(19) DANMARK

(10) **DK/EP 3612838 T3**

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: ***G 01 N 33/49 (2006.01)***

(45) Oversættelsen bekendtgjort den: **2024-10-21**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2024-09-25**

(86) Europæisk ansøgning nr.: **18724652.5**

(86) Europæisk indleveringsdag: **2018-04-20**

(87) Den europæiske ansøgnings publiceringsdag: **2020-02-26**

(86) International ansøgning nr.: **US2018028630**

(87) Internationalt publikationsnr.: **WO2018195468**

(30) Prioritet: **2017-04-20 US 201762488045 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Hemosonics, LLC, 400 Preston Avenue , Suite 250, Charlottesville, VA 22903, USA**

(72) Opfinder: **HIGGINS, Timothy, 400 Preston Avenue , Suite 250, Charlottesville, Virginia 22903, USA**
HOMYK, Andrew, 400 Preston Avenue, Suite 250, Charlottesville, Virginia 22903, USA
COREY, F. Scott, 400 Preston Avenue , Suite 250, Charlottesville, Virginia 22903, USA
REGAN, Franklin F. IV, 400 Preston Avenue , Suite 250, Charlottesville, Virginia 22903, USA
WALKER, William F., 400 Preston Avenue, Suite 250, Charlottesville, Virginia 22903, USA
BRYANT, David, 400 Preston Avenue , Suite 250, Charlottesville, Virginia 22903, USA
GIVENS, Thomas, 400 Preston Avenue , Suite 250, Charlottesville, Virginia 22903, USA
VIOLA, Francesco, 400 Simerville Road, Chapel Hill, NC 27517, USA

(74) Fuldmægtig i Danmark: **NORDIC PATENT SERVICE A/S, Bredgade 30, 1260 København K, Danmark**

(54) Benævnelse: **ENGANGSSYSTEM TIL ANALYSE AF HÆMOSTATISK FUNKTION**

(56) Fremdragne publikationer:
EP-A2- 3 001 196
WO-A1-02/50535
WO-A1-2015/184433
DE-U1- 202014 002 289
US-A1- 2008 261 261
US-B1- 6 750 053
US-B2- 9 272 280

DESCRIPTION

Description

GOVERNMENT LICENSE RIGHTS

[0001] The invention was made with government support under grant R44HL103030 awarded by National Heart Lung and Blood Institute. The government has certain rights in the invention.

RELATED APPLICATIONS

[0002] This application claims priority to, and the benefit of, U.S. Provisional Appl. no. 62/488,045, filed April 20, 2017, titled "Disposable System for Analysis of Hemostatic Function," .

TECHNICAL FIELD

[0003] The present application relates to an apparatus according to claim 1.

BACKGROUND

[0004] Hemostasis, the physiological control of bleeding, is a complex process incorporating the vasculature, platelets, coagulation factors, fibrinolytic proteins, and a variety of activators and inhibitors. Disruption of hemostasis plays a central role in the onset of myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis and excessive bleeding. Consequently, *in vitro* diagnostics (IVD) are critically needed to quantify hemostatic function/dysfunction and direct appropriate treatment.

[0005] The process of coagulation is highly dependent, among other things, on the temperature at which it takes place. Under normal conditions, coagulation occurs at body temperature, which is optimal for the proper enzymatic action of the clotting factors in the cascade.

[0006] Preparation of the blood to be tested is also important, as the manner a blood sample is prepared prior to its evaluation can affect, for example, the actions of the vasculature components, platelets and other cellular components, coagulation factors, fibrinolytic

components, and any inhibitor or activator of hemostasis.

[0007] US9272280 discloses a device for evaluation of hemostasis that comprises test chambers configured to receive blood of a test sample whereby each test chamber comprises a reagent or combination of reagents. The device comprises a channel in communication with the test chambers and a heat exchanger in communication with the channel.

SUMMARY

[0008] Provided is an apparatus according to claim 1. For example, provided are disposable systems for analysis of hemostasis function. The disposable system, in some embodiments, includes a multi-channel or multi-chamber test cartridge device configured to operate with a testing system for evaluation of hemostasis in a subject by in vitro evaluation of a test sample from the subject. The disposable system, in some embodiments, is configured to interrogate the test sample to evaluate clot stiffness, strength, or other mechanical properties of the test sample to assess the function of various physiological processes occur during coagulation and/or dissolution of the resulting clot. The sample can include in whole, or in part, whole blood, plasma, platelet rich plasma, or platelet poor plasma. Furthermore, the sample can include one or more reagent (such as anticoagulants or anti-platelet drugs that might be present in the blood as collected), or one or more pharmacological treatment (such as in the case of heparin or low molecular weight heparin) or other inert components (such as polystyrene beads) that are added to the test sample before the cartridge device being used. The disposable system facilitates the point of care evaluation of hemostasis of a test sample that is robust (e.g., can be performed in non-laboratory environment), rapid (e.g., only to take a few minutes to perform), easy-to-use and provides clear results (e.g., that are direct to the functional components of hemostasis), and facilitates identification of exact hemostasis defects. The exemplified device automates one or more pre-measurement steps that minimizes sample manipulation steps required for the user, thereby improving test reproducibility and/or test quality. The disposable system, in some embodiments, includes a plurality of testing circuits each having a pathway defined by channels and chambers configured to prepare a test sample of blood for evaluation by a measurement device. In each testing circuit, a portion of the test sample is introduced to a reagent or combination of reagents specific to that testing circuit.

[0009] The disposable system, in some embodiments, is configured to condition the respective test samples prior to, during, and/or after the mixing with the reagent(s), to optimize the proper actions of applicable blood component and chemistry (e.g., vasculature components, platelets or other cellular components, coagulation factors, fibrinolytic components, and any other inhibitor or activator of hemostatic function, etc.) being evaluated.

[0010] In an aspect, an apparatus (e.g., a cartridge) is disclosed for the assessment of hemostasis. The apparatus includes a housing; an input port integrally formed with the housing that is structurally configured to establish fluidic communication and evacuate contents of a

sample holding tube; and a first chamber in fluidic communication with the input port, the first chamber being configured to receive a sample contained in the sample holding tube and to condition the received sample to a desired temperature (e.g., a pre-defined temperature range) before the received sample is allowed to contact one or more reagents located in one or more fluidic circuits downstream to the first chamber, wherein each of the one or more fluidic circuits comprises i) a second chamber in fluidic communication with the first chamber that meters the sample in the first chamber into an aliquot, wherein the metered sample is introduced to a reagent, or a combination of reagents, (e.g., in the form of lyophilized reagent bead) located in a corresponding fluidic circuit (e.g., a reagent pocket) to form a mixed sample and ii) a testing chamber in fluidic communication with the second chamber, the testing chamber being structurally configured for interrogation by a measurement system configured to determine properties (e.g., mechanical properties or viscoelastic properties) of the mixed sample.

[0011] In some embodiments, at least one of the one or more fluidic circuits comprise one or more pockets (e.g., each configured to house a lyophilized reagent bead comprising a reagent, or a combination of reagents).

[0012] In some embodiments, at least one of the one or more fluidic circuits comprise one or more liquid-retaining pockets (e.g., each configured to house an assay, in liquid form, comprising the reagent, or a combination of reagents).

[0013] In some embodiments, at least one of the one or more fluidic circuits includes one or more lyophilized reagents that are located on one or more surfaces thereof (e.g., lyophilized on each of the surfaces; lyophilized as films placed on, or adhered to, one or more of the surfaces).

[0014] In some embodiments, at least one of the one or more fluidic circuits includes one or more reagents that are processed onto surfaces thereof (e.g., dried on the surfaces; spray coated on the surfaces; baked onto the surfaces).

[0015] In some embodiments, the input port is communicatively coupled to a pressure port, wherein pressure applied to the pressure port causes the evacuation of the contents of the sample holding tube through the input port to first chamber.

[0016] In some embodiments, the input port comprises a needle assembly.

[0017] In some embodiments, the needle assembly comprises the input port and a second port, wherein the second port is configured to vent a liquid or gas into the sample holding tube so as to promote evacuation of the contents therein. The input port, in some embodiments, is located (e.g., concentrically located) within a second port configured to vent a liquid or gas into the sample holding tube so as to cause evacuation of the contents of the sample holding tube.

[0018] In some embodiments, the input port comprises a luer lock configured to connect to the

sample holding tube, wherein the sample holding tube is a syringe.

[0019] In some embodiments, the input port is communicatively coupled to a first pressure port, wherein pressure when applied to the first pressure port causes the evacuation of the contents of the sample holding tube through the input port to the first chamber.

[0020] In some embodiments, the first chamber is configured to mate with a corresponding thermal regulating system (e.g., heating/cooling system) of the measurement system to condition the received sample to, or near, the desired temperature.

[0021] In some embodiments, the shape and/or materials of the first chamber are optimized to facilitate thermal regulation (e.g., heating and/or cooling) of the sample to, or near, the desired temperature.

[0022] In some embodiments, the first chamber is configured to mate with a corresponding thermal regulating surface of a sub-system component of the measurement system to condition the received sample to, or near, the desired temperature. In some embodiments, a channel portion of the one or more fluidic circuits is configured to mate with a corresponding heating/cooling system of the measurement system to condition the received sample to, or near, the desired temperature.

[0023] In some embodiments, a channel portion of the one or more fluidic circuits is configured to mate with a corresponding thermal regulating system of the measurement system to condition the received sample to the desired temperature. In some embodiments, the first chamber and/or the channel portion of the one or more fluidic circuits is in physical proximity (e.g., physical contact or near contact) with a sensor configured to measure a temperature of the sample received in the first chamber.

[0024] In some embodiments, the sensor is selected from group consisting of a thermistor, a thermocouple, and an optical sensor (e.g., an IR sensor).

[0025] In some embodiments, the apparatus includes a first pressure port in fluidic communication with the first chamber, the first pressure port being configured to receive negative or differential pressure (e.g., for filling the first chamber); and a filter positioned within the first pressure port in at least one of the fluidic circuits (e.g., such that the filter is clogged by the sample received in the first chamber when the first chamber is full). The filter, in some embodiments, is configured to allow air to move through the first pressure port but prevent fluid from moving there through.

[0026] In some embodiments, the apparatus includes a first pressure port configured to receive negative or differential pressure for filling the first chamber; and a first fluidic pathway extending from the first pressure port to the first chamber, wherein the filter is positioned within the first pressure port.

[0027] In some embodiments, for each of the one or more fluidic circuits, the fluidic communication between the first chamber and the second chamber is through a second fluid pathway originating from a side of the first chamber (e.g., a side wall, a bottom wall, and etc.) (e.g., such that bubbles present in the received sample are trapped away from the second chamber).

[0028] In some embodiments, each of the one or more fluidic circuits comprises a third fluid pathway in fluidic communication with the second chamber, wherein the third fluidic pathway leads a second pressure port configured receive negative or differential pressure for filling the second chamber.

[0029] In some embodiments, the second pressure port has a second filter therein, wherein the second filter is configured to clog when the second chamber is filled.

[0030] In some embodiments, the apparatus includes one or more fluidic pathways in fluidic communication with the second pressure port for all of the one or more fluidic circuits, wherein the one or more fluidic pathways are configured to provide the negative pressure to the second pressure port for all of the one or more fluidic circuits.

[0031] In some embodiments, for each of the one or more fluidic circuits, the second chamber is in fluidic communication with a vent port, wherein the vent port is configured to be closed while the sample is metered into the aliquot in the second chamber and further configured to be open to atmospheric pressure after the sample is metered into the aliquot in the second chamber.

[0032] In some embodiments, each of the one or more fluidic circuits comprises a third set of fluid pathways in fluidic communication between a respective second chamber (e.g., metering chamber) and test chamber, wherein a portion of third set of fluid pathways are arranged as a serpentine-shaped conduit or channel.

[0033] In some embodiments, each of the one or more fluidic circuits further comprises a serpentine reservoir between the testing chamber and the second chamber.

[0034] In some embodiments, the metered sample is alternatively directed through portions of the one or more fluidic circuits to facilitate mixing of the metered sample and the reagent, or a combination of reagents.

[0035] In some embodiments, the metered sample is alternatively and multiplicatively directed, for each of the one or more fluidic circuits, between a first position (e.g., the second chamber) in a fluidic circuit a second position (e.g., a position in the serpentine reservoir) in the fluidic circuit.

[0036] In some embodiments, each of the one or more fluidic circuits further comprises a third pressure port in fluidic communication with the second chamber and the testing chamber, the

third pressure port configured to receive negative or differential pressure (e.g., for drawing the aliquot from the second chamber to the testing chamber), wherein the third pressure port is further configured to alternately receive alternating pressure, e.g., for alternately drawing the aliquot from the second chamber along the serpentine reservoir and pushing the aliquot through the serpentine reservoir to the second chamber.

[0037] In some embodiments, the serpentine reservoir includes an optical detection zone to facilitate optical detection of the metered sample in the serpentine reservoir or a location of the sample in the serpentine reservoir.

[0038] In some embodiments, each of the one or more fluidic circuits further comprises a mixing pathway between the testing chamber and the second chamber, the mixing pathway comprising one or more ferromagnetic beads or bars therein.

[0039] In some embodiments, at least one of the one or more fluidic circuits comprises one or more quality testing portals.

[0040] In some embodiments, the one or more quality testing portals is configured to be sensed optically, wherein the quality testing port is transparent.

[0041] In some embodiments, the one or more quality testing portals is configured to be sensed electrically, wherein quality testing port comprises one or more sensing electrodes.

[0042] In some embodiments, the one or more quality testing ports is configured to be sampled for characteristics for the metered sample (e.g., for pressure, presence of flow, flow rate, temperature).

[0043] In some embodiments, for each of the one or more fluidic circuits, the testing chamber comprises a mechanism to couple energy into the testing chamber to perform the measurements such as in the case of a lens configured to direct ultrasonic pulses into to the testing chamber.

[0044] In another aspect, an apparatus is disclosed for the assessment of hemostasis, the apparatus comprising: a housing; an input port integrally formed with the housing that is structurally capable of establishing fluidic communication with, and evacuating contents of, a sample holding tube; a first chamber that is in fluidic communication with the input port that receives the sample contained in the evacuated tube and whereby the sample temperature is adjusted to a desired temperature before the sample contacting one or more reagents; one or more second chambers that are in fluidic communication with the first chamber, the one or more second chamber being configured to meter the sample in the first chamber into one or more aliquots; one or more reagent pockets each filled with one or more lyophilized reagent bead that are in fluidic communication with each of the aliquot chambers and permits the sample present in each aliquot to be mixed with said one or more reagent beads; and one or more testing chambers that are in fluidic communications with the aliquot chambers and that

are structurally capable of being interrogated to determine the sample viscoelastic properties after such sample has been mixed with the one or more reagents.

[0045] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes an intrinsic pathway activator (e.g., kaolin, celite, glass, ellagic acid, micronized silica, Hageman factor, etc.) or a combination therewith.

[0046] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes an extrinsic pathway activator (e.g., tissue factor, recombinant tissue factor, thromboplastin, etc.) or a combination therewith.

[0047] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes a coagulation activator (e.g., thrombin, factor Xa, reptilase, ecarin, Russell's viper venom or other snake venoms, etc.) or a combination therewith.

[0048] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes a platelet activator or platelet inhibitor (e.g., GPIIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban, roxifiban, orbofiban), cytochalasin D, blebbistatin, PARI inhibitors, PAR4 inhibitors, glycoprotein IB inhibitors, TRAP, ADP, arachidonic acid, ADP inhibitors, non-steroidal anti-inflammatory drugs, platelet activating factor, ristocetin, epinephrine, etc.) or a combination therewith.

[0049] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes a fibrinolytic functions activator or inhibitor (e.g., tPA, uKA, streptokinase, TAFIa, plasmin/plasminogen, aprotinin, epsilon-aminocaproic acid, tranexamic acid, plasminogen activator inhibitor 1 (PAI1), α2-antiplasmin (α2-AP), or plasmin-antiplasmin complexes, carboxypeptidase inhibitor) or a combination therewith.

[0050] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes FXIIIa inhibitors or a combination therewith.

[0051] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuit includes thrombomodulin or a combination therewith.
In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuit includes low molecular weight heparin or a combination therewith.

[0052] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes Hexadimethrine bromide (polybrene) or a combination therewith.

[0053] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes heparin or a combination therewith.

[0054] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes corn trypsin inhibitor or a combination therewith.

[0055] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes adenosine or a combination therewith.

[0056] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes GPRP (Gly-Pro-Arg-Pro) or a combination therewith.

[0057] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes calcium or a combination therewith.

[0058] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes fibronectin or a combination therewith.

[0059] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes collagen or a combination therewith.

[0060] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes an immuno-detection reagent or a combination therewith.

[0061] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes heparinase I or a combination therewith.

[0062] In some embodiments, the reagent, or combination of reagents, located in the one or more fluidic circuits includes endothelial cells or activated endothelial cells.

[0063] In some embodiments, the measurement system is selected from the group consisting of a sonorheometry-based system, thromboelastography-based system, a thromboelastometry-based system, an optical-based system, a fluorescence-based system, a colorimetric-based system, an aggregometry-based system, a resonance-based system, and an electrical impedance-based system.

[0064] In another aspect, a method is disclosed of mixing a sample with one or more reagents in an apparatus (e.g., a cartridge) and testing the mixed sample for the assessment of hemostasis. The method includes receiving a plurality of metered samples of from a plurality of metering chambers that received test fluid from a sample holding tube (e.g., via a mechanical coupling that connects the apparatus to the sample holding tube or via an opening to which sample from the sample holding tube is placed); alternately and multiplicatively flowing each of the aliquots until the aliquot is mixed with a reagent, or a combination of reagents, to form a mixed aliquot, wherein the at least one aliquot alternately and cyclically flowed i) in a first direction from the metering chamber through one or more reagent pocket, with the one or more reagents therein (e.g., lyophilized reagent bead), and along a serpentine pathway in communication with the metering chamber until at least a portion of the aliquot reaches a detection zone located in, or after, the serpentine pathway and ii) in a second direction from the detection zone reversed to the first direction through at least a portion of the serpentine

pathway toward the metering chamber until a trigger event; and driving the mixed aliquot in a testing chamber in fluidic communication with the metering chamber, wherein the testing chamber is structurally configured for interrogation by a measurement system configured to determine properties (e.g., mechanical properties or viscoelastic properties) of the mixed aliquot, and wherein an interrogation of the testing chamber is performed with the mixed aliquot located therein.

[0065] In some embodiments, the method includes receiving the fluid in a first chamber configured to substantially adjust the temperature of the test sample toward body temperature or other desired temperatures, wherein the metered sample received in the metering chamber is received from the first chamber.

[0066] In some embodiments, the test fluid is moved into the first chamber in response to an applied pressure that is applied by, or generated from, the measurement system.

[0067] In some embodiments, the method includes conditioning the test fluid in the first chamber to, or substantially near, a desired temperature, wherein the test fluid is mixed with the one or more reagents following exit from the first chamber.

[0068] In some embodiments, the method includes isolating (e.g., blocking via a valve) the test fluid in the metering chamber to prevent the test fluid from contacting the one or more reagents during the filling of the metering chamber.

[0069] In some embodiments, a second applied positive or negative pressure is applied by, or generated from, the measurement system (e.g., applied at a second pressure port in communication with the) at a second port in communication with the serpentine pathway so as to move the at least one aliquot in the second direction.

[0070] In some embodiments, the first applied positive or negative pressure is applied by, or generated from, the measurement system in reversed so as to move the at least one aliquot in the second direction.

[0071] In some embodiments, the operation of receiving the mixed aliquot in the testing chamber further comprises receiving a negative pressure via the third pressure port, wherein the third pressure port is further in fluid communication with the testing chamber.

[0072] In some embodiments, the testing chamber is downstream of the serpentine pathway and the third pressure port is downstream of the testing chamber.

[0073] These and other features and advantages of the present invention will become more readily apparent to those skilled in the art upon consideration of the following detailed description and accompanying drawings, which describe both the preferred and alternative embodiments of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0074] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate embodiments and together with the description, serve to explain the principles of the methods and systems:

FIG. 1 shows a perspective view of an example biological sample input of a cartridge for use in a disposable system, in accordance with an illustrative embodiment.

FIG. 2 shows a side cross-sectional view of the example biological sample input of FIG. 1 with a casing, in accordance with an illustrative embodiment.

FIG. 3 shows a side cross-sectional view of the example biological sample input of FIG. 2 with a sample holding tube attached thereon, in accordance with an illustrative embodiment.

FIG. 4 shows a detailed view of the example biological sample input of FIG. 3, in accordance with an illustrative embodiment.

FIGS. 5A and 5B each shows the biological fluid pathways of four testing circuits (e.g., Hemostasis testing circuits) that are located on a sample preparation plane, in accordance with an illustrative embodiment. FIG. 5B further shows the cartridge body of FIG. 5A further coupled to a sample holding tube, in accordance with an illustrative embodiment.

FIGS. 6A and 6B show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with labels corresponding to the heating chamber filling.

FIGS. 6C and 6D show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with labels corresponding to the sample chamber filling.

FIGS. 6EC and 6F show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with labels corresponding to the sample mixing and test chamber filling.

FIG. 7 shows the back-side of the cartridge of FIG. 5A and includes an interconnection plane that interfaces to the sample preparation plane, that collectively form the biological fluid pathways for the testing circuits, in accordance with an illustrative embodiment.

FIG. 8 shows portions of the biological fluid pathways that are on the interconnection plane of FIG. 7, in accordance with an illustrative embodiment.

FIG. 9 shows an example testing chamber section for use with the example cartridge, in accordance with an illustrative embodiment.

FIG. 10 shows a cross-sectional view of an example testing chamber in the example testing chamber section, in accordance with an illustrative embodiment.

FIG. 11 shows a detailed cross-sectional view of the example testing chamber of FIG. 10, in accordance with an illustrative embodiment.

FIG. 12 shows a cross-sectional view of the disposable system operatively coupled to a measurement system, in accordance with an illustrative embodiment.

FIG. 13 shows an example shear modulus versus time curve, in accordance with an illustrative embodiment.

FIG. 14 shows an example of shear modulus curves obtained with an activator of coagulation and with and without a fibrinolysis inhibitor. A differential comparison of these curves can provide information about the fibrinolytic activity of the sample.

FIG. 15 shows potential embodiments of differential metrics that can be measured from shear modulus curves obtained with an activator of coagulation and with and without a fibrinolysis inhibitor.

FIG. 16 shows a photograph of an exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9 for use in a disposable system, in accordance with an illustrative embodiment.

Fig. 17 shows a front view of the exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9 in accordance with an illustrative embodiment.

Fig. 18 shows a front view of the exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9, in accordance with an illustrative embodiments.

DETAILED DESCRIPTION

[0075] The present invention now will be described more fully hereinafter with reference to specific embodiments of the invention. Indeed, the invention can 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 satisfy applicable legal requirements.

[0076] As used in the specification, and in the appended claims, the singular forms "a," "an," "the," include plural referents unless the context clearly dictates otherwise.

[0077] The term "comprising" and variations thereof as used herein are used synonymously with the term "including" and variations thereof and are open, non-limiting terms.

[0078] As used throughout, by a "subject" is meant an individual. The subject may be a vertebrate, more specifically a mammal (e.g., a human, horse, pig, rabbit, dog, sheep, goat, non- human primate, cow, cat, guinea pig or rodent), a fish, a bird or a reptile or an amphibian. The term does not denote a particular age or sex.

[0079] The apparatus described here includes a single-use cartridge apparatus configured to facilitate in vitro assessment of one or more hemostatic functions. Hemostatic function refers to a functional role of various blood components such coagulation factors, fibrinogen, platelets, fibrinolytic factors, and components of the vasculature. The cartridge apparatus and associated measurement system, in some embodiments, are configured to assess hemostatic function by measuring changes in at least one mechanical property of the tested sample when such sample is exposed to one or more reagents. In some embodiments, the cartridge apparatus and its test chambers are configured to facilitate measurements of viscoelastic properties, e.g., based on interrogation using ultrasound pulses or ultrasonic energy. However, other interrogation systems may be used with a cartridge apparatus with the features described herein. Examples of other .interrogation systems includes, for example, but not limited to, systems that employ cup/pin technologies (such as in the case of thromboelastography and thromboelastometry), oscillating piston to measure changes in mechanical impedance, optical sensing, fluorescence sensing, colorimetric sensing, aggregometry, resonance sensing, or electrical impedance sensing, among others.

[0080] A broad array of reagents can be utilized in the cartridge apparatus, including intrinsic pathway activators (without limitations kaolin, Hageman factor, celite, glass, ellagic acid, micronized silica etc), extrinsic pathway activators (without limitations tissue factor, recombinant tissue factor, thromboplastin, etc), other coagulation activators (without limitations thrombin, factor Xa, reptilase, ecarin, Russell's viper venom or other snake venoms, etc), platelet activators or platelet inhibitors (without limitations GPIIb/IIIa inhibitors (such as abciximab, eptifibatide, tirofiban, roxifiban, orbofiban), cytochalasin D, blebbistatin, PARI inhibitors, PAR4 inhibitors, glycoprotein IB inhibitors, TRAP, ADP, arachidonic acid, ADP inhibitors, non-steroidal anti-inflammatory drugs, etc.), fibrinolytic function activators or fibrinolytic function inhibitors (without limitations tPA, uKA, streptokinase, TAFIa, plasmin/plasminogen, aprotinin, epsilon- aminocaproic acid, tranexamic acid, plasminogen activator inhibitor 1 (PAI1), α2-antiplasmin (α2-AP), or plasmin-antiplasmin complexes, carboxypeptidase inhibitor, etc.), and others (FXIIIa inhibitors, Hexadimethrine bromide (polybrene), heparinase (e.g., heparinase I), ristocetin, heparin, low molecular weight heparin, corn trypsin inhibitor, adenosine, GPRP, calcium, fibronectin, collagen, epinephrine, immuno-detection reagents, direct thrombin inhibitors, factor Xa inhibitors, reagents aimed at reversing or eliminating the effects of the new oral anticoagulants (such as the direct thrombin inhibitors and the factor Xa inhibitors), thrombomodulin, etc.). Additional non-functional reagents could also be used to preserve the functionality of the other reagents (buffers and stabilizers for lyophilization or drying, dyes, etc.).

[0081] Reagents, in some embodiments, are placed and stored in chambers (e.g., pockets located within a fluidic circuit) in the cartridge apparatus but in alternative embodiments reagents can be placed and stored in various chambers or fluidic channels in the fluidic circuit of the cartridge apparatus. A fluidic circuit generally refers to one or more fluidic pathways established between sample preparation and the one or more test chambers where samples are ultimately measured.

[0082] In some embodiments, reagents are placed and stored in the cartridge apparatus in liquid forms or can be lyophilized in spheres (such as in the case of the Lyopheres™ produced by BioLyph LLC), lyophilized in films, lyophilized on the plastic surfaces, dried on the plastic surfaces, or spray coated, etc., in order to improve shelf-life stability. A person of ordinary skills in the art should recognize that these reagents are not fully inclusive and other reagents or reagent combinations that are inhibitors or activators of one or more hemostatic functions could be used in this cartridge.

[0083] The cartridge apparatus disclosed here is a component of a measurement system (e.g., a hemostasis measurement system). The measurement system (also referred to as the instrument) includes at least an interface element which couples between the cartridge apparatus and a measuring element configured to measures viscoelastic properties or mechanical properties of a sample processed within the cartridge apparatus. The measured viscoelastic properties or mechanical properties are outputted as results to a user interface. An example user interface is described in commonly assigned U.S. Pub. No. 2011/0252352 to Viola et al., which is incorporated by reference herein in its entirety.

[0084] In some embodiments, the interface element includes one or more heating and/or cooling elements.

[0085] In some embodiments, the interface element includes a fluidic manifold that facilitate connection to one or more pump elements and one or more valves.

[0086] In some embodiments, the interface element includes one or more sensors, e.g., configured to perform hemostasis measurements. The one or more sensors, in some embodiments, includes ultrasound sensors. In other embodiments, the one or more sensors includes other interrogative devices that is based on thromboelastography, thromboelastometry (e.g., a thromboelastography-based system or a thromboelastometry-based system), or that measures changes in mechanical impedance, changes in perturbation as observed via an optical-based system (e.g., having an optical sensor), fluorescence, colorimetric-based system, aggregometry-based system (e.g., having optical sensor, acoustic sensor, or electrodes that measure aggregation with the test sample), resonance-based system (e.g., having optical, acoustic, or mechanical position sensors that measures the sample when the sample is at, or near resonance), electrical impedance-based system (e.g., having electrodes configured to measure electrical impedance), or a combination thereof.

[0087] In some embodiments, the interface element includes a mechanical clamp configured to position the cartridge apparatus in a desired orientation with respect to the components (the one or more sensors, the fluidic manifold, the heating and/or cooling elements, and etc.) of the measurement system. When the interface element is interfaced with the components of the measurement system, the cartridge apparatus, in some embodiments, is driven via a series of controlled actions orchestrated by the measurement system to prepare the test sample for measurement. In some embodiments, the preparation operations include sample aspiration of a sample from a sample container (also referred to as a sample holding tube), sample heating

and/or cooling, sample metering, sample mixing with reagents, and sample measurement. Each step, with reference to various embodiments, is described below. After measurements are completed, the results are output in the instrument user interface.
In some embodiments, the cartridge apparatus and its internal components are the only component that directly contact with a sample to be analyzed.

[0088] In some embodiments, the cartridge includes computer readable information that can be optically or communicatively interrogated (e.g., RFID tags, computer readable medium such as flash ICs, QR codes, BAR codes, and etc.) and/or human readable information (e.g., labels).

[0089] The various embodiments described below does not utilize any active valve element in the cartridge design, but instead relies on a fluidic manifold and one or more valves placed in the instrument. Fluid is moved through the various cartridge components via pressure differential and/or gravity and/or material properties (such as in the case of hydrophobicity or hydrophilicity) and/or capillary forces.

[0090] In these embodiments, the cartridge is configured to couple with the instrument via one or more connection ports that are aligned via alignment slots. The connection ports include one or more pressure ports and one or more vent ports. However, in alternative embodiments, actuated valves (such as in the case of elastomeric valves) can be included in the cartridge design to control fluid flow. These valves are actuated, in some embodiments, by corresponding hardware and software components in the measurement system.

[0091] The surface properties and texture of the cartridge surfaces in direct contact with the sample can be optimized to promote sample adhesion and/or sample flow. In some embodiments, the test chamber's interior surface and/or other interior surfaces of the fluidic circuit within the cartridge apparatus are plasma treated to optimize the surface energy and texture for adhesion of specific plasma proteins. In other embodiments, test chamber's interior surface and/or other interior surfaces of the fluidic circuit are treated with surface roughness texturing, material coating (such as in the case of gold plating), biological material coating (such as in the case of fibronectin or collagen coating, for example), raw material selection (e.g., use of specific plastic or other materials for the plate that does not require additional treatment), etc. Such treatments maybe performed independently, or in conjunction with, a plasma treatment. Similarly, the cartridge materials can be selected or manipulated to achieve the desired hydrophobicity or hydrophilicity. These properties can be changed by plasma treatment or by surface coatings.

[0092] As described in more details below, the cartridge and the associated measurement system can utilize one or more sensors of one or more types (e.g., optics, pressure, ultrasound, etc.) as part of the automated operations of the cartridge. In addition, the outputs of such one or more sensor(s) can be further utilized to perform quality control checks. These checks may be performed before, during, or after cartridge testing to ensure function of one or more of the subsystems (for example, ultrasound or other interrogation system, fluidics, fluid

level, clamping, cartridge positioning/orientation system, or temperature control), ensure the cartridge is functional, ensure correct sample preparation before measurements are performed or have been performed for the measurement, and may also be used to accept or reject a test result or even to abort testing before initiation of measurements.

[0093] Note that in the discussion below a fluidic circuit includes a channel with fluidic component that connects one or more chambers together. Fluid circuit is also referred to as a testing channel in a multitude of channels that can be individually and controllably processed within a single cartridge apparatus.

Cartridge Input Section

[0094] FIGS. 1, 2, 3, and 4 are schematic illustrations of an example biological sample input section of a cartridge **100** for evaluating hemostasis. Specifically, FIG. 1 shows a perspective view of an example biological sample input of a cartridge for use in disposable system, in accordance with an illustrative embodiment. FIG. 2 shows a side view of the example biological sample input of FIG. 1 with a casing, in accordance with an illustrative embodiment. FIG. 3 shows a side cross-sectional view of the example biological sample input of FIG. 2 with a sample holding tube attached thereon, in accordance with an illustrative embodiment. FIG. 4 shows a detailed view of the example biological sample input of FIG. 3, in accordance with an illustrative embodiment. In alternative embodiments, the input section of the cartridge comprises a well to which fluid sample can be placed, for example, by way of a pipette or tube.

[0095] In some embodiments, and as shown in FIG. 1, the cartridge **100** has a dual connection tab **28a, 28b** for coupling the cartridge **100** to a sample container guide **1** (shown in FIG. 2). As shown in FIG. 2, the sample container guide **1**, when mated with the cartridge **100**, aligns a sample container **2** to a sample input port **3** of the cartridge **100.** The cartridge **100** also includes an alignment tab **29** that is configured to slide into an alignment groove **30** of the sample container guide **1** to further stabilize the coupling of the sample container guide **1** to the cartridge **100.** The sample container guide **1** can further provide a hard stop **5** (shown in FIG. 3) to hold the sample container **2** at the appropriate height to establish fluidic communication with the cartridge **100.**

[0096] In various embodiments, the sample container **2** is an evacuated tube (also referred to herein as the sample holding tube **2**) such as a BD Vacutainer™ tube, and the sample input port **3** comprises one or more needles required for sample transferring **3a** and venting **4** (see FIG. 1). Though shown as concentric in the figures, the needles can be configured to be concentric, side by side, or integrated. In some embodiments, and as shown in FIG. 1, the sample transferring needle **3a** includes inlets (**3b** and **3d**) and an outlet **3c** that terminates in a sample inlet chamber **26** of the cartridge **100.** The sample inlet chamber **26** is in fluid communication with an inlet pathway **8** that leads to a retention/heating chamber **6** (see FIG. 5A). In some embodiments, and as shown in FIG. 1, the venting needle **4** includes an outlet **4a**

that is configured to terminate within the sample container **2** when attached and is spaced apart from the inlet **3d** so as to minimize bubbles being drawn into the inlets **3b** and **3d.** The venting needle **4** also has an inlet **4b** that terminates in a venting inlet chamber **27** of the cartridge. The venting inlet chamber **27** is in fluid communication with a vent pathway **9** that, in some embodiments, terminates at a filter chamber **9a** (shown in FIG. 5A) housing a filter. An alternative sample container **2** can be utilized, such as a syringe, which requires a luer lock connection on the cartridge 100. And, as noted above, in other embodiments, the input section of the cartridge comprises a well to which fluid sample can be placed, for example, by way of a pipette or tube.

Vent Pathway

[0097] FIGS. 5A, 5B, 7, and 8 are schematic illustrations of biological fluid pathways of the example cartridge **100** in accordance to an embodiment. Specifically, FIGS. 5A and 5B each shows the biological fluid pathways of four testing circuits (corresponding to test chambers 16a, 16b, 16c, and 16d, shown in FIG. 5A), also referred to herein as Hemostasis testing circuits, that are located on a sample preparation plane, in accordance with an illustrative embodiment. Though shown with four testing circuits, additional circuits or less may be included, including, e.g., two, three, five, six, seven, eight, and etc. FIG. 5B further shows of the cartridge body of FIG. 5A further coupled to a sample holding tube **2**, in accordance with an illustrative embodiment. FIG. 7 shows the back-side of the cartridge of FIG. 5A and includes an interconnection plane that interfaces to the sample preparation plane, that collectively form the biological fluid pathways for the testing circuits, in accordance with an illustrative embodiment. FIG. 8 shows portions of the biological fluid pathways that are on the interconnection plane of FIG. 7, in accordance with an illustrative embodiment.

[0098] As noted above, the biological fluid pathways are formed on, and across, multiple planes defined in the cartridge **100.** A first plane of fluid pathways of the cartridge **100** is shown in FIGS. 5A and 5B. The first plane of fluid pathways of the cartridge **100** may alternatively be referred to as a front plane of the cartridge **100.** FIGS. 7 and 8 each shows a second plane of fluid pathways of the cartridge **100** in which FIG. 8 shows the fluid pathways in the second plane isolated from the remainder of the structure of the cartridge **100** for ease of understanding. The second plane of fluid pathways of the cartridge **100** may alternatively be referred to as a back plane of the cartridge **100.** The fluid pathways between the first and second planes are connected by fluidic vias that traverse across the various planes of the cartridge **100.**

[0099] As discussed above in relation to FIG. 1, in some embodiments, the venting inlet chamber **27** is in fluid communication with a vent pathway **9.** The vent pathway **9** may terminate at a filter chamber **9a** (shown in FIG. 5A), which may house a filter therein. The filter chamber **9a** in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a vent port **22i** (shown in FIG. 8) in the second plane of fluid pathways of the cartridge **100.** As discussed in more detail below, cartridge **100** couples with the measurement system

(also referred to herein as the instrument) via the vent port **22i** to provide atmospheric pressure to vent pathway **9.**

Heatins Chamber Pathway

[0100] As discussed above in relation to FIG. 1, in some embodiments, the sample transferring needle outlet **3c** terminates in a sample inlet chamber **26** of the cartridge **100.** The sample inlet chamber **26** is in fluid communication with an inlet pathway **8.** The sample inlet pathway **8** provides a fluid communication pathway between the sample inlet chamber **26** and a retaining/heating chamber **6** (also referred to herein as heating chamber **6** or as a "first chamber") (shown in FIG. 5A). The label "first", "second", and "third" as used herein is provided merely as labels and do not intended to connote a sequence. The heating chamber **6** is configured to mate with a corresponding thermal regulating (e.g., heating/cooling) system in the measurement system to warm or cool the sample toward or to, or near, a pre-defined temperature.

[0101] The heating chamber 6, as provided herein, facilitate uniform conditioning of the test fluid prior to the fluid be metered or aliquoted to their respective testing, thus reducing variability in the test sample that can affect subsequent measurements and analysis. The shape of the heating chamber **6** can be optimized for heating/cooling transfer, as in the case here in which a thin cross-section with thin walls is used. The materials of the cartridge **100** can also be optimized to facilitate heating/cooling. In some embodiments, the sample heating/cooling conditioning stage can also be implemented in one or more chamber/channels of the cartridge design and it is not limited to just occur within just the heating chamber **6.** In some embodiments, a stirring, rotating, or oscillating element (not shown) can be placed in the heating chamber **6** that may be controlled by the measurement system to promote uniform temperature heating or cooling. In other embodiments, test fluid in the heating chamber 6 may be vibrated by the measurement system vibrating the cartridge **100** to promote uniform temperature conditioning of the test fluid.

[0102] In some embodiments, temperature measurement is conducted of the test sample in the cartridge **100.** To measure the temperature, a sensor can be incorporated in the measurement system or in the cartridge **100.** In some embodiments, a thermistor or thermocouple can be placed in physical contact with the cartridge **100**, or biological sample (such as blood). In other embodiments, an IR thermometer is pointed at the cartridge **100** or biological sample. In either case the cartridge **100** may incorporate a small well through which the incoming blood passes, rather than having direct contact with the blood. In some embodiments, the temperature of the test sample may be assessed at or near the heating chamber 6. In other embodiments, the temperature of the test sample may be assessed while the test sample is flowing through channels as it is directed toward the test chambers **16.**

[0103] Referring now to FIGS. 5A, 5B, and 8, the sample inlet pathway **8** terminates at a first corner **6a** of the heating chamber **6**, shown as the top left corner of heating chamber **6** in

FIGS. 5A and 5B. In some embodiments, chambers along the fluid pathways are generally filled from the top as to prevent blood to backflow into the inlet. A fill outlet channel **10a** extends from a second corner **6b** of the heating chamber **6** opposite from the first corner **6a.**

[0104] The fill outlet channel **10a** extends to a filter chamber **10** with a filter therein. The filter chamber **10** (e.g., as shown in FIGS. 5A and 5B) in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a heating-chamber fill channel **10b** shown in the second plane of fluid pathways of the cartridge **100** (see FIG. 8). The fill conduit **10b** is in fluid communication with a pressure port **22a** (see also Fig. 8) that facilitate filling of the heating chamber **6.** The conduit 10b is a part of a network of conduits used to consolidate pressure ports (e.g., **22a** as discussed, as well as **22b-22i** to be later discussed) of the cartridge **100** to one or more areas to which the measurement system can coupled with its pressure control interfaces. Such configuration reduces the complexity of the measurement system to control fluid movement within the cartridge **100.** Indeed, the conduits that handles the control of movement of the fluid sample in the first plane of the cartridge **100** is primarily placed in the second plane of the cartridge **100.** FIGS. 6A and 6B show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with additional labels corresponding to the description of this section.

Heating Chamber Fill

[0105] In operation, the instrument's fluid pump aspirates the sample through the input port **3** (see FIGS. 1-2) via the connection ports **22** (see FIG. 7) (also referred to herein as pressure ports) and into the heating chamber **6** (see FIG. 5A or 5B) of the cartridge **100.** For example, the instrument's fluid pump may be in communication with and apply differential pressure (e.g., positive or negative) to a pressure port **22a** (see FIG. 8). This in turn creates an applied pressure along the fill conduit **10b**, within the heating chamber **6**, and along the inlet pathway **8** to aspirate the sample into the heating chamber **6**. At the same time, the inner vent needle **4** is linked to the isolated pathway **9** that receives atmospheric pressure from the instrument via the vent port **22i** (see FIG. 8) to neutralize pressure in the sample container **2** as the sample is aspirated into the heating chamber **6** of the cartridge **100**. During filling of the heating chamber **6**, all other ports (e.g., **22b-22i**) are closed, e.g., by the measurement system.

[0106] When the heating chamber **6** is filled, the filter within filter chamber **10** is clogged and creates a pressure spike that is detected by the instrument, causing the instrument to turn off the fluidic pump. The instrument may also close the vent port **22i** or otherwise discontinue supplying atmospheric pressure via vent port **22i** upon detecting the pressure spike. Alternative filling detection techniques could also be used, i.e., optical sensors placed at the desired fill level, volumetric control, fixed time of pressure alteration (negative and/or positive pressures), ultrasound detectors placed at the desired fill level, etc. The sample remains in the heating chamber until the desired temperature is reached, which can for example be at or near body temperature of a normal and typical subject (e.g., about 37°C for a healthy person). In other instances, other desired temperatures may be warranted. The shape of the heating

chamber **6** and the channels leading to the sample metering chambers **11** (described below) are configured so that bubbles that might be present in the fluid sample are trapped away from the rest of the fluidic circuit. The shape of the inlet pathway **8** includes an anti-siphon feature **8a** (see FIG. 5A and 5B) and is configured to reduce the occurrence of bubbles forming in the heating chamber 6 and prevent siphoning to and from the sample container **2.** To this end, additional unprocessed test sample (e.g., un-warmed blood) is prevented from being siphoned into the heating chamber following the first drawn test sample being heated and/or cooled, e.g., when the processed test sample is pulled into the metering chamber **11** (also referred to herein as sample chamber **11** and "second" chamber). FIGS. 6A and 6B also show labels corresponding to the description of this section.

Sample Aliquot (Metering) Chambers Pathway

[0107] Referring to FIG. 5A, 5B, and 8, a first side **6c** of the heating chamber **6** (see FIG. 5A) extends between the first corner **6a** and the second corner **6b.**

[0108] One or more of outlet ports **6e-6h** (see FIG. 5A) are arranged along the length of the second side **6d** of the heating chamber. Each of the one or more outlet ports **6e-6h** may be arranged in a different one of the valleys along the second side **6d** of the heating chamber in which the valleys direct the sample into conduits leading to each respective test channel. A test channel, in some embodiments, refers to the associated fluidic pathway structures and testing chamber, collectively, used to perform a measurement for a given aliquot sample. In some embodiments, and as shown in FIG. 5B, each of the one or more outlet ports **6e-6h** in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a first end of a corresponding one or more channels **20a-20d** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100**, collectively referred to as channels **20** (see Fig. 5B). A second end of each of the one or more channels **20a-20d** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100** is likewise in fluid communication with a first end of a corresponding one or more channels **11a-11d** (see FIG. 5B) in in the first plane of fluid pathways of the cartridge **100.** A second end of each of the one or more channels **11a-11d** terminates in a corresponding one or more sample chambers **11** (shown in duplicates ("x4") in FIG. 5B with an "o" symbol therein). In the example shown in FIGS. 5A, 5B, 7, and 8, there are four sample chambers **11.** More or fewer sample chambers **11** and corresponding fluid communication pathways with the heating chamber **6** may be present on the cartridge **100** in some configurations.

[0109] The sample chambers **11** are fed by the one or more channels **20** originating from the bottom of the heating chamber **6.** This geometric configuration avoids bubbles being drawn into the sample chambers **11** as the bubbles rise to the upper portion of the heating chamber **6.**

[0110] Each of the sample chambers **11** has a corresponding fill channel **11e** that is in fluid communication with a corresponding filter chamber **12** (shown in duplicates ("x4") in FIG. 5B

with a "+" symbol) with a filter therein. The filter chamber **12** in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a channel **12a** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100.** The channel **12a** is in fluid communication with a pressure port **22g** (see FIG. 8).

[0111] In some configurations, when more than one sample chamber **11** are implemented on the cartridge **100**, the channel **12a** (see FIG. 8) is in fluid communication with all of the sample chambers **11** (see Fig. 5B) via corresponding fill channels **11e** and filter chambers **12.** Accordingly, channel **12a** acts as a manifold for applying negative pressure to all of the sample chambers **11** via a single pressure port **22g.** Therefore, a separate pressure port is beneficially not needed for filling each of the sample chambers **11.** FIGS. 6C and 6D show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with additional labels corresponding to the description of this section.

Heatins Chamber Vent Pathway

[0112] Referring to FIG. 5A, 5B, and 8, the heating chamber **6** comprises a vent pathway **31a, 31b, 31c** along the first side **6c** of the heating chamber for venting the heating chamber **6** as the sample chambers **11** are filled. The vent pathway **31** (not shown) includes the fluid pathway through conduit elements **31a-31d.** Channels **31a-31b** terminate at one end in the heating chamber **6** along the first side **6c** and terminate at the other end at a filter chamber **31c** with a filter therein. Accordingly, channels **31a-b** provide a fluid pathway between the heating chamber **6** and the filter chamber **31c.** The filter chamber **31c** (see FIG. 5A) in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a channel **31d** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100**, which in turn is in fluid communication with a vent port **22c** (see FIG. 8). As discussed in more detail below, cartridge **100** couples with the instrument via the vent port **22c** for the instrument to provide atmospheric pressure to vent the heating chamber **6.** FIGS. 6C and 6D also show labels corresponding to the description of this section.

***Sample* Chamber Vent Pathway**

[0113] Referring to FIGS. 5A, 5B, and 8 each of the sample chambers **11** includes a vent pathway **18** that terminates at a first end in a corresponding sample chamber **11.** A second end of the vent pathway **18** in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a vent manifold **18** in the second plan of fluid pathways of the cartridge **100.** When more than one sample chamber **11** is present, all of the vent pathways **18** (see FIG. 5B) of the sample chambers are in fluid communication with the vent manifold **18a** (see FIG. 8). The vent manifold **18a** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100** is further in fluid communication with a first end of a channel **18b** (see FIG. 5B) in the first plane of fluid pathways. A second end of channel **18b** (see FIG. 5B) is in fluid

communication with a filter chamber **18c** (see FIG. 5B) with a filter therein. Filter chamber **18c** (see FIG. 5B) in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a vent port **22e** (see FIG. 8). FIGS. 6C and 6D also show labels corresponding to the description of this section.

Sample Aliquot (Metering) Chambers Fill

[0114] During operation, once the sample is at, or near, the desired temperature, the sample is aliquoted (or metered) into one or more independent sample chambers **11** (see FIG. 5B). Referring to FIGS. 5B unless indicated otherwise, in various embodiments, the sample chambers are filled by applying a negative pressure at pressure port **22g** (see FIG. 8) via a pump in the instrument while venting the heating chamber **6** by way of the vent port **22c** (see FIG. 8). Each filter chamber **12** has a filter therein that will clog when the corresponding sample chamber **11** is filled and will trigger the pressure sensor of the instrument to turn the pump off, similar to filling the heating chamber **6.** As discussed above, alternative filling detection techniques could be used. In various embodiments, all the sample chambers **11** are controlled by a single valve and fluidic pathway in the instrument via pressure port **22g** (see FIG. 8). The cutoff pressure will not trigger until all sample chambers' filters clog in the corresponding filter chambers **12.** The sample chambers **11** are used to separate samples into independent functional channels, aliquot a known volume of sample, and stage the sample for mixing with reagents. While the sample chambers **11** are filled, pressure ports **22b, 22d, 22f, and 22h** (see FIG. 8) as well as vent port **22e** (see FIG. 8) are closed by the instrument so as to prevent fluid from leaking past the location **19**, arranged below the sample chambers **11.** Once the sample chambers **11** have been filled, the vent port **22e** (see FIG. 8) is opened to atmospheric pressure so that the one or more sample chambers **11** can be fluidically separated from each other and the heating chamber **6.** Vent port **22e** (see FIG. 8) remains open to atmosphere during sample mixing as discussed below. FIGS. 6C and 6D also show labels corresponding to the description of this section.

***Mixing* and Testing Pathway**

[0115] Referring to FIGS. 5B unless indicated otherwise, each of the sample chambers **11** is in fluid communication with a corresponding one or more reagent pocket **14** (see FIG. 5A) configured to house at least one lyophilized bead comprising a reagent. As shown in FIGS. 5A and 5B, two reagent pockets **14** (shown as 14a and 14b in FIG. 5A for one of the test channels) are provided. In other embodiments, a single reagent pocket is used for each testing channel. In yet other embodiments, more than two reagent pockets **14** are used for each testing channel. The reagent pockets **14** are in turn in fluid communication with a serpentine channel **13** (see FIG 5A, and shown with a duplication symbol ("x4"). Each of the serpentine channel **13** has a first end in fluid communication with the reagent pockets and a second end that terminates at an optical detection zone **15.** As discussed below, the instrument (i.e.,

measurement system) may optically interrogate the optical detection zone **15** of the cartridge **100** to facilitate the control of a pump that facilitates mixing of the individual aliquots with the corresponding reagent(s). Each of the serpentine channel **13** (see FIG. 5A) is in fluid communication with a test chamber **16** (see FIG. 5B, with duplication symbol "x4") which in turn is in fluid communication with a filter chamber **17**, with a filter therein. The filter chamber **17** in the first plane of fluid pathways of the cartridge **100** is in fluid communication with a first end of a corresponding one of fluid channels **17a-17d** (see FIG. 8) in the second plane of fluid pathways of the cartridge **100.** A second end of each of the fluid communication channels **17a-17d** (see FIG. 8) are in fluid communication with a corresponding pressure port **22b, 22d, 22f, and 22h** (see FIG. 8). The cartridge **100** couples with instrument via the pressure ports **22b, 22d, 22f, and 22h** (see FIG. 8) to supply positive and negative pressure to facilitate mixing and testing of the sample as described below. FIGS. 6E and 6F also show a front perspective view and a back perspective view of FIGS. 5A, 5B, and 8 with additional labels corresponding to the description of this section.

Sample Mixing

[0116] Referring to FIG. 5B unless indicated otherwise, each individual aliquot in the sample chambers **11** is pulled into a separate reservoir or channel (a serpentine channel pathway **13** (see FIG. 5A) in various embodiments) and brought into contact with the channel specific reagent, located in one (or both) of the two reagent pockets **14** (see FIG. 5A). Specifically, a pump in the instrument applies negative pressure to pressure ports **22b, 22d, 22f,** and **22h** (see FIG. 8) to draw the sample through the reagent pockets **14** (see FIG. 5A) and serpentine channel pathway **13** (see FIG. 5A). The reagents and sample are kept separate from each other during sample chamber **11** filling so as to avoid reagents floating on the blood and getting trapped in the filter in filter chambers **12**, as well as to ensure fluidic isolation of the one or more sample chamber **11** from the heating chamber **6.** To this end, precise time of when the test sample is in contact with the reagents can be measured thereby facilitating accurate and precise clot time measurements (e.g., from when mixing begins). In addition, the reagents and test samples are kept separated from one another, in some embodiments, until all channels are metered to prevent undesired siphoning of test samples from other channels or from the unprocessed sample in the fluidic pathways. The sample is aspirated through the serpentine channel **13** (see FIG. 5A) until it triggers an optical sensor in the instrument (detection zone is top of serpentine channel near the optical detection zone **15** (see FIG. 5A)) which closes off the channel from the pump. Mixing in the serpentine channels or zones, or region, therein can be controlled by one or more independent valves and pathways that allow individual channel control. Alternative sensor techniques could be utilized: pressure, pass through optical sensors, ultrasound detection, time, volumetric control, etc. Once all the channels' optical sensors trigger, the pump reverses and applies positive pressure to pressure ports **22b, 22d, 22f,** and **22h** (see FIG. 8). The positive pressure pushes the biological sample, such as blood, down the serpentine path **13** (see FIG. 5A) for a designated time, or until a second set of optical sensors in the instrument is tripped (in an alternative embodiment). This process, to pull the sample up the serpentine path **13** (see FIG. 5A) to the optical detection zone where it is

detected by an optical sensor of the instrument and push back for a given time, repeats until full sample mixing is achieved. FIGS. 6E and 6F also show labels corresponding to the description of this section.

[0117] Other sensors (e.g., impedance sensors), pressure sensor, and etc., may be used. Alternatively, additional sensors may be used to detect both ends of the optical detection zone. Alternate pathway geometries, obstructions to create turbulence, cycle numbers, and cycle speed are all design alternatives that can be used with varying test types to achieve optimal results. In alternative embodiments, mixing could be achieved with one or more ferromagnetic beads or bars placed within the cartridge and controlled by the instrument.

Test Chamber Filling

[0118] Referring to FIGS. 5A, 5B, and 8, one or more testing chambers **16** are filled after mixing is completed. Using one or more independent valves and pathways, each testing chamber **16** is filled with a sample via the application of pressure perturbations (negative and/or positive pressure) at pressure ports **22b, 22d, 22f**, and **22h**. Specifically, the instrument pump will apply negative pressure to pressure ports **22b, 22d, 22f,** and **22h** until all of the filters are clogged in the one or more filter chambers and cause a pressure spike to cause the instrument to turn the pump off, similar to filling the heating chamber **6.** As discussed above, alternative filling detection techniques could be used. The testing chambers **16** have design features such as the ridges **24a** which prevent the formation of bubbles in the testing chambers **16** during filling. Once filled, the instrument begins viscoelastic testing of the sample. FIGS. 6E and 6F also show labels corresponding to the description of this section.

[0119] In some embodiments, the cartridge apparatus includes, at least, four independent fluidic circuits configured with different sets of reagents for measurements (and/or sample preparation) to be performed in parallel. The measurements are performed per channel of the, at least, four channels of the cartridge. The measurement, in some embodiments, include viscoelastic properties such as a sample shear modulus. The measurement, in another embodiment, includes other properties such as viscosity, elastic modulus, or any other mechanical property of the sample, or combinations thereof.

[0120] Table 1 provides an example set of reagents and measurement parameters for use in an example cartridge apparatus (e.g., apparatus **100**, among others). As shown in Table 1, Channel #1 in the example cartridge apparatus is interrogated to measure clot time of the test sample in the presence of kaolin, which is an activator of the intrinsic pathway of coagulation. As shown in Table 1, Channel #2 is interrogated to measure clot time of the test sample in the presence of kaolin and in further presence of heparinase I, which is a neutralizer of the anticoagulant heparin. As shown in Table 1, Channel #3 is interrogated to measure overall clot stiffness of the test sample in the presence of i) thromboplastin, which is an activator of the extrinsic pathway of coagulation, and ii) polybrene, which is a neutralizer of the anticoagulant heparin. As shown in Table 1, Channel #4 is interrogated to measure clot stiffness of the test

sample with the same reagents as channel #3, but with the addition of abciximab (e.g., Clotinab® and/or ReoPro®), which is an inhibitor of platelet aggregation/contraction. As shown in Table 1, when the assay is configured to operate with citrated whole blood samples, calcium is added to all the reagent formulations.

Table 1. Reagents utilized in a preferred embodiment

Channel #	Reagents	Measurement(units)
1	Kaolin, calcium, buffers and stabilizers	Clot time (Seconds)
2	Kaolin, heparinase I, calcium, buffers and stabilizers	Clot time (Seconds)
3	Thromboplastin, polybrene, calcium, buffers and stabilizers	Clot stiffness (hecto Pascals)
4	Thromboplastin, polybrene, abciximab (and/or cytochalasin D), calcium, buffers and stabilizers	Clot stiffness (hecto Pascals)

[0121] Table 2 provides an additional example set of reagents and measurements for use in an example cartridge apparatus (e.g., apparatus **100**, among others). As shown in Table 2, channel #2 includes an extrinsic pathway activator with inhibition of fibrinolysis by tranexamic acid (TXA). In addition to the measurements previously presented in Table 1, channels #2, channel #3, and channel #4 are interrogated to also measure clot stiffness changes, which, for example, can be related to the fibrinolytic process. In some embodiments, other channels can include reagents that inhibit fibrinolysis and can also be interrogated to measure clot stiffness changes. For example, channel #4 could also include TXA or other fibrinolysis inhibitor in order to measure clot stiffness in the absence of fibrinolysis.

Table 2. Reagents utilized in a preferred embodiment

Channel #	Reagents	Measurement (units)
1	Kaolin, calcium, buffers and stabilizers	Clot time (Seconds)
2	Thromboplastin, polybrene, calcium, tranexamic acid, buffers and stabilizers	Clot stiffness (hectoPascals) and Clot stiffness change
3	Thromboplastin, polybrene, calcium, buffers and stabilizers	Clot stiffness (hecto Pascals) and clot stiffness change
4	Thromboplastin, polybrene, abciximab (and/or cytochalasin D), calcium, buffers and stabilizers	Clot stiffness (hecto Pascals) and clot stiffness change

[0122] In some embodiments, clot time and clot stiffness are measured by analyzing a shear modulus (clot stiffness) versus time curve that is generated within each measurement channel in the cartridge. Fig. 13 shows an example shear module versus time curve, in accordance with an illustrative embodiment. Clot time may be determined by identifying when the clot

stiffness meets or exceeds a threshold value, or when the first or higher derivative of such property being measured meets or exceeds a threshold value, or at the point of maximum acceleration in the rate of clot stiffness, or some combination of the above methods. Clot stiffness may be estimated by the clot stiffness at a fixed time after clot time, or the maximum overall clot stiffness measured within some time limit, or the clot stiffness at the point of maximum rate of change in clot stiffness, or some combination of the above methods. Similar methods can also be applied to measure the effects of fibrinolysis (i.e., clot dissolution) and the corresponding reduction in clot stiffness. In some embodiments, clot stiffness changes can be calculated as percentage drop in clot stiffness over a fixed time window, as a rate of change of clot stiffness over time, as area under or over the clot stiffness vs time curve within a predefined time window, as the time required to achieve a predefined drop in clot stiffness, or combinations thereof. Similar curves and similar measurements to those just described can be formed by plotting the Young's modulus, viscosity, or other viscoelastic property of the sample being measured.

Table 3. Parameters reported from measurement of the preferred embodiments discussed in relation to Table 1.

Hemostatic Index	**Units**	**Description**	**Measurement**
Clot Time	Minutes (min)	Clot time in citrated whole blood	Clot time measured from channel # 1 with kaolin activation (intrinsic pathway)
Heparinase Clot Time	Minutes (min)	Clot time in citrated whole blood with heparin neutralization	Clot time measured from channel #2 with kaolin activation and heparinase I
Clot Stiffness	hecto Pascals (hPa)	Stiffness of the whole blood clot	Clot stiffness measured from channel #3 with thromboplastin activation (extrinsic pathway) and polybrene
Fibrinogen Contribution	hecto Pascals (hPa)	Contribution of functional fibrinogen to clot stiffness	Clot stiffness measured from channel#4 with thromboplastin activation, polybrene, and abciximab
Clot Time Ratio	Unit less	Assessment of residual heparin anticoagulation	Calculated ratio of clot time values from channels #1 and #2
Platelet Contribution	hecto Pascals (hPa)	Contribution of platelet activity to clot stiffness	Calculated from subtraction of the clot stiffness values from channels #3 and #4

[0123] A person of ordinary skills in the art should recognize that clot time and clot stiffness can be estimated using a number of methodologies and criteria. Clot times and clot stiffness values obtained from the, at least, four channels / measurements may be combined to provide, at least, six parameters can depict a functional status of the patient's hemostatic system. The

indexes are summarized in Table 3. Relationship between results (clot time, clot stiffness, clot stiffness change, etc.) from different channels may be verified to be within expected ranges as additional quality control checks to verify instrument, cartridge, and sample function.

[0124] In other embodiments, other reagents can be used and other hemostatic indexes or output parameters can be obtained such as in the case of a fibrinolytic index, indexes corresponding to the functionality of anti-platelet treatments, indexes corresponding to the functionality of anti-coagulation treatments, etc.

[0125] For example, one or more fibrinolysis indexes could be formed using the clot stiffness changes measured in any of the channels presented in Table 2, but preferably channels #3 and #4. Alternatively, a fibrinolysis index could be formed by differential combination of the clot stiffness changes measured in channels #2 and channel #3 presented in Table 2. Such combination could be in the form of a ratio, a difference, or combinations thereof. One of the benefit of using a combination of clot stiffness changes measured with and without an anti-fibrinoltyic reagent is the ability to mitigate the interfering effects of non-fibrinolysis driven reductions in clot stiffness values. In some embodiments, TXA or other fibrinolysis inhibitor reagent can be included in both channel #2 and channel #4 of the example cartridge of Table 2. With such modifications the parameters Clot Stiffness, Platelet Contribution, and Fibrinogen Contribution could be derived without the influence of fibrinolysis by combination of the clot stiffness measurements obtained in channel #2 and channel #4.

[0126] As discussed above, an example user interface is described in commonly assigned U.S. Pub. No. 2011/0252352 to Viola et al., which is incorporated by reference herein in its entirety. The example user interface may be used to display the measured hemostatic indexes as discussed in relation to Table 4, among other parameters.

Table 4. Parameters reported from measurement of the preferred embodiments discussed in relation to Table 2.

Hemostatic Index	**Units**	**Description**	**Measurement**
Clot Time	Minutes (min)	Clot time in citrated whole blood	Clot time measured from channel # 1 with kaolin activation (intrinsic pathway)
Clot Stiffness	hecto Pascals (hPa)	Stiffness of the whole blood clot	Clot stiffness measured from channel #3 with thromboplastin activation (extrinsic pathway) and polybrene
Fibrinogen Contribution	hecto Pascals (hPa)	Contribution of functional fibrinogen to clot stiffness	Clot stiffness measured from channel #4 with thromboplastin activation, polybrene, and abciximab
Platelet Contribution	hecto Pascals	Contribution of platelet activity to clot stiffness	Calculated from subtraction of the clot stiffness values from

Hemostatic Index	Units	Description	Measurement
	(hPa)		channels #3 and #4
Clot Stiffness Change	% or hPa/sec or sec	Clot stiffness change over time	Changes (% or rate of change) in clot stiffness measured from channels #2 and #3
Clot Reduction Differential	% or hPa/sec, or no units	Differential rate of clot stiffness changes with and without anti-fibrinolytic	Differential comparison of clot stiffness change measured in channels #2 and #3.

[0127] As noted before, in various embodiments, the testing chambers 16 are shaped to facilitate ultrasound testing of viscoelastic properties of the sample, but alternative geometries can also be implemented to facilitate other types of testing. Such an ultrasound testing system is described in commonly assigned U.S. Patent No. 9,726,647 and U.S. Pub. No. 2016/0139159, both of which are hereby incorporated by reference in their entirety. Ultrasound transducers in the measuring system connect with the testing chambers **16** of the cartridge **100** via compliant and deformable elastomers **21** which are affixed to a testing block **21d** on the cartridge **100.**

[0128] Example elastomeric materials optionally include, Dynaflex D3202, Versaflex OM 9-802CL, Maxelast 54740, RTP 6035, Versaflex CL2003X, among others. Referring now to FIG. 9 unless indicated otherwise, the testing block **21d** is aligned with the testing chambers **16** (see FIG. 5B) via alignment slots **23** and **24** on the cartridge **100.** Referring still to FIG. 9, the elastomers **21** may be affixed to the testing block **21d** via a flange **21a** on the elastomers **21.** The flange **21a** may have a plurality of alignment holes **21b** that may receive corresponding alignment pegs (not shown) from the testing block **21d.** The soft elastomers **21** may also each include a lens **21c** that focuses ultrasound energy within the sample at the testing chambers **16.**

[0129] FIG. 16 shows a photograph of an exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9 for use in a disposable system, in accordance with an illustrative embodiment. Fig. 17 shows a front view of the exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9, in accordance with an illustrative embodiment. Fig. 18 shows a front view of the exemplary cartridge of FIGS. 1, 2, 3, 4, 5A, 5B, 7, 8, and 9, in accordance with an illustrative embodiments.

[0130] As described in U.S. Patent No. 9,272,280, which is incorporated by reference herein in its entirety, in various embodiments, the consumable cartridge contains a lens assembly that focuses ultrasound energy within the sample that can be used to generate streaming and mixing. The lens assembly, or sound focusing assembly, is designed using a soft material, such as a thermoplastic elastomer **134** (previously referred to as 21), in conjunction with a rigid

substrate **132** (e.g., formed of testing block 21d), such as polystyrene as shown in FIGS. 10, 11, and 12. This combination provides a dry ultrasound coupling that does not require the use of any fluid or gel couplant. Note that the same lens and ultrasound driver used for hemostasis measurement can be used in this matter to provide mixing. Increasing acoustic energy for mixing can be delivered by, for example, increasing pulse length, pulse amplitude or pulse repetition frequency.

[0131] Referring now to FIG. 10, a top cross-sectional view of the testing chamber **116** (referred to previously as testing chamber 16) is shown. To seal each test chamber, e.g. test chamber **116**, a lens assembly **131** includes a rigid substrate **132** and a couplant **134** that can be positioned at the back end of each test chamber.

[0132] Referring still to Fig. 10, each couplant **134** comprises an elastomeric material. Optionally, the elastomeric material is a thermoplastic elastomer (TPE). Example elastomeric materials optionally include, Dynaflex D3202, Versaflex OM 9-802CL, Maxelast 54740, RTP 6035, Versaflex CL2003X, among others. Optionally the couplant is over-molded to the rigid substrate. Optionally the couplant is mechanically anchored to the rigid substrate.

[0133] Referring still to Fig. 10, between each couplant **134** and the open space of each test chamber is a rigid substrate **132.** The rigid substrate and the couplant form an interface that focuses ultrasound transmitted (e.g. lens assembly) by an ultrasonic transducer into the chamber's open space and onto any biological fluid and/or reagents in the chamber. The rigid substrate of the lens can comprise a material which allows sound to pass and that can act to focus ultrasound at some level within the space. Optionally, the rigid substrate comprises a styrene.

[0134] Referring now to Fig. 11, The lens assembly may be glued or welded to the surface **101** of the testing block **21d** (shown in FIG. 11 as element 132) to secure the lens in place in an orientation that allows the desired focusing of sound. Alternatively, the lens assembly is optionally manufactured together with the surface **101** of the testing block **21d.** In this regard, the rigid substrate **132** can be molded with the surface **101** of the testing block **21d** and the couplant **134** can be overmolded or mechanically anchored on the rigid substrate. A wide variety of materials can be used to construct the device. For example, plastics can be used for single use, disposable cartridges.

[0135] Referring still to FIG. 11, each of the test chambers **116** can have a lens assembly positioned over the large opening of each chamber's open space. In this way, each chamber can be separately interrogated by focused ultrasound.

[0136] Referring still to FIG. 11, when placed in the instrument, the couplant **134** can be placed in acoustic communication with a transducer for supplying ultrasound through the lens assembly and into a test chamber **116.** Optionally, an intermediate layer of an acoustically permeable material is positioned between an ultrasonic transducer and the couplant. For example, and intermediate layer or block of Rexolite® or TPX® can be used. The intermediate

layer can be forced against the couplant and can be in acoustic contact with the transducer.

[0137] Referring still to FIG. 11, sound generated by a transducer passes through the intermediate layer, through the couplant, through the rigid substrate, and is focused within the biological sample, such as blood, and reagent in the test chamber. Some of the sound directed into chamber contacts the distal interior surface **111** of the test chamber, which is defined by the surface **126.** Optionally, the surface is polystyrene. The distal interior surface has a known geometry and is positioned at a known distance from the ultrasound source. The distal interior surface **111** is used as a calibrated reflector, which is used to estimate the speed of sound and attenuation of sound in a test chamber at base line and during the process of clot formation and clot dissolution. These measurements can be used, for example, to estimate hematocrit of the subject along with the indexes of hemostasis. The sound generated by the transducer can be focused within the biological sample in a test chamber using a parabolic mirror that is coupled to the biological sample using an elastomer.

[0138] Other example cartridge apparatus and measurement system, and methods thereof, are described in U.S. Patent No. 9,031,701; U.S. Provisional Appl. No. 61/443,084; U.S. Patent No. 9,410,971; U.S. Provisional Appl. No. 61/443,088; U.S. Publication No. 2011/0252352; published PCT Publication No. WO2011/127436; U.S. Publication No. 2012/0294767; U.S. Patent No. 7,892,188; U.S. Patent No. 8,740,818; and U.S. Publication 2016/0274067.

[0139] As noted, the cartridge and features described herein can be modified for use with other types of measurement systems such as thromboelastography-based systems, thromboelastometry-based systems, optical-based systems, fluorescence-based systems, colorimetric-based systems, aggregometry-based systems, resonance-based system, and an electrical impedance-based system, among others.

[0140] Many modifications and other embodiments of the invention set forth herein will come to mind to one skilled in the art to which this invention pertains having the benefit of the teachings presented in the foregoing description. Therefore, it is to be understood that the invention is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.
Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

[0141] As used in the claims, the term "first", "second", and "third" are provided merely as labels and do not intended to connote a sequence.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US62488045 [0002]
- US9272280B [0007] [0130]
- US20110252352A [0083] [0126] [0138]
- US9726647B [0127]
- US20160139159A [0127]
- US9031701B [0138]
- US61443084 [0138]
- US9410971B [0138]
- US61443088 [0138]
- WO2011127436A [0138]
- US20120294767A [0138]
- US7892188B [0138]
- US8740818B [0138]
- US20160274067A [0138]

PATENTKRAV

1. Anordning, der omfatter:

et hus;

en indgangsåbning (3), der er dannet integreret med huset, og som og strukturelt er konfigureret til at modtage indhold af et prøveopbevaringsrør (2); og

et første kammer (6) i fluidforbindelse med indgangsåbningen, hvilket første kammer er et varmekammer konfigureret til at modtage en prøve indeholdt i prøveopbevaringsrøret og til at tilbageholde og konditionere den modtagne prøve til, eller nær, en ønsket temperatur, før den modtagne prøve får lov til at komme i kontakt med ét eller flere reagenser, der befinder sig i ét eller flere fluidkredsløb nedstrøms for det første kammer,

hvor hvert af det ene eller flere fluidkredsløb omfatter i) et andet kammer (11) i fluidforbindelse med det første kammer, der afmåler prøven i det første kammer i en alikvot, hvor den afmålte prøve introduceres for et reagens eller en kombination af reagenser, der befinder sig i et tilsvarende fluidkredsløb for at danne en blandet prøve, og ii) et testkammer (16) i fluidforbindelse med det andet kammer, hvor testkammeret er strukturelt konfigureret til forespørgsel fra et målesystem konfigureret til at bestemme mindst én viskoelastisk egenskab ved den blandede prøve.

2. Anordning ifølge krav 1, hvor mindst ét af det ene eller flere fluidkredsløb omfatter én eller flere lommer (14) konfigureret til at rumme mindst én frysetørret kugle omfattende reagenset, eller kombinationen af reagenser, eller hvor mindst ét af det ene eller flere fluidkredsløb omfatter én eller flere lommer indeholdende væske til at rumme reagenset eller kombinationen af reagenser.

3. Anordning ifølge krav 1 eller 2, hvor indgangsåbningen er forbindelsesmæssigt koblet til en første trykåbning (22), hvor tryk, når det påføres den første trykåbning, bevirker udledning af indhold fra prøveopbevaringsrøret gennem indgangsåbningen til det første kammer.

4. Anordning ifølge et hvilket som helst af krav 1-3, hvor indgangsåbningen danner en del af en nåle- (4) enhed strukturelt konfigureret til at etablere fluidforbindelse og udlede prøveopbevaringsrørets indhold.

5. Anordning ifølge krav 4, hvor nåleenheden omfatter indgangsåbningen og en anden åbning, hvor den anden åbning er konfigureret til at indføre en væske eller gas ind i prøveopbevaringsrøret for således at fremme udledning af indhold deri.

6. Anordning ifølge et hvilket som helst af krav 1-5, hvor det første kammer er konfigureret til at passe sammen med en tilsvarende termisk regulerende flade af en undersystemskomponent af målesystemet for at konditionere den modtagne prøve til, eller nær, den ønskede temperatur.

7. Anordning ifølge et hvilket som helst af krav 1-6, hvor en kanaldel af det ene eller flere fluidkredsløb er konfigureret til at passe sammen med et tilsvarende termisk reguleringssystem i målesystemet for at konditionere den modtagne prøve til den ønskede temperatur, og hvor det første kammer og/eller kanaldelen af det ene eller flere fluidkredsløb er i fysisk nærhed af en sensor i målesystemet, der er konfigureret til at måle en temperatur på prøven modtaget i det første kammer.

8. Anordning ifølge et hvilket som helst af krav 1-7, hvor hvert af det ene eller flere fluidkredsløb omfatter et tredje sæt af fluidbaner (13) i fluidforbindelse mellem et tilsvarende andet kammer og testkammer, hvor en del af tredje sæt af fluidbaner er indrettet som et slangeformet rør, hvor hvert af anden kamre er forbundet med en anden trykåbning (22), hvor tryk, når det påføres den anden trykåbning, bevirker fyldning af det andet kammer, og hvor hvert af anden kamre er forbundet med en ventilationsåbning (22), hvor ventilationsåbningen er konfigureret til at være lukket, mens prøven afmåles i alikvoten i det andet kammer, og endvidere konfigureret til at åbnes for atmosfærisk tryk, efter at prøven er afmålt i alikvoten i det andet kammer.

9. Anordning ifølge et hvilket som helst af krav 1-8, hvor det slangeformet rør danner et slangeformet reservoir mellem testkammeret og det andet kammer, og hvor en afmålt prøve dirigeres gennem dele af det slangeformede rør for at fremme blanding af den afmålte prøve og reagenset eller kombinationen af reagenser.

10. Anordning ifølge krav 9, hvor hvert af testkamrene er forbundet med en tredje trykåbning (22), hvor påføring af tryk på den tredje trykåbning bevirker, at testprøven strømmer mod testkammeret gennem et tilsvarende slangeformet kanal, og hvor påføring af tryk på den tredje

trykåbning i en omvendt retning bevirker, at testprøven strømmer væk fra testkammeret gennem den tilsvarende slangeformede kanal.

11. Anordning ifølge et hvilket som helst af krav 1-10, hvor mindst ét af det ene eller flere fluidkredsløb omfatter én eller flere kvalitetstestportaler, hvor den ene eller flere kvalitetstestportaler er konfigureret til at blive detekteret optisk eller elektrisk.

12. Anordning ifølge et hvilket som helst af krav 1-11, hvor testkammeret omfatter en linse konfigureret til at dirigere ultralydsimpulser genereret af målesystemet ind i testkammeret.

13. Anordning ifølge et hvilket som helst af krav 1-12, hvor mindst ét af reagenserne, eller kombinationen af reagenser, der befinder sig i det ene eller flere fluidkredsløb, vælges fra gruppen bestående af en intrinsisk baneaktivator, en extrinsisk baneaktivator og en koaguleringsaktivator, eller

hvor mindst ét af reagenserne, eller kombinationen af reagenser, der befinder sig i det ene eller flere fluidkredsløb, vælges fra gruppen bestående af en blodpladeaktivator, en blodpladehæmmer, en fibrinolytisk funktionshæmmer, eller

hvor mindst ét af reagenserne, eller kombinationen af reagenser, der befinder sig i det ene eller flere fluidkredsløb, vælges fra gruppen bestående af en FXIIIa-hæmmer, thrombomodulin, polybren, heparin, majs-trypsinhæmmer, adenosin, GPRP (Gly-Pro-Arg-Pro), calcium, fibronectin, collagen, et immuno-detekteringsreagsen og heparinase I eller en kombination deraf.

14. Anordning ifølge et hvilket som helst af krav 1-13, hvor målesystemet vælges fra gruppen bestående af et sonorheometribaseret system, thromboelastografibaseret system, et thromboelastometribaseret system, et optisk baseret system, et fluorescensbaseret system, et kolorimetrisk baseret system, et aggregometribaseret system, et resonansbaseret system og et elektrisk impedansbaseret system.

15. Anordning ifølge et hvilket som helst af krav 1-14 omfattende:

mindst fire testkanaler, hvor en første testkanal omfatter en intrinsisk baneaktivator, hvor en anden testkanal omfatter en extrinsisk baneaktivator og en fibrinolytisk funktionshæmmer, hvor en tredje testkanal omfatter en extrinsisk baneaktivator, og hvor en fjerde testkanal omfatter den extrinsisk baneaktivator og en blodpladehæmmer, og hvor den anden kanal, tredje kanal og

den fjerde kanal hver indbefatter hexadimethrinbromid (polybren) eller en fibrinolytisk funktionshæmmer.

DRAWINGS

Drawing

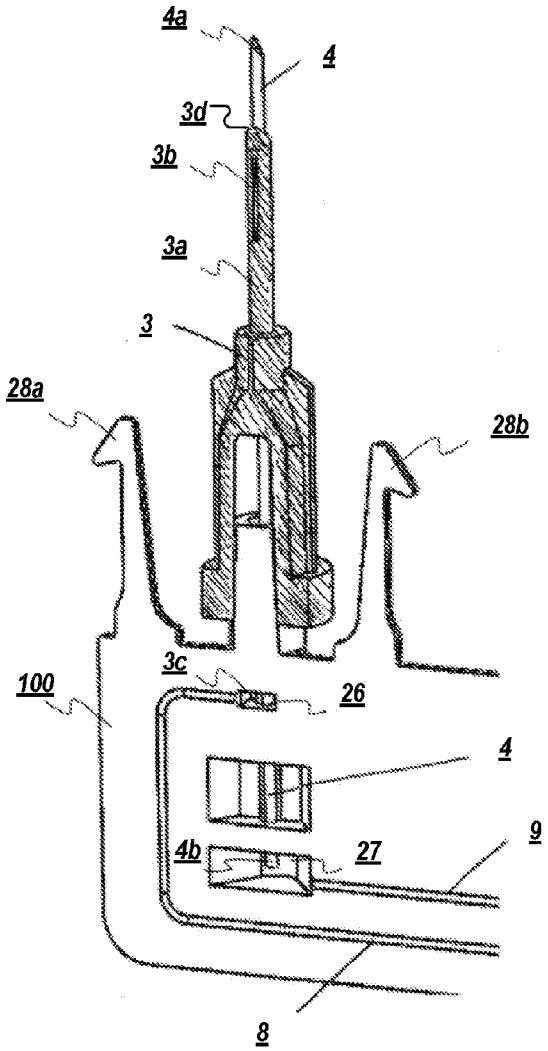

FIG. 1

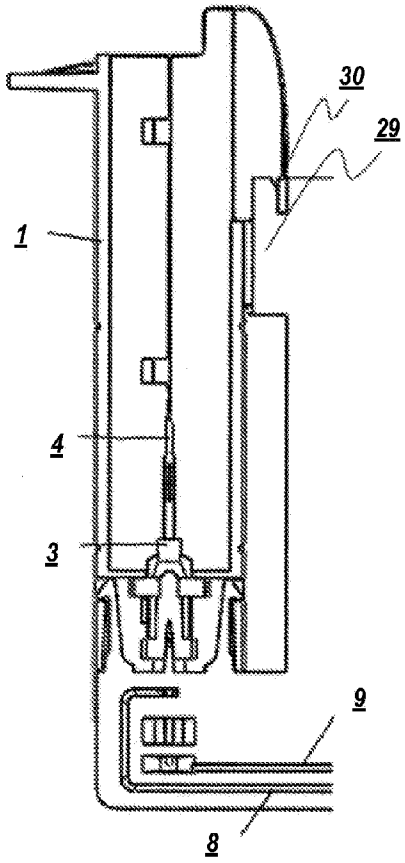

FIG. 2

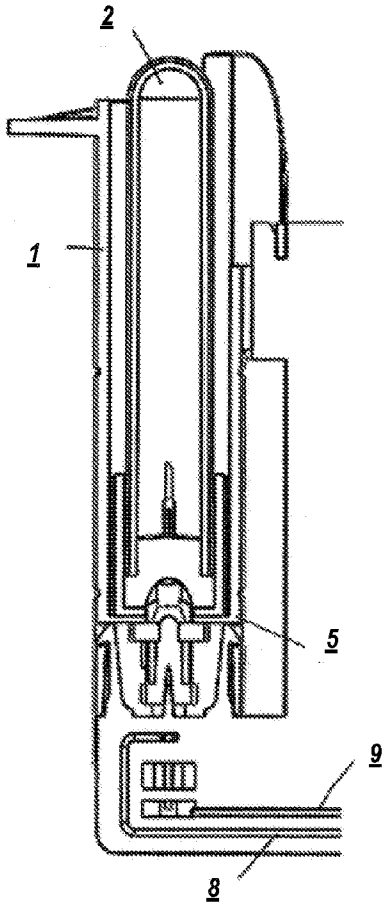

FIG. 3

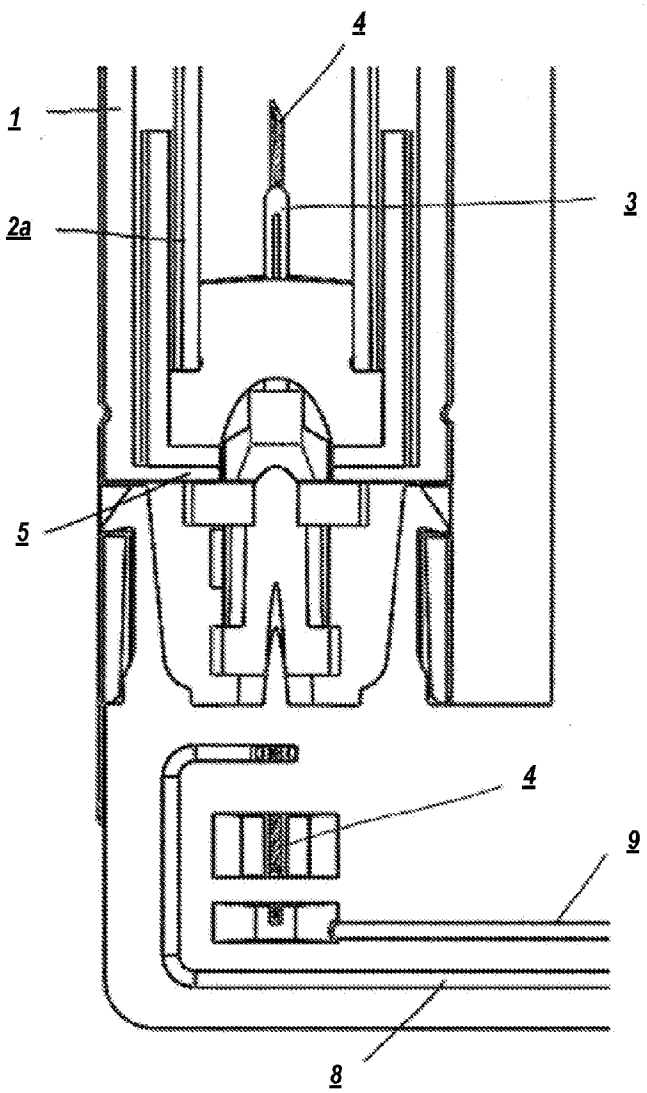

FIG. 4

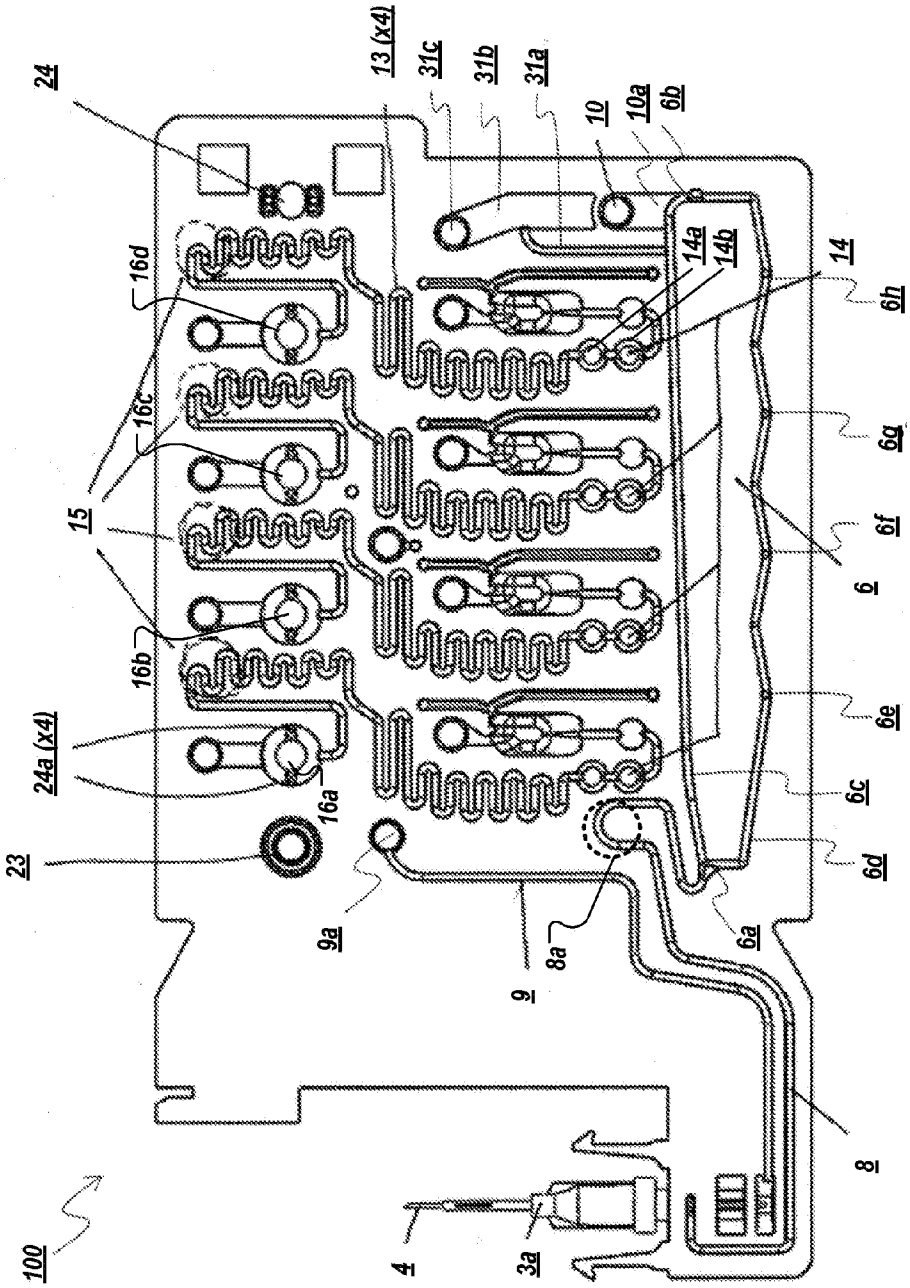
24
13 (x4)
31c
31b
31a
10
10a
6b
16d
14a
14b
14
6h
16c
6g
15
6f
6
16b
6e
24a (x4)
16a
6c
23
6d
9a
8a
6a
9
8
100
4
3a

FIG. 5A

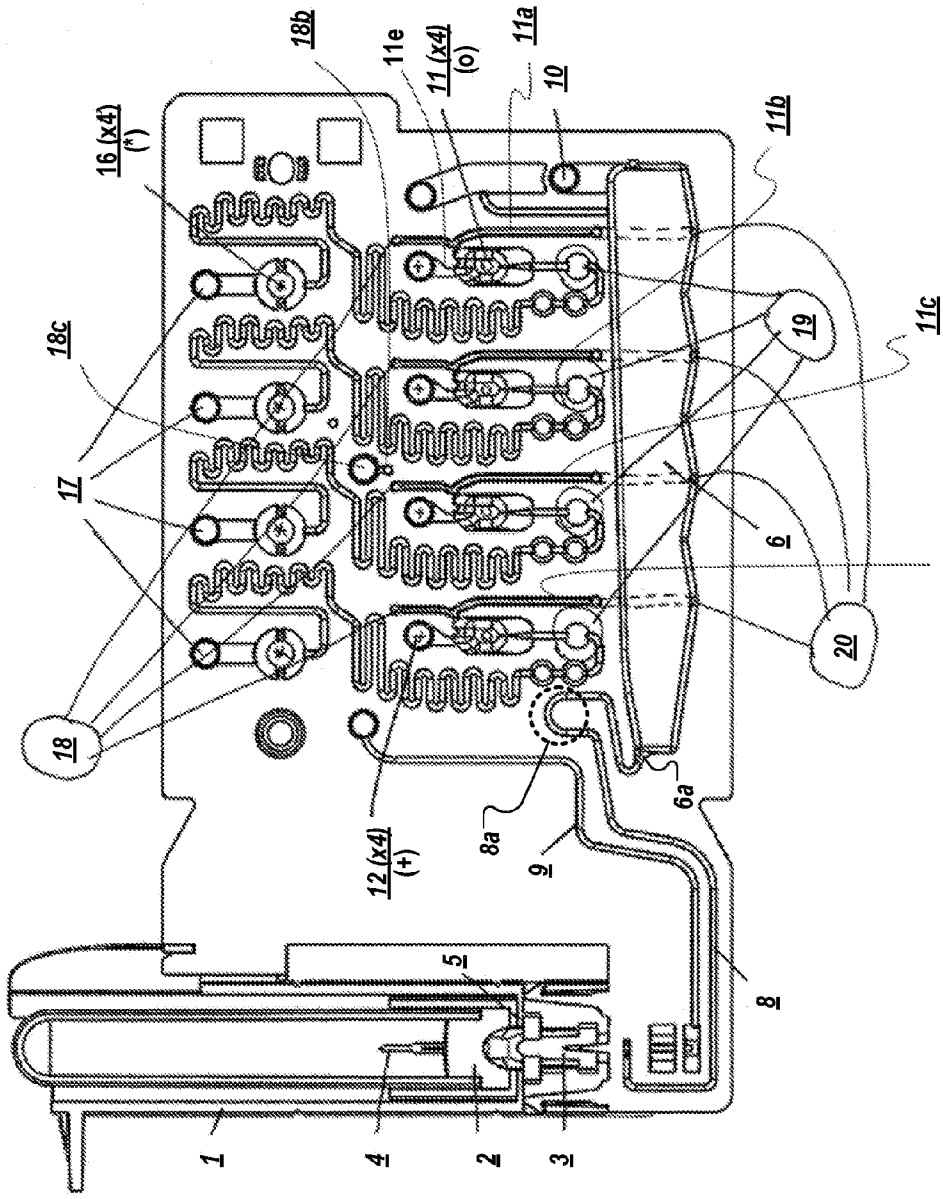
18b
11e
11 (x4)
(o)
11a
10
16 (x4)
(*)
11b
18c
19
11c
17
6
11d
20
18
6a
8a
9
12 (x4)
(+)
5
8
1
4
2
3

FIG. 5B

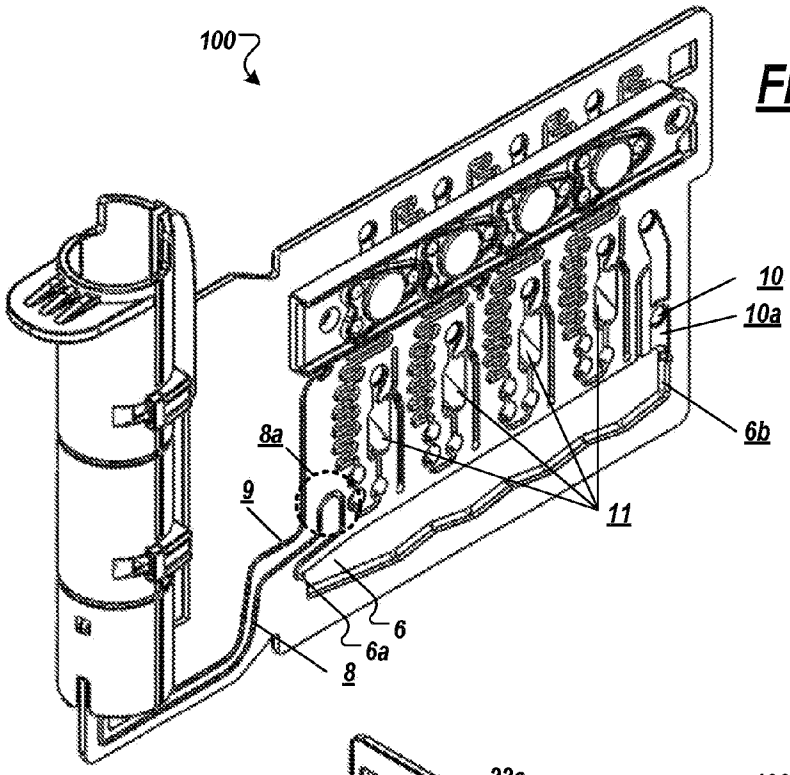
100
10
10a
6b
8a
9
11
6
6a
8

FIG. 6A

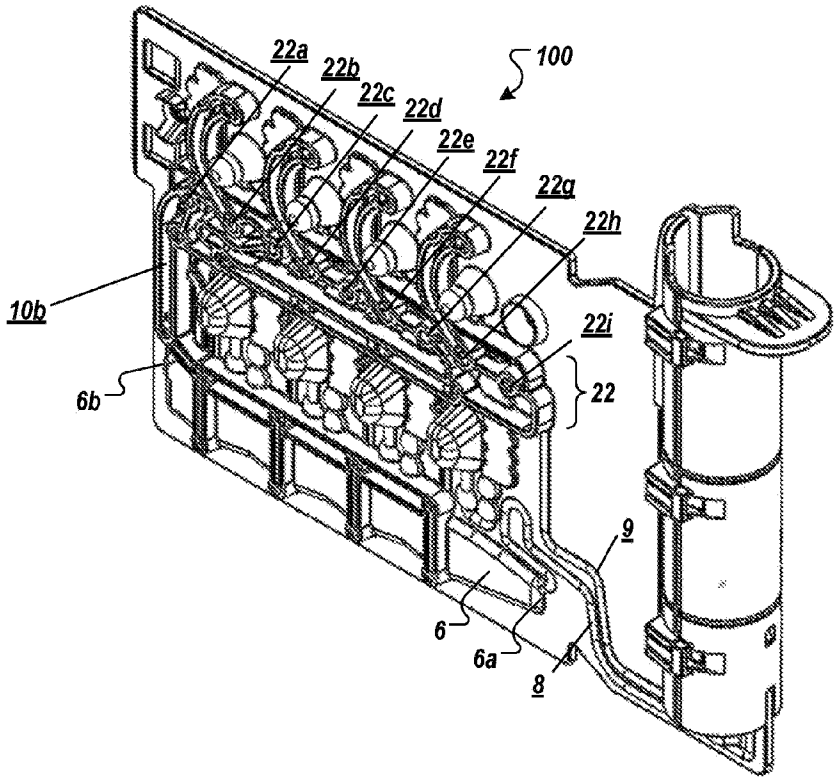
100
22a
22b
22c
22d
22e
22f
22g
22h
22i
22
10b
6b
9
6
6a
8

FIG. 6B

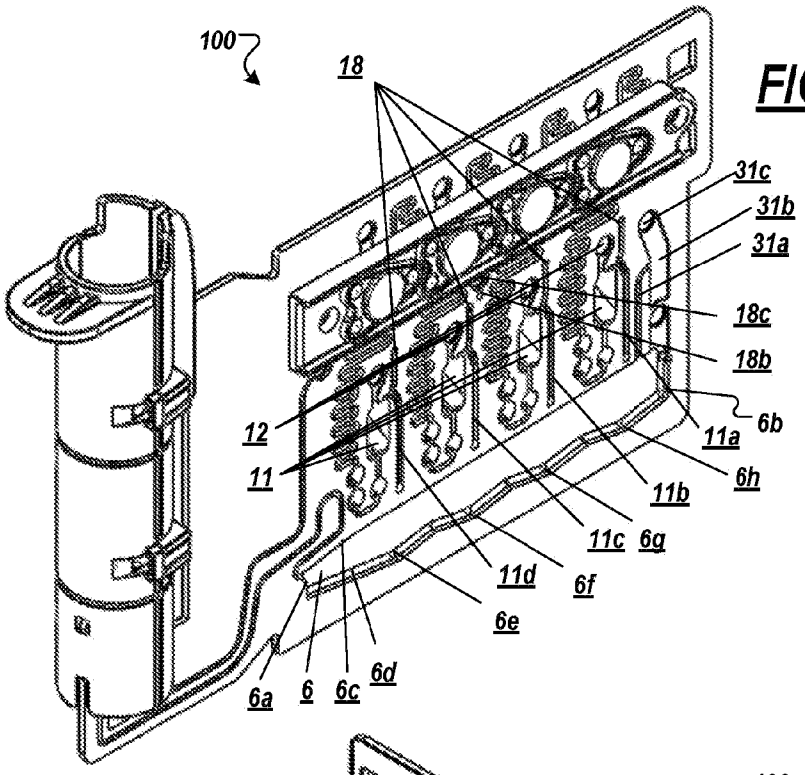
100
18
31c
31b
31a
18c
18b
6b
12
11
11a
6h
11b
11c
6g
11d
6f
6e
6a
6
6c
6d

FIG. 6C

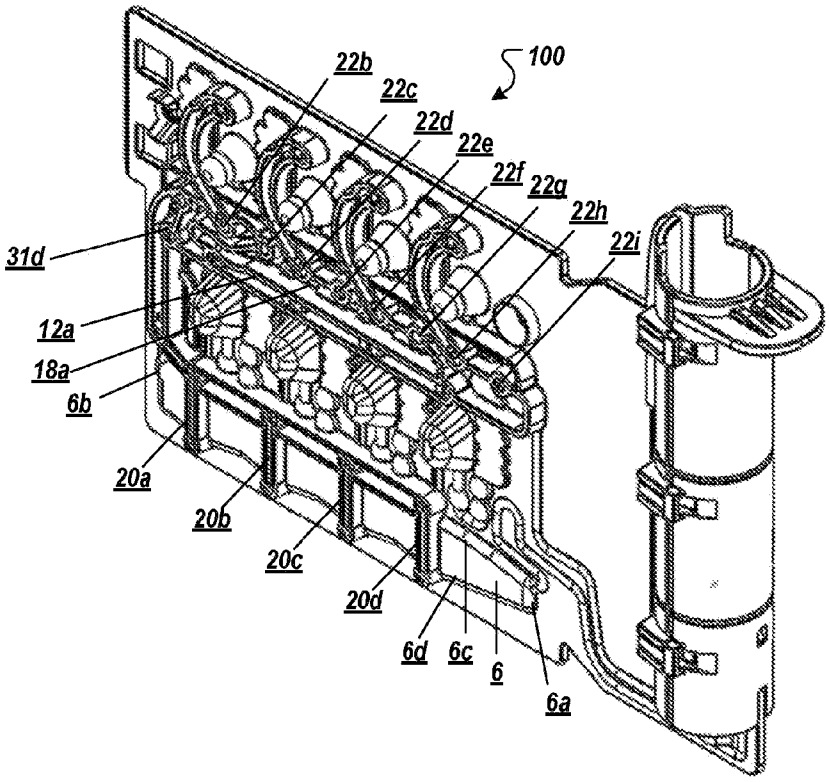
100
22b
22c
22d
22e
22f
22g
22h
22i
31d
12a
18a
6b
20a
20b
20c
20d
6d
6c
6
6a

FIG. 6D

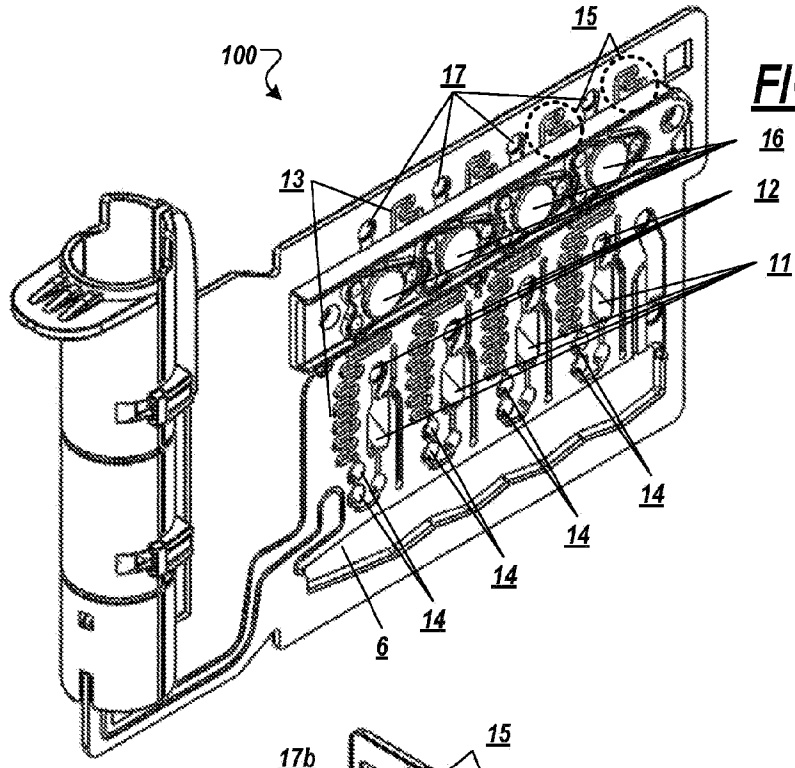
100
15
17
16
13
12
11
14
14
14
14
6

FIG. 6E

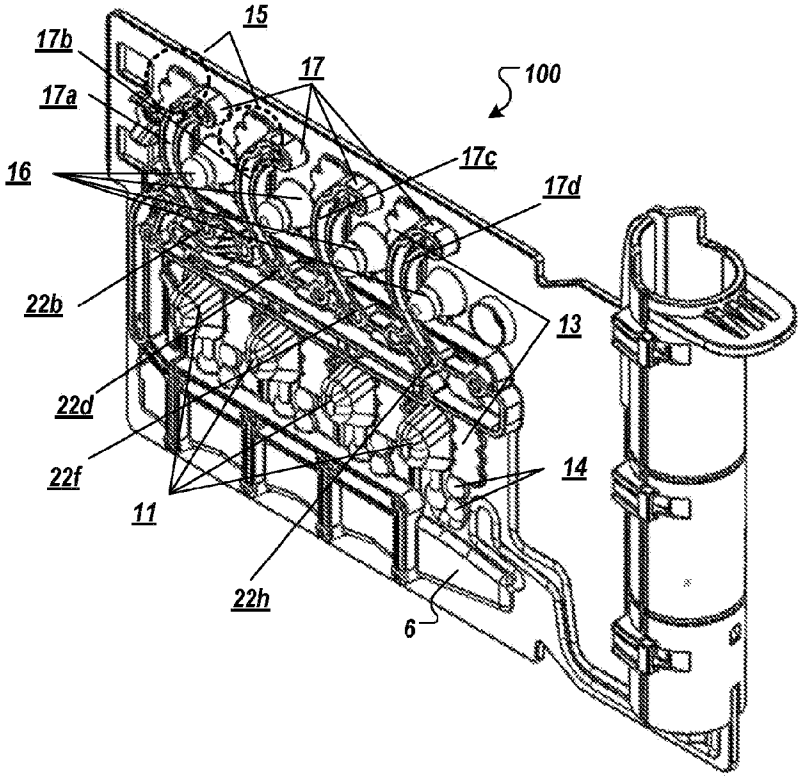
15
17b
17
17a
100
16
17c
17d
22b
13
22d
22f
14
11
22h
6

FIG. 6F

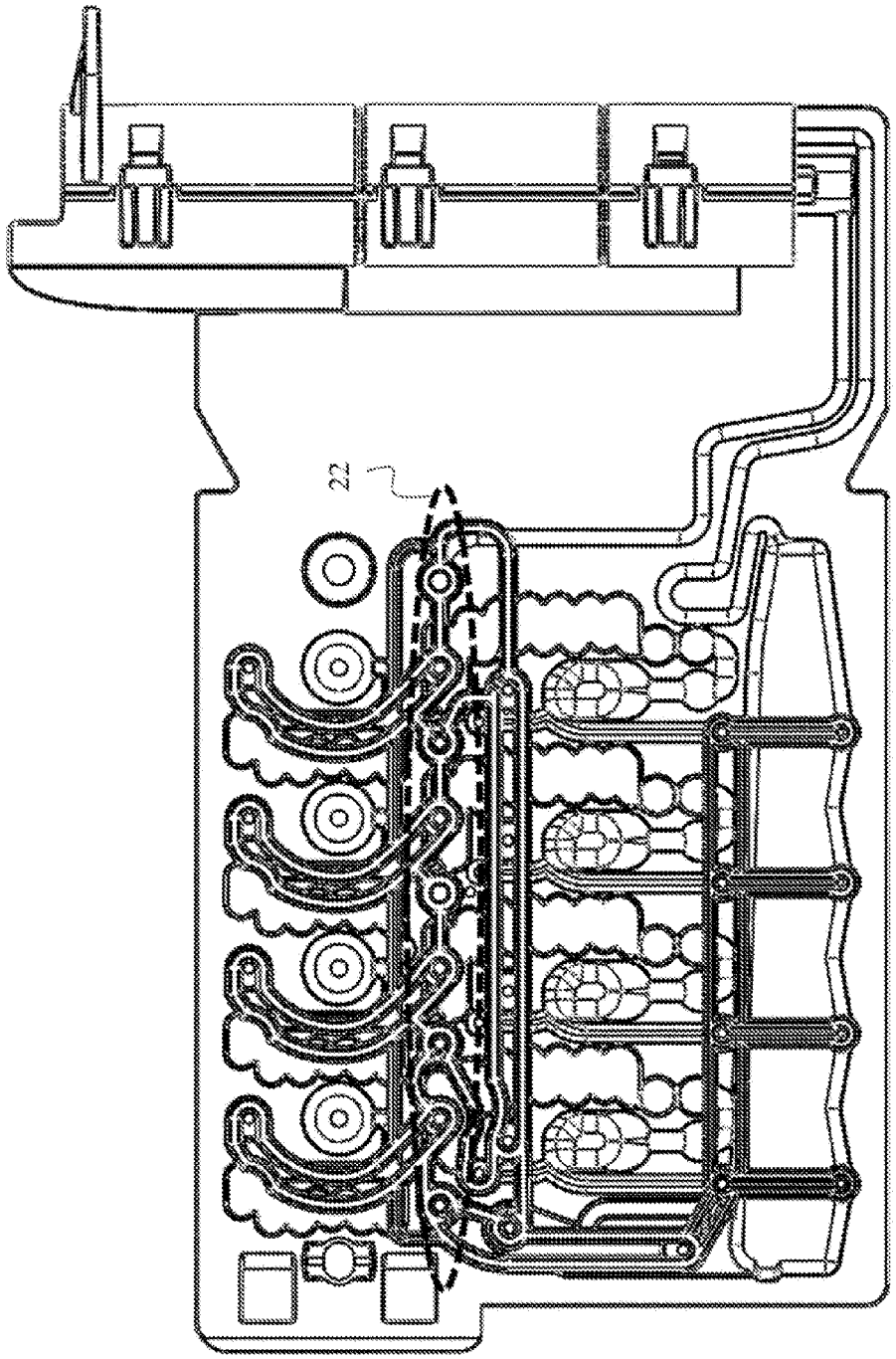

FIG. 7

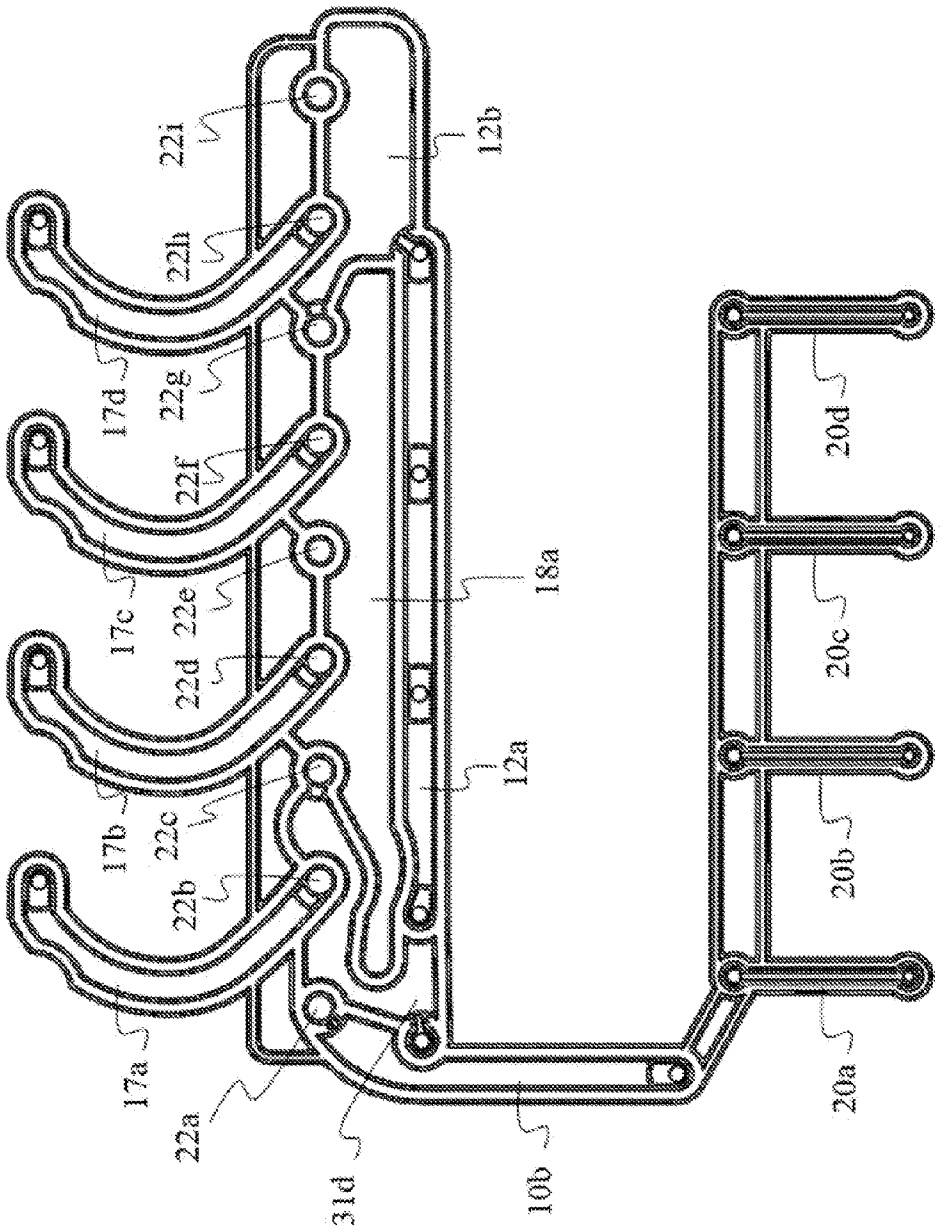
22i
12b
22h
17d
22g
22f
17c
22e
22d
18a
12a
17b
22c
22b
17a
22a
31d
10b
20d
20c
20b
20a

FIG. 8

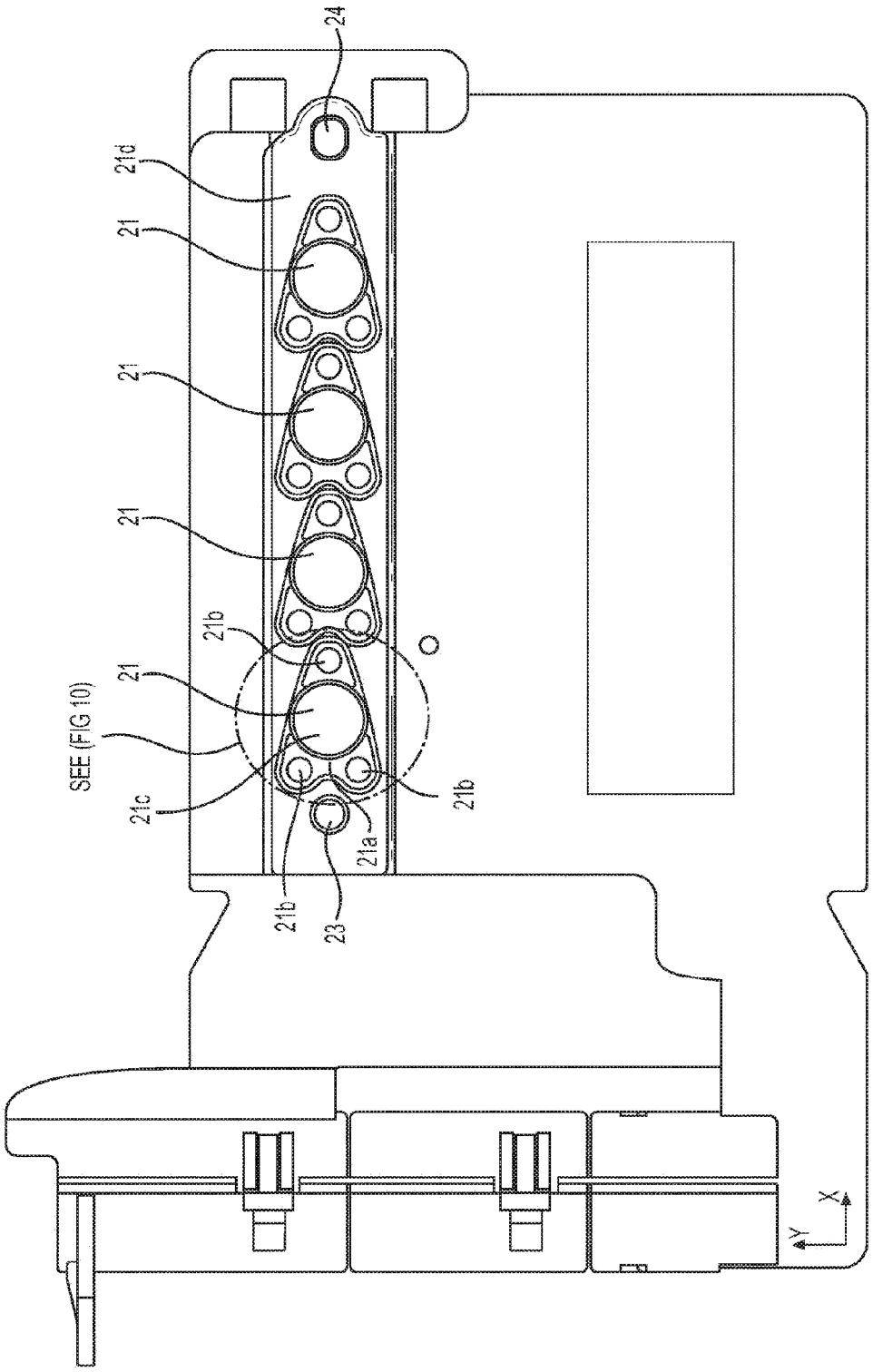

FIG. 9

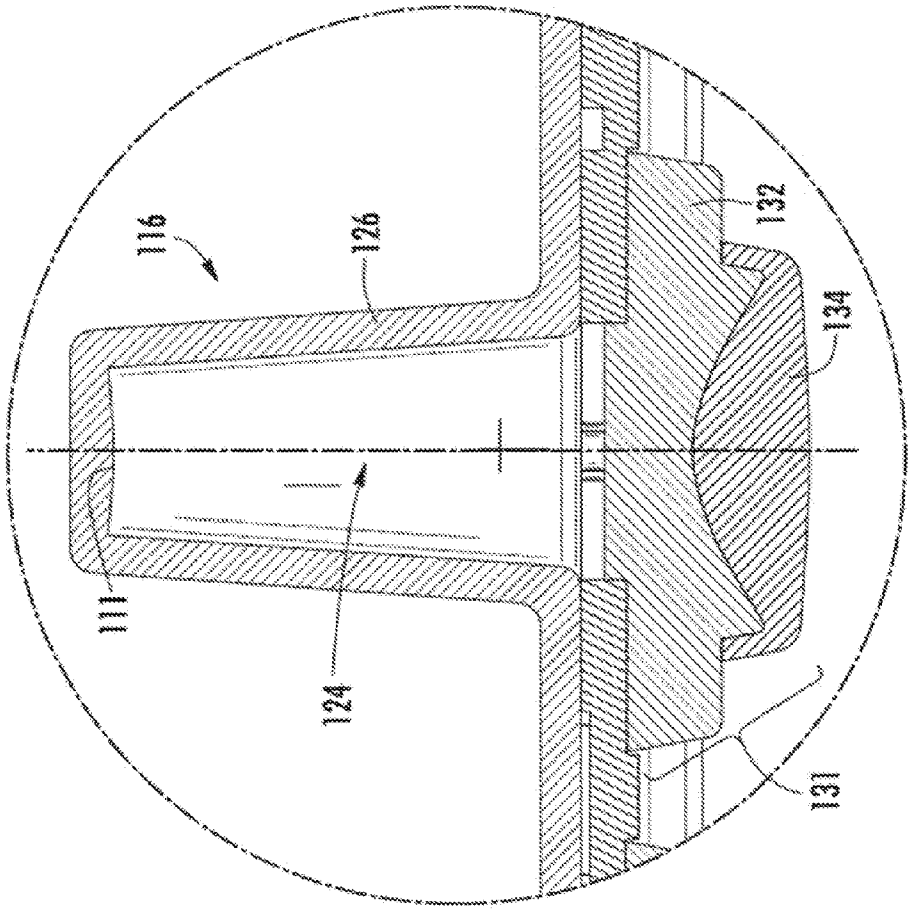

FIG. 10

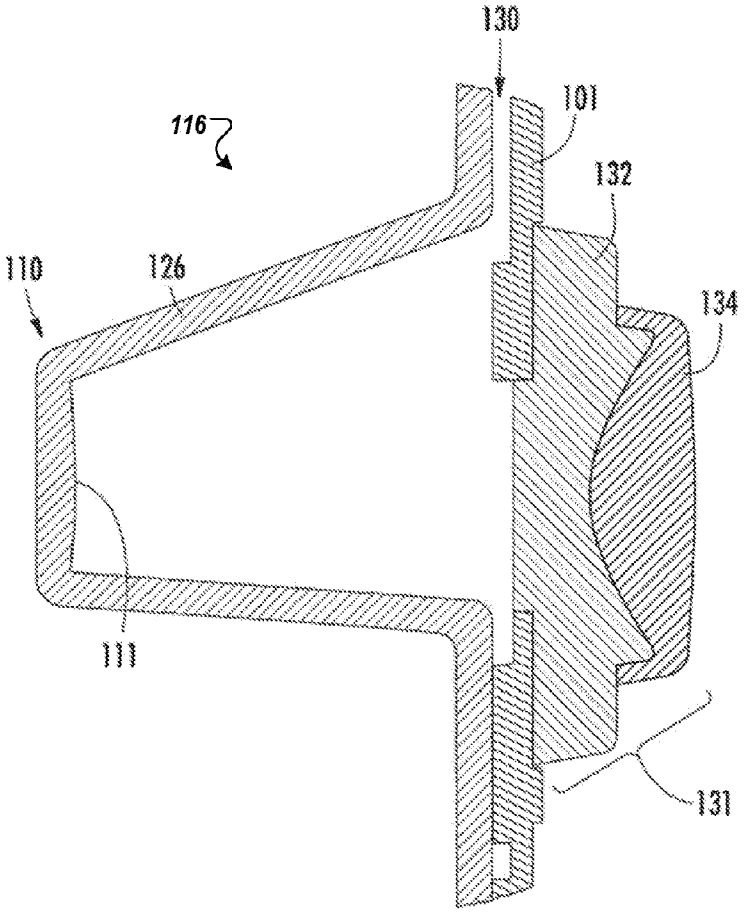

FIG. 11

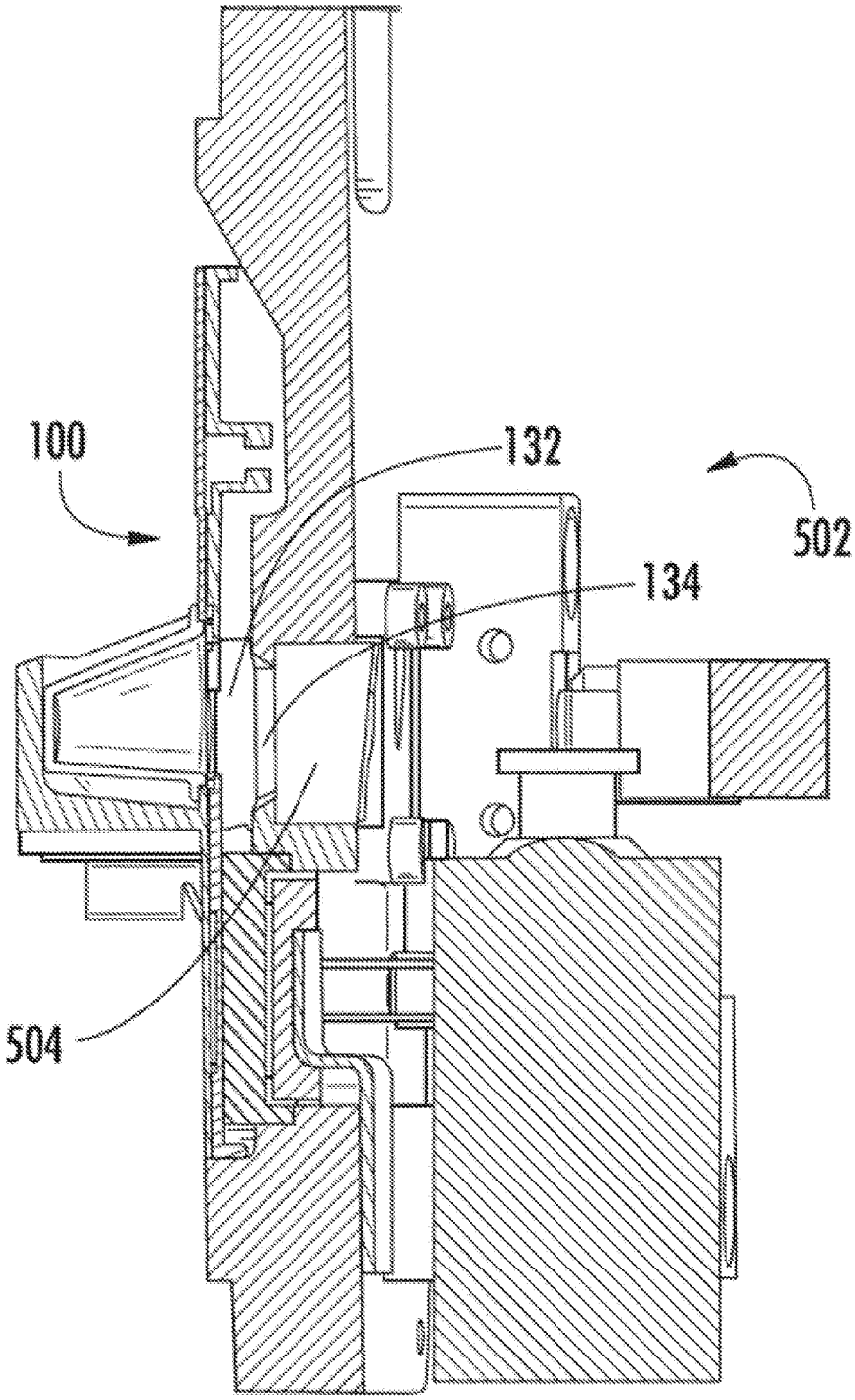

FIG. 12

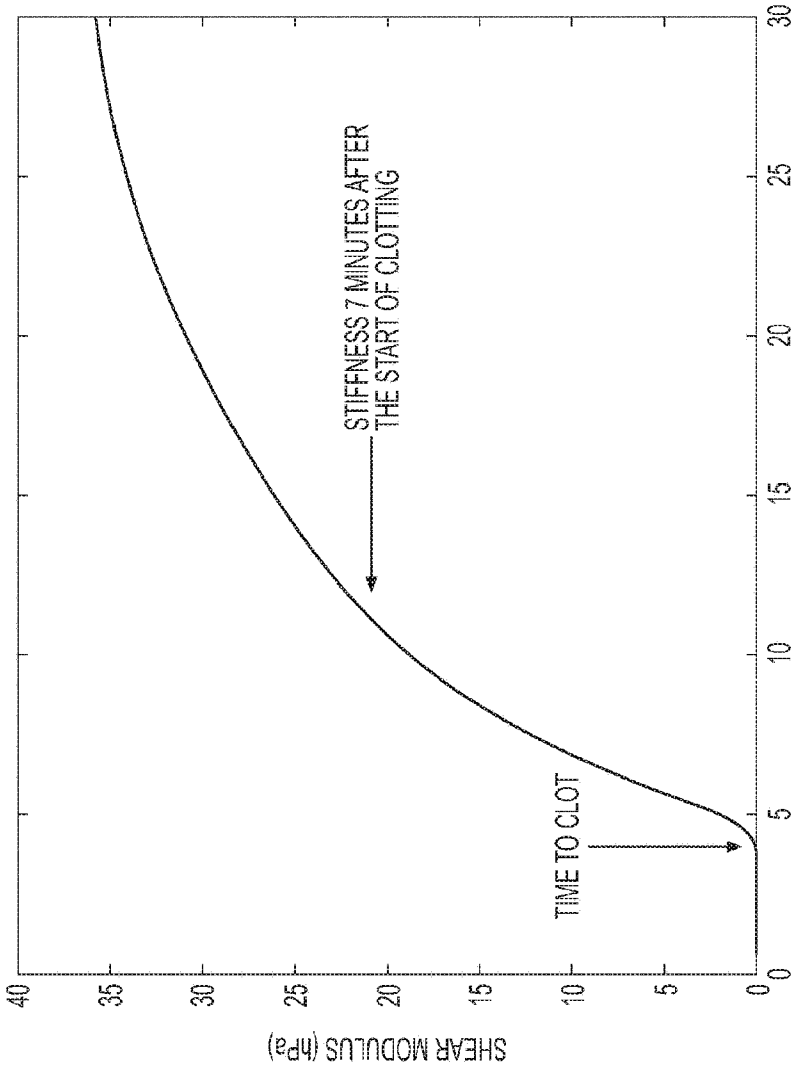
SHEAR MODULUS (hPa)
TIME (MINUTES)
STIFFNESS 7 MINUTES AFTER THE START OF CLOTTING
TIME TO CLOT
0
5
10
15
20
25
30
35
40

FIG. 13

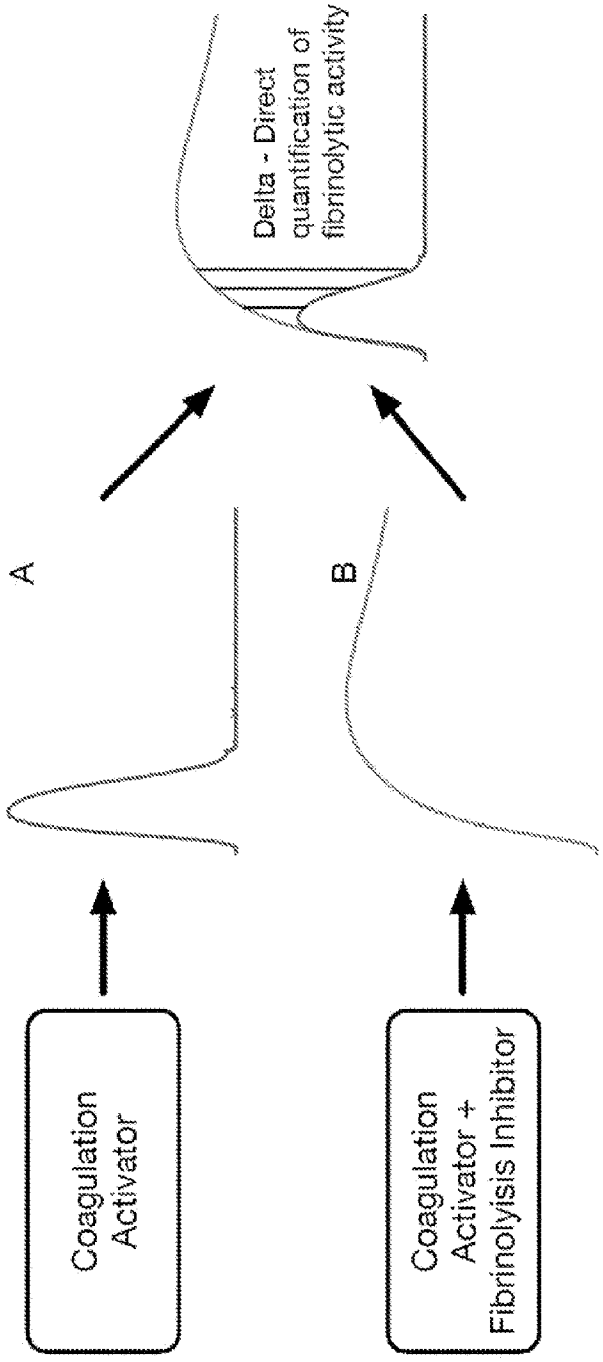
Coagulation Activator
Coagulation Activator + Fibrinolysis Inhibitor
A
B
Delta - Direct quantification of fibrinolytic activity

FIG. 14

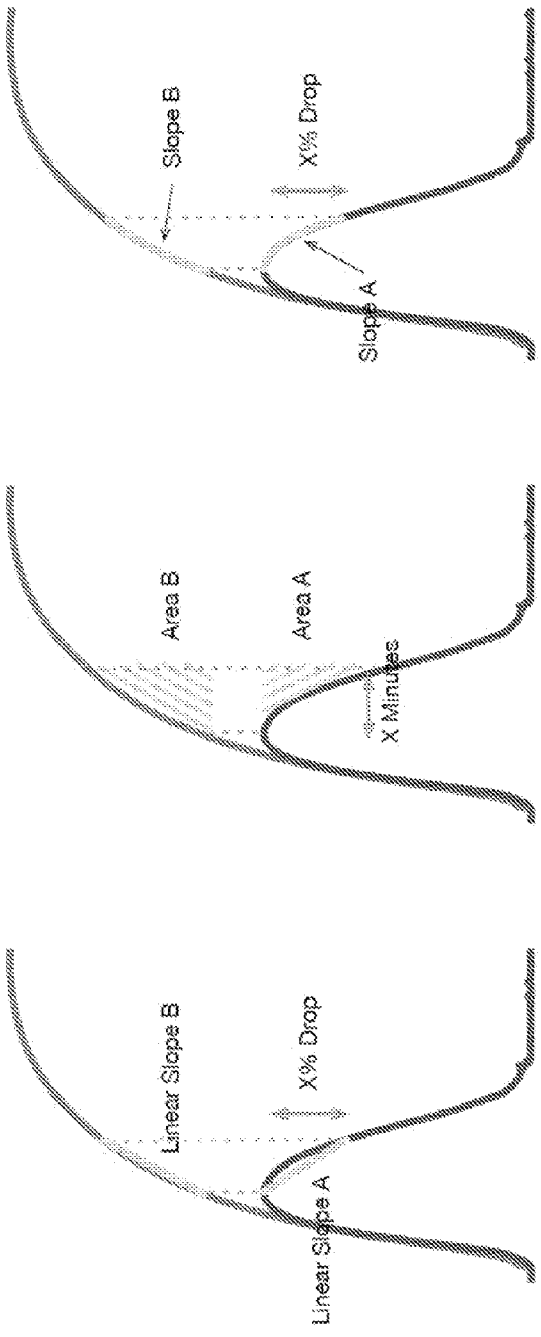
Slope B
X% Drop
Slope A
Area B
Area A
X Minutes
Linear Slope B
X% Drop
Linear Slope A

FIG. 15

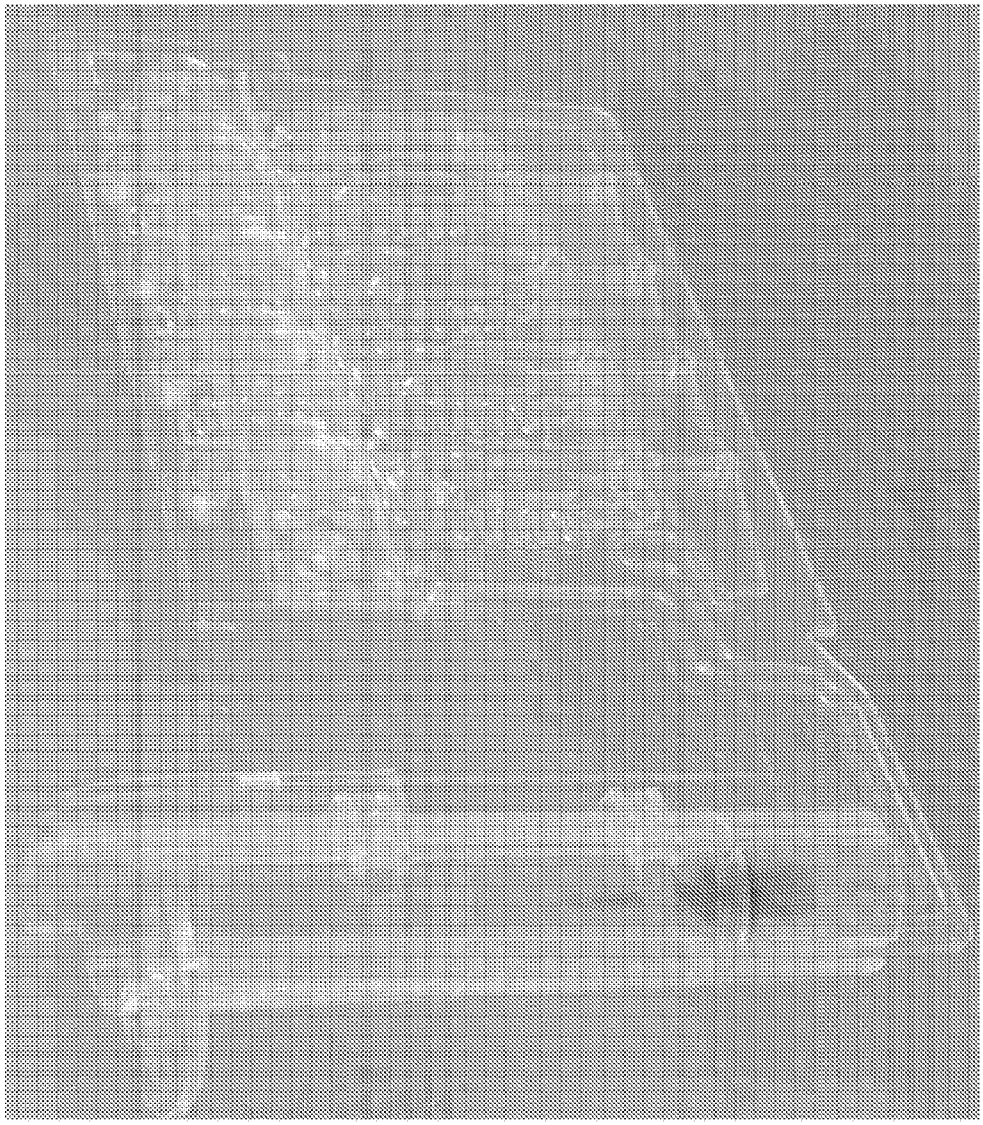

FIG. 16

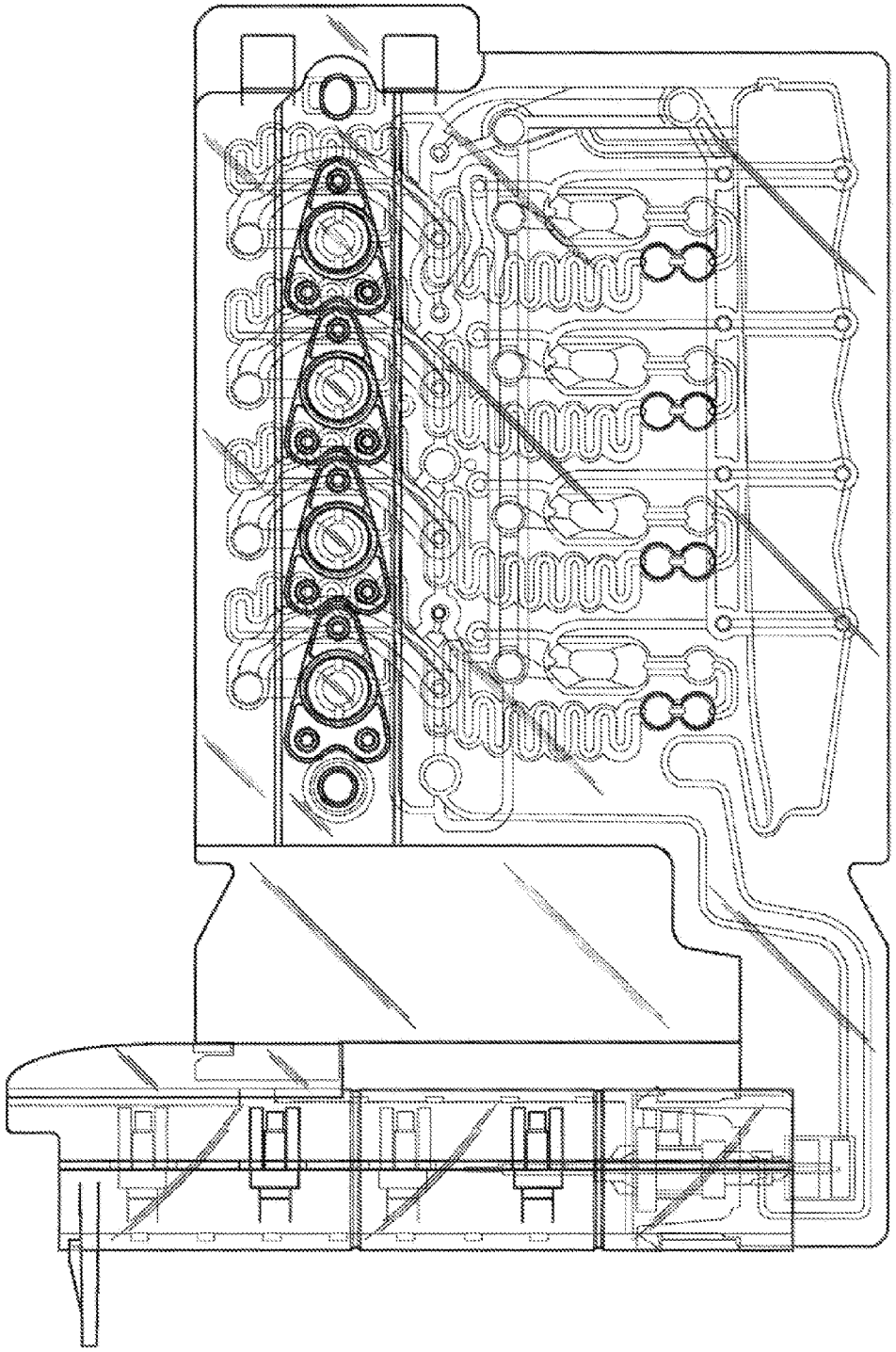

FIG. 17

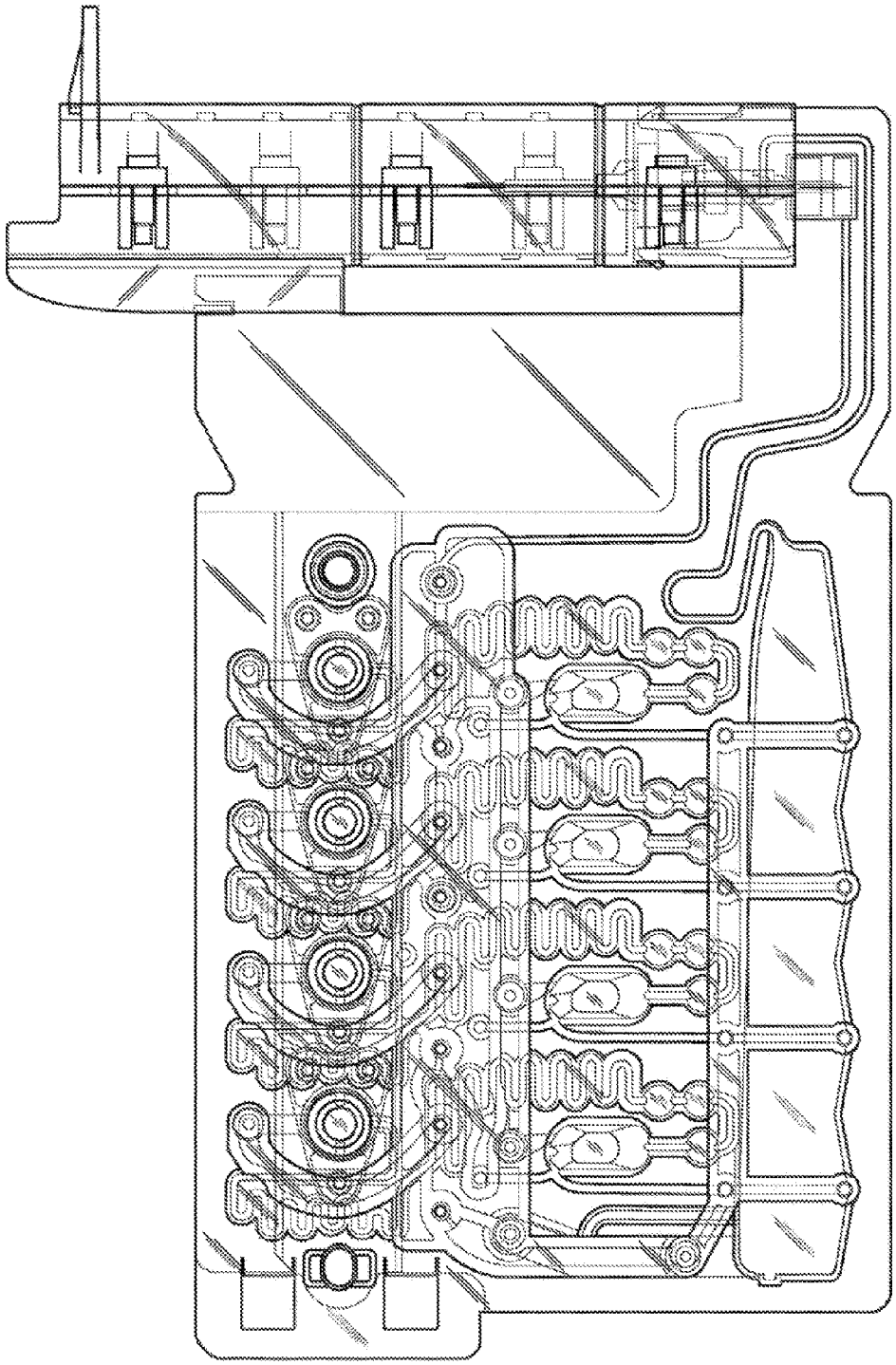

FIG. 18