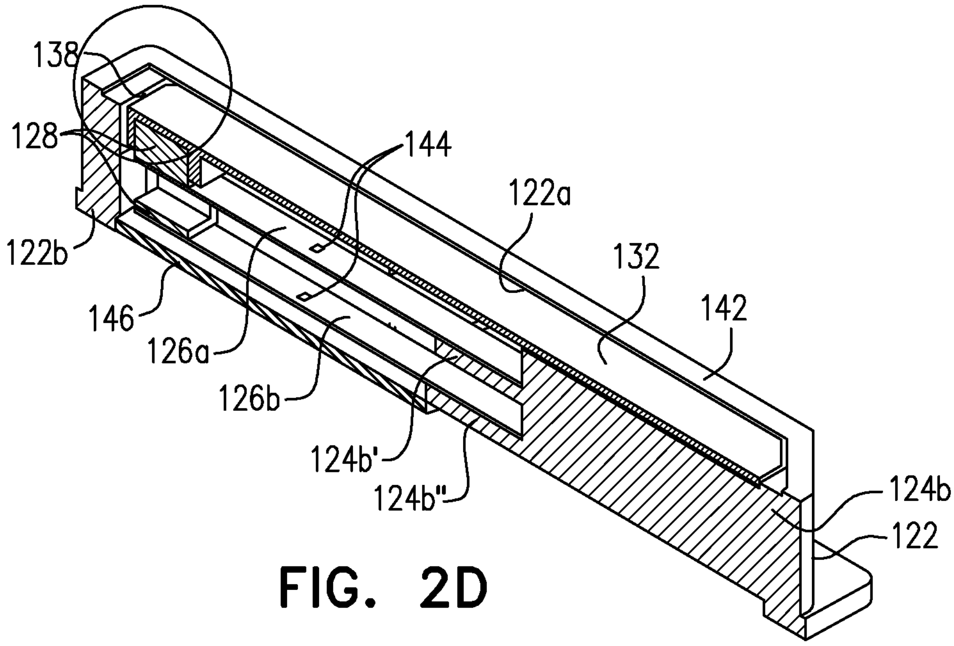

138
128
144
122a
122b
132
142
146
126a
126b
124b'
124b"
124b
122

FIG. 2D

FIG. 3A

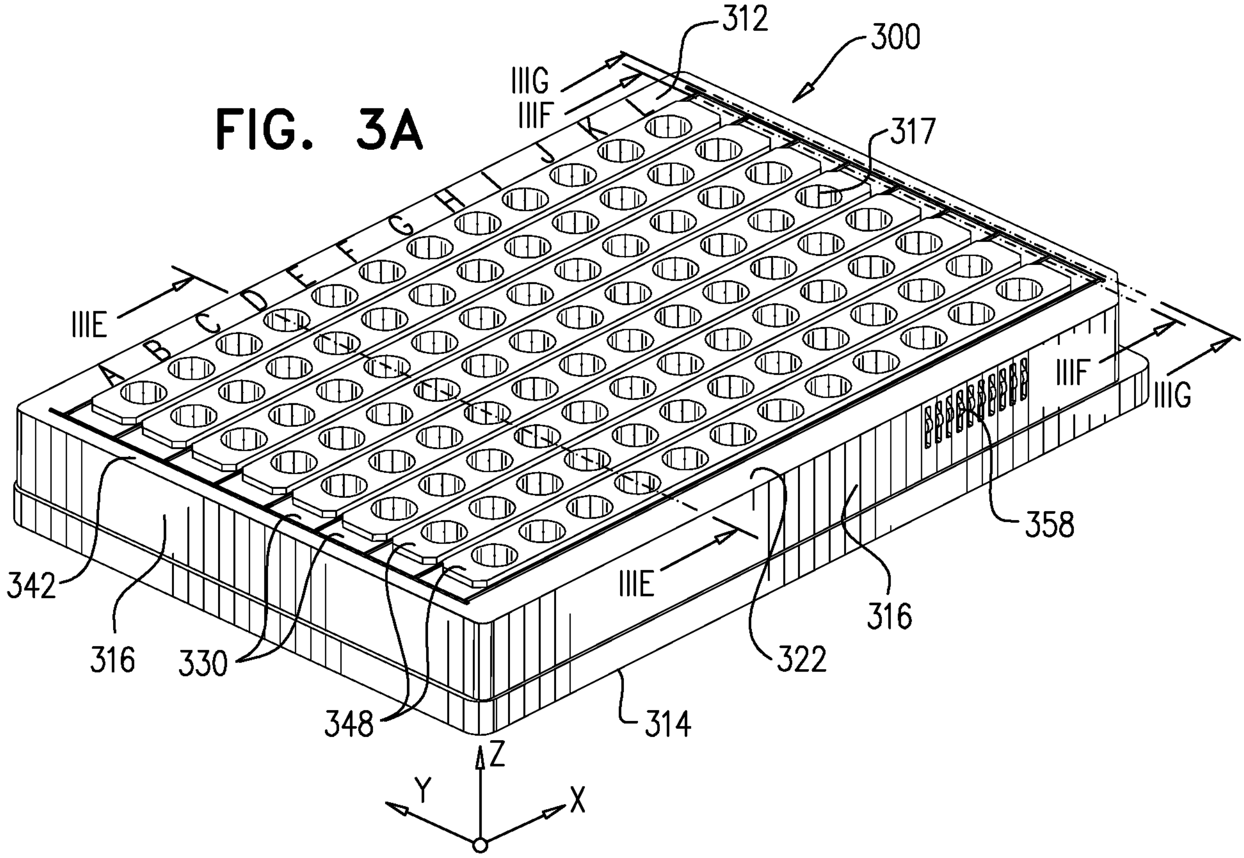
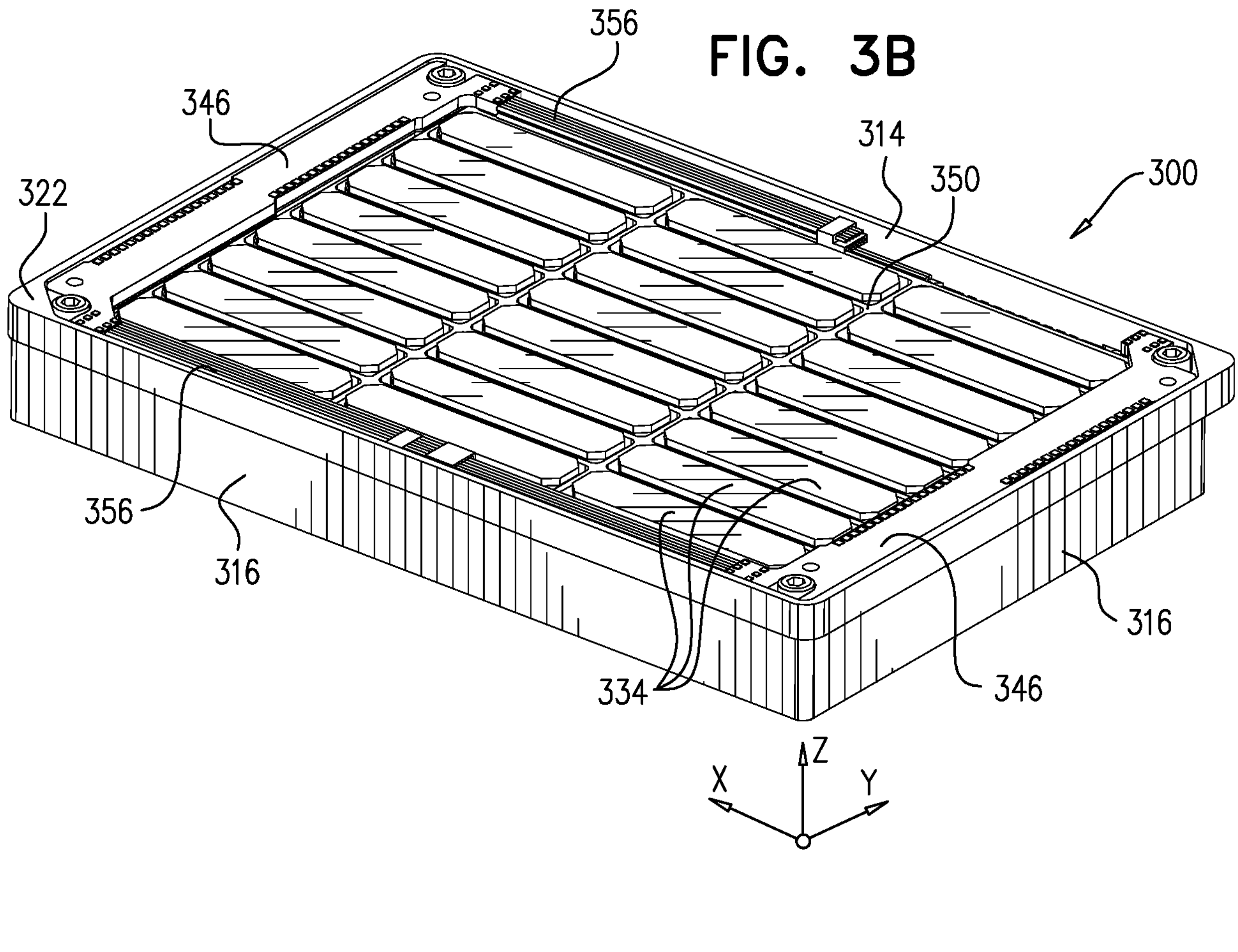

312
300
IIIG
IIIF
317
A
B
C
D
E
F
G
H
I
J
K
L
IIIE
IIIF
IIIG
358
342
316
330
348
IIIE
322
316
314
Z
Y
X

FIG. 3B


356
346
314
350
300
322
356
316
334
346
316
Z
X
Y

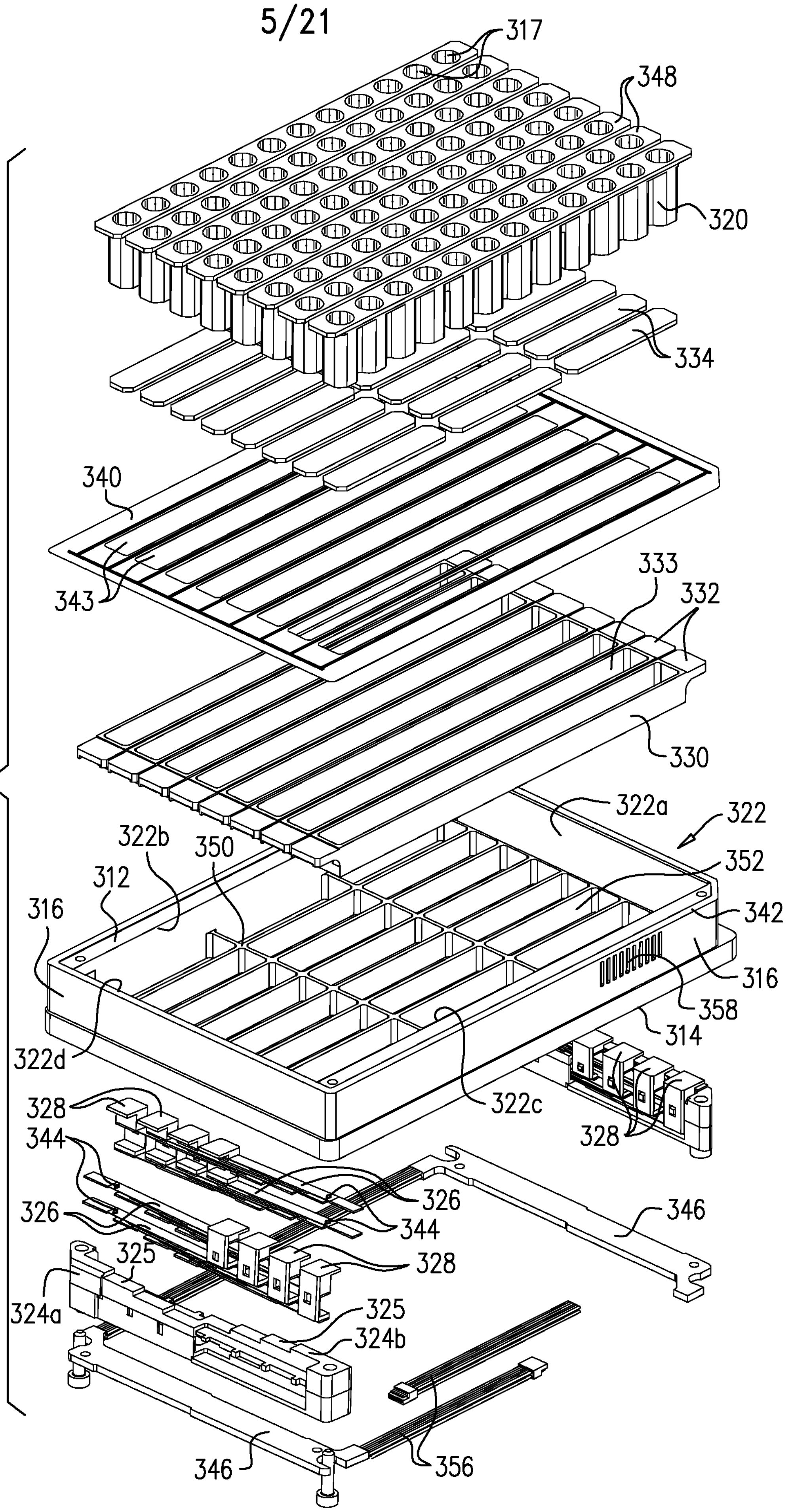

317
348
320
334
340
343
300
333
332
330
322a
322
322b
350
352
312
342
316
316
358
314
322d
322c
328
328
344
326
326
344
346
325
328
324a
325
324b
346
356

FIG. 3C

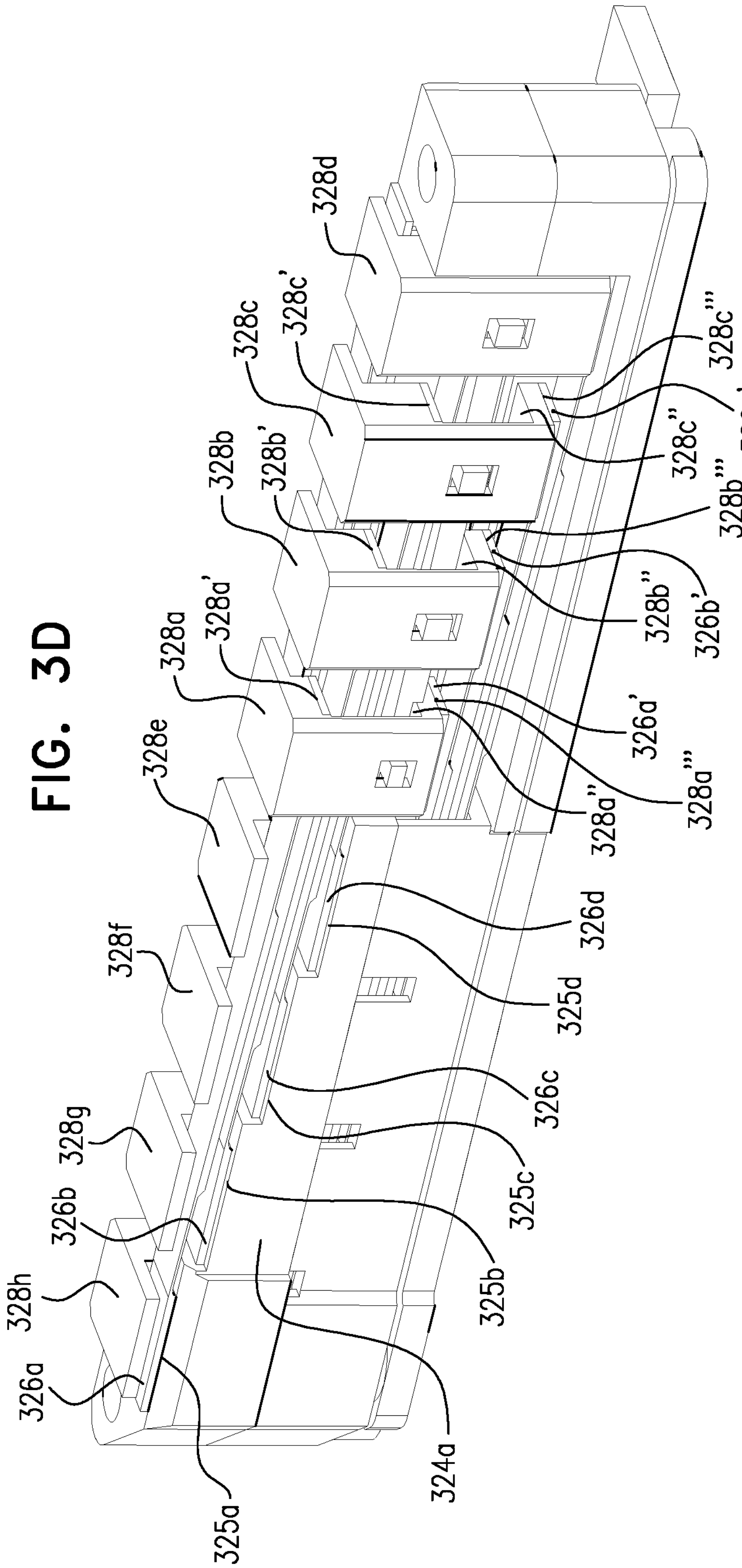

328d
328c
328c'
328b
328b'
328a
328a'
328e
328f
328g
326b
328h
326a
325a
324a
325b
325c
326c
325d
326d
328a''
328a'''
326a'
328b''
326b'
328b'''
328c''
326c'
328c'''

FIG. 3D

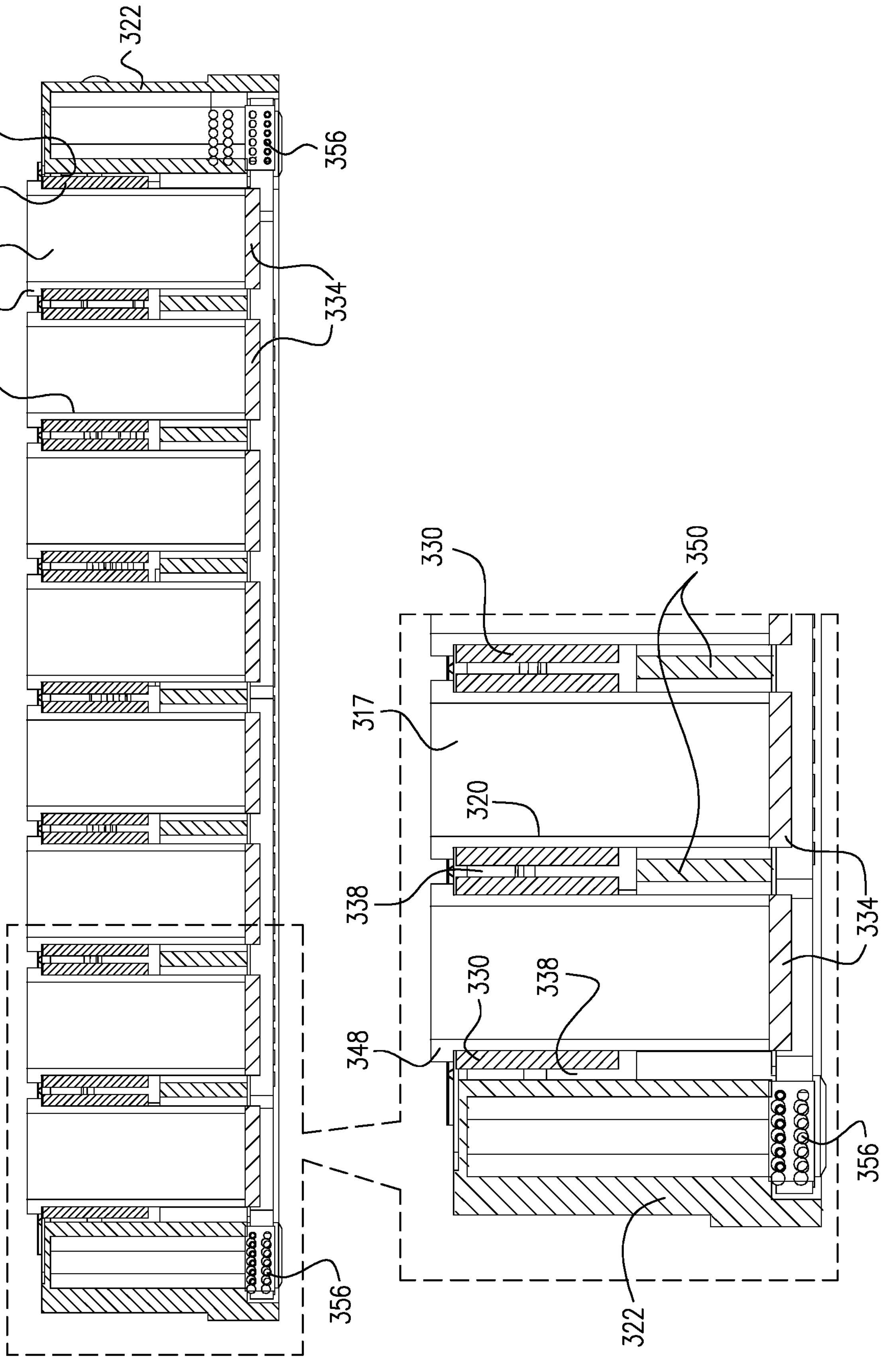
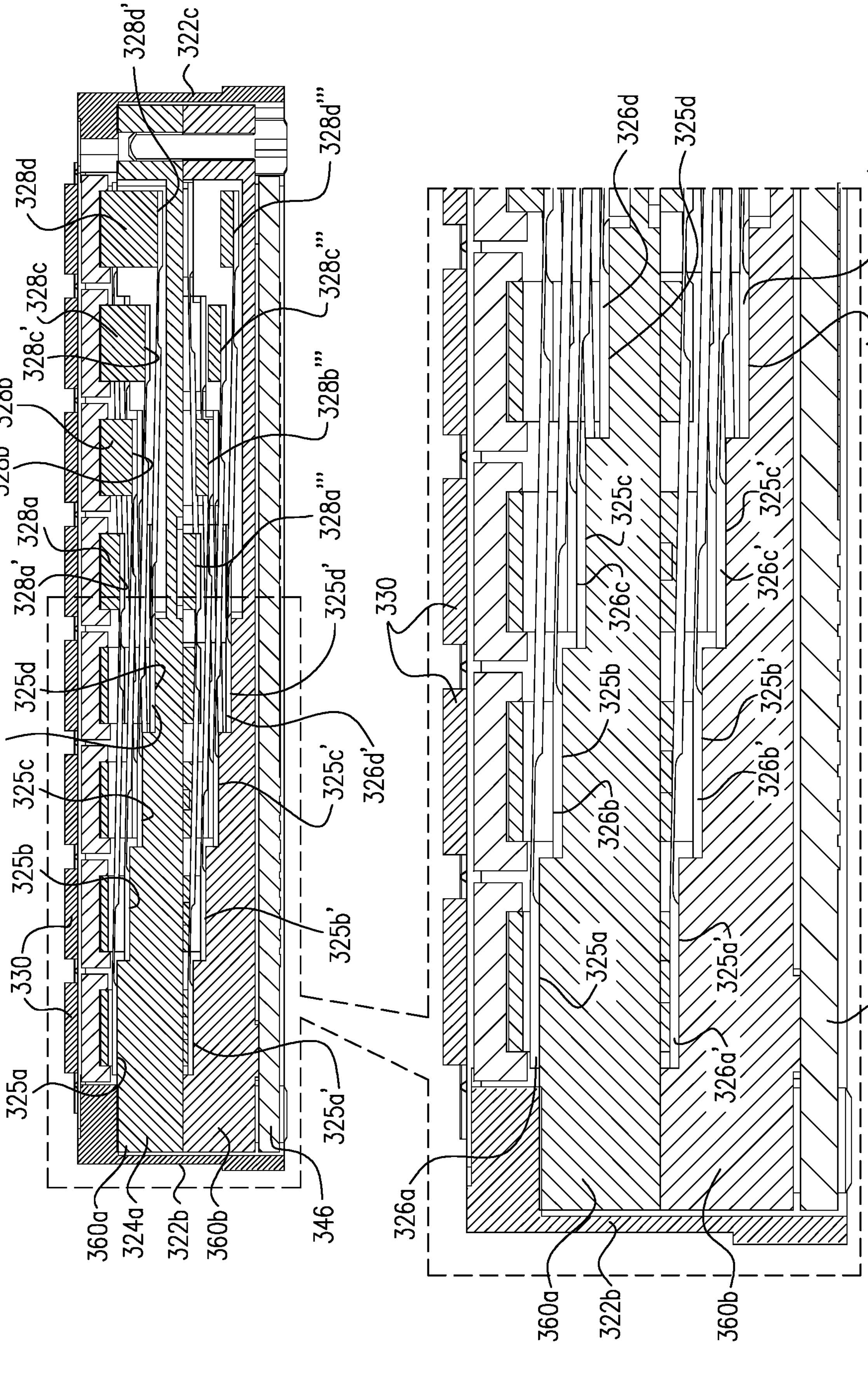


FIG. 3E



328d'
322c
328d
328d'''
328c
328c'
328c'''
328b
328b'
328b'''
328a
328a'
328a'''
325d'
325d
326d
325c
325c'
326d'
325b
325b'
330
325a
325a'
360a
324a
322b
360b
346
326d
325d
326d'
325d'
330
325c
326c
325c'
326c'
325b
326b
325b'
326b'
325a
325a'
326a'
326a
346
360a
322b
360b

FIG. 3F

FIG. 3G

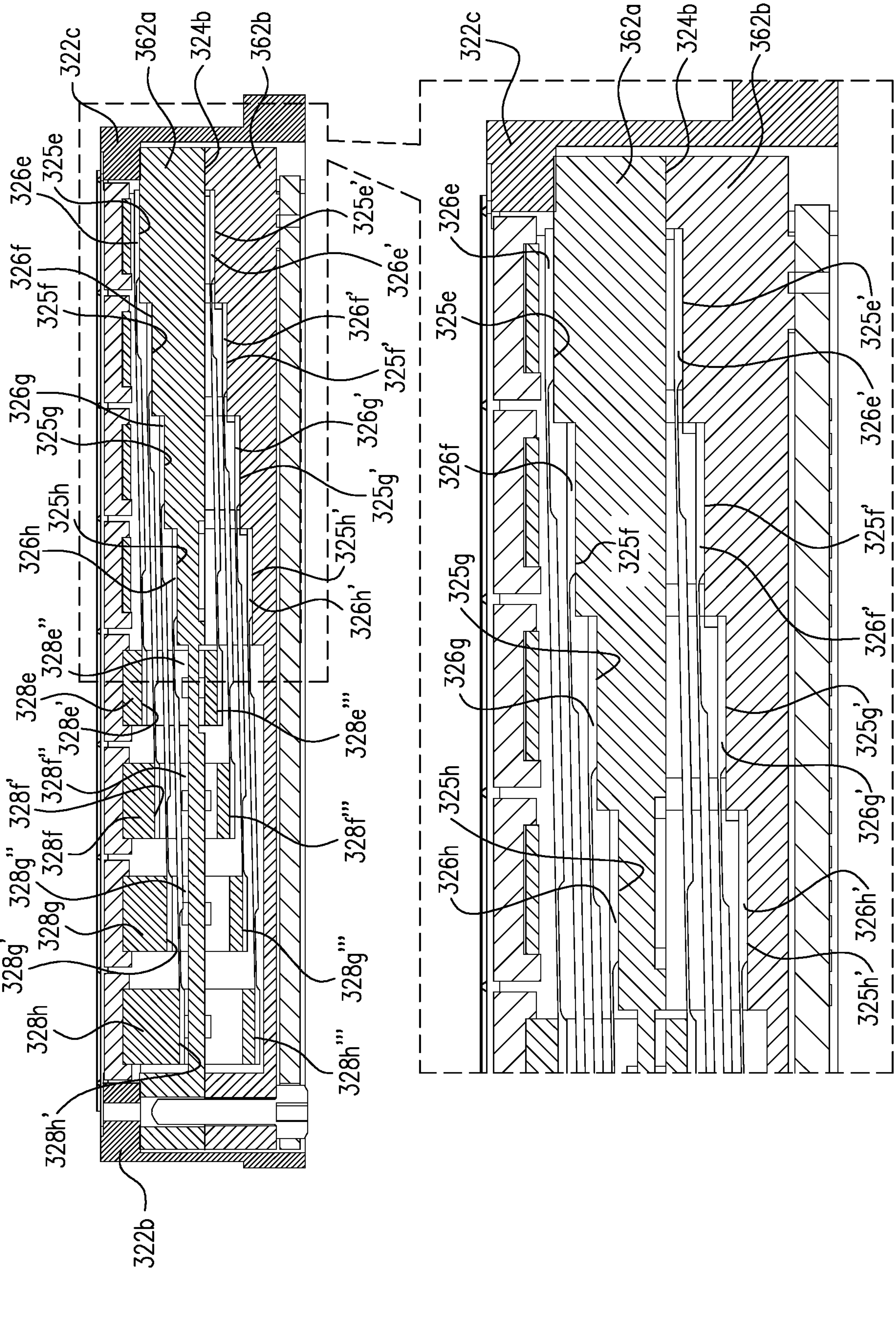
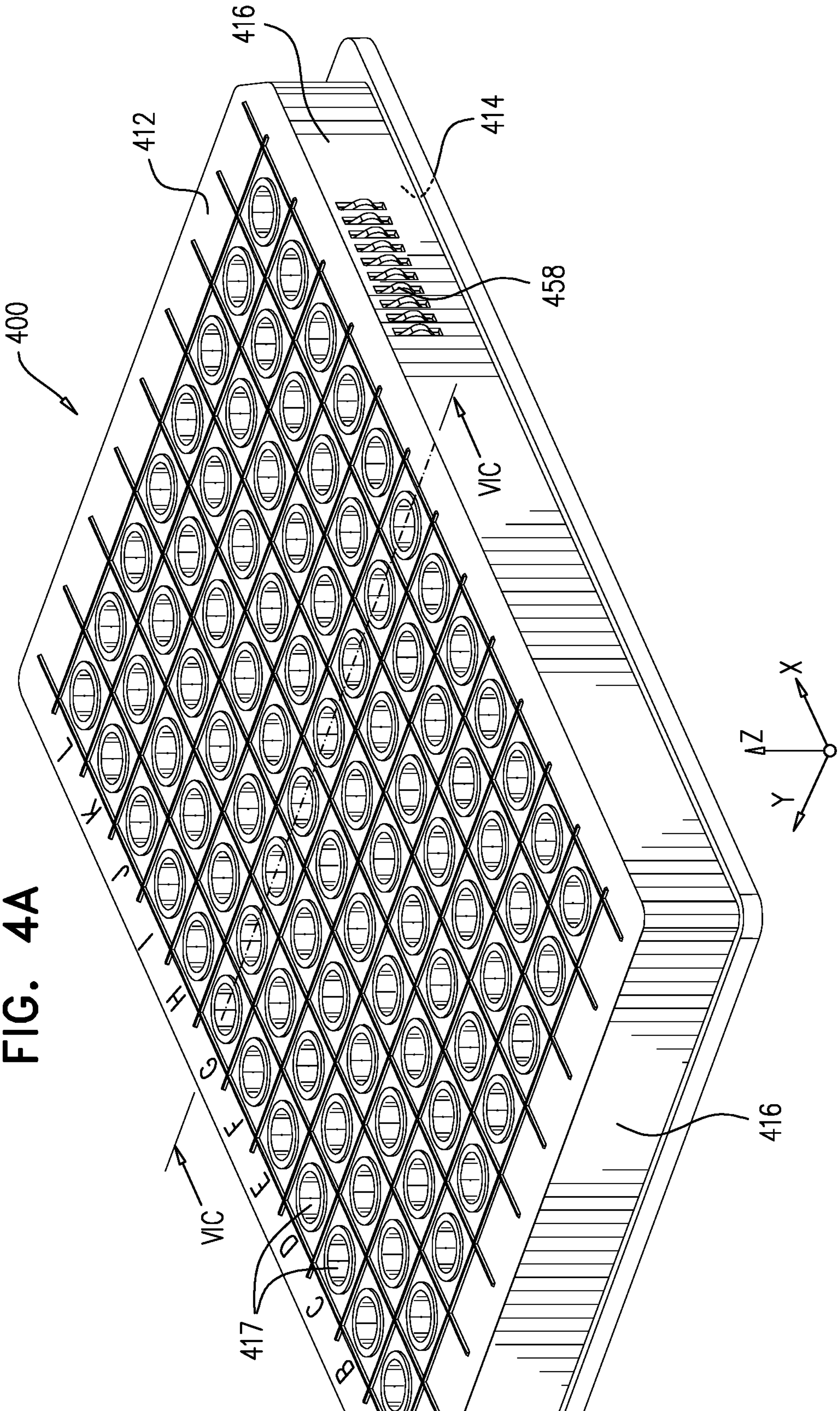
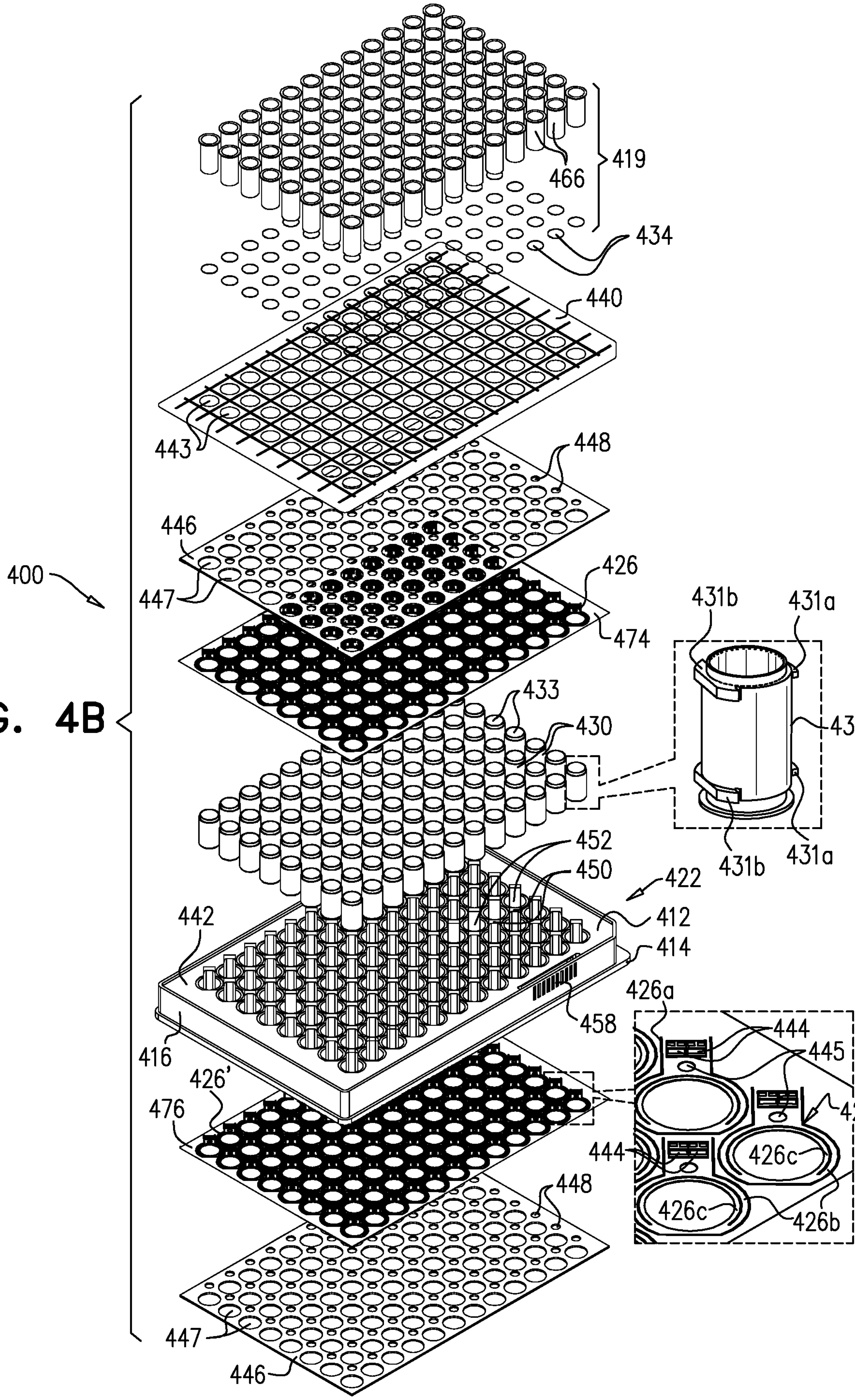

322c
362a
324b
362b
326e
325e
325e'
326e'
326f
325f
326f'
325f'
326g
325g
326g'
325g'
325h
326h
325h'
326h'
328e''
328e
328e'
328e'''
328f'
328f''
328f
328f'''
328g''
328g
328g'
328g'''
328h
328h'''
328h'
322b

FIG. 4A




419
466
434
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443
448
446
447
426
474
400
433
430
431b
431a
430
431b
431a
452
450
422
442
412
414
458
416
426a
444
445
426'
476
444
426c
426c
426b
448
447
446

FIG. 4B

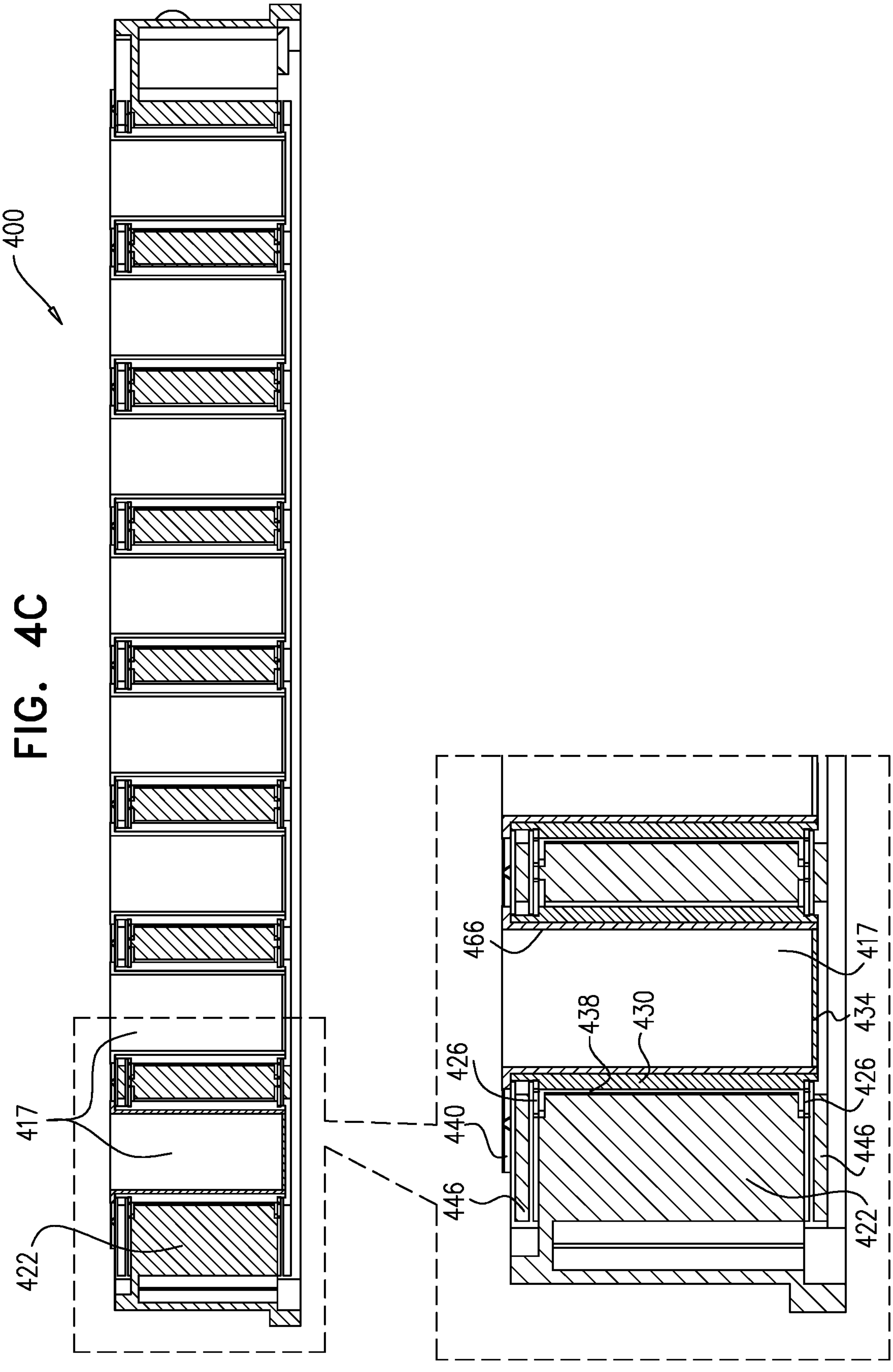

FIG. 4C

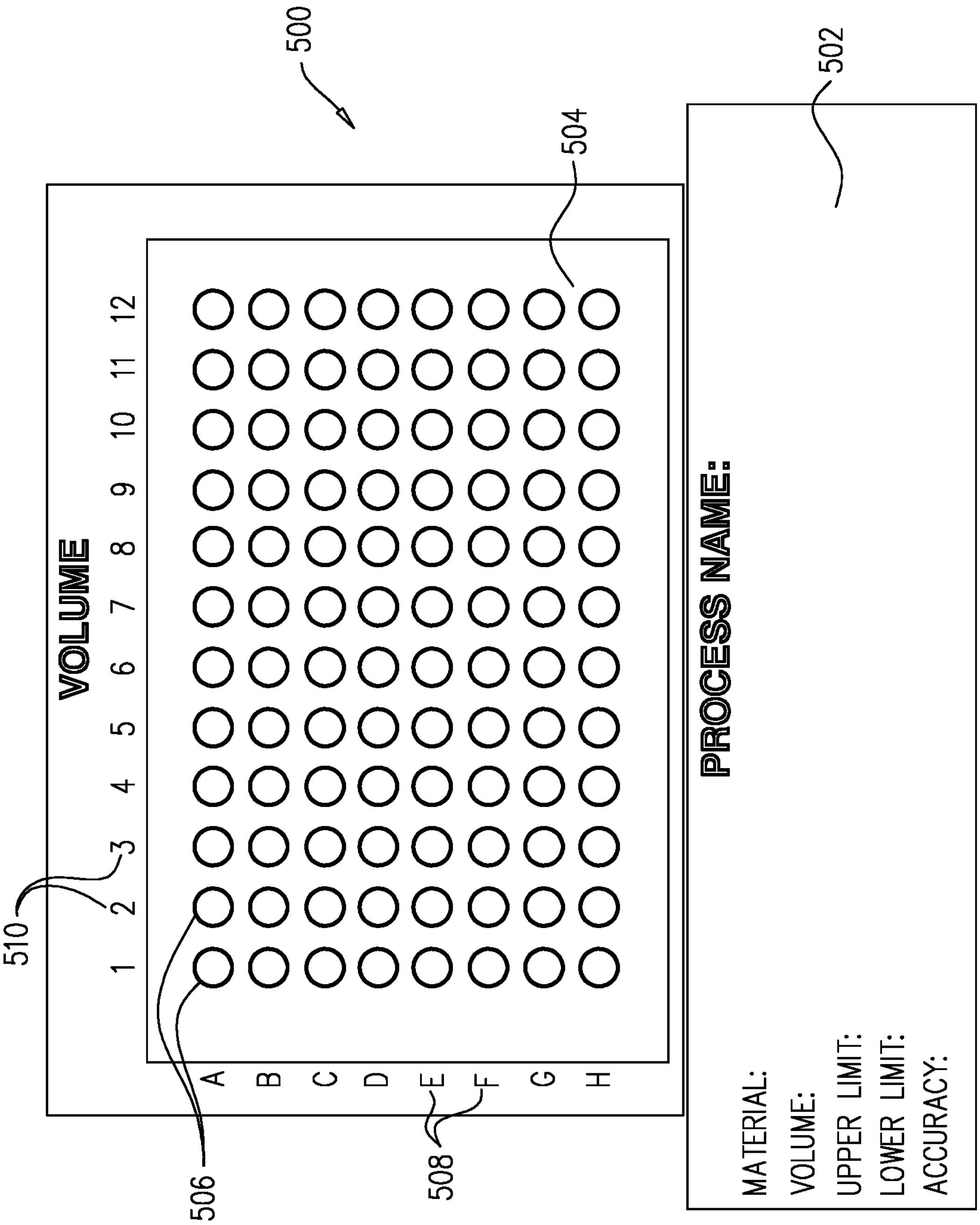
500
502
504
VOLUME
1 2 3 4 5 6 7 8 9 10 11 12
A B C D E F G H
510
506
508
PROCESS NAME:
MATERIAL:
VOLUME:
UPPER LIMIT:
LOWER LIMIT:
ACCURACY:

FIG. 5A

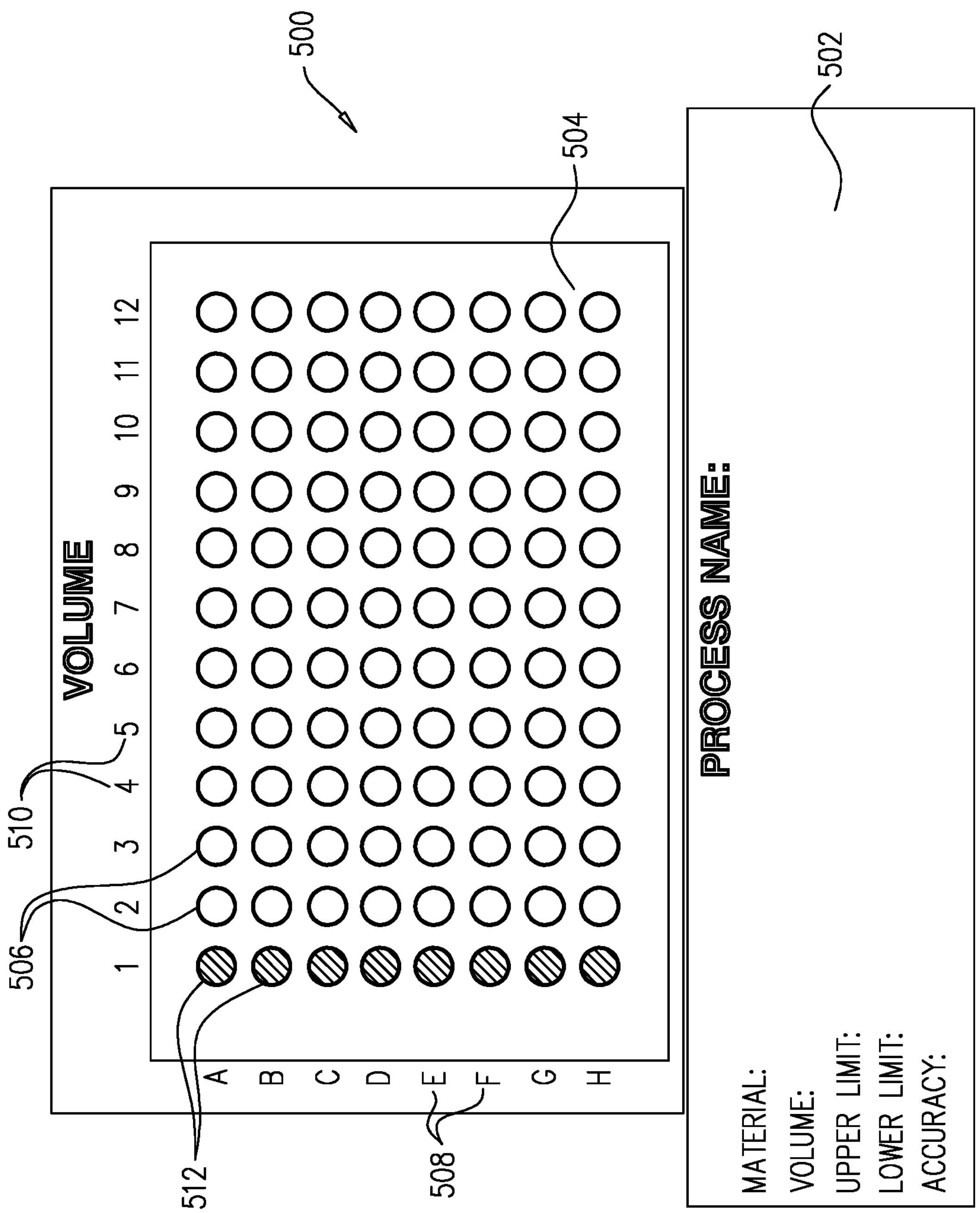
500
502
504
VOLUME
1 2 3 4 5 6 7 8 9 10 11 12
A B C D E F G H
506
508
510
512
PROCESS NAME:
MATERIAL:
VOLUME:
UPPER LIMIT:
LOWER LIMIT:
ACCURACY:

FIG. 5B

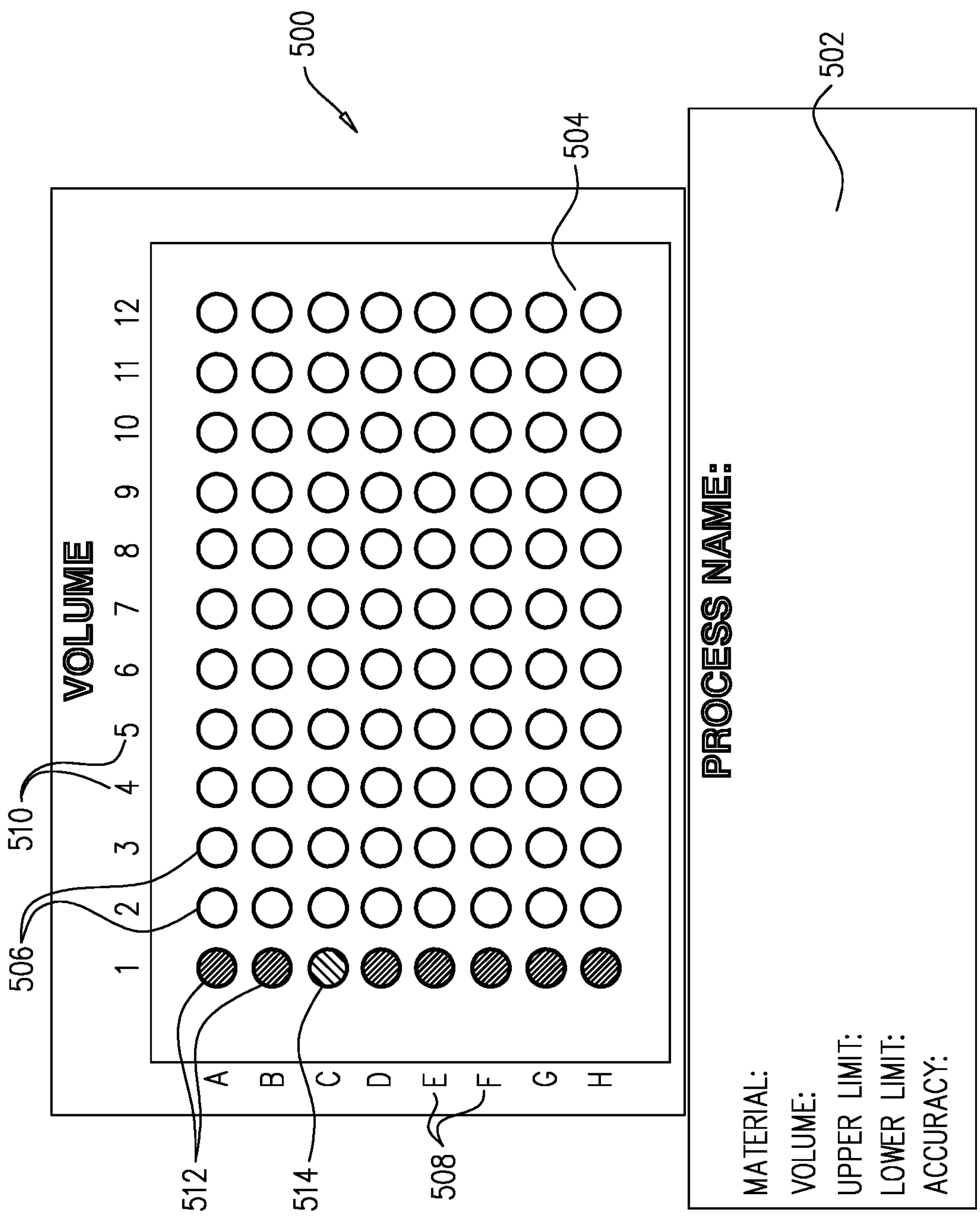
500
502
504
506
508
510
512
514
VOLUME
1 2 3 4 5 6 7 8 9 10 11 12
A B C D E F G H
PROCESS NAME:
MATERIAL:
VOLUME:
UPPER LIMIT:
LOWER LIMIT:
ACCURACY:

FIG. 5C

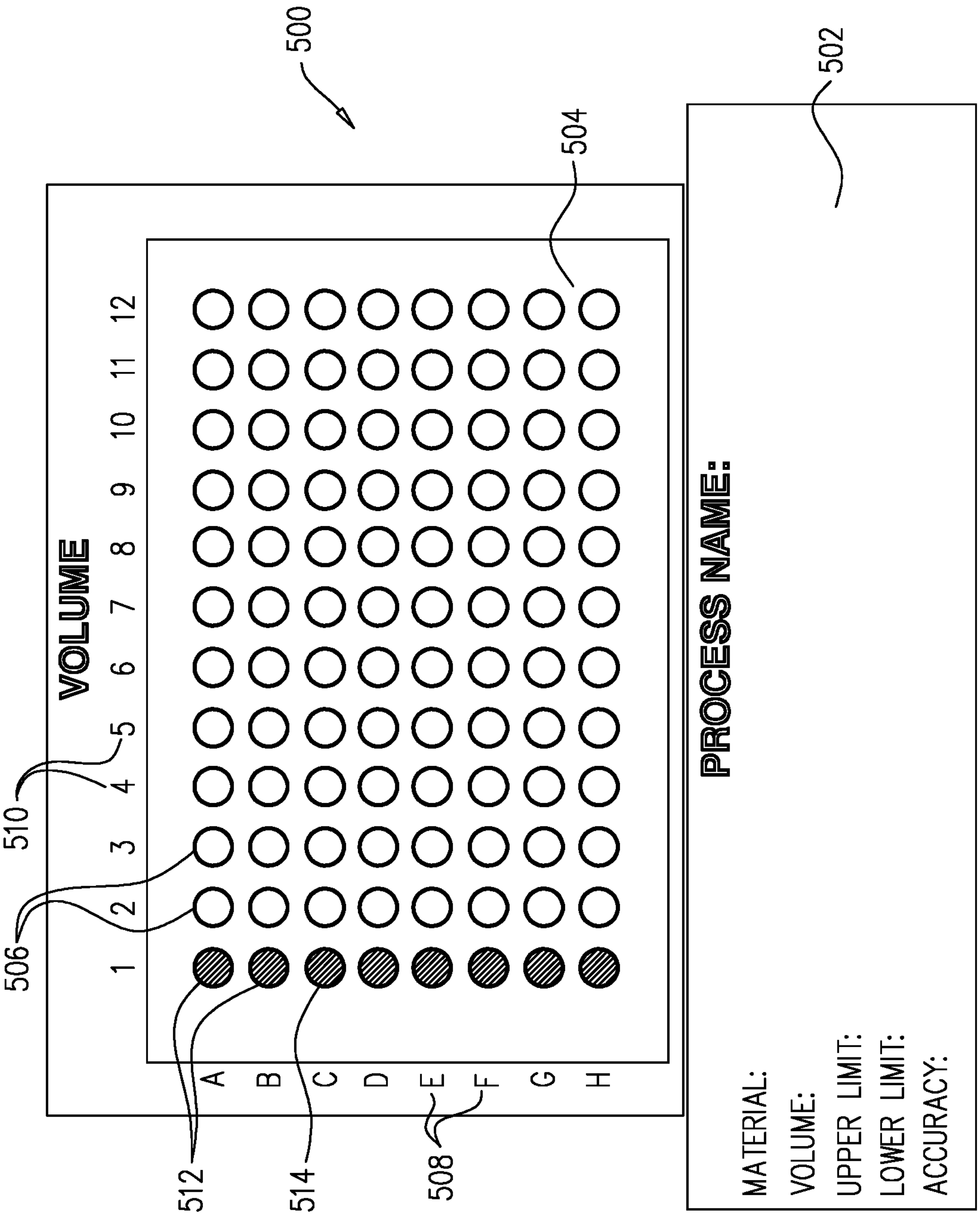
500
502
504
VOLUME
1
2
3
4
5
6
7
8
9
10
11
12
A
B
C
D
E
F
G
H
PROCESS NAME:
MATERIAL:
VOLUME:
UPPER LIMIT:
LOWER LIMIT:
ACCURACY:
506
508
510
512
514

FIG. 5D

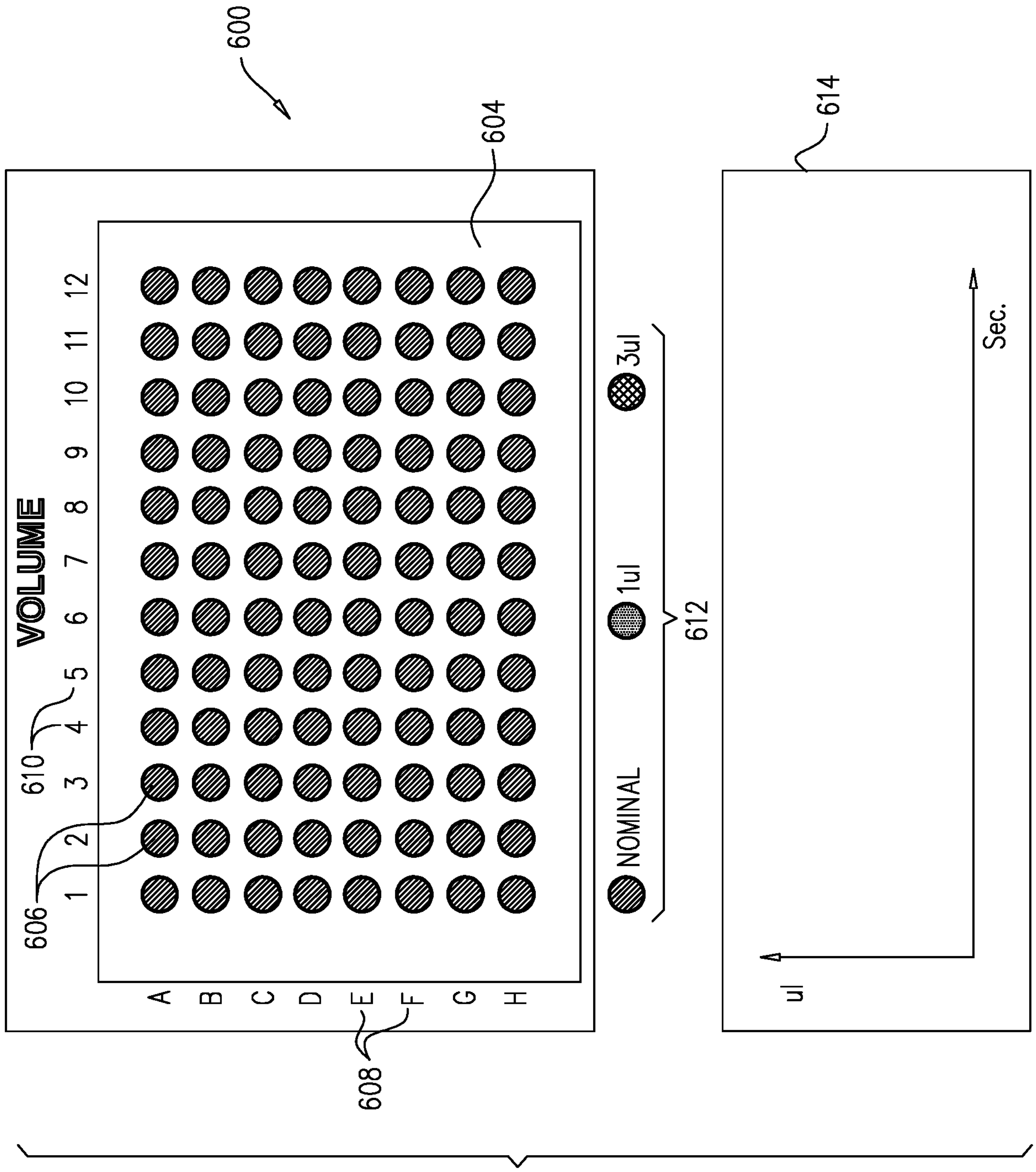
600
604
614
VOLUME
1
2
3
4
5
6
7
8
9
10
11
12
A
B
C
D
E
F
G
H
606
610
608
NOMINAL
1ul
3ul
612
Sec.
ul

FIG. 6A

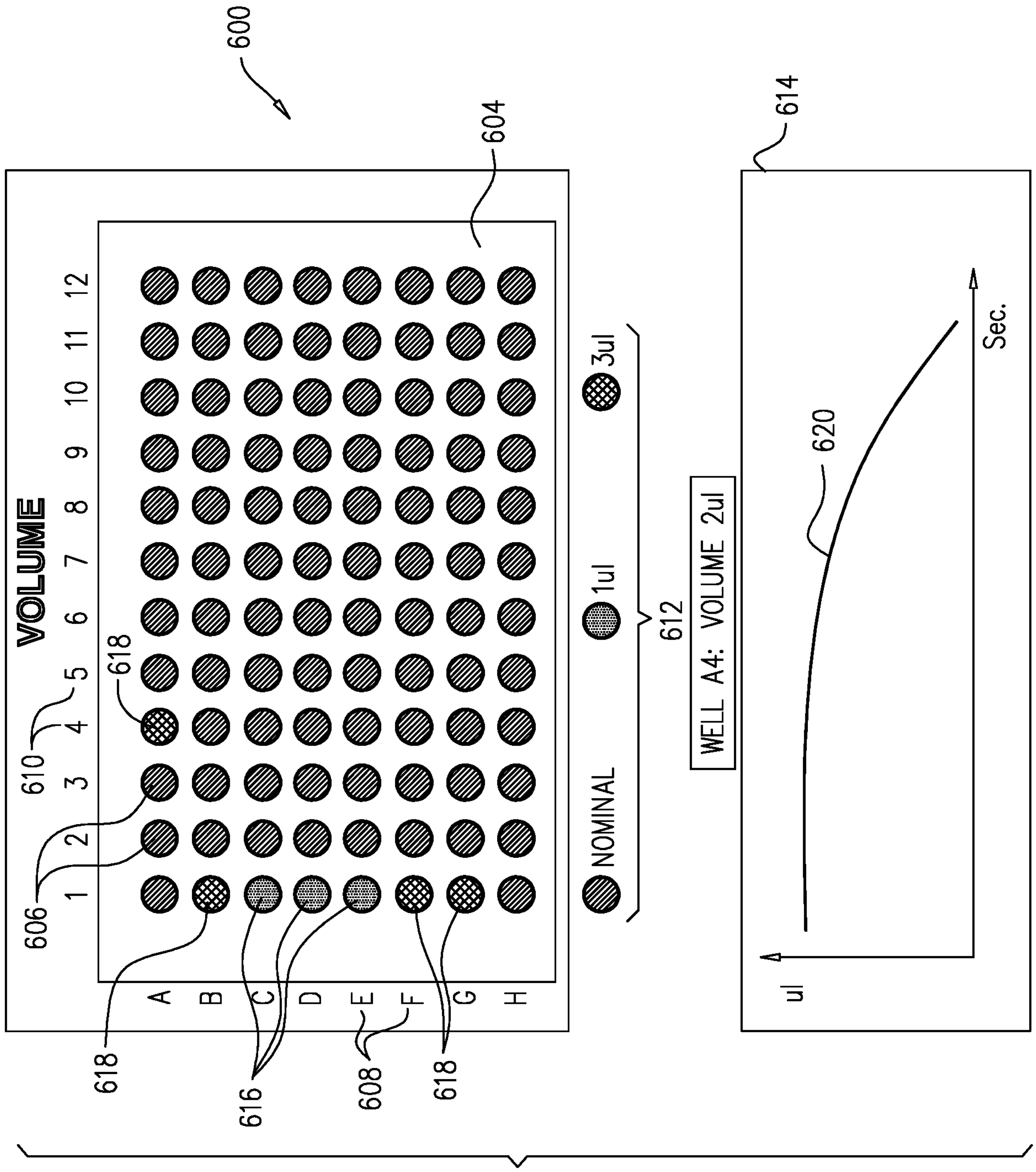
600
604
VOLUME
1
2
3
4
5
6
7
8
9
10
11
12
A
B
C
D
E
F
G
H
606
610
618
616
608
NOMINAL
1ul
3ul
612
WELL A4: VOLUME 2ul
614
620
ul
Sec.

FIG. 6B

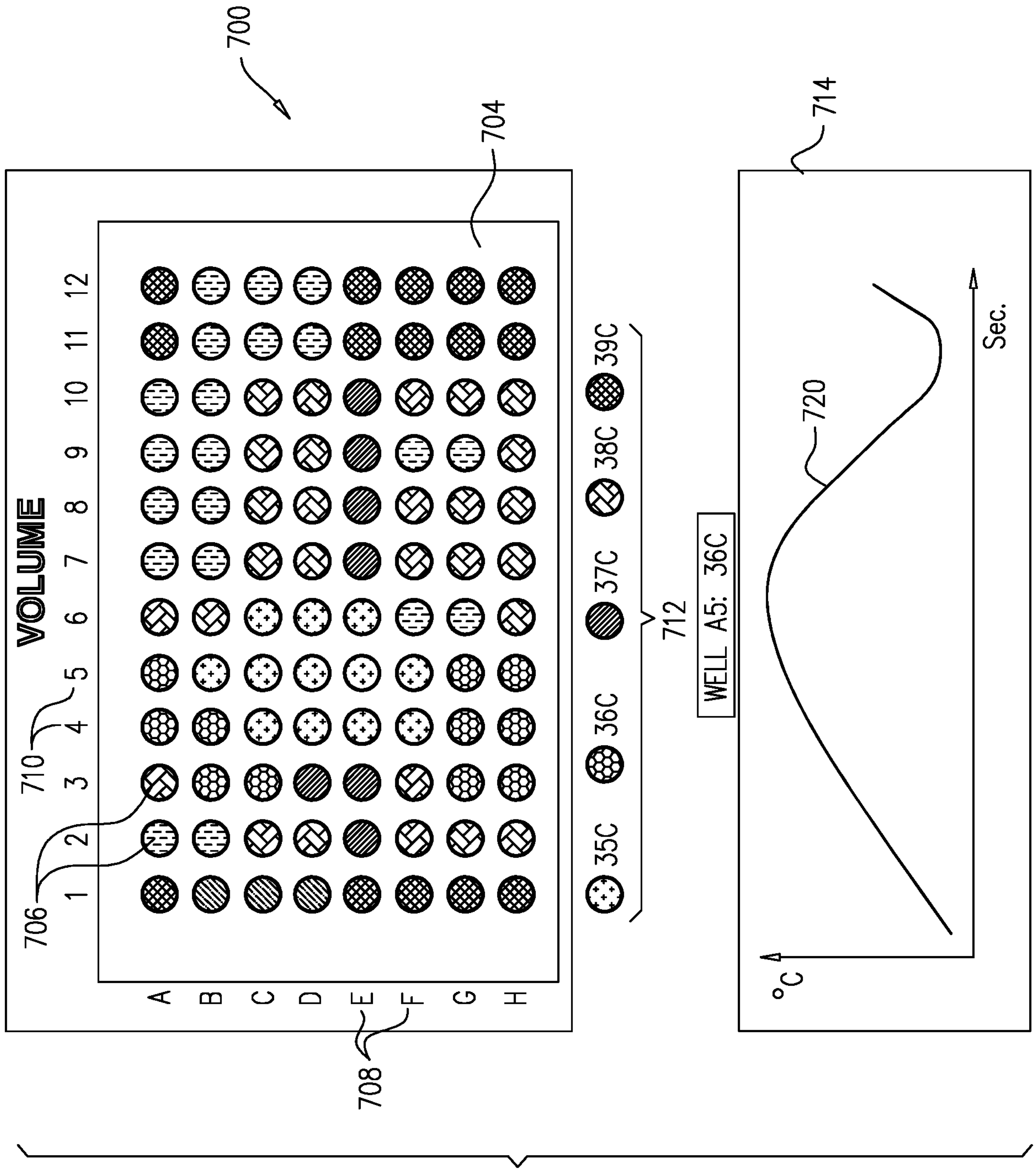
700
704
714
VOLUME
1 2 3 4 5 6 7 8 9 10 11 12
A B C D E F G H
706
708
710
712
35C
36C
37C
38C
39C
WELL A5: 36C
720
°C
Sec.

FIG. 7

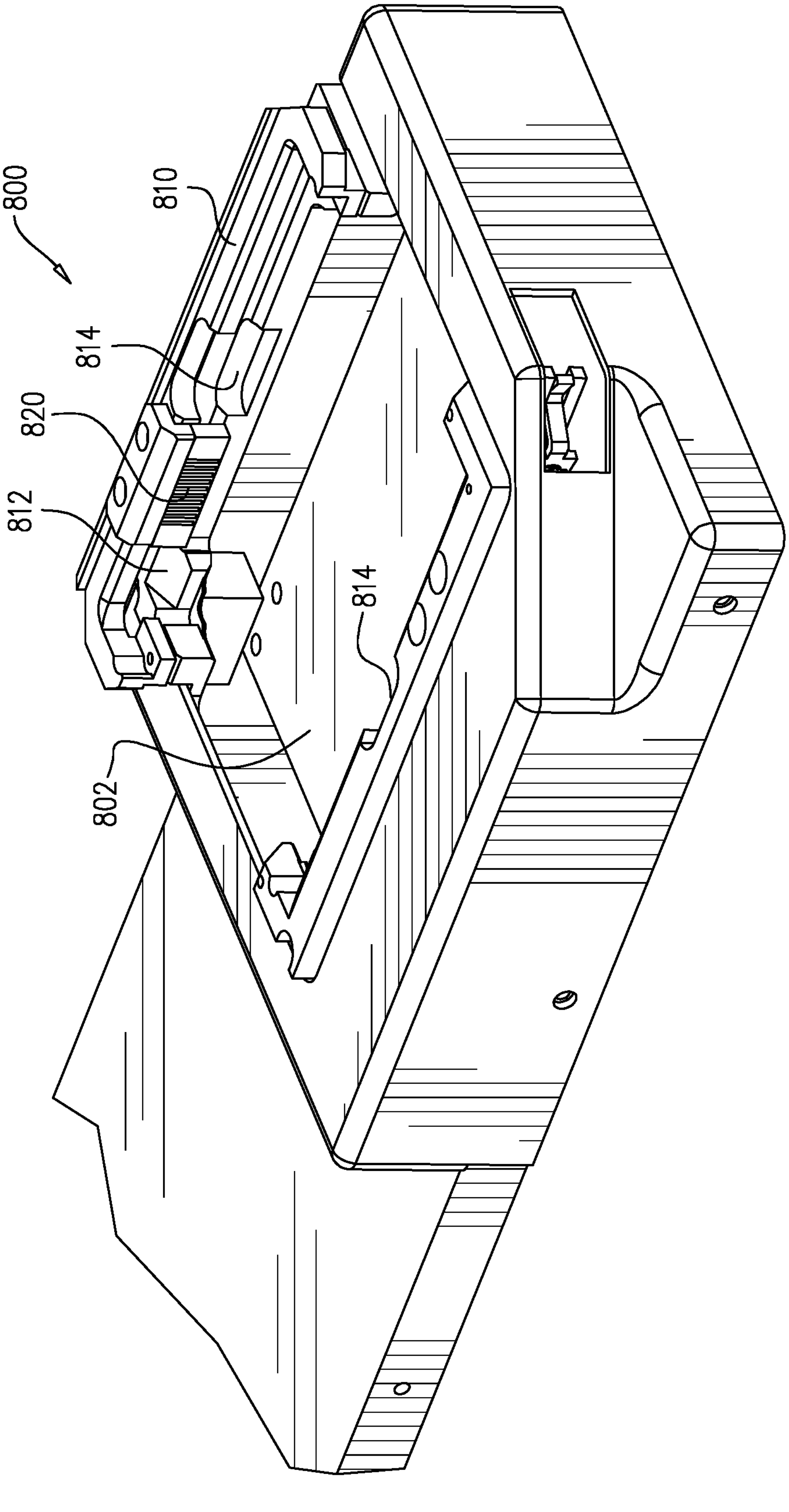

FIG. 8

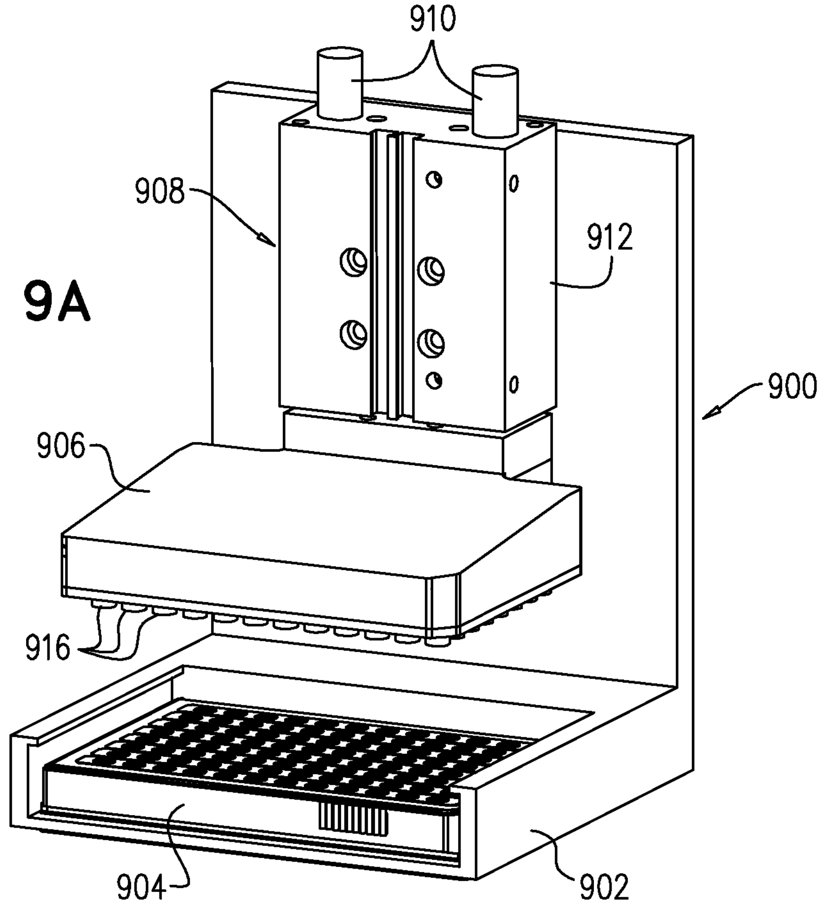
910
908
912
900
906
916
904
902

FIG. 9A

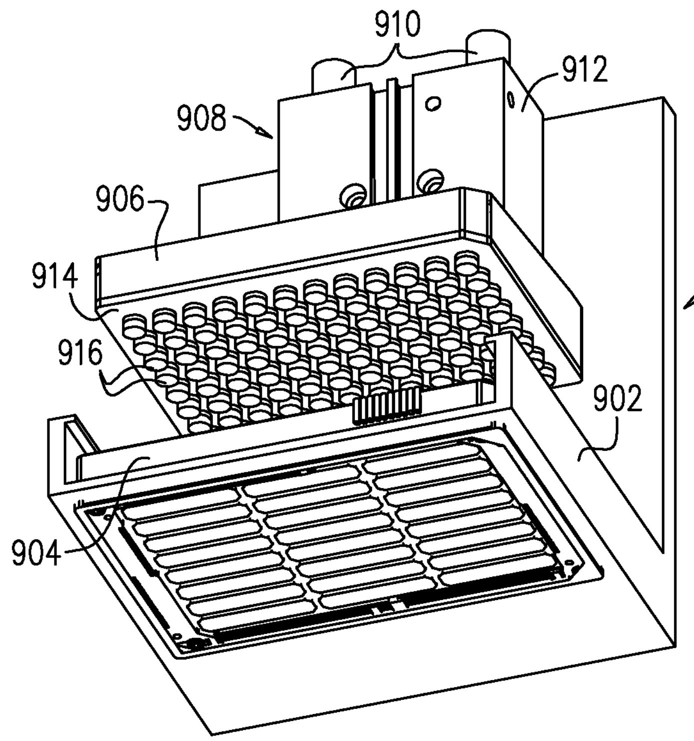
910
908
912
906
914
916
900
902
904

FIG. 9B