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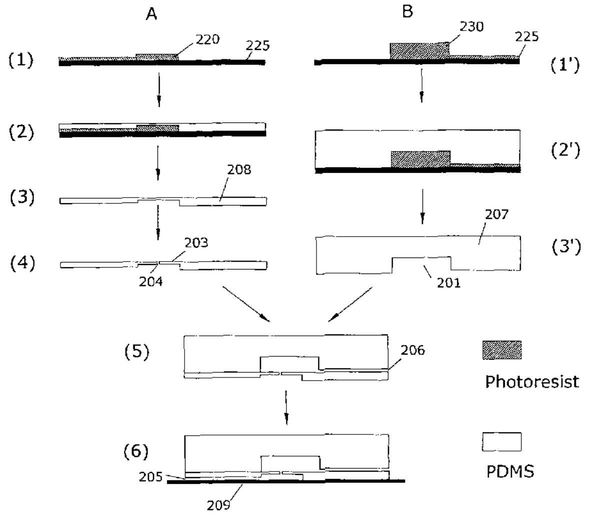

(57) Abstract: The present invention is a robust, microfluidic check valve and a method of using the check valve in microfluidic devices. The check valve is comprised two stacked chambers that are separated by a pore-containing membrane. The membrane is composed of an elastomeric material and can be configured in normally open or normally closed state. The normally open check valve can be implemented so that the degree of back pressure necessary to close the valve can be set. The normally closed embodiment can maintain a closed state with essentially no back pressure. Both the normally open and the normally closed version can be readily produced by multilayer soft lithographic techniques and may retain effective functioning through many thousands of opening and closing cycles without failure. Such check valves can substitute for active valve structures in microfluidic devices and, when appropriately implemented, can simplify the design, manufacture, and/or operation of the devices containing them.

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MICROFLUIDIC CHECK VALVES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Patent Application No. 60/849,223, filed October 4, 2006, the content of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Microfluidic devices can be used for analytical, preparative, metering, and other manipulative functions on a scale not imagined until recently. The advantages of microfluidic devices include conservation of precious reagents and samples, high density and throughput of sample analysis or synthesis, fluidic precision and accuracy at a level scarcely visible to the unaided eye, and a space reduction accompanying the replacement of counterpart equipment operating at the macrofluidic scale. Associated with the reduction in size and the increased density of microfluidic devices is increased complexity and higher engineering and fabrication costs associated with increasingly intricate device architecture. The present invention, a microfluidic check valve and it method of use, can reduce the complexity of microfluidic chips and simplify their operation.

BRIEF SUMMARY OF THE INVENTION

[0003] The present invention is a robust, microfluidic check valve and a method of using the check valve in microfluidic devices. The check valve is comprised two stacked chambers that are separated by a pore-containing membrane. The membrane is composed of an elastomeric material and can be configured in normally open or normally closed state. The normally open check valve can be implemented so that the degree of back pressure necessary to close the valve can be set. The normally closed embodiment can maintain a closed state with essentially no back pressure. Both the normally open and the normally closed version can be readily produced by multilayer soft lithographic techniques and may retain effective functioning through many thousands of opening and closing cycles without failure. Such check valves can substitute for active valve structures in microfluidic devices and, when appropriately implemented, can simplify the design, manufacture, and/or operation of the devices containing them.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] Fig. 1 provides an illustration of a microfluidic check valve in an embodiment;

[0005] Fig. 2 illustrates a method for fabrication of a microfluidic check valve in an embodiment;

[0006] Fig. 3 illustrates the flow rate through a microfluidic check valve as a function of applied pressure in one embodiment; and

[0007] Fig. 4 is a micrograph of check valves fabricated in series using the methods illustrated in Fig. 2.

[0008] Fig. 5 is a diagram of a microfluidic check valve.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The invention provides a microfluidic check valve that is easily manufactured and incorporated into microfluidic devices. The check valve is characterized as having exceptionally low activation pressure to open or close, minimal dead volume, and essentially no back flow. The valves of the present invention can withstand thousands of opening and closing cycles and survive the high end of pressures that are encountered in microfluidic devices. The invention provides for a microfluidic device comprising, an inlet channel, a check valve, and an outlet channel wherein, in the absence of outlet channel flow restrictions, an inlet channel pressure of less than 5 psi (pounds per square inch) is required to produce flow to the outlet channel and wherein substantially no flow occurs from the outlet channel to the inlet channel when an outlet pressure exceeds the inlet channel pressure by about 3 psi. In a further embodiment, the check valve will allow flow to occur from the inlet channel to the outlet channel with an inlet channel pressure of less than 3 psi, 2 psi, 1 psi, 0.5 psi or 0.2 PSI. The initial inlet pressure required to open the check valve will, in some cases, exceed the pressure required to open the check valve in subsequent opening. The opening pressures recited above represent the average opening pressures of 10 repeated openings and closings within a 30 minutes period. In an embodiment, the check valve will close when the pressure in the outlet channel exceeds the pressure in the inlet channel by 2 psi, 1 psi, 0.5 psi, 0.25 psi, 0.1 psi, or 0.05 psi. In a further embodiment, the check valve will close when the pressure in the outlet channel exceeds the pressure in the inlet channel by 0.005 psi.

[0010] The check valves of the present invention are further characterized by a very low dead volume. The check valves my have a dead volume of 100 nL (nanoliters) or less, 50 nL or less, 25 nL or less, 15 nL or less, 10 nL, or less, 5 nL or less, 4 nL or less, 2.5 nL or less, or, in a further embodiment, about 1 nL.

[0011] The invention further relates to a check valve having a dead volume of less than 100 nL, the check valve comprising, an outlet chamber in fluidic communication with an outlet channel, an inlet chamber in fluidic communication with an inlet channel, and a deflectable membrane between the outlet chamber from the inlet chamber, the membrane having a fluidic channel that places the inlet chamber in fluidic communication with the outlet chamber. The check valve may be further defined in this embodiment wherein the inlet and outlet chambers of the check valve have a columnar shape and the footprint of the columns defining either the inlet or outlet chamber that is selected from the group consisting of a polygon, a quadrangle, a square, an oval, a circle, or a partially rounded polygon. For some applications, circular footprints are preferred. In other applications, polygonal footprints are preferred. In particular, quadrilateral or square footprints may be preferred for some applications. Polygonal footprints can also be used for the chambers, and, in some instances, a rounded polygon or an oval footprint may be desired.

[0012] In a further embodiment (Fig. 5), the footprint of the inlet chamber has a shortest internal width, A, and the inlet chamber has a height, B, the footprint of the outlet chamber has a shortest internal width, C, and the outlet chamber has a height, D. In an embodiment, the membrane channel has a width, E, and a membrane thickness, F (Fig. 5). The check valves of the invention will typically have a ratio of C to A is greater than or equal to about1.2, a ratio of D to B is greater than or equal to about 1.4, and a ratio of A to E is greater than or equal to about 1.9. In further embodiments, the ratio of C to A is equal to or less than about 1.5, equal to or less than about 1.75, equal to or less than about 2, equal to or less that about 2.5, equal to or less than about 3, or greater than 3. The ratio of D to B can be equal to about 1.6 or less, equal to or less than about 1.8, equal to or less than about 2, equal to or less than about 2.5, or equal to or less than about 3, or greater than 3. The ratio of A to E can be equal to or less than about 2.2, equal to or less than about 2.5, equal to or less than about 2.8, equal to or less than about 3, or greater than 3. The membrane thickness, F, can be from about 2 to about 100 um, preferably from about 2 to about 75 um, preferably from about 2 to about 50 um, more preferably from about 2 to about 25 um. In some embodiments, it is preferred that F is less than about 25 um. In some embodiments it is preferred that F is equal to or less than about 10 um. In other embodiments, it is preferred that F is equal to or less than 5 um in thickness. The membrane (503) should have a Young's modulus of about 100 MPA (megapascals) or less. In other embodiments, the Young's modulus of the membrane is about 75 MPA or less, about 50 MPa or less, about 25 MPa or less, about 10 MPa or less, about 8 MPa or less, about 5 MPa or less, or about 2 MPa or less.

[0013] The check valves of the invention may be constructed wherein the fluidic channel of the membrane defines an axis and the inlet chamber and the outlet chamber are substantially axially aligned. This may result in a configuration, for example where the output chamber and the inlet chamber are arranged so as to appear as concentric circles around a central axis that is the membrane fluid channel. In other embodiments, the chambers may be offset from each other. The geometrical shapes of the chamber footprints may be the same or different with, for example, the input chamber having a quadrilateral footprint, such as a square, and the outlet chamber having a substantially circular footprint.

[0014] The check valves of the invention are generally constructed of three layers; an upper layer defining the outlet chamber and, optionally, an outlet channel; a bottom layer defining the inlet chamber, and, optionally, an inlet channel; and a middle layer that, minimally, defines the membrane layer. In a preferred embodiment, the middle membrane layer is integral to the bottom layer that defines the input chamber. For example, the bottom layer might be prepared from an elastomeric material that is cast such that the top of the input chamber defines the membrane. The microfluidic devices of the invention may be conveniently constructed out of elastomer materials in their entirety, but this is not required or, in some cases, preferred. Non-elastomeric materials such as glass, steel, brass, copper, silicon, quartz, and hard plastics may be used to form the upper and/or lower layers. These layers may be prepared by machining, etching, casting, molding, embossing, vacuum forming, or similar methodologies. Elastomeric layers may also be prepared and used as described below. Elastomers used in the present invention may have a Young's modulus of from about 1 kilopascal (KPa) to about 2.5 gigapascals (GPa). Ranges of Young's moduli used for elastomeric materials for the present invention include from about 1 KPa to about 2 GPa, from about 50 KPa to about 500 MPa, from about 50 KPa to about 100 MPa, from about 50 KPa, to about 100 MPa, from about 100 KPa to about 10 MPa, from about 100 KPa to about 1 MPa, from about 200 KPa to about 500 MPa, from about 200 KPa to about 100 MPa, and from about 200 KPa to about 10 MPa.

[0015] Preferred Layer and Channel Dimensions:

[0016] Microfabricated refers to the size of features of an elastomeric structure fabricated in accordance with an embodiment of the present invention. In general, variation in at least one dimension of microfabricated structures is controlled to the micron level, with at least one dimension being microscopic (i.e. below 1000 µm). Microfabrication typically involves semiconductor or MEMS fabrication techniques such as photolithography and spincoating that are designed for to produce feature dimensions on the microscopic level, with at least some of the dimension of the microfabricated structure requiring a microscope to reasonably resolve/image the structure.

[0017] In preferred aspects, flow channels preferably have width-to-depth ratios of about 10:1. A non-exclusive list of other ranges of width-to-depth ratios in accordance with embodiments of the present invention is 0.1:1 to 100:1, more preferably 1:1 to 50:1, more preferably 2:1 to 20:1, and most preferably 3:1 to 15:1. In an exemplary aspect, flow channels have widths of about 1 to 1000 microns. A non-exclusive list of other ranges of widths of flow channels in accordance with embodiments of the present invention is 0.01 to 1000 microns, more preferably 0.05 to 1000 microns, more preferably 0.2 to 500 microns, more preferably 1 to 250 microns, and most preferably 10 to 200 microns. Exemplary channel widths include 0.1 µm, 1 µm, 2 µm, 5 µm, 10 µm, 20 µm, 30 µm, 40 µm, 50 µm, 60 µm, 70 µm, 80 µm, 90 µm, 100 µm, 110 µm, 120 µm, 130 µm, 140 µm, 150 µm, 160 µm, 170 µm, 180 µm, 190 µm, 200 µm, 210 µm, 220 µm, 230 µm, 240 µm, and 250 µm.

[0018] Flow channels have depths of about 1 to 100 microns. A non-exclusive list of other ranges of depths of flow channels in accordance with embodiments of the present invention is 0.01 to 1000 microns, more preferably 0.05 to 500 microns, more preferably 0.2 to 250 microns, and more preferably 1 to 100 microns, more preferably 2 to 20 microns, and most preferably 5 to 10 microns. Exemplary channel depths include including 0.01 µm, 0.02 µm, 0.05 µm, 0.1 µm, 0.2 µm, 0.5 µm, 1 µm, 2 µm, 3 µm, 4 µm, 5 µm, 7.5 µm, 10 µm, 12.5 µm, 15 µm, 17.5 µm, 20 µm, 22.5 µm, 25 µm, 30 µm, 40 µm, 50 µm, 75 µm, 100 µm, 150 µm, 200 µm, and 250 µm.

[0019] Elastomeric layers may be cast thick for mechanical stability. In an exemplary embodiment, a layer is 50 microns to over a centimeter thick, and more preferably approximately 4 mm thick. A non-exclusive list of ranges of thickness of the elastomer layer in accordance with other embodiments of the present invention is between about 0.1 micron to 1 cm, 1 micron to 1 cm, 10 microns to 0.5 cm, 100 microns to 10 mm.

[0020] Accordingly, membranes separating flow channels have a typical thickness of between about 0.01 and 1000 microns, more preferably 0.05 to 500 microns, more preferably 0.2 to 250, more preferably 1 to 100 microns, more preferably 2 to 50 microns, and most preferably 5 to 40 microns. Exemplary membrane thicknesses include 0.01 μm, 0.02 μm, 0.03 μm, 0.05 μm, 0.1 μm, 0.2 μm, 0.3 μm, 0.5 μm, 1 μm, 2 μm, 3 μm, 5 μm, 7.5 μm, 10 μm, 12.5 μm, 15 μm, 17.5 μm, 20 μm, 22.5 μm, 25 μm, 30 μm, 40 μm, 50 μm, 75 μm, 100 μm, 150 μm, 200 μm, 250 μm, 300 μm, 400 μm, 500 μm, 750 μm, and 1000 μm.

[0021] Fig. 5 illustrates an embodiment of a microfluidic check valve of the present invention. An upper layer (507) defines an outlet chamber (501) that is in fluidic communication with and outlet channel (506). The outlet chamber has a height, D, and a chamber width, C. The upper layer is adhered to, pressed onto, or bonded to the membrane (503) with its flow channel (504) opening into the outlet chamber. The membrane has a thickness, F, and a flow channel width (or diameter), E. The membrane layer is adhered to, pressed onto, bonded to, or integral with the bottom layer (508) which defines the input chamber (502) and the input flow channel (505). The input chamber has a width (or diameter), A, and a height, B. The layer 508 is adhered to, pressed onto, or bonded to a substrate (either hard or elastomeric) (509) that forms the inlet channel (505).

[0022] The microfluidic devices disclosed herein are typically constructed at least in part from elastomeric materials and constructed by single and multilayer soft lithography (MSL) techniques and/or sacrificial-layer encapsulation methods (see, e.g., Unger et al. (2000) Science 288:113-116, and PCT Publication WO 01/01025, both of which are incorporated by reference herein in their entirety for all purposes). Utilizing such methods, microfluidic devices can be designed in which solution flow through flow channels of the device is controlled, at least in part, with one or more control channels that are separated from the flow channel by an elastomeric membrane or segment. This membrane or segment can be deflected into or retracted from the flow channel with which a control channel is associated by applying an actuation force to the control channels. By controlling the degree to which the membrane is deflected into or retracted out from the flow channel, solution flow can be slowed or entirely blocked through the flow channel. Using combinations of control and flow channels of this type, one can prepare a variety of different types of valves and pumps for regulating solution flow as described in extensive detail in Unger et al. (2000) Science 288:113-116, and PCT Publication WO/02/43615 and WO 01/01025. The present invention provides an advancement of microfluidic architecture by providing a device that can be integrated into known types of microfluidic devices and facilitate one way flow into and through critical regions of such devices.

[0023] The invention also provides a method of flowing a fluid in a microfluidic device in a single direction along a flow path. The method comprises providing (a) providing a check valve having a dead volume of less than 100 nL, the check valve comprising, an outlet chamber in fluidic communication with an outlet channel, an inlet chamber in fluidic communication with an inlet channel, a deflectable membrane between the outlet chamber from the inlet chamber, the membrane having a fluidic channel that places the inlet chamber in fluidic communication with the outlet chamber, (b) flowing a fluid in the inlet channel to form an inlet channel fluidic pressure such that the fluid appears in the outlet channel and forms an outlet channel fluidic pressure, (c) raising the fluidic pressure in the outlet channel or lowering the fluidic pressure in the inlet channel such that the fluidic pressure in the outlet channel exceeds the fluidic pressure of the inlet channel, and (d) deflecting the membrane to close the check valve to seal off a flow of fluid from the outlet channel to the inlet channel.

[0024] The check valve may be further defined in this embodiment wherein the inlet and outlet chambers of the check valve have a columnar shape and the footprint of the columns defining either the inlet or outlet chamber that is selected from the group consisting of a polygon, a quadrangle, a square, an oval, a circle, or a partially rounded polygon. For some applications, circular footprints are preferred. In other applications, polygonal footprints are preferred. In particular, quadrilateral or square footprints may be preferred for some applications. Polygonal footprints can also be used for the chambers, and, in some instances, a rounded polygon or an oval footprint may be desired.

[0025] In a further embodiment (Fig. 5), the footprint of the inlet chamber has a shortest internal width, A, and the inlet chamber has a height, B, the footprint of the outlet chamber has a shortest internal width, C, and the outlet chamber has a height, D. In an embodiment, the membrane channel has a width, E, and a membrane thickness, F (Fig. 5). The check valves of the invention will typically have a ratio of C to A is greater than or equal to about1.2, a ratio of D to B is greater than or equal to about 1.4, and a ratio of A to E is greater than or equal to about 1.9. In further embodiments, the ratio of C to A is equal to or less than about 1.5, equal to or less than about 1.75, equal to or less than about 2, equal to or less that about 2.5, equal to or less than about 3, or greater than 3. The ratio of D to B can be equal to about 1.6 or less, equal to or less than about 1.8, equal to or less than about 2, equal to or less than about 2.5, or equal to or less than about 3, or greater than 3. The ratio of A to E can be equal to or less than about 2.2, equal to or less than about 2.5, equal to or less than about 2.8, equal to or less than about 3, or greater than 3. The membrane thickness, F, can be from about 2 to about 100 um, preferably from about 2 to about 75 um, preferably from about 2 to about 50 um, more preferably from about 2 to about 25 um. In some embodiments, it is preferred that F is less than about 25 um. In some embodiments it is preferred that F is equal to or less than about 10 um. In other embodiments, it is preferred that F is equal to or less than 5 um in thickness. The membrane (503) should have a Young's modulus of about 100 MPA (megapascals) or less. In other embodiments, the Young's modulus of the membrane is about 75 MPA or less, about 50 MPa or less, about 25 MPa or less, about 10 MPa or less, about 8 MPa or less, about 5 MPa or less, or about 2 MPa or less.

[0026] Soft Lithographic Bonding:

[0027] Preferably, elastomeric layers are bonded together chemically, using chemistry that is intrinsic to the polymers comprising the patterned elastomer layers. Most preferably, the bonding comprises two component "addition cure" bonding.

[0028] In one aspect, the various layers of elastomer are bound together in a heterogeneous bonding in which the layers have a different chemistry. Alternatively, a homogenous bonding may be used in which all layers would be of the same chemistry. Thirdly, the respective elastomer layers may optionally be glued together by an adhesive instead. In a fourth aspect, the elastomeric layers may be thermoset elastomers bonded together by heating.

[0029] In one aspect of homogeneous bonding, the elastomeric layers are composed of the same elastomer material, with the same chemical entity in one layer reacting with the same chemical entity in the other layer to bond the layers together. In one embodiment, bonding between polymer chains of like elastomer layers may result from activation of a crosslinking agent due to light, heat, or chemical reaction with a separate chemical species.

[0030] Alternatively in a heterogeneous aspect, the elastomeric layers are composed of different elastomeric materials, with a first chemical entity in one layer reacting with a second chemical entity in another layer. In one exemplary heterogeneous aspect, the bonding process used to bind respective elastomeric layers together may comprise bonding together two layers of RTV 615 silicone. RTV 615 silicone is a two-part addition-cure silicone rubber. Part A contains vinyl groups and catalyst; part B contains silicon hydride (Si--H) groups. The conventional ratio for RTV 615 is 10A:1B. For bonding, one layer may be made with 30A:1B (i.e. excess vinyl groups) and the other with 3A:1B (i.e. excess Si--H groups). Each layer is cured separately. When the two layers are brought into contact and heated at elevated temperature, they bond irreversibly forming a monolithic elastomeric substrate.

[0031] Alternatively, other bonding methods may be used, including activating the elastomer surface, for example by plasma exposure, so that the elastomer layers/substrate will bond when placed in contact. For example, one possible approach to bonding together elastomer layers composed of the same material is set forth by Duffy et al, "Rapid Prototyping of Microfluidic Systems in Poly (dimethylsiloxane)", Analytical Chemistry (1998), 70, 4974-4984, incorporated herein by reference. This paper discusses that exposing polydimethylsiloxane (PDMS) layers to oxygen plasma causes oxidation of the surface, with irreversible bonding occurring when the two oxidized layers are placed into contact.

[0032] Yet another approach to bonding together successive layers of elastomer is to utilize the adhesive properties of uncured elastomer. Specifically, a thin layer of uncured elastomer such as RTV 615 is applied on top of a first cured elastomeric layer. Next, a second cured elastomeric layer is placed on top of the uncured elastomeric layer. The thin middle layer of uncured elastomer is then cured to produce a monolithic elastomeric structure. Alternatively, uncured elastomer can be applied to the bottom of a first cured elastomer layer, with the first cured elastomer layer placed on top of a second cured elastomer layer. Curing the middle thin elastomer layer again results in formation of a monolithic elastomeric structure.

[0033] Elastomeric layers may be created by spin-coating an RTV mixture on microfabricated mold at 2000 rpm for 30 seconds yielding a thickness of approximately 40 microns. Additional elastomeric layers may be created by spin-coating an RTV mixture on microfabricated mold. Both layers may be separately baked or cured at about 80°C. for 1.5 hours. The additional elastomeric layer may be bonded onto first elastomeric layer at about 80°C for about 1.5 hours.

[0034] Suitable Elastomeric Materials:

[0035] Allcock et al, Contemporary Polymer Chemistry, 2nd Ed. describes elastomers in general as polymers existing at a temperature between their glass transition temperature and liquefaction temperature. Elastomeric materials exhibit elastic properties because the polymer chains readily undergo torsional motion to permit uncoiling of the backbone chains in response to a force, with the backbone chains recoiling to assume the prior shape in the absence of the force. In general, elastomers deform when force is applied, but then return to their original shape when the force is removed. The elasticity exhibited by elastomeric materials may be characterized by a Young's modulus.

[0036] The systems of the present invention may be fabricated from a wide variety of elastomers. In an exemplary aspect, elastomeric layers may preferably be fabricated from silicone rubber. However, other suitable elastomers may also be used.

[0037] In an exemplary aspect of the present invention, the present systems are fabricated from an elastomeric polymer such as GE RTV 615 (formulation), a vinyl-silane crosslinked (type) silicone elastomer (family). However, the present systems are not limited to this one formulation, type or even this family of polymer; rather, nearly any elastomeric polymer is suitable. An important requirement for the preferred method of fabrication of the present microvalves is the ability to bond multiple layers of elastomers together. In the case of multilayer soft lithography, layers of elastomer are cured separately and then bonded together. This scheme requires that cured layers possess sufficient reactivity to bond together. Either the layers may be of the same type, and are capable of bonding to themselves, or they may be of two different types, and are capable of bonding to each other. Other possibilities include the use an adhesive between layers and the use of thermoset elastomers.

[0038] Given the tremendous diversity of polymer chemistries, precursors, synthetic methods, reaction conditions, and potential additives, there are a huge number of possible elastomer systems that could be used to make monolithic elastomeric microvalves and pumps. Variations in the materials used will most likely be driven by the need for particular material properties, i.e. solvent resistance, stiffness, gas permeability, or temperature stability.

[0039] There are many, many types of elastomeric polymers. A brief description of the most common classes of elastomers is presented here, with the intent of showing that even with relatively "standard" polymers, many possibilities for bonding exist. Common elastomeric polymers include polyisoprene, polybutadiene, polychloroprene, polyisobutylene, poly(styrene-butadiene-styrene), the polyurethanes, and silicones.

[0040] Polyisoprene, polybutadiene, polychloroprene:

[0041] Polyisoprene, polybutadiene, and polychloroprene are all polymerized from diene monomers, and therefore have one double bond per monomer when polymerized. This double bond allows the polymers to be converted to elastomers by vulcanization (essentially, sulfur is used to form crosslinks between the double bonds by heating). This would easily allow homogeneous multilayer soft lithography by incomplete vulcanization of the layers to be bonded; photoresist encapsulation would be possible by a similar mechanism.

[0042] Polyisobutylene:

Pure polyisobutylene has no double bonds, but is crosslinked to use as an elastomer by including a small amount ($\approx 1\%$) of isoprene in the polymerization. The isoprene monomers give pendant double bonds on the polyisobutylene backbone, which may then be vulcanized as above.

[0043] Poly(styrene-butadiene-styrene):

[0044] Poly(styrene-butadiene-styrene) is produced by living anionic polymerization (that is, there is no natural chain-terminating step in the reaction), so "live" polymer ends can exist in the cured polymer. This makes it a natural candidate for the present photoresist encapsulation system (where there will be plenty of unreacted monomer in the liquid layer poured on top of the cured layer). Incomplete curing would allow homogeneous multilayer soft lithography (A to A bonding). The chemistry also facilitates making one layer with extra butadiene ("A") and coupling agent and the other layer ("B") with a butadiene deficit (for heterogeneous multilayer soft lithography). SBS is a "thermoset elastomer", meaning that above a certain temperature it melts and becomes plastic (as opposed to elastic); reducing the temperature yields the elastomer again. Thus, layers can be bonded together by heating.

[0045] Polyurethanes:

[0046] Polyurethanes are produced from di-isocyanates (A--A) and di-alcohols or di-amines (B--B); since there are a large variety of di-isocyanates and di-alcohols/amines, the number of different types of polyurethanes is huge. The A vs. B nature of the polymers, however, would make them useful for heterogeneous multilayer soft lithography just as RTV 615 is: by using excess A--A in one layer and excess B--B in the other layer.

[0047] Silicones:

[0048] Silicone polymers probably have the greatest structural variety, and almost certainly have the greatest number of commercially available formulations. The vinyl-to-(Si--H) crosslinking of RTV 615 (which allows both heterogeneous multilayer soft lithography and photoresist encapsulation) has already been discussed, but this is only one of several crosslinking methods used in silicone polymer chemistry.

[0049] Cross Linking Agents:

[0050] In addition to the use of the simple "pure" polymers discussed above, crosslinking agents may be added. Some agents (like the monomers bearing pendant double bonds for vulcanization) are suitable for allowing homogeneous (A to A) multilayer soft lithography or photoresist encapsulation; in such an approach the same agent is incorporated into both elastomer layers. Complementary agents (i.e. one monomer bearing a pendant double bond, and another bearing a pendant Si--H group) are suitable for heterogeneous (A to B) multilayer soft lithography. In this approach complementary agents are added to adjacent layers.

[0051] Other Materials:

[0052] In addition, polymers incorporating materials such as chlorosilanes or methyl-, ethyl-, and phenylsilanes, and polydimethylsiloxane (PDMS) such as Dow Chemical Corp. Sylgard 182, 184 or 186, or aliphatic urethane diacrylates such as (but not limited to) Ebecryl 270 or Irr 245 from UCB Chemical may also be used.

[0053] The following is a non-exclusive list of elastomeric materials which may be utilized in connection with the present invention: polyisoprene, polybutadiene, polychloroprene, polyisobutylene, poly(styrene-butadiene-styrene), the polyurethanes, and silicone polymers; or poly(bis(fluoroaLkoxy)phosphazene) (PNF, Eypel-F), poly(carborane-siloxanes) (Dexsil), poly(acrylonitrile-butadiene) (nitrile rubber), poly(1-butene), poly(chlorotrifluoroethylene-vinylidene fluoride) copolymers (Kel-F), poly(ethyl vinyl ether), poly(vinylidene fluoride), poly(vinylidene fluoride-hexafluoropropylene) copolymer (Viton), elastomeric compositions of polyvinylchloride (PVC), polysulfone, polycarbonate, polymethylmethacrylate (PMMA), and polytertrafluoroethylene (Teflon).

[0054] Doping and Dilution:

[0055] Elastomers may also be "doped" with uncrosslinkable polymer chains of the same class. For instance RTV 615 may be diluted with GE SF96-50 Silicone Fluid. This serves to reduce the viscosity of the uncured elastomer and reduces the Young's modulus of the cured elastomer. Essentially, the crosslink-capable polymer chains are spread further apart by the addition of "inert" polymer chains, so this is called "dilution". RTV 615 cures at up to 90% dilution, with a dramatic reduction in Young's modulus.

[0056] Other examples of doping of elastomer material may include the introduction of electrically conducting or magnetic species, as described in detail below in conjunction with alternative methods of actuating the membrane of the device. Should it be desired, doping with fine particles of material having an index of refraction different than the elastomeric material (i.e. silica, diamond, sapphire) is also contemplated as a system for altering the refractive index of the material. Strongly absorbing or opaque particles may be added to render the elastomer colored or opaque to incident radiation. This may conceivably be beneficial in an optically addressable system.

[0057] Finally, by doping the elastomer with specific chemical species, these doped chemical species may be presented at the elastomer surface, thus serving as anchors or starting points for further chemical derivitization.

[0058] The microfluidic check valves of the present invention can be incorporated into devices in which fluids must be contained under various levels of pressurization. Such applications may include loading reactant solutions into a sealed reaction chamber, moving biological entities, such as cells, into a detection region of a device while preventing the backwards flow of the solution (and biological entities contained therein), or providing for the semi-permanent activation of control channels and associated structures, such as valves.

[0059] Example 1

[0060] Figure 1 depicts the functional process for a normally closed check valve. At its original normally closed state, (a), the membrane (103) with a pore (flow channel) (104) is relaxed and the portion of the membrane containing the pore rests on the floor (109) of the bottom chamber (102). The valve is closed do to the portion of the membrane surrounding the pore touching the substrate and thereby sealing the bottom chamber. When a forward pressure is applied, (b), the membrane is raised by the flowing liquid which then passes through the membrane pore. When the forward pressure ceases and both the top and bottom chambers are filled with liquid, the membrane returns to the normally close state (c). When reverse pressure is applied, the liquid in the top chamber (101) exerts a pressure on the membrane and the channel is closed (d). There is substantially no back flow under this condition.

[0061] Example 2

[0062] Figure 2 depicts a fabrication process for a microfluidic check valve. In this Example, the microfluidic check valve utilized two elastomeric layers bonded to each other and attached to a substrate. The substrate could be elastomeric or made of a rigid material. Column A shows the fabrication of the bottom (inlet) chamber (201) and the membrane (203) with a pore (flow channel) (204). Column B shows the fabrication of the top (outlet) chamber (201). The fabrication of the bottom chamber begins with a photoresist lithographic process that produces a mold (220 and 225) defining a chamber with a thin membrane roof and an inlet channel (Column A (1)). An uncured, liquid elastomeric compound such as polydimethylsiloxane (PDMS) is spin-layered onto the mold to evenly distribute the elastomeric liquid on the surface of the mold (Column A (2)) and the elastomeric liquid is cured or is allowed to cure. The elastomer is pealed off the mold, and the mold (Column A (3)) and a hole (204) is punched in the membrane roof (203) of the bottom chamber (Column A (4)). The top chamber is fabricated by a similar process, i.e. by spin-layering an elastomeric liquid on lithographically produced spin mold (230 and 225) that defines the top chamber (201) and the outlet flow channel (206), curing the spun elastomeric layer (207), and removing the cured elastomer with the molded features (Column B (1'), (2') and (3')). The two elastomeric layers are assembled by bonding the layer defining the top chamber onto the elastomeric layer defining the bottom chamber, membrane, and pore. The layers are aligned such that the cavity defining the top chamber is aligned with the membrane roof of the bottom chamber so that sufficient membrane remains unbonded and pliable to allow actuation (5). Assembly of the microfluidic check valve is completed by attachment of the bonded elastomeric structure to a substrate (carrier) by gluing or bonding the side of the elastomeric structure with the cavity defining the bottom chamber to the substrate (209) so that connections to liquid flow channels are obtained (6). Alternate embodiments are possible including a flow channel defined in the carrier to make direct connection to the bottom chamber of connection to a recess in the elastomeric structure that defines an input flow channel leading to the bottom chamber.

Example 3

[0063] Figure 3 shows the flow rates (nL/s) through the microfluidic check valves and through an open channel with no check valve. When forward pressure (positive values) is applied, the flow rates increase linearly as a function of pressure. Very little fluidic resistance is imposed on the flow channels by the inclusion of the check valve. The check valves were prepared from PDMS with circular footprint chambers. The widths (chamber diameters) are given in Table 1. The heights of the outlet chambers were 100 um. The heights of the inlet chambers were 15 um.

[0064] The behavior of an open channel without check valve is plotted (upper line at the lower pressures and flow rates) as a comparison. The average of all the channels with the various check valves is also plotted (upper line at low pressures and flow rates). As can be seen in Figure 3, the difference in behavior between an open channel and the channels with check valves is very similar. There is a minimum pressure value for to begin fluid flow for all of the channels with or without a check valve. The minimum pressure is about 2.5 pounds per square inch (psi) to 3 psi in this Example. When backward pressure (negative values) is applied, no backward flow was observed thus confirming the function of the microfluidic check valves. There is no leakage or fluidically available dead volume associated with the channels equipped with the normally close check valves.

Table 1. Example 3 Check Valve Chamber Diameters.

Check Valve No.	Upper Chamber Diameter (μm)	Lower Chamber Diameter (μm)
1	600	400
2	800	400
3	1000	400
4	700	300
5	900	300

[0065] Two microfluidic check valves were fabricated by the methods outlined in Example 2. The check valves were placed in series through the use of a via that connects the upper outlet flow channel of a first check valve with the lower inlet flow channel of a second check valve. A micrograph of the two check valves connected in series is shown in Figure 4.

[0066] While the above provides a full and complete disclosure of certain embodiments of the present invention, various modifications, alternate constructions and equivalents may be employed as desired. Therefore, the above description and illustrations should not be construed as limiting the invention, which is defined by the appended claims.

Claims:

1. A microfluidic device comprising:

   an inlet channel,

   a check valve,

   an outlet channel,

   wherein, in the absence of outlet channel flow restrictions, an inlet channel pressure of less than 4 psi is required to produce flow to the outlet channel and wherein substantially no flow occurs from the outlet channel to the inlet channel when an outlet pressure exceeds the inlet channel pressure by about 2 psi.

2. The microfluidic device of claim 1 wherein the dead volume of the check valve is 10 nL or less.

3. The microfluidic device of claim 1 wherein the dead volume of the check valve is 4 nL or less.

4. The microfluidic device of claim 2 wherein substantially no flow occurs from the outlet channel to the inlet channel when an outlet channel pressure exceeds the inlet channel pressure by about 1 psi.

5. The microfluidic device of claim 4 wherein an inlet channel pressure of less than 1 psi is required to produce flow to the outlet channel.

6. A microfluidic device comprising:

   a check valve having a dead volume of less than 100 nL, the check valve comprising,

   an outlet chamber in fluidic communication with an outlet channel,

   an inlet chamber in fluidic communication with an inlet channel,

   a deflectable membrane between the outlet chamber from the inlet chamber, the membrane having a fluidic channel that places the inlet chamber in fluidic communication with the outlet chamber.

7. The microfluidic device of claim 6 wherein the inlet chamber has a shortest internal width, A, and a height, B, the outlet chamber has a shortest internal width, C, and a height, D, the membrane channel has a width, E, and a membrane thickness, F,

   wherein the ratio of C to A is greater than or equal to 1.2,

   the ratio of D to B is greater than or equal to 1.4,

   the ratio of A to E is greater than or equal to 1.9, and, F is equal to or less than 100 um.

8. The microfluidic device of claim 7 wherein B is about 5 um to about 50 um.

9. The microfluidic device of claim 7 wherein E is about 40 um to about 200 um.

10. The microfluidic device of claim 7 wherein the ratio of C to A is equal to or greater than 1.5.

11. The microfluidic device of claim 7 wherein the ratio of D to B is greater than or equal to 1.75.

12. The microfluidic device of claim 7 wherein the ratio of A to E is greater than or equal to 2.5.

13. The microfluidic check valve of claim 6 wherein the dead volume of the check valve is 50 nL or less.

14. The microfluidic device of claim 6 wherein the dead volume of the check valve is 10 nL or less.

15. The microfluidic device of claim 6 wherein the dead volume of the check valve is 4 nL or less.

16. The microfluidic device of claim 6 wherein the dead volume is 1 nL or less.

17. The microfluidic device of claim 6 wherein the inlet chamber and the outlet chamber each have a footprint that is selected from the group consisting of a polygon, a quadrangle, a square, an oval, a circle, or a partially rounded polygon.

18. The microfluidic device of claim 6 wherein the membrane has a Young's modulus equal to or less than about 100 MPa.

19. The microfluidic device of claim 18 wherein the membrane has a Young's modulus equal to or less than about 50 MPa.

20. The microfluidic device of claim 19 wherein the membrane has a Young's modulus equal to or less than about 10 MPa.

21. The microfluidic device of claim 6 wherein the fluidic channel of the membrane defines an axis and the inlet chamber and the outlet chamber are substantially axially aligned.

22. A microfluidic device of claim 1 wherein the outlet channel is in fluidic communication with a reaction chamber.

23. The microfluidic device of claim 6 wherein the outlet channel is in fluidic communication with a reaction chamber.

24. A method of flowing a fluid in a microfluidic device comprising;

(a) providing a check valve having a dead volume of less than 100 nL, the check valve comprising,

an outlet chamber in fluidic communication with an outlet channel,

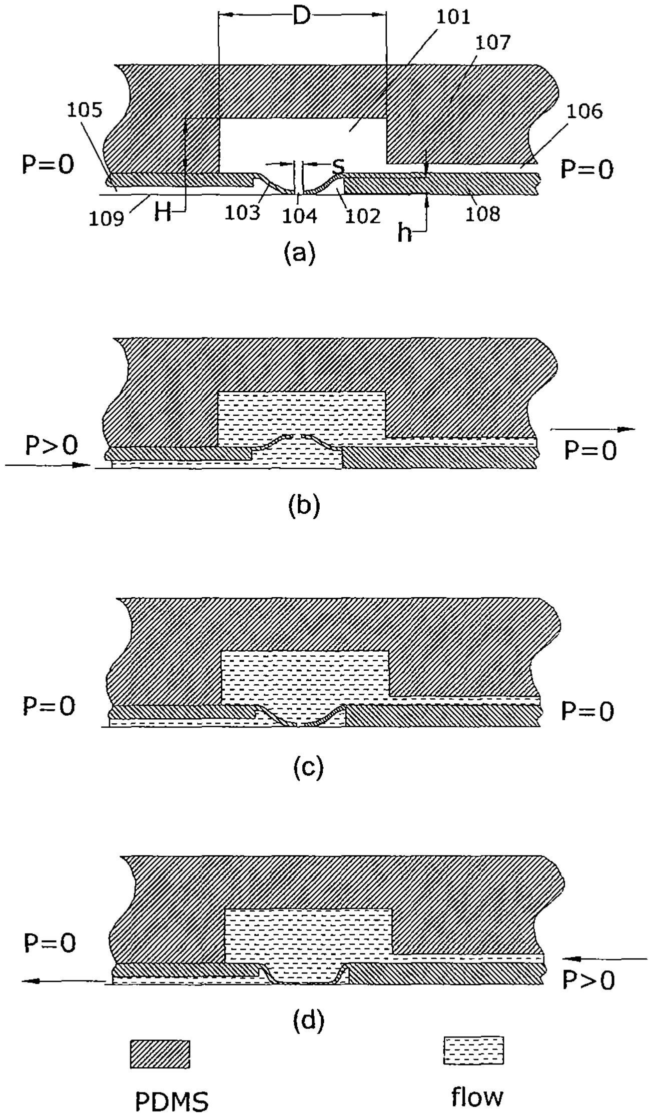
an inlet chamber in fluidic communication with an inlet channel,

a deflectable membrane between the outlet chamber from the inlet chamber, the membrane having a fluidic channel that places the inlet chamber in fluidic communication with the outlet chamber,

(b) flowing a fluid in the inlet channel such that the fluid appears in the outlet channel,

(c) raising the fluidic pressure in the outlet channel or lowering the fluidic pressure in the inlet channel such that the fluidic pressure in the outlet channel exceed the fluidic pressure of the inlet channel, and

(d) closing the check valve to seal off a flow of fluid from the outlet channel to the inlet channel.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105
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H
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104
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108
h
(a)
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(b)
P=0
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(c)
P=0
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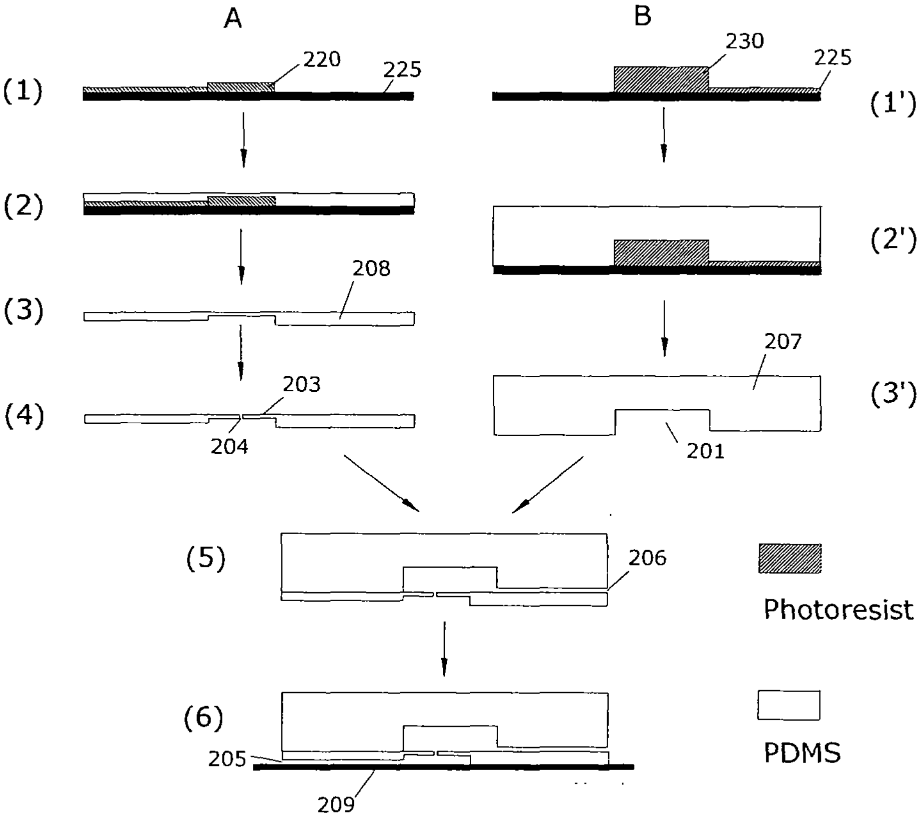
(d)
PDMS
flow

Fig. 1.


A
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225
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208
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205
209

Fig 2

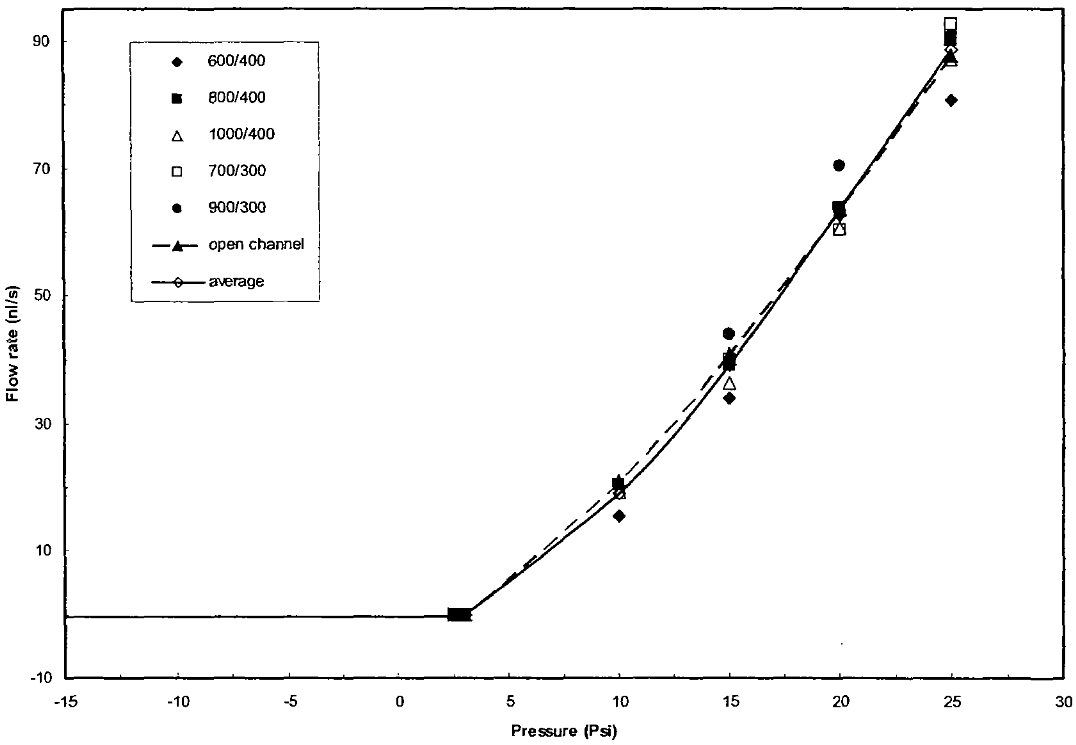
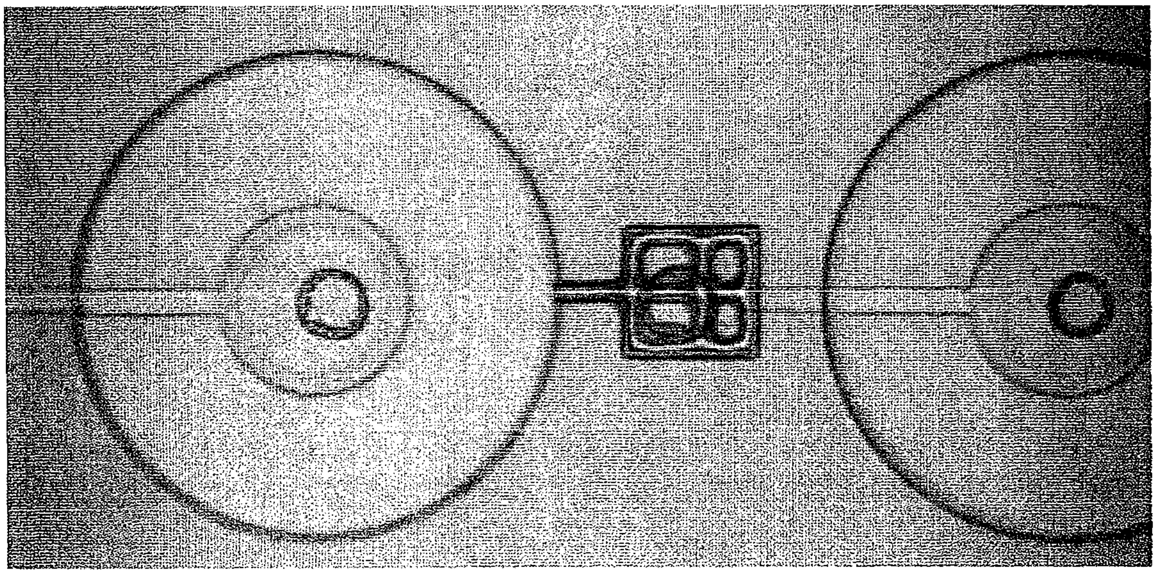


Fig 3. Flow rate changes as a function of applied pressure

Figure 4



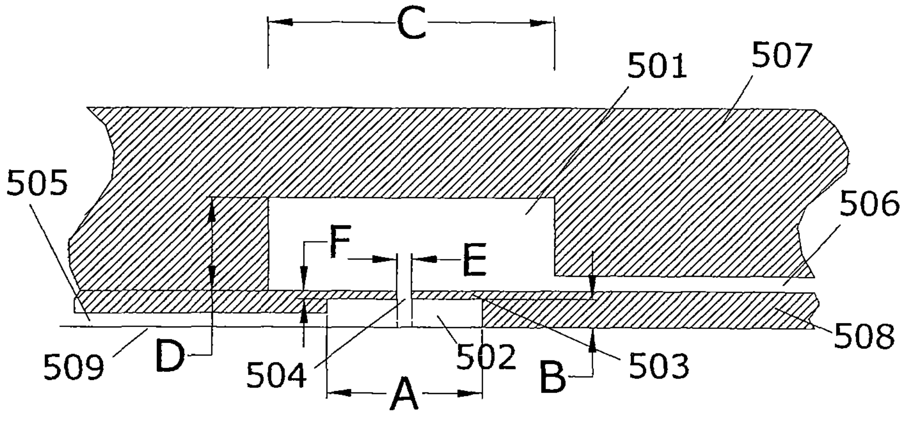


Fig 5