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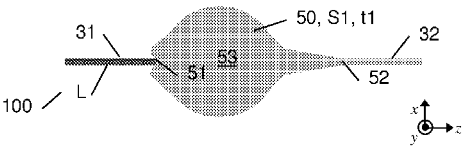

FIG. 2.A

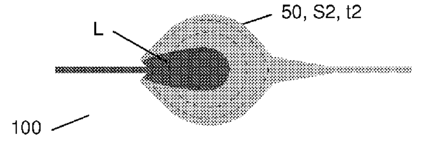

FIG. 2.B

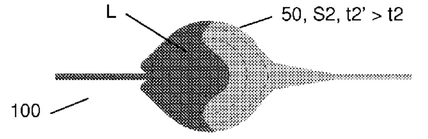

FIG. 2.C

(57) **Abstract**: The invention is notably directed to a microfluidic device (100) comprising: a first microchannel (31), a second microchannel (32), and a valve (50) comprising at least an input port (51) and an output port (52), said ports respectively connected to the first microchannel and the second microchannel, the valve designed to control a flow of a liquid (L) along a flow direction (z) defined by the ports, wherein the valve further comprises one or more walls (54, 56, 58, 20) joining the ports and defining a hollow chamber (53) that is wider than each of the microchannels in a direction perpendicular to the flow direction, said walls at least partly deformable along a deformation direction (– y) intersecting the flow direction, such that the walls can be given at least a first deformation state (S1) and a second deformation state (S2), the liquid being pulled along the flow direction substantially more in the second deformation state than in the first deformation state, by capillarity.

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MICROFLUIDIC DEVICE WITH DEFORMABLE VALVE

FIELD OF THE INVENTION

The invention relates in general to the field of microfluidic devices and methods of fabrication and operation thereof. In particular, it is directed to microfluidic devices equipped with microvalves.

BACKGROUND OF THE INVENTION

Microfluidics generally refers to microfabricated devices, which are used for pumping, sampling, mixing, analyzing and dosing liquids. Prominent features thereof originate from the peculiar behavior that liquids exhibit at the micrometer length scale (see Brody J P, Yager P, Goldstein R E and Austin R H 1996 Biotechnology at low Reynolds Numbers *Biophys. J.* 71 3430–3441 and Knight J B, Vishwanath A, Brody J P and Austin R H 1998 Hydrodynamic Focusing on a Silicon Chip: Mixing Nanoliter in Microseconds *Phys. Rev. Lett.* 80 3863–3866). Flow of liquids in microfluidics is typically laminar. Volumes well below one nanoliter can be reached by fabricating structures with lateral dimensions in the micrometer range. Reactions that are limited at large scales (by diffusion of reactants) can be accelerated (see Squires T M and Quake S R 2005 Microfluidics: Fluid physics at the nanoliter scale *Rev. Mod. Phys.* 77 977–1026). Finally, parallel streams of liquids can possibly be accurately and reproducibility controlled, allowing for chemical reactions and gradients to be made at liquid/liquid and liquid/solid interfaces (Kenis P J A, Ismagilov R F and Whitesides G M 1999 Microfabrication Inside Capillaries Using Multiphase Laminar Flow Patterning *Science* 285 83–85). Microfluidics are accordingly used for various applications in life sciences.

Many microfluidic devices have user chip interfaces and closed flowpaths. Closed flowpaths facilitate the integration of functional elements (e.g. heaters, mixers, pumps, UV detector, valves, etc.) into one device while minimizing problems related to leaks and evaporation.

The analysis of liquid samples often requires a series of steps (e.g. filtration, dissolution of reagents, heating, washing, reading of signal, etc). For portable diagnostic devices, this requires accurate flow control using various pumping and valve principles. It is usually a challenge to obtain valves that are simple, inexpensive to fabricate and easy to operate.

Two categories of valves for microfluidic devices (or “microvalves”) can generally be identified: (i) the active valves and (ii) the passive valves.

Active microvalves usually have increased fabrication complexity, are expensive to fabricate, and need power for actuation. They further need external peripheral and also need power to stay in “on” or “off” state. An example is the “abrupt junction passive microvalve”. Such a microvalve requires active pumping to pump aqueous liquids inside hydrophobic structures, where they can be pinned at constriction. Increasing the pumping pressure results in pushing liquid through the valve. As it may be realized, such a solution is however not compatible with capillary-driven microfluidics. It further requires active pumping and actuation, i.e., additional peripherals. In addition, liquid tend to break in larger volume before a constriction.

Next, passive microvalves usually lack interactivity (i.e. they impose predefined opening or closing conditions), require complex fabrication of integration of chemicals. In addition, passive valves that are initially in closed state usually have problems with venting of air.

The following references address various types of microvalves that have been developed so far:

- Liu *et al.* Anal. Chem. 2004, 76, 1824-1831.
- Ahn *et al.* Proc. of the IEEE, Vol. 92, No. 1, January 2004, pp 154 – 173.
- Zoval *et al.* Proc. of the IEEE, Vol. 92, No. 1, January 2004, pp 140 – 153.

BRIEF SUMMARY OF THE INVENTION

According to a first aspect, the present invention is embodied as a microfluidic device comprising: a first microchannel, a second microchannel, and a valve comprising at least an input port and an output port, said ports respectively connected to the first microchannel and the second microchannel, the valve designed to control a flow of a liquid along a flow direction defined by the ports, wherein, the valve further comprises one or more walls joining the ports and defining a hollow chamber that is wider than each of the microchannels in a direction perpendicular to the flow direction, said walls at least partly deformable along a deformation direction intersecting the flow direction, such that the walls can be given at least a first deformation state and a second deformation state, such that the liquid can be pulled along the flow direction substantially more in the second deformation state than in the first deformation state.

In other embodiments, said microfluidic device may comprise one or more of the following features:

- the first deformation state and the second deformation state respectively induce a first capillary pressure and a second capillary pressure for the liquid, the first capillary pressure being substantially larger than the second capillary pressure, typically by more than 1000 N/m^2, and the first capillary pressure having preferably a same order of magnitude as a capillary pressure induced in a portion upstream the first microchannel, said upstream portion preferably corresponding to a portion comprising a loading pad for loading liquid into the device;

- the first deformation state is essentially a non-deformed state and the second state is essentially a deformed state, and an average dimension of the hollow chamber along the deformation direction exhibits a ratio between the second deformation state and the first deformation state, which is between 0.1 and 0.9, preferably between 0.5 and 0.75, and the walls at least partly deformable are preferably non-permanently deformable, and more preferably resiliently deformable;

- a characteristic dimension of the hollow chamber is substantially larger than a characteristic dimension of each of the first and the second microchannels, wherein said characteristic dimensions are measured in a same plane, perpendicular to the deformation direction, and preferably measured in a direction perpendicular to both the deformation direction and the flow direction;

- depths of each of the microchannels and the hollow chamber, as measured along the deformation direction, are essentially equal;

- at least portions of each of the first microchannel and the second microchannel at the level of the ports are grooves open on an upper surface of a first layer, and the hollow chamber is defined by a depression open on the upper surface of the first layer, the grooves and the depression being closed by a lower surface of a second layer, and the first layer and/or the second layer are at least partly deformable and preferably exhibit a tensile strength between 1 and 60 Mpa, and more preferably between 20 and 60 Mpa;

- an opening angle θ_{add} of the chamber at the level of the input port, as measured between a flow direction and a portion of said one or more walls delimiting the hollow chamber at the input port, is between 90° and 180°, preferably between 110° and 160°, and more preferably substantially equal to 135°;

- an opening angle θ_{out} of the chamber at the level of the output port, as measured between a direction opposite to the flow direction and a portion of said one or more walls delimiting the hollow chamber at the output port, is between 0° and 90°, preferably between 20° and 70°, and more preferably substantially equal to

35°, and, preferably, the profile of the valve along the flow direction is essentially tear-shaped;

- a minimal length/width ratio of the hollow chamber is between 3/1 and 1/1, the length measured along the flow direction and the width measured perpendicularly to both the length and the deformation direction;

- the valve comprises sidewalls at least partly indented, the indented sidewalls exhibiting protrusions protruding outwardly;

- the valve further comprises wettable pillars extending from a lower wall to an upper wall of the valve, the pillars distribution being substantially denser at the level of one of the ports or preferably each of the ports than at the centre of the valve;

- the microfluidic device further comprises one or more reservoirs connecting the hollow chamber; and

- the microfluidic device further comprises a loading pad upstream the first microchannel, and preferably comprises a reaction chamber downstream the valve, and more preferably comprises reagent zone and a capillary pump, respectively inserted in a liquid path of the first microchannel and the second microchannel.

According to a further aspect, the invention is embodied as a microfluidic device, comprising n sets, $n \geq 2$, each of the sets comprising a first microchannel, a second microchannels and a valve configured similarly as said first microchannel, said second microchannel and said valve of the device according to any one of the above embodiments.

According to a final aspect, the invention is embodied as a method for controlling a liquid flow in a device according to any one of the above embodiments, comprising steps of:
- filling the first microchannel with liquid; and
- deforming said one or more walls at least partly deformable such that liquid is pulled through the hollow chamber from the first microchannel to the second microchannel.

Devices and methods embodying the present invention will now be described, by way of non-limiting examples, and in reference to the accompanying drawings.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

- FIGS. 1.A – 1.B are section views of a device according to embodiments (with section cut through a valve), and illustrating a basic principle of this invention;
- FIGS. 2.A – 2.C are top views of the device of FIGS. 1.A – 1.B, and illustrating the same principle;
- FIGS. 3.A – 3.B are partial 3D views (wireframe) of a device, where the microchannels/valve chamber are formed as grooves/depression provided in a layer of the device, according to embodiments;
- FIG. 4 is a theoretical model illustrating capillary pressure variations along a device according to embodiments;
- FIG. 5.A – 12 depict various alternate embodiments of a device, according to the invention; and
- FIGS. 13.A – 13.D show time sequence fluorescence microscope images, wherein liquid is passing a microvalve, according to applied embodiments.

DETAILED DESCRIPTION OF THE INVENTION

As an introduction to the following description, it is first pointed at general aspects of the invention, directed to microfluidic devices equipped with a valve designed to control a liquid flow. Such a valve has a hollow chamber, typically between two ports, respectively connecting to microchannels. The chamber enlarges a flowpath: it is wider than the microchannels (in a direction perpendicular to the flow direction). Next, the walls delimiting the chamber are at least partly deformable, in a direction perpendicular to a flow direction that is defined by the ports. Typically, a flexible material is used for at least portions of the walls, which can be pressed (e.g., with a rod or stylus), such as to increase the capillary pressure (in absolute terms) and pull the liquid through the valve. Deforming the valve shall therefore determine how a liquid is pulled along the flow direction, by capillarity. This invention relies on a simple external actuation means and the simplicity and efficiency of capillary-driven flow. The present valve further benefits from a simple fabrication; it does not require power to keep the valve in the “on” or “off” state; very small power is required for the deformation of the valve, which can easily be carried out by an operator him- or herself.

Specific embodiments shall now be described in details, which typically make it possible to achieve no (or negligible) dead volumes and fast switching times. Furthermore, such embodiments do typically not require the use of:

- heat sensitive materials (e.g., wax);
- light sensitive material (light-triggered wetting);
- sample-responsive material (e.g. pH-sensitive hydrogel); or
- chemical composition of the sample to convert a hydrophobic barrier into a hydrophilic zone.

In addition, as air is not compressed by filling liquid, there is no need for vents. The fabrication challenge furthermore remains low compared to other known solutions. Indeed, present embodiments do not require to provide structures with different depths and tilted sidewalls or complementary matching shapes. They also do not require to fabricate and assemble mating parts for occluding the flowpath. Finally, valve mechanisms according to present embodiments are actually not critically sensitive to particles, or dust, etc., in contrast to most of the known valve concepts, which are based on heterogeneous structures where sealing, bonding, etc., is critical.

Referring to FIGS. 1.A – 2.C, a microfluidic device 100 according to embodiments typically comprises: a first microchannel 31, a second microchannel 32, and a valve 50 comprising an input port 51 and an output port 52 (only two ports are described, for simplicity). Ports 51, 52 are respectively connected to input/output microchannels 31, 32. The valve is generally designed to control a flow of a liquid L along the flow direction as defined by the ports.

More in details, this valve has one or more walls 54, 56, 58, 20 joining the ports, such as to define a hollow chamber or cavity 53. The latter is wider than the microchannels in at least one direction, e.g., direction x, which direction is perpendicular to the flow direction z, such as to enlarge the flowpath. At least portions of these walls (typically the upper wall 20) are made of a deformable or flexible material. The exact geometry of the walls is not important, as long as they enlarge the flowpath compared to the microchannels and are at least partly deformable, in a direction intersecting the flow direction z (preferably perpendicularly to direction z). In the depicted example, there are four distinct walls 54, 56, 58, 20 (top, bottom and sides).

However, the hollow chamber could, in variants, be defined by bulb-shaped walls (possibly a single, continuous wall), joining the ports, and at least partly deformable along a deformation direction intersecting the flow direction. In that case, the chamber would be wider than the microchannels in any radial direction (the chamber would typically exhibit cylindrical symmetry with the main axis being that of the flow direction z), such as to enlarge the flowpath perpendicularly to direction z. The walls could be made of a flexible material, deformable along any radial direction (i.e., perpendicularly to direction z). As the skilled reader may appreciate, many other configurations could be defined similarly, e.g., intermediate configurations between the two configurations as defined above.

In all cases, the valve may exhibit two deformation states (or more), notably a first deformation state S1 distinct from a second deformation state S2. As depicted in FIGS. 1.A – 2.C, liquid is pulled along the flow direction substantially more in one of the states (here state S2) than in the other state (S1). Different degrees of flow control can be achieved, up to (in principle) a full on-off switch, as to be discussed later.

The operation principle of this valve is better described in terms of capillary pressures as experienced by a liquid propagating through the device 100. By convention, an “attractive” capillary pressure is assumed negative, according to thermodynamics standards. The distinct deformation states induce distinct capillary pressures for a liquid L filling the device 100, as illustrated in FIG. 2.A – C, which in turn makes it possible to modify the way the liquid L is pulled throughout the chamber 53.

In the following, one assumes, for the sake of exemplification, that:

- Liquid is filled from the left side (i.e., from the first microchannel 31, see FIGS. 2, 4, and 5 to 13); and
- The second deformation state S2 is a deformed state (substantial stress applied, like in FIG. 1.B), while the first state S1 essentially corresponds to a non-deformed state (no specific stress applied, FIG. 1.B). The extent of deformations conferred by the two states S1, S2 is such that a first capillary pressure P1 (as induced by state S1, non-deformed) must be substantially larger than capillary pressure P2 as experienced by a liquid when the valve is in the deformation state S2. This shall be quantified later by way of examples.

A typical device may be operated as follows, see FIGS. 1 – 2:

- First, FIG. 2.A (non-deformed state S1, time t1): a liquid L is filled from microchannel 31, where it reaches port 51. There, the liquid slows down or even stops, because of the large capillary pressure P1 induced by non-deformed state S1. The inside of the valve’s chamber 53 is so far such as depicted in FIG. 1.A. In that respect, the valve is preferably configured such as to enlarge (e.g., abruptly) the wettable flowpath when going from microchannel 31 to chamber 53. This enlargement results in increasing the capillary pressure (or reducing it in absolute terms), at least when the chamber is not deformed, and this, sufficiently to slow down the liquid, or possibly stop it. The precise behavior of the liquid will depend on the nature of the liquid, the precise geometry of the chamber at the level of the input port 51, the chemical surface state, etc., as many parameters that shall discussed in more details below;

- Second, as depicted in FIG. 1.B (state S2, time t2 > t1), the valve is deformed, e.g., pressed at the center towards – *y*, thanks to a push rod or the like. As the valve's walls are deformed along deformation axis *y*, which axis intersects the flow direction *z*, the local dimension (along *y*) of the chamber is reduced, which enhances capillary effects. Thus, the valve can be regarded as being more capillary active in one of the states than in the other.
- As a result of the deformation (FIG. 2.B), capillary pressure drops and liquid is pulled along the flow direction, i.e., at least substantially more in deformed state S2 than in initial state S1. In FIG. 1.B, the two arrows point at regions that still exhibit high capillary pressure, even when the chamber is deformed, compared to the center. As a result, liquid propagates first towards the center (time t2), i.e., the most deformed region where capillary pressure is the lowest (negative values are assumed).
- Eventually (state S2, time t2' > t2, FIG. 2.C), liquid propagates to other regions of the chamber, having higher capillary pressure. Maintaining the deformation allows for the liquid to advance towards port 51, until it reaches the second microchannel 32 (not shown).

Preferably, the walls of the valve are non-permanently deformable, such as to allow for reverting to a non-deformed state. More preferably, they are resiliently deformable, to allow for re-using the valve. Yet, for some applications where e.g., single use of valves is expected, the valves' walls need not be non-permanently (or resiliently) deformable. On the contrary, one may prefer permanently deformable valves to prevent from re-using the device (single-use test chip, etc.), be it for security reasons. Another possibility would be to rely on a flexible material, yet configured to exhibit a snapping effect, e.g., once deformed, the chamber cannot easily revert to its initial geometry.

As said, we assumed that the first state is a non-deformed state and the second state a deformed state, for the sake of exemplification. Yet, the skilled person shall appreciate that various configurations/scenarios fall under the same principle as described above, i.e., that the liquid be pulled along the flow direction substantially more in one state than in the other. For example, the chamber could be initially deformed (e.g., pressed on the sides to increase the mean height along *z*) and maintained in this deformed state, such as to be capillary inactive and prevent liquid to flow through the valve. Restoring a non-deformed state of the valve, wherein the valve is capillary active would prompt the liquid to flow through. This actually depends on the deformation direction, *vs.* the flow direction and the general geometry of the chamber.

Concerning now the deformation direction: it was so far only assumed that this direction had to intersect the flow direction z, i.e., with a non-zero angle. Preferably yet, simplest designs are obtained for configurations where the deformation direction (y) is perpendicular to the flow direction z. In this respect, in the examples of FIGS. 1 – 2, the valve 50 is created by enlarging the wettable flowpath along the x axis i.e., perpendicular to both the flow direction z and the deformation direction y. Here, a characteristic dimension of the chamber 53 along x (e. g., measured in the main plane of the chamber 53) is substantially larger than the characteristic dimension of the microchannels along the same axis x. In this case, deforming the valve essentially along y (actually in the direction $-y$), allow the liquid to more easily contact both lower and upper walls 58, 11 and propagates towards output port 53, by capillarity. Yet, deforming the valve along x may in principle allow the same, provided that side walls 54, 56 can be sufficiently deformed to get close enough to each other and allow the liquid to propagate. Thus, one understands that the deformation direction must have a component (e.g., along x or y) perpendicular to the flow direction z. This is why the valve (i.e., its walls) must be at least partly deformable along a deformation direction *intersecting* the flow direction z.

Preferably yet, the valve is essentially deformable along y (rather than x), as in the examples of FIGS. 1 – 2, such that the deformation direction y intersects both the flow direction z and the enlargement direction x. This is advantageous in terms of fabrication process, inasmuch as the depths of the microchannels and the chamber can in this case be essentially the same, subject to machining tool precision. This is illustrated in FIGS. 3.A – 3.B (wireframe pictures), where the microchannels 31, 32 and the chamber 53 are shown to be provided as grooves/depression in a single layer 10. More precisely, each of microchannels 31, 32 (or at least end portions thereof at the level of respective ports 51, 52) are grooves open on the upper surface 11 of the first layer 10. Similarly, the hollow chamber is essentially delimitated by a depression 53 open on the upper surface 11. As seen in FIG. 3.B, the grooves and depression are closeable by the lower surface of the second layer 20 (i.e., the lower surface 21 in FIG. 1.A). Such a design is easily manufactured, owing to the single machining depth necessary here.

Incidentally, note that not all the walls 54, 56, 58, 20 need be deformable. For example, only the upper wall 20 need be deformable (as illustrated in FIG. 1.B). Conversely (or in addition), the wall 54, 56 could be deformable too, or at least portions thereof. Similarly, only the lower wall 58 could be made deformable, etc.

When a two-layer manufacture process is contemplated, then at least one of the layers 10, 20 can be made of a deformable material. Having one of the layers 10, 20 (or both) made of a flexible material is simpler in terms of fabrication steps.

The deformable layer preferably exhibits a tensile strength between 1 and 60 MPa. It can for example be made of a poly(dimethylsiloxane) elastomer, for which typical tensile strengths vary between 1 and 10 MPa. They can otherwise advantageously be made of a plastic material. One preferred example is a polyolefin copolymer, easier to fabricate in large numbers using mold injection or embossing techniques. Thermoplastic materials are suitable candidates, typically having a tensile strength between 20 and 60 MPa, see e.g., the Polymer Data Handbook, Oxford University Press, 1999. Another example of a suitable material is Sylgard 184^{TM} poly(dimethylsiloxane), the latter having a Young's modulus of about 2.5 MPa. The material chosen should preferably not be brittle.

FIG. 4 is a graphic representing the variations of capillary pressures as experienced by a liquid propagating through the device 100. Capillary pressures are expressed in N/m^2. The various curves represent: a "closed" state of the valve (full line); an "open" state (dotted line) and an intermediate, partly deformed state (dashed line). Consistently with the embodiments of FIGS. 1 – 3, the closed/open states respectively correspond to non-deformed/deformed states. These curves all result from a theoretical model of a device 100, the latter depicted in the same drawing. The position of the liquid in the device is expressed in mm. This device 100 comprises:

- A loading pad 60 (region *R1*) for loading liquid into the device,
- A loading channel (region *R2*), for bringing liquid to:
- A narrowing channel (region *R3*), itself leading to:
- A first microchannel (region *R4*);
- Then, the flowpath abruptly enlarges when entering the chamber of the valve 50 (region *R5*), until it reaches a maximal width (i.e., its characteristic *x*-dimension);
- Next, the flowpath width continuously decreases with an approximately constant slope (region *R6*), until it reaches:
- A next section (53') of the valve's chamber, where the flowpath width still decreases but now with a smaller slope (region *R7*). Such a section provides a useful intermediate profile between region *R6* and the next region *R7*, the latter corresponding to:
- The output microchannel (region *R8*).

In this model, the cover (i.e., layer 20 in FIG. 3.B) is made of a flexible material, e.g., Sylgard 184^{TM}. The microfluidic chip (i.e., layer 10 in FIGS. 3.A –

3.B) is microfabricated in silicon and has a native oxide treated to have an advancing contact angle with water of 45°. The cover typically has an advancing contact angle with water of 110°. As seen from the curves, the capillary pressure experienced by the liquid (typically water) typically drops with narrowing sections. As a comment, capillary pressure would reach values close to zero for cavities having extended dimensions (depth and width); it should even (theoretically) reach zero for infinite depth and width. The capillary pressure typically reaches a minimum at the level of the microchannels (regions *R4* and *R8*). In regions *R5* – *R7*, the capillary pressure suddenly increases, because of the abrupt enlargement of the valve's chamber. In the closed state (non-deformed, full line), capillary pressure reaches a level (typically > – 1 000 N/m^2) that is similar to (i.e., has a same order of magnitude of) that in the loading pad (region *R1*), higher than in the loading channel (region *R2*), and substantially higher than in the input microchannel (region *R4*). As a result, liquid essentially stops at the input port. Typically, the PDMS cover (layer 20) lies 60 μm above layer surface 58, when not deformed.

Next, opening the valve (i.e., deforming it in direction – *y*), allows to achieve subsequent deformation states where capillary pressure substantially decreases (dashed and doted lines). In the "open" state, the PDMS layer 20 is typically pressed down to 20 μm (on average) above the lower layer 10, which corresponds to a stretch ratio of $\lambda = 1/3$. Thus an order of magnitude of the deformation within the hollow chamber (and along the deformation axis) is typically $e = \lambda - 1 = -2/3$. In fact, a suitable stretch ratio is one that allows the chamber to pass from a state that is clearly capillary inactive to a state that is clearly capillary active, with respect to the liquid considered. Typical stretch ratios would thus more generally be comprised between 0.1 and 0.75, and possibly between 0.1 and 0.5, as exemplified above.

As seen, the differences of capillary pressures between the maxima in the closed and open states can be as high as 2000 N/m^2. It is typically more than 1000 N/m^2. Since the lowered capillary pressure is now below the capillary pressure as experienced in regions *R1* – *R2*, the liquids, seeking to lower its potential energy, shall be pulled through the valve to reach region *R8*.

Incidentally, we note that, irrespective of the exact configuration of the device 100 (whether it comprises a loading pad, a loading channel, etc. or not) and the exact values of capillary pressures experienced by liquid propagating through the device, as long as distinct deformation states can be defined for the valve (with deformation intersecting axis *z*), liquid shall necessarily be pulled along the flow direction more in one of theses states than in the other. Indeed, the modification of the geometry along the deformation axis results in that capillary effects are more effective in one state than in the other. Accordingly, and referring back to FIGS. 1 – 3, a core idea of the present invention is to provide a valve with a hollow chamber 53, which enlarges the flowpath and is deformable along a direction intersecting the flow direction. A valve mechanism is accordingly obtained, which allows for controlling a flow of liquid along a flowpath.

In preferred embodiments, the chamber is provided with additional geometrical features to make the valve more effective, e.g., to achieve an effective “stop-valve”, rather than a means merely impacting the liquid flow dynamics. In this regards, it can be realized that a bulb design such as represented in FIG. 5.A, where the flowpath is seen to enlarge at the level of the input port, results in slowing down the liquid at the input port rather than stopping it clearly (i.e., before deforming the chamber). Of course, the actual behavior of the liquid shall depend on the precise geometrical features of the chamber, the nature of the liquid, the chemical surface state of the flowpath, etc., as said earlier.

Now, it can be realized that the entrance opening angle θ_{add} of the chamber 53, i.e., at the level of the input port 51, impacts the propensity of the liquid to wet the flowpath at the input port and, thus, the flow dynamics. Therefore, embodiments of the present invention provide an entrance opening angle θ_{add} that is “negative”. More precisely, if this entrance angle θ_{add} is measured between the flow direction z and the portion of the valve that delimitates the chamber at the input port 51, then this angle is preferably set between 90° and 180°, see e.g., FIG. 6.B, which zooms on the input port region of FIG. 6.A. Preferably, this angle is comprised between 110° and 160°, a suitable value being typically 135°. Thus, considering a situation where liquid fills a microchannel with an advancing contact angle θ_{adv}, the enlargement, i.e., the widening at the entrance in the chamber adds an angle component θ_{add} that challenges the propagation of the meniscus into the chamber of the valve. This increases the stability of the valve in its blocking state.

Similarly, the output geometry also impacts the flow dynamics. It has been found that the angle θ_{out}, i.e., at the level of the output port, should be less than the opening angle θ_{add}. Note that the angle θ_{out} is this time measured between direction $-z$ (i.e., opposite to the flow direction z) and the portion of the valve delimiting the chamber at the output port. Thus, θ_{out} is between 0° and 90°. Preferably, it is set between 20° and 70°, a typical, suitable value being 35°.

As a result of the preferred angle values and x-enlargement, the profile of the valve along the flow direction is essentially tear-shaped, as illustrated in the preferred examples shown in FIGS. 5 – 9.

More generally, the geometry of the inlet can be optimized in various ways, be it to pin the liquid at the entrance of the valve and prevent it from creeping along corners and sidewalls. This is especially true when the walls of the valve are hydrophilic, or when the liquid has surfactants or has a lower surface tension. As said, some optimization can be performed in respect of opening angles θ_{add} and θ_{out}.

Other geometrical parameters shall impact the valve efficiency. Notably, it was found that minimal length/width ratios of the inner chamber 53 should preferably be between 3/1 and 1/1, as depicted in FIGS. 5.A to 5.C, where this ratio passes from approximately 1/1 to 3/1. Note that, here, the "inner chamber" represent the chamber 53, yet excluding the intermediate section 53' leading to the output channel, as denoted by dashed lines FIG. 5.A. The higher the minimal length/width ratio, the more progressive the profile toward the output channel, which allows for reducing dead volume and risk of air entrapment. Incidentally, the width of the chamber is typically 200 – 1800 µm, preferably about 600 µm. In the above examples, the length and width are measured along directions z and x, respectively. More generally, the characteristic width of the chamber is measured in a plane (x, z), perpendicular to the deformation direction.

Thus, as described above in reference to FIGS. 1 – 6, three important parameters of the valve are its depth (y-axis), its width (or, say, its characteristic lateral dimension along x-axis) and length (z-axis). Of course, the actual number of such parameters depends on the symmetry given to the chamber. The width and depth for instance reduce to one (radial) parameter if the chamber is constrained to have cylindrical symmetry. Similarly, only one radial parameter results from spherical symmetry. Now, such parameters (i.e., the depth and width in FIGS. 1 – 6) combine with the Young's modulus of the deformable wall (i.e., the cover) to define the critical actuation pressure. This pressure is what needs to be applied on the cover where the valve is located to trigger a flow from the inlet to the outlet. As evoked earlier, since it is easier and more economical to produce microfluidic chips wherein structures have all the same depth, it is particularly convenient to vary the width rather than the depth to set the critical pressure. Typically, the characteristic lateral dimension corresponds to the maximum width of the valve. For modeling purposes, it is also possible to approximate a section of the valve to a circle, in which case the characteristic lateral dimension becomes the diameter of the valve. The cover is typically made from poly(dimethylsiloxane) (or PDMS) such as Sylgard 184^{TM}, which has a Young's modulus of ~2.5 MPa.

Next, the propagation of thin liquid films along corners and surfaces can be hard to prevent, especially when a valve is desired to block a liquid for a long time and/or if there are temperature and pressure changes. A further reduction of liquid creeping can be achieved by creating indentations (protrusions or teeth 72, 74) along sidewalls 54, 56 of the valve, as depicted in FIGS. 7.A – 7.C, 8.A, 8.B, and 9.C, 9.D. Such indentations 72, 74 protrude outwardly, i.e., they have a main component on the *x*-direction. Indented paths increase the peripheral surface offered to the liquid, typically by a factor 4/3 (FIGS. 7.A, 7.B). Indentations near the outlet (FIGS. 7.A, 7.B, 8.A, 8.B, 9.C, and 9.D) are particularly useful because they enable trapping and slowing down small droplets of condensing liquid. In FIG. 7.C, the path is indented on most of the valve periphery. In FIGS. 8.B, 9.C, and 9.D, tapered indentations are provided, such as to provide entrance angle with high value "added" angles. More generally, the shapes of indentation can be optimized concurrently with opening angles θ_{add} and/or θ_{out}, as illustrated in FIG. 8.A.

Next, the valve 50 may further comprise wettable pillars 86 (or pinning structures, represented as white dots in FIGS. 9 – 10). Such pillars typically extend from the lower wall 10, 58 to the upper wall 20 of the valve 50. The pillars distribution is substantially denser at the level of one of the ports (i.e., the input port), or even each of the ports (input and output ports), than at the centre of the valve.

Pinning structures can help to stop a liquid filling front in a wettable channel at a precise location, if needed. An example is a line or rectangular posts with narrow spacing, forming a channel. When the liquid filling the structure reaches the outlet of a narrow channel, the advancing liquid meniscus is challenged by the surface tension of the liquid. The energetically most favorable state is reached when the liquid meniscus bows out of the channel with a radius of curvature of half the channel width. Referring more specifically to:

- FIG. 9.A, here rectangular posts are provided at the entrance (input port). Rectangular posts in a semi-circle distribute the liquid to many pinning channels. Post dimensions are typically 40×40 μm^2 with a spacing of 20 μm;
- FIG. 9.B, circular posts distribute the liquid to one single line of pinning rectangular posts (pinning line). Diameter of circular posts is e.g., 70 μm;
- FIG. 9.C, structures are provided to distribute and pin the liquid filling front. It combines with indented walls (with added angles) to stop creeping of liquid along the corners;
- FIG. 9.D, rectangular posts distribute the liquid to a pinning line. Corrugated walls and indented walls with added angles can be added to stop creeping of liquid at channel walls, if needed.

In addition, the microfluidic device 100 may further comprises one or more reservoirs 90, 92 connecting the hollow chamber 53, e.g., through respective ports as depicted in FIGS. 10.A – C.

Added angles, pining structures and reservoirs are as many optional features which can be combined for optimizing a device according to the invention. For example, in FIGS. 10.A – B, sidewalls of the valve are placed away from the central area of the chamber by creating side reservoirs 90, 92. In FIGS. 10.A and 10.B, pinning the liquid filling front using pillars, added angles, and side cavities decreases further creeping of liquid along walls of the valve. Building on this principle, the flow of liquid can even be constrained to a narrow incoming path toward the valve area using (wettable) pillars, FIG. 10.C. In this limit case, the valve was found to be particularly stable. More in details, here the flowpath critically depends on pillar structures, as the flow path of the liquid filling the chip is defined by the pillars, e.g., circular posts 86 (typical diameter and spacing being ~100 μm). Liquid enters the structure from the left and fills the volume between the posts with liquid. In the center of the stop valve, where pillars are absent, the capillary pressure approaches zero: the liquid cannot proceed any further and filling is stopped. To have the liquid pass the other side, the chamber 53 is deformed, as described earlier.

Next, a microfluidic device according to embodiments may further comprises a number of additional features, such as

- A loading pad 60 (FIGS. 4, 11, 12), i.e., upstream the first microchannel, to load liquid into the device,
- A reaction chamber 70 downstream the valve 50 (FIG. 11),
- A reagent zone 82 (FIG. 11), e.g., inserted between the loading pad and the first microchannel, and
- A capillary pump (84), inserted downstream the valve 50, preferably after the reaction chamber 70,
- Etc.

FIG. 11 shows a design of a microfluidic chip having a loading pad able to receive 2 μL of liquid, a reagent zone 82, a mechanical stop valve 50, a reaction chamber 70 and a capillary pump 84 as described above. This design can for instance be transferred into silicon using reactive ion etching (typical depth of channels in the silicon chip: 60 μm). A PDMS cover is placed on top (not shown) to cover the channels and pumps. In the area of the reaction chamber, the PDMS cover comprises lines of biological receptor molecules (e.g. avidin or other biomolecules), which cross the reaction chambers perpendicularly and are facing the lumen of the reaction chamber. In this chip, an assay can be done in the reaction chamber located after the valve and before the capillary pump.

Note, however, that present embodiments are not at all limited to applications with biological receptor molecules or, even, receptor molecules. One may for instance want to use a microfluidic chip for testing metabolites that are not biological although present in the human body (like citrate or other metabolites). Also, keeping the previous example of metabolites, detection could for example be performed by using an enzymatic reaction and not a ligand-receptor binding. The skilled person may appreciate that various other applications can be contemplated with microfluidic devices as provided herein.

More generally, peripherals for experiments using chips having the valves disclosed herein can be:

- A heating stage underneath the reagent zone (as some assays require labeling analytes using various temperatures or dissociating analyte molecules);
- A cooling stage underneath the loading pad (for example to limit evaporation, especially if very small volumes of sample are used or enhance the stability of reagents/analytes);
- A fluorescence reader, e.g., above the reaction chamber (to read signal of the assay through the cover) or under the reaction chamber in the case of a plastic chip;
- A piston (e.g. a solenoid that can be programmed to exert a precise pressure at a given time onto the valve); and
- A pipetting robot (for automatic loading of samples and reagents onto the loading pad and/or reagent zone.

Such peripherals are however not requirements for a valve mechanism as described herein.

Next, some of the concepts described above may be parallelized. For example, a microfluidic device may, in embodiments, comprise n sets, $n \geq 2$, each comprising first and second microchannels and a valve configured as described above.

For example, a microfluidic chip with nine channels for parallel detection of analytes is disclosed in FIG. 12. The dimensions of the chip are approximately 52×47 mm^2. Flow direction on the chip is left to right. The chip comprises a common loading pad onto which 10 μL of sample can be pipetted. A system of channels pulls the liquid from the pad and distributes it equally into nine distinct flow paths. All paths are typically made equal (in length and therefore hydraulic resistance) using serpentines. Each flow path leads to a reagent zone which can hold a liquid volume of 0.5 μL. Each reagent zone is followed by a microchannel that comprises a mechanical stop valve 50 to interrupt the filling of the chip with liquid. Each valve is followed by a reaction chamber. The nine reaction chambers are kept proximal and parallel to ease the reading of signals using optical systems. Each reaction chamber is connected to a capillary pump that can hold a liquid volume of 1 μL.

Microfluidic devices such as described above can notably be applied to biological assays. For instance, FIGS. 13.A – 13.D reflect time sequence fluorescence microscope images showing molecular grade water containing biotinylated 997 bp dsDNA PCR product with Bryt™ Green dye (fluorescent when it is intercalated in double strand DNA), passing the valve (from left to right). Taking as an example the detection of PCR products composed of nucleotides (double-stranded DNA, each having 997 bases), an assay for detecting this PCR product in a sample utilizing the valve and chip shown in FIG 11 was done. First, 1 µL of Bryt™ Green dye and 1 µL of 2 µM biotinylated 20 bases single-stranded DNA probe were pipetted in a reagent zone 82 of a chip (without having the cover in place) and dried. Second, 1 µL of sample containing 10 nM 997 bp PCR product in Tris-EDTA buffer solution was pipetted in a loading pad 60. The liquid meniscus filled a hybridization chamber 81, a first microchannel 31, and stopped at the input port 51. The filling of the sample from the loading pad until the input port approximately took 30 s and when the sample reached the reagent zone, it dissolved the Bryt™ Green dye and biotinylated 20 bases single-stranded DNA probe. Third, the area of the reagent zone of the chip was heated to 95°C and cooled down to room temperature. The heating of liquid in the reagent zone sometimes resulted in the formation of an air bubble in the reagent zone. It was found possible to remove it by applying a pressure (approximately 1 bar above ambient pressure) using a custom-made pressurization chamber. During the heating step, the double strand PCR product melted (the strands separated) and the biotinylated single-stranded DNA bound its complementary sequence in the PCR product during cooling. This process typically took around 10 min during which the valve 50 was stopping the liquid. Fourth, by pressing a push nod 110 on top of the PDMS above the cavity 53 (e.g. using the tip of a pencil) the PDMS was deformed into the channel and the liquid was pulled into the cavity. Fifth, the liquid then passed through the second microchannel 32, through the reaction chamber 70, and reached the capillary pump 84. In the reaction chamber 70, the biotinylated probes annealed to PCR products were captured on avidin receptors patterned on the PDMS surface facing the lumen of the reaction chamber. The captured PCR product analytes were quantified by means of surface fluorescence using a fluorescence microscope.

Applications are however not limited to biological assays. The types of reagent, liquid compositions, temperatures and incubation time can be varied. Many types of samples with analytes to be detected can be added to the loading pad and many different types of reagents (chemicals, dyes, enzymes, oligonucleotides, antibodies, etc.) can be added in the reagent zone. The volumes, type of microstructures in the chip, size of the chip, materials used for the chip and cover can be varied. The geometry of the valve can be varied to adjust for different mechanical properties of the cover. The valves and microfluidic chip can be used under ambient conditions as well as within a pressurized chamber.

While the present invention has been described with reference to certain embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the present invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the present invention without departing from its scope. Therefore, it is intended that the present invention not be limited to the particular embodiment disclosed, but that the present invention will include all embodiments falling within the scope of the appended claims. For example, present devices may be embodied with conduits inserted through each of the superimposed layers 10, 20 of FIGS. 3.A – 3.B, in opposite or same directions, and possibly connected through microchannels. Several designs of microchannels could be contemplated. Several superimposed layers similar to layers 10, 20 can be fabricated, with conduits inserted though two or more layers and microchannels grooved at several interfaces, such as to enable fluid communication between three or more layers, etc. Interface layers could still be provided between a pair of layers 10, 20, etc.

CLAIMS

1. A microfluidic device (100) comprising: a first microchannel (31), a second microchannel (32), and a valve (50) comprising at least an input port (51) and an output port (52), said ports respectively connected to the first microchannel and the second microchannel, the valve designed to control a flow of a liquid (L) along a flow direction (*z*) defined by the ports,
wherein,
the valve further comprises one or more walls (54, 56, 58, 20) joining the ports and defining a hollow chamber (53) that is wider than each of the microchannels in a direction perpendicular to the flow direction, said walls at least partly deformable along a deformation direction (– *y*) intersecting the flow direction, such that the walls can be given at least a first deformation state (S1) and a second deformation state (S2), such that the liquid can be pulled along the flow direction substantially more in the second deformation state than in the first deformation state.

2. The device of claim 1, wherein the first deformation state and the second deformation state respectively induce a first capillary pressure and a second capillary pressure for the liquid, the first capillary pressure being substantially larger than the second capillary pressure, typically by more than 1000 N/m^2, and the first capillary pressure having preferably a same order of magnitude as a capillary pressure induced in a portion (*R1*) upstream the first microchannel, said upstream portion preferably corresponding to a portion comprising a loading pad (60) for loading liquid into the device.

3. The device of claim 1 or 2, wherein,
the first deformation state is essentially a non-deformed state and the second state is essentially a deformed state,
and wherein an average dimension of the hollow chamber along the deformation direction exhibits a ratio between the second deformation state and the first deformation state, which is between 0.1 and 0.9, preferably between 0.5 and 0.75, and wherein the walls at least partly deformable are preferably non-permanently deformable, and more preferably resiliently deformable.

4. The device of claim 1, 2 or 3, wherein a characteristic dimension of the hollow chamber is substantially larger than a characteristic dimension of each of the first and the second microchannels, wherein said characteristic dimensions are measured in a same plane (*x*, *z*), perpendicular to the deformation direction, and preferably measured in a direction (*x*) perpendicular to both the deformation direction and the flow direction.

5. The device of claim 4, wherein depths of each of the microchannels and the hollow chamber, as measured along the deformation direction, are essentially equal.

6. The device of any one of claims 1 to 5, wherein at least portions of each of the first microchannel and the second microchannel at the level of the ports are grooves open on an upper surface (11) of a first layer (10), and the hollow chamber is defined by a depression (53, 53') open on the upper surface of the first layer, the grooves and the depression being closed by a lower surface (21) of a second layer (20), and wherein the first layer and/or the second layer are at least partly deformable and preferably exhibit a tensile strength between 1 and 60 Mpa, and more preferably between 20 and 60 Mpa.

7. The device of any one of claims 1 to 6, wherein an opening angle θ_{add} of the chamber at the level of the input port, as measured between a flow direction and a portion of said one or more walls delimiting the hollow chamber at the input port, is between 90° and 180°, preferably between 110° and 160°, and more preferably substantially equal to 135°.

8. The device of claim 7, wherein an opening angle θ_{out} of the chamber at the level of the output port, as measured between a direction opposite to the flow direction and a portion of said one or more walls delimiting the hollow chamber at the output port, is between 0° and 90°, preferably between 20° and 70°, and more preferably substantially equal to 35°, and wherein, preferably, the profile of the valve along the flow direction is essentially tear-shaped.

9. The device of any one of claims 1 to 8, wherein a minimal length/width ratio of the hollow chamber is between 3/1 and 1/1, the length measured along the flow direction and the width measured perpendicularly to both the length and the deformation direction.

10. The device of claim 9, wherein the valve comprises sidewalls at least partly indented, the indented sidewalls exhibiting protrusions (72, 74) protruding outwardly.

11. The device of any one of claims 1 to 10, wherein the valve further comprises wettable pillars (86) extending from a lower wall (10, 58) to an upper wall (20) of the valve, the pillars distribution being substantially denser at the level of one of the ports or preferably each of the ports than at the centre of the valve.

12. The device of any one of claims 1 to 11, wherein the microfluidic device further comprises one or more reservoirs (90, 92) connecting the hollow chamber.

13. The device according to any one of claims 1 to 12, wherein the microfluidic device further comprises a loading pad (60) upstream the first microchannel, and preferably comprises a reaction chamber (70) downstream the valve, and more preferably comprises reagent zone (82) and a capillary pump (84), respectively inserted in a liquid path of the first microchannel and the second microchannel.

14. A microfluidic device, comprising *n* sets, $n \geq 2$, each of the sets comprising a first microchannel, a second microchannels and a valve configured similarly as said first microchannel, said second microchannel and said valve of the device according to any one of claims 1 to 13.

15. A method for controlling a liquid flow in a device according to any one of claims 1 to 14, comprising steps of:
- filling the first microchannel (31) with liquid (L); and
- deforming (S1, S2) said one or more walls at least partly deformable such that liquid is pulled through the hollow chamber (53) from the first microchannel (31) to the second microchannel (32).

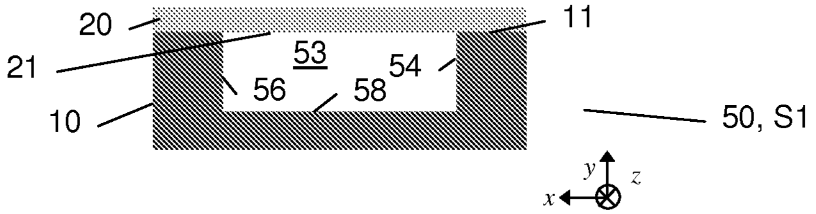


FIG. 1.A

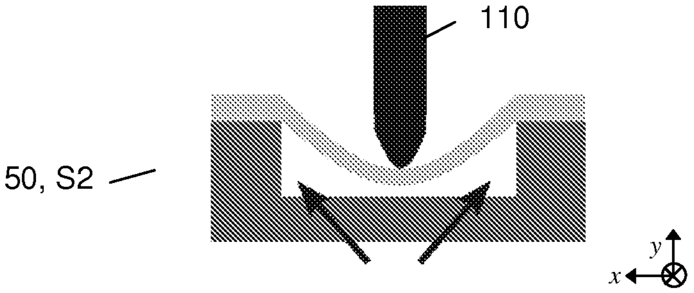


FIG. 1.B

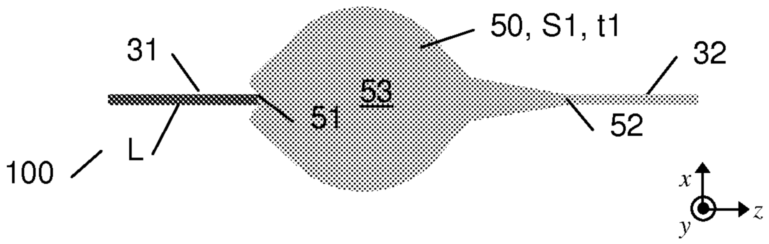


FIG. 2.A

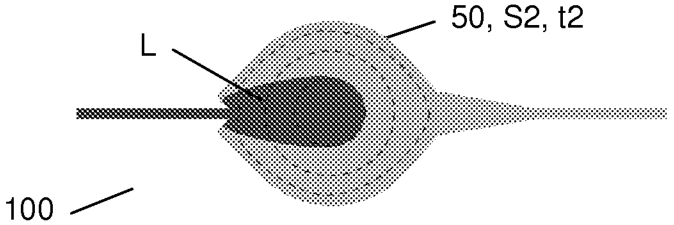


FIG. 2.B

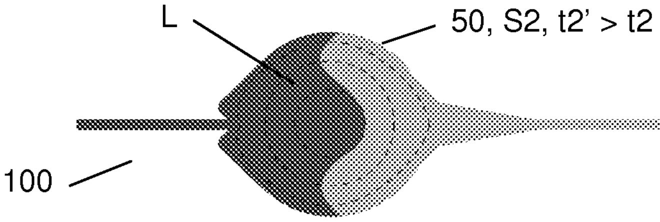


FIG. 2.C

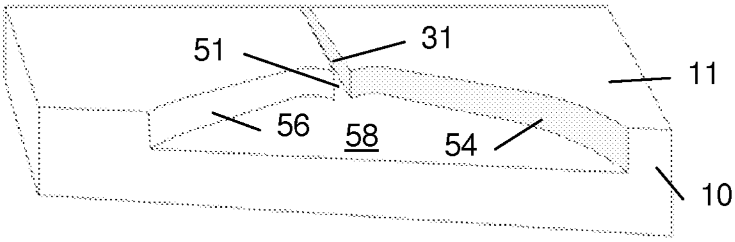


FIG. 3.A

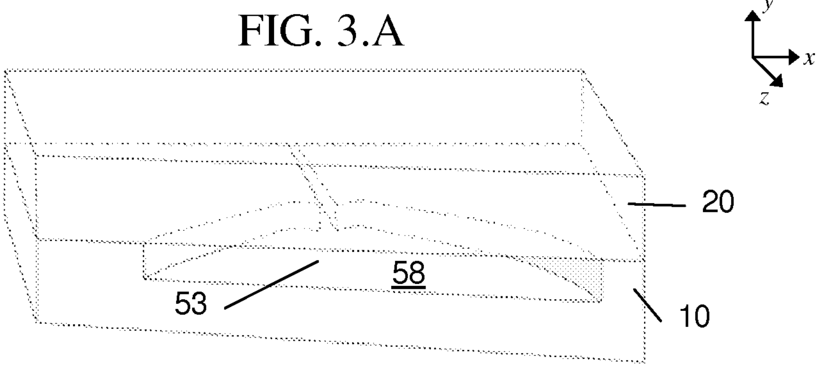


FIG. 3.B

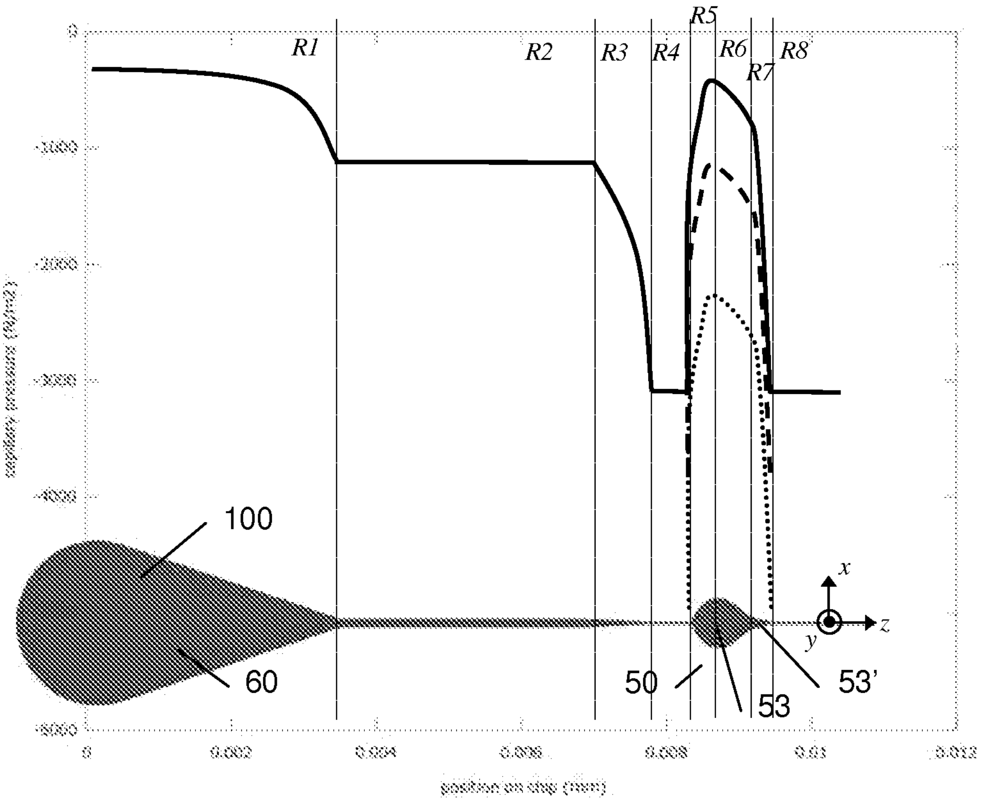


FIG. 4.

FIG. 5.A

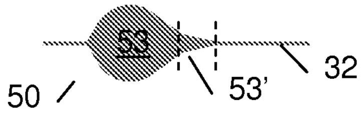
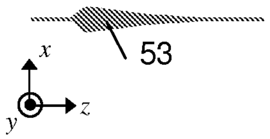


FIG. 5.B

FIG. 5.C



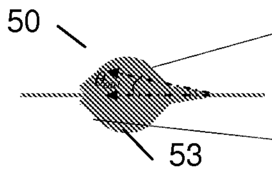


FIG. 6.A

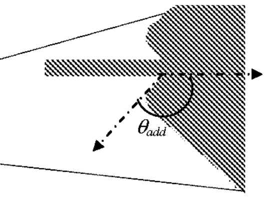


FIG. 6.B

FIG. 6.C

FIG. 6.D

FIG. 7.A FIG. 7.B

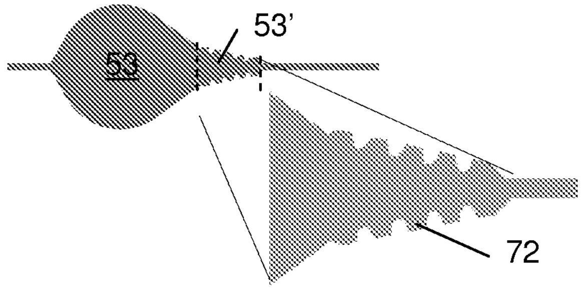
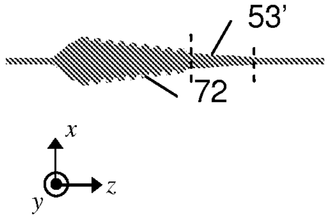


FIG. 7.C



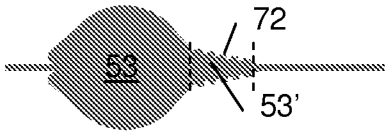


FIG. 8.A

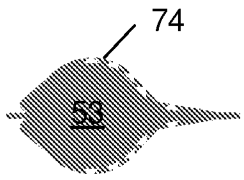


FIG. 8.B

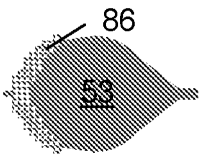


FIG. 9.A

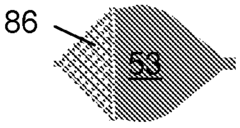


FIG. 9.B

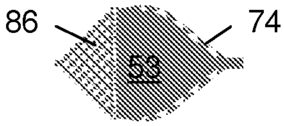


FIG. 9.C

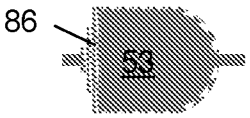
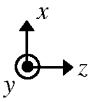


FIG. 9.D



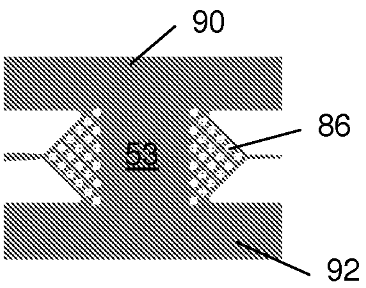


FIG. 10.A

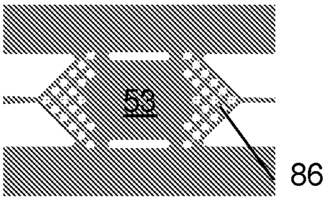


FIG. 10.B

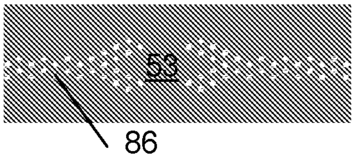
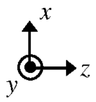


FIG. 10.C



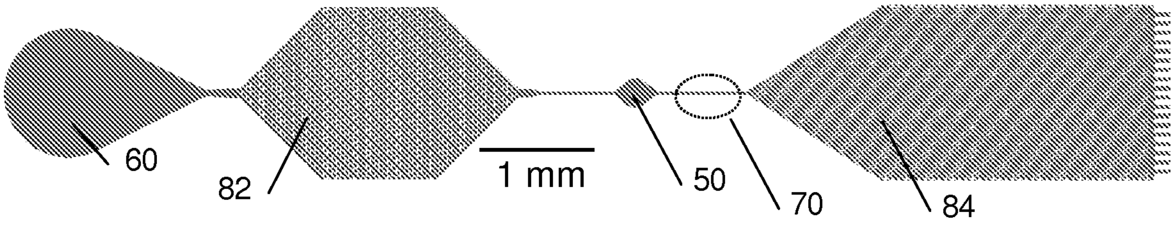


FIG. 11.

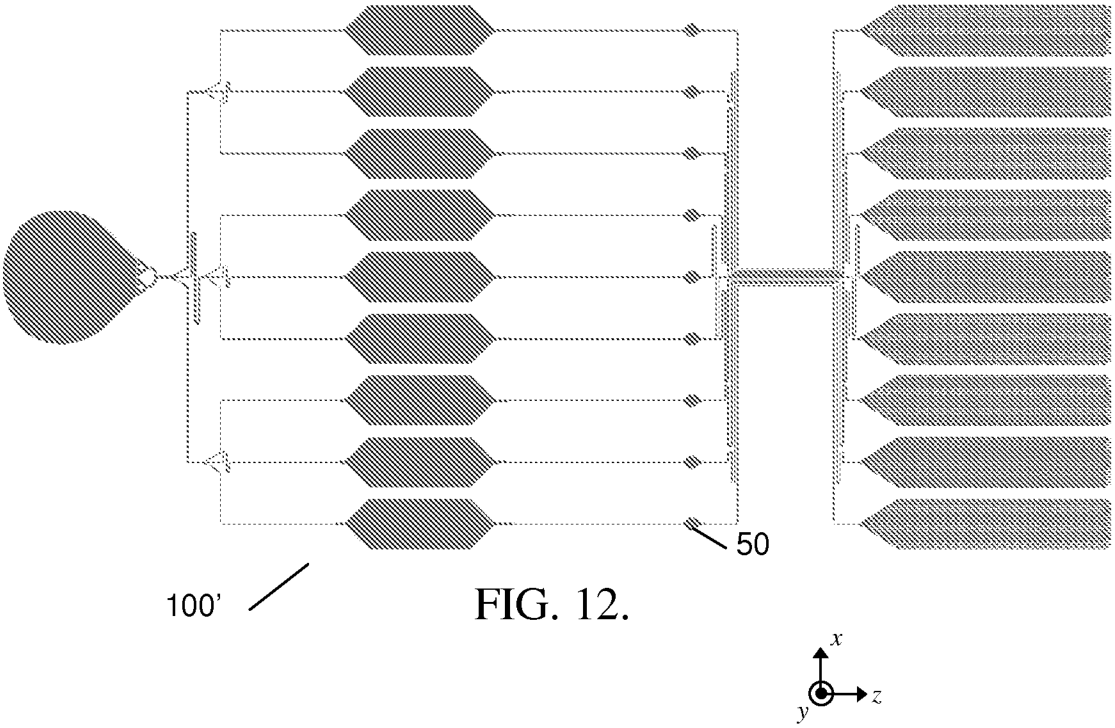


FIG. 12.

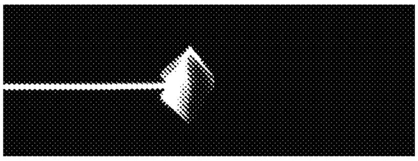


FIG. 13.A

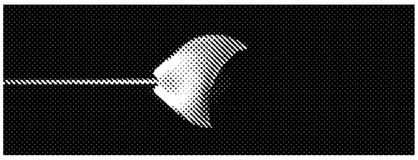


FIG. 13.B

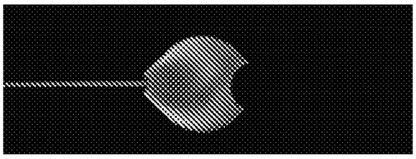


FIG. 13.C

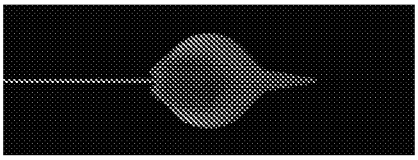


FIG. 13.D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/055643

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. F04B53/10(2006.01)i, B81B3/00(2006.01)i, F16K7/16(2006.01)i, G01N37/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. F04B53/10, B81B3/00, F16K7/16, G01N37/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2013
Registered utility model specifications of Japan 1996-2013
Published registered utility model applications of Japan 1994-2013

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	JP 2010-107051 A (SEIKO INSTRUMENTS INC.) 2010.05.13, [0019]-[0023], Fig.1-2 (No Family)	1, 4-5, 9, 14 2-3, 6-8, 10-13, 15
A	WO 2008/105308 A1 (KONICAMINOLTA HOLDINGS, INC.) 2008.09.04, [0011]-[0020], Fig.1-3 & JP 4169115 B & US 2010/0101660 A1	1-15
A	JP 2006-167719 A (KONICAMINOLTA HOLDINGS, INC.) 2006.06.29, [0040]-[0045], Fig.2-4 (No Family)	1-15
A	JP 2005-299597 A (TAMA-TLO, LTD.) 2005.10.27, [0026]-[0049], Fig.1-12 (No Family)	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"&" document member of the same patent family

Date of the actual completion of the international search
01.03.2013

Date of mailing of the international search report
12.03.2013

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