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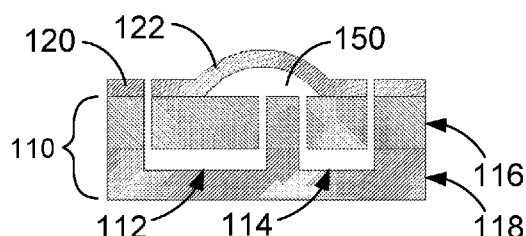
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RESERVOIRS, AND APPLICATIONS OF SAME

FIG. 1B

(57) Abstract: Aspects of the disclosure relate to pressure regulation sys-
tems, pressure-activated valves, and passive pressurized fluid reservoirs
thereof, and applications of the same. The pressure-activated valve includes
a substrate and a membrane disposed thereon. The substrate has an input
fluidic channel and an output fluidic channel formed therein. The membrane
includes a center region and a peripheral region surrounding the center re-
gion and bound to the substrate. The center region covers one end of the
input fluidic channel and one end of the output fluidic channel. The center
region of the membrane is controlled to deform by pressure to switch be-
tween an open state and a closed state, allowing the input fluidic channel
and the output fluidic channel to be in communication with each other in
the open state and not in communication with each other in the closed state.

**PRESSURE REGULATION SYSTEM, PRESSURE RELEASE VALVES
THEREOF, PASSIVE PRESSURIZED FLUID RESERVOIRS, AND
APPLICATIONS OF SAME**

STATEMENT AS TO RIGHTS UNDER FEDERALLY-SPONSORED RESEARCH

This invention was made with government support under Grant Nos. 5UG3TR002097-02, U01CA202229 and HHSN271201700044C awarded by the National Institutes of Health, Grant No. 83573601 awarded by the U. S. Environmental Protection Agency, Grant No. 2017-17081500003 awarded by the Intelligence Advanced Research Projects Activity, and Grant No. CBMXCEL-XL1-2-001 awarded by the Defense Threat Reduction Agency through Subcontract 468746 by Los Alamos National Laboratory (LANL). The government has certain rights in the invention.

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application Serial Nos. 62/719,868, and 62/868,303, filed August 20, 2018 and June 28, 2019, respectively.

This application is also a continuation-in-part application of U.S. Patent Application Serial No. 15/820,506, filed November 22, 2017, now allowed, which is a divisional application of U.S. Patent Application Serial No. 13/877,925, filed July 16, 2013, now abandoned, which is a national stage entry of PCT Application Serial No. PCT/US2011/055432, filed October 7, 2011, which claims priority to and the benefit of, U.S. Provisional Patent Application Serial No. 61/390,982, filed October 7, 2010.

This application is also a continuation-in-part application of U.S. Patent Application Serial No. 16/049,025, filed July 30, 2018, which is a continuation application of U.S. Patent Application Serial No. 14/363,074, filed June 5, 2014, now U.S. Patent No. 10,078,075, is a national stage entry of PCT Application Serial No. PCT/US2012/068771, filed December 10, 2012, which claims priority to and the benefit of U.S. Provisional Patent Application Serial Nos. No. 61/569,145, 61/697,204 and 61/717,441, filed December 9, 2011, September 5, 2012 and October 23, 2012, respectively.

This application is also a continuation-in-part application of U.S. Patent Application Serial No. 16/012,900, filed June 20, 2018, which is a divisional application of U.S. Patent Application Serial No. 15/191,092 (the '092 application), filed June 23, 2016, now U.S. Patent

No. 10,023,832, which claims priority to and the benefit of U.S. Provisional Patent Application Serial Nos. 62/183,571, 62/193,029, 62/276,047 and 62/295,306, filed June 23, 2015, July 15, 2015, January 7, 2016 and February 15, 2016, respectively. The '092 application is also a continuation-in-part application of U.S. Patent Application Serial Nos. 13/877,925, 14/363,074, 5 14/646,300 (the '300 application) and 14/651,174 (the '174 application), filed July 16, 2013, June 5, 2014, May 20, 2015 and June 10, 2015, respectively. The '300 application, now U.S. Patent No. 9,874,285, is a national stage entry of PCT Application Serial No.

PCT/US2013/071026, filed November 20, 2013, which claims priority to and the benefit of U.S. Provisional Patent Application Serial Nos. 61/729,149, 61/808,455, and 61/822,081, filed 10 November 21, 2012, April 4, 2013 and May 10, 2013, respectively. The '174 application, now U.S. Patent No. 9,618,129, is a national stage entry of PCT Application Serial No.

PCT/US2013/071324, filed November 21, 2013, which claims priority to and the benefit of U.S. Provisional Patent Application Serial Nos. 61/808,455 and 61/822,081, filed April 4, 2013 and May 10, 2013, respectively.

15 This application is also a continuation-in-part application of U.S. Patent Application Serial No. 16/511,379, filed July 15, 2019, which is a divisional application of U.S. Patent Application Serial No. 15/776,524, filed May 16, 2018, now allowed, which is a national stage entry of PCT Application Serial No. PCT/US2016/063586 (the '586 application), filed November 23, 2016, which claims priority to and the benefit of, U.S. Provisional Patent 20 Application Serial No. 62/259,327, filed November 24, 2015. The '586 application is also a continuation-in-part application of U.S. Patent Application Serial Nos. 13/877,925, 14/363,074, 14/646,300, 14/651,174 and 15/191,092, filed July 16, 2013, June 5, 2014, May 20, 2015, June 10, 2015 and June 23, 2016, respectively.

This application is also a continuation-in-part application of PCT Patent Application 25 Serial No. PCT/US2019/034285 (the '285 application), filed May 29, 2019, which claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 62/677,468, filed May 29, 2018. The '285 application is also a continuation-in-part application of U.S. Patent Application Serial Nos. 15/776,524 and 16/012,900, filed May 16, 2018 and June 20, 2018, respectively.

30 Each of the above-identified applications is incorporated herein by reference in its entirety.

Some references, which may include patents, patent applications, and various

publications, are cited and discussed in the description of the invention. The citation and/or discussion of such references is provided merely to clarify the description of the invention and is not an admission that any such reference is “prior art” to the invention described herein. All references cited and discussed in this specification are incorporated herein by reference in their
5 entireties and to the same extent as if each reference was individually incorporated by reference.

FIELD OF THE INVENTION

The invention relates generally to microfluidic systems, and more particularly to a pressure regulation system, pressure sensitive valves, and passive pressurized fluid reservoirs
10 thereof, and applications of the same.

BACKGROUND INFORMATION

The background description provided herein is for the purpose of generally presenting the context of the invention. The subject matter discussed in the background of the invention section
15 should not be assumed to be prior art merely as a result of its mention in the background of the invention section. Similarly, a problem mentioned in the background of the invention section or associated with the subject matter of the background of the invention section should not be assumed to have been previously recognized in the prior art. The subject matter in the background of the invention section merely represents different approaches, which in and of
20 themselves may also be inventions. Work of the presently named inventors, to the extent it is described in the background of the invention section, as well as aspects of the description that may not otherwise qualify as prior art at the time of filing, are neither expressly nor impliedly admitted as prior art against the invention.

Generally, the liquid flow through microfluidic channels and devices used in biological
25 research is driven by relatively low pressure gradients, typically less than one atmosphere of pressure, and often as low as several centimeters of water. In certain circumstances when microfluidic devices are using sources of constant or metered fluid flows, the local pressure can spike, causing rupture damage to either the pump itself or downstream devices and thereby potentially causing hazardous leakage of fluids. Such spikes could be the result of delayed
30 opening of a valve while a pump is running, the kinking of a tube, or some other transient obstruction in the fluid flow path.

Therefore, a heretofore unaddressed need exists in the art to address the aforementioned

deficiencies and inadequacies.

SUMMARY OF THE INVENTION

One aspect of the present invention relates to a pressure activated valve, which includes:
5 a substrate, having an input fluidic channel and an output fluidic channel formed therein; and a
membrane disposed on the substrate, wherein the membrane includes a center region and a
peripheral region surrounding the center region and bound to the substrate, and the center region
covers one end of the input fluidic channel and one end of the output fluidic channel. The center
region of the membrane is controlled to deform by pressure to switch between an open state and
10 a closed state, allowing the input fluidic channel and the output fluidic channel to be in
communication with each other in the open state and not in communication with each other in
the closed state.

In certain embodiments, a default state of the center region of the membrane is the closed
state, and the center region of the membrane is attached to the substrate such that the input
15 fluidic channel and the output fluidic channel are not in communication with each other in the
closed state.

In certain embodiments, in response to a pressure, the center region of the membrane
deforms to switch to the open state and form a space between the center region and the substrate,
allowing the input fluidic channel and the output fluidic channel to communicate with each other
20 through the space.

In certain embodiments, when an output pressure in the output fluidic channel exceeds a
pressure threshold, the center region of the membrane deforms to switch to the open state.

In certain embodiments, the peripheral region of the membrane includes an inlet port in
communication with the other end of the input fluidic channel and an outlet port in
25 communication with the other end of the output fluidic channel.

In certain embodiments, the input fluidic channel comprises: a first vertical input hole in
communication with the inlet port; a second vertical input hole covered by the center region of
the membrane; and a horizontal input channel connecting the first vertical input hole to the
second vertical input hole; and the output fluidic channel comprises: a first vertical output hole in
30 communication with the outlet port; a second vertical output hole covered by the center region of
the membrane; and a horizontal output channel connecting the first vertical output hole to the
second vertical output hole.

In certain embodiments, the center region of the membrane is in a circular shape.

In certain embodiments, the one end of the input fluidic channel covered by the center region is located at or relatively close to a center of the circular shape of the center region, and the one end of the output fluidic channel covered by the center region is located relatively close
5 to an outer edge of the circular shape of the center region.

In certain embodiments, the center region of the membrane is in a non-circular shape.

In certain embodiments, a minimum distance between the one end of the output fluidic channel covered by the center region and an outer edge of the non-circular shape of the center region is shorter than a minimum distance between the one end of the input fluidic channel
10 covered by the center region and the outer edge of the non-circular shape of the center region.

In certain embodiments, the pressure activated valve further includes a pressure adjustment means provided on the center region of the membrane, wherein the pressure adjustment means is configured to generate a pressure on the center region.

In certain embodiments, the pressure adjustment means is a spring.

15 In certain embodiments, the pressure adjustment means comprises a pressurized gas or fluid.

Another aspect of the present invention relates to a pressure regulation system, which includes a pressure activated valve as described above. In certain embodiments, the pressure regulation system is a rotary planar peristaltic micropump (RPPM).

20 A further aspect of the present invention relates to a pressure activated valve functioning as a non-linear fluidic capacitor, which includes: a substrate, having a fluidic channel formed therein; and a membrane disposed on the substrate, wherein the membrane includes a center region and a peripheral region surrounding the center region and bound to the substrate, and the center region covers one end of the fluidic channel. The center region of the membrane is
25 controlled to deform by fluid pressure provided in the fluidic channel to switch between an open state and a closed state, allowing a space to store fluid between the center region of the membrane and the substrate in the open state.

In certain embodiments, a default state of the center region of the membrane is the closed state, and the center region of the membrane is attached to the substrate such that no space exists
30 between the center region of the membrane and the substrate in the closed state.

In certain embodiments, the center region of the membrane is in a circular shape.

A further aspect of the present invention relates to a passive pressure relief valve, which

includes: an upper housing having a cylindrical cavity; a spring disposed in the cylindrical cavity; a fluidic device disposed below the spring, wherein the fluidic device has a straight channel running through a bowl formed by a membrane; and a base plate, disposed below the fluidic device. The spring is compressed upon the membrane that forms the bowl of the fluidic device to close the bowl.

In certain embodiments, the cylindrical cavity of the upper housing aligns with the bowl of the fluidic device.

In certain embodiments, a bottom portion of the upper housing fits the spring.

In certain embodiments, a bottom portion of the upper housing does not fit with the spring.

In certain embodiments, the fluidic device is formed by Polydimethylsiloxane (PDMS).

In a further aspect, a passive pressurized fluid reservoir includes: a chamber comprising a base and a cap; a spring disposed in the base of the chamber, wherein the cap has a column extending out to hold the spring; a capsule, wherein the spring is disposed within the capsule; a bellows pouch, disposed in the base of the chamber below the capsule; wherein a fluid flows into the bellows pouch such that the bellows pouch expands to push the capsule into the cap to compress the spring, and the spring pushes the fluid out of the bellows pouch.

In certain embodiments, the bellows pouch is made of a plastic material.

In certain embodiments, the base and the cap of the chamber and the capsule are 3D-printed.

In yet another aspect of the present invention, a ridge pump is provided. The ridge pump includes: a support plate; a ridge chip, having a plurality of protrusions formed on a first surface facing the support plate, a plateau formed on a second surface away from the support plate, and a protruding ridge disposed on the plateau, wherein the support plate mates with the protrusions to form a fluid channel between the ridge chip and support plate, and the protruding ridge is in relation to the fluid channel allowing the support plate to gradually engage and disengage with the fluid channel; and a pressure limiting structure, comprising: a membrane disposed on the plateau of the ridge chip covering the fluidic channel; and pressure adjustment means disposed on the membrane, configured to generate a pressure on the membrane to maintain the fluidic channel in a closed state. The pressure limiting structure is controlled by a fluidic pressure in the fluidic channel to switch the fluidic channel between the closed state to an open state, wherein the fluidic channel is switched to the open state when the fluidic pressure is greater than the

pressure generated by the pressure adjustment means, and the fluidic channel is switched to the closed state when the fluidic pressure is not greater than the pressure generated by the pressure adjustment means..

In certain embodiments, the pressure adjustment means is a helical spring.

5 In certain embodiments, the protruding ridge comprises a ridge portion and two ramps connecting the plateau to two ends of the ridge portion, a height of each of the two ramps gradually increases from the plateau to the two ends of the ridge portion, and a height of the ridge portion equals the greatest height of each of the two ramps.

10 In certain embodiments, a pressure regulation system may include the ridge pump as described above.

These and other aspects of the invention will become apparent from the following description of the preferred embodiment taken in conjunction with the following drawings, although variations and modifications therein may be affected without departing from the spirit and scope of the novel concepts of the disclosure.

15

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings illustrate one or more embodiments of the invention and, together with the written description, serve to explain the principles of the invention. Wherever possible, the same reference numbers are used throughout the drawings to refer to the same or
20 like elements of an embodiment.

FIG. 1A shows a top view of a pressure sensitive valve according to one embodiment of the invention.

FIG. 1B shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 1A in an open pressurized state.

25 FIG. 1C shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 1A in a closed state.

FIG. 2A shows a top view of a pressure sensitive valve according to one embodiment of the invention.

30 FIG. 2B shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 2A in an open pressurized state.

FIG. 2C shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 2A in a closed state.

FIG. 3A shows a top view of a pressure sensitive valve according to one embodiment of the invention.

FIG. 3B shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 3A in an open pressurized state.

5 FIG. 3C shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 3A in a closed state.

FIGS. 3D-3G show schematic cross sectional views of the pressure sensitive valve shown in FIG. 3A illustrating the non-linear fluidic capacitor and variable fluidic resistance features of the design.

10 FIG. 4A shows a top view of a pressure sensitive valve according to one embodiment of the invention.

FIG. 4B shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 4A in an open state.

15 FIG. 4C shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 4A in a closed state.

FIG. 5A schematically shows a pressure sensitive valve in a closed state according to one embodiment of the invention.

FIG. 5B schematically shows the pressure sensitive valve as shown in FIG. 5A in an open state.

20 FIG. 6A shows a top view of a pressure sensitive valve according to one embodiment of the invention.

FIG. 6B shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 6A in an open state.

25 FIG. 6C shows a cross-sectional view of the pressure sensitive valve as shown in FIG. 6A in a closed state.

FIG. 7 schematically shows a pump with a pressure sensitive bypass valve in a closed state according to one embodiment of the invention.

FIG. 8A schematically shows a perspective view of a RPPM having a pressure sensitive valve according to one embodiment of the invention.

30 FIG. 8B schematically shows a ridge chip of the RPPM as shown in FIG. 8A.

FIG. 8C schematically shows plain view and cross-sectional views of the ridge chip as shown in FIG. 8B.

FIG. 8D schematically shows a plurality of locations along the ridge of the ridge pump as shown in FIG. 8A.

FIG. 8E shows a cross-section of the ridge at location 4 in the uncompressed ridge pump as shown in FIG. 8D.

5 FIG. 8F shows a cross-section of the ridge at location 1 in the compressed ridge pump as shown in FIG. 8D.

FIG. 8G shows a cross-section of the ridge at location 2 in the compressed ridge pump as shown in FIG. 8D.

10 FIG. 8H shows a cross-section of the ridge at location 3 in the compressed ridge pump as shown in FIG. 8D.

FIG. 8I shows the height of the protruding ridge as a function of the angle around the ridge pump chip as shown in FIG. 8A.

15 FIG. 8J shows the relationship between the height of the protruding ridge of the ridge chip and the elastomeric volume displacement as a function of angle according to certain embodiments of the invention.

FIG. 9A shows a top view of a non-linear fluidic capacitor according to one embodiment of the invention.

FIG. 9B shows a cross-sectional view of the non-linear fluidic capacitor as shown in FIG. 9A in an open state.

20 FIG. 9C shows a cross-sectional view of the non-linear fluidic capacitor as shown in FIG. 9A in a closed state.

FIG. 10 schematically shows a pressure pump for multiple-organ perfusion according to one embodiment of the present invention.

25 FIG. 11A shows the pump speed of the pumps for each of the three valve settings in FIG. 10.

FIG. 11B shows the pressure within each of the three reservoirs in FIG. 10.

FIG. 12A schematically shows a plan-view of a bypass valve according to one embodiment of the present invention.

30 FIG. 12B schematically shows a cross-section view of a bypass valve in its open state according to one embodiment of the present invention.

FIG. 12C schematically shows a cross-section view of a bypass valve in its closed state according to one embodiment of the present invention.

FIG. 12D shows a mask to prevent adherence of the PDMS in the central valve region according to one embodiment of the present invention.

FIG. 12E shows an alignment guide of the PDMS mask to create the central, non-adherent region of the bypass valve membrane in FIGS. 12B and 12C.

5 FIG. 12F shows the PDMS mask and alignment jig positioned over a real valve body fabricated from PDMS according to one embodiment of the present invention.

FIG. 13A shows the complete arrangement of the passive pressure relief valve according to one embodiment of the present invention.

10 FIG. 13B shows the upper housing for the long spring of the passive pressure relief valve as shown in FIG. 13A according to one embodiment of the present invention.

FIG. 13C shows the upper housing for a short spring of the passive pressure relief valve as shown in FIG. 13A according to one embodiment of the present invention.

FIG. 13D shows the design of the channels in the PDMS fluidic device in FIG. 13A according to one embodiment of the present invention.

15 FIG. 13E shows the base plate of the passive pressure relief valve as shown in FIG. 13A.

FIG. 13F shows the spring cap of the passive pressure relief valve as shown in FIG. 13A.

FIG. 14 shows a pressurized planar bellows reservoir according to one embodiment of the present invention.

20 FIG. 15A schematically shows a passive pressurized vertical bellows fluid reservoir according to one embodiment of the present invention.

FIG. 15B shows a cap of the chamber of the passive pressurized fluid reservoir as shown in FIG. 15A.

FIG. 15C shows the base of the chamber of the passive pressurized fluid reservoir as shown in FIG. 15A.

25 FIG. 15D shows the spring capsule of the passive pressurized fluid reservoir as shown in FIG. 15A.

FIG. 15E shows the plastic cylindrical bellows pouch of the passive pressurized fluid reservoir as shown in FIG. 15A.

30 FIG. 15F shows the plastic cylindrical bellows pouch as shown in FIG. 15E in combination with the spring of the passive pressurized fluid reservoir as shown in FIG. 15A.

FIG. 15G shows the plastic bellows pouch as shown in FIG. 15E from a different viewing angle.

FIG. 15H shows the plastic bellows pouch as shown in FIG. 15G in combination with the spring of the passive pressurized fluid reservoir as shown in FIG. 15A.

DETAILED DESCRIPTION OF THE INVENTION

5 The invention will now be described more fully hereinafter with reference to the accompanying drawings, in which exemplary embodiments of the invention are shown. The invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to
10 those skilled in the art. Like reference numerals refer to like elements throughout.

 The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used. Certain terms that are used to describe the invention are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner regarding the description of the
15 invention. For convenience, certain terms may be highlighted, for example using italics and/or quotation marks. The use of highlighting and/or capital letters has no influence on the scope and meaning of a term; the scope and meaning of a term are the same, in the same context, whether or not it is highlighted and/or in capital letters. It will be appreciated that the same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for
20 any one or more of the terms discussed herein, nor is any special significance to be placed upon whether or not a term is elaborated or discussed herein. Synonyms for certain terms are provided. A recital of one or more synonyms does not exclude the use of other synonyms. The use of examples anywhere in this specification, including examples of any terms discussed herein, is illustrative only and in no way limits the scope and meaning of the invention or of any
25 exemplified term. Likewise, the invention is not limited to various embodiments given in this specification.

 It will be understood that when an element is referred to as being “on” another element, it can be directly on the other element or intervening elements may be present therebetween. In contrast, when an element is referred to as being “directly on” another element, there are no
30 intervening elements present. As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

 It will be understood that, although the terms first, second, third, etc. may be used herein

to describe various elements, components, regions, layers and/or sections, these elements, components, regions, layers and/or sections should not be limited by these terms. These terms are only used to distinguish one element, component, region, layer or section from another element, component, region, layer or section. Thus, a first element, component, region, layer or section discussed below can be termed a second element, component, region, layer or section without departing from the teachings of the invention.

It will be understood that when an element is referred to as being “on,” “attached” to, “connected” to, “coupled” with, “contacting,” etc., another element, it can be directly on, attached to, connected to, coupled with or contacting the other element or intervening elements may also be present. In contrast, when an element is referred to as being, for example, “directly on,” “directly attached” to, “directly connected” to, “directly coupled” with or “directly contacting” another element, there are no intervening elements present. It will also be appreciated by those of skill in the art that references to a structure or feature that is disposed “adjacent” to another feature may have portions that overlap or underlie the adjacent feature.

The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms “comprises” and/or “comprising,” or “includes” and/or “including” or “has” and/or “having” when used in this specification specify the presence of stated features, regions, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, regions, integers, steps, operations, elements, components, and/or groups thereof.

Furthermore, relative terms, such as “lower” or “bottom” and “upper” or “top,” may be used herein to describe one element's relationship to another element as illustrated in the figures.

It will be understood that relative terms are intended to encompass different orientations of the device in addition to the orientation shown in the figures. For example, if the device in one of the figures is turned over, elements described as being on the “lower” side of other elements would then be oriented on the “upper” sides of the other elements. The exemplary term “lower” can, therefore, encompass both an orientation of lower and upper, depending on the particular orientation of the figure. Similarly, if the device in one of the figures is turned over, elements described as “below” or “beneath” other elements would then be oriented “above” the other elements. The exemplary terms “below” or “beneath” can, therefore, encompass both an

orientation of above and below.

Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. It will be further understood that terms, such as those defined in commonly
5 used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the relevant art and the present disclosure, and will not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

As used herein, “around,” “about,” “substantially” or “approximately” shall generally mean within 20 percent, preferably within 10 percent, and more preferably within 5 percent of a
10 given value or range. Numerical quantities given herein are approximate, meaning that the terms “around,” “about,” “substantially” or “approximately” can be inferred if not expressly stated.

As used herein, the terms “comprise” or “comprising,” “include” or “including,” “carry” or “carrying,” “has/have” or “having,” “contain” or “containing,” “involve” or “involving” and the like are to be understood to be open-ended, *i.e.*, to mean including but not limited to.

15 As used herein, the phrase “at least one of A, B, and C” should be construed to mean a logical (A or B or C), using a non-exclusive logical OR. As used herein, the term “and/or” includes any and all combinations of one or more of the associated listed items.

The description below is merely illustrative in nature and is in no way intended to limit the invention, its application, or uses. The broad teachings of the invention can be implemented
20 in a variety of forms. Therefore, while this invention includes particular examples, the true scope of the invention should not be so limited since other modifications will become apparent upon a study of the drawings, the specification, and the following claims. For purposes of clarity, the same reference numbers will be used in the drawings to identify similar elements. It should be understood that one or more steps within a method may be executed in different order (or
25 concurrently) without altering the principles of the invention.

As discussed above, when microfluidic devices are using pumps as active sources of constant or metered fluid flows, the local pressure can spike, causing rupture damage to either the pump itself or downstream devices and thereby potentially causing hazardous leakage of fluids. Such spikes could be the result of delayed opening of a valve while a pump is running,
30 the kinking of a tube, or some other transient obstruction in the fluid flow path. Accordingly it is good engineering practice to provide pumps with a pressure regulation system that will prevent pressure transients and their associated problems.

In certain aspect of the present invention, two categories of passive pressure relief devices are provided, which can be integrally fabricated as part of a microfluidic pumping system. One category relies on the intrinsic elastomeric properties of the material used to fabricate the rotary planar peristaltic micropumps (RPPMs), and the other augments this with
5 additional adjustable springs or other pressure adjustment features for the purpose of providing field adjustable pressure relief and regulation.

One aspect of the present invention relates to a pressure-activated valve, which is also known as a pressure sensitive valve, a pressure release valve or a pressure limiting valve. The pressure-activated valve utilizes flexible elastomeric membranes, which will deform when
10 pressure is applied to one side of the membrane. This effect can be utilized to construct valves which will remain closed to fluid flow at low pressures, but will become open to fluid flows at higher pressures.

FIGS. 1A-1C schematically show a pressure sensitive valve according to one embodiment of the present invention. The pressure sensitive valve 100 is formed by a substrate
15 110 and a membrane 120 disposed on the substrate 110. Specifically, the membrane 120 is a flexible elastomeric membrane, which includes a pressure-sensitive center region 122 and a peripheral region 124 surrounding the center region 122. The peripheral region 124 is bound to the substrate 110, and includes an inlet port 130 and an outlet port 140. The center region 122 covers the substrate 110 but is not fixed or attached to the substrate 110. In this case, the center
20 region 122 of the membrane 120 can be controlled to deform by pressure to switch between the open state and a closed state.

As shown in FIGS. 1B and 1C, the substrate 110 is formed with an input fluidic channel 112 and an output fluidic channel 114 therein. Specifically, the substrate 110 is formed by a via layer 116 and a channel layer 118 stacked together, where the via layer 116 may be provided
25 with multiple vertical holes, and the channel layer 118 may be provided with horizontal channels. As shown in FIG. 1C, the input fluidic channel 112 includes a first vertical input hole 112A in communication with the inlet port 130, a second vertical input hole 112B covered by the center region 122 of the membrane 120, and a horizontal input channel 112C connecting the first vertical input hole 112A to the second vertical input hole 112B. In other words, the first vertical
30 input hole 112A and the second vertical input hole 112B respectively form two ends of the input fluidic channel 112. The output fluidic channel 114 includes a first vertical output hole 114A in communication with the outlet port 140, a second vertical output hole 114B covered by the

center region 122 of the membrane 120, and a horizontal output channel 114C connecting the first vertical output hole 114A to the second vertical output hole 114B. In other words, the first vertical output hole 114A and the second vertical output hole 114B respectively form two ends of the output fluidic channel 114. Thus, one end 112B of the input fluidic channel 112 and one
5 end 114B of the output fluidic channel 114 are covered by the center region 122 of the membrane 120. The other end 112A of the input fluidic channel 112 is in communication with the inlet port 130, and the other end 114A of the output fluidic channel 114 is in communication with the outlet port 140.

As shown in FIG. 1A, the center region 122 of the membrane 120 is in a circular shape.
10 In certain embodiments, a default state of the center region 122 of the membrane 120 is the closed state as shown in FIG. 1C, where the center region 122 of the membrane 120 presses against the substrate 110 because of the passive stiffness of the membrane 120, such that the input fluidic channel 112 and the output fluidic channel 114 are not in communication with each other. In comparison, when a pressurized fluid is provided through one of the input fluidic
15 channel 112 and the output fluidic channel 114, the center region 122 of the membrane 120 may, in response to the pressure, deform to switch to the open state as shown in FIG. 1B. In this case, a space 150 is formed between the center region 122 and the substrate 110, allowing the input fluidic channel 112 and the output fluidic channel 114 to communicate with each other through the space 150.

As shown in FIG. 1A, the one end 112B of the input fluidic channel 112 covered by the center region 122 is located at or relatively close to a center of the circular shape of the center region 122, and the one end 114B of the output fluidic channel 114 covered by the center region 122 is located relatively close to an outer edge of the circular shape of the center region 122. In different embodiments, the location of these channel ends can be altered in accordance with the
25 application of the device and the elastic properties of the material used to form membrane 120.

As discussed above, the peripheral region 124 of the membrane 120 is rigidly bound to the substrate 110 to form a circular edge surrounding the center region 122. In operation, when the input pressure of the pressurized fluid provided through the input fluidic channel 112 exceeds a certain threshold, the center region 122 of the membrane 120 deforms to an extent to form the
30 space 150, allowing fluid to flow from the input fluidic channel 112 to the output fluidic channel 114.

The membrane 120 is a flexible elastomeric membrane, which can be implemented in a

variety of elastomeric materials. In certain embodiments, the elastomeric materials may be hydrophobic elastomers such as Polydimethylsiloxane (PDMS) or other elastomers which have been coated with hydrophobic materials. In this case, an energy barrier is created for aqueous fluids that, in combination with the elastic tension of the membrane 120 and the weak adhesive forces that hold the elastomer and the underlying substrate 110 together act to keep the valve 100 closed to fluid flow at low fluid pressures relative to the atmospheric pressure present on opposite side of the membrane 120.

As discussed above, the center region 122 of the membrane 120 is in the circular shape. The one end 112B of the input fluidic channel 112 covered by the center region 122 is located at or relatively close to a center of the circular shape of the center region 122, and the one end 114B of the output fluidic channel 114 covered by the center region 122 is located relatively close to an outer edge of the circular shape of the center region 122. The placement of the end 112B of the input fluidic channel 112 and the end 114B of the output fluidic channel 114 in the center region 122 are important parameters affecting the performance of this pressure sensitive valve 100. Additional parameters of importance are the thickness of the membrane 120 and the Young's modulus of the elastomeric material forming the membrane 120, as well as the hydrophobicity of the surfaces.

In certain embodiments, the center region of the membrane is not limited to be in the circular shape, and other geometric valve designs which rely on the same elastomeric membrane features can be adopted. For example, FIGS. 2A-2C schematically show a pressure sensitive valve according to another embodiment of the present invention. The pressure sensitive valve 200 as shown in FIGS. 2A-2C is different from the pressure sensitive valve 100 as shown in FIGS. 1A-1C mainly in that, as shown in FIG. 2A, the center region 222 of the membrane 220 is in a non-circular shape. Specifically, the pressure sensitive valve 200 is formed by a substrate 210 and a membrane 220 disposed on the substrate 210. The membrane 220 is a flexible elastomeric membrane, which includes a pressure-sensitive center region 222 and a peripheral region 224 surrounding the center region 222. The peripheral region 224 is rigidly attached to and bound to the substrate 210, and includes an inlet port 230 and an outlet port 240. The center region 222 covers the substrate 210 but is not fixed or attached to the substrate 210. As shown in FIG. 2A, the center region 222 of the membrane 220 is in a triangular cone shape. Correspondingly, the exact placement of the inlet port 230 and the outlet port 240 as well as the end 212B of the input fluidic channel 212 and the end 214B of the output fluidic channel 214

covered by the center region 222, which are the critical parameters influencing device performance, are also different.

FIGS. 3A-3C schematically show a pressure sensitive valve according to a further embodiment of the present invention. The pressure sensitive valve 300 as shown in FIGS. 3A-3C is different from the pressure sensitive valve 100 as shown in FIGS. 1A-1C mainly in that, as shown in FIGS. 3B and 3C, the substrate 310 is formed in one single layer. In other words, the fluidic channels 312 and 314 are built into the single layer of the substrate 310 and connect directly to the underside of the membrane 320, thus eliminating the need for a via layer or a vertical hole containing layer in the substrate 310. Further, similar to the pressure sensitive valve 200 as shown in FIGS. 2A-2C, the center region 322 of the membrane 320 is also in the same triangular cone shape, but the exact placement of the inlet port 330 and the outlet port 340 is different. Specifically, as shown in FIG. 3A, the inlet port 230 and the outlet port 340 are both located on the same side (bottom side of FIG. 3A) of the center region 322 and are connected to the center region 322 of the membrane by channels 312 and 314, respectively.

As shown in FIG. 3A, all but the end 314B of the output fluidic channel 314 is covered and sealed by the regions of membrane 320 that are outside of the center region 322. The end 314B is located just inside the outer edge of the center region 322. Similarly, the outer section of the input fluidic channel 312 is covered and sealed by the regions of membrane 320 that are outside of the center region 322. The input fluidic channel 312 extends into the center region 322 with the channel end 312B. In other words, a minimum distance between the end 314B of the output fluidic channel 314 exposed within the center region 322 and an outer edge of the center region 322 is shorter than a minimum distance between the end 312B of the input fluidic channel 312 and the outer edge of the center region 322. In operation, the center region 322 of the membrane 320 above the end 312B of the input fluidic channel 312 will be easier for fluid to deform than it will be for fluid to deform the center region 322 of the membrane 320 immediately above the end 314B of the output fluidic channel 314. This is because the proximity of constrained membrane edge (i.e., the outer edge of the center region 322) is a parameter which affects the ability of fluid to deform the membrane 320. Thus, the exact shape of the center region 322 of the membrane 320 and placement of input and output access channels determine device performance of the pressure sensitive valve 300.

As shown in schematically in FIG. 3D-3G the invention in certain embodiments incorporates features of non-linear fluidic capacitance and variable fluidic resistance that can be

useful in fluidic circuits to control pressure pulsations and overpressure control circuits associated with fluidic pumps. Specifically, FIG. 3D shows the valve in a completely closed state, where both the inlet channel 312 and the outlet channel 314 are closed. FIG. 3E shows the valve in a fluidic capacitor state, where the inlet channel is open as the fluidic capacitor, and the outlet channel is closed. FIG. 3F shows the valve in a partially open state, where the inlet channel is open and the outlet channel is partially open as a leaky fluidic capacitor. FIG. 3G shows the valve in a completely open state, where both the inlet channel and the outlet channel are open as the leaky fluidic capacitor. At very low input port fluidic pressure as shown in FIG. 3D, there is no distension of the flexible membrane 320 that covers both the input and output channels 312 and 314. At somewhat higher input port pressures as shown in FIG. 3E, the membrane 320 in the vicinity of the input port 312B distends thus creating a fluidic capacitor 350C which can have the effect of dampening fluidic pressure changes in the vicinity of the input port 312B. At this low input pressure range the output port 314 remains closed and there is no flow from the input port 312 to the output port 314. The localized inflation of the distensible elastomeric membrane 320 will have a larger spatial extent at higher input pressures as shown in FIG. 3F. Here the output port 314 is partially opened by the elastomeric distensible membrane 320 and fluid can flow through the relatively high resistance channel connecting the input port 312 to the output port 314. The distended elastomeric membrane 320 in this geometry continues to act as a non-linear fluidic capacitor. At even higher input port pressures (FIG. 3G) the output port 314 can be completely opened thus providing a relatively lower fluidic resistance path between the input port 312 and the output port 314. In the pressure sensitive valve as described in the embodiments above, the pressure controlling the center region of the membrane to switch between the open state and the closed state is the pressure provided by the pressurized fluid.

In other embodiments, the input fluidic channel 312 and the output fluidic channel 314 can extend down through the thickness of layer 310, rather than first come across the upper surface of layer 310 before descending to the back side via ports 330 and 340.

In certain embodiments, additional pressure adjustment devices or features such as springs or other devices may be provided for the purpose of providing field adjustable pressure relief and regulation. For example, FIGS. 4A-4C schematically show a pressure sensitive valve according to one embodiment of the present invention. Specifically, the pressure sensitive valve 400 is modified from the embodiment of FIGS. 1A-1C, and includes all of the components identical to those in the pressure sensitive valve 100 as shown in FIGS. 1A-1C, which are not

herein elaborated. In addition, the pressure sensitive valve 400 further includes a support structure 410 and a helical spring 420 connected between the support structure 410 and the center region 122 of the membrane. In this case, the helical spring 420 may provide additional pressure to the center region 122 in order to assist switching the pressure sensitive valve 400 between the open state as shown in FIG. 4B and the closed state as shown in FIG. 4C.

In certain embodiments, the additional pressure adjustment features can be implemented by a pressurized fluid, liquid or gas. For example, FIGS. 5A and 5B schematically show a pressure sensitive valve according to another embodiment of the present invention. As shown in FIG. 5A, the pressure sensitive valve 500 utilizes the concept of an RPPM, which has a pump body 510 and a distensible membrane 520 containing pressurized water 525 disposed between the input fluidic channel 530 and the output fluidic channel 540. The input fluidic channel 530 is connected to an inlet having the pressure P_1 , and the output fluidic channel 540 is connected to an outlet having the pressure P_2 . The pressurized water 525 has the pressure P_3 . By adjusting the pressure P_3 of the pressurized water 525, the pressure sensitive valve 500 can switch between the closed state as shown in FIG. 5A and the open state as shown in FIG. 5B. In particular, when $P_3 > P_2 > P_1$, the pressurized water 525 will press the membrane 520 to block the channel between the input fluidic channel 530 and the output fluidic channel 540, such that the input fluidic channel 530 and the output fluidic channel 540 are not in communication with each other, and the pressure sensitive valve 500 is in the closed state. when the pressure P_3 of the pressurized water 525 is reduced such that $P_2 > P_3 > P_1$, the pressure P_2 provided by the fluid in the output fluidic channel 540 will push the membrane 520 upward, such that the input fluidic channel 530 and the output fluidic channel 540 are in communication with each other to switch the pressure sensitive valve 500 to the open state.

FIGS. 6A-6C schematically show a pressure sensitive valve according to one embodiment of the present invention. Specifically, the pressure sensitive valve 600 is modified from the embodiment of FIGS. 1A-1C, and includes all of the components identical to those in the pressure sensitive valve 100 as shown in FIGS. 1A-1C, which are not herein elaborated. In addition, the pressure sensitive valve 600 further includes a chamber 610 covering the center region 122 of the membrane 120, where the chamber 610 is filled with pressurized gas 620. In this case, by adjusting the pressure of the pressurized gas 620 in the chamber 610, additional pressure may be provided to the center region 122 in order to assist switching the pressure sensitive valve 600 between the open state as shown in FIG. 6B and the closed state as shown in

FIG. 6C.

The additional pressure adjustment devices or features are not limited to the spring as shown in FIGS. 4A-4C, pressurized water as shown in FIGS. 5A and 5B, or pressurized gas as shown in FIGS. 6A-6C. For example, FIG. 7 schematically shows a pump with a pressure-sensitive bypass valve according to one embodiment of the present invention, where a bypass valve 710 is provided between the inlet and the outlet of a U-shaped, rotary planar peristaltic micropump channel to prevent excessive pressure being generated by the pump should its outlet 714 be blocked downstream of the pump. The pump would generate an excessive pressure $P_2 \gg P_1$ such that the pressure-sensitive bypass valve 710 would open, redirecting the fluid being delivered to the output 714 of the pump back to its input 712, thereby equalizing P_2 to the lower input pressure P_1 . In certain embodiments, the bypass valve 710 can be a turn valve.

FIGS. 8A-8D shows an implementation of the pressure-sensitive bypass valve in a circular, through-plate rotary planar peristaltic micropump (RPPM). Pump chip 810 has a pumping channel 823 and a pump actuator ridge 801. The details of this pump are described below. This particular implementation of the RPPM has a spring-loaded pressure-sensitive bypass valve across the input and output channels as illustrated schematically in FIG. 7. Other spring geometries and implementations would also support the integration of a pressure sensitive valve to an RPPM.

In a rotary planar peristaltic pump, the entry and exit of rolling actuators (e.g., balls or rollers) create transient changes in the fluid flow at the outlet of the pump. As the pump runs, these fluctuations take the form of a series of pressure changes, some of which can go negative, resulting in reverse flow. In vascularized microbio reactors such as the NVU Puck, reverse flow can adversely affect endothelial polarization. Hence it is critical to create a pump whose roll-on/roll-off fluctuations in pump flow rate are minimized, and never are negative.

A possible means to reduce pump fluctuations might be to create a fluidic channel of constant height that lies beneath the surface and whose radial distance from the axis of rotation of the actuator varies as a function of angle. Analysis of this approach indicates that X-Y fluidic channel steering is not an effective means for addressing the problem, whereas the introduction of Z-axis variability introduced in this invention can successfully reduce pump pulsatility and prevent backflow.

The key problem can be described as follows. When implementing a rotary planar peristaltic pump, independent of scale, a pinch point where the roller closes the fluid path must

be made at the beginning of the pumping path. This pinch point displaces some volume. In addition the pinch point must be made to move along a length of the fluid path in order to displace an additional volume of fluid. Before this pinch point is released, another pinch point must be applied back at the beginning of the pumping path, otherwise reverse flow will occur
5 when the pump's outlet has a higher fluid pressure than the inlet. Because the introduction of a pinch point has an associated volume displacement, this volume must be filled when releasing the pinch point at the end of the pumping path. If the volume of the pinch point is greater than the displacement of the next pinch point's advancement, then the flow at the output of the pump must reverse to fill this volume. If the velocity of the front of the pinch point becomes zero or
10 negative this will also cause stop flow or reverse flow respectively.

Steering the fluid path out from under the pinch point does not address this problem: steering the fluidic channel out from under the compression zone causes a change in relative velocity of the compression zone as the radius of displacement changes. If the fluidic is driven to a larger radius, this causes an under-pressure condition in the captured volume and will result
15 in backwards flow when the compression zone opens at the output of the pump. As the trailing edge of the leading compression zone accelerates (increases in linear velocity resulting from increasing channel radius), the leading edge of the same compression zone approaches zero velocity relative to the channel. This causes the fluid velocity at the output of the pump to be near zero when the compression zone opens. If the displacement of the leading edge of the next
20 compression zone is equal to the removal volume of the present compression zone then the flow will remain at zero. If the removal volume of the present compression zone is greater than the displacement of the next compression zone, then the flow will be negative. Steering the fluidic out from under the compression path has as its best case scenario a small stop flow.

In one aspect, this invention addresses the peristaltic pinch-point problem with a
25 compression ridge with tapered onset and offset. The ridge does not eliminate the need for proper alignment of the compression path versus the fluid path since the velocity of the compression path will vary along the length of any rotating compression path that is misaligned. This variation in velocity results in either an over pressure or under pressure in the captured volume between adjacent compression areas. As soon as the leading compression area is opened
30 to the output fluidic path, either a positive flow spike or a negative flow spike will result. The change in pressure may also contribute to bubble formation.

The roll-off ramp plays a critical role in reducing fluctuations and reverse flow. When

the compression surface of an actuator ball or roller is on the pump ridge, it is displacing a specific volume of the elastomer. This volume displacement can be seen to remove some volume of the fluid path directly under the compression surface. As the ridge cross-section changes at the ramp, the volume displacement is reduced. By careful design of the shape and steepness of the slope of cross-sectional change, the reduction in fluid displacement per degree of rotation can be set to a value less than that of the volume displacement of the next advancing compression zone. This insures that the flow rate does not become zero or negative. Since the fluid channel follows the compression ridge there is no velocity change in the compression zone. With the present invention, the angular change in the volume displacement of the elastomer allows the pinch point to be effectively lifted straight up instead of being driven off to one side of the fluid path.

For example, FIGS. 8A-8C schematically shows a RPPM according to one embodiment of the present invention. Specifically, the RPPM is in the form of a ridge pump, which includes a pressure-limiting valve or shunt formed by a membrane 880 and a pressure adjustment means 870. As shown in FIG. 8A, the pressure adjustment means 870 is a helical spring. The pressure-limiting shunt prevents the pump from developing very high pressures should a down-stream channel become blocked or a valve left closed. The dotted region in FIG. 8A demarcates a region where the pump membrane 880 is not bonded to the underlying fluidics channels 823 to create a bypass valve membrane as shown in FIG. 4B. The pressure at which the unattached membrane 880 enclosed by the dots lifts off from the two underlying channel stubs can be controlled by the helical spring 870. When the pressure in the delivery side of the pump exceeds the threshold pressure, the valve opens and the pressure is released by the fluid flowing into the lower-pressure input channel. The elegance of this approach is that it allows a pump that is somewhat “stiff” and delivers metered volumes, to become “soft” above a threshold pressure, thereby protecting the pump and downstream devices from being ruptured by downstream blockages.

FIG. 8B schematically shows an RPPM ridge fluidic chip as also shown in FIG. 8A. As shown in FIG. 8B, the ridge chip 810 includes a protruding ridge 801 disposed on a zero-elevation plateau 802. The protruding ridge 801 is a circular-segment cross-section of varying height, and is molded into the actuator-facing surface of the fluidic ridge chip 800 and superimposed over the channel path 823 (not shown in FIG. 8B; see FIG. 8C). The protruding ridge 801 includes a constant-elevation ridge portion 803 and two ramps 804 connecting the

plateau 802 to two ends of the ridge portion 803 along the swept path of actuator rollers 835 (not shown in FIG. 8B; see FIGS. 8F-8H). In this embodiment, the ridge portion 803 includes one quarter of the swept path (90° , as shown in 805), the plateau portion 806 (i.e., the plateau portion not occupied by the protruding ridge 801) spans 108° of the swept path (as shown in 816), and each ramp 804 spans 81° of the swept path. As shown in FIG. 8A, the bypass valve membrane 880 (as well as the helical spring 870 disposed on the membrane 880) may be located on the plateau portion 806 of the ridge chip 810 and is not covered by the protruding ridge 801.

The pump fluidic chip 810 is molded from a liquid silicone rubber or other elastomeric material. Access ports 824 are punched into protrusions 860 that mate with through-holes in a corresponding fluidic support plate.

The protruding ridge 801 serves several purposes. Firstly, the ramps 804 allow roller bearings to gently roll onto and off of the working region, thereby reducing pulsatility in the fluid flow profile and eliminating backflow caused by rollers abruptly departing from the working region causing the channel to snap open. Secondly, it focuses the force of an actuator (not shown in FIG. 8B) onto the regions of desired compression, namely, the path of the fluidic channel. Such focusing reduces compression and friction in non-active regions of the pump fluidic, for example the ridge-free plateau region 816 by reducing the overall contact area necessary for pumping, and increases pressure in the active regions. Thirdly, the protruding ridge 801 allows for larger tolerances in alignment between the fluidic ridge chip 810 and the corresponding actuator by decreasing the necessary contact area between rollers 835 and the protruding ridge 801.

As shown in FIG. 8F-8H, roller bearings 835 compress and pinch off channel(s) 823 as they contact and compress fluidic chip 810 and thereby restrict the cross section of the channel 834, and at a pinch point, reducing that cross-section to zero (FIG. 8H). As roller bearings 835 progress around the circumference of the channel pattern 823 shown in FIG. 8A, fluid contained by the channel is propelled in the direction of actuator rotation. As rollers 835 leave a compressed region of their path, the elastomeric material relaxes, the pinched-off channel re-opens, and fluid is drawn into the newly-available volume.

FIGS. 8D-8H schematically show a plurality of stages of the ridge pump as shown in FIG. 8A. Specifically, FIG. 8D shows the different locations 1-4. As shown in FIG. 8E, at location 4, the roller 835 is absent and the elastomeric fluidic device 830 is relaxed to its uncompressed dimensions (because the protruding ridge 801 is not compressed by the roller).

As shown in FIG. 8F, at location 1, the roller 835 does not yet contact the protruding ridge, and the elastomeric fluidic device 830 remains uncompressed. As shown in FIG. 8G, when the roller 835 moves above the tapered portion (i.e., the ramps 804) of the protruding ridge 801 at location 2, the height of the ridge of the ramp 804 is insufficient to make contact with the roller 835. As shown in FIG. 8H, once the roller 835 moves to location 3, it contacts the ramp 804 and compresses the fluidic channel 834 to create a closed channel 837. The angle at which this first occurs defines the pinch point.

Referring back to FIG. 8E, the ridge pump 830 has an upper layer 801 (i.e., the ridge chip) and a lower layer 832. The upper layer ridge chip 801 has on its upper surface the protruding ridge 801 and the fluidic channel 834, which has a circular-segment cross section. By eliminating the vertical sidewalls seen in other microfluidic channels, the efficacy by which channels 834 are completely sealed closed is increased.

The location of the starting and stopping angles of the ramp is critical to the proper function of the pump. FIG. 8I shows the function of the height of the protruding ridge to angle of the ridge chip as shown in FIG. 8A. As shown in FIG. 8I, the height of the protruding ridge 801 is shown as a function of angle around the central axis of the fluidic chip 810 and the actuator. The choice of these angles is critical to the proper function of this invention. FIG. 8J shows the relationship between the height of the protruding ridge of the ridge chip and elastomeric volume displacement according to certain embodiments of the invention.

Not only does this approach protect the pump and downstream devices from rupturing by any more distant blockages, this type of pump can be used to pressurize a reservoir to whatever pressure at which the bypass valve is set. In terms of an RPPM-RPV system that provides regular fluid changes to each well of a well-plate, i.e., a well-plate feeder, this creates the possibility of a single pump-valve pair to maintain pressure in multiple reservoirs, each connected to the pump by one of the valve ports. When the pump is connected to a particular reservoir, the pressure in the reservoir increases to the maximum delivered by the pump. If the valve is then switched to the next reservoir, that reservoir can be filled while the input to the first reservoir is blocked by the closed valve so that the first reservoir can only drain slowly, at a rate determined by the fluidic resistance of the downstream device. Some embodiments of spring-loaded pressurized reservoirs can provide flows of 1 to to 3 μL per minute, for example, that could be delivered over a reservoir pressure range of 2 to 6 psi. An adjustable downstream throttling or TURN valve, or the downstream device would provide the resistance that limits the flow. In some embodiments,

a single pump, a 24-port valve, and 24 reservoirs would be able to maintain a gently-oscillating flow in each well of a 24-well plate. This would obviate the need for compressed gas lines to pressurize reservoirs, as is currently the case in the Nortis and Emulate organ-chip platforms. The design of this system will have to be optimized to particular down-stream chips such as those produced by CFDRC/SynVivo.

In certain embodiments, the pressure-sensitive valve can function as a non-linear fluidic capacitor. For example, FIGS. 9A-9C schematically show a non-linear fluidic capacitor according to one embodiment of the present invention. Specifically, the non-linear fluidic capacitor 900 has a substrate 910 and a membrane 920 disposed on the substrate 910. The membrane 920 is a flexible elastomeric membrane, which includes a pressure-sensitive center region 922 and a peripheral region 924 surrounding the center region 922. The peripheral region 924 is bound to the substrate 910. The center region 922 is in a circular shape, and covers the substrate 910 but is not fixed or attached to the substrate 910. In this case, the center region 922 of the membrane 920 can be controlled to deform by pressure to switch between the open state and a closed state. The substrate 910 has a fluidic channel 912 therein, which is covered by the center region 922 of the membrane 920 and functions as an outlet port. Thus, the center region 922 of the membrane 920 may be controlled by the fluid pressure provided by the fluidic channel 912. The non-linear fluidic capacitor 900 is provided for fluid pressures lower than the threshold pressure at which the single port (i.e., the fluidic channel 912) becomes accessible to fluid pressure. Once the threshold pressure has been exceeded, the elastomeric membrane begins to deform, thus creating a fluidic capacitor that has a maximum volume determined by the elasticity of the membrane 922. This state is shown in FIG. 9B. However, the capacitance of the device is not constant, but depends on the stress-strain curve of the deformable elastic membrane 920.

In certain embodiments, the pressure sensitive valves as described in the above embodiments may be utilized in a pressure regulation system to control the pressure of the fluid therein.

FIG. 10 schematically shows a pressure pump for multiple-organ perfusion according to one embodiment of the present invention. In this figure a media reservoir provides a source of fluid to the fluidic pump which is equipped with an overpressure fluidic valve that reroutes the output of the pump back to the input of the pump whenever the overpressure threshold of the fluidic valve has been exceeded. This has two important functions: (1) when the multiplexing valve connected to the output of the pump is momentarily completely closed during the

switching interval between the three illustrated bellows reservoirs, this overpressure valve prevents damage to the fluidic pump mechanism and (2) when the switching valve is routing the fluid to any one of the bellows spring loaded reservoirs, the overpressure threshold of this fluidic valve will act as a pressure regulator to ensure that each spring loaded bellows reservoir will be repressurized to the same extent, thus providing a uniform periodic pressure loading of each of the bellows reservoirs.

FIG. 11A shows the timing of fluid delivery by the single pump to each of the 3 reservoirs configured as in FIG. 10. Periodic refreshing of fluid levels is required to keep fluid available for flowing under spring loaded bellows control to the organ modules FIG. 11B shows the pressure profile within each of the three bellows reservoirs after initial start-up of the fluidic pump / multiplexing valve set-up. Note that for this particular bellows output fluidic resistance and this particular refresh multiplexing rate the relative output pressures provided by each of the bellows remains in a similar narrow band after initial start-up of the multiplexing procedure.

FIGS. 12A-12C schematically show a bypass valve according to one embodiment of the present invention. Specifically, the bypass valve 1200 is a modification of the non-linear fluidic capacitor 900 as shown in FIGS. 9A-9C, with the only difference being that two fluidic channels 912 are provided in the substrate 910 to form the bypass valve 1200.

FIG. 12D shows a PDMS mask according to one embodiment of the present invention, and FIG. 12E shows an alignment guide of the PDMS mask to create the non-adherent region of the bypass valve membrane in FIGS. 12B and 12C. As shown in FIG. 12D, the PDMS mask 1210 includes multiple legs, which fit into holes in the PDMS. Circular extension lies flush on the surface of the PDMS to prevent plasma treatment. The alignment guide 1220 as shown in FIG. 12E is used to punch holes for the legs of the PDMS mask 1210 as shown in FIG. 12D. FIG. 12F shows the PDMS mask and alignment jig positioned over a real PDMS valve body fabricated from PDMS according to one embodiment of the present invention.

Another aspect of the present invention relates to a passive pressure relief valve. FIGS. 13A-13F show one particular embodiment of a passive pressure relief valve for microfluidic devices. The passive pressure relief valve was designed to be inexpensive and easily manufactured and used. The system takes advantage of the properties of long yet very soft springs, which at a high fractional compression can provide the desired force on the valve membrane that changes relatively little while changing compression during use. FIG. 13A shows the complete arrangement of the passive pressure relief valve according to one

embodiment of the present invention. As shown in FIG. 13A, the fluidic device 1330 is sandwiched between the upper housing 1350 and the base plate 1340, with gauge 4-48 screws holding the setup together. This aligns the cylindrical cavity 1320 of the upper housing 1350 with a shallow bowl in the fluidic device 1334. A spring 1310 is lowered into the cavity 1320 and then compressed with a gauge 10-32 screw. The compressed spring 1310 presses upon the bowl in the fluidic layer, closing it.

There are two designs of the upper housing 1350 (FIG. 13B and 13C): one that has a larger internal diameter and one that fits the springs used tighter (and includes chambers for the spring caps)

FIG. 13B shows the upper housing for the long spring of the passive pressure relief valve as shown in FIG. 13A. As shown in FIG. 13B, the upper housing 1350 which holds the spring 1310 and the base plate 1340 which sandwiches the PDMS fluidic are both 3D printed using a Formlabs Form 2 printer with their “durable” resin. The bottom portion of the upper housing 1350 fits the spring 1310 snugly to minimize kinking of the spring 1310. A 3 mm portion at the top of the upper housing 1350 and the bottom of the spring 1310 are slightly wider to hold the spring caps. Further, the top half of the jig 1350 is threaded and large enough for the screw. When fluid runs into the PDMS device it pushes against the spring 1310. With sufficient input pressure, the spring 1310 will raise enough that fluid can flow through the device.

FIG. 13C shows the upper housing for a short spring of the passive pressure relief valve as shown in FIG. 13A according to one embodiment of the present invention. In comparison to the upper housing 1350 as shown in FIG. 13B, the upper housing 1360 as shown in FIG. 13C has a wider interior chamber, which is 6 mm across the entire way down and does not fit the spring 1310 as snugly. However, the screw can be brought all the way to the bottom of the jig 1360.

FIG. 13D shows the design of the channels in the PDMS fluidic device according to one embodiment of the present invention. The channels 1332 in the fluidic device 1330 are around 0.2 mm deep and the bowl 1334 is around 0.4 mm deep. The channels 1332 are of semi-circular cross section and are identical on both sides of the bowl, thus the device is bidirectional.

FIG. 13E shows the base plate of the passive pressure relief valve as shown in FIG. 13A. The base plate 1340 as shown in FIG. 13E is designed to hold gauge 4-48 screws. In the center there is a cavity through which the user can observe the alignment and operator of the spring 1310 on the PDMS bowl.

FIG. 13F shows the spring cap of the passive pressure relief valve as shown in FIG. 13A.

In certain embodiments, the spring cap 1370 is a 3D printed part that is placed on both the upper and lower ends of the spring 1310 to both prevent the spring 1310 from getting caught in the cavity 1329 and distribute the force evenly across the PDMS bowl 1334 in fluidic device 1330.

FIG. 14 shows a pressurized reservoir 1400 according to one embodiment of the present invention. The reservoir volume 1410 is determined by the extent by which the planar bellows membrane 1420 is distended by the pressurized fluid delivered to the reservoir through port 1430. Spring 1440 determines the pressure-volume relationship of this system.

Another aspect of the present invention relates to a passive pressurized fluid reservoir. The passive pressurized fluid reservoir takes advantage of the properties of long yet soft springs under high compression, which can reach a desired force that changes relatively little while changing compression during use. FIGS. 15A-15H schematically shows a passive pressurized fluid reservoir according to one embodiment of the present invention. The passive pressurized fluid reservoir 1500 may function as a fluidic capacitor. As shown in FIG. 15A, the passive pressurized fluid reservoir 1500 includes a spring 1510 contained within a 3D printed capsule 1520, which is 1.5 inch in length. The device includes a cap 1530 and base 1540 screwed together with a larger cylindrical cavity in the center. This cavity holds a plastic “bellows”-style pouch 1550 that expands to contain fluid from an outside source. On top of this capsule rests the spring capsule 1520. As fluid flows into the bellows 1550 it will expand, pushing the capsule 1520 into the cap 1530 and further compressing the spring 1510. The spring 1510 then applies a force back onto the bellows 1550, expelling fluid and compressing the bellows 1550. The 3D printed parts are made using a Formlabs Form 2 printer with their “durable” resin. In one embodiment, the passive pressurized fluid reservoir uses a long, soft spring 1510 as the applied force does not change much with changes in compression. All of the components of the passive pressurized fluid reservoir 1500 can be screwed together with gauge 4-48 screws. With high fluidic resistance on the output side, the device 1500 can maintain fluid flows for times on the order of hours.

FIG. 15B shows a cap of the chamber of the passive pressurized fluid reservoir as shown in FIG. 15A. Specifically, the cap 1530 is a 3D printed cap. A column extends from the center of the cap 1530 that pushes onto the spring 1510 and holds it in the capsule 1520. The threads are sized for gauge 4-48 screws.

FIG. 15C shows the base of the chamber of the passive pressurized fluid reservoir as shown in FIG. 15A. Specifically, the base is a 3D printed base. The base 1540 is also threaded

for gauge 4-48 screws. The bellows 1550 and the spring capsule 1520 rest inside the hollow center of the base.

FIG. 15D shows the spring capsule of the passive pressurized fluid reservoir as shown in FIG. 15A. Specifically, the spring capsule 1520 is a 3D printed capsule. One end of the spring capsule 1520 is closed off and the other end has a cavity for the spring 1510. The capsule 1520 is hollow to reduce weight and materials.

FIGS. 15E-15H show the plastic bellows pouch of the passive pressurized fluid reservoir as shown in FIG. 15A. The bellows pouch 1550, at full expansion, holds 7.33 mL. During operation, the bellows pouch 1550 can change length by up to 16 mm.

The foregoing description of the exemplary embodiments of the invention has been presented only for the purposes of illustration and description and is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Many modifications and variations are possible in light of the above teaching.

The embodiments were chosen and described in order to explain the principles of the invention and their practical application so as to enable others skilled in the art to utilize the invention and various embodiments and with various modifications as are suited to the particular use contemplated. Alternative embodiments will become apparent to those skilled in the art to which the invention pertains without departing from its spirit and scope. Accordingly, the scope of the invention is defined by the appended claims rather than the foregoing description and the exemplary embodiments described therein.

CLAIMS

What is claimed is:

1. A pressure-activated valve, comprising:
 - a substrate, having an input fluidic channel and an output fluidic channel formed therein; and
 - a membrane disposed on the substrate, wherein the membrane includes a center region and a peripheral region surrounding the center region and bound to the substrate, and the center region covers one end of the input fluidic channel and one end of the output fluidic channel;
 - wherein the center region of the membrane is controlled to deform by pressure to switch between an open state and a closed state, allowing the input fluidic channel and the output fluidic channel to be in communication with each other in the open state and not in communication with each other in the closed state.
2. The pressure-activated valve of claim 1, wherein a default state of the center region of the membrane is the closed state, and the center region of the membrane is attached to the substrate such that the input fluidic channel and the output fluidic channel are not in communication with each other in the closed state.
3. The pressure-activated valve of claim 2, wherein in response to a pressure, the center region of the membrane deforms to switch to the open state and form a space between the center region and the substrate, allowing the input fluidic channel and the output fluidic channel to communicate with each other through the space.
4. The pressure-activated valve of claim 2, wherein when an output pressure in the output fluidic channel exceeds a pressure threshold, the center region of the membrane deforms to switch to the open state.
5. The pressure-activated valve of claim 1, wherein the peripheral region of the membrane includes an inlet port in communication with the other end of the input fluidic channel and an outlet port in communication with the other end of the output fluidic channel.

6. The pressure-activated valve of claim 5, wherein:
 - the input fluidic channel comprises:
 - a first vertical input hole in communication with the inlet port;
 - a second vertical input hole covered by the center region of the membrane;
 - and
 - a horizontal input channel connecting the first vertical input hole to the second vertical input hole; and
 - the output fluidic channel comprises:
 - a first vertical output hole in communication with the outlet port;
 - a second vertical output hole covered by the center region of the membrane; and
 - a horizontal output channel connecting the first vertical output hole to the second vertical output hole.
7. The pressure-activated valve of claim 1, wherein the center region of the membrane is in a circular shape.
8. The pressure-activated valve of claim 7, wherein the one end of the input fluidic channel covered by the center region is located at or relatively close to a center of the circular shape of the center region, and the one end of the output fluidic channel covered by the center region is located relatively close to an outer edge of the circular shape of the center region.
9. The pressure-activated valve of claim 1, wherein the center region of the membrane is in a non-circular shape.
10. The pressure-activated valve of claim 9, wherein a minimum distance between the one end of the output fluidic channel covered by the center region and an outer edge of the non-circular shape of the center region is shorter than a minimum distance between the one end of the input fluidic channel covered by the center region and the outer edge of the non-circular shape of the center region.

11. The pressure-activated valve of claim 1, further comprising a pressure adjustment means provided on the center region of the membrane, wherein the pressure adjustment means is configured to generate a pressure on the center region.
12. The pressure-activated valve of claim 10, wherein the pressure adjustment means is a spring.
13. The pressure-activated valve of claim 10, wherein the pressure adjustment means comprises a pressurized gas or fluid.
14. A pressure regulation system, comprising a pressure-activated valve of claim 1.
15. The pressure regulation system of claim 14, being a rotary planar peristaltic micropump (RPPM).
16. A pressure-activated valve incorporating a non-linear fluidic capacitor, comprising:
 - a substrate, having a fluidic channel formed therein; and
 - a membrane disposed on the substrate, wherein the membrane includes a center region and a peripheral region surrounding the center region and bound to the substrate, and the center region covers, in one location, one end of a fluidic input channel and, in another location, one end of a fluidic output channel ;

wherein the center region of the membrane is influenced by certain magnitudes of the input fluidic port fluidic pressure to create an enclosed fluid-filled localized region in the vicinity of the input channel bounded by the membrane and the substrate that act like a fluidic capacitor due to the extendability of the elastomeric membrane, and

wherein the central region of the membrane is further influenced by certain even higher magnitudes of input port fluidic pressure to create fluid-filled space that connects the input port to the output port thereby acting like a input pressure controlled valve.
17. The pressure-activated valve of claim 16, wherein a default state of the center region of the membrane is the closed state, and the center region of the membrane is attached to the

- substrate such that no space exists between the center region of the membrane and the substrate in the closed state.
18. The pressure-activated valve of claim 16, wherein the center region of the membrane is in a circular shape.
 19. The pressure-activated valve of claim 16 wherein the center region of the membrane is in a non-circular shape.
 20. A passive pressure relief valve, comprising:
 - an upper housing having a cylindrical cavity;
 - a spring disposed in the cylindrical cavity;
 - a fluidic device disposed below the spring, wherein the fluidic device has a straight channel running through a bowl formed by a membrane; and
 - a base plate, disposed below the fluidic device,wherein the spring is compressed upon the membrane that forms the bowl of the fluidic device to close the bowl.
 21. The passive pressure relief valve of claim 20, wherein the cylindrical cavity of the upper housing aligns with the bowl of the fluidic device.
 22. The passive pressure relief valve of claim 21, wherein a bottom portion of the upper housing fits the spring.
 23. The passive pressure relief valve of claim 21, wherein a bottom portion of the upper housing does not fit with the spring.
 24. The passive pressure relief valve of claim 20, wherein the fluidic device is formed by Polydimethylsiloxane (PDMS).
 25. A passive pressurized fluid reservoir, comprising:
 - a chamber comprising a base and a cap;

a spring disposed in the base of the chamber, wherein the cap has a column extending out to hold the spring;
a capsule, wherein the spring is disposed within the capsule;
a bellows pouch, disposed in the base of the chamber below the capsule;
wherein a fluid flows into the bellows pouch such that the bellows pouch expands to push the capsule into the cap to compress the spring, and the spring pushes the fluid out of the bellows pouch.

26. The passive pressurized fluid reservoir of claim 25, wherein the bellows pouch is made of a plastic material.
27. The passive pressurized fluid reservoir of claim 25, wherein the base and the cap of the chamber and the capsule are 3D-printed.
28. A ridge pump, comprising:
a support plate;
a ridge pump fluidic chip with an internal fluidic pumping channel created by sealing the channels with the pump membrane, having a plurality of protrusions formed on a first surface facing the support plate, a plateau formed on a second surface away from the support plate, and a protruding ridge disposed on the plateau, wherein the support plate mates with the protrusions to hold the ridge chip on the support plate, and the protruding ridge is in relation to the fluid channel allowing the pump actuator to gradually engage and disengage with the fluid channel; and
a pressure limiting structure, comprising:
a membrane disposed on the plateau of the ridge chip covering the fluidic bypass channel; and
a pressure adjustment means disposed on the bypass channel membrane, configured to generate a pressure on the membrane to maintain the fluidic channel in a closed state;
wherein the pressure limiting structure is controlled by a fluidic pressure in the fluidic channel to switch the fluidic channel between the closed state to an open state, wherein the fluidic channel is switched to the open state when the fluidic pressure is

greater than the pressure generated by the pressure adjustment means, and the fluidic channel is switched to the closed state when the fluidic pressure is not greater than the pressure generated by the pressure adjustment means.

29. The ridge pump of claim 28, wherein the pressure adjustment means is a helical spring.
30. The ridge pump of claim 28, wherein the protruding ridge comprises a ridge portion and two ramps connecting the plateau to two ends of the ridge portion, a height of each of the two ramps gradually increases from the plateau to the two ends of the ridge portion, and a height of the ridge portion equals the greatest height of each of the two ramps.
31. A pressure regulation system, comprising a ridge pump of claim 28.

100

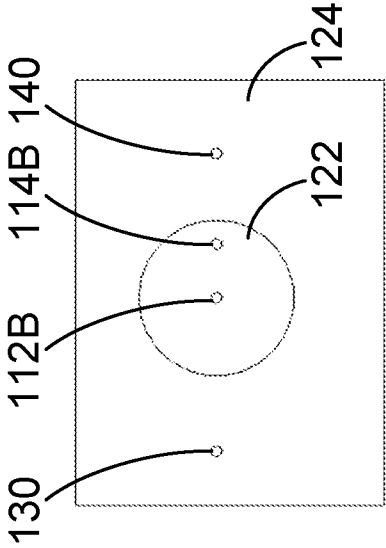


FIG. 1A

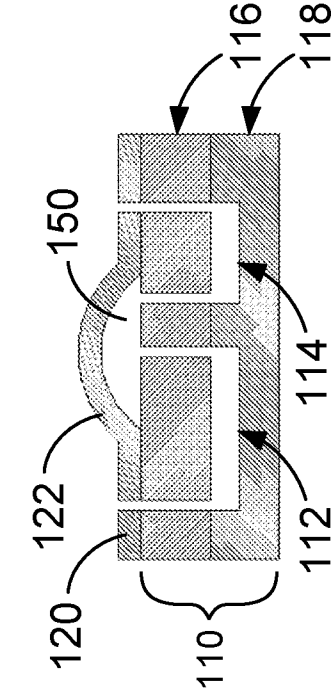


FIG. 1B

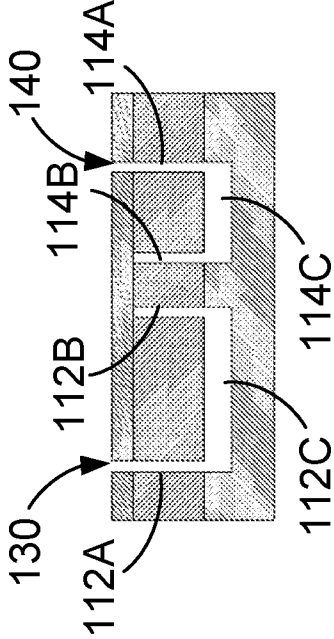


FIG. 1C

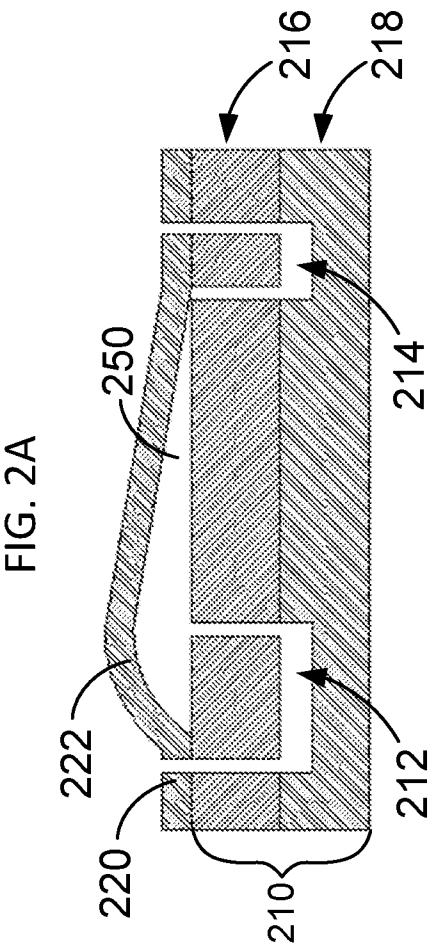
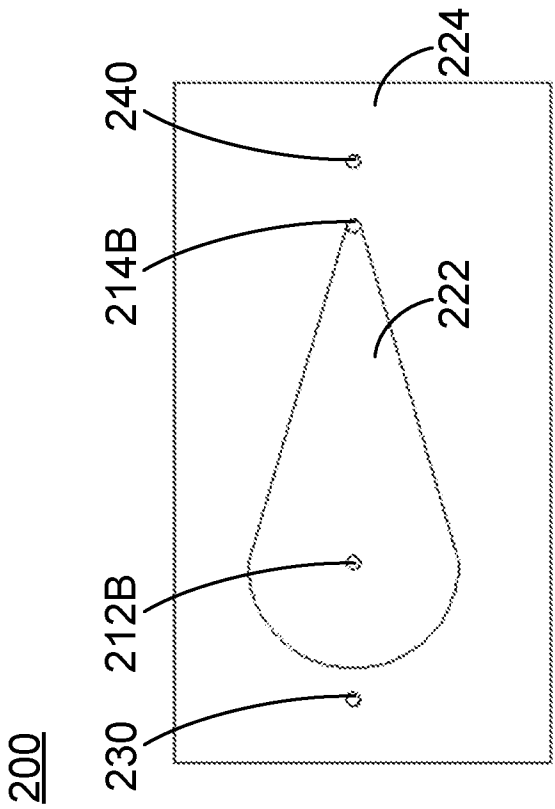


FIG. 2B

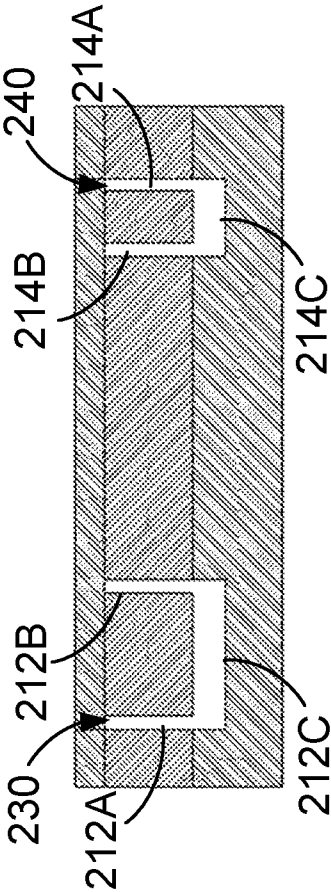


FIG. 2C

300

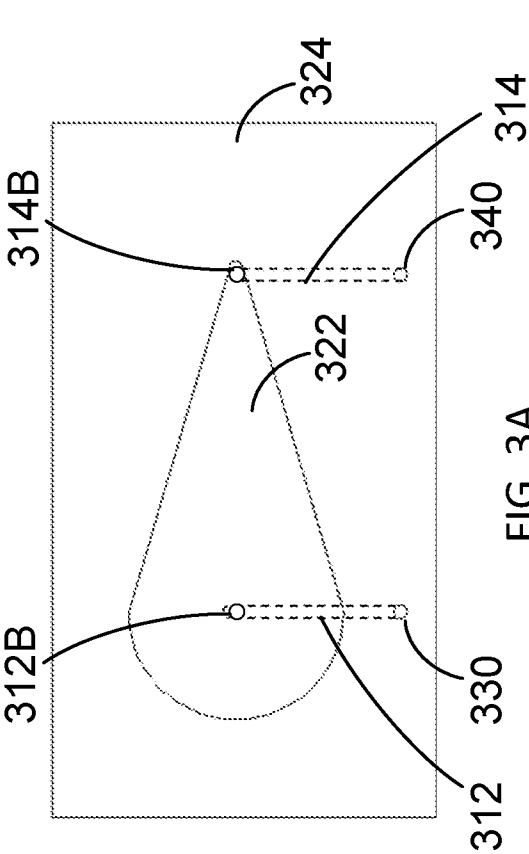


FIG. 3A

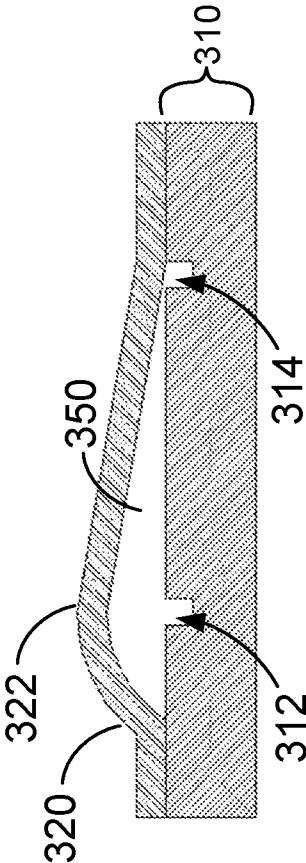


FIG. 3B

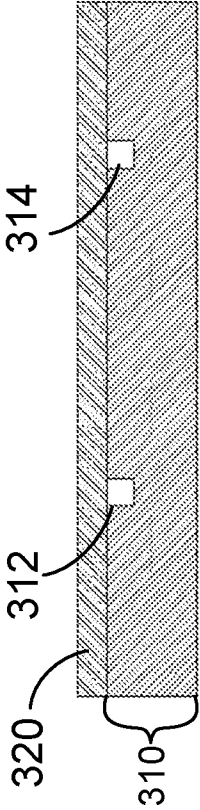


FIG. 3C

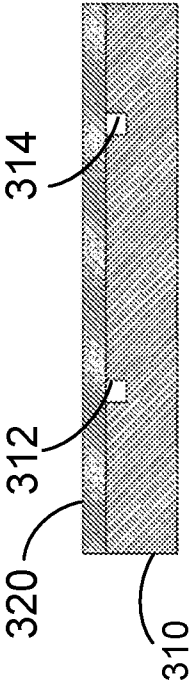


FIG. 3D

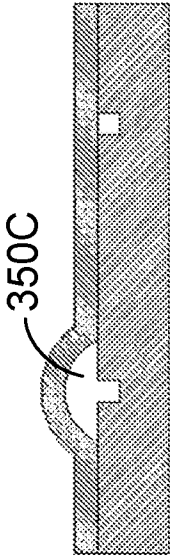


FIG. 3E

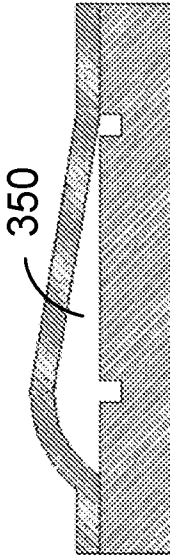


FIG. 3F

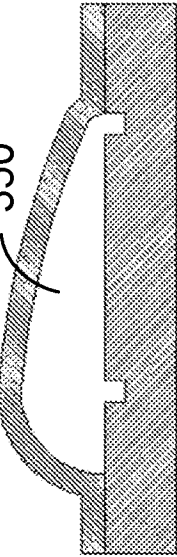


FIG. 3G

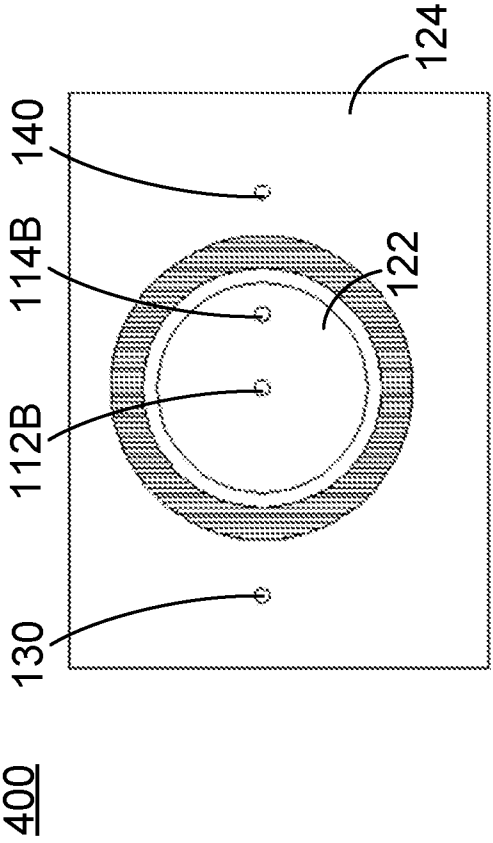


FIG. 4A

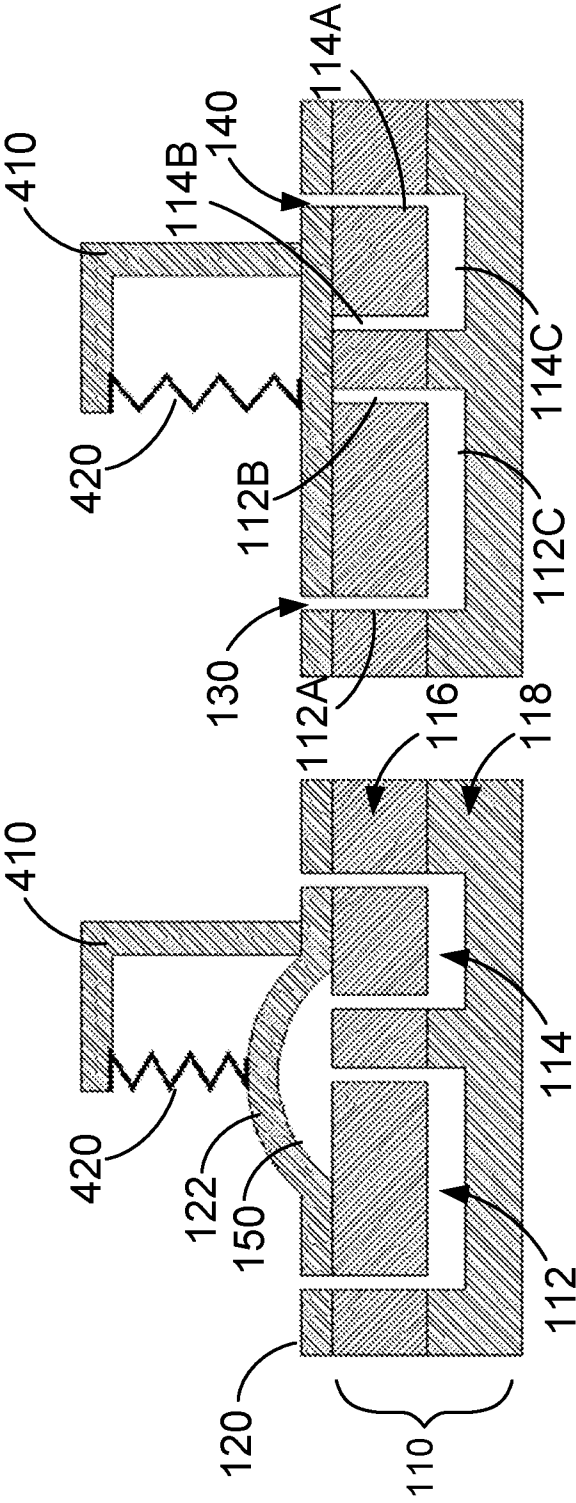


FIG. 4B

FIG. 4C

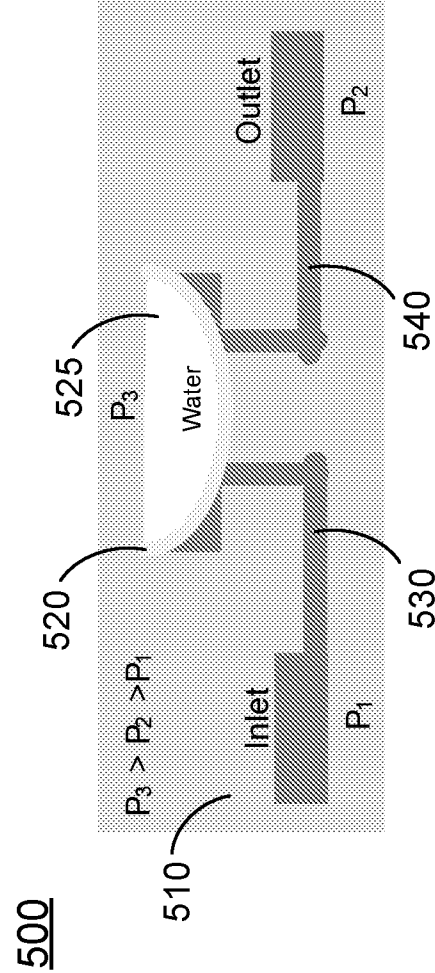


FIG. 5A

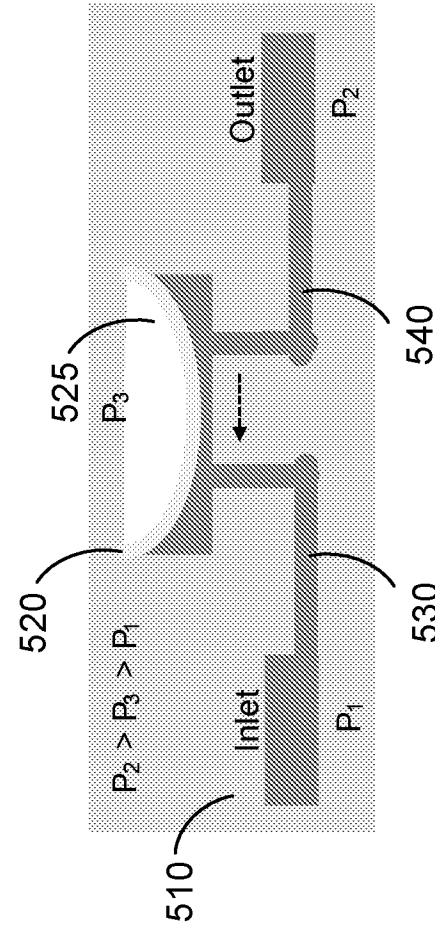


FIG. 5B

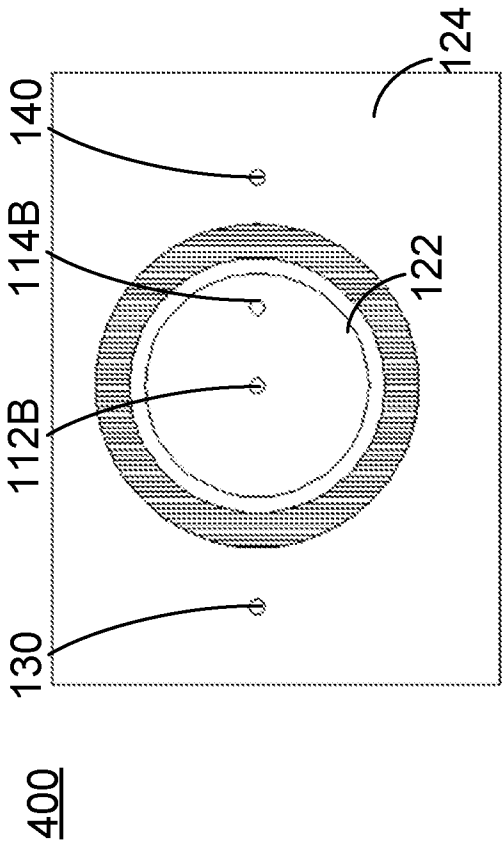


FIG. 6A

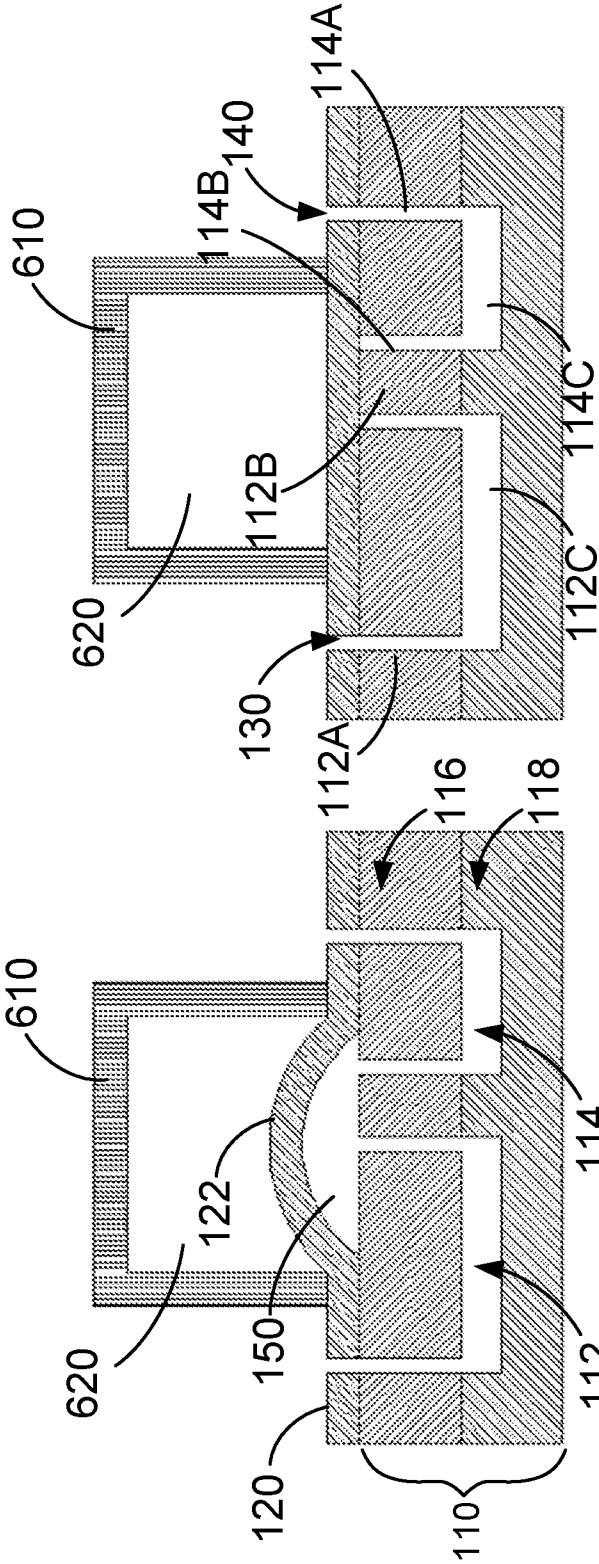


FIG. 6C

FIG. 6B

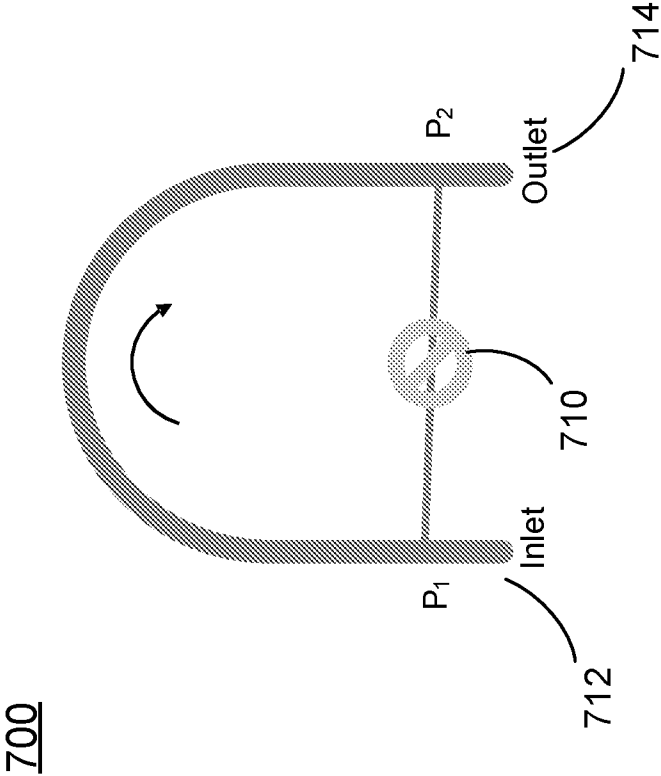


FIG. 7

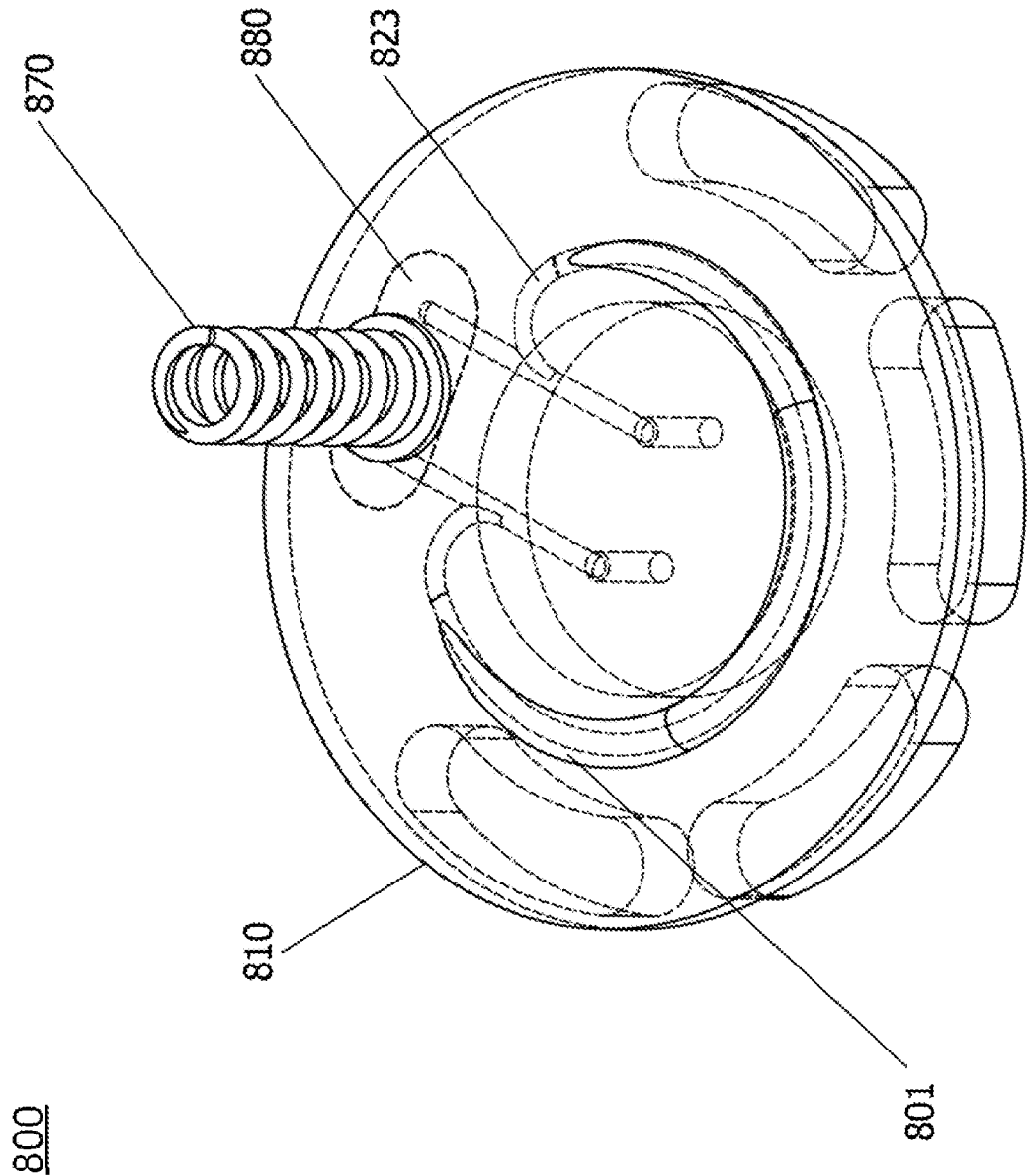


FIG. 8A

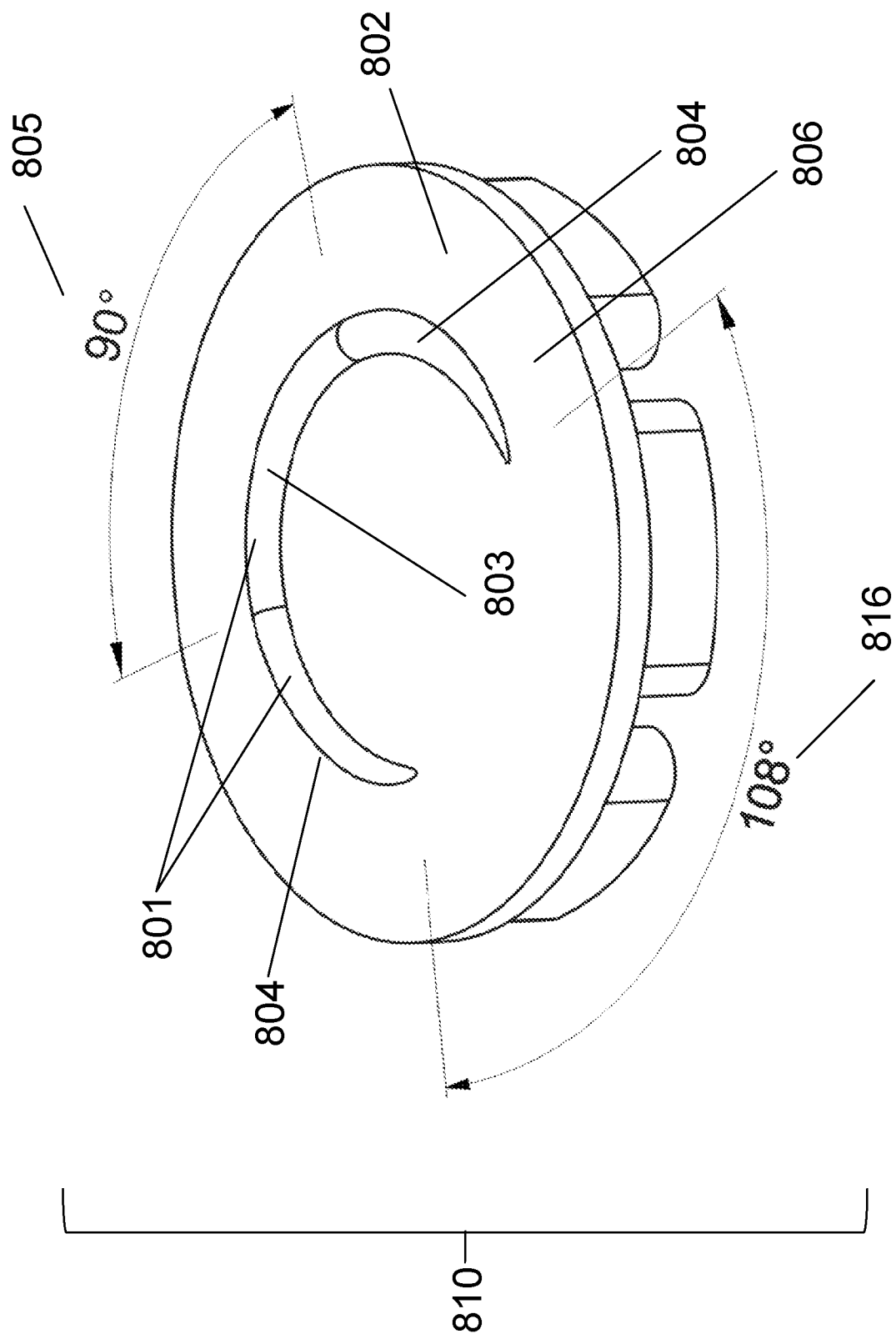


FIG. 8B

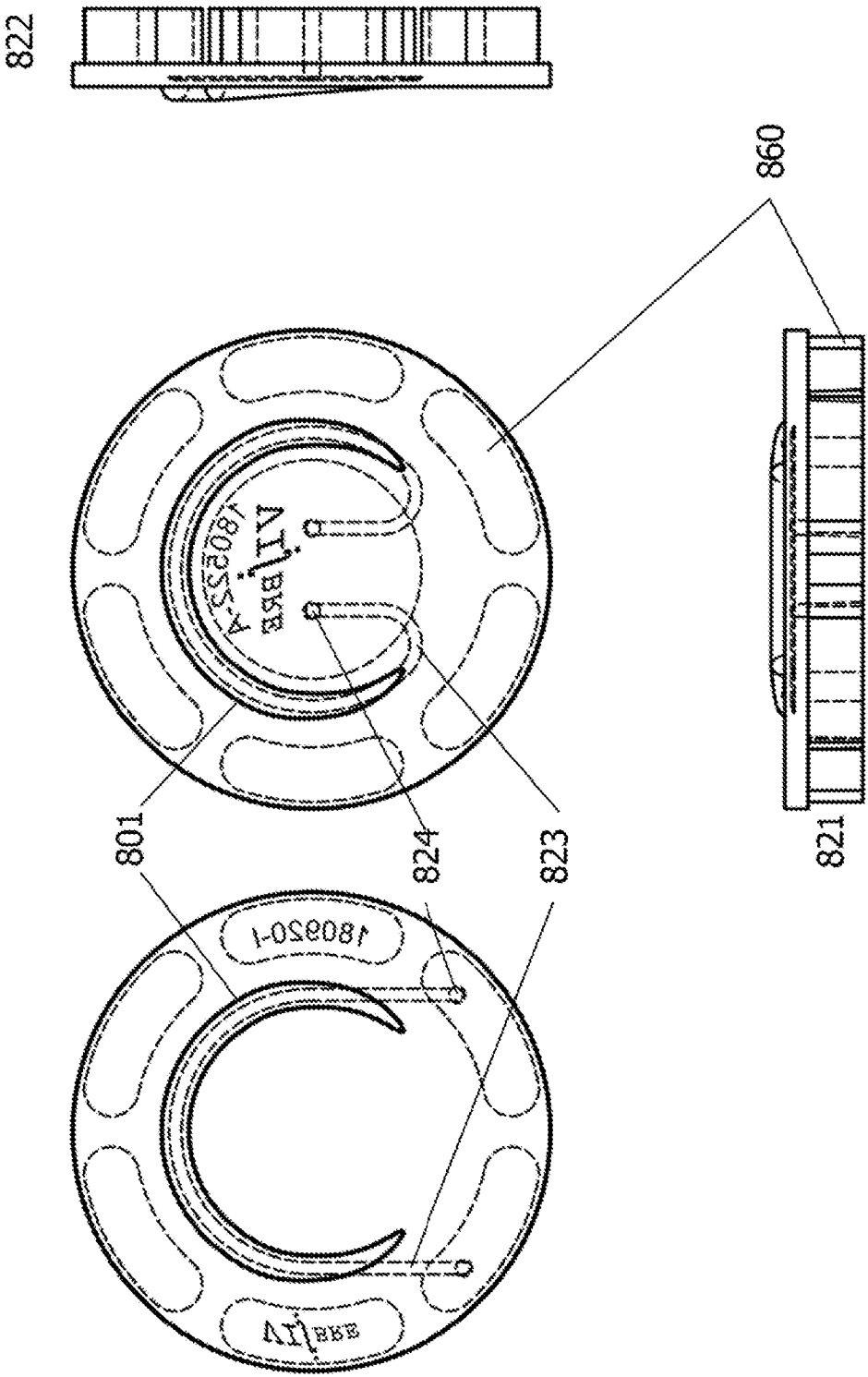


FIG. 8C

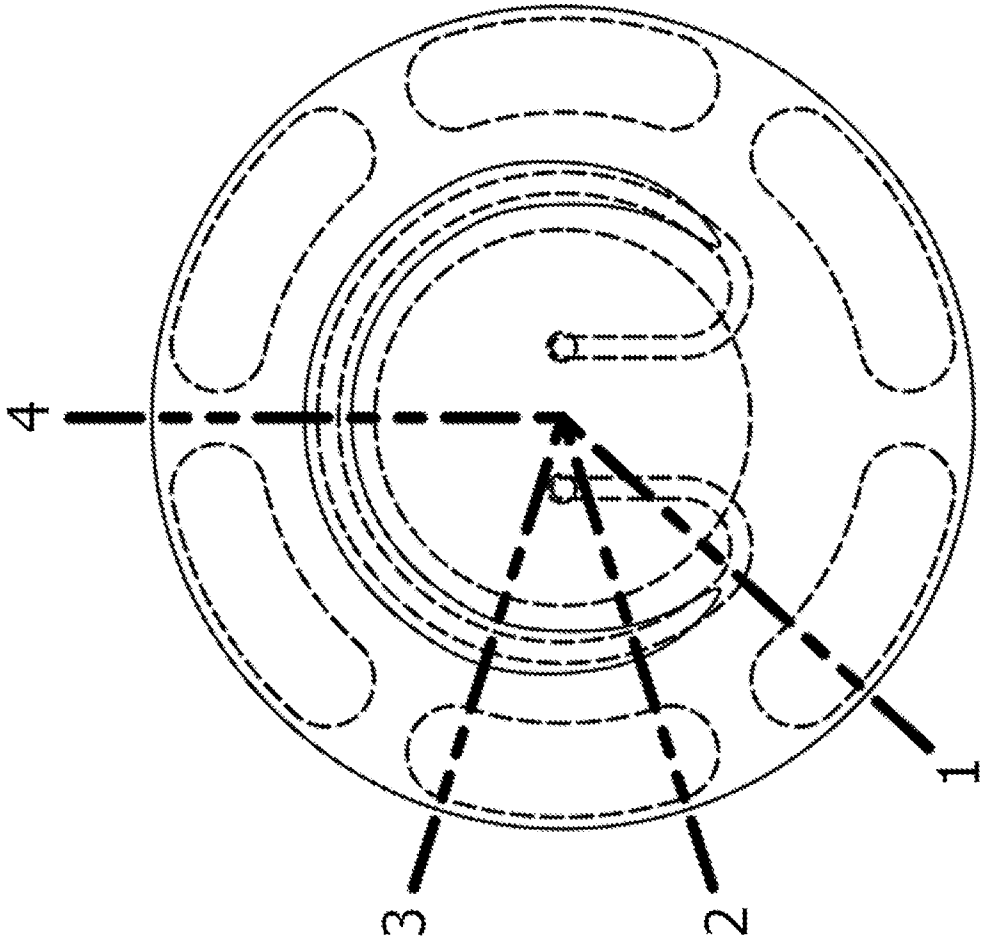


FIG. 8D

830

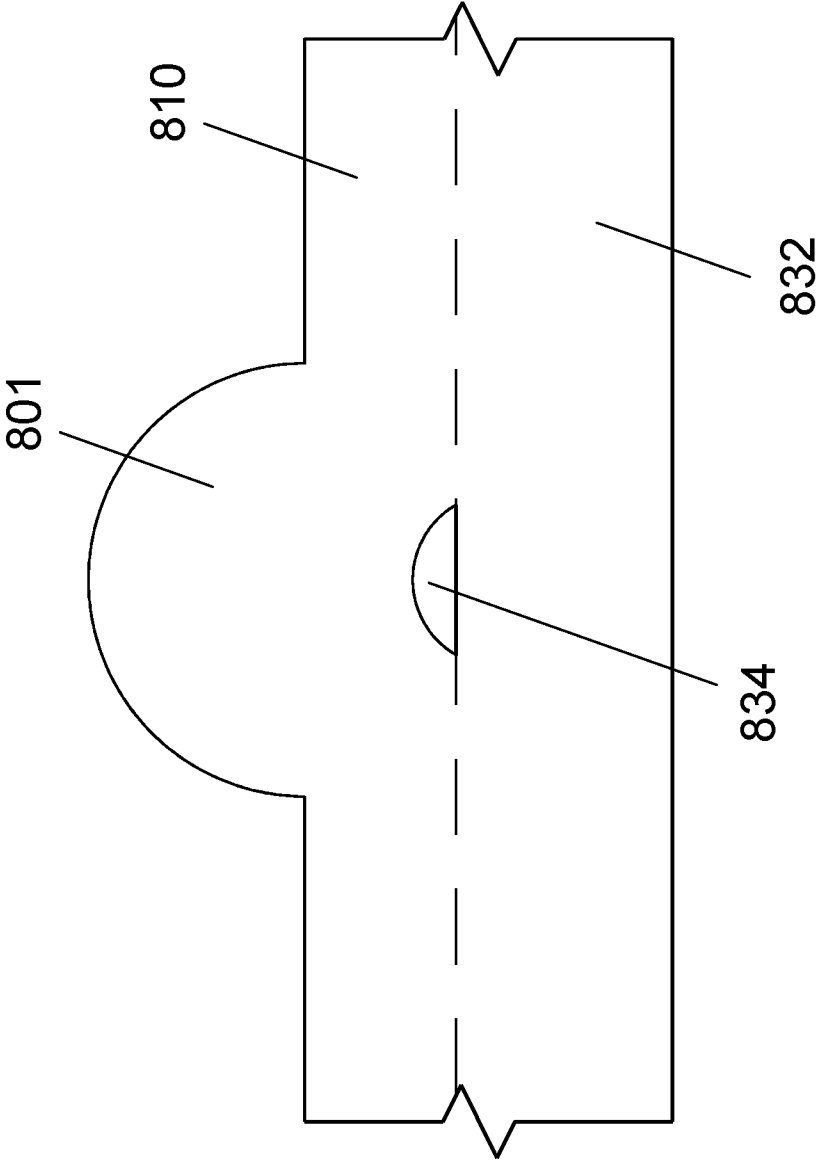


FIG. 8E

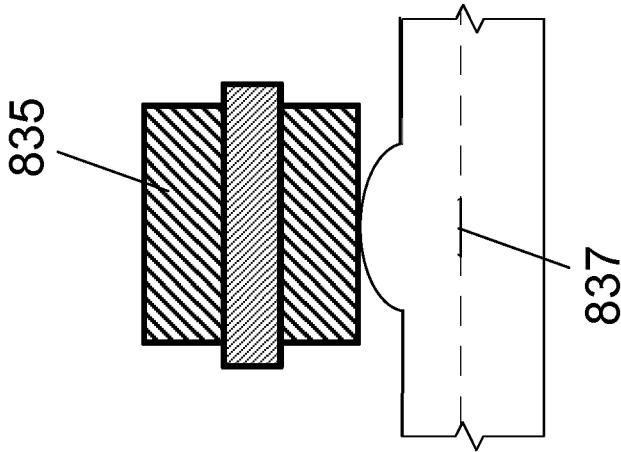


FIG. 8F

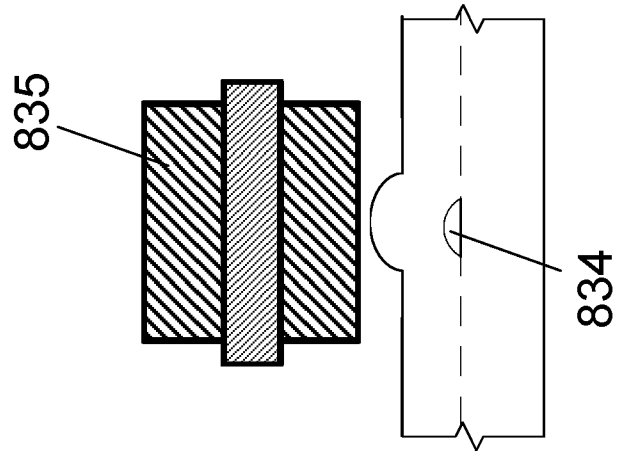


FIG. 8G

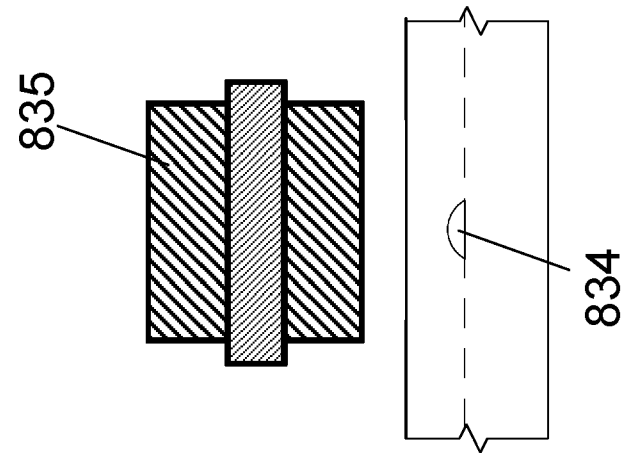


FIG. 8H

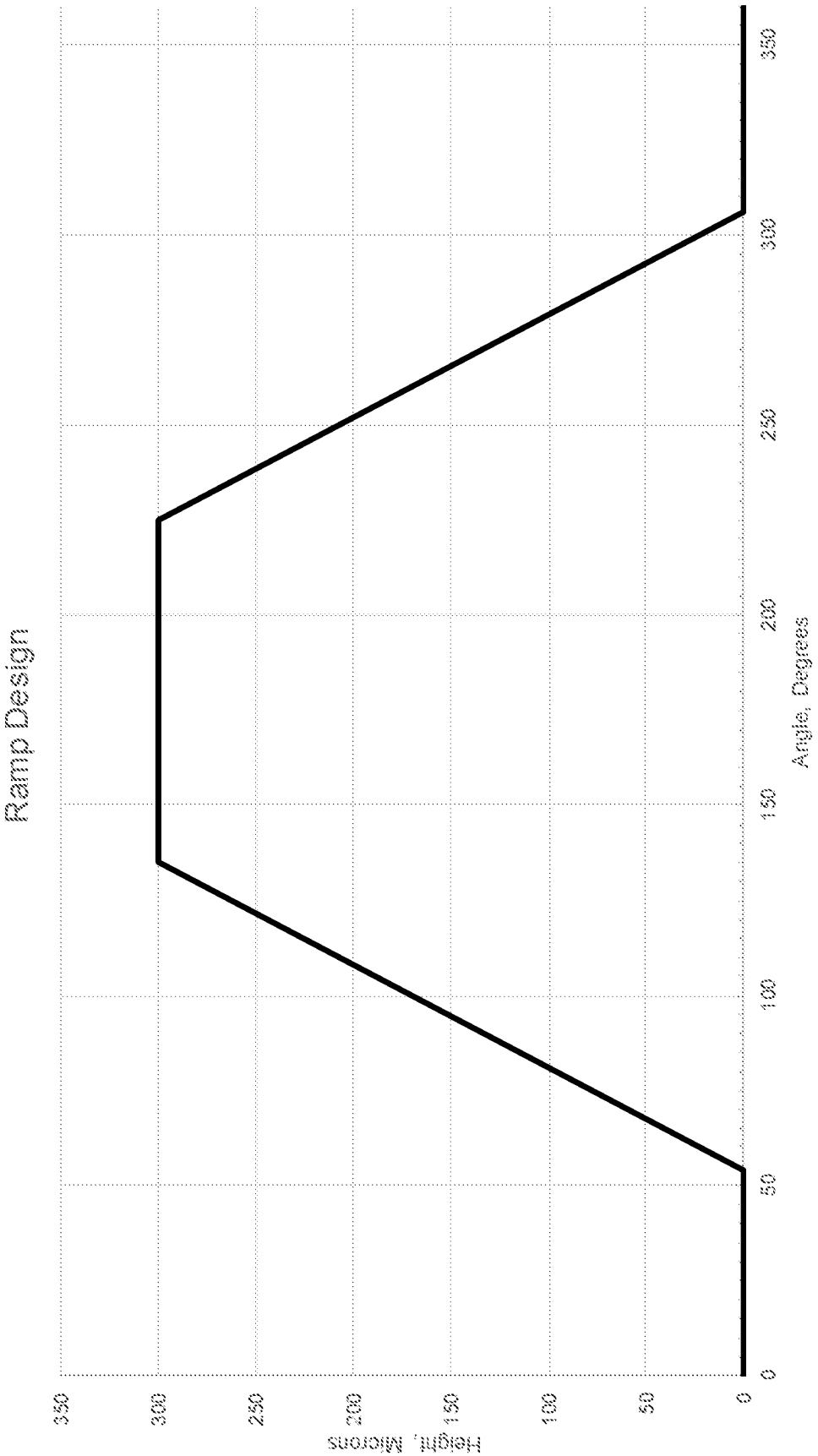


FIG. 8I

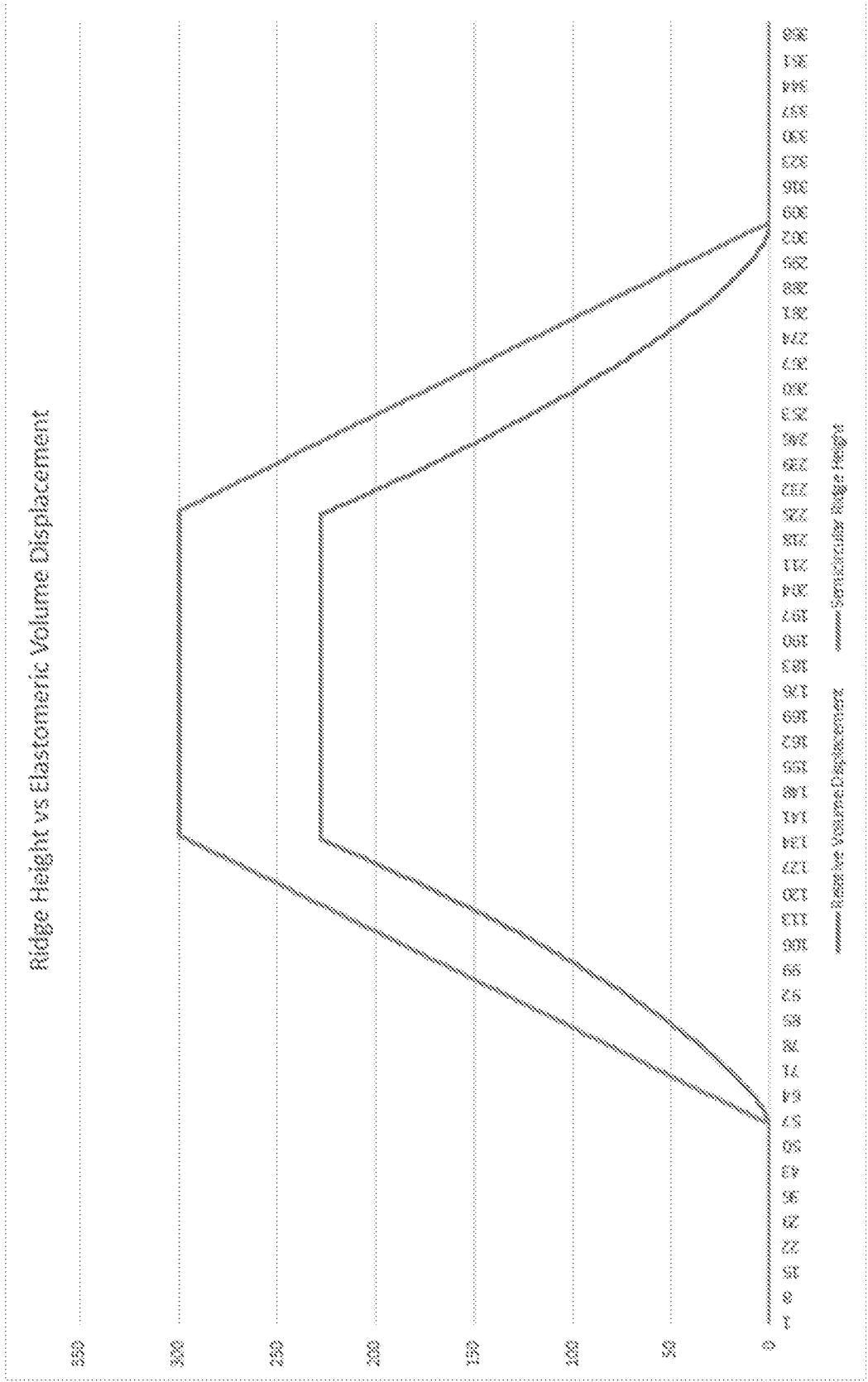


FIG. 8J

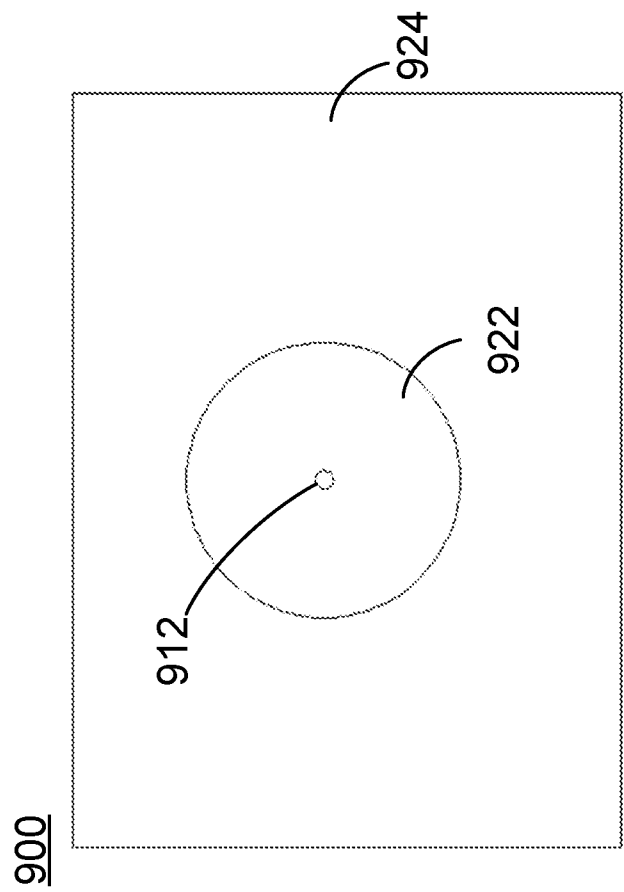


FIG. 9A

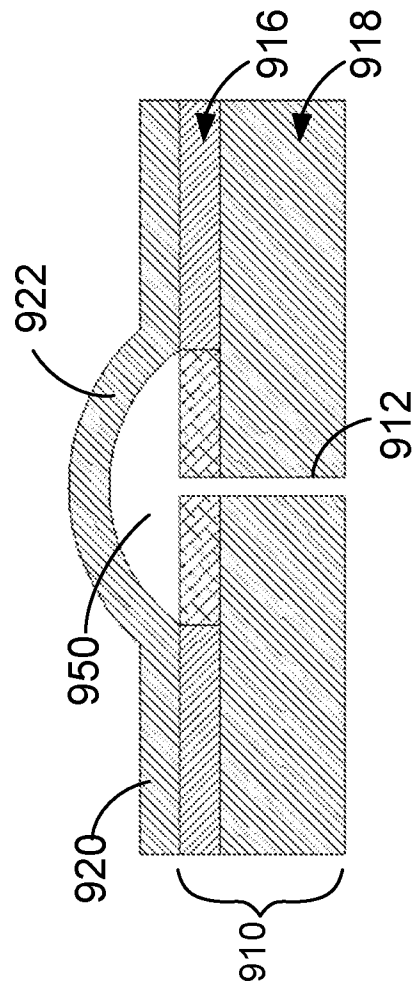


FIG. 9B

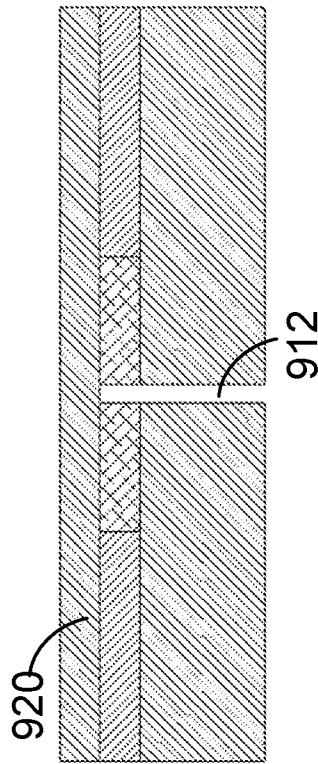


FIG. 9C

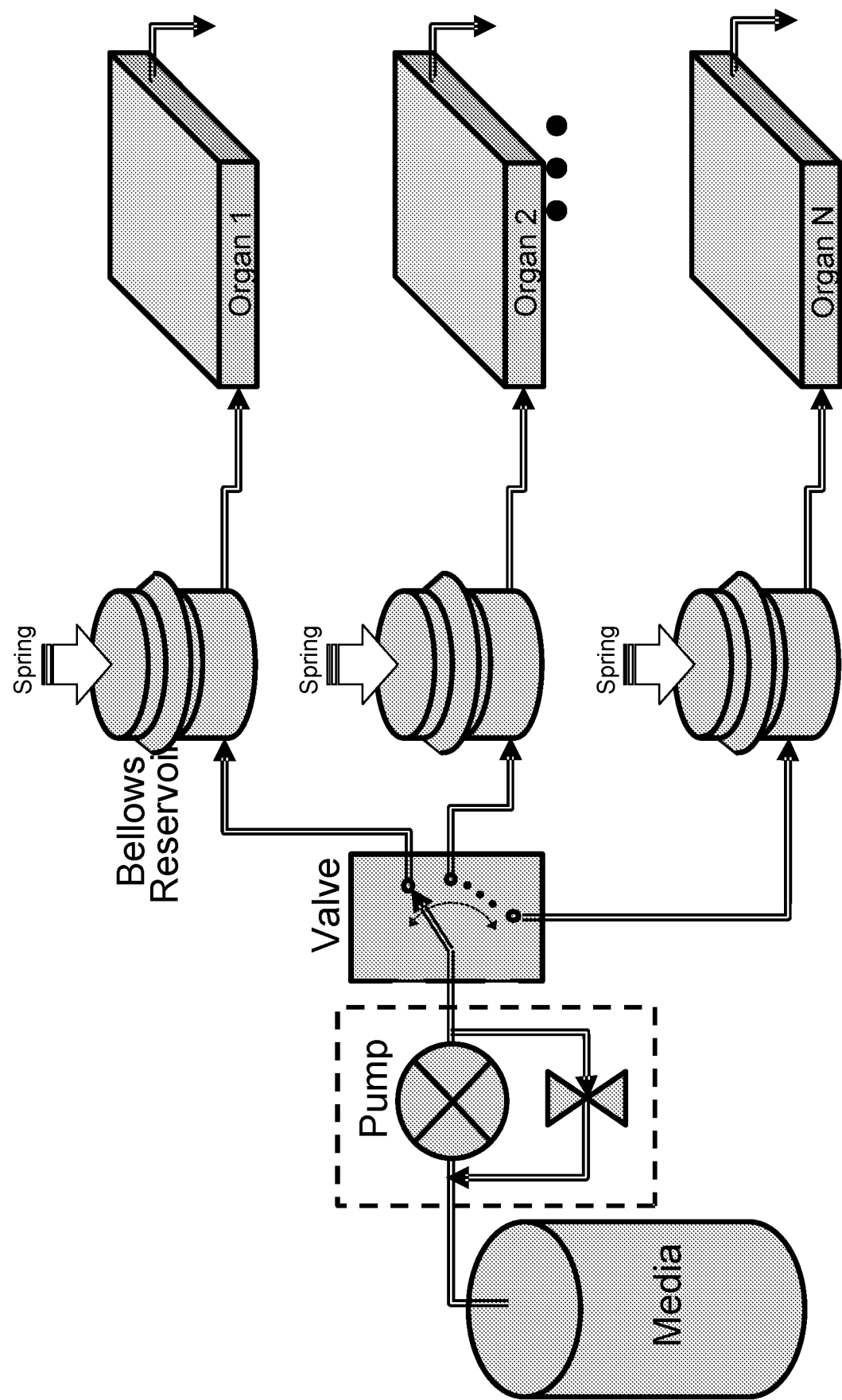


FIG. 10

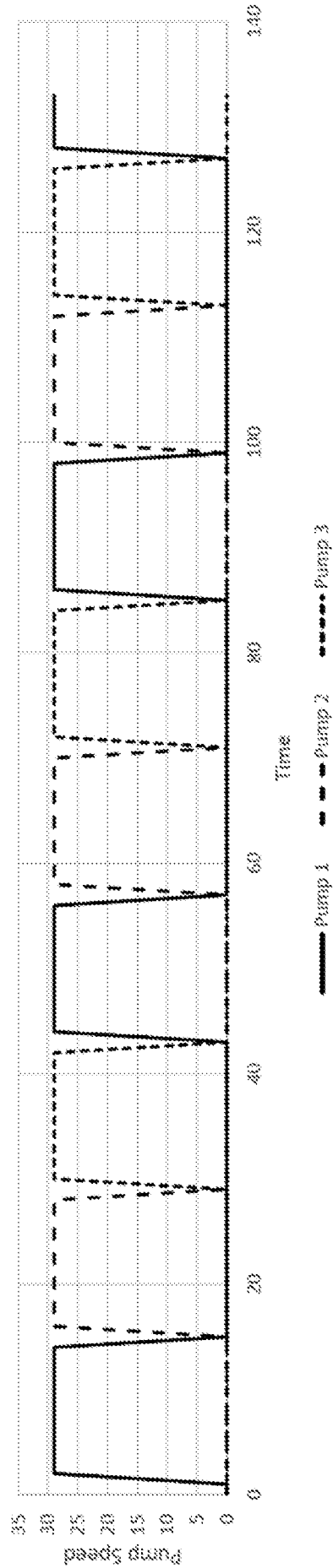


FIG. 11A

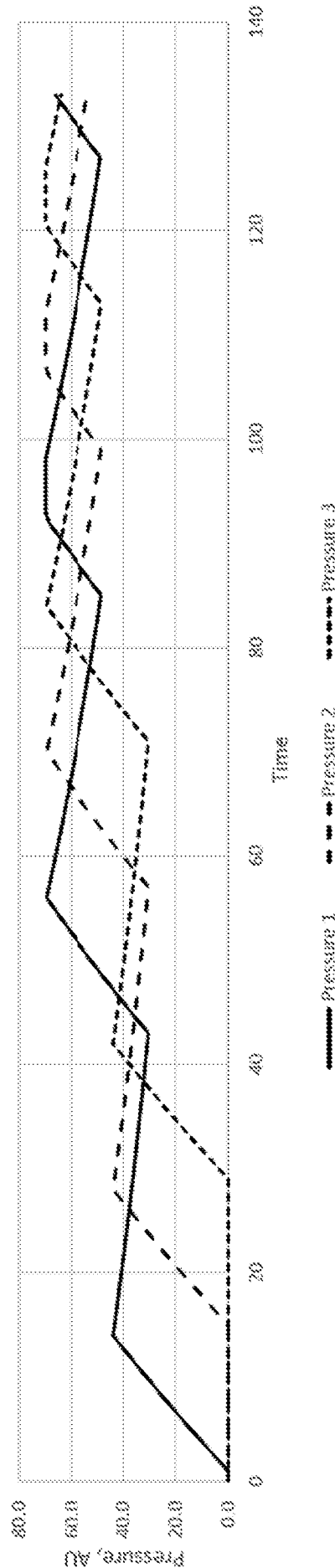


FIG. 11B

1200

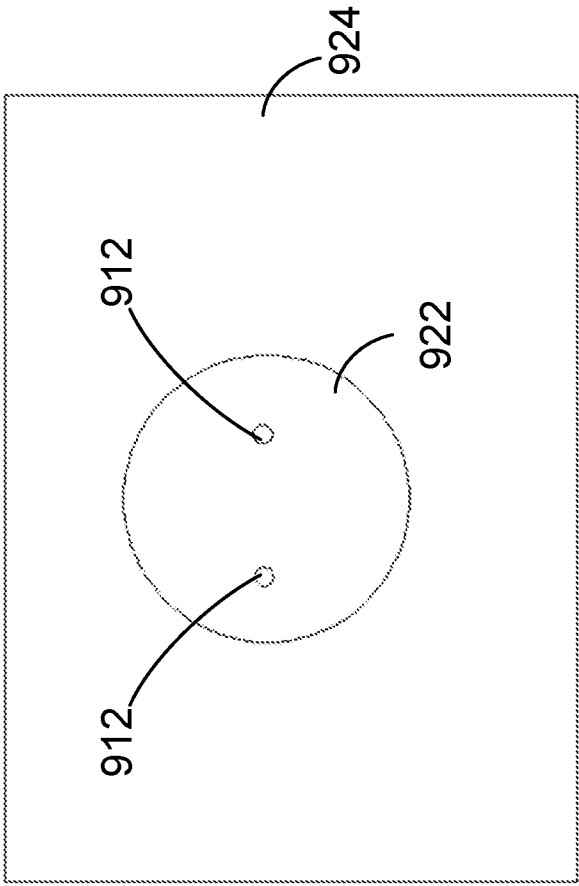


FIG. 12A

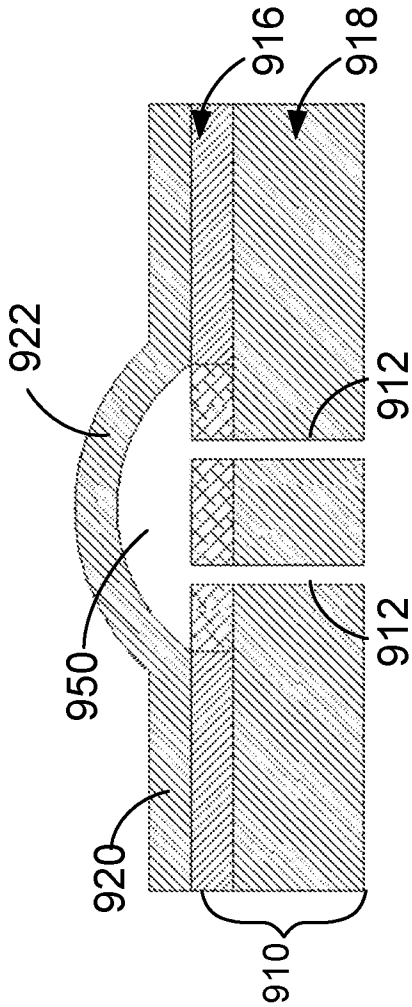


FIG. 12B

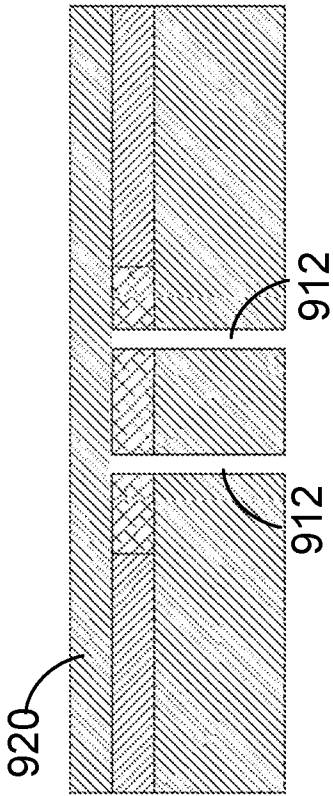


FIG. 12C

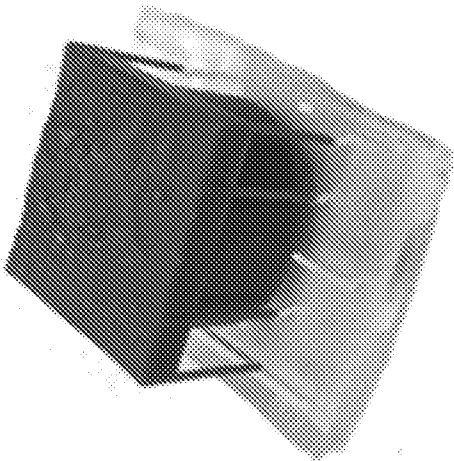


FIG. 12D

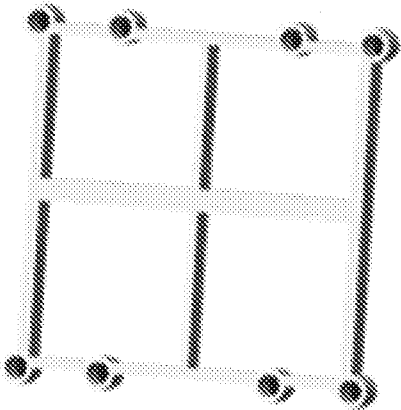


FIG. 12E

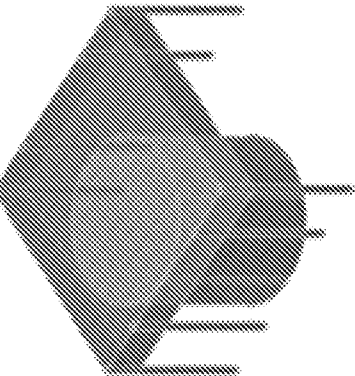


FIG. 12F

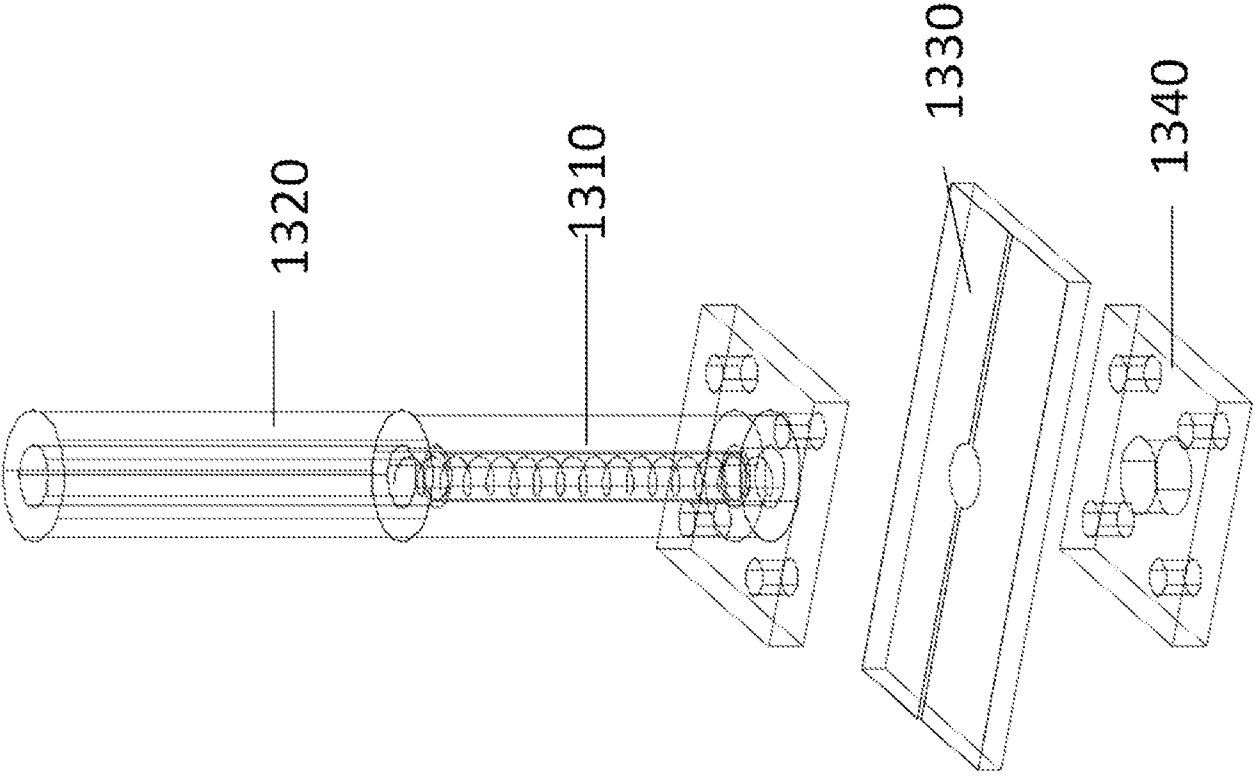


FIG. 13A

1300

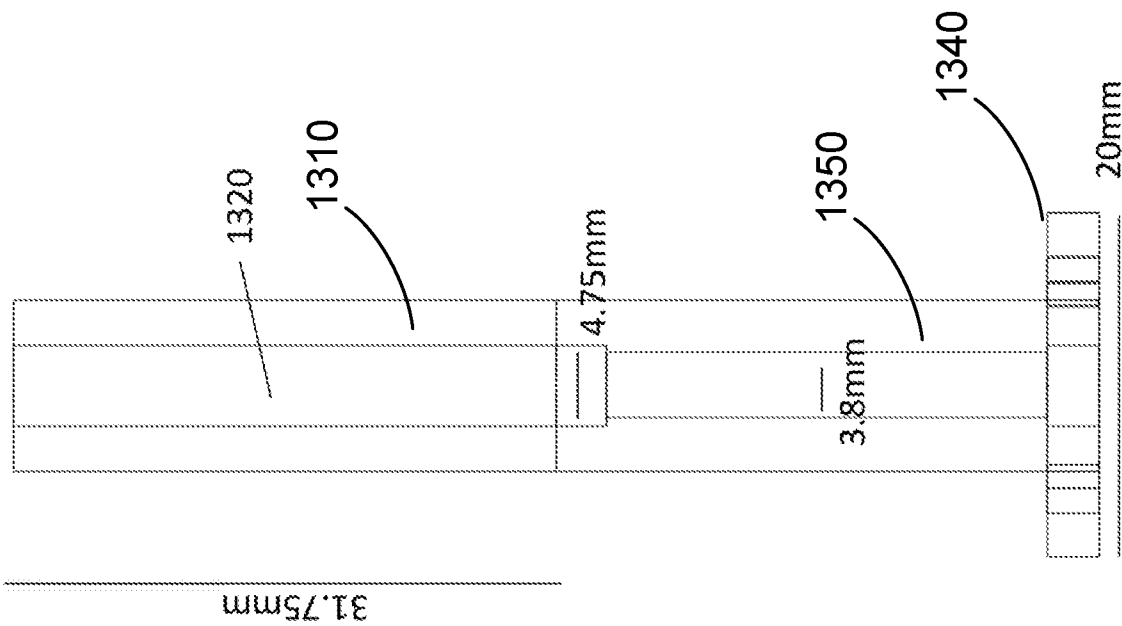


FIG. 13B

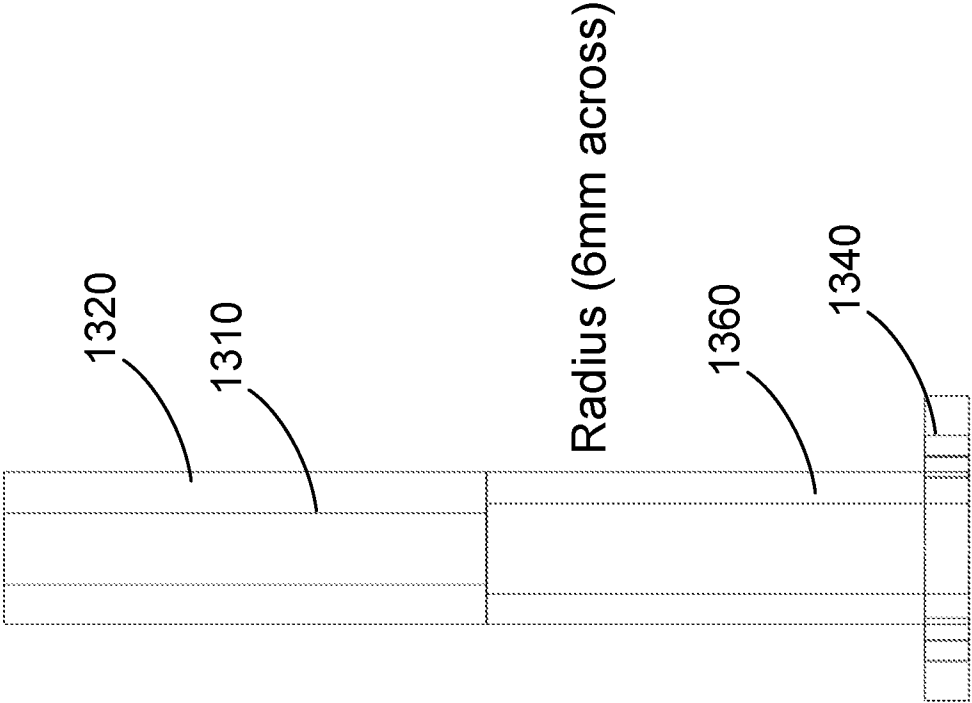


FIG. 13C

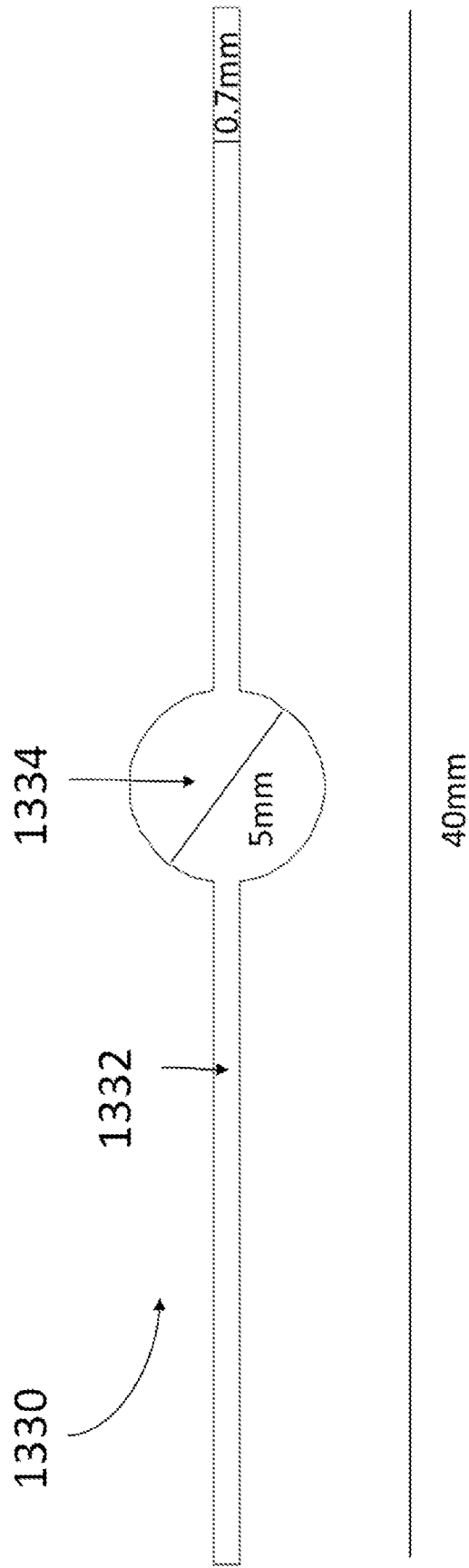


FIG. 13D

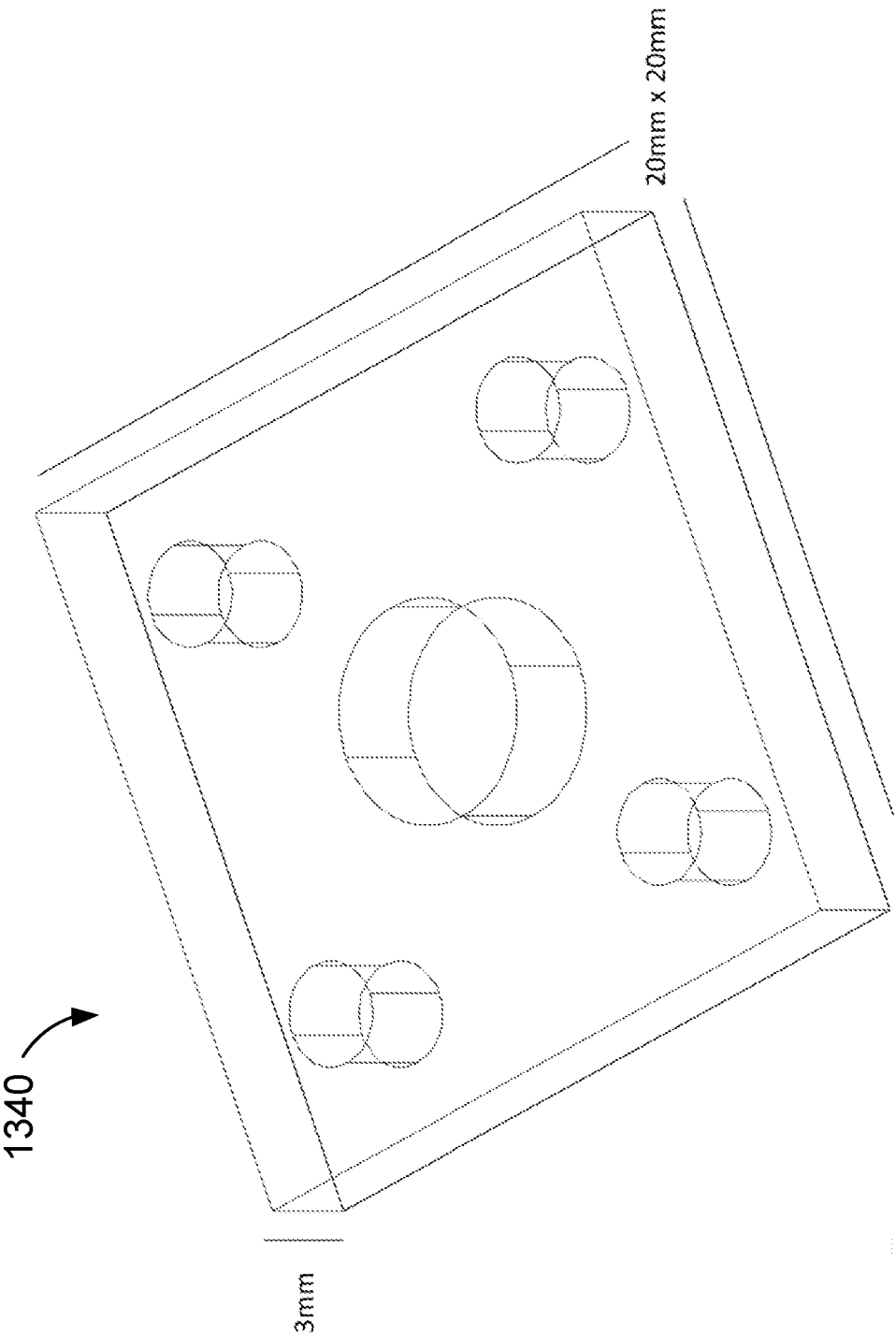


FIG. 13E

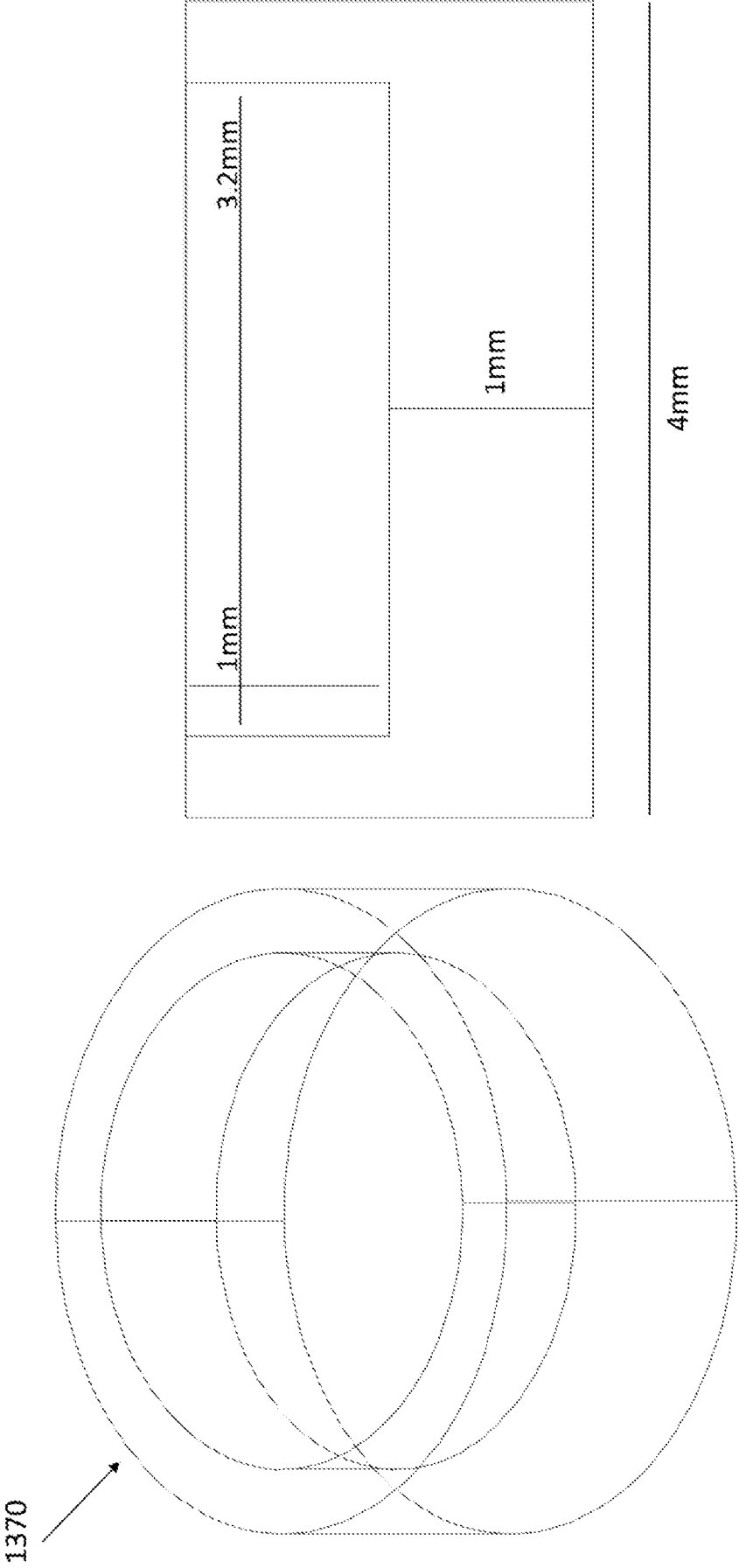


FIG. 13F

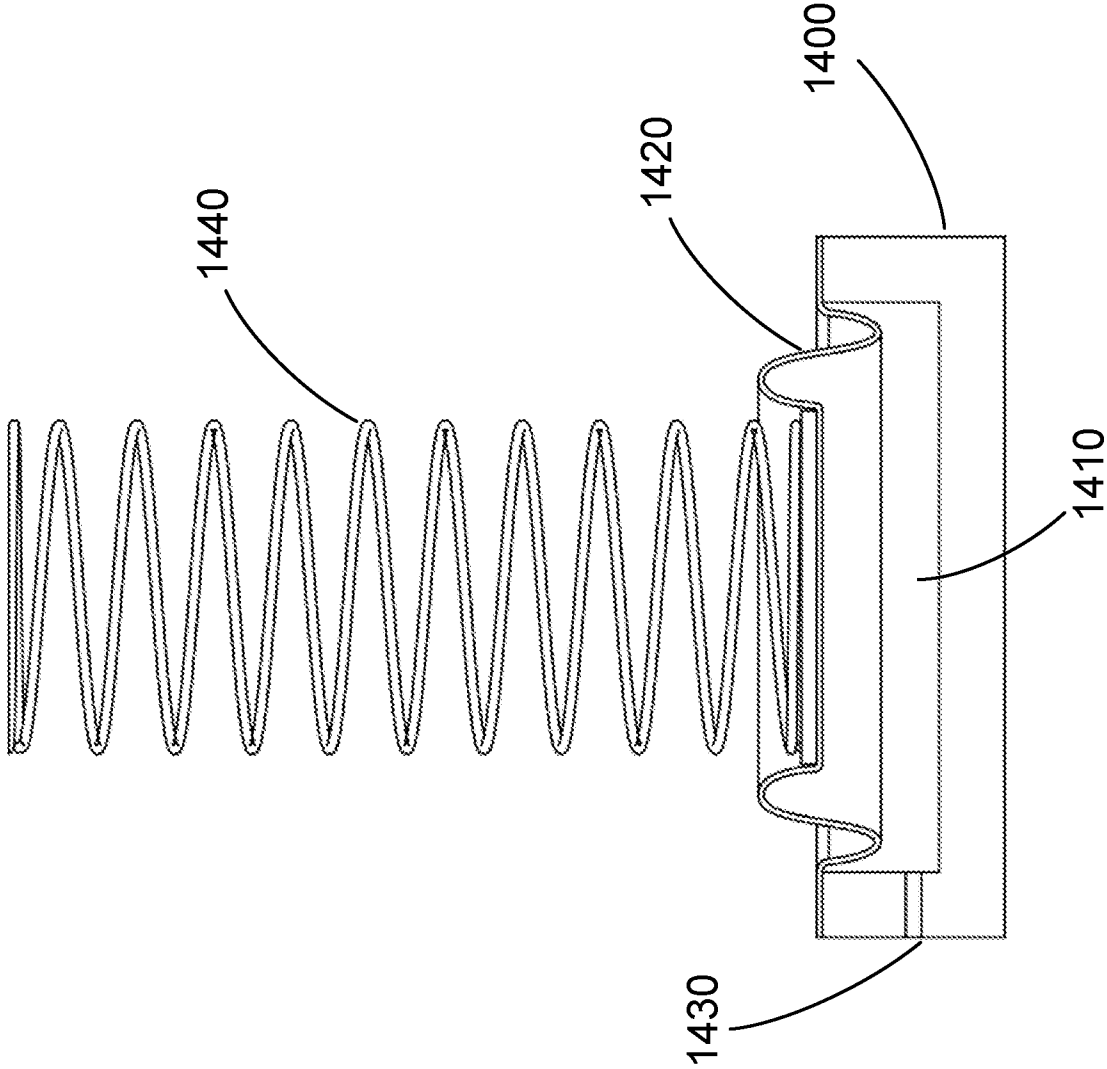


FIG. 14

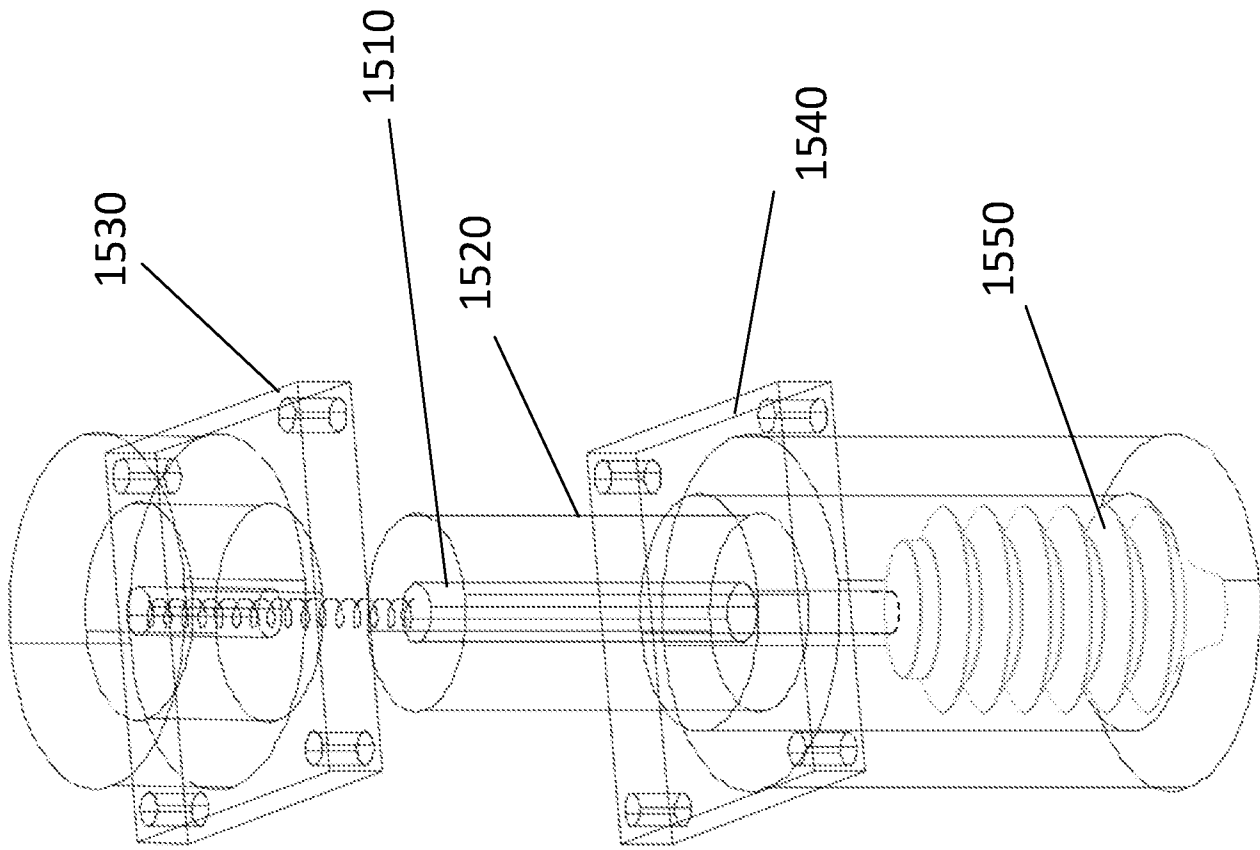


FIG. 15A

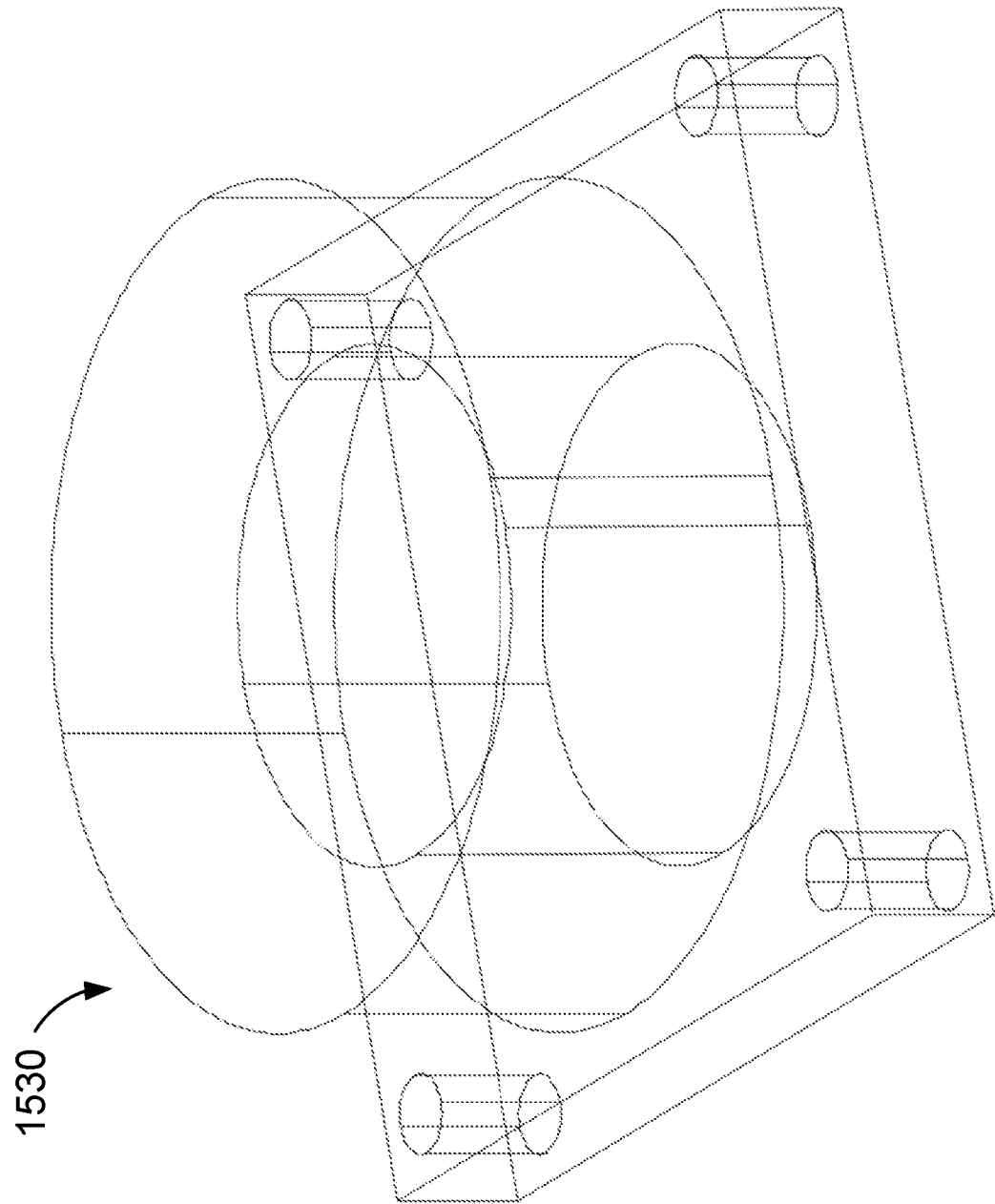


FIG. 15B

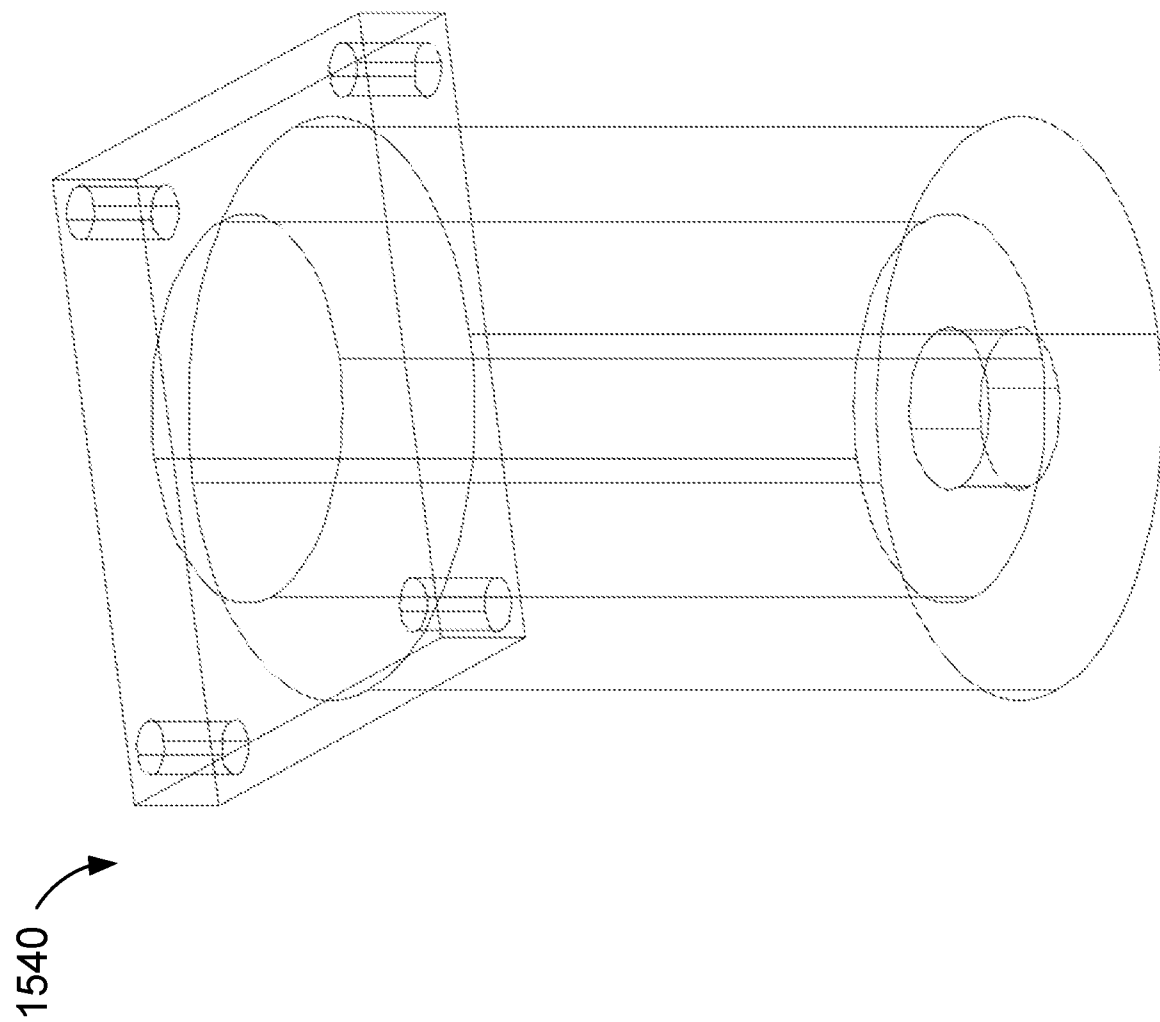
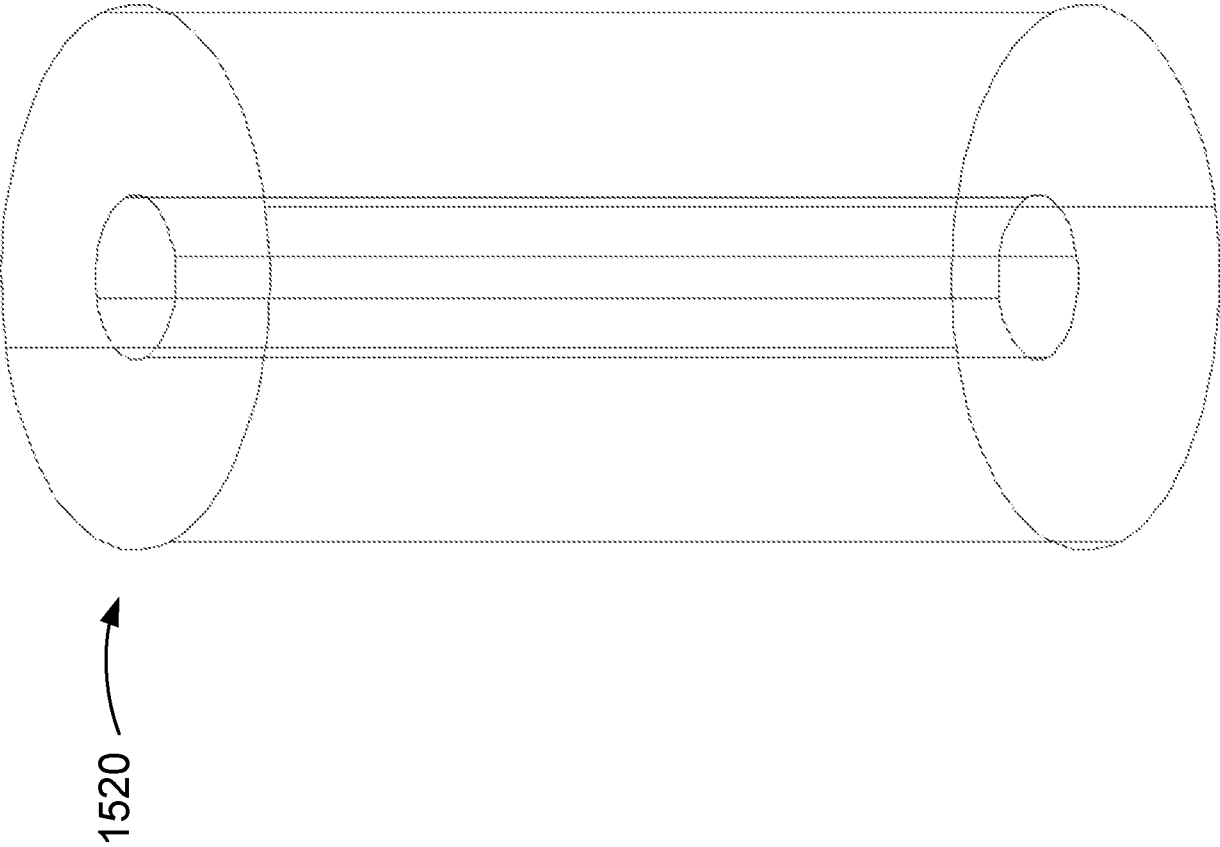


FIG. 15C



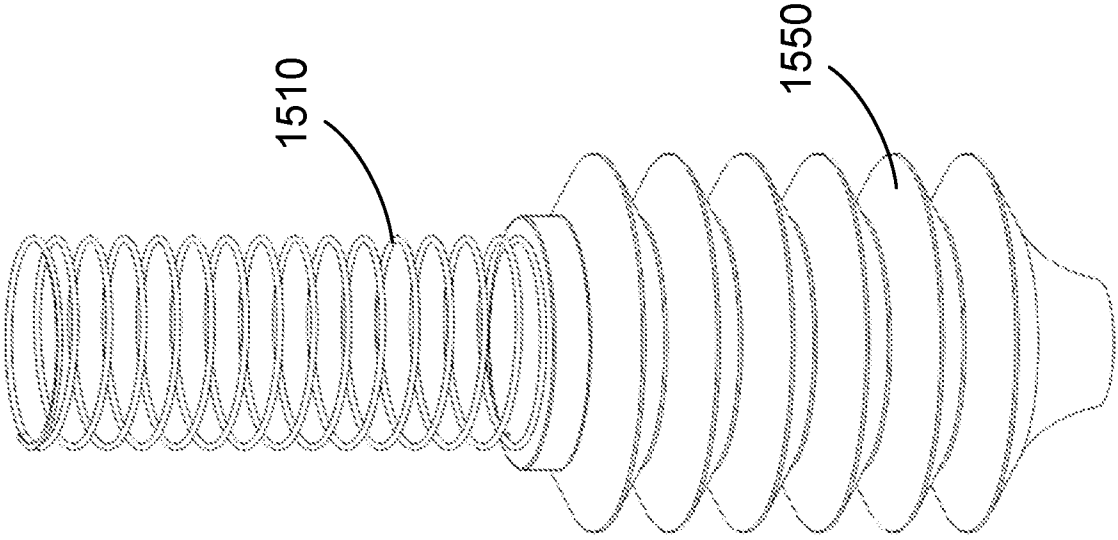


FIG. 15F

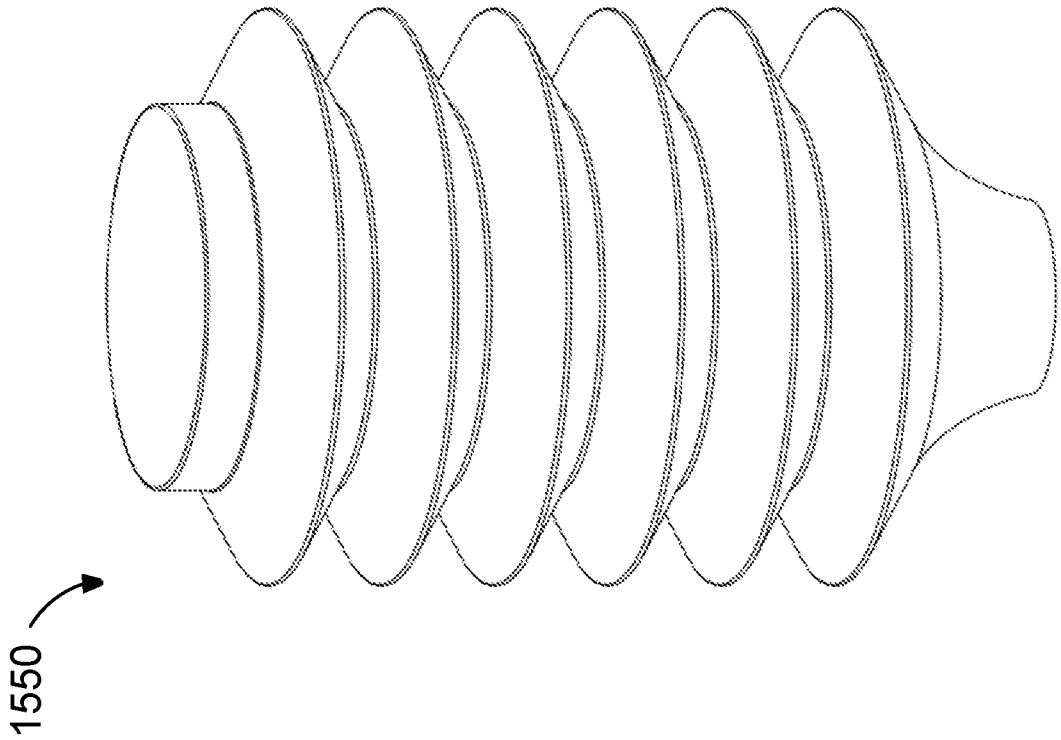


FIG. 15E

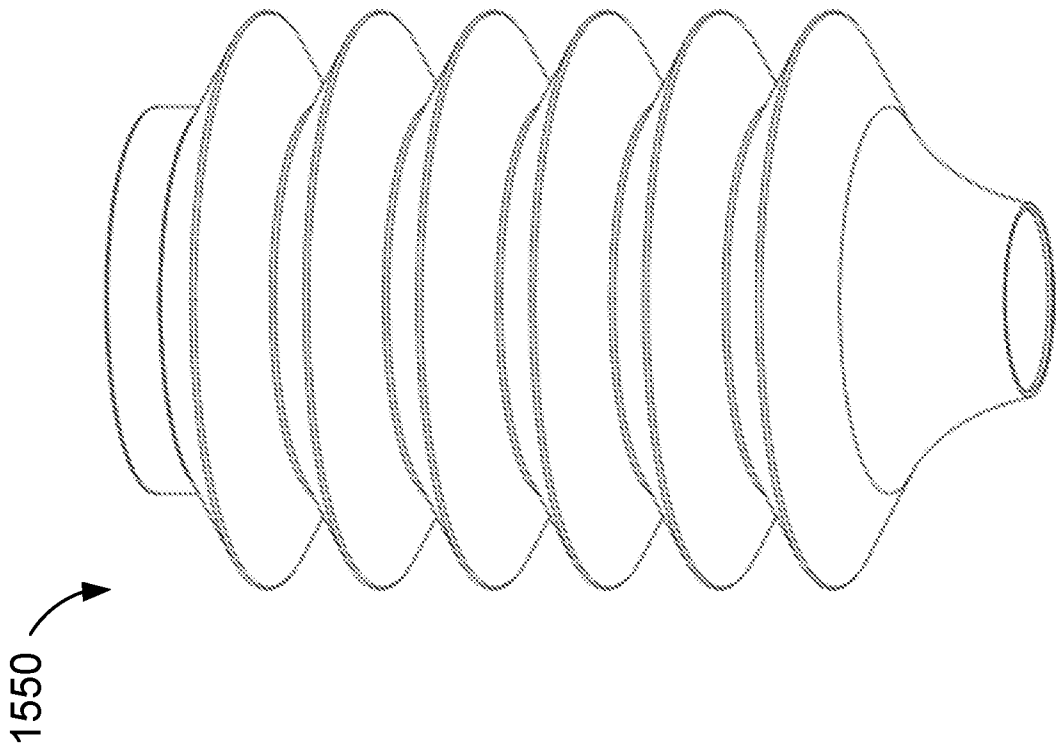


FIG. 15G

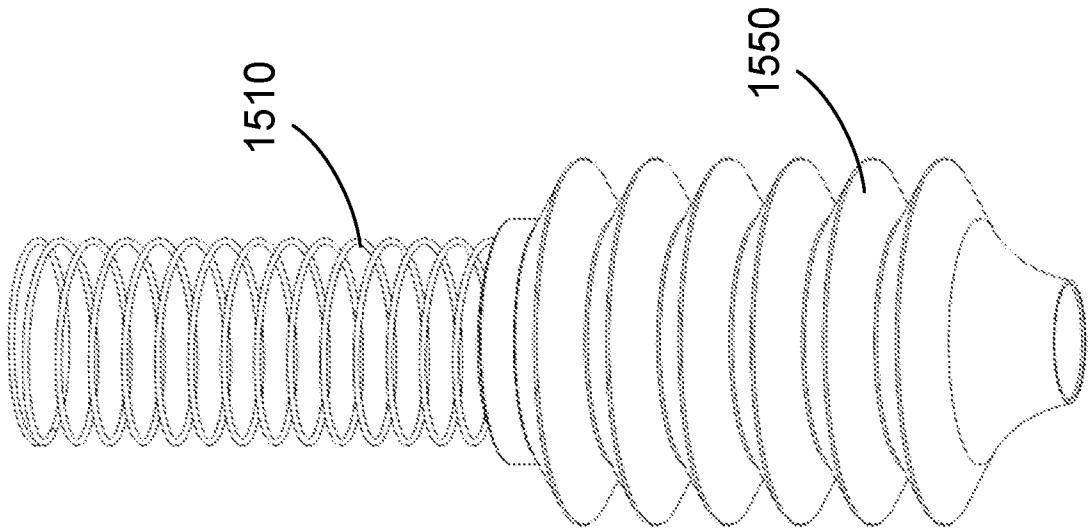


FIG. 15H