US 20160003229A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2016/0003229 A1**

(43) **Pub. Date: Jan. 7, 2016**

Mescher et al.

(54) **ELECTROMAGNETICALLY-ACTUATED MICROFLUIDIC FLOW REGULATORS AND RELATED APPLICATIONS**

(71) Applicant: **The Charles Stark Draper Laboratory, Inc.**, Cambridge, MA (US)

(72) Inventors: **Mark J. Mescher**, West Newton, MA (US); **Jason O. Fiering**, Boston, MA (US); **Christopher E. Dube**, Lexington, MA (US)

(21) Appl. No.: **14/795,551**

(22) Filed: **Jul. 9, 2015**

Related U.S. Application Data

(63) Continuation of application No. 11/169,211, filed on Jun. 28, 2005, now abandoned, which is a continuation-in-part of application No. 11/046,540, filed on Jan. 28, 2005, now Pat. No. 7,867,193, said application No. 11/169,211 is a continuation-in-part of application No. 10/601,606, filed on Jun. 23, 2003, now abandoned.

(60) Provisional application No. 60/540,283, filed on Jan. 29, 2004, provisional application No. 60/602,691, filed on Aug. 19, 2004, provisional application No. 60/390,773, filed on Jun. 21, 2002.

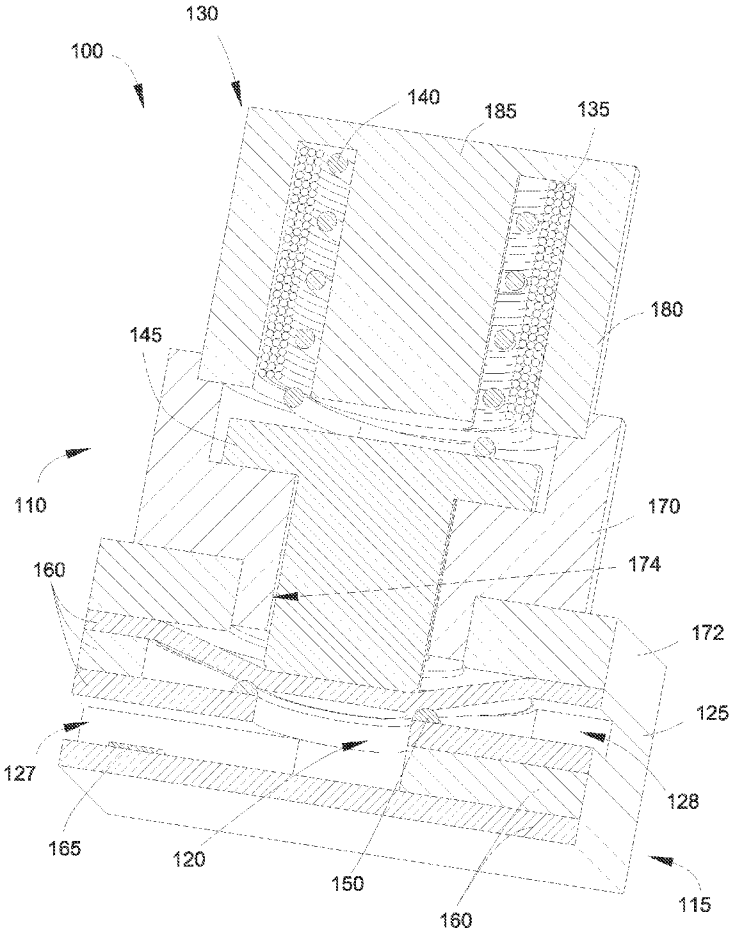
Publication Classification

(51) **Int. Cl.**
F04B 43/04 (2006.01)

(52) **U.S. Cl.**
CPC ***F04B 43/043*** (2013.01)

(57) **ABSTRACT**

A variable, closed-loop apparatus for regulating a microfluidic flow that employs a low-power deflection assembly, which is surface-mounted over a flexible membrane overlying a chamber integrated into a microfabricated platform. A flexible membrane, movable between two positions, sealingly overlies the chamber. One of the positions of the membrane restricts the flow through the chamber to a greater degree than the other position. A deflection assembly disposed on the substrate over the membrane unidirectionally deflects the membrane, thereby regulating the flow through the chamber.



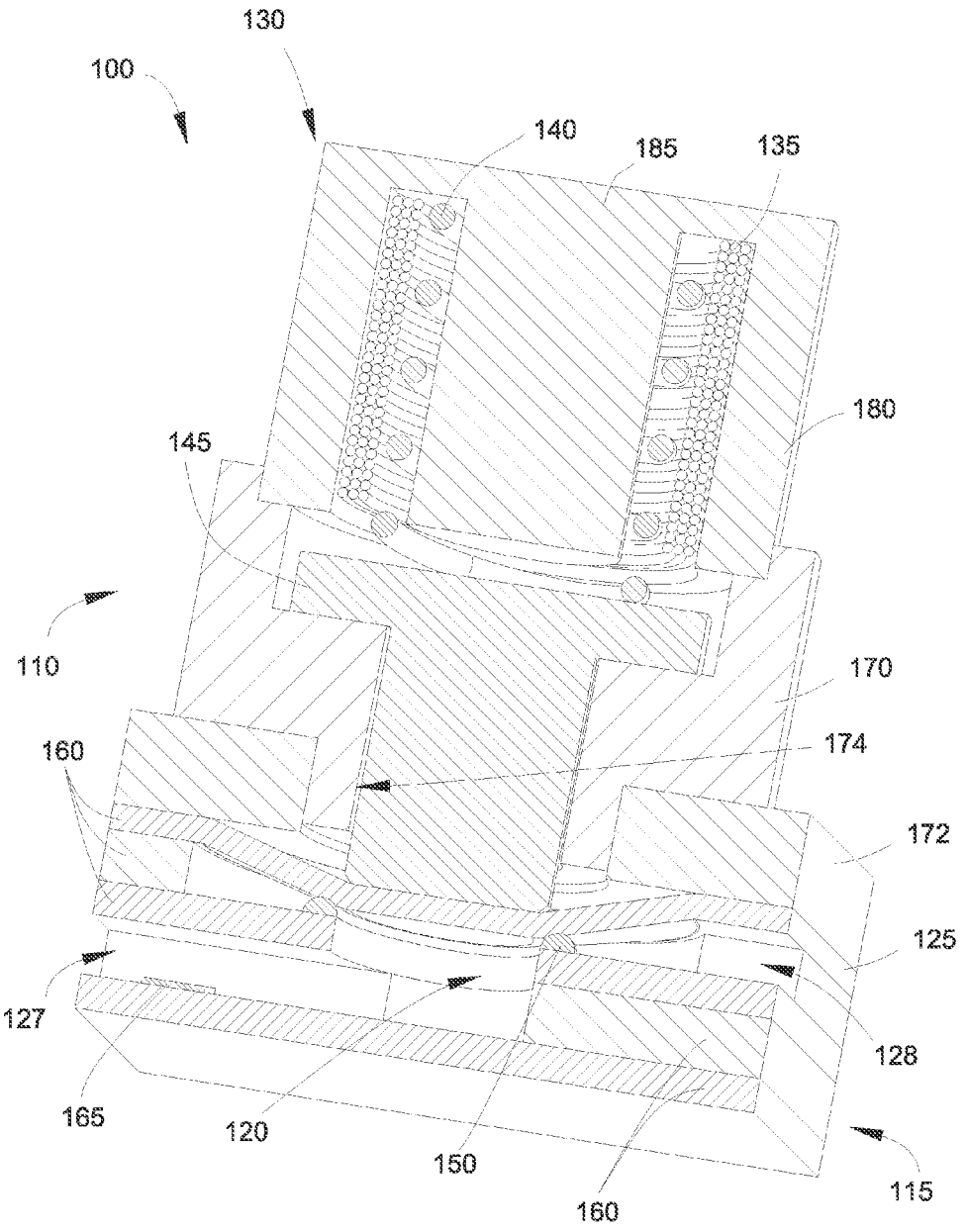

130
100
140
185
135
180
145
110
170
160
174
172
125
127
128
165
120
150
160
115

FIG. 1A

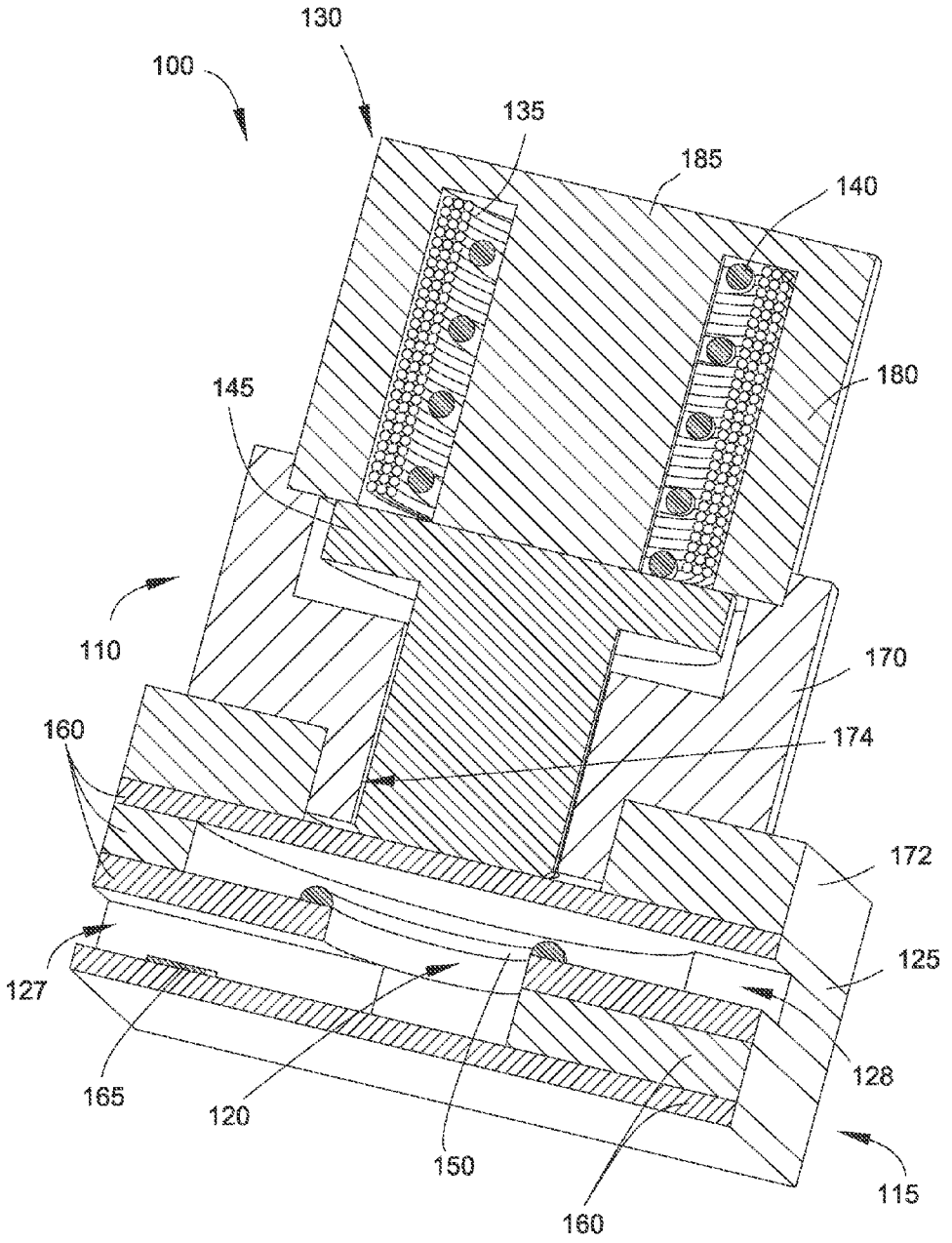

130
100
135
185
140
180
145
110
170
160
174
172
125
127
128
165
120
150
115
160

FIG. 1B

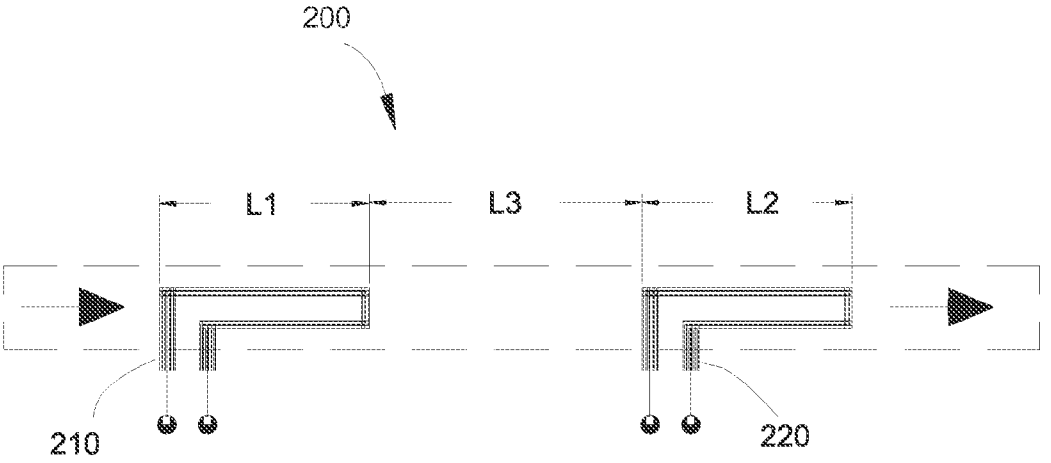

200
L1
L3
L2
210
220

FIG. 2A

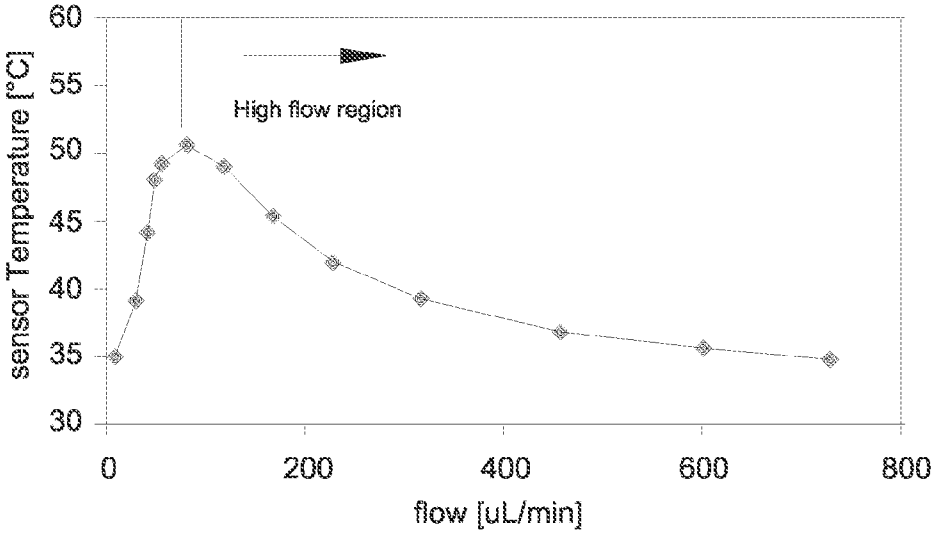

60
55
50
45
40
35
30
sensor Temperature [°C]
High flow region
0
200
400
600
800
flow [uL/min]

FIG. 2B

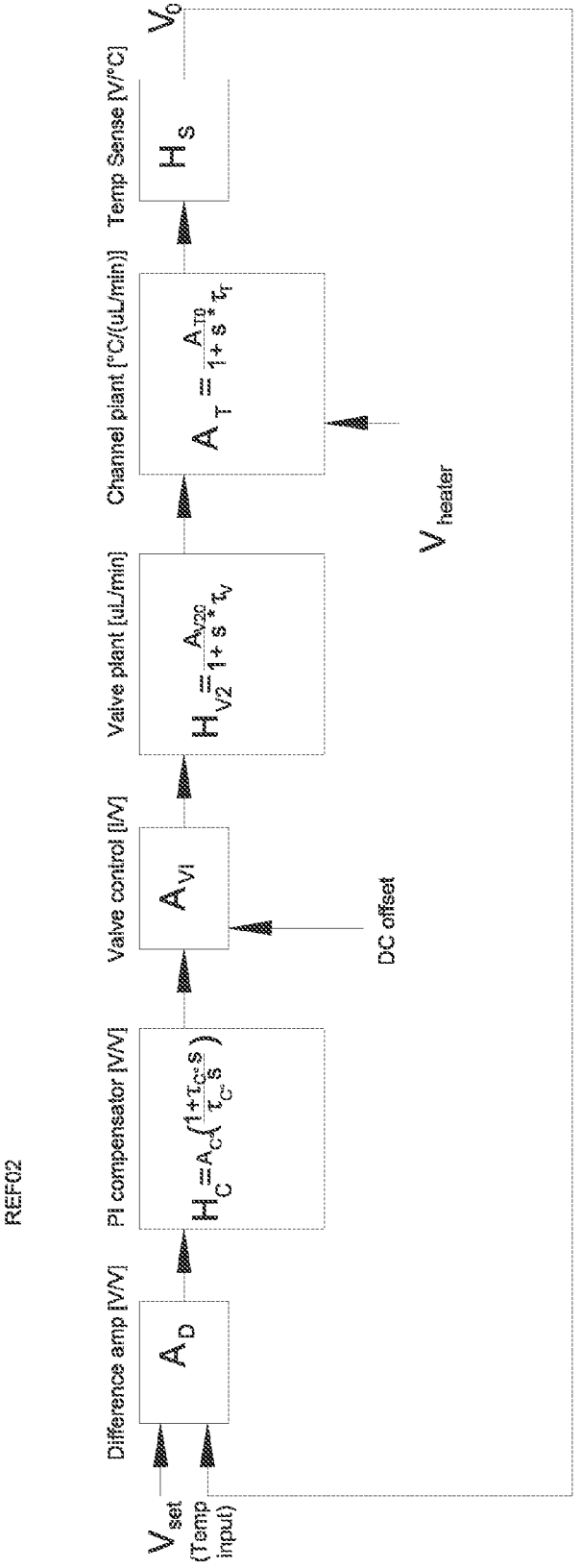

REF02
Difference amp [V/V]
PI compensator [V/V]
Valve control [l/V]
Valve plant [uL/min]
Channel plant [°C/(uL/min)]
Temp Sense [V/°C]
V_{set} (Temp input)
A_D
$H_C = A_C(\frac{1+\tau_{C'}s}{\tau_{C''}s})$
A_{VI}
$H_{V2} = \frac{A_{V20}}{1+s*\tau_V}$
$A_T = \frac{A_{T0}}{1+s*\tau_T}$
H_S
V_O
DC offset
V_{heater}

FIG. 3A

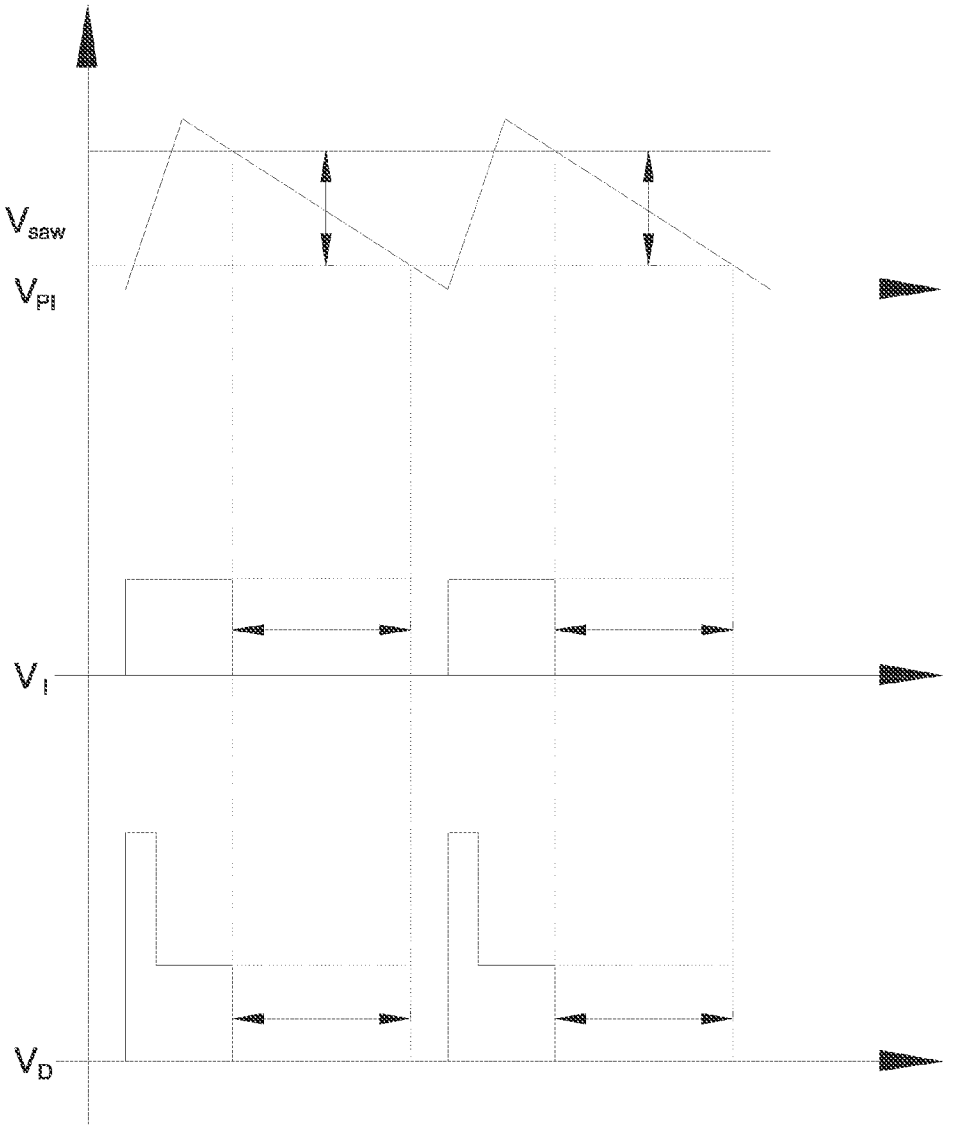


FIG. 3B

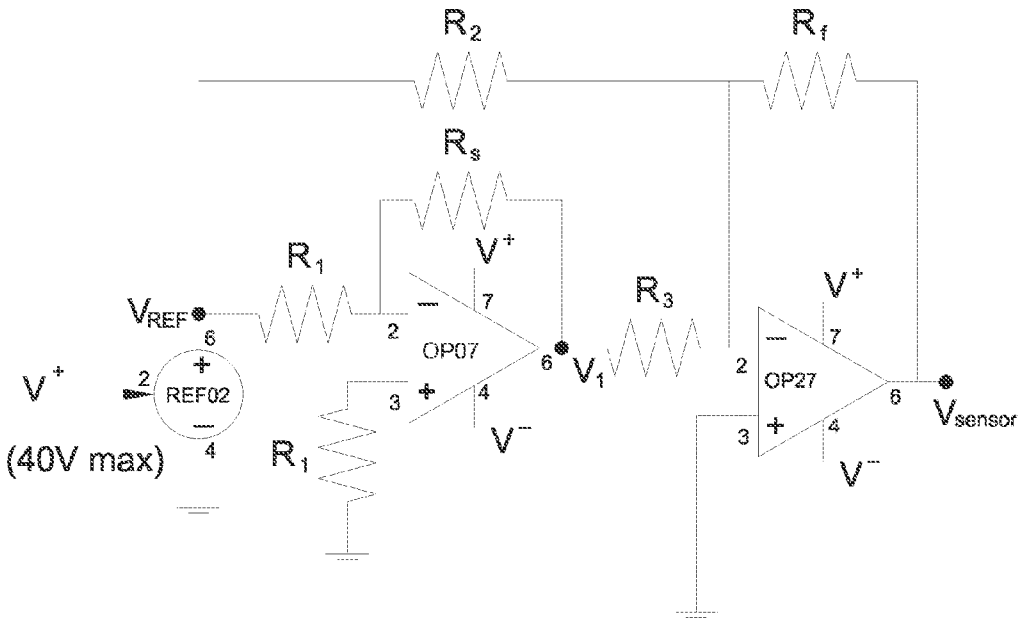


FIG. 4A

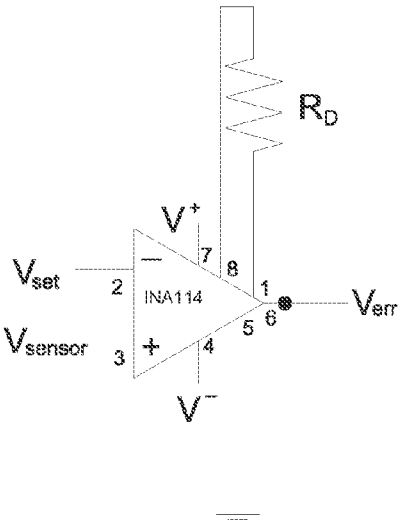


FIG. 4B

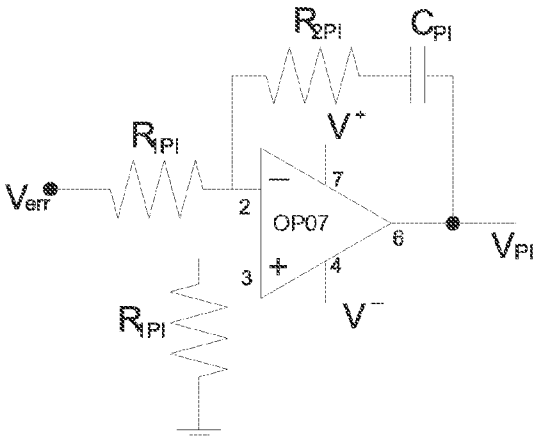


FIG. 4C

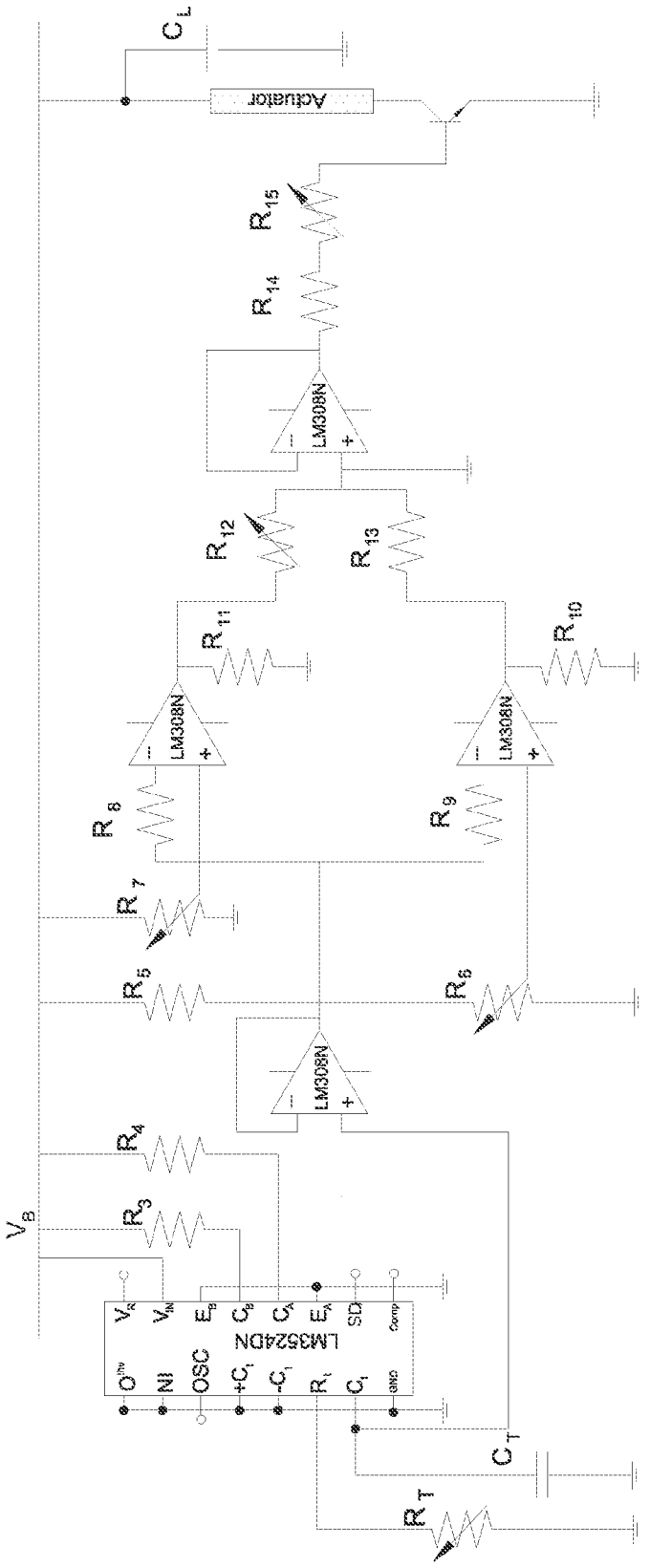

C L
Actuator
R 15
R 14
LM308N
R 12
R 13
R 11
R 10
LM308N
LM308N
R 8
R 9
R 7
R 5
R 6
LM308N
R 4
R 3
V B
LM3524DN
C T
R T

FIG. 4D

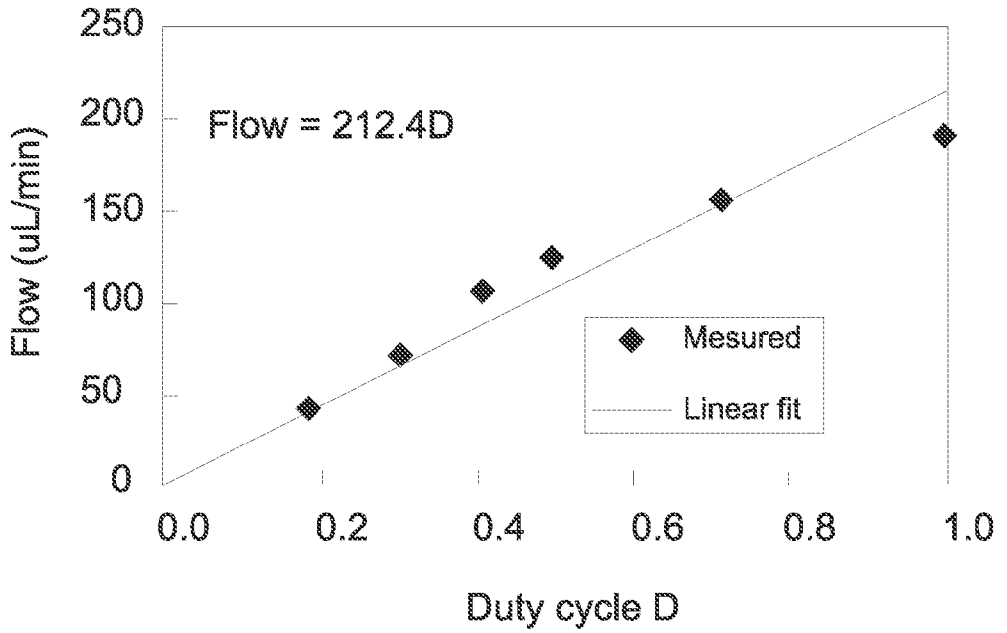

250
200
150
100
50
0
Flow (uL/min)
Flow = 212.4D
Mesured
Linear fit
0.0
0.2
0.4
0.6
0.8
1.0
Duty cycle D

FIG. 5A

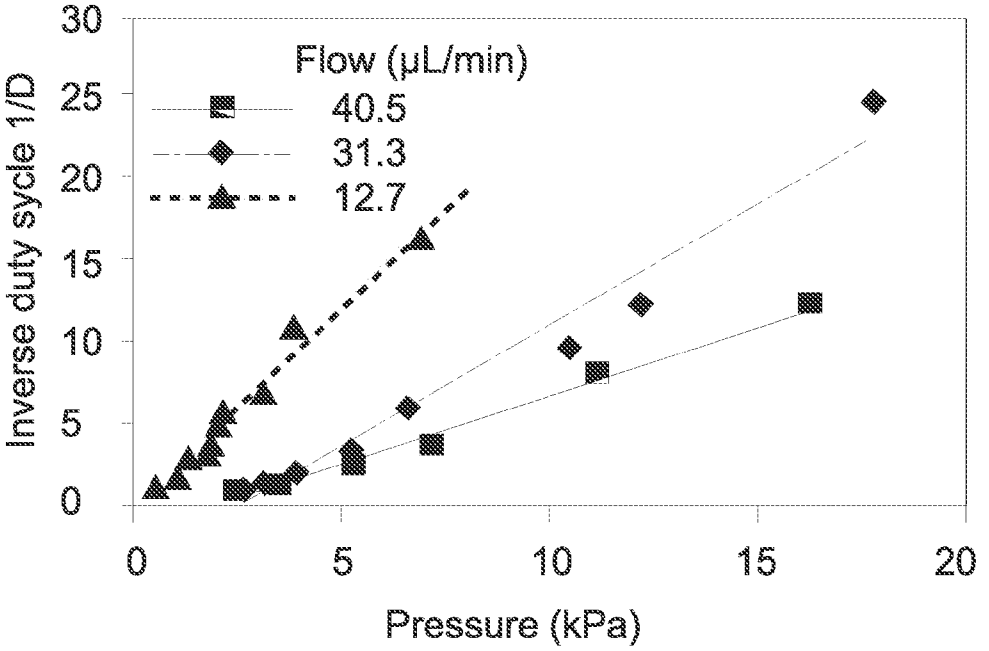

Inverse duty sycle 1/D
Flow (µL/min)
40.5
31.3
12.7
Pressure (kPa)
0
5
10
15
20
25
30

FIG. 5B

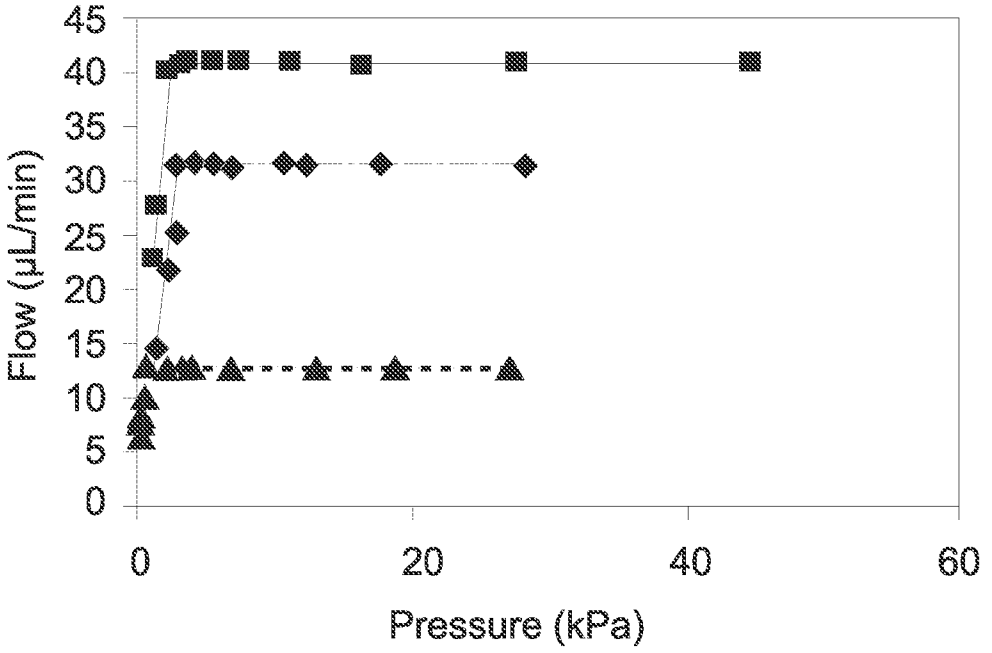

Flow (µL/min)
Pressure (kPa)
0
5
10
15
20
25
30
35
40
45
0
20
40
60

FIG. 5C

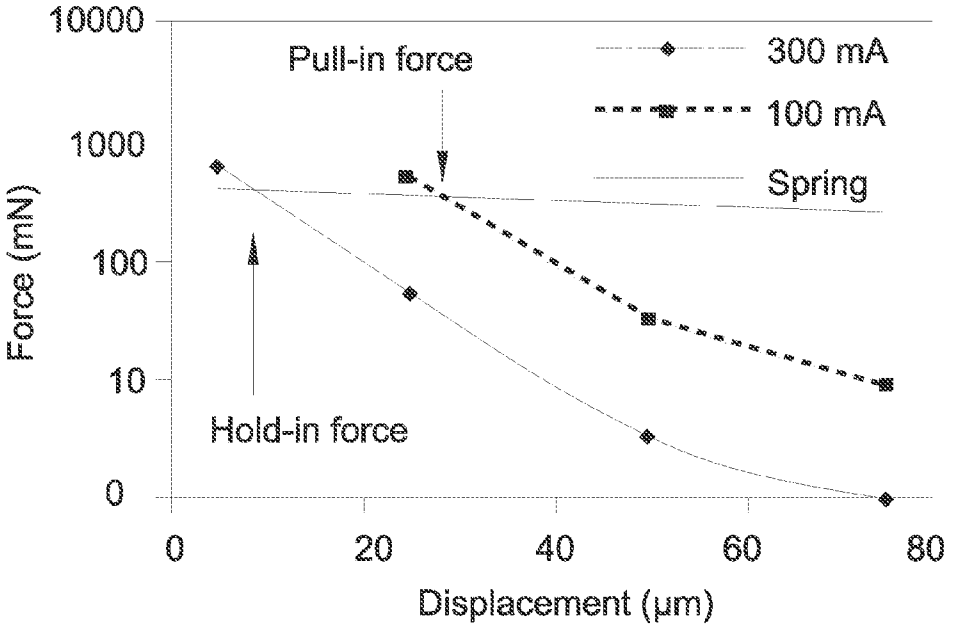

10000
1000
100
10
0
Force (mN)
Pull-in force
Hold-in force
300 mA
100 mA
Spring
0
20
40
60
80
Displacement (μm)

FIG. 6

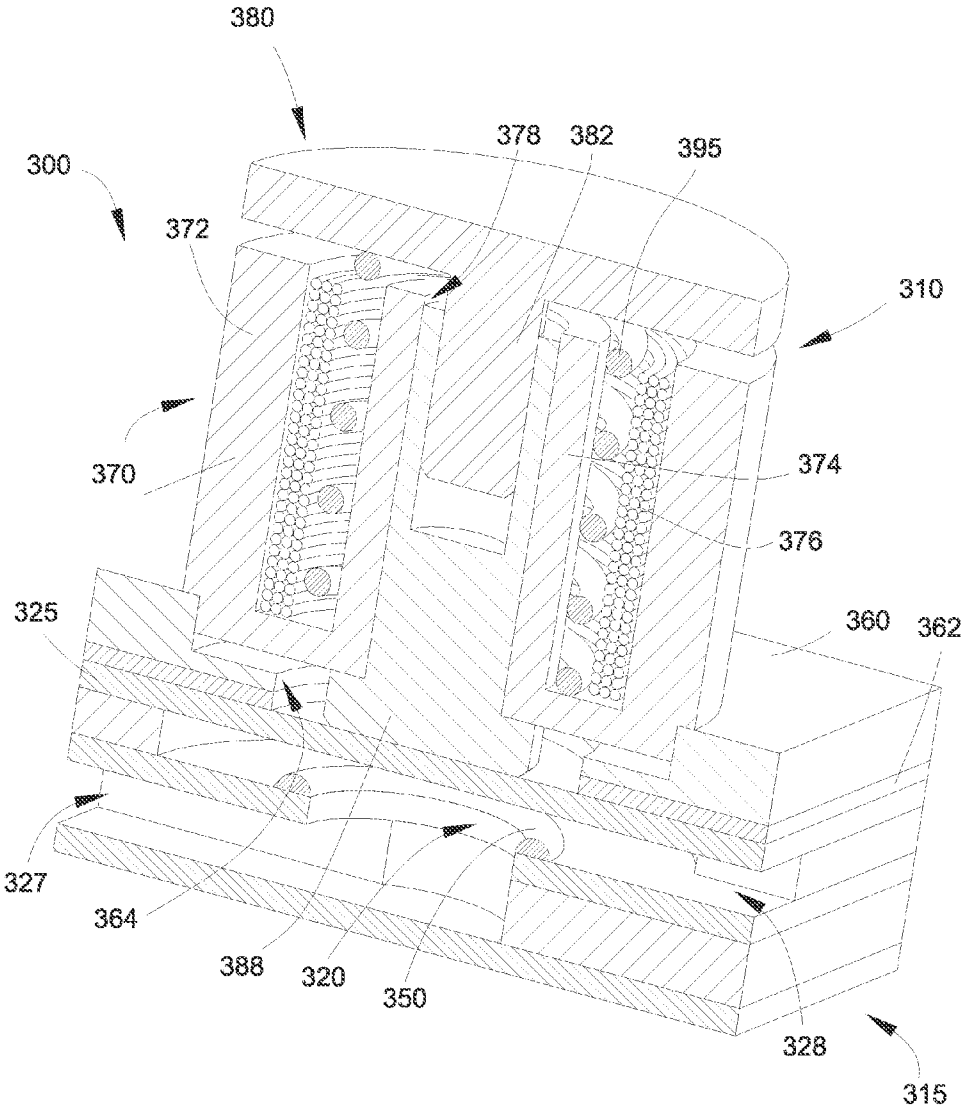

380
300
372
378
382
395
310
370
374
376
325
360
362
327
364
388
320
350
328
315

FIG. 7

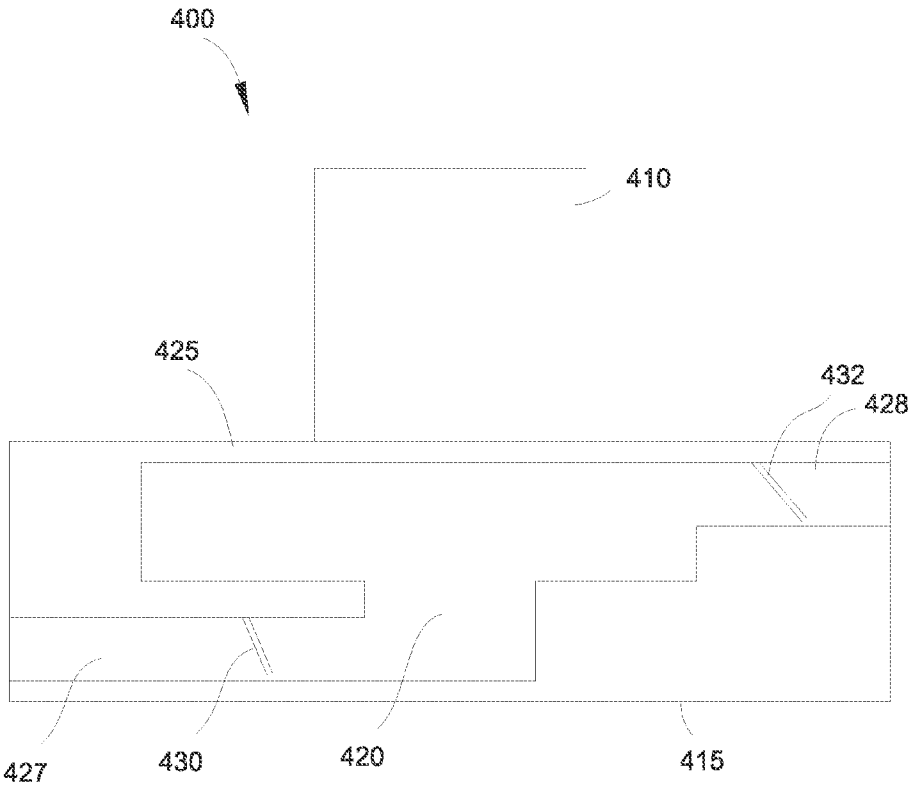


FIG. 8A

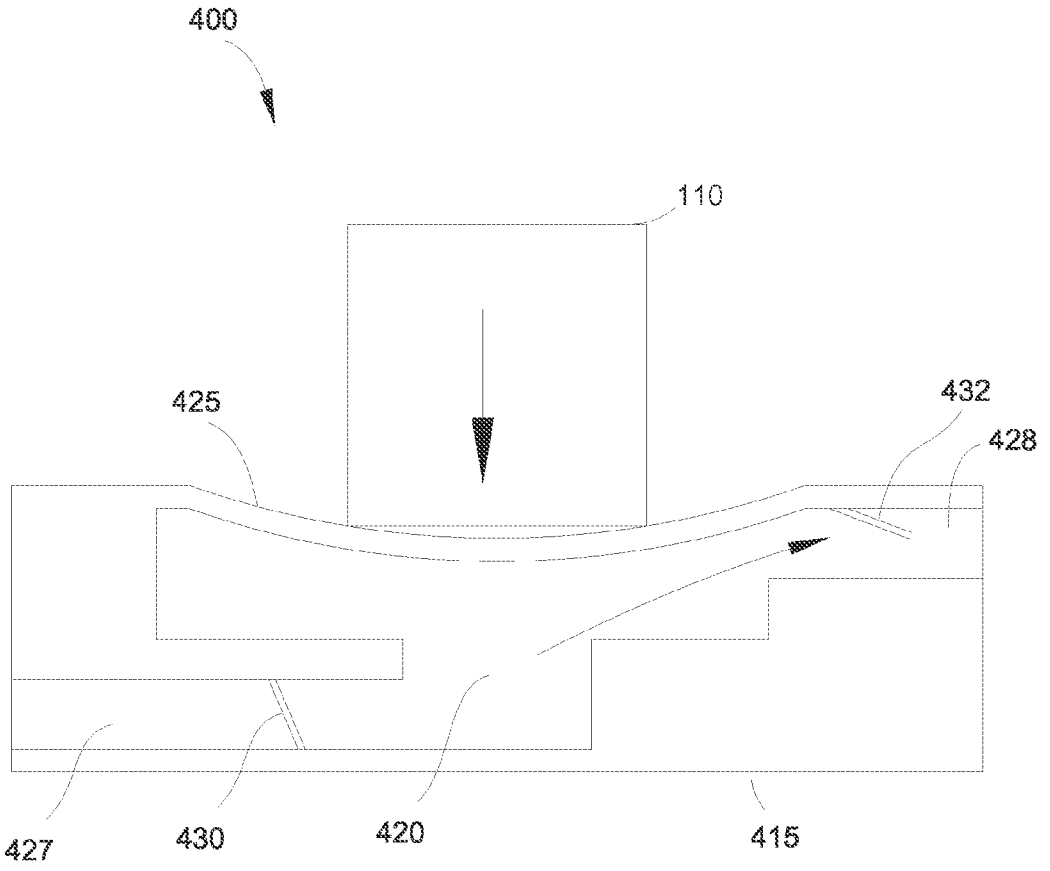


FIG. 8B

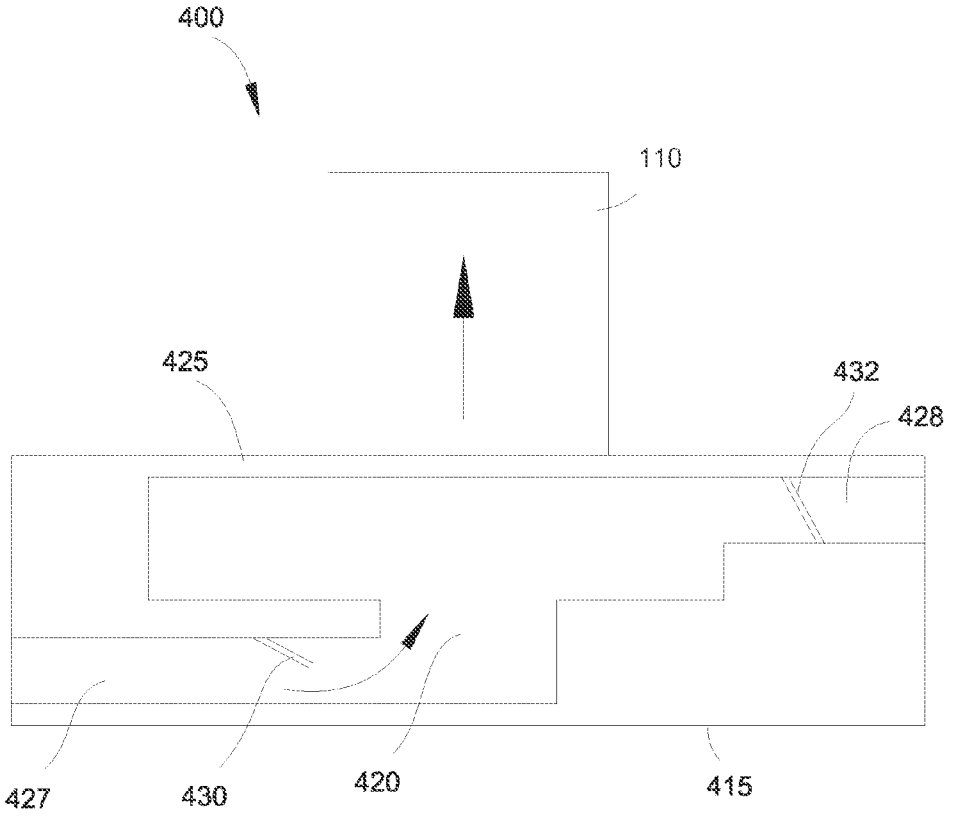


FIG. 8C

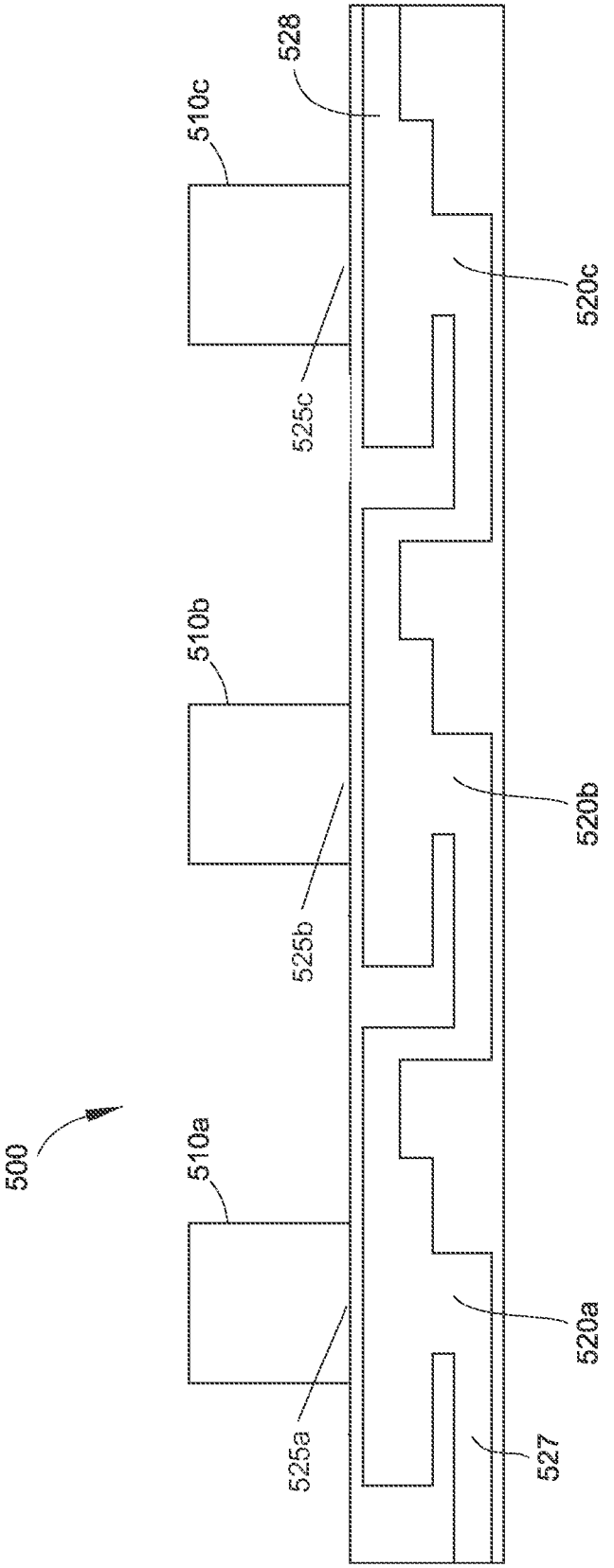


FIG. 9

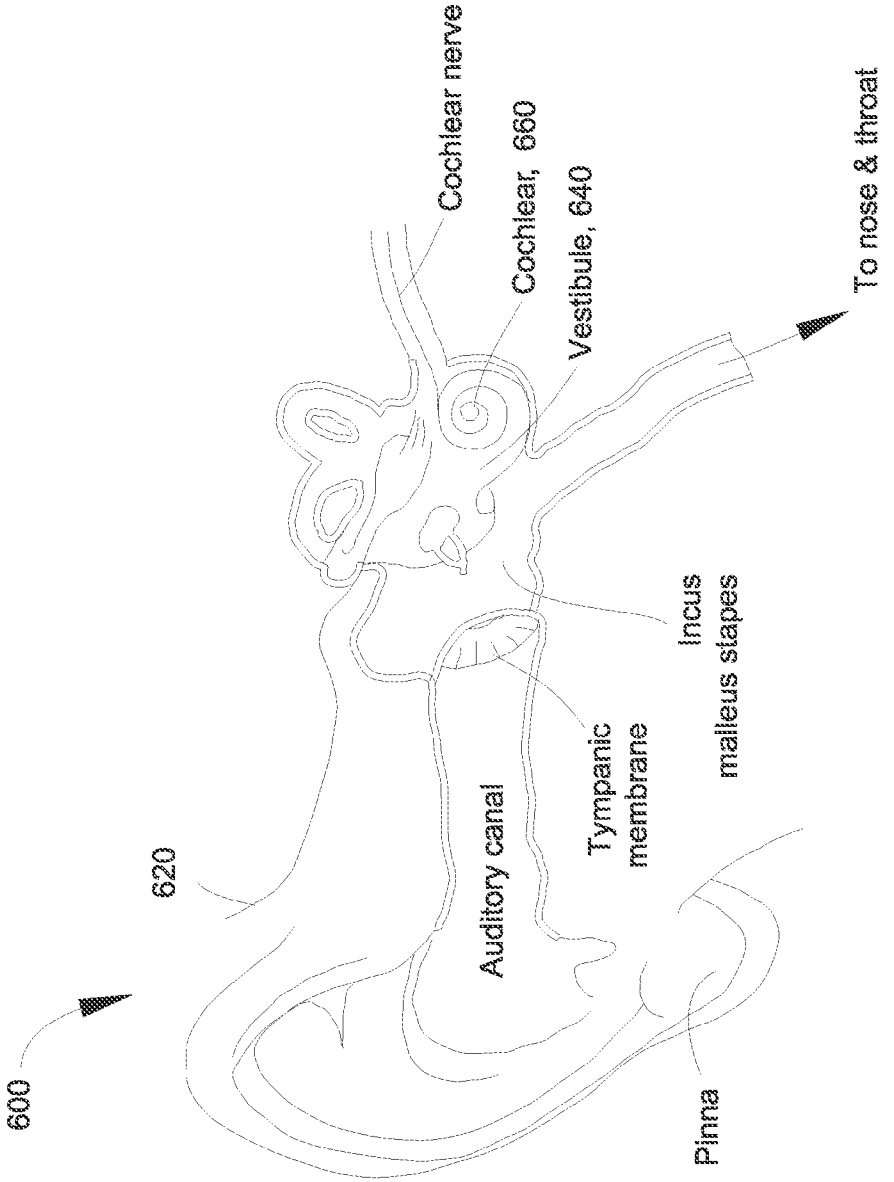

600
620
Auditory canal
Tympanic membrane
Incus
malleus stapes
Pinna
Cochlear nerve
Cochlear, 660
Vestibule, 640
To nose & throat

FIG. 10

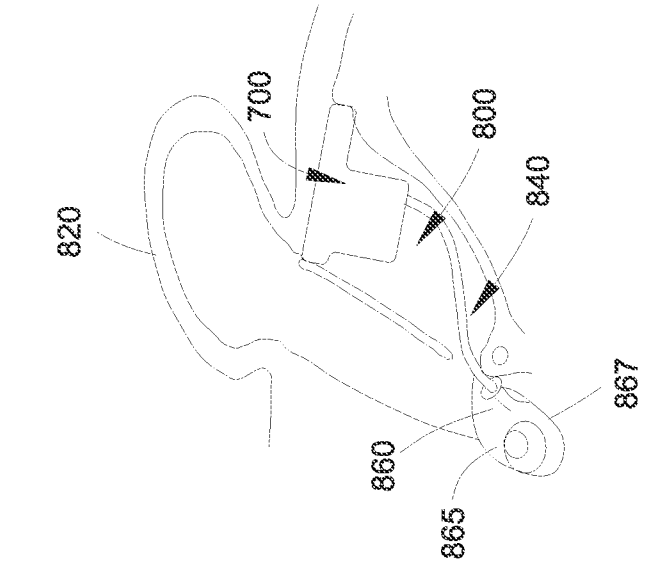


FIG. 11B

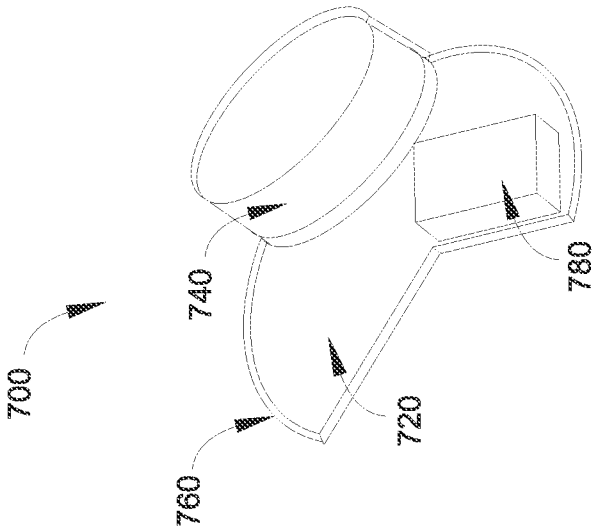


FIG. 11A

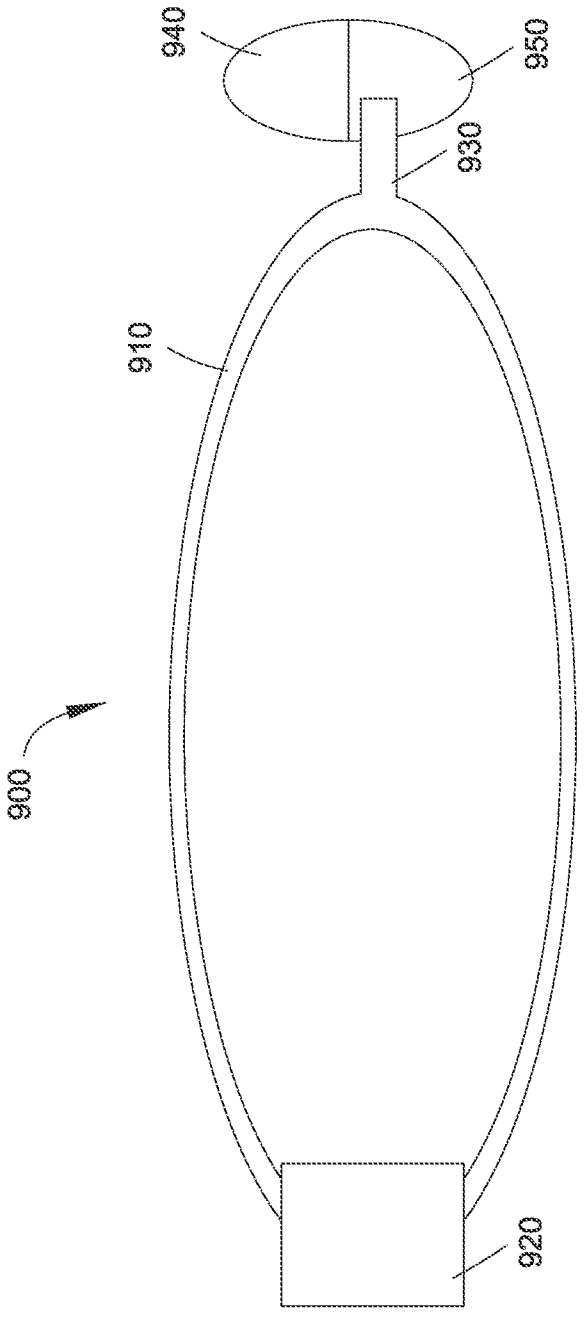


FIG. 12A

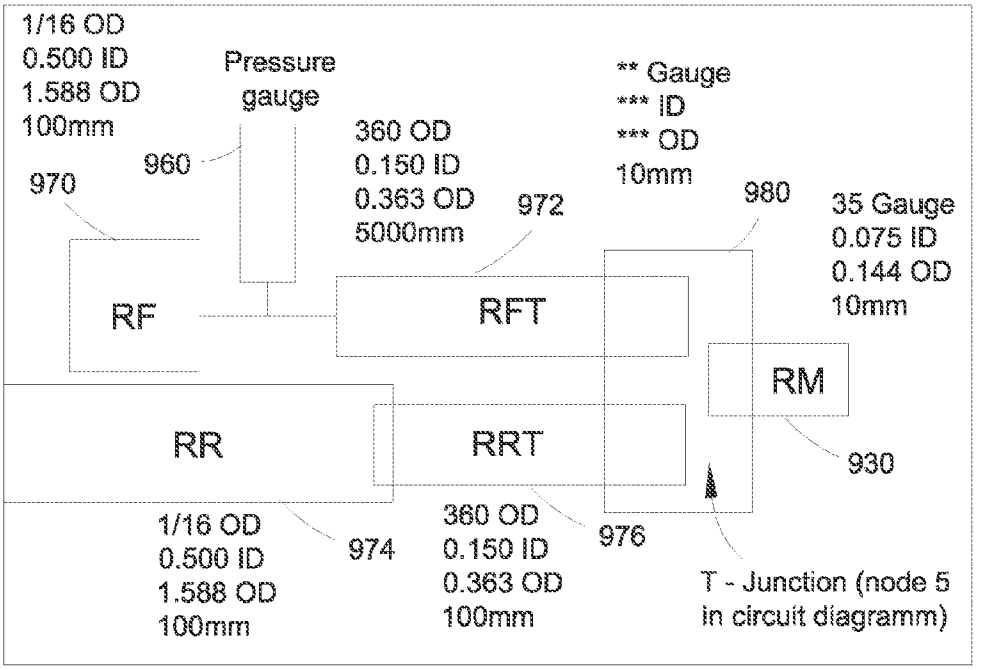


FIG. 12B

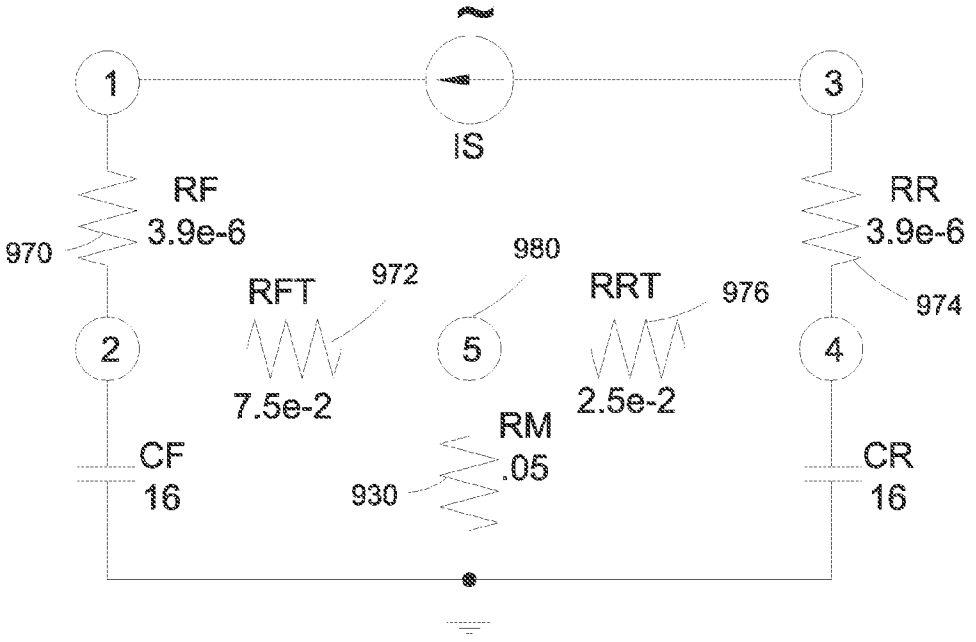


FIG. 12C

ELECTROMAGNETICALLY-ACTUATED MICROFLUIDIC FLOW REGULATORS AND RELATED APPLICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 11/046,540, filed Jan. 28, 2005, which claims priority to and the benefit of U.S. provisional application Ser. No. 60/540,283, filed Jan. 29, 2004, and U.S. provisional application Ser. No. 60/602,691, filed Aug. 19, 2004. This application is also a continuation-in-part of U.S. patent application Ser. No. 10/601,606, filed Jun. 23, 2003, which claims priority to and the benefit of U.S. provisional application Ser. No. 60/390,773, filed Jun. 21, 2002. Disclosures of all of these applications are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of flow control systems, and, more particularly, to electromagnetically-actuated microfluidic flow regulators mounted over substrates for manipulating small quantities of fluids at low flow rates.

BACKGROUND OF THE INVENTION

[0003] Emerging microsystems present solutions to many previously intractable engineering challenges, particularly in the fields of biotechnology, drug delivery, and analytical chemistry. The extension to new areas of microfabrication methods developed to create integrated circuits has spawned microelectromechanical system (MEMS) devices capable of performing the functions of conventional sensors and actuators at a fraction of the size and cost. For example, the resulting miniaturization enables complete systems to be integrated into drug delivery devices small enough to be implanted in close proximity to an organ to be treated. In addition, complex automated drug-dosing regimens can be programmed into the system or even implemented to respond to sensor input of physiological measurements. Several emerging technologies allow controlled release of drug in dried or lyophilized form from discrete compartments.

[0004] Such applications typically require flow regulators to control the transport of small quantities of fluids at low flow rates. In addition to automated drug delivery, other examples of such applications include portable diagnostic and sensor systems, microdispensers, microfluidic analytical instruments, micropropulsion systems, and many others. Specifically, in these applications, it is desirable to enable precisely controlled transport of small volumes of fluids using microfluidic valves. Such valves can control the release of fluids from a positive pressure reservoir, or can switch and route fluids to multiple reaction chambers and sensing sites. Also, it is desirable to modify some of these active valve designs to perform as micropumps.

[0005] To meet the above demands, a number of flow control approaches have been developed for microsystems, including systems utilizing thermopneumatic and osmotically-expandable chambers; electrostatic, piezoelectric, and shape-memory alloy membranes; electrochemical gas generation; and/or permanent and electromagnets, as well as systems based on electro- or thermocapillary motion of droplets. Drawbacks of these known approaches, however, include high cost of fabrication, dependence on specific properties of the fluid to be controlled, high power consumption, and unreliable performance over a range of pressures, as well as limited control functionality.

[0006] In addition, modern microsystems often integrate microfluidic components such as channels, pumps, valves, and the like with electronic components in a common platform for use in numerous applications, such as DNA analysis, drug delivery, detection of chemicals, analytes and biomolecules, tissue engineering, environmental sampling, and microdispensing. Typical, conventional platforms integrate individual microfluidic and electronic components by first assembling the components on a common substrate and then interconnecting the fluidic components to the other components of the system with an interface such as microtubules. Manufacture of these prior-art platforms for microsystems requires multiple placement steps of the various components on the substrate, dispensing of adhesive to attach the components to the substrate, and using discrete wires to electrically interconnect the various components. Moreover, these conventional platforms typically employ silicon and glass materials because these materials can easily be precisely machined.

[0007] These prior-art approaches suffer from several distinct disadvantages. Interconnecting the individual microfluidic and electronic components with delicate microtubules can be time consuming, expensive, and unreliable. Moreover, as the number of components of the system increases, so does the overall length of microtubule utilized. This, in turn, increases the total system volume of fluid and, therefore, increases the size of the samples required for analysis. Increased fluid volume also results in a decrease in performance due to longer system response time, and also decreases the functionality and reliability of the microsystem. The requirement of multiple placement steps to position the microfluidic and electronic components on the substrate and using discrete wires to interconnect the various components complicates the manufacturing processes, decreases reliability, and increases costs. Moreover, silicon and glass materials are more expensive than other readily available materials, such as polymers.

[0008] In view of the above, there is a need in the art for a low-power flow-regulating system, which is reliable, versatile, relatively easy and inexpensive to manufacture, as well as suitable for portability and programmable control in variety of diverse applications. For example, in the field of automated drug delivery, it is desirable to provide an implantable, versatile long-term drug delivery system for treatment of inner-ear disorders that is capable of delivering therapeutically effective amounts of drugs over long periods of time, with the ability to control and regulate the sequence and rate of delivery.

[0009] Also, it is desirable to provide a reliable, polymer-based integrated electrofluidic platform which eliminates the need for microtubules and discrete wires to interconnect individual fluidic and electronic components, as well as eliminates multiple placement steps in order to integrate the various components of the microsystem.

SUMMARY OF THE INVENTION

[0010] It is an object of the present invention to provide a flow control system that addresses the disadvantages of known approaches. Specifically, various implementations of the invention generally focus on a variable, closed-loop appa-

ratus for regulating a microfluidic flow that employs a low-power deflection assembly, which is surface-mounted over a flexible membrane overlying a chamber integrated into a microfabricated platform. In various embodiments, to minimize power consumption and optimize the operation, the apparatus relies on magnetic force for deflection of the membrane towards either forward or retracted position thereof.

[0011] In a microvalve configuration, in many embodiments, the membrane seals against a micromachined valve seat. When configured as a pump, in some embodiments, micromachined check valves upstream and downstream of the membrane within a microfabricated platform convert compression of the membrane into directional flow of fluid. In other embodiments, three or more sequentially disposed flow regulators operate in a predetermined order out of phase to achieve peristaltic pumping. In many embodiments, pumps and valves populate a hybrid microfluidic/printed circuit board alongside standard electronic components.

[0012] In general, in one aspect, the invention features an apparatus for regulating a microfluidic flow. The apparatus includes a substrate that defines a fluid-conducting chamber. A flexible membrane, movable between a first position and a second position, sealingly overlies the chamber. One of the positions of the membrane restricts the flow through the chamber to a greater degree than the other position. The apparatus also includes an electromagnetically-driven assembly disposed on the substrate over the membrane for unidirectionally deflecting the membrane from the first position to the second position, thereby regulating the flow through the chamber. The electromagnetically-driven assembly can be removably attached, i.e. reattachable to the substrate, or be permanently attached to it.

[0013] Embodiments of this aspect of the invention may include one or more of the following features. The membrane may be made of a polymer, such as, for example, polyimide, and have a thickness ranging from about 20 μm to 30 μm. A height of the electromagnetically-driven assembly may range from about 3.5 mm to about 5 mm.

[0014] The electromagnetically-driven assembly may move the membrane only from the first position to the second position (i.e. unidirectionally) but not from the second position to the first position. For example, the apparatus may include a resilient means, such as, for example, a spring, for urging the membrane towards the first position. In one embodiment, the second position of the membrane restricts the flow through the chamber to a greater degree than the first position. In certain versions of this embodiment, upon deactivation of the electromagnetically-driven assembly, the membrane elastically reverts into the first position. In other versions, upon deactivation of the electromagnetically-driven assembly, the membrane is movable into the first position by the flow through the chamber. In another embodiment, the first position of the membrane restricts the flow through the chamber to a greater degree than the second position. In some versions of this embodiment, a valve seat is disposed in the chamber generally opposite to the membrane, such that the membrane is elastically engageable against the valve seat by the resilient means and deflectable away from the valve seat towards the second position by the electromagnetically-driven assembly. The valve seat can be made of polymer and may be attached to the interior surface of the chamber using a dry adhesive.

[0015] In various embodiments of the invention, the electromagnetically-driven assembly includes an actuator and a magnetizable member. When the electric field is applied to the magnetizable member, the actuator is movable towards the magnetizable member by magnetic force. The actuator may be made of a material having high magnetic permeability, such as, for example, stainless steel or iron-cobalt alloy.

[0016] In some embodiments, the actuator is fixedly attached to the flexible membrane, such that the membrane is movable when the magnetic force is applied to the actuator by the magnetizable member. In other embodiments, when the magnetic force is applied to the actuator, the membrane is movable by the flow through the chamber. The magnetizable member may include an inner core member and a wire coil surrounding the inner core member. In various embodiments of the invention, the magnetizable member further includes an outer core member, such that the inner core member is axially disposed in the outer core member. At least one of the core members may include, or consist essentially of, a second material having high magnetic permeability. The inner core member may be integrally formed with the outer core member as a unitary structure. In certain embodiments, a spring is disposed between the inner core member and the wire coil. The spring urges the membrane towards one of two positions of the membrane, which restricts the flow through the chamber to a greater degree than the other position.

[0017] In an alternative embodiment in response to axial movement of the actuator when the magnetic force is applied to the actuator, the membrane is movable towards one of two positions of the membrane, which restricts the flow through the chamber to a greater degree than the other position. In this embodiment, the magnetizable member includes an inner core member defining an axial lumen therethrough and a wire coil surrounding the inner core member. The actuator is at least partially slidably disposed in the lumen. In some versions of this embodiment, the magnetizable member also includes an outer core member such that the inner core being axially disposed in the outer core member. At least one of the core members may include, or consist essentially of, a third material having high magnetic permeability. The inner core member can be integrally formed with the outer core member as a unitary structure. In a particular version of this embodiment, the electromagnetically-driven assembly includes a plunger connected to the actuator and at least partially disposed in the lumen for urging the membrane between two positions in response to axial movement of the actuator when the magnetic force is applied to the actuator. The plunger may include, or consist essentially of, a fourth material having low magnetic permeability.

[0018] In various embodiments, the apparatus also includes a power source in electric communication with the electromagnetically-driven assembly, such as, for example, a battery, for supplying the electric current to it. A flow sensor can be disposed in the chamber of the substrate for generating a signal in response to the flow through the chamber. A control system can be included for varying a duty cycle of the electromagnetically-driven assembly in response to the signal from the flow sensor. As discussed in more detail below, the substrate may be microfabricated and include a plurality of laminated polymer layers, at least one of which comprising polyimide. Also, the substrate can be fabricated by or in conjunction with known precision methods of manufacturing printed circuit boards. In some embodiments of the invention, the substrate includes a top layer defining an aperture for exposing the membrane, such that the electromagnetically-

driven assembly is to the top layer over the aperture. The top layer may be substantially rigid and include, or consist essentially of, ceramic.

[0019] Generally, in another aspect, the invention features a peristaltic micropump that includes a substrate defining a fluid-conducting chamber and at least three flexible membranes sealingly overlying the chamber. Each of the membranes is movable between a first position and a second position; one of the positions of each of the membranes restricts the flow through the chamber to a greater degree than the other position. The micropump further includes at least three electromagnetically-driven assemblies sequentially disposed on the substrate. Each assembly is associated with one of the membranes and disposed thereover for unidirectionally deflecting the membrane such that each of the membranes is moved from the one position to the other position in a predetermined order, thereby causing a directional flow through the chamber.

[0020] In yet another aspect, the invention features on a micropump that includes a substrate that defines a fluid-conducting chamber, as well as a first lumen and a second lumen in fluid communication with the chamber. A first check valve is disposed in the first lumen, and a second check valve is disposed in the second lumen. At least one of the check valves may include a plurality of laminated polymer layers. The micropump also includes a flexible membrane that is movable between two positions. The membrane sealingly overlies the chamber. One of two positions of the membrane restricting the flow through the chamber to a greater degree than the other position. The micropump further includes an electromagnetically-driven assembly disposed on the substrate over the membrane for unidirectionally deflecting the membrane between two positions, thereby causing a directional flow through the chamber.

[0021] In general, in still another aspect, the invention is directed to a drug delivery system employing a microfluidic flow regulator. Specifically, in this aspect, the invention features an implantable drug delivery apparatus for delivering a drug into a bodily fluid in a body cavity of a patient over a period of time. The apparatus includes a hollow member that defines at least one lumen for facilitating a unidirectional recirculating flow of a therapeutic fluid through the lumen. The therapeutic fluid can contain a bodily fluid, such as, for example, perilymph, and a drug. The apparatus also includes a microfluidic flow regulator, such as one or more of micropumps described above, for controlling the flow rate of the therapeutic fluid through the hollow member, and an interface member in communication with at least one lumen of the hollow member. The device thus allows for the controlled delivery of the therapeutic fluid to a predetermined location in the bodily cavity of the patient, such as, for example, a cochlea of a human ear. To facilitate the recirculation of the therapeutic fluid through the hollow member a pump can be included within the apparatus. In one embodiment of the invention this pump may be a microelectromechanical (MEMS) microfluidic pump. The micropump can be operated at a predetermined frequency, which can be either substantially constant or modulated depending upon the requirements of the system. In a particular embodiment, a flow rate of less than about one microliter per minute.

[0022] In various embodiments, control of the flow pattern of the therapeutic fluid through the hollow member is implemented through the use of a control system in electric communication with the micropump. Performance parameters regarding the flow pattern of the therapeutic fluid can also be detected by the addition of sensors to the apparatus. The information from these sensors can then be transmitted to a remote device through the use of receiving and transmitting electronics in both the remote device and the apparatus. This configuration can also allow electric signals to be sent from the remote device to the apparatus.

[0023] In another aspect, the invention stems from the realization that an innovative integrated electrofluidic system can be achieved not by attaching numerous individual fluidic and electronic components on the surface of a common substrate and then interconnecting the components with microtubules, but instead by utilizing a commercially available, low-cost polymer material with a thin layer of adhesive which is machined and processed to define microfluidic and/or electronic components directly on the polymer material; additional layers of the polymer/adhesive material are added and additional microfluidic and/or electronic components may be defined; the layers are then laminated with the thin layer of adhesive which efficiently seats and bonds the layers. As a result, the microfluidic and/or electronic components are embedded within the system.

[0024] In a particular embodiment, the substrate may include a plurality of laminated layers forming the embedded microfluidic system. The substrate may include a polyimide material, such as, for example, KAPTON, available from DuPont High Performance Materials of Circleville, Ohio. The layers may be laminated using a phenolic resin adhesive, such as, for example, R/FLEX, available from Rogers Corporation of Rogers, Conn. The phenolic resin adhesive may be etched to a thickness of 3 to 10 μm. The phenolic resin adhesive may be selectively removed from regions where bonding is undesirable between the layers and/or between a layer and an electrofluidic and/or a microfluidic component. The microfluidic system may include a valve, a pump, a reservoir, a mixer, at least one channel, a filter, a dispenser, a reactor, a heater, a concentrator, a pressurizing device or a cooling device.

[0025] Generally, in still another aspect, the invention features a method for manufacturing of an apparatus for regulating a microfluidic flow. The method includes the step of providing a plurality of platform layers. Each platform layer has an adhesive layer disposed thereon. Included in the plurality of platform layers is a layer that defines a flexible membrane. The method also includes the step of forming at least one aperture in each layer of a portion of the plurality of platform layers. An electromagnetically-driven assembly is disposed over the membrane, and the plurality of platform layers are laminated to form a substrate that defines a chamber such that the membrane overlies the chamber. The membrane is movable between two positions, one of which restricts the flow through the chamber to a greater degree than the other. The membrane is unidirectionally deflectable by the electromagnetically-driven assembly to regulate the flow through the chamber.

[0026] Embodiments of this aspect of the invention include the following features. At least one of adhesive layers can be thinned. At least one of the platform layers may include, or consist essentially of, polyimide. At least one of the adhesive layers may include, or consist essentially of, a phenolic resin. The method may also include the step of machining some of the plurality of platform layers to define at least one electronic component. The machining step may further include defining at least one additional feature of the substrate. An additional

layer can be disposed over the membrane-defining layer. This additional layer can define an opening for exposing the membrane, such that the electromagnetically-driven assembly can be attached to the second layer over the opening.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The objects and features of the invention can be better understood with reference to the drawings described below, and the appended claims. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the drawings, like numerals are used to indicate like parts throughout the various views.

[0028] FIGS. **1**A-**1**B depict cross-sectional views of the apparatus for regulating a microfluidic flow, in closed and open positions, respectively, according to one embodiment of the invention.

[0029] FIG. **2**A depicts a schematic diagram of the flow control sensor suitable for use with the apparatus of FIGS. **1**A-**1**B.

[0030] FIG. **2**B depicts a plot representing two flow sensing modes of the sensor of FIG. **2**A.

[0031] FIG. **3**A depict a drive circuit diagram of the control system for the apparatus of FIGS. **1**A-**1**B.

[0032] FIG. **3**B depicts waveforms generated at various points in the circuit shown in FIG. **3**A.

[0033] FIGS. **4**A-**4**D depict circuit diagrams of various components of the control system of FIG. **3**A.

[0034] FIGS. **5**A-**5**B depict plots of open loop flow rate of water versus duty cycle of 11 Hz and the inverse duty cycle as a function of the inlet pressure, respectively, for the apparatus of FIGS. **1**A-**1**B.

[0035] FIG. **5**C depicts a plot of the active flow control using the apparatus of FIGS. **1**A-**1**B at three different set-points.

[0036] FIG. **6** depicts a plot of the force generated by the electromagnetically-driven assembly as a function of the displacement of the actuator of the apparatus of FIGS. **1**A-**1**B.

[0037] FIG. **7** depicts a cross-sectional view of the apparatus for regulating a microfluidic flow according to another embodiment of the invention.

[0038] FIG. **8**A depicts a schematic view of the apparatus for regulating a microfluidic flow shown in FIGS. **1**A-**1**B and FIG. **7** configured to operate as a micropump.

[0039] FIGS. **8**B-**8**C depict a schematic view of one embodiment of the micropump of FIG. **8**A at different stages of its operation.

[0040] FIG. **9** depicts a schematic view of the peristaltic micropump including three or more electromagnetically-driven assemblies sequentially disposed on the substrate, according to various embodiments of the invention.

[0041] FIG. **10** depicts a sketch of a human inner ear with an implanted drug delivery system, in accordance with various embodiments of the invention.

[0042] FIG. **11**A depicts a schematic view of an exemplary drug delivery apparatus that includes a pump, reservoir, electronics and battery system, in accordance with one embodiment of the invention.

[0043] FIG. **11**B depicts a sketch of an exemplary drug delivery apparatus implanted in the mastoid cavity of a human ear.

[0044] FIG. **12**A is a schematic view of a recirculating drug delivery apparatus in accordance with some embodiments of the invention. FIGS. **12**B-**12**C depict schematic diagrams for the drug delivery apparatus of FIG. **10**.

DETAILED DESCRIPTION

[0045] As mentioned above, various aspects of the invention contemplate a variable, closed-loop apparatus for regulating a microfluidic flow employing a low-power deflection assembly, which is surface-mounted over a flexible membrane that overlies a chamber integrated into a substrate, thereby allowing for modular flexibility and rapid prototyping. In various embodiments, to minimize power consumption and optimize the operation, the apparatus relies on magnetic force for deflection of the membrane towards either forward or retracted position thereof. While generally described in conjunction with a microfabricated substrate, various aspects of the invention may employ a substrate fabricated using known precision non-microscale methods of manufacturing printed circuit boards.

[0046] Referring to FIGS. **1**A-**1**B, in various embodiments, an apparatus **100** for regulating a microfluidic flow includes an electromagnetically-driven assembly **110** fabricated by conventional machining techniques and surface-mounted onto a substrate **115** over a fluid-conducting chamber **120** covered by a flexible membrane **125**. The substrate **115** defines the chamber **120**, as well as an inflow channel **127** and an outflow channel **128**. The channels are in fluid communication with the chamber. The flexible membrane **125** overlies the chamber sealing it from the outside environment.

[0047] The electromagnetically-driven assembly **110**, discussed in more detail below, includes a magnetizable member **130** containing a wire coil **135**; a resilient means, such as, for example, a spring **140**. The electromagnetically-driven assembly further includes an actuator **145** disposed between the magnetizable member and the substrate. In certain embodiments, when the electromagnetically-driven assembly is deactivated, i.e. at zero power, the resilient means urges the actuator towards the membrane, thereby deflecting and pressing it against a microfabricated valve seat **150**.

[0048] In some embodiments, the substrate is microfabricated by laminating a plurality of stacked polymer platform layers **160** that are micromachined prior to lamination to define the features of the substrate **115**, including the chamber **120**, the channels **127**, **128**, the membrane **125**, and/or the valve seat **150**, as discussed in more detail in a co-pending patent application Ser. No. 10/601,606 entitled "Integrated Electrofluidic System and Method" ("'606 application"), incorporated herein by reference in its entirety. For example, at least one aperture can be formed in each layer of a certain portion of the plurality of platform layers, such that desired interior features are defined when the layer are aligned in a predetermined manner and then laminated. The substrate can also be fabricated by or in conjunction with known precision methods of manufacturing printed circuit boards. In a particular embodiment, the channels **127**, **128** are disposed within different layers of the substrate, such that the inflow channel **127** is disposed below the outflow channel **128**. The layers may be formed from a polyimide material, such as, for example, KAPTON film, available from DuPont High Performance Materials of Circleville, Ohio. The layers may be laminated to form the resulting substrate using a phenolic resin adhesive, such as, for example, R/FLEX adhesive, available from Rogers Corporation of Rogers, Conn. The phenolic resin adhesive may be thinned to a thickness ranging from about 3 μm to 10 μm by etching, such as, for example, plasma

etching. The phenolic resin adhesive may be selectively removed from regions where bonding is undesirable between the layers and/or between a layer and an electrofluidic and/or a microfluidic component. In some embodiments, the membrane is part of a top layer positioned over the chamber when the platform layers are laminated.

[0049] The apparatus **100** may also include a sensor device connected to or integrated within the substrate. In some embodiments, the sensor device is mounted on the substrate and electrically interconnected to other components of the apparatus using standard surface mounting techniques known to those skilled in the art, such as, for example, utilizing liquid adhesives or soldering. With continued reference to FIG. **1**A, in other embodiments of the invention, the sensor **165** is a two-element, thin-film anemometer device integrated between the layers **160** within the substrate **115**, for example, within the fluid-conducting chamber **120**, the inflow channel **127**, or the outflow channel **128**, as shown in FIGS. **1**A-**1**B. Various implementations of this sensor are disclosed in the '606 application, as well as in an article by Dube et al. entitled "A Si-Based FPW Sensor Array System with Polymer Microfluidics Integrated on a PCB," *Proceedings IEEE Sensors* 2002, Orlando, Fla., 460-465 (2002), incorporated herein by reference. In one particular embodiment, the sensor is a flow sensor that includes a resistive heater and a resistive temperature detector positioned in the inflow channel. As fluid flows over the resistive heater, the fluid transfers heat from the resistive heater to the resistive temperature detector. This heat transfer creates a change in temperature at the temperature detector, which causes a change in resistance of the detector that may be used as a quantitative measure of flow rate. In another particular embodiment, the sensor is a mass sensor device, such as flexure plate wave device.

[0050] The flexible membrane **125** can be made of a polymer, such as, for example, polyimide, and have a thickness ranging from about 20 μm to 30 μm, preferably between 22 μm and 27 μm, for example, about 25 μm. The radius of the membrane may range from about 500 μm to about 900 μm. As mentioned above, the membrane can be part of one of layers **160** that is disposed on top of the stack upon lamination. The membrane is generally movable between two positions, with one of the positions of the membrane restricting the flow from the inflow channel to the outflow channel through the chamber to a greater degree than the other position. For example, in various embodiments, when deflected inwardly towards the bottom of the chamber (or the valve seat disposed, thereon), the membrane reduces or completely blocks the flow through the chamber. Specifically, the membrane blocks the flow when completely deflected inwardly until it is pressed against the bottom of the chamber, or, in the embodiment shown in FIGS. **1**A-**1**B, the valve seat **150** disposed in the bottom part of the chamber generally opposite to the membrane. The valve seat can be made of polymer and may be attached to the interior surface of the chamber using a dry adhesive. Alternatively, the valve seat can be micromachined as disclosed in the '606 application along with other interior features of the substrate. In some embodiments of the invention, the valve seat has a generally toroidal shape and defines a lumen therethrough in communication with the channel **127**. The inner diameter of the valve seat may range from about 150 μm to 200 μm, for example, is about 170 μm. The outer diameter of the valve seat may range from about 300 μm to 400 μm, for example, is about 340 μm.

[0051] With further reference to FIGS. **1**A-**1**B, in various embodiments of the invention, as mentioned above, the apparatus **100** includes the electromagnetically-driven assembly **110** surface-mounted onto the substrate **115** over the flexible membrane **125** for unidirectionally deflecting the membrane from the first position to the second position, thereby regulating the flow through the chamber. In some embodiments, the electromagnetically-driven assembly is mounted onto the top layer of the substrate after the substrate is formed by laminating the layers **160**. In other embodiments, the assembly is attached to one of the layers **160** that defines the membrane **125** and then the layers are laminated to fabricate the substrate. The electromagnetically-driven assembly can be removably attached, i.e. reattachable to the substrate, or be permanently attached to it.

[0052] The assembly **110** includes a base member **170** either fixedly or removably mounted onto the substrate **115** using any suitable mounting method known in the art, such as, for example, bonding, welding, employing adhesives, clamps, or screws. In a particular embodiment of the invention, a rigid ceramic layer **172**, for example, a layer of MACOR machinable glass ceramic available from Corning, Inc. of Corning, N.Y., is bonded to the substrate, thereby forming a rigid mounting plate for the base member. The base member defines a lumen **174** axially disposed therethrough and extending to the membrane. The actuator **145** is slidably disposed in the lumen and, in some embodiments, is attached to the membrane by an adhesive or other means. The assembly further includes the magnetizable member **130** fixedly disposed over the base member and attached thereto by any method known in the art, for example, using an adhesive, such that the actuator is generally disposed between the magnetizable member and the membrane. In various embodiments, the magnetizable member includes an outer core member **180** and an inner core member **185** axially disposed in the outer core member. The outer core member serves as a housing for the wire coil **135**, which is disposed within the outer core member surrounding the inner core member. The actuator, the inner core member, and/or the outer core member can include, or consist essentially of, a material having high magnetic permeability, such as, for example, 416 stainless steel or an iron-cobalt alloy. In some embodiments, the inner core member is integrally formed with the outer core member as a unitary core structure by conventional metal processing techniques. In other embodiments, the outer core member is not included, such that the inner core member, having the wire coil wound thereover, is connected directly to the base member.

[0053] The total height H of the electromagnetically-driven assembly **110** ranges from about 3 mm to about 5 mm, for example, is about 4.1 mm. Outer diameter D of each of the base member **170** and the magnetizable member **130** is less than about 5 mm, for example, is about 4.3 mm.

[0054] The apparatus **100** further includes a power source (not shown) in electric communication with the wire coil, such as, for example, a battery, for supplying the electric current that actuates the electromagnetically-driven assembly. In various embodiments, a control system discussed in more detail below is included for varying a duty cycle of the electromagnetically-driven assembly.

[0055] Still referring to FIG. **1**A-**1**B, as mentioned above, the electromagnetically-driven assembly **110** further includes the resilient means disposed within the magnetizable member **130** in contact with the actuator **145** for elastically biasing the

actuator towards the substrate. In one embodiment, the resilient means is a spring **140** surrounding the inner core member **185** underneath the wire coil **135**. In a particular embodiment, the spring generates a biasing force ranging from 0.30 N to 0.40 N, preferably, about 0.34 N, such that, when the electromagnetically-driven assembly is deactivated, the resilient means urges the actuator towards the membrane, thereby deflecting and pressing it against the microfabricated valve seat **150** yielding a normally-closed valve.

[0056] Referring to FIG. **1**B, in operation, when the electric current is conducted through the wire coil **135** from the power source, as skilled artisans will readily recognize, a magnetic force is generated in the magnetizable member **130** through electromagnetic induction, attracting the actuator **145** towards the inner core member **185** of the magnetizable member.

[0057] As mentioned above, in some embodiments, the actuator is fixedly attached to the flexible membrane. In such embodiments, the membrane is pulled upward and is movable away from the valve seat **150** (or the bottom portion of the chamber **120**) against the biasing force of the spring **140** when the magnetic force is applied to the actuator by the magnetizable member, thereby opening fluid communication between the channels **127**, **128** through the chamber **120**. Still referring to FIG. **1**B, in other embodiments, the actuator is not attached to the membrane. In these embodiments, when the magnetic force is applied to the actuator such that it is attracted to the core member **185**, the membrane is no longer constrained by the actuator and is movable upward and away from the valve seat by the flow through the chamber. The power applied to the electromagnetically-driven assembly for counteracting the biasing force of the spring may range from about 10 to about 40 mW, for example, is about 35 mW. Conversely, when the electromagnetically-driven assembly is deactivated, i.e. at zero power, the spring urges the actuator back towards the membrane, thereby deflecting the membrane down towards the interior of the chamber and pressing it against the valve seat, thereby restricting the flow. If a square wave current of appropriate amplitude is applied to the coil, the valve will open and close periodically. Further, if the duty cycle of the current signal is varied, the average flow through the valve will vary (the average must be taken over a time interval that is large compared to the period of the current signal driving the actuator). This variation in average flow will be generally proportional to the duty cycle of the current signal, as discussed in more detail below.

[0058] With continued reference to FIGS. **1**A-**1**B, as mentioned above, control of the flow pattern of the fluid through the chamber **120** is implemented through the use of a control system in electric communication with the apparatus **100**. Performance parameters regarding the flow pattern can be detected by the addition of sensors to the apparatus as described above. The information from these sensors can then be transmitted to a remote device through the use of receiving and transmitting electronics in both the remote device and the apparatus. This configuration can also allow electric signals to be sent from the remote device to the apparatus. Thus, in various embodiments, the apparatus includes the control system for varying a duty cycle of the electromagnetically-driven assembly. The control system uses a position-integral controller, whereby the sensor output is compared to a reference voltage and integrated. The resulting error signal is compared to a sawtooth to generate a controlled duty cycle drive signal. In a particular embodiment, a power-efficient bi-level current drive uses a 3 ms high-level current pulse for pull-in and a low-level current to hold the apparatus in the open state. Flow through the channel **127** through the chamber **120** to the channel **128** is controlled by variation of the duty cycle of the apparatus **100**. As mentioned above, in some embodiments, in order to detect the flow parameters, the control system employs the sensor **165** integrated between the layers **160** within the substrate **115**, for example, within the fluid-conducting chamber **120**, the inflow channel **127**, or the outflow channel **128**, as shown in FIGS. **1**A-**1**B.

[0059] Referring to FIG. **2**A, in one particular embodiment, the flow sensor is a two-element, thin-film anemometer device **200** that includes a resistive heater **210** and a resistive temperature detector **220**. The heater trace heats fluid in the channel immediately above it, such as for example, an inflow channel or the outflow channel. As fluid flows over the resistive heater, it transports this heat from the resistive heater to the resistive temperature detector over a gap L**3**, inducing a temperature increase in the detector. This temperature change at the temperature detector causes a change in resistance of the detector that may be used as a quantitative measure of flow rate. In some embodiments of the invention, length L**1** of the heater ranges from about 1400 μm to about 1500 μm, for example, is about 1460 μm. Also, length L**2** of the temperature detector may range from about 1700 μm to about 1850 μm, for example, is about 1780 μm. In many embodiments, the length L**3** of the gap between the heater and the temperature detector ranges from about 3000 μm to about 4000 μm, for example, is about 3380 μm.

[0060] For flow rates, the heater is able to induce a large temperature change in the fluid. The temperature of the fluid drops as it flows through the channel, dispersing heat to the channel walls. Thus for low flow rates, the temperature at the detector will increase with increasing flow rates because less heat is lost to the channel walls while the fluid traverses from the heater to the detector. At higher flow rates, the fluid flows by the heater so rapidly that it does not pick up as much heat per unit volume. Thus for high flow rates, the detector temperature decreases with increasing flow rate because less heat is picked up by the detector. This behavior is characterized by the plot shown in FIG. **2**B, depicting a data plot showing two modes of flow sensor: temperature of detector initially increases with flow because less heat is lost to channel walls in between heater and detector, but temperature ultimately begins to drop as flow increases further because heat transfer from the heater to the fluid may not occur rapidly enough.

[0061] The flow is controlled by a proportional-integral (PI) controller which integrates the sensor error signal, i.e. actual temperature deviation from a setpoint, which is then used to drive the nonlinear duty-cycle drive of the valve. At least two distinct readout methods can be used to do flow rate sensing. The flow setpoint can be set by either the sensor's heater power or by its temperature setpoint. In one case, power to the heater is held constant and the temperature of the sensor indicates the flow rate. In a second case, the temperature of the sensor is held constant and the heater power required to maintain the temperature gives an indication of the flow. In either instance, preliminary calibration is contemplated to accurately determine flow parameters.

[0062] One exemplary control scheme using a PI controller as depicted in FIG. **3**A. Referring to FIG. **3**A, the sensor output V_0 is compared to a reference voltage V_{set}, which defines a temperature setpoint. The difference signal is amplified and integrated. This error signal is then compared to a

sawtooth waveform. The resulting valve drive signal is shown in FIG. **3**B, wherein error signal V_{PI} is compared to a sawtooth signal V_{saw}, variable duty-cycle signal, and variable duty-cycle signal after addition of high-voltage pull-in pulse. A power-efficient bi-level current drive uses a short high-level current pulse for pull-in and a low-level current to hold the valve in the open state. Some of many possible implementations of the circuits used to implement the various components of the control system are temperature detector readout circuit, where Rs is the RTD sensing element (FIG. **4**A), PI compensator, include an difference amplifier (FIG. **4**B), and integrator (FIG. **4**C), as well as a duty-cycle control circuit (FIG. **4**D)

[0063] Thus, in many embodiments of the invention, flow control against a varying head pressure of water was achieved by controlling the valve duty cycle in response to the output of the flow sensor. As shown in FIG. **5**A, in one example, open loop flow rate of water was measured versus valve duty cycle at 11 Hz, with constant head pressure of 10 kPa applied. FIG. **5**B depicts an active flow control at three different setpoints, whereby the inverse duty cycle is plotted as a function inlet pressure, showing the expected linear dependence. In this example, the flow was regulated to better than 1% at multiple setpoints in the range of 10-45 μL/min over at least one order of magnitude of pressure, as shown in FIG. **5**C In this example, the system maintains a flow setpoint against a wide pressure range, but it has a low pressure cutoff due to the passive resistance of the fully open valve and a high pressure cutoff due to the valve's leak resistance when closed.

[0064] In a specific example, the force generated by the electromagnetically-driven assembly was measured by suspending the magnetizable member at fixed distances from the actuator using plastic shims. The minimum current required to resist the gravitational force on the core was recorded and is depicted in FIG. **6**.

[0065] The invention further contemplates an alternative design for an electromagnetically-driven assembly of the apparatus for regulating a microfluidic flow. Referring now to FIG. **7**, in some embodiments, an apparatus **300** includes an electromagnetically-driven assembly **310** surface-mounted onto a substrate **315** over a fluid-conducting chamber **320** covered by a flexible membrane **325**. As described above with reference to FIGS. **1**A-**1**B, the substrate defines the chamber **320**, as well as an inflow channel **327** and an outflow channel **328** in fluid communication with the chamber. The flexible membrane **325**, which can be either a separate structure or an integral part of the substrate, overlies the chamber sealing it from the outside environment. The membrane is generally movable between two positions, with one of the positions of the membrane restricting the flow from the channel **327** to the channel **328** through the chamber to a greater degree than the other position. For example, in various embodiments, when deflected down towards the interior of the chamber, the membrane reduces or completely blocks the flow through the chamber. Specifically, the membrane blocks the flow when completely deflected inwardly until it is pressed against either the bottom of the chamber, or, as shown in FIG. **7**, the valve seat **350** disposed in the bottom part of the chamber generally opposite to the membrane. The valve seat can be made of polymer and may be attached to the interior surface of the chamber using a dry adhesive. Alternatively, the valve seat can be micromachined as disclosed in the '606 application along with other interior features of the substrate. In some embodiments of the invention, the valve seat has a generally toroidal shape and defines a lumen therethrough in communication with the channel **327**.

[0066] As mentioned above, the electromagnetically-driven assembly **310** is surface-mounted onto the substrate **315** over the flexible membrane **325** for unidirectionally deflecting the membrane between two positions, thereby regulating the flow through the chamber. Dimensions of the electromagnetically-driven assembly **310** are within the ranges disclosed above is connection with the embodiment shown in FIGS. **1**A-**1**B.

[0067] The electromagnetically-driven assembly includes a base member **360**, either fixedly or releasably mounted onto the substrate using any suitable mounting method known in the art. For example, as described above with reference to FIGS. **1**A-**1**B, in a particular embodiment of the invention, a rigid ceramic layer **362**, for example, a layer of MACOR machinable glass ceramic available from Corning, Inc. of Corning, N.Y., is bonded to the substrate, thereby forming a rigid mounting plate for the base member. The base member defines a lumen **364** axially disposed therethrough and extending to the membrane.

[0068] The assembly further includes a magnetizable member **370** disposed over the base member and attached thereto by any method known in the art, for example, using an adhesive. The magnetizable member includes an outer core member **372** attached to the base member and an inner core member **374** axially disposed in the outer core member. The outer core member serves as a housing for the wire coil **376** is disposed within the core member surrounding the inner core member. In some embodiments, the inner core member is integrally formed with the outer core member as a unitary core structure by conventional metal processing techniques. The inner core member defines a lumen **378** axially disposed therethrough and extending to the membrane. In other embodiments, the outer core member is not included, such that the inner core member, having the wire coil wound thereover, is connected directly to the base member.

[0069] An actuator **380** is disposed over the magnetizable member **370**. In a particular embodiment of the invention, the actuator includes a protrusion **382** at least partially extending into the lumen **378**.

[0070] In some embodiments, the protrusion of the actuator extends to the membrane, such that the membrane is deflectable downward by protrusion upon the axial movement of the actuator. In other embodiments, as shown in FIG. **7**, a plunger **388** is slidably disposed in the lumens **364**, **378** and is dimensioned to contact the membrane **325** at least upon downward movement of the plunger. In certain versions of this embodiment, the plunger is attached to the actuator, for example, by having a cavity in its top portion dimensioned to at least partially receive and secure the protrusion therein. The actuator, the inner core member, and/or the outer core member may include, or consist essentially of, a material having high magnetic permeability, such as, for example, 416 stainless steel or an iron-cobalt alloy. The plunger is preferably formed from a lightweight material having low magnetic permeability, such as, for example, aluminum or plastic.

[0071] The apparatus **300** further includes a power source (not shown) in electric communication with the wire coil, such as, for example, a battery, for supplying the electric current to it thereby actuating the electromagnetically-driven assembly. In various embodiments, a control system discussed above is included for varying a duty cycle of the electromagnetically-driven assembly.

[0072] Still referring to FIG. **7**, in operation, when the electric current is conducted through the wire coil **376** from the power source, as skilled artisans would readily recognize, a magnetic force is generated in the magnetizable member **370** through electromagnetic induction, attracting the actuator **380** downward towards the inner core member **374** of the magnetizable member. Downward movement of the actuator urges the plunger **388** towards the membrane **325**, thereby deflecting the membrane inwardly and pressing it against the bottom portion of the chamber (or, in some embodiments, the valve seat **350** disposed thereon), thereby restricting the flow. Conversely, when the electromagnetically-driven assembly **310** is deactivated, i.e. at zero power, in some versions of this embodiment, the membrane elastically reverts away from the bottom of the chamber, i.e. into the open position, thereby opening fluid communication between the channels **327** and **328** through the chamber **320**, yielding a normally-open valve. In other versions, upon deactivation of the electromagnetically-driven assembly, the membrane is no longer constrained by the plunger and/or the actuator and is movable upwards and away from the valve seat (or the bottom of the chamber) into the open position by the flow through the chamber.

[0073] Additionally, a resilient means, such as, for example, a spring **395** can be provided in contact with the actuator **380** for elastically biasing the actuator and plunger **388** away from the membrane, thereby further facilitating the normally-open state of the apparatus. In a particular embodiment, the spring is disposed within the outer core member **372** and surrounds the inner core member **374** underneath the wire coil **376**. The spring may generate a biasing force ranging from 0.30 N to 0.40 N, preferably, about 0.34 N, such that, when the electromagnetically-driven assembly is deactivated, the resilient means urges the actuator and the plunger away from the membrane.

[0074] In yet another aspect, the apparatus for regulating a microfluidic flow is configured to perform as a micropump. Referring to FIG. **8**A, in various embodiments, a micropump **400** includes an electromagnetically-driven assembly **410** configured according to any of the embodiments described above (with reference to FIGS. **1**A-**1**B and FIG. **7**) that is surface-mounted onto a substrate **415** over a fluid-conducting chamber **420** covered by a flexible membrane **425**. The substrate defines an inflow channel **427** and an outflow channel **428** in fluid communication with the chamber. The flexible membrane **425**, which can be either a separate structure or an integral part of the substrate, overlies the chamber sealing it from the outside environment. The membrane is generally movable between two positions, with one of the positions of the membrane restricting the flow from the inflow channel to the outflow channel through the chamber to a greater degree than the other position. Further, an inflow check valve **430** is disposed in the channel **427**, and an outflow check valve **432** is disposed in the channel **428**. At least one of the check valves can be micromachined as disclosed in the '606 application along with, for example, a valve seat, and other interior features of the substrate. In some embodiments, at least one of the check valves includes a plurality of laminated polymer layers.

[0075] As skilled artisans will readily recognize, operating the electromagnetically-driven assembly to deflect the membrane between the open and closed positions (or vice-versa) alternately opens and doses the check valves, and thereby converts compression of the membrane into a directional flow of fluid through the chamber from the inflow channel to the outflow channel. Specifically, referring now to FIGS. **1**A-**1**B and **8**B-**8**C, in one embodiment, the micropump **400** includes the electromagnetically-driven assembly **110**. In operation, during the first phase, the electromagnetically-driven assembly is actuated causing the membrane **425** to deflect downward towards the bottom of the chamber, as shown in FIG. **8**B. This movement of the membrane increases the pressure in the chamber **120** and causes the outflow check valve to open, the inflow check valve to close, and the fluid to exit the chamber through the outflow channel. Then, during the second phase the electromagnetically-driven assembly is deactivated, such that the resiliency urges the membrane upward and away from the bottom of the chamber towards its initial position. This movement of the membrane forces the fluid to enter the chamber through the inflow channel, opening the inflow check valve and closing the outflow check valve, as shown in FIG. **8**C.

[0076] In another aspect, the invention contemplates a peristaltic micropump. As generally recognized in the art, peristaltic pumping employs rotating rollers pressed against special flexible tubing to create a pressurized flow. The tube is compressed at a number of points in contact with the rollers or shoes. The media is moved through the tube with each rotating motion. The individual components of peristaltic pumps include a pump head, drive, and tubing. Peristaltic pumps are also referred to as flexible member pumps, flexible tube pumps, dispensing pumps, or dosing pumps. The advantages of peristaltic pumps are that the components of the pump may be chosen when the integrity of the media is a requirement of the application since the fluid type does not contact any internal parts. Seals and valves are typically not needed as in other known pumps.

[0077] Referring to FIG. **9**, in one embodiment, three or more apparatuses for regulating a microfluidic flow can be configured to perform as a peristaltic micropump **500**, whereby three or more electromagnetically-driven assemblies **510***a*, **510***b*, and **510***c*, each configured according to any of the embodiments described above with reference to FIGS. **1**A-**1**B and FIG. **7** are sequentially disposed over the common substrate **515** defining fluid-conducting chambers **520***a*, **520***b*, and **520***c*, and are actuated in a predetermined order out of phase to achieve peristaltic pumping. Specifically, each assembly is associated with one of the membranes **525***a*, **525***b*, and **525***c* and disposed thereover for unidirectionally deflecting the membrane. Each of the membranes is movable between a first position and a second position; one of the positions of each of the membranes restricts the flow through the chamber to a greater degree than the other position. The assemblies are actuated such that each of the membranes is moved from the forward position to the retracted position, or vice versa, in a predetermined order, thereby causing a directional flow from an inflow channel **527** to an outflow channel **528** through the chambers **520**.

[0078] As mentioned above, in the field of automated drug delivery, it is desirable to provide an implantable, versatile long-term drug-delivery system for treatment of inner-ear disorders that is capable of delivering therapeutically effective amounts of drugs over long periods of time, with the ability to control and regulate the sequence and rate of delivery. Whereas conventional drug infusers utilize macroscale machined components to pump liquid drugs from a reservoir, the apparatus for regulating a microfluidic flow according to various embodiments of the invention facilitates replacement

of these components with a synthesis of micropumps and MEMS solutions for drug storage and release, which will result in smaller devices with greater functionality. This will enable the opening of the inner ear and other previously inaccessible locations in the body for new direct treatment, without the side effects of systemic delivery.

[0079] Microfluidics and microelectromechanical systems (MEMS) capability can be used for drug delivery applications, to allow or provide a controlled rate, low drug volume, and/or liquid formulation (e.g. for an implantable inner ear delivery system). In an exemplary embodiment, a fluidic system having a closed loop microfluidic flow controller can be used with animal test apparatus. In one embodiment of the current invention, an implanted recirculating delivery system can be used in therapy for hearing loss and Meniere's disease.

[0080] In some embodiments, the micromechanical device for intracochlear drug delivery discloses utilizing a surgical approach that is similar to cochlear implantation, but minimizes cochlear insult. The implementation concept includes a double-lumen intracochlear catheter inserted into the scala tympani through a cochteostomy adjacent to the round window. In its implanted position, it is similar to cochlear implants that also traverse the tympanomastoid cavity with electrodes positioned within the cochlea, except that the depth of insertion is much less.

[0081] In accordance with the invention, drug delivery to the ear relies on a method in which a recirculating stream of fluid from the patient is passed through a device and is infused remotely rather than within the tissue, which enables recirculation and control of very low flow rates (e.g., less than 1 microliter/minute) as required in the confined volume of the inner ear. A specific application with respect to inner ear diseases provides for direct infusion of the cochlea through a catheter, using an implanted device to programmably and continually deliver drugs through the catheter.

[0082] The recirculating fluid permits the reservoir to contain a highly concentrated solution, and therefore can potentially produce a device that operates for years without refilling. This greatly reduces the risk of microbial contamination during refill. Another benefit is using a vehicle that is inherently biochemically compatible. In addition, the perilymph may circulate through the catheter at a rate that is independent of the drug delivery rate. Thus these parameters can be optimized separately. It is likely that frequent circulation of the perilymph will maintain potency in the catheter, whereas a slow one-way drug infusion would occlude. Finally, because there is controlled supply of liquid solvent, it is not necessary to use a liquid drug reservoir. The drug storage may take any number of forms, such as microchip arrays, bio-erodible polymers, or even hybrid combinations of these drug delivery methods.

[0083] In a specific exemplary embodiment, a microfluidic pump, according to any of the embodiments described above with reference to FIGS. **8**A-**8**C and FIG. **9**, recirculates human perilymph, which is withdrawn and returned to the inner ear through a catheter, implanted through the round window membrane or adjacent tissue. Drugs are injected into this recirculating stream from one or more reservoirs by one or more microvalves and/or one or more other drug release methods.

[0084] As used herein, the term "drug" is understood to mean any natural or synthetic, organic or inorganic, physiologically or pharmacologically active substance capable of producing a localized or systemic prophylactic and/or therapeutic effect upon administration. A drug includes (i) any active drug, (ii) any drug precursor or pro-drug that may be metabolized within the animal to produce an active drug, (iii) combinations of drugs, (iv) combinations of drug precursors, (v) combinations of a drug with a drug precursor, and (vi) any of the foregoing in combination with a pharmaceutically acceptable carrier, excipient, or formulating agent.

[0085] The drug or drugs of interest may be stored in the apparatus either in pure form or as a formulation, for example, in combination with a pharmaceutically acceptable carrier or encapsulated within a release system. A release system can include a matrix of a biodegradable material or a material which releases incorporated drug by diffusion. The drugs can be homogeneously or heterogeneously distributed within the release system. A variety of release systems may be useful in the practice of the invention; however, the choice of the appropriate system will depend upon rate of drug release required by a particular drug regime. Both non-degradable and degradable release systems can be used. Suitable release systems include polymers and polymeric matrices, non-polymeric matrices, or inorganic and organic excipients and diluents such as, but not limited to, calcium carbonate and sugar. Release systems may be natural or synthetic. However, synthetic release systems are preferred because generally they are more reliable, more reproducible and produce more defined release profiles. The release system material can be selected so that drugs having different molecular weights are released from a particular cavity by diffusion through or degradation of the material. Biodegradable polymers, bioerodible hydrogels, and protein delivery systems currently are preferred for drug release via diffusion or degradation.

[0086] Representative synthetic, biodegradable polymers include, for example: polyamides such as poly(amino acids) and poly(peptides); polyesters such as poly(lactic acid), poly (glycolic acid), poly(lactic-co-glycolic acid), and poly(caprolactone); poly(anhydrides); polyorthoesters; polycarbonates; and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), copolymers and mixtures thereof. Representative synthetic, non-degradable polymers include, for example polyethers such as poly(ethylene oxide), poly(ethylene glycol), and poly(tetramethylene oxide); vinyl polymers-polyacrylates and polymethacrylates such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic and methacrylic acids, and others such as poly(vinyl alcohol), poly(vinyl pyrolidone), and poly(vinyl acetate); poly(urethanes); cellulose and its derivatives such as alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, and various cellulose acetates; polysiloxanes; and any chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skated in the art), copolymers and mixtures thereof.

[0087] Preferably, the storage capabilities of the apparatus are such that it holds sufficient amount of the drug to provide a continuous delivery over the extended delivery period, e.g., several weeks, months, or even longer. The storage volume needed thus depends on characteristics such as drug solubility, drug delivery rate, period of delivery, drug's half life, etc. Once implanted, the device continuously delivers the drug for prolonged period of time until replenishment.

[0088] In various embodiments of the invention, communication with a remote device external to the patient's body

and capable of controlling of the infusion rate allows for modification of the therapy in response to a patient's symptoms and reactions. This feature may include control of the recirculation rate to allow different dosage schemes, such as, but not be limited to, either steady low concentrations or intermittent high concentrations of drugs. Variation of the dosage based on the time of day can also be desirable.

[0089] In addition to performance features, a number of safety features may also be included in embodiments of the invention. Exemplary features may include, but are not limited to, automatic shutoff control if pressure or flow sensors give abnormal readings and self-diagnostic routines which may run automatically or upon prompting from an external controller. In one embodiment of the invention, telemetry can enable a physician to interrogate settings, identify low battery or other alarm signals, and obtain device identification or serial number. A clinician may communicate with the device by means of a hand-held module connected to a personal computer, or through another analogous communication device.

[0090] The ability to communicate with implanted electronic devices has been well established over the last 25 years (e.g. with pacemaker systems). As such, communicating with and controlling the drug delivery device does not pose a major problem. Nonetheless, the communication subsystem facilitates reliable and robust operation, since minimal service and adjustment is possible after installation.

[0091] As a result of its ubiquitous application, communication via the wireless RF technique offers one approach for remote communication. In addition to enabling a small low-cost device, the RF technique also provides a convenient means by which the battery energy may be replenished. Although recent studies have concentrated on frequencies above a few hundred megahertz, these studies have been motivated by the need to distribute real-time image information. The bandwidth requirements for the drug delivery device are much more modest. A frequency of 10 MHz helps minimize attenuation due to skin effect, while at the same time allows use of a small, low profile antenna.

[0092] Several additional physical means are also available for coupling communication signals from the implanted device to an external interrogator or programmer. In one embodiment of the invention, mechanical (acoustic) waves may provide a communication mechanism. The acoustic technique is enabled by the recent availability of miniature transducers fabricated with MEMS technology. Further embodiments may include, but not be limited to, the use of optical means or direct volume conduction to communicate with an implanted device.

[0093] One embodiment of the current invention can be seen in FIG. **10**. Referring to FIG. **10**, an implanted recirculating delivery system directs fluid to and from the cochlea of a human ear **600**. A double lumen catheter **620** is implanted a body and is in communication with the vestibule **640** and cochlea **660** of the inner ear. This arrangement allows a fluid to recirculate between the cochlea and an external or internally planted pump (not shown).

[0094] An exemplary embodiment of the invention with an electronic device embedded within the mastoid cavity of a human ear is illustrated in FIGS. **11**A and **11**B. Referring to FIG. **11**A, in one embodiment, a device **700** includes a micropump **720** connected to a reservoir **740**. The flow rate produced by the pump, and the rate at which a drug is released by the reservoir, can be controlled by a control system **760** integrated within the device. Power can be supplied to the system through a battery **780**, which can also be embedded in the device. Alternative embodiments of the device, may incorporate additional features, such as but not limited to further reservoirs or additional electronic features, but can also be simplified by removing attachments shown herein, such as the reservoir. For example, drug storage within the device can be achieved through a number of methods such as, but not limited to, the use of a fluid chamber with a valve connection, the addition of bio-erodible polymers, the addition of multiple reservoirs containing multiplier drugs, and the addition of storage devices capable of delivering said or powdered drug formulations.

[0095] The device **700** illustrated in FIG. **11**A can be implanted within a mastoid cavity **800** of a human ear, in accordance with one embodiment of the invention, as shown in FIG. **11**B. In this embodiment, the device **700**, incorporating the micropump **720**, reservoir **740**, control system **760**, and battery **780**, is implanted behind the pinna **820** of a human ear, within the mastoid cavity. The device is connected to a double-lumen catheter **840**, which connects to an interface member, such as, for example, a cannula **860**, which is implanted into the vestibule **865** of a human ear, thus allowing fluid communication with a cochlea **867**.

[0096] Various configurations of the device allow a drug, or drugs, to be mixed with the therapeutic fluid recirculating within the double-lumen catheter. Depending upon the requirements of the system, the infusion of a drug into the therapeutic fluid can be constant or modulated. The flow rate of the therapeutic fluid within the system can also be controlled through the control of the micropump, which can either be held at a substantially constant frequency or modulated. The control system in the device can control the flow and infusion rate, and also provides the possibility of monitoring the performance of the device, send information regarding the flow parameters to a remote device, and receive information from a remote device. In various embodiments, the device includes a regulating system that is used to determine optimal drug delivery rates. In some embodiments, the regulating system is part of the control system. In one particular embodiment, a biosensor of the regulating system detects a level of a particular molecule of the drug and thereby enables the regulating system to automatically determine the quantity of the drug to release from the reservoir. Also, a sensor of the regulating system may also measure the concentration of drug in the perilymph and provide feedback to regulate the drug release rate from the reservoir or increase the flow rate by the pump.

[0097] A schematic for the basic fluid circuit is shown in FIG. **12**A-**12**C. Referring to FIG. **12**A, in one embodiment, a drug delivery system **900** has been designed without a distinct supply reservoir. As a result, it recirculates a constant net volume of fluid through a loop of tubing **910** driven by a micropump **920**. The recirculating stream communicates through a lumen of a cannula **930** with the cochlea **940**, depicted here for simplicity as an open reservoir containing fluid **950**. Delivery occurs through transport outside of the system: fluid expelled during the first half pump cycle equilibrates with the fluid in the outside reservoir, either through diffusion or mixing, thus the fluid drawn in during the next half cycle is less concentrated and net delivery occurs, albeit decreasing over time. In various embodiments, design of the system enhances mixing by achieving an oscillatory flow of sufficient amplitude to completely expel the fluid contained in

the cannula during a cycle. Otherwise "fresh" compound would not be delivered each cycle, in effect, mixing would largely be dominated by diffusion in the small volume of the cannula.

[0098] FIGS. **12**B and **12**C, respectively, depict a plumbing diagram for the recirculating fluidic delivery system and its equivalent lumped-element electric circuit schematic. FIG. **12**B depicts a schematic diagram for the system **900**, with the addition of a pressure gauge **960**. The pressure gauge is connected to the feed leg of the hollow member, which comprises two sections of differing diameter **970** and **972**. The return leg of the hollow member comprises the two sections of differing diameter **974** and **976**. The hollow member connects through a T-junction **980** to the cannula **930**. FIG. **12**C depicts a circuit representation of the system of FIG. **12**B. Here, the resistance of the sections of each hollow member sections is shown, along with the resistance within the cannula and the capacitance in the feed and return leg sections **974** and **976**. By appropriate selection of the geometric properties of the cannula and hollow member sections, the flow pattern properties within the system, and the resulting drug delivery rates to the cochlea, can be controlled. In a particular embodiment of the invention, selection of the system's geometric properties and the operational properties of the micropump can produce a reciprocating flow within the system. In this configuration, the fluid capacitance and fluid resistance of within the delivery system can be selected and, optionally, controllably altered, to provide an oscillating flow through a single cannula. This flow regime can have a number of important benefits, such as, but not limited to, improving mixing of the drug and perilymph within the delivery system and cochlea, carefully controlling the rate of drug delivery to the cochlea, and helping to avoid occlusion within the tubing. This configuration also allows for a transport of fluid into and out of the cochlea using only a single interface member.

[0099] In some embodiments, the micropump driving the fluid is a reciprocating solenoid pump (such as a Wilson Greatbatch WGL 05) with a 0.5 μL fixed stroke volume operating up to 20 psi. The transition time of the pump stroke is preferably much smaller than the pump cycle time, which is 0.33 sec minimum (3 Hz maximum pumping frequency). The nominal feed and return tubing between the pump and T-junction are each approximately 50 cm long with negligible resistance, having an I.D. of 1.0 mm. These tubes may function as the primary source of compliance (CF and CR described below) and may vary in material from silicone (modulus ~10 MPa) to PEEK (modulus 1 GPa). The T-junction capillaries are rigid (fused silica). The tubes represented by RFT and RRT should have I.D. less than 250 μm (not necessarily equal) and length of at least 10 mm. The cannula is assumed fixed, because of surgical constraints, with I.D. 75 μm and length 20 mm.

[0100] To satisfy the above condition, one half of a flow cycle generates a fluid flow volume of at least that of the mixing tube volume.

$$V_M = \frac{\pi}{4} \cdot D_{IM}^2 \cdot L_M = 0.088\ \mu\text{L} \qquad \text{(Formula 1)}$$

[0101] Given the circuit configuration, it may be difficult to achieve this without some capacitance in the system. Specifically, with the fluidic capacitors shown in FIG. **12**C removed, there is no loop that includes the mixing output leg RM through which fluid can flow. Equivalently, there is no storage capability in the pump loop which allows fluid to be stored in such a way that the flow rates in the T-feed and T-return sections can be unequal at the same instant in time, which is the only condition under which fluid may flow in the cannula.

[0102] In one embodiment of the fluidic delivery system described above, the micropump can be configured to operate continuously at a predetermined frequency. In a second embodiment, the micropump input can be modulated so that it periodically turns on and off at some frequency much lower than the pump cycle frequency, and also more slowly than the largest system time constant.

[0103] In order to analyze the system described above with reference to FIGS. **12**A-**12**C, a number of system parameters are calculated for the component geometry and properties, and a number of simplifying approximations need to be made. For example, the pump pulse time is estimated to be of the order of milliseconds. Also, the resistance to fluid flow of a tube with circular and constant cross section can be given by;

$$R = \frac{128\eta \cdot L}{\pi \cdot D_I^4} \qquad \text{(Formula 2)}$$

where η is the dynamic viscosity, L the tube length, and D_I the inner diameter.

[0104] For an expandable piece of tubing, the capacity to store fluid can be approximated by;

$$C = \frac{dV}{dP} = \frac{\pi \cdot L \cdot D_I^3}{2 \cdot E_Y \cdot (D_O - D_I)} \qquad \text{(Formula 3)}$$

where E_Y is the elastic modulus, D_O is the outer diameter, and D_I again refers to the tube inner diameter. Alternatively, to use the compressibility of a length of air bubble in a portion of tubing, the capacitance can be described approximately by;

$$C = \frac{L_0 \cdot \pi \cdot D_I^2 \cdot P_0}{4 \cdot P^2} \qquad \text{(Formula 4)}$$

where L_0 is the length of the bubble when at pressure P_0, and P is the bubble pressure. It should be noted that this expression describes a non-linear element (i.e. it is dependent on the pressure). For analysis, the average pressure of the bubble (i.e. $P=P_{avg}$) gives reasonably accurate estimates of the bubble capacity as long as the average is large compared to its maximum deviation from that average.

[0105] Laplace domain analysis of the circuit yields the transfer function

$$\frac{I_0}{I_S} = \frac{-A_0 \cdot \omega_n^2 \cdot s}{(s^2 + 2 \cdot \zeta \cdot \omega_n \cdot s + \omega_n^2)} = \frac{-A_0 \cdot \omega_n^2 \cdot s}{(s + \omega_H) \cdot (s + \omega_L)} \qquad \text{(Formula 5)}$$

where I_0 is the fluid flow through the output tube, I_S is the source flow, and the system gain, undamped natural frequency, damping ratio, and high and low frequency poles are given respectively by:

$$A_0 = R_{FT} \cdot C_F - R_{RT} \cdot C_R \quad \text{(Formula 6)}$$

$$\omega_n = [C_F \cdot C_R \cdot (R_{FT} \cdot R_{RT} + R_{FT} \cdot R_M + R_M \cdot R_{RT})]^{-\frac{1}{2}} \quad \text{(Formula 7)}$$

$$\zeta = \frac{\omega_n \cdot (R_M \cdot C_R + R_{FT} \cdot C_F + R_{RT} \cdot C_R + R_M \cdot C_F)}{2} \quad \text{(Formula 8)}$$

$$\omega_H = \left(\zeta + \sqrt{\zeta^2 - 1}\right) \cdot \omega_n \quad \text{(Formula 9)}$$
$$\omega_L = \left(\zeta - \sqrt{\zeta^2 - 1}\right) \cdot \omega_n$$

[0106] It can be shown, by taking partial derivates of Formula (8) with respect to the various circuit elements, that the damping ratio for this system is always greater than or equal to one, and in fact is only equal to one in two trivial non-useful scenarios, and thus the system never has an under-damped decaying-oscillation response to an impulse or unit step input.

[0107] The invention may be embodied in other specific forms without departing form the spirit or essential characteristics thereof. The foregoing embodiments, therefore, are to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. An apparatus for regulating a microfluidic flow, the apparatus comprising:

a substrate defining a fluid-conducting chamber;

a flexible membrane sealingly overlying the chamber, the membrane movable between a first position and a second position, one of the positions of the membrane restricting the flow through the chamber to a greater degree than the other position; and

an electromagnetically-driven assembly disposed on the substrate over the membrane for unidirectionally deflecting the membrane from the first position to the second position, thereby regulating the flow through the chamber.

2-49. (canceled)

* * * * *