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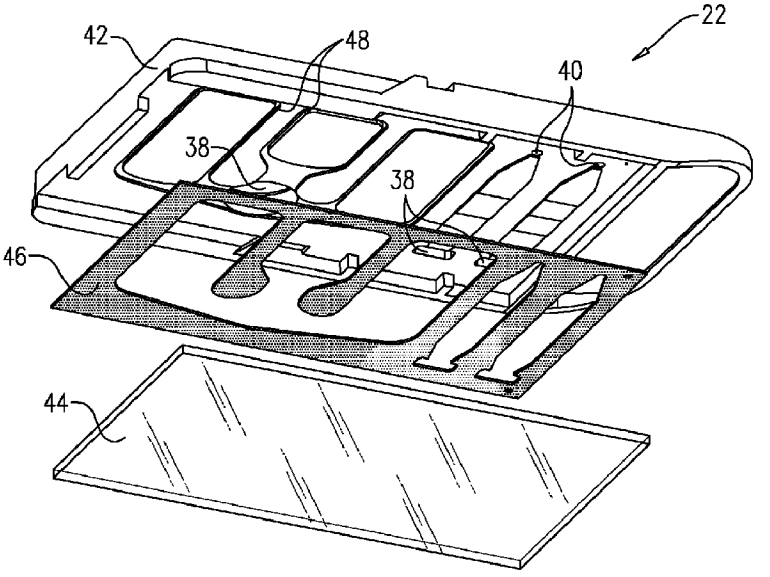

FIG. 4C

(57) Abrégé/Abstract:
Apparatus and methods are described including a sample carrier (22) configured to carry a portion of a bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions. An optical measurement device (24)

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(57) Abrégé(suite)/Abstract(continued):
performs optical measurements upon the portion of the bodily sample that is housed within the sample carrier (22), and at least partially photobleaches an area within the portion of the sample carrier (22) by causing the area to fluoresce. By detecting that the area within the portion of the sample carrier (22) has been photobleached, an output is generated indicating that at least a portion of the sample carrier (22) is contaminated or that optical measurements cannot be performed on the portion of the sample carrier (22), or the optical measurement device (24) is prevented from performing optical measurements upon a sample portion housed within the given portion of the sample carrier (22).

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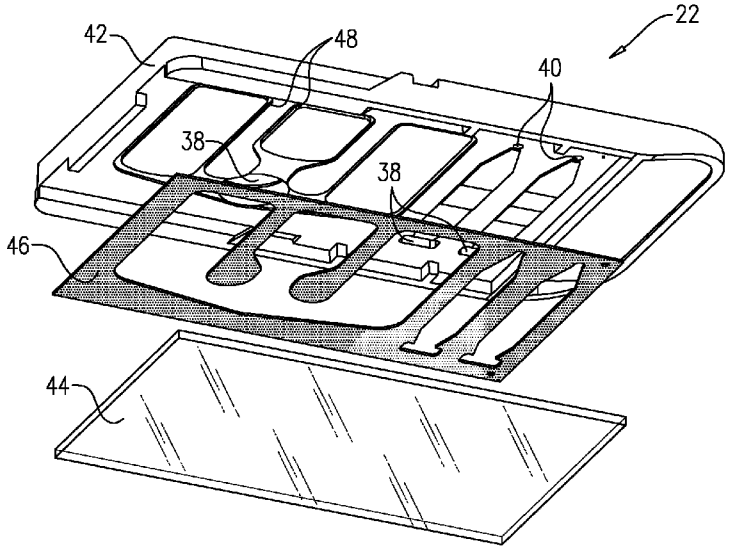

FIG. 4C

(57) Abstract: Apparatus and methods are described including a sample carrier (22) configured to carry a portion of a bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions. An optical measurement device (24) performs optical measurements upon the portion of the bodily sample that is housed within the sample carrier (22), and at least partially photobleaches an area within the portion of the sample carrier (22) by causing the area to fluoresce. By detecting that the area within the portion of the sample carrier (22) has been photobleached, an output is generated indicating that at least a portion of the sample carrier (22) is contaminated or that optical measurements cannot be performed on the portion of the sample carrier (22), or the optical measurement device (24) is prevented from performing optical measurements upon a sample portion housed within the given portion of the sample carrier (22).

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SAMPLE CARRIER FOR OPTICAL MEASUREMENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority from U.S. Provisional Patent Application No. 62/585,621 to Yorav-Raphael, filed Nov. 14, 2017, entitled "Sample carrier for optical measurements."

The above-referenced application is incorporated herein by reference.

FIELD OF EMBODIMENTS OF THE INVENTION

Some applications of the presently disclosed subject matter relate generally to sample carriers that are used for optical measurements, and in particular, to sample carriers that are used for microscopic measurements that are performed upon bodily samples.

BACKGROUND

In some optics-based methods (e.g., diagnostic, and/or analytic methods), a property of a biological sample, such as a blood sample, is determined by performing an optical measurement. For example, the density of a component (e.g., a count of the component per unit volume) may be determined by counting the component within a microscopic image. Similarly, the concentration and/or density of a component may be measured by performing optical absorption, transmittance, fluorescence, and/or luminescence measurements upon the sample. Typically, the sample is placed into a sample carrier and the measurements are performed with respect to a portion of the sample that is contained within a chamber of the sample carrier. The measurements that are performed upon the portion of the sample that is contained within the chamber of the sample carrier are analyzed in order to determine a property of the sample.

For some applications, diagnostic tests are performed on a sample carrier that is filled with a bodily sample that is taken from a subject. In such cases, there is a risk that a user will try to reuse the cartridge (e.g. after washing it). This could lead to the risk of erroneous results in diagnosing a subsequent sample that is placed in the sample carrier after is has already been used, e.g. due to cross-contamination, and/or debris being left in the sample carrier from its previous use.

SUMMARY OF EMBODIMENTS

For some applications of the present invention, a sample carrier is configured to house the bodily sample, and at least a portion of the sample carrier is configured to fluoresce, at least under certain conditions. For some applications, the portion of the sample carrier is analyzed, in order to determine whether the portion or an area thereof has undergone photobleaching. In response to detecting that the portion or the area thereof has undergone photobleaching, it is determined that the sample carrier, or a portion thereof (e.g., a chamber thereof) has already been used, and/or the number of times the sample carrier or the portion thereof (e.g., a chamber thereof) has been used. For some applications, the above steps are performed by a computer processor. For some applications, in response to detecting that the sample carrier, or a portion thereof (e.g., a chamber thereof) has already been used, or that the usage of the sample carrier, or a portion thereof (e.g., a chamber thereof) has exceeded a given threshold, the computer processor (a) generates an output indicating that the sample carrier, or the portion thereof (e.g., the chamber thereof), should not be used, (b) generates an output indicating that the sample carrier, or the portion thereof (e.g., the chamber thereof) is contaminated, and/or (c) prevents the optical measurement device from performing optical measurements upon the sample carrier, or the portion thereof (e.g., the chamber thereof).

For some applications, a given area of the sample carrier is marked by photobleaching the area when the sample carrier is used. For example, an optical measurement device may be configured to photobleach a given area of the sample carrier, when the sample carrier is placed inside the optical measurement device, and/or when the optical measurement device performs an optical measurement on the sample carrier. For some applications, the optical measurement is configured to photobleach a given area of the sample carrier automatically, by virtue of performing optical measurements upon the sample carrier. For example, the optical measurement device may be a microscope system that performs fluorescent imaging upon the sample. For some applications, the excitation wavelength that is emitted by the microscope system, in order to cause the sample to fluoresce, also photobleaches the given area of the sample carrier. For some applications, prior to photobleaching the given area, the computer processor verifies that the sample carrier has not already been used, using the techniques described hereinabove.

For some applications, the sample carrier is configured to be reused, but only a limited number of times. For some such applications, each time the sample carrier is used, a respective different area of the sample carrier is photobleached, such that the computer processor may then determine how many times the sample carrier has been used by detecting the number and/or locations of photobleached areas upon the sample carrier.

For some applications, the above-described photobleaching effect is used by a manufacturer of sample carriers to encode manufacturing information regarding the sample carrier, in a manner that is not visible to the naked eye. For example, such information may include an authenticity mark (to reduce the likelihood of counterfeit sample carriers being utilized), sample carrier type, manufacturing date, expiry date, manufacturing location, date required for accurate performance of the test (e.g. calibration date pertaining to the sample carrier, or batch of sample carriers). For some such applications, the mark is marked using a geometric pattern that includes lines, figures, barcodes, alphanumeric characters, etc.

There is therefore provided, in accordance with some applications of the present invention, apparatus for use with a bodily sample, the apparatus including:

a sample carrier configured to carry a portion of the bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions; and

an optical measurement device configured to:

perform optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

at least partially photobleach an area within the portion of the sample carrier by causing the area to fluoresce.

In some applications, the apparatus further includes an optical measurement unit that is configured to house the sample carrier while the optical measurement device performs the optical measurements upon the portion of the bodily sample, and the optical measurement device is configured to photobleach the given area of the sample carrier, in response to the sample carrier being placed inside the optical measurement unit.

In some applications, wherein the sample carrier is configured to be used for a plurality of measurements by the optical measurement device, and wherein the optical measurement device is configured to photobleach a respective different area of the sample

carrier, each time the sample carrier is used for measurements by the optical measurement device.

In some applications, the apparatus further includes:

an output device; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to generate an output upon the output device indicating that at least a portion of the sample carrier is contaminated.

In some applications, the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to generate the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

In some applications, the apparatus further includes:

an output device; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to generate an output upon the output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier.

In some applications, the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to generate the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

In some applications, the apparatus further includes at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to prevent the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

In some applications, wherein the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to prevent the optical measurement device from performing the optical measurements, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

In some applications, the optical measurement device is configured to photobleach the given area of the sample carrier by virtue of performing optical measurements upon the sample.

In some applications, the optical measurement device is configured to illuminate the sample, in order to perform optical measurements on the sample, and the optical measurement device is configured to photobleach the given area of the sample carrier by virtue of illuminating the sample.

There is further provided, in accordance with some applications of the present invention, a method for use with a bodily sample, the method including:

placing a portion of the bodily sample within a sample carrier, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions; and

while the portion of the bodily sample is housed within the sample carrier, performing optical measurements upon the portion of the bodily sample that is housed within the sample carrier, using an optical measurement device; and

at least partially photobleaching an area within the portion of the sample carrier by causing the area to fluoresce.

There is further provided, in accordance with some applications of the present invention, apparatus for use with a bodily sample and an output device, the apparatus including:

a sample carrier configured to carry the bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions;

an optical measurement device configured to perform optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured, in response to detecting that an area within the portion of the sample carrier has been photobleached, to perform an action selected from the group consisting of: generating an output upon the output device indicating that at least a portion of the sample carrier is contaminated, generating an output upon the output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier, and preventing the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

In some applications, the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to perform the selected action, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

There is further provided, in accordance with some applications of the present invention, a method for use with a bodily sample and an output device, the method including:

placing a portion of the bodily sample inside a sample carrier, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions;

performing optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

using at least one computer processor, in response to detecting that an area within the portion of the sample carrier has been photobleached, performing an action selected from the group consisting of: generating an output upon the output device indicating that at least a portion of the sample carrier is contaminated, generating an output upon the output device

indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier, and preventing the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

There is further provided, in accordance with some applications of the present invention, apparatus for use with a bodily sample and a microscope having an imaging module, the apparatus including:

at least one chamber configured for housing therein a portion of the bodily sample, the chamber including an upper inner surface, and a lower inner surface,

wherein the upper inner surface includes a first mark and the lower inner surface includes a second mark; and

a computer processor configured to:

focus the imaging module on the first marking and register an indication of a first focusing distance between the imaging module and the first marking;

focus the imaging module on the second marking and register an indication of a second focusing distance between the imaging module and the second marking; and

determine a height of the chamber, based upon a difference between the first focusing distance and the second focusing distance.

There is further provided, in accordance with some applications of the present invention, a method for use with a bodily sample and a microscope having an imaging module, the method including:

placing a portion of the bodily sample inside at least one chamber, the chamber including an upper inner surface, and a lower inner surface, the upper inner surface including a first mark and the lower inner surface including a second mark; and

using at least one computer processor:

focusing the imaging module on the first marking and registering an indication of a first focusing distance between the imaging module and the first marking;

focusing the imaging module on the second marking and registering an indication of a second focusing distance between the imaging module and the second marking; and

determining a height of the chamber, based upon a difference between the first focusing distance and the second focusing distance.

The present invention will be more fully understood from the following detailed description of embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a block diagram showing components of a biological sample analysis system, in accordance some applications of the present invention;

Figs. 2A, 2B, 2C, and 2D are schematic illustrations of respective views of a sample carrier, in accordance with some applications of the present invention;

Figs. 3A and 3B show photobleaching patterns that were detected upon a sample carrier immediately after being exposed to short-term fluorescent excitation (Fig. 3A), and one week after the exposure (Fig. 3B), in accordance with some applications of the present invention;

Fig. 3C is a plot of the fluorescent emission from the sample carrier measured along the length of the sample carrier, immediately after the sample carrier was exposed to the short-term fluorescent excitation, one week after the sample carrier was exposed to the short-term fluorescent excitation, and three weeks after the sample carrier was exposed to the short-term fluorescent excitation, in accordance with some applications of the present invention;

Figs. 4A, 4B, and 4C are schematic illustrations of respective views of a sample carrier that is used for performing both microscopic measurements and optical density measurements, in accordance with some applications of the present invention;

Figs. 5A, 5B, and 5C are schematic illustrations of respective views of a sample carrier that is used for performing both microscopic measurements and optical density measurements, in accordance with some applications of the present invention;

Fig. 6 is a schematic illustration of a sample carrier that includes markings on its upper and lower surfaces, in accordance with some applications of the present invention;

Fig. 7A is a schematic top view of an irregular pattern of a sample carrier, in accordance with some applications of the present invention;

Fig. 7B is a schematic diagram illustrating the irregular pattern shown in Fig. 7A when tilted, in accordance with some applications of the present invention;

Figs. 8A, 8B, 8C, and 8D are schematic top views of portions of the irregular pattern shown in Fig. 7A as viewed through an observation field of an imaging module of an optical measurement device, in accordance with some applications of the present invention;

Figs. 9A, 9B, 9C, and 9D are schematic top views of portions of the irregular pattern shown in Fig. 7B as viewed through an observation field of an imaging module of an optical measurement device, in accordance with some applications of the present invention;

Figs. 10A, 10B, and 10C are schematic top views of some examples of irregular patterns, in accordance with some applications of the present invention;

Fig. 11A is a schematic illustration of a 3D irregular pattern on a sample carrier, in accordance with some applications of the present invention;

Fig. 11B is a schematic 3D illustration of a portion of the 3D irregular pattern shown in Fig. 11A, in accordance with some applications of the present invention;

Figs. 11C, 11D, 11E, and 11F are schematic 2D top views of the portion shown in Fig. 11B, taken at respective different focal lengths of an optical field of an imaging module of an optical measurement device, in accordance with some applications of the present invention;

Fig. 12 is a schematic XY position chart demonstrating some possible planar positions of a sample carrier with respect to an imaging module of an optical measurement device, in accordance with some applications of the present invention.

DETAILED DESCRIPTION OF EMBODIMENTS

Reference is now made to Fig. 1, which is block diagram showing components of a biological sample analysis system 20, in accordance with some applications of the present invention. Typically, a biological sample (e.g., a blood sample) is placed into a sample carrier 22. While the sample is disposed in the sample carrier, optical measurements are performed upon the sample using one or more optical measurement devices 24. For example, the optical measurement devices may include a microscope (e.g., a digital microscope), a spectrophotometer, a photometer, a spectrometer, a camera, a spectral camera, a hyperspectral camera, a fluorometer, a spectrofluorometer, and/or a photodetector

(such as a photodiode, a photoresistor, and/or a phototransistor). For some applications, the optical measurement devices include dedicated light sources (such as light emitting diodes, incandescent light sources, etc.) and/or optical elements for manipulating light collection and/or light emission (such as lenses, diffusers, filters, etc.). For some applications, a microscope system is used that is generally similar to the microscope system described in US 2014/0347459 to Greenfield, which is incorporated herein by reference.

A computer processor 28 typically receives and processes optical measurements that are performed by the optical measurement device. Further typically, the computer processor controls the acquisition of optical measurements that are performed by the one or more optical measurement devices. The computer processor communicates with a memory 30. A user (e.g., a laboratory technician) sends instructions to the computer processor via a user interface 32. For some applications, the user interface includes a keyboard, a mouse, a joystick, a touchscreen device (such as a smartphone or a tablet computer), a touchpad, a trackball, a voice-command interface, and/or other types of user interfaces that are known in the art. Typically, the computer processor generates an output via an output device 34. Further typically, the output device includes a display, such as a monitor, and the output includes an output that is displayed on the display. For some applications, the processor generates an output on a different type of visual, text, graphics, tactile, audio, and/or video output device, e.g., speakers, headphones, a smartphone, or a tablet computer. For some applications, user interface 32 acts as both an input interface and an output interface, i.e., it acts as an input/output interface. For some applications, the processor generates an output on a computer-readable medium (e.g., a non-transitory computer-readable medium), such as a disk, or a portable USB drive, and/or generates an output on a printer.

For some applications, optical measurement device 24 (and/or computer processor 28 and memory 30) is housed inside an optical measurement unit 31. In order to perform the optical measurements upon the sample, sample carrier 22 is placed inside the optical measurement unit.

Reference is now made to Figs. 2A and 2B, which are schematic illustrations of respective views of sample carrier 22, in accordance with some applications of the present invention. Figs. 2A shows a top view of the sample carrier (the top cover of the sample carrier being shown as being opaque in Fig. 2A, for illustrative purposes), and Fig. 2B shows a bottom view (in which the sample carrier has been rotated around its short edge with

respect to the view shown in Fig. 2A). For some applications, sample carrier 22 includes a plurality of chambers 36, e.g., five chambers as shown in Fig. 2A. Typically, the chambers are filled with a bodily sample, such as blood via sample inlet holes 38. For some applications, the chambers define one or more outlet holes 40. The outlet holes are configured to facilitate filling of the chambers with the bodily sample, by allowing air that is present in the chambers to be released from the chambers. Typically, as shown, the outlet holes are located longitudinally opposite the inlet holes (with respect to a sample chamber of the sample carrier). For some applications, the outlet holes thus provide a more efficient mechanism of air escape than if the outlet holes were to be disposed closer to the inlet holes.

Reference is made to Fig. 2C, which shows an exploded view of sample carrier 22, in accordance with some applications of the present invention. For some applications, the sample carrier includes at least three components: a molded component 42, a glass sheet 44, and an adhesive layer 46 configured to adhere the glass sheet to an underside of the molded component. Reference is also made to Fig. 2D, which shows the molded component and the adhesive layer in the absence of the glass sheet, for illustrative purposes. The molded component is typically made of a polymer (e.g., a plastic) that is molded (e.g., via injection molding) to provide the chambers with a desired geometrical shape. For example, as shown, the molded component is typically molded to define inlet holes 38, outlet holes 40, and gutters 48 which surround the central portion of each of the chambers. The gutters typically facilitate filling of the chambers with the bodily sample, by allowing air to flow to the outlet holes, and/or by allowing the bodily sample to flow around the central portion of the chamber.

As described hereinabove, while the sample is disposed in the sample carrier, optical measurements are performed upon the sample using one or more optical measurement devices 24. Typically, the sample is viewed by the optical measurement device via the glass layer, glass being transparent at least to wavelengths that are typically used by the optical measurement device. Typically, the sample carrier is inserted into optical measurement unit 31, which houses the optical measurement device while the optical measurements are performed. Typically, the optical measurement unit houses the sample carrier such that the molded layer is disposed above the glass layer, and such that the optical measurement unit is disposed below the glass layer of the sample carrier and is able to perform optical measurements upon the sample via the glass layer. The sample carrier is formed by adhering

the glass sheet to the molded component. For example, the glass sheet and the molded component may be bonded to each other during manufacture or assembly (e.g. using thermal bonding, solvent-assisted bonding, ultrasonic welding, laser welding, heat staking, adhesive, mechanical clamping and/or additional substrates). For some applications, the glass layer and the molded component are bonded to each other during manufacture or assembly using adhesive layer 46.

For some applications, diagnostic tests are performed on a sample carrier that is filled with a bodily sample that is taken from a subject. In such cases, there is a risk that a user will try to reuse the cartridge (e.g. after washing it). This could lead to the risk of erroneous results in diagnosing a subsequent sample that is placed in the sample carrier after is has already been used, e.g. due to cross-contamination, and/or debris being left in the sample carrier from its previous use. For some applications, as shown in Figs 2A-D, a sample carrier defines a plurality of chambers, which facilitates multiple samples being placed within respective chambers of a single cartridge, and/or multiple types of diagnostic tests being performed on respective portions of a single sample that is placed in respective chambers. In such cases, it may be desirable to enable the user to perform the various tests at respective different times. However, it is further desirable that the user does not reuse the same chamber, whether deliberately or accidentally. In some cases, a sample carrier may be configured to be reused, but for a limited number of times. For some applications, in order to prevent reuse of a sample carrier, reuse of a chamber of a sample carrier, and/or reuse of a sample carrier more than a given number of times, photobleaching apparatus and techniques are used, as described in further detail hereinbelow with reference to Figs. 3A, 3B, and 3C.

For some applications, a portion of sample carrier 22 is configured to fluoresce, at least under certain conditions. For example, the portion of the sample carrier may be configured to fluoresce when exposed to light emitted by optical measurement device 24 (e.g., brightfield light or fluorescent light that is emitted by a microscope system). Or, the portion of the sample carrier may be configured to fluoresce when placed within optical measurement unit 31 in which optical measurement device 24 is housed. As described hereinabove, for some applications, sample carrier 22 includes adhesive layer 46. For some applications, the adhesive layer, or a portion thereof, is configured to fluoresce in the above-described manner (e.g., by an adhesive material within the adhesive layer being configured

to fluoresce, by the adhesive layer containing an additional material that is configured to fluoresce, and/or by the adhesive layer being coated with such a material). For some applications, the adhesive layer is a pressure-sensitive adhesive, at least a portion of which is configured to fluoresce. For example, the pressure-sensitive adhesive may be an acrylic-based pressure-sensitive adhesive, at least a portion of which is configured to fluoresce. For some applications, the portion of the sample carrier that is configured to fluoresce is further configured to undergo photobleaching in areas that are exposed to fluorescent excitation (e.g. in the UV part of the electromagnetic spectrum). For example, such areas may be configured to undergo photobleaching when exposed to fluorescent excitation for less than one minute, less than 10 seconds, or less than 1 second. Typically, the area that is photobleached can be viewed using the optical measurement device 24 (e.g., the microscope system), and further typically, the photobleaching remains visible for at least one week, e.g., at least one month, or one year.

Reference is now made to Figs. 3A and 3B, which show photobleached spots 50 on microscope images of a sample carrier immediately after being exposed to short-term fluorescent excitation (Fig. 3A), and one week after the exposure (Fig. 3B), in accordance with some applications of the present invention. The diameter of the spot shown in Figs. 3A and 3B is approximately 2 mm, and as shown, it is visible in the microscope images.

Reference is also made to Fig. 3C, which is a plot of the fluorescent emission from the sample carrier (y-axis) measured along the length of the sample carrier (x-axis), immediately after the sample carrier was exposed to the short-term fluorescent excitation (the curve with the uppermost peak between 200 and 300 along the x-axis), one week after the sample carrier was exposed to the short-term fluorescent excitation (the curve with the middle peak between 200 and 300 along the x-axis), and three weeks after the sample carrier was exposed to the short-term fluorescent excitation (the curve with the lowest peak between 200 and 300 along the x-axis), in accordance with some applications of the present invention. The plots were normalized to have equal intensities at the darkest spot.

In accordance with the effect that is demonstrated in Figs. 3A-C, for some applications of the present invention, a portion of a sample carrier is analyzed, in order to determine whether the portion or an area thereof has undergone photobleaching. In response to detecting that the portion has undergone photobleaching, it is determined that the sample carrier, or a portion thereof (e.g., a chamber thereof) has already been used, and/or the

number of times the sample carrier or the portion thereof (e.g., a chamber thereof) has been used. For some applications, the above steps are performed by computer processor 28. For some applications, in response to detecting that the sample carrier, or a portion thereof (e.g., a chamber thereof) has already been used, or that the usage of the sample carrier, or a portion thereof (e.g., a chamber thereof) has exceeded a given threshold, the computer processor generates an output indicating that the sample carrier, or the portion thereof (e.g., the chamber thereof), should not be used, generates an output indicating that the sample carrier, or the portion thereof (e.g., the chamber thereof) is contaminated, and/or prevents the optical measurement device from performing optical measurements upon the sample carrier, or the portion thereof (e.g., the chamber thereof).

For some applications, a given area of the sample carrier is marked by photobleaching the area when the sample carrier is used. For example, optical measurement device 24 may be configured to photobleach a given area of the sample carrier when the sample carrier is placed inside optical measurement unit 31 that houses the sample carrier while optical measurements are performed upon the portion of the sample. Alternatively or additionally, optical measurement device 24 may be configured to photobleach a given area of the sample carrier when the optical measurement device performs an optical measurement on the sample carrier. For some applications, the optical measurement device is configured to photobleach a given area of the sample carrier automatically, by virtue of performing optical measurements upon the sample carrier (i.e., without having to perform any activity specifically for the purpose of causing the photobleaching, which the optical measurement device would not have been performing in any event, in order to perform the optical measurements). For example, the optical measurement device may be a microscope system that performs fluorescent imaging upon the sample by exciting the sample and/or a stained portion of the sample with light that corresponds to an excitation wavelength of the sample and/or the stained portion of the sample, such that the light causes the sample and/or the stained portion of the sample to fluoresce. The light that is emitted by the microscope system, in order to cause the sample and/or the stained portion of the sample to fluoresce, may also photobleach the given area of the sample carrier. For some applications, prior to photobleaching the given area, the computer processor verifies that the sample carrier has not already been used, using the techniques described hereinabove.

As described hereinabove, for some applications, the sample carrier is configured to be reused, but only a limited number of times. For some such applications, each time the sample carrier is used, a respective different area of the sample carrier is photobleached, such that the computer processor may then determine how many times the sample carrier has been used by detecting the number and/or locations of photobleached areas upon the sample carrier.

For some applications, the above-described photobleaching effect is used by a manufacturer of sample carriers to encode manufacturing information regarding the sample carrier, in a manner which is not visible to the naked eye. For example, such information may include an authenticity mark (to reduce the likelihood of counterfeit sample carriers being utilized), sample carrier type, manufacturing date, expiry date, manufacturing location, date required for accurate performance of the test (e.g. calibration date pertaining to the sample carrier, or batch of sample carriers). For some such applications, the marking is marked using a geometric pattern that includes lines, figures, barcodes, alphanumeric characters, etc.

For some applications, a sample carrier that contains a given sample is analyzed more than once by the optical measurement devices. For example, the sample may be analyzed and then re-analyzed at certain time intervals. For some applications, respective portions of the same sample are placed in respective chambers of the sample carrier and are analyzed at respective time intervals. For some applications, in order to ensure that the same sample is being re-analyzed, the optical measurement device is configured to mark the sample carrier, via photobleaching, in a given manner. Subsequently, when the sample carrier is placed back inside the optical measurement unit, or a different optical measurement unit for the re-analysis, the computer processor verifies that it is the same sample carrier by identifying the marks on the sample carrier.

It is noted that the above-described apparatus and methods, which relate to photobleaching a portion of a sample carrier that is configured to fluoresce at least under certain conditions, is not limited to any particular design of the sample carrier. Rather, any design of sample carrier may be configured to incorporate such a portion. Similarly, the above-described apparatus and methods, which relate to photobleaching a portion of a sample carrier that is configured to fluoresce at least under certain conditions, is not limited to any particular portion of a sample carrier. Rather, any portion of a sample carrier may be

configured to have such characteristics. For example, any portion of the molded component, the adhesive layer, or the glass sheet of a sample carrier as described herein may be configured in this manner.

Reference is now made to Figs. 4A, 4B, 4C, and 4D, which are schematic illustrations of respective views of sample carrier 22, the sample carrier being configured for facilitating both microscopic measurements, and optical density measurements with respect to the sample, in accordance with some applications of the present invention. Figs. 4A shows a top view of the sample carrier (the top cover of the sample carrier being shown as being opaque in Fig. 4A, for illustrative purposes), Fig. 4B shows a bottom view (in which the sample carrier has been rotated around its long edge with respect to the view shown in Fig. 4A), and Fig. 4C shows an exploded side view.

For some applications, a sample carrier as shown in Figs. 4A-C is used when performing a complete blood count on a blood sample. For some applications, the sample carrier includes a first set 52 of chambers, which are used for performing microscopic analysis upon the sample, and a second set 54 of chambers, which are used for performing optical density measurements upon the sample. As described hereinabove with reference to Figs. 2A-D, for some applications, the sample carrier is made of a molded component 42, a glass sheet 44 and an adhesive layer 46, as shown in Fig. 4C. For some applications, the adhesive layer is configured to fluoresce and/or to become photobleached, as described hereinabove. Typically, the molded component is configured to define inlet holes 38, outlet holes 40, and/or gutters 48, which are generally as described hereinabove.

As described in WO 17/195205 to Pollack, which is incorporated herein by reference, for some applications, chambers belonging to set 54 (which is used for optical density measurements), typically define at least a first region 56 (which is typically deeper) and a second region 58 (which is typically shallower), the height of the chambers varying between the first and second regions in a predefined manner.

Typically, in order to perform optical analysis upon the sample, it is desirable to know the optical path length, the volume, and/or the thickness of the portion of the sample upon which the optical measurements were performed, as precisely as possible. Further typically, the optical measurements are performed upon a portion of the sample disposed in a sample carrier that is defined by two or more opposing surfaces. In order to provide the

desired level of precision, it is desirable for the two or more opposing surfaces to be separated by a distance that is correspondingly tightly set or tightly controlled. However, in some manufacture or assembly processes, the distance between the opposing surfaces may vary substantially. For example, the upper and lower surfaces of the chambers as shown in Figs. 4A-C are defined respectively by the molded component, and the glass sheet, the molded component and glass sheet being coupled to one another via the adhesive layer. Although the adhesive layer has a nominal thickness, it is typically the case that, for example, due to variation in the manufactured thickness of the pressure-sensitive adhesive or in the pressure applied during its application, the actual thickness of the layer is different from the nominal thickness. For example, molded component and the glass sheet may be bonded using a pressure-sensitive adhesive layer with a nominal thickness that is configured to separate the opposing surfaces by a separation of 100 micrometers. In such a case, variation in the manufactured thickness of the pressure-sensitive adhesive layer or in the pressure applied during its application may result in a final thickness that may lie, for example, as far as 20 micrometers greater or less than the nominal thickness.

Typically, an optical measurement is performed on the sample. For example, the density of a component may be determined by performing a count of the component within a microscopic image. Similarly, the concentration and/or density of a component may be measured by performing optical absorption, transmittance, fluorescence, and/or luminescence measurements upon the sample. Without being bound by theory, an uncertainty of 20 percent in the distance separating the two opposing surfaces (as described in the above example), may, in turn, correspond to 20 percent uncertainty in parameters of the sample that are derived from the optical measurements that are performed upon the sample (such as, the derived concentration and/or density of a component within the sample), e.g., as described in WO 17/195205 to Pollack, which is incorporated herein by reference.

In accordance with some applications of the present invention, the above-described problems associated with uncertainty relating to the height of a sample chamber are at least partially overcome. Referring again to Fig. 4A, sample chambers belonging to set 54 define first region 56 and second region 58. The heights of first region 56 and second region 58 of the sample chamber are defined by a lower surface that is defined by the glass sheet and by an upper surface that is defined by the molded component. The upper surface at the second region is stepped with respect to the upper surface at the first region. The step between the

upper surface at the first and second regions, provides a predefined height difference Δh between the regions, such that even if the absolute height of the regions is not known to a sufficient degree of accuracy, the height difference Δh is known to a sufficient degree of accuracy to determine a parameter of the sample, using the techniques described herein, and as described in WO 17/195205 to Pollack, which is incorporated herein by reference.

As described hereinabove, the molded component is shaped to define a stepped surface such as to define the manner in which the height of the chambers belonging to set 54 varies between the first and second regions. Typically, relative manufacturing tolerances within a single substrate, and especially between nearby surfaces, are tighter than manufacturing tolerances on positioning between different substrates or even between opposing surfaces lying within the same substrate. Therefore, it is typically the case that by having a single substrate define the manner in which the height of the one or more sample chambers varies between the first and second regions, the height difference between the first and second regions is relatively precise. For example, the molded component may be manufactured with relatively tight tolerances, for example, using injection molding, embossing or machining.

As described with reference to WO 17/195205 to Pollack, which is incorporated herein by reference, for some applications, chambers belonging to set 52 (which is used for microscopy measurements) have different heights from each other, in order to facilitate different measurands being measured using microscope images of respective chambers, and/or different chambers being used for microscopic analysis of respective sample types. For example, if a blood sample, and/or a monolayer formed by the sample, has a relatively low density of red blood cells, then measurements may be performed within a chamber of the sample carrier having a relatively great height, such that there is a sufficient density of cells, and/or such that there is a sufficient density of cells within the monolayer formed by the sample, to provide statistically reliable data. Such measurements may include, for example red blood cell density measurements, measurements of other cellular attributes, (such as counts of abnormal red blood cells, red blood cells that include intracellular bodies (e.g., pathogens, Howell-Jolly bodies), etc.), and/or hemoglobin concentration. Conversely, if a blood sample, and/or a monolayer formed by the sample, has a relatively high density of red blood cells, then such measurements may be performed upon a chamber of the sample carrier having a relatively low height, for example, such that there is a sufficient sparsity of

cells, and/or such that there is a sufficient sparsity of cells within the monolayer of cells formed by the sample, that the cells can be identified within microscopic images. For some applications, such methods are performed even without the variation in height between the chambers belonging to set 52 being precisely known.

For some applications, based upon the measurand that is being measured, the chamber within the sample carrier upon which to perform optical measurements is selected. For example, a chamber of the sample carrier having a relatively great height may be used to perform a white blood cell count (e.g., to reduce statistical errors which may result from a low count in a shallower region), white blood cell differentiation, and/or to detect more rare forms of white blood cells. Conversely, in order to determine mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), red blood cell distribution width (RDW), red blood cell morphologic features, and/or red blood cell abnormalities, microscopic images may be obtained from a chamber of the sample chamber having a relatively low height, since in such chambers the cells are relatively sparsely distributed across the area of the region, and/or form a monolayer in which the cells are relatively sparsely distributed. Similarly, in order to count platelets, classify platelets, and/or extract any other attributes (such as volume) of platelets, microscopic images may be obtained from a chamber of the sample chamber having a relatively low height, since within such chambers there are fewer red blood cells which overlap (fully or partially) with the platelets in microscopic images, and/or in a monolayer.

In accordance with the above-described examples, it is preferable to use a chamber of the sample carrier having a lower height for performing optical measurements for measuring some measurands within a sample (such as a blood sample), whereas it is preferable to use a chamber of the sample carrier having a greater height for performing optical measurements for measuring other measurands within such a sample. Therefore, for some applications, a first measurand within a sample is measured, by performing a first optical measurement upon (e.g., by acquiring microscopic images of) a portion of the sample that is disposed within a first chamber belonging to set 52 of the sample carrier, and a second measurand of the same sample is measured, by performing a second optical measurement upon (e.g., by acquiring microscopic images of) a portion of the sample that is disposed within a second chamber of set 52 of the sample carrier. For some applications, the first

and second measurands are normalized with respect to each other, for example, using techniques as described in WO 17/195208 to Zait, which is incorporated herein by reference.

Reference is now made to Figs. 5A, 5B, and 5C, which are schematic illustrations of respective views of sample carrier 22, the sample carrier being configured for use in performing both microscopic measurements, and optical density measurements, in accordance with some applications of the present invention. Fig. 5A shows a bottom view of the sample carrier, with the bottom surface being transparent, such that features of the chambers of the sample carrier may be observed. Figs. 5B and 5C show top views of the sample carrier in which the top layer of the sample carrier is opaque (and in which the sample carrier has been rotated around its long edge with respect to the view shown in Fig. 5A).

Sample carrier as shown in Figs. 5A, 5B, and 5C is generally similar to that shown in Figs. 4A-C, and described with reference thereto, except for differences described hereinbelow. For some applications, the sample carrier includes first set 52 of chambers, which are used for performing microscopic analysis upon the sample, and second set 54 of chambers, which are used for performing optical density measurements upon the sample. For some applications, the second set of chambers, which are used for performing optical density measurements upon the sample includes only a single chamber, as shown. For some applications, there is a plurality of chambers within the first set 52 of chambers, which are used for performing microscopic analysis upon the sample, and each of the chambers defines an outlet hole 40 (which is generally as described hereinabove). For some such applications, the outlet holes of each of the chambers belonging to the first set of chambers are disposed in close proximity to each other (as shown in Fig. 5B), e.g., such that the holes are disposed along a line measuring less than 1 cm long. For example, there may be respective channels 51 leading from each of the chambers to its outlet hole, such that the outlet holes are disposed in close proximity to each other.

For some applications, a cover 60 (shown in Fig. 5C) is reversibly (or, optionally, irreversibly) coupled to the sample carrier, such as to cover the outlet holes. For example, the cover may include paper, sponge or filter material that has an adhesive backing. Typically, the cover is configured to prevent the sample from leaking out of the sample carrier, thereby reducing the likelihood of the optical measuring device becoming contaminated by leakage from the sample carrier. For some applications, the cover is configured to control the rate of filling of the first set 52 of chambers, by limiting the rate of

air flow out of the chambers. For some applications (not shown), a cover that is generally similar to cover 60 is placed over outlet holes associated with second set 54 of chambers.

For some applications, sample carrier 22 is shaped to define a reservoir 39 that is adjacent to inlet hole 38. Typically, the reservoir is configured to allow the user to fill the chambers of the sample carrier with the bodily sample, such that, on the one hand, the user is not required to insert a precise volume of the bodily sample into the inlet hole, and yet, on the other hand, the inlet hole is left substantially free of liquids.

Reference is now made to Fig. 6 which is a schematic illustration showing a bottom view of sample carrier 22, a chamber of the sample carrier including a first marking 62 on its lower inner surface (i.e., the inner surface of the glass layer), and a second marking 64 on its upper inner surface (e.g., the inner surface of the substrate layer), in accordance with some applications of the present invention. In the view shown in Fig. 6, the inner surface of the substrate layer is visible through the transparent glass layer. In accordance with respective applications, the markings may constitute lines, or other shapes (e.g., alphanumeric characters). The markings may be imprinted on the sample carrier, drawn on the sample carrier, etched on the sample carrier, engraved on the sample carrier, glued on the sample carrier, embedded within the sample carrier, may constitute protrusions and/or indentations within the sample carrier and/or other visible features of the sample carrier, and/or may be attached to the sample carrier.

Typically, a sample fills a volume having a height that is defined by the upper and lower surfaces. For example, the volume of a portion of the sample in one of the chambers is defined by the area of the chamber multiplied by the height of the chamber. However, in some cases, the exact height of the chamber is not known, for example, for the reasons provided hereinabove. For some applications, the computer processor determines the height of the chamber by focusing an imaging module of the optical measurement device on first marking 62 and registering an indication of the focusing distance F1 associated with the first marking. The computer processor also focuses the imaging module of the optical measurement device on second marking 64 and registers an indication of the focusing distance F2 associated with the second marking. The computer processor then determines the height of the chamber, based upon the difference between F1 and F2. For some applications, the computer processor determines the volume of the chamber, or a portion thereof, based upon the determined height of the chamber. Typically, the computer

processor determines a property of the sample at least partially based upon the determined height of the chamber, for example, using techniques as described hereinabove.

There is typically a degree of variation in the positioning of the sample carrier with respect to an imaging module of optical measurement device 24. For example, placement of the sample carrier on a microscope stage can vary significantly in view of the required imaging resolution (due for example to limitations of the microscope, variation in the sample carrier, variations in placement by an operator of the device, etc.). Therefore, in accordance with some applications, the positioning of the sample carrier with respect to an imaging module of optical measurement device 24 is determined, in accordance with the techniques described herein.

For some applications, the imaging module of the optical measurement device and a stage upon which the sample carrier is placed are initially positioned such that a visible mark on the sample carrier appears within the observation field of the imaging module. This is followed by scanning a portion of the sample carrier surface until sufficient information is available to define the sample carrier's position and/or orientation at least with respect to the X-Y plane. (In the present application, the term Z-axis is used to refer to the optical axis of the optical system, and the X-Y plane is used to denote the plane that is perpendicular to the optical axis, as is common in the art.)

Reference is now made to Figs. 7A and 7B, in which an example of an irregular pattern 70 is shown, the pattern including a set of vertical lines 72 and horizontal lines 74 confined within a square boundary 76, in accordance with some applications of the present invention. Fig. 7B shows the irregular pattern shown in Fig. 7A in an orientation that is tilted with respect to that shown in Fig. 7A. For some applications, an irregular pattern, such as that shown in Figs. 7A-B, is marked upon sample carrier 22. Optical measurement device, which typically includes a microscope system, images the sample carrier via an observation field. Typically, such observation fields image sub-portions within chambers of the sample carrier.

It may be observed that the spacing between the vertical lines 72 is irregular, i.e. the distance between each two neighboring vertical lines 72 is different than any of two other neighboring vertical lines 72. The same design is applied to the horizontal lines. By way of

example, the irregular pattern may measure about 2.7 X 2.7 mm^2, while the observation field may measure about 0.6 X 0.8 mm^2.

It is noted that while irregular pattern 70 and the observation field are shown as being essentially rectangular or square, any other shape may be used. For example, a round or other shape observation field may be selected, for example based on optical limitations which may provide a better image in a portion of a diagnostic field.

As described hereinabove, the optical measurement device is typically used to capture images of the sample using an observation field O.F. (also referred herein as an orientation field), which has a predetermined size and shape, and through which (when properly place above the sample carrier) a portion of the sample carrier can be viewed. The irregular pattern is designed with a resolution that is complementary to the observation field size so that in any lateral X-Y position of the observation field over the irregular pattern, the portion of the irregular pattern observed through the observation field is unique to that specific position and detectable at the set resolution of the device. Optionally, an observation field may be a diagnostic field or a portion thereof. In some embodiments, an observation field is assembled using a plurality of adjacent diagnostic fields, such that the combined information from two or more diagnostic fields is used as an observation field.

Reference is now made to Figs. 8A, 8B, 8C, and 8D, in which examples of the pattern corresponding to respective observation fields are shown, in accordance with some applications of the present invention. It may be observed that the image of the portion of the irregular pattern captured at different positions of the observation field is different for each such position. The irregular pattern is designed so that the images captured at any two different X-Y positions will yield different visible portions of the irregular pattern.

It is also noted that, typically, the resolution of the irregular pattern is designed to be complementary to the size and shape of the observation field, such that it is typically not the case that the observation field is smaller than the distance between two neighboring lines of the pattern (either horizontal or vertical), so that an observation field never includes a single line, an empty space or the sole thickness of a single line. Typically, the only exception to this configuration is an irregular pattern designed specifically so that such a single line, empty space and/or sole thickness can occur in a single position of the observation field across the entire irregular pattern.

Since each position of the observation field corresponds to its own unique pattern, the computer processor typically determines the position of the irregular pattern with respect to the observation field. Since the irregular pattern is fixedly associated with the sample carrier, the computer processor thereby determines the location, and optionally orientation, of the sample carrier that is imaged within the observation field.

Reference is now made to Figs. 9A, 9B, 9C, and 9D, in which some additional examples of the pattern corresponding to respective observation fields are shown, in accordance with some applications of the present invention. It is noted, with reference to the examples shown in Figs. 9A-D, that not only the X-Y position of the irregular pattern be determined via the observation field, but also the orientation thereof. Thus, for some applications, the computer processor determines which portion of the sample carrier is being imaged in a given observation field, as well as the orientation of the sample carrier within the observation field, based upon the irregular pattern that is identified within the observation field.

In accordance with some applications, the irregular pattern is imprinted on the sample carrier, drawn on the sample carrier, etched on the sample carrier, engraved on the sample carrier, glued on the sample carrier, embedded within the sample carrier, constitutes protrusions and/or indentations within the sample carrier, and/or other visible features of the sample carrier, and/or is attached to the sample carrier. Typically, the irregular pattern (e.g., a 2D pattern as described with reference to Figs. 7A-10C, and/or a 3D pattern as described with reference to Fig. 11A-11F) is formed upon the inner surface of the molded layer of the sample carrier. Alternatively or additionally, the irregular pattern is formed on a surface of the glass layer of the sample carrier. For some applications, an irregular pattern as described with reference to any one of Fig. 7A-12 is used on a sample carrier having different characteristics to the sample carriers described with reference to Figs. 2A-6.

Reference is now made to Figs. 10A, 10B and 10C, in which three additional examples of irregular patterns are shown, in accordance with some applications of the present invention. The examples that are shown are as follows:

Fig. 10A - a set of concentric circles of uniquely different diameters, and being overlapped by a rectangular wave pattern;

Fig. 10B - a set of circles of uniquely different diameters and varying line thicknesses, and which are not concentric; and

Fig. 10C - a spiral configuration of varying line thickness.

Each of the patterns shown in Figs. 10A to 10C provides a unique image to respective observation fields that are disposed at different X-Y positions above the irregular pattern. In addition, each of the patterns shown in Figs. 10A to 10C provides a unique image to respective observation fields that are disposed at different angular orientations above the irregular pattern, such that it is possible to distinguish between angular positions that are separated by less than 5 degrees.

In principle, it should be appreciated that while a single irregular pattern may be sufficient for determining both location and orientation of the sample carrier, the subject matter of the present disclosure does not exclude the use of two or more such patterns in a single carrier/chamber, potentially allowing for more accurate results.

For some applications, the irregular pattern is a 3D pattern having elements thereof located at different heights along the Z-axis. Optionally, the maximum height of the 3D pattern relative to the minimum height measures about 10 μm. For some applications, the 3D pattern is marked on a surface having the same position along the optical axis of the imaging module of the optical measurement device as the surface upon which the sample is to be imaged. For example, the 3D pattern may be located on the surface and/or be embedded within the material.

It should be noted that according to some applications, a 3D pattern is used such that even a single image, or no more than 10 images, are needed to provide sufficient information to determine the position, and optionally also orientation of the sample carrier, with respect to an imaging module of an optical measurement device, both with respect to an XY plane of the observation field and along the optical axis of the imaging module.

For some applications, the 3D pattern is associated with a 2D pattern or mark as described above (either juxtaposed therewith or being a part thereof), so that once information is gathered from the 2D mark or pattern (regarding the position, and optionally orientation, of the sample carrier with respect to an X-Y plane of the visual examination zone), a single image of the 3D pattern is enough to determine the location of the sample carrier along the optical axis of an imaging module.

Reference is now made to Fig. 11A in which a 3D pattern 80 is shown, in which the irregular pattern is reflected not only in the 2D grid design, but also in varying depths of different areas of the pattern, in accordance with some applications of the present invention. In particular, the 3D pattern is in the form of an irregular grid of rectangular portions, each rectangle having a top at a certain depth from the surface, such that at least some different rectangles have different depths.

Reference is also made to Fig. 11B, in which a portion of the 3D pattern is shown (e.g. a portion of the pattern observed by the observation field O.F.), comprising nine rectangles sq1 to sq9, each rectangle being at one of four depths D0 to D3, in accordance with some applications of the present invention. Specifically, the arrangement shown in Fig. 11B is as follows:

Rectangle No.	**Depth**
sq1, sq3, sq8	D0
sq2, sq6	D1
sq4, sq9	D2
sq5, sq7	D3

Reference is also made to Figs. 11C to 11F, each showing an example of an image of the 3D portion taken by the imaging module of the optical measurement device at depths D0 to D3 respectively, in accordance with some applications of the present invention. It may be observed that, at each focal length of the imaging module of the optical measurement device, corresponding to each of the depths D0 to D3, the image received is such that the boundaries of the rectangles at that depth/focal length are clearly visible (indicated by the solid lines), while the remainder of the rectangles (which are not located at that depth/focal length) are not in focus (indicated by the dashed lines).

Thus, for some applications, the 3D feature of the irregular pattern is used by computer processor 28 to provide an additional degree of accuracy for determining the position of the sample carrier with respect to the imaging module of the optical measurement device. Alternatively or additionally, the 3D feature of the irregular pattern is used by computer processor 28 to provide an indication as to the focal length of the imaging module

of the optical measurement device. A single image taken of the 3D pattern may provide sufficient information regarding the position of the grid in the X-Y plane as well as along the optical axis of the imaging module of the optical measurement device. Optionally, once the X-Y position is known, an image (e.g., a single image) of the 3D pattern is taken at the known X-Y position, and the computer processor derives the location of the 3D pattern along the optical axis of the imaging module of the optical measurement device using the image.

It should be appreciated that the depths D0 to D3 are not necessarily equally spaced, and the height differences between respective pairs of consecutive height levels can be different from each other.

Reference is now made to Fig. 12, which is a schematic illustration of the spatial arrangement of an irregular pattern of a sample carrier with respect to an observation field O.F. of the imaging module of optical measurement device 24, in accordance with some applications of the present invention. As shown, a sample carrier may be located in one of a plurality of X-Y positions with respect to the observation field. In this example, two extreme positions, Position A and Position B, of the sample carrier with respect to the observation field are depicted, the positions differing in location by a length *Lx* along the X-axis, and by a length *Ly* along the Y-axis. The spatial arrangement of the irregular pattern along the carrier is typically such that at least a portion of the irregular pattern falls within the observation field, regardless of the relative position of the carrier with respect to the optical device. Thus, the position of the sample carrier with respect to the imaging module of the optical measurement device does not affect the optical measurement device's ability to operate properly.

For some applications, the sample as described herein is a sample that includes blood or components thereof (e.g., a diluted or non-diluted whole blood sample, a sample including predominantly red blood cells, or a diluted sample including predominantly red blood cells), and parameters are determined relating to components in the blood such as platelets, white blood cells, anomalous white blood cells, circulating tumor cells, red blood cells, reticulocytes, Howell-Jolly bodies, etc.

In general, it is noted that although some applications of the present invention have been described with respect to a blood sample, the scope of the present invention includes applying the apparatus and methods described herein to a variety of samples. For some

applications, the sample is a biological sample, such as, blood, saliva, semen, sweat, sputum, vaginal fluid, stool, breast milk, bronchoalveolar lavage, gastric lavage, tears and/or nasal discharge. The biological sample may be from any living creature, and is typically from warm blooded animals. For some applications, the biological sample is a sample from a mammal, e.g., from a human body. For some applications, the sample is taken from any domestic animal, zoo animals and farm animals, including but not limited to dogs, cats, horses, cows and sheep. Alternatively or additionally, the biological sample is taken from animals that act as disease vectors including deer or rats.

For some applications, similar techniques to those described hereinabove are applied to a non-bodily sample. For some applications, the sample is an environmental sample, such as, a water (e.g. groundwater) sample, surface swab, soil sample, air sample, or any combination thereof. In some embodiments, the sample is a food sample, such as, a meat sample, dairy sample, water sample, wash-liquid sample, beverage sample, and/or any combination thereof.

Applications of the invention described herein can take the form of a computer program product accessible from a computer-usable or computer-readable medium (e.g., a non-transitory computer-readable medium) providing program code for use by or in connection with a computer or any instruction execution system, such as computer processor 28. For the purposes of this description, a computer-usable or computer readable medium can be any apparatus that can comprise, store, communicate, propagate, or transport the program for use by or in connection with the instruction execution system, apparatus, or device. The medium can be an electronic, magnetic, optical, electromagnetic, infrared, or semiconductor system (or apparatus or device) or a propagation medium. Typically, the computer-usable or computer readable medium is a non-transitory computer-usable or computer readable medium.

Examples of a computer-readable medium include a semiconductor or solid state memory, magnetic tape, a removable computer diskette, a random-access memory (RAM), a read-only memory (ROM), a rigid magnetic disk and an optical disk. Current examples of optical disks include compact disk-read only memory (CD-ROM), compact disk-read/write (CD-R/W) and DVD.

A data processing system suitable for storing and/or executing program code will include at least one processor (e.g., computer processor 28) coupled directly or indirectly to memory elements (e.g., memory 30) through a system bus. The memory elements can include local memory employed during actual execution of the program code, bulk storage, and cache memories which provide temporary storage of at least some program code in order to reduce the number of times code must be retrieved from bulk storage during execution. The system can read the inventive instructions on the program storage devices and follow these instructions to execute the methodology of the embodiments of the invention.

Network adapters may be coupled to the processor to enable the processor to become coupled to other processors or remote printers or storage devices through intervening private or public networks. Modems, cable modem and Ethernet cards are just a few of the currently available types of network adapters.

Computer program code for carrying out operations of the present invention may be written in any combination of one or more programming languages, including an object-oriented programming language such as Java, Smalltalk, C++ or the like and conventional procedural programming languages, such as the C programming language or similar programming languages.

It will be understood that algorithms described herein, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general-purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer (e.g., computer processor 28) or other programmable data processing apparatus, create means for implementing the functions/acts specified in the algorithms described in the present application. These computer program instructions may also be stored in a computer-readable medium (e.g., a non-transitory computer-readable medium) that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable medium produce an article of manufacture including instruction means which implement the function/act specified in the flowchart blocks and algorithms. The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer implemented process such that the

instructions which execute on the computer or other programmable apparatus provide processes for implementing the functions/acts specified in the algorithms described in the present application.

Computer processor 28 is typically a hardware device programmed with computer program instructions to produce a special purpose computer. For example, when programmed to perform the algorithms described herein, computer processor 28 typically acts as a special purpose sample-analysis computer processor. Typically, the operations described herein that are performed by computer processor 28 transform the physical state of memory 30, which is a real physical article, to have a different magnetic polarity, electrical charge, or the like depending on the technology of the memory that is used.

There is provided, in accordance with some applications of the present invention, the following inventive concepts:

Inventive concept 1. Apparatus comprising:

a sample carrier configured to carry a sample; and

an optical measurement device configured to perform optical measurements upon the sample, the optical measurement device defining an observation field,

the sample carrier comprising a surface that comprises at least one irregular pattern, such that any portion of the surface of the sample carrier having a shape and area that corresponds to the observation field of the optical measurement device and that contains at least a portion of the pattern has a geometric pattern unique to that portion.

Inventive concept 2. The apparatus according to inventive concept 1, wherein the irregular pattern is configured to facilitate determining a position of the sample carrier with respect to a plane of the observation field, based on a single image of any portion of the surface of the sample carrier that contains a portion of the pattern having a geometric pattern unique to that portion.

Inventive concept 3. The apparatus according to inventive concept 1, wherein the irregular pattern has a given orientation with respect to the surface of the sample carrier, such that the sample carrier facilitates determining orientation of the sample carrier with respect to the observation field of the optical measurement device

Inventive concept 4. The apparatus according to inventive concept 1, wherein the irregular pattern is present on the surface of the carrier using one or more techniques selected from the group consisting of: drawing, embossing, etching, carving, and adhering.

Inventive concept 5. The apparatus according to inventive concept 1, wherein the surface of the sample carrier that comprise the irregular pattern comprises a surface of a sample chamber that is configured to carry the sample therein.

Inventive concept 6. The apparatus according to inventive concept 1, wherein the carrier comprises a cover, and wherein the surface of the sample carrier that comprise the irregular pattern comprises a surface of the cover.

Inventive concept 7. The apparatus according to inventive concept 1, wherein the surface of the sample carrier that comprise the irregular pattern comprises a surface of the sample carrier that is located on the sample carrier outside any chamber.

Inventive concept 8. The apparatus according to inventive concept 1, wherein the optical measurement device comprises a microscope.

Inventive concept 9. The apparatus according to inventive concept 1, wherein the sample carrier comprises two or more irregular patterns.

Inventive concept 10. The apparatus according to inventive concept 1, wherein the said sample carrier comprises two or more chambers, each configured to carry a portion of the sample therein.

Inventive concept 11. The sample carrier according to inventive concept 10, wherein at least one of said at least one irregular pattern is located on a surface of each of said two or more chambers.

Inventive concept 12. A sample carrier configured for containing a sample to be analyzed by an optical measurement device having a maximal visual examining zone of area A at a diagnostic imaging magnification, wherein the initial imaging position of the carrier may vary by a length L in at least one of the X and Y axis of a plane being perpendicular to the optic axis of the optic device and having a visual examining zone of area S, said sample carrier comprising at least one irregular pattern having an area A', where $A' = f(A,L)$; such that any image having the same shape and area as that of the visual examining zone taken at

an expected initial location of the irregular pattern would comprise a portion of the pattern that has a geometric pattern unique to that portion.

Inventive concept 13. A sample carrier configured for containing a sample to be analyzed by an optical measurement device the carrier comprising at least one irregular geometric pattern having an area of at least 6mm^2 such that any portion of the pattern having the same size and shape and having an area of 0.3 mm^2 or more and comprising at least a portion of the pattern has a geometric pattern unique to that portion.

Inventive concept 14. The sample carrier of inventive concept 13, wherein an inscribing circle of said irregular geometric pattern measures at least 3mm in diameter, and does not measure less than 2mm in two perpendicular directions.

Inventive concept 15. The sample carrier of inventive concept 13, wherein the inscribing circle of said portion measures at least 0.5 mm in diameter, and does not measure less than 0.4 mm in two perpendicular directions.

Inventive concept 16. An automated microscope configured to analyze a sample within a sample carrier comprising:

an optical module;

a support for holding a sample carrier; and

a controller configured to:

operate the optical module to capture ten orientation images or less of the sample carrier at a predetermined location; and

analyze the images to deduce at least one of a position and orientation of the carrier or a portion thereof with respect to at least one of an XY plane and a z axis of the microscope,

wherein the sample carrier comprises at least one irregular pattern and the irregular pattern is sized and positioned on a sample carrier surface such that at least one of said ten orientation images or less shows the irregular pattern or a part thereof without searching.

Inventive concept 17. An automated microscope according to inventive concept 16, wherein the irregular pattern is patterned such that any portion of an orientation image that shows the irregular pattern or a part thereof shows a geometric pattern unique to that portion.

Inventive concept 18. An automated microscope according to inventive concept 16, wherein the irregular pattern is sized, shaped and positioned such that one image per pattern is sufficient for determining at least one of a position and orientation of the sample carrier.

Inventive concept 19. A sample carrier for a microscope, comprising at least one chamber configured for containing therein a sample to be analyzed, said chamber comprising:

a cavity with a platform disposed therein and having a platform surface elevated above a floor surface of the cavity; and

a cover covering said cavity spaced from said platform surface;

wherein said platform surface comprises a first mark and a said cover comprises on a surface thereof a second mark, wherein the focusing distance between the first mark and the second mark allows determining a vertical length of the space between said platform surface and a bottom surface of said cover.

Inventive concept 20. A sample carrier for a microscope according to inventive concept 19, wherein the second mark is on the bottom surface of said cover.

Inventive concept 21. A sample carrier for a microscope according to inventive concept 19, wherein the first mark and second mark overlap along the Z axis.

Inventive concept 22. A sample carrier for a microscope according to inventive concept 19, wherein at least one of the first mark and second mark comprises an irregular pattern.

Inventive concept 23. A method for determining a volume of a portion of a fluid sample in a sample carrier of inventive concept 19, comprising:

introducing the fluid sample into said sample carrier such that the sample fills a volume having a height defined between said platform surface and a bottom surface of said cover;

determining an area A of a portion of said platform surface;

focusing an optical module of the microscope on said first mark and registering an indication of the focusing distance F_1 for said first mark;

focusing an optical module of the microscope on said second mark and registering an indication of the focusing distance F_2 for said second mark; and

determining based on F_1, F_2 and A, a volume of the fluid sample located on said portion of the platform surface.

The apparatus and methods described herein may be used in conjunction with apparatus and methods described in any one of the following patent applications, all of which are incorporated herein by reference:

US 2012/0169863 to Bachelet;

US 2014/0347459 to Greenfield;

US 2015/0037806 to Pollak;

US 2015/0316477 to Pollak;

US 2016/0208306 to Pollak;

US 2016/0246046 to Yorav Raphael;

US 2016/0279633 to Bachelet;

US 2018/0246313 to Eshel;

WO 16/030897 to Yorav Raphael;

WO 17/046799 to Eshel;

WO 17/168411 to Eshel;

WO 17/195205 to Pollack; and

WO 17/195208 to Zait.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

CLAIMS

1. Apparatus for use with a bodily sample, the apparatus comprising:

a sample carrier configured to carry a portion of the bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions; and

an optical measurement device configured to:

perform optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

at least partially photobleach an area within the portion of the sample carrier by causing the area to fluoresce.

2. The apparatus according to claim 1, further comprising an optical measurement unit that is configured to house the sample carrier while the optical measurement device performs the optical measurements upon the portion of the bodily sample, wherein the optical measurement device is configured to photobleach the given area of the sample carrier, in response to the sample carrier being placed inside the optical measurement unit.

3. The apparatus according to claim 1, wherein the sample carrier is configured to be used for a plurality of measurements by the optical measurement device, and wherein the optical measurement device is configured to photobleach a respective different area of the sample carrier, each time the sample carrier is used for measurements by the optical measurement device.

4. The apparatus according to any one of claims 1-3, further comprising:

an output device; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to generate an output upon the output device indicating that at least a portion of the sample carrier is contaminated.

5. The apparatus according to claim 4, wherein the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to generate the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

6. The apparatus according to any one of claims 1-3, further comprising:

an output device; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to generate an output upon the output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier.

7. The apparatus according to claim 6, wherein the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to generate the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

8. The apparatus according to any one of claims 1-3, further comprising at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured:

to detect that the area within the portion of the sample carrier has been photobleached, and

in response thereto, to prevent the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

9. The apparatus according to claim 8, wherein the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to prevent the optical measurement device from performing the optical measurements, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

10. The apparatus according to any one of claims 1-3, wherein the optical measurement device is configured to photobleach the given area of the sample carrier by virtue of performing optical measurements upon the sample.

11. The apparatus according to claim 10, wherein the optical measurement device is configured to illuminate the sample, in order to perform optical measurements on the sample, and wherein the optical measurement device is configured to photobleach the given area of the sample carrier by virtue of illuminating the sample.

12. A method for use with a bodily sample, the method comprising:

placing a portion of the bodily sample within a sample carrier, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions; and

while the portion of the bodily sample is housed within the sample carrier, performing optical measurements upon the portion of the bodily sample that is housed within the sample carrier, using an optical measurement device; and

at least partially photobleaching an area within the portion of the sample carrier by causing the area to fluoresce.

13. The method according to claim 12, wherein at least partially photobleaching the area within the portion of the sample carrier by causing the area to fluoresce comprises placing the sample carrier inside an optical measurement unit.

14. The method according to claim 12, wherein the sample carrier is configured to be used for a plurality of measurements by the optical measurement device, and wherein at least partially photobleaching the area within the portion of the sample carrier by causing the area to fluoresce comprises photobleaching a respective different area of the sample carrier, each time the sample carrier is used for measurements by the optical measurement device.

15. The method according to any one of claims 12-14, further comprising, using at least one computer processor:

detecting that the area within the portion of the sample carrier has been photobleached; and

in response thereto, generating an output upon an output device indicating that at least a portion of the sample carrier is contaminated.

16. The method according to claim 15,

further comprising determining that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached,

wherein generating the output on the output device comprises generating the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

17. The method according to any one of claims 12-14, further comprising, using at least one computer processor:

detecting that the area within the portion of the sample carrier has been photobleached; and

in response thereto, generating an output upon an output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier.

18. The method according to claim 17,

further comprising determining that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached,

wherein generating the output on the output device comprises generating the output on the output device, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

19. The method according to any one of claims 12-14, further comprising, using at least one computer processor:

detecting that the area within the portion of the sample carrier has been photobleached; and

in response thereto, preventing the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

20. The method according to claim 19,

further comprising determining that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached,

wherein preventing the optical measurement device from performing the optical measurements comprises preventing the optical measurement device from performing the optical measurements, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

21. The method according to any one of claims 12-14, wherein at least partially photobleaching the area within the portion of the sample carrier by causing the area to fluoresce comprises causing the area to fluoresce by virtue of performing optical measurements upon the sample.

22. The method according to claim 21, wherein performing optical measurements upon the sample comprises illuminating the sample in order to perform optical measurements on the sample, and by causing the area to fluoresce comprises by causing the area to fluoresce by virtue of illuminating the sample.

23. Apparatus for use with a bodily sample and an output device, the apparatus comprising:

a sample carrier configured to carry the bodily sample, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions;

an optical measurement device configured to perform optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

at least one computer processor that is operatively coupled to the optical measurement device, the computer processor being configured, in response to detecting that an area within the portion of the sample carrier has been photobleached, to perform an action selected from the group consisting of: generating an output upon the output device indicating that at least a portion of the sample carrier is contaminated, generating an output upon the output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier, and preventing the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

24. The apparatus according to claim 23, wherein the computer processor is configured:

to determine that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

to perform the selected action, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

25. A method for use with a bodily sample and an output device, the method comprising:

placing a portion of the bodily sample inside a sample carrier, at least a portion of the sample carrier being configured to fluoresce, at least under certain conditions;

performing optical measurements upon the portion of the bodily sample that is housed within the sample carrier; and

using at least one computer processor, in response to detecting that an area within the portion of the sample carrier has been photobleached, performing an action selected from the group consisting of: generating an output upon the output device indicating that at least a portion of the sample carrier is contaminated, generating an output upon the output device indicating that optical measurements cannot be performed on at least a portion of the sample that is housed within a given portion of the sample carrier, and preventing the optical measurement device from performing optical measurements upon at least a portion of the sample that is housed within a given portion of the sample carrier.

26. The method according to claim 25, wherein performing the selected action comprises:

determining that at least a portion of the sample carrier has been used more than a given number of times, based upon detecting that an area within of the portion of the sample carrier has been photobleached; and

performing the selected action, in response to determining that at least the portion of the sample carrier has been used more than the given number of times.

27. Apparatus for use with a bodily sample and a microscope having an imaging module, the apparatus comprising:

at least one chamber configured for housing therein a portion of the bodily sample, the chamber comprising an upper inner surface, and a lower inner surface,

wherein the upper inner surface comprises a first mark and the lower inner surface comprises a second mark; and

at least one computer processor configured to:

focus the imaging module on the first marking and register an indication of a first focusing distance between the imaging module and the first marking;

focus the imaging module on the second marking and register an indication of a second focusing distance between the imaging module and the second marking; and

determine a height of the chamber, based upon a difference between the first focusing distance and the second focusing distance.

28. A method for use with a bodily sample and a microscope having an imaging module, the method comprising:

placing a portion of the bodily sample inside at least one chamber, the chamber including an upper inner surface, and a lower inner surface, the upper inner surface including a first mark and the lower inner surface including a second mark; and

using at least one computer processor:

focusing the imaging module on the first marking and registering an indication of a first focusing distance between the imaging module and the first marking;

focusing the imaging module on the second marking and registering an indication of a second focusing distance between the imaging module and the second marking; and

determining a height of the chamber, based upon a difference between the first focusing distance and the second focusing distance.

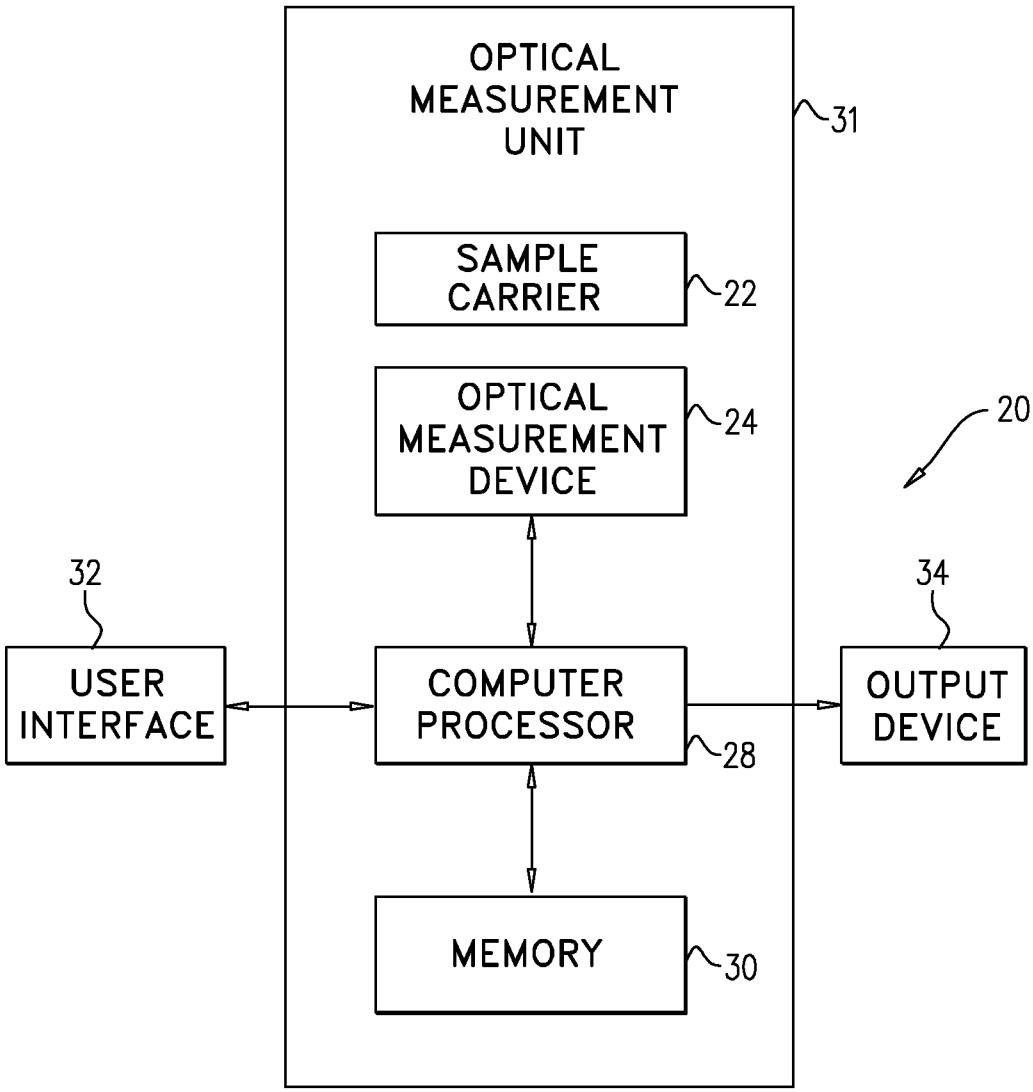
OPTICAL MEASUREMENT UNIT
31
SAMPLE CARRIER
22
OPTICAL MEASUREMENT DEVICE
24
20
32
34
USER INTERFACE
COMPUTER PROCESSOR
28
OUTPUT DEVICE
MEMORY
30

FIG. 1

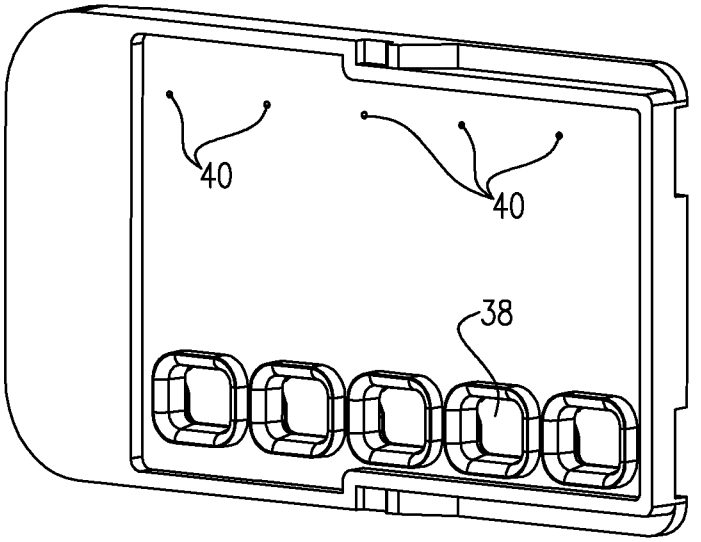

FIG. 2A

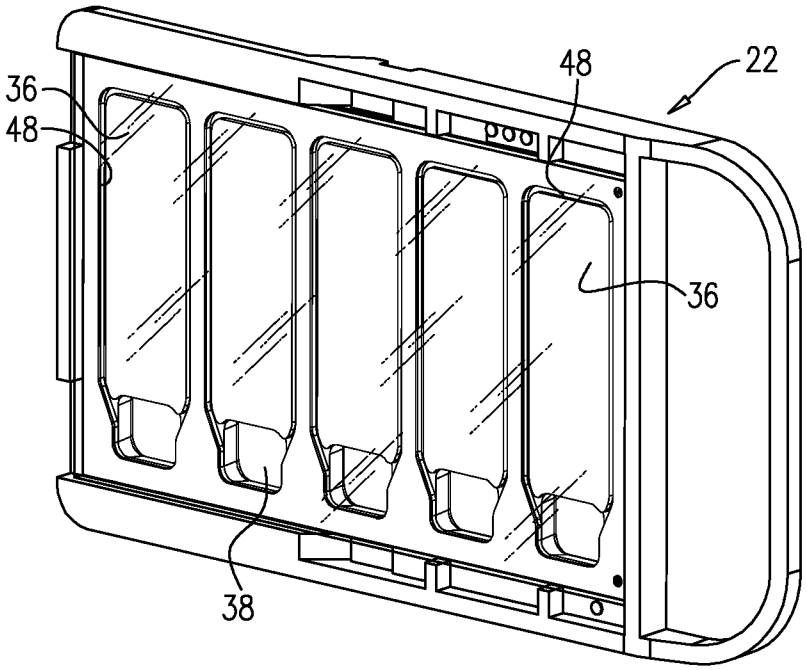

FIG. 2B

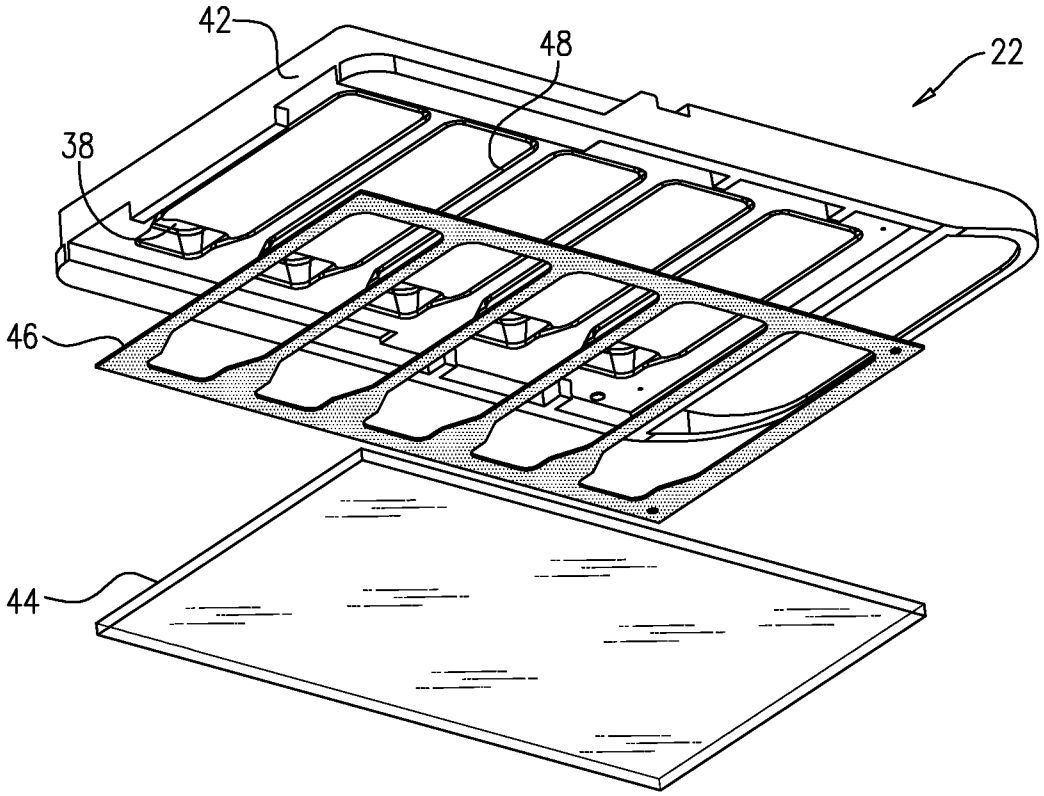

FIG. 2C

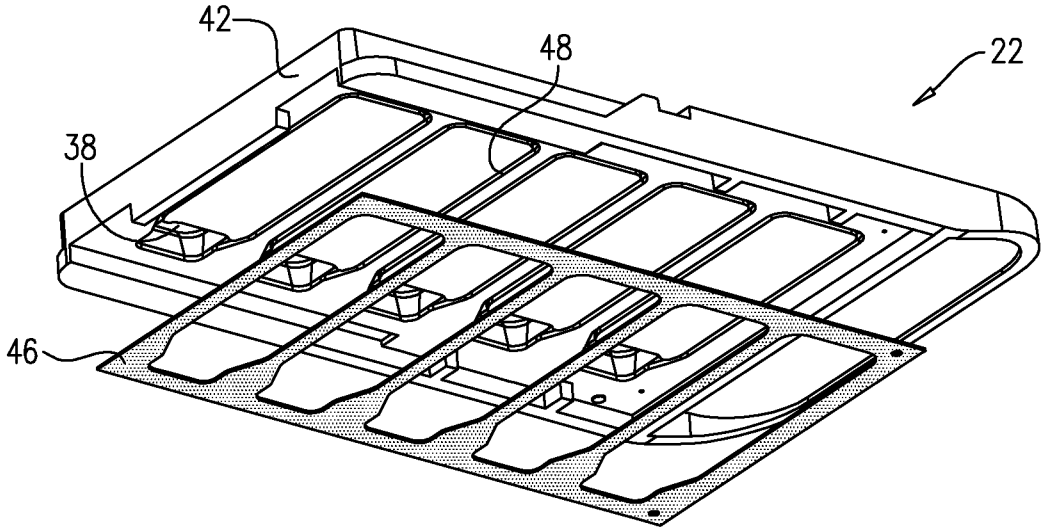

FIG. 2D

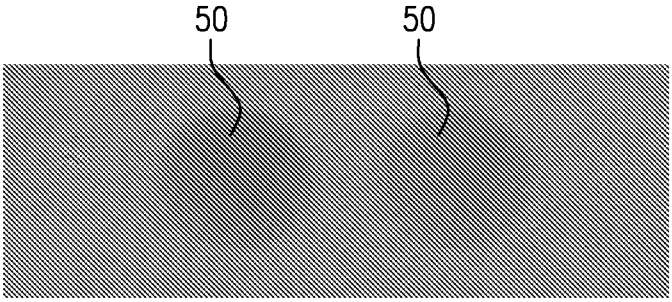

FIG. 3A

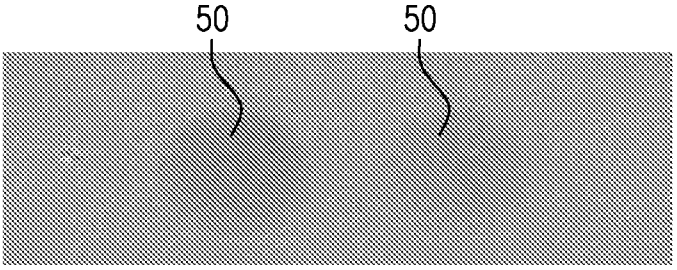

FIG. 3B

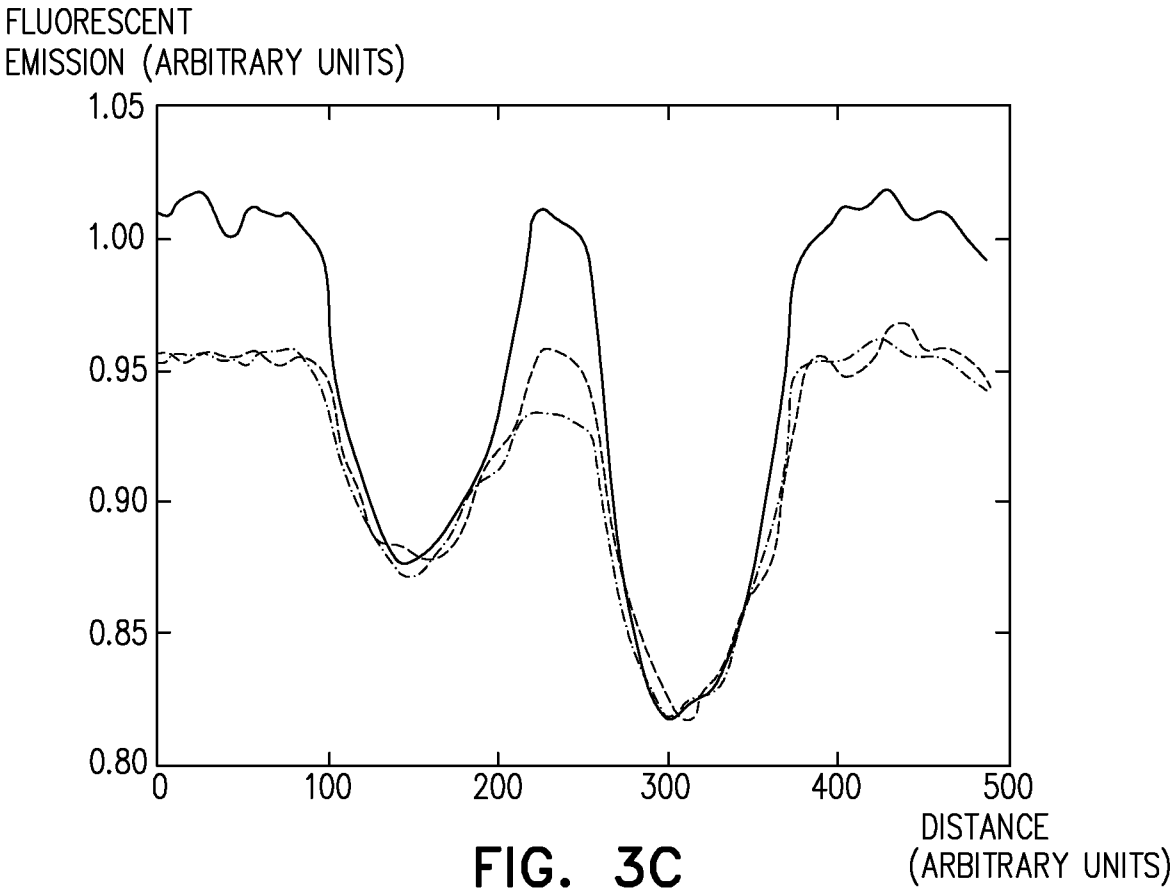

FIG. 3C

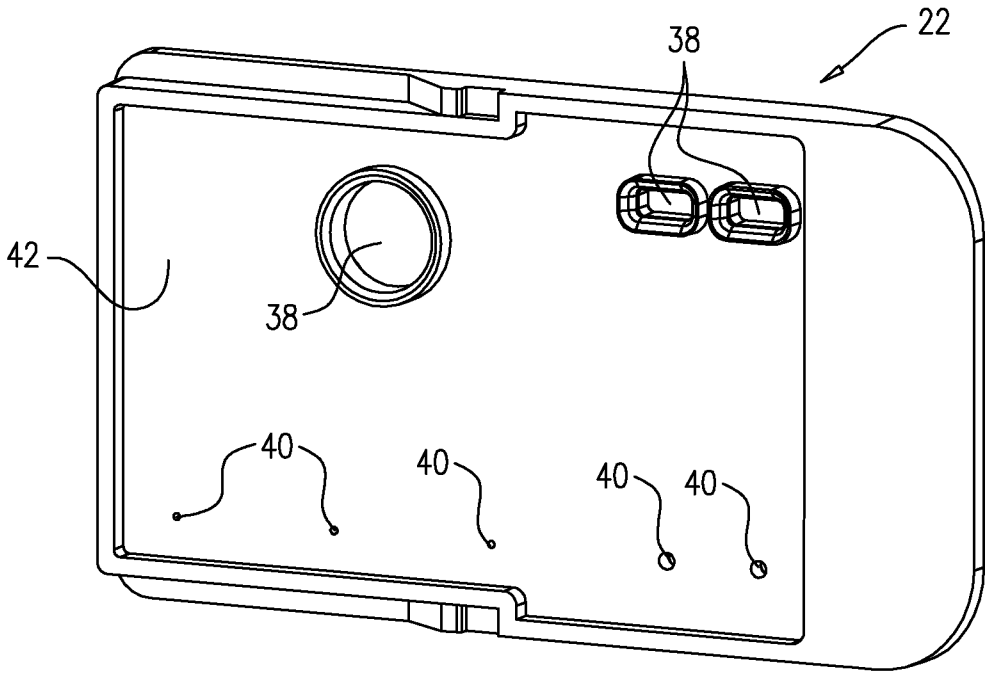

FIG. 4A

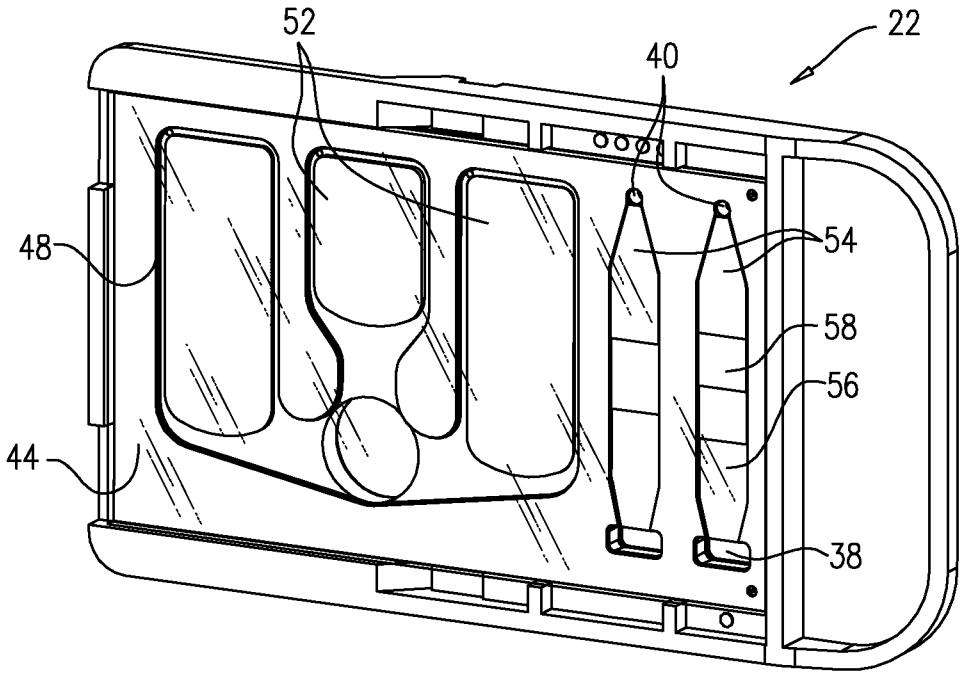

FIG. 4B

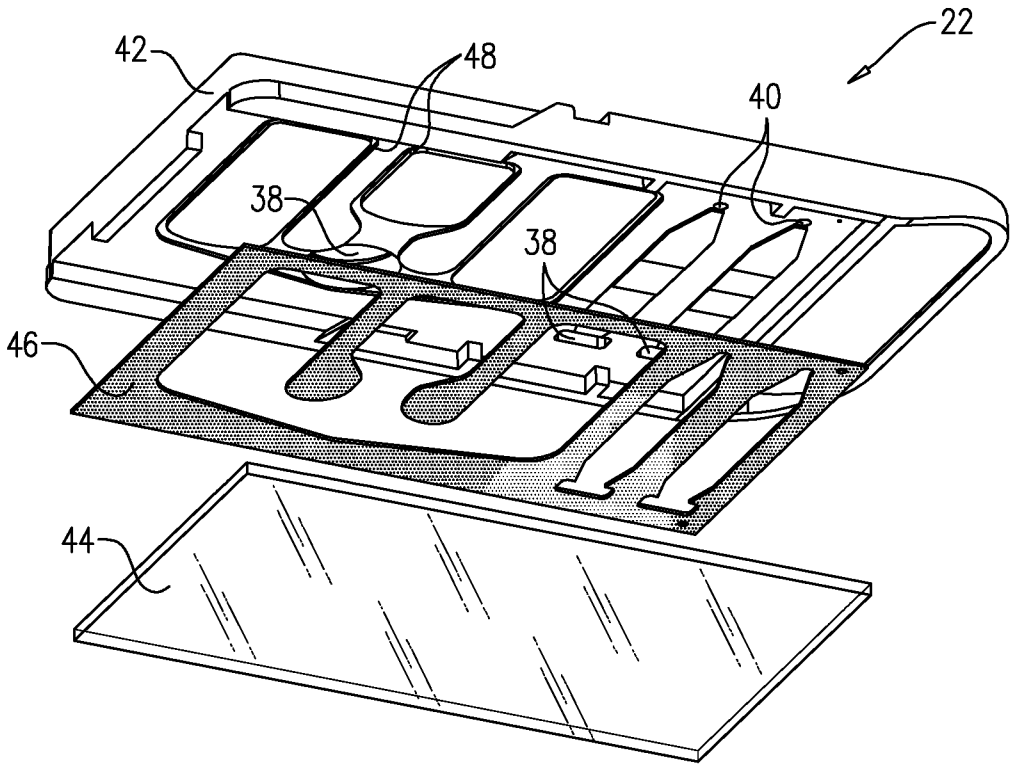

FIG. 4C

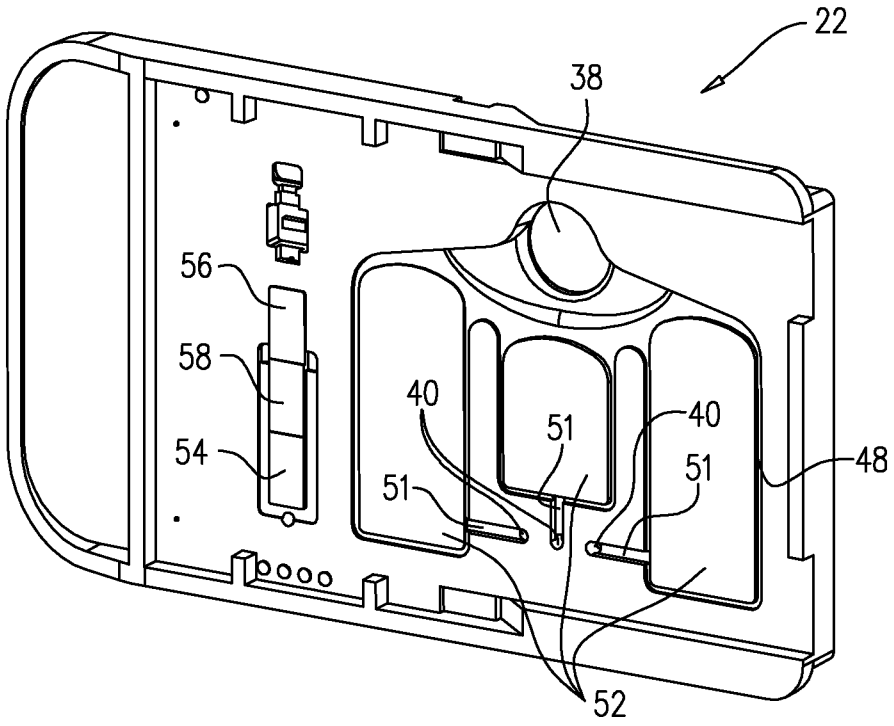

FIG. 5A

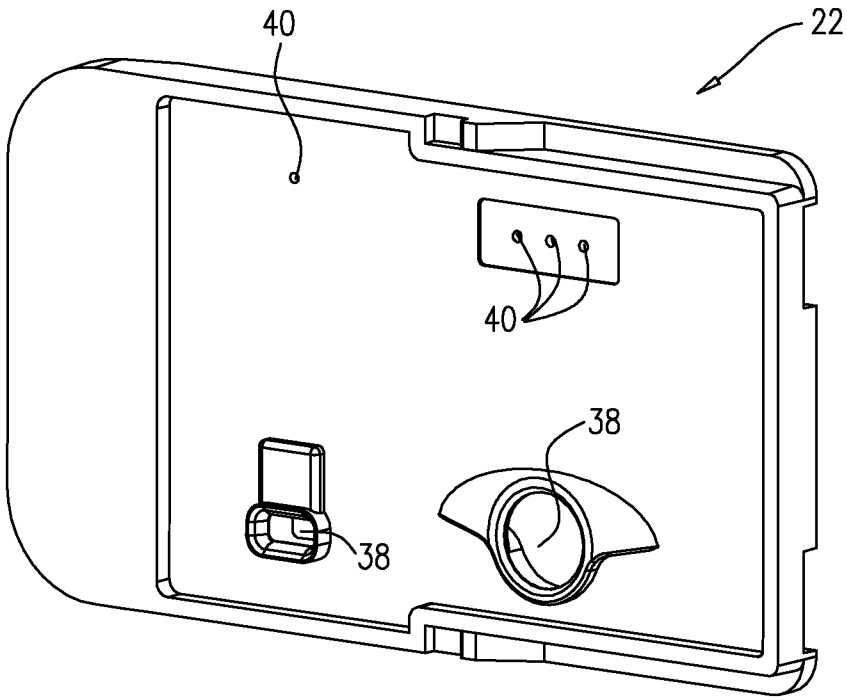

FIG. 5B

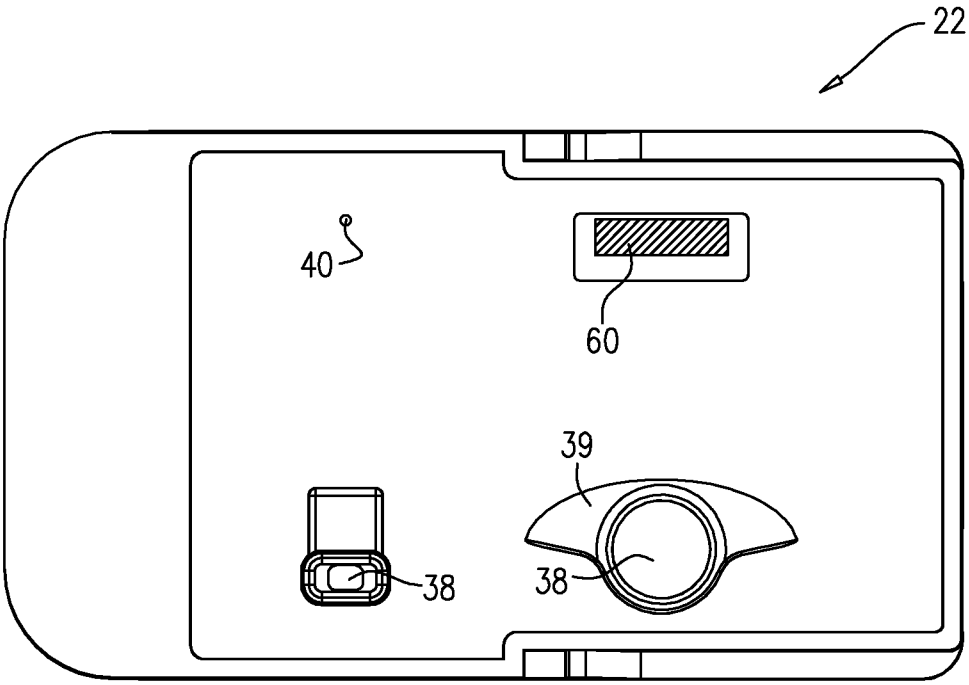

FIG. 5C

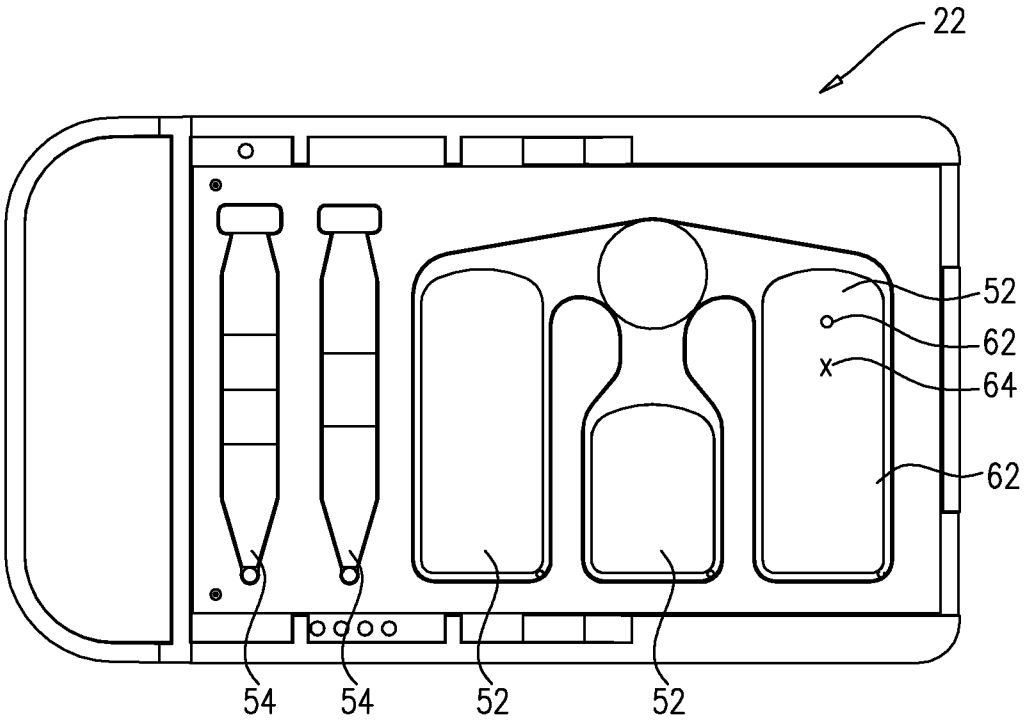

FIG. 6

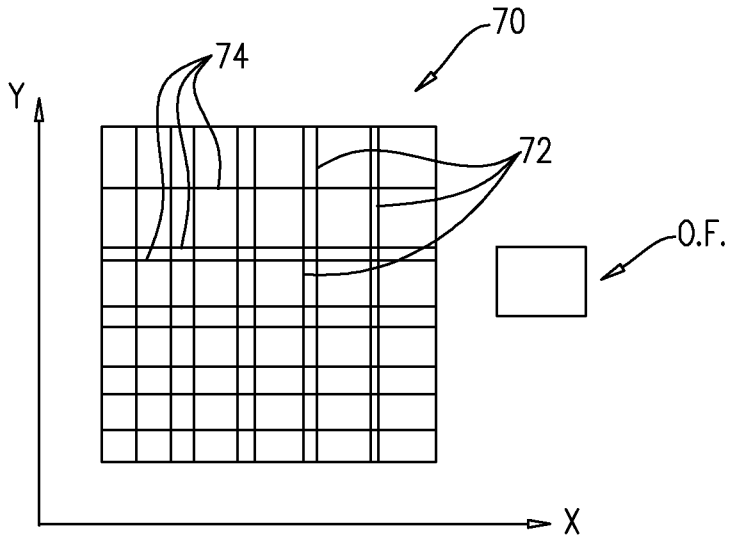

FIG. 7A

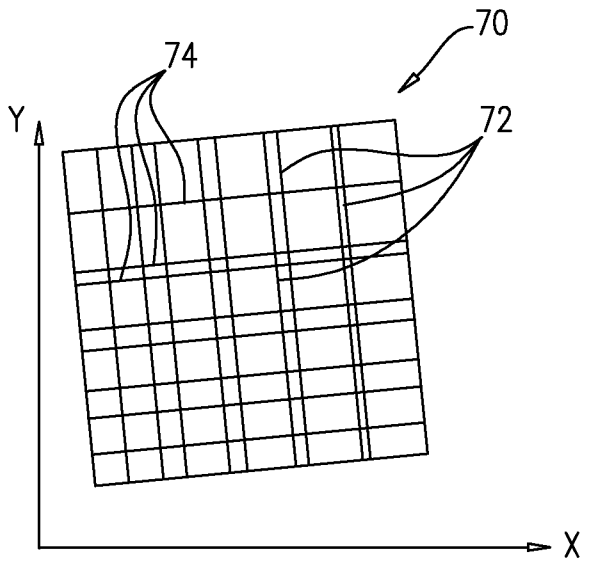

FIG. 7B

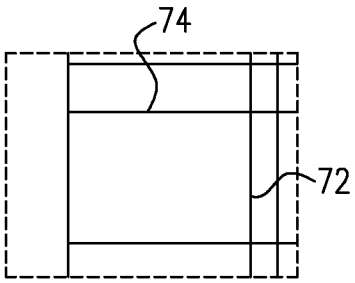

FIG. 8A

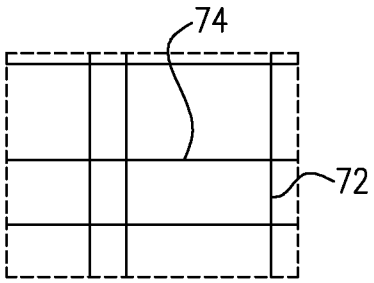

FIG. 8B

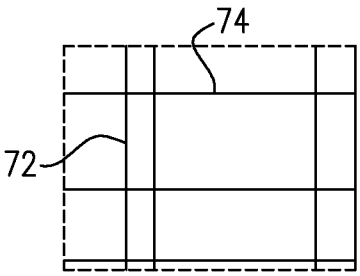

FIG. 8C

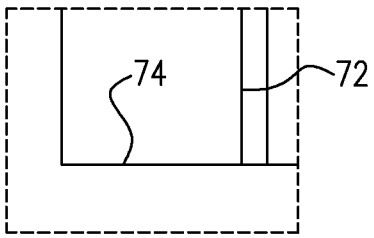

FIG. 8D

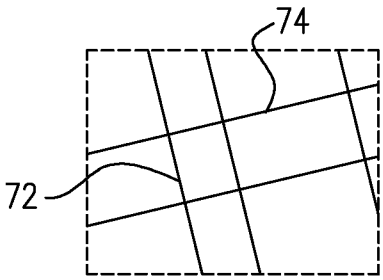

FIG. 9A

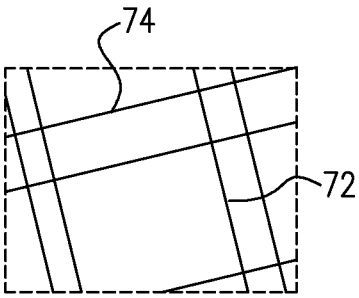

FIG. 9B

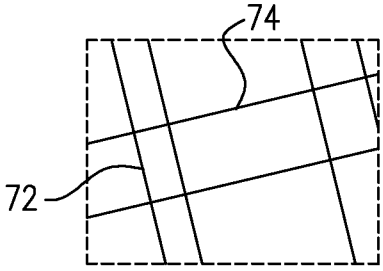

FIG. 9C

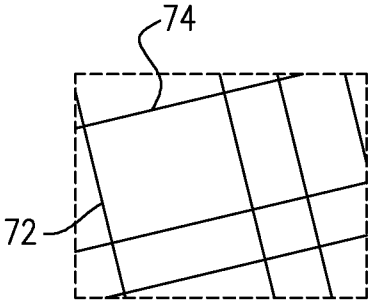

FIG. 9D

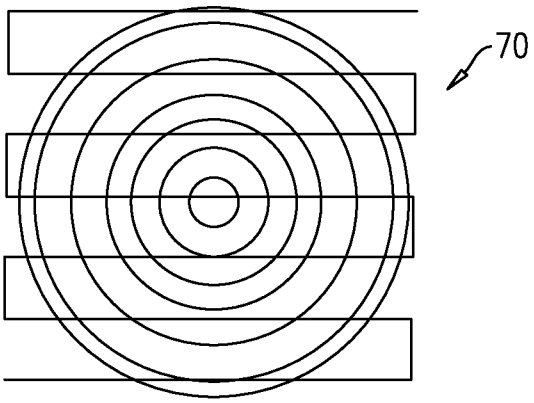

FIG. 10A

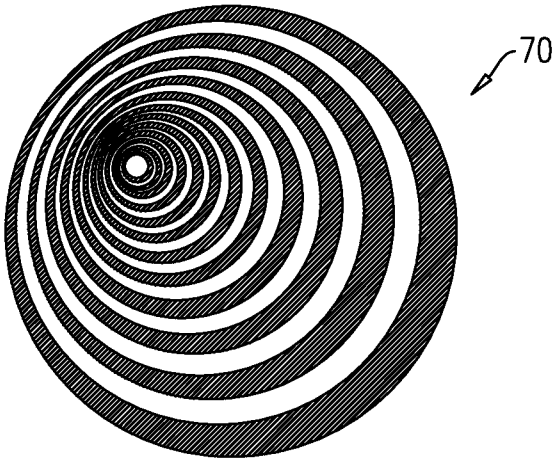

FIG. 10B

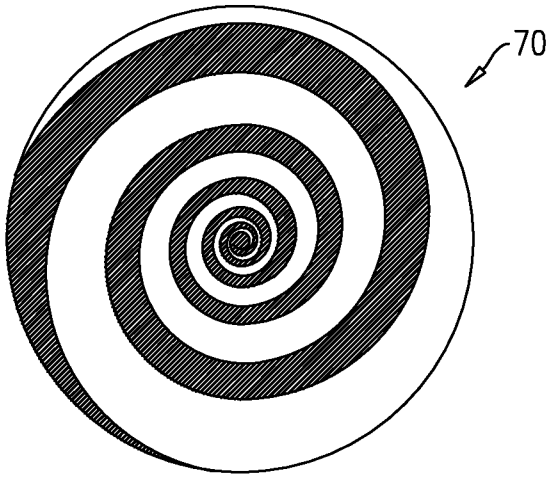

FIG. 10C

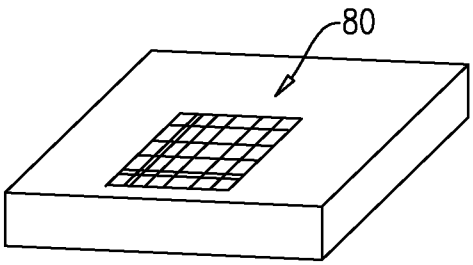

FIG. 11A

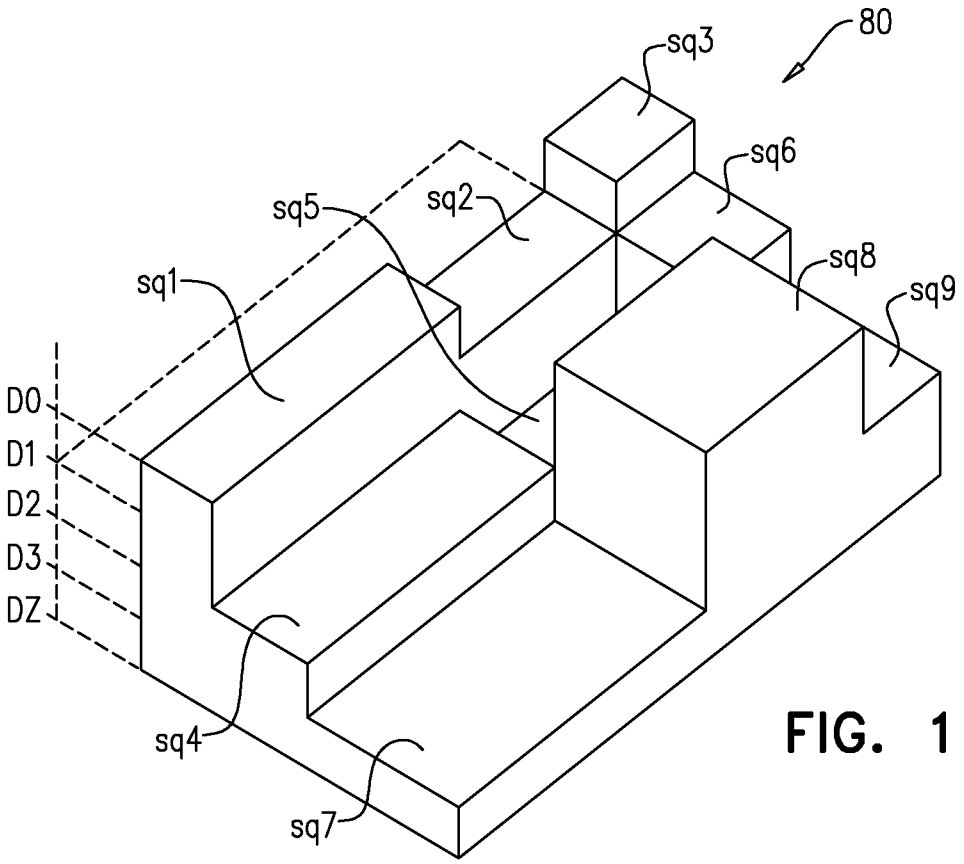

FIG. 11B

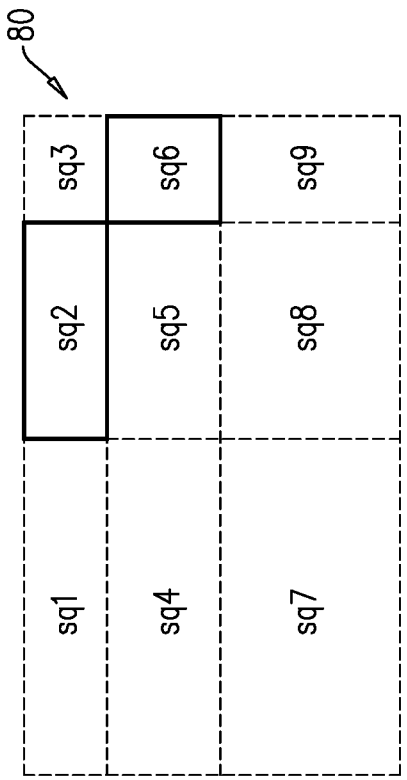

FIG. 11D

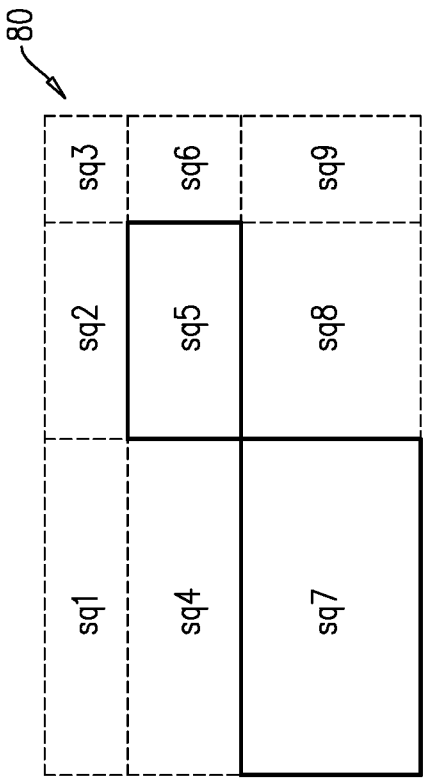

FIG. 11F

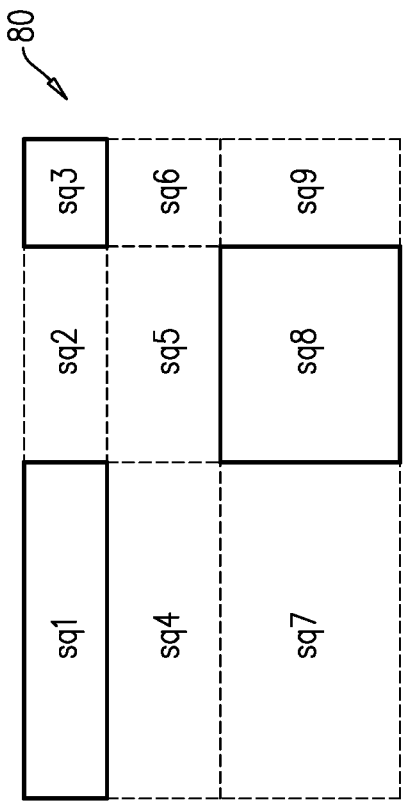

FIG. 11C

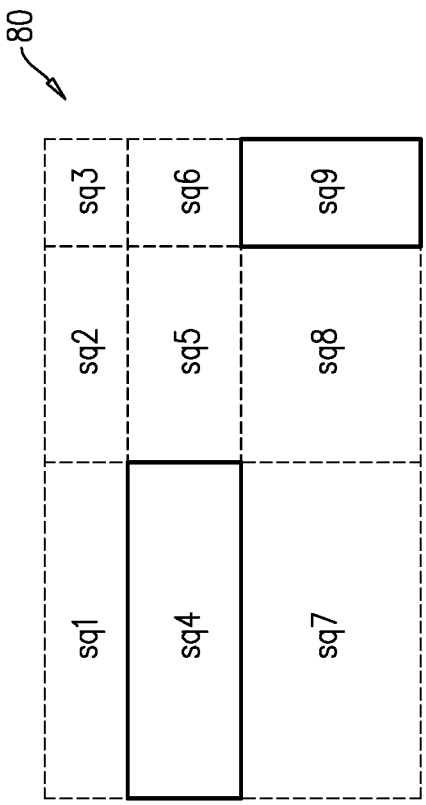

FIG. 11E

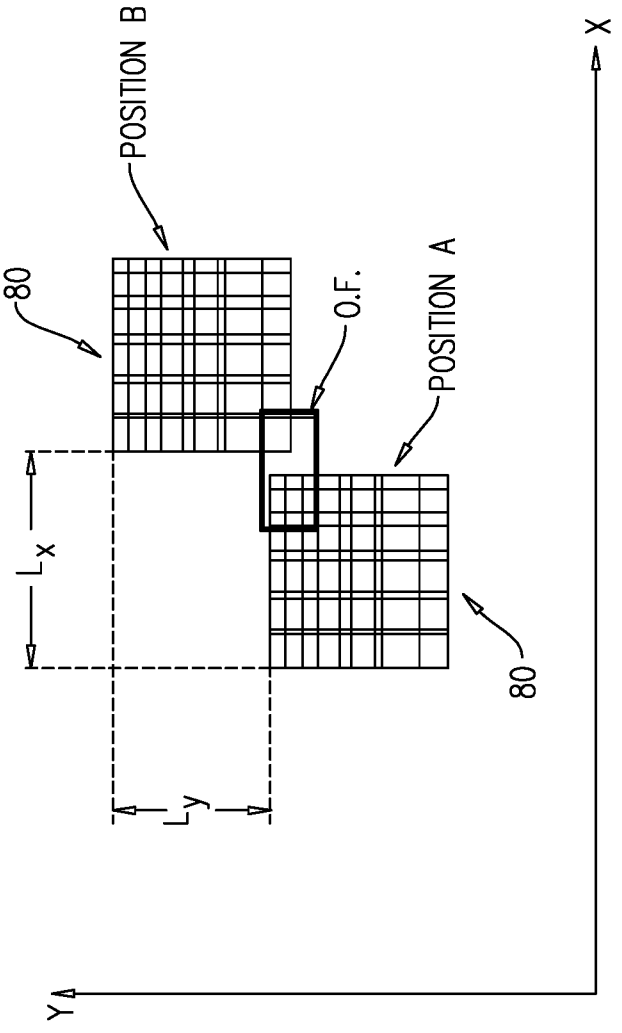

FIG. 12

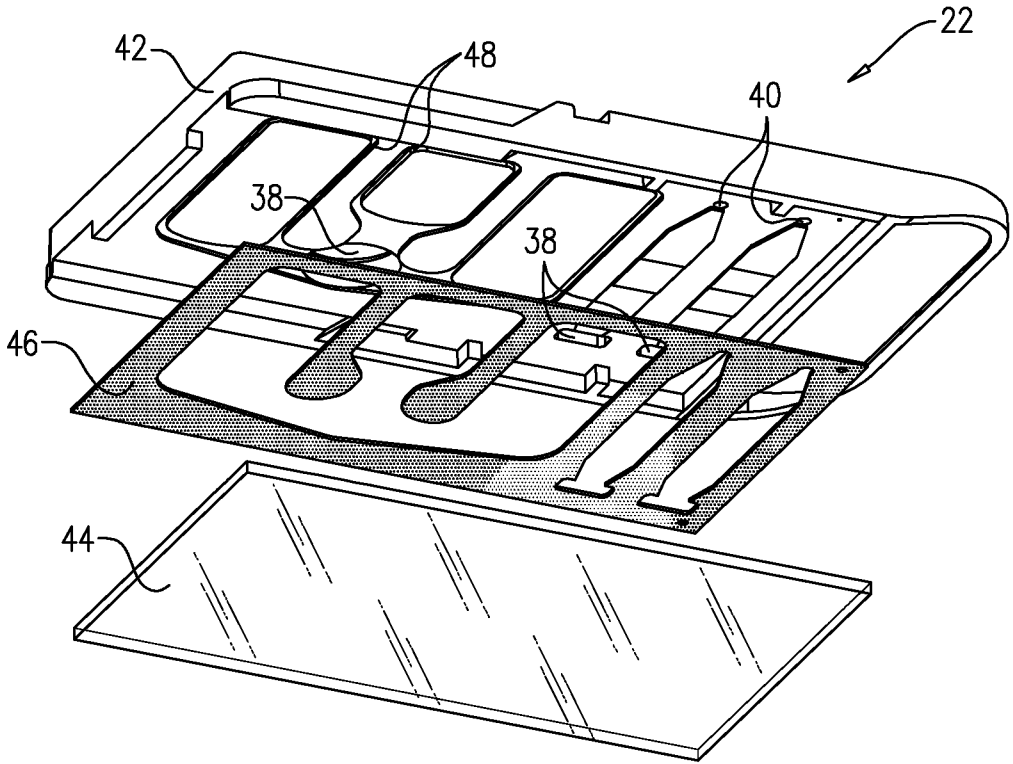

FIG. 4C