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(71) Applicant: FLUIDIC ANALYTICS LIMITED [GB/GB]; Unit 5, Chesterton Mill, French's Road, Cambridge CB4 3NP (GB).

(72) Inventors: DOUGLAS, Anthony; 274 Glenalmond Avenue, Cambridge CB2 8DS (GB). KNOWLES, Tuomas Pertti Jonathan; 22 Aylestone Road, Cambridge CB4 1HF (GB). MUELLER, Thomas; Ottenbergstrasse 32A, 8049 Zuerich (CH). LYNN, Andrew; Unit 5, Chesterton Mill, French's Road, Cambridge CB4 3NP (GB).

(74) Agent: STRATAGEM INTELLECTUAL PROPERTY MANAGEMENT LIMITED; Meridian Court, Comberton Road, Toft, Cambridge CB23 2RY (GB).

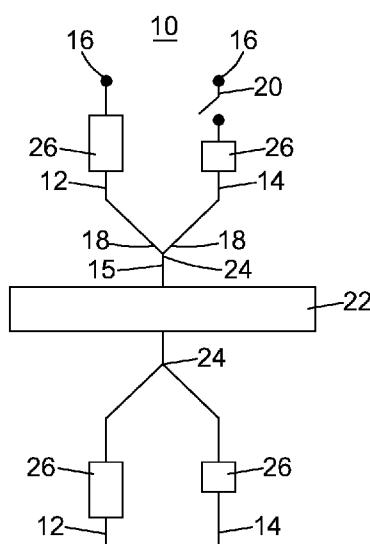
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(54) Title: IMPROVEMENTS IN OR RELATING TO A FLUID FLOW CONTROLLER FOR MICROFLUIDIC DEVICES



(57) Abstract: A fluid flow controller for introducing fluids into a microfluidic device is provided. The fluid flow controller comprising, at least one high resistance fluid pathway provided between an inlet port and a connection port; at least one low resistance fluid pathway between the inlet and connection port; and at least one valve configured to enable fluid flow through the high resistance fluid pathway, the low resistance fluid pathway or both.

Fig. 1A

IMPROVEMENTS IN OR RELATING TO A FLUID FLOW CONTROLLER FOR MICROFLUIDIC DEVICES

This invention relates to improvements in or relating to a fluid flow controller and in particular, a fluid flow controller for controlling the flow of a fluid into a microfluidic device.

5 Microfluidic devices offer many desirable capabilities for example, the ability to use very small quantities of biological or chemical samples and reagents such as 10 proteins, carbohydrates or DNA. In addition, microfluidic devices also have the ability to analyse, separate and detect fluids contained within the samples or reagents with high resolution and sensitivity.

15 Fluid handling, pumping and manipulation often play a critical role in introducing fluids into the microfluidic devices. In most microfluidic devices, a fluid flow can be manipulated by external means such as applying pressure to the fluid pathways or using a flow pump.

20 Pressure can be accurately and precisely controlled in microfluidic devices with the use of pressure actuators. However, controlling the flow rates in microfluidic devices can often be a challenge. This problem can be exacerbated when using inexpensive microfluidic chips.

25 Controlling the flow rates of fluids in a microfluidic device may be achieved with the use of a flow pump. However, a flow pump typically has a slow response to changes in the desired fluid flow. For example, it can take several minutes for changes in the flow rates to occur within the microfluidic device.

30 In addition, controlling the flow of fluids may include applying pressure over a large resistance in the fluid pathways. However, this can often be a time-consuming process as the large resistance may decrease the flow rate of fluids through the

channel.

It is against this background that the invention has arisen.

5 According to the present invention there is provided, a fluid flow controller for introducing fluids into a microfluidic device, the controller comprising: at least one high resistance fluid pathway provided between an inlet port and a connection port; at least one low resistance fluid pathway between the inlet and connection port; and at least one valve configured to enable fluid flow through the high 10 resistance fluid pathway, the low resistance fluid pathway or both or none.

The fluid flow controller, which can be used for introducing fluids into a microfluidic device, is particularly advantageous as it may provide a means for controlling the flow of fluids through one or more high resistance fluid pathways and/or one or 15 more low resistance fluid pathways.

In normal operation the fluids flow through the high resistance pathways. However, if it is desired to bypass the device, then access can be enabled to the low resistance fluid pathway. This allows the fluid that would otherwise have 20 flowed through the high resistance fluid pathway to flow instead through the bypass or low resistance fluid pathway.

In some embodiments, when access is enabled to the low resistance fluid pathway, the high resistance fluid pathways are closed off. This configuration 25 ensures that all of the fluid bypasses the high resistance pathways completely.

In some embodiments, when access is enabled to the low resistance fluid pathway, the high resistance fluid pathways remain accessible, but as a result of the difference in resistance fluid will preferentially flow through the low resistance 30 fluid pathway. However, a small proportion of the fluid will flow through the high resistance fluid pathway thus ensuring that the same fluid is flowing through all pathways and ensuring that no bubbles of air enter any part of the device.

The resistance of the high and low resistance fluid pathway may be dictated by one or more of the following: the cross sectional area of the pathway, the length of the pathway and the surface roughness of the pathway, as well as the viscosity of
5 the fluid. In some embodiments, the cross sectional area of the low resistance pathway may be 0.1 mm to 2 mm, and the length of the low resistance pathway may be between 1 and 1000mm, for example 100 mm in length.

In some embodiments, there is provided a network of interlinked high resistance
10 fluid pathways one or more inlet ports to one or more connection ports.

In some embodiments, each high resistance fluid pathway has a corresponding low resistance fluid pathway. This embodiment is particularly useful where different high resistance pathways are carrying different fluids and each of those
15 high resistance pathways may need to be bypassed. The provision of a separate low resistance pathway for each high resistance pathway means that all of the high resistance pathways can be bypassed without the fluids mixing in the low resistance pathways.

20 A plurality of high resistance fluid pathways and a plurality of low resistance fluid pathways may be provided in an array. A plurality of high resistance fluid pathways and a plurality of low resistance fluid pathways can be advantageous to connect to a microfluidic chip as it can be used to control the flow rates of several fluids.

25 The controller may further comprise a manifold including a plurality of valves for controlling the array of fluid pathways. In the context of microfluidic devices, valves are advantageous in that they may enable the microfluidic device to be used for performing complex fluid handling procedures. For example, the valves could be
30 used to control the direction of fluids that flow through the array of fluid pathways.

The plurality of valves is particularly advantageous because it can be used to enable the fluids to partially or completely bypass one or more fluid pathways. In some embodiments, the valve may be opened to permit the fluids to flow through the low resistance fluid pathways, thereby enabling the fluids to partially or 5 completely bypass the high resistance fluid pathways. In some embodiments, the valve may be closed, enabling the fluids to flow along the high resistance fluid pathway only. In other embodiments, the valve may be provided on the low resistance fluid pathway to permit the flow of fluids through both the high and low resistance fluid pathways.

10

The resistance of the low resistance fluid pathway can be several orders of magnitude smaller than the resistance of the chip, for example up to 100000 times smaller. The resistance of the high resistance fluid pathway can be several orders of magnitude larger than the chip resistance, for example between 3 and 3000 15 times larger.

For example, the low resistance fluid pathway may have a resistance 1000 times smaller than the chip resistance and the high resistance fluid pathway may have a resistance 100 times larger than the chip resistance.

20

The high resistance fluid pathway may have a resistance of between 1 mbar / μ l/h and 1000 mbar / μ l/h. The low resistance fluid pathway may have a resistance in the range of 1×10^{-5} mbar / μ l/hr and 100 mbar / μ l/hr.

25

The use of bypasses is particularly appropriate for systems deploying low precision chips so that the high resistance fluid pathway can be used for flow control.

30

The resistance of the low resistance fluid pathway can be 1 to 10,000,000 times less than the resistance of the high resistance fluid pathway

In some embodiments, the high resistance fluid pathway may have a resistance of 1 mbar / μ l/h to 1000 mbar / μ l/h, or it may exceed 100, 200, 400, 800 or 1000 mbar / μ l/h. In some embodiments, the high resistance fluid pathway may have a resistance of less than 1000, 800, 400, 200, 100 or 50 mbar / μ l/h. Preferably, the 5 high resistance fluid pathway has a resistance of 10 mbar / μ l/h.

In some embodiments, the low resistance fluid pathway may have a resistance of 0.00001 mbar / μ l/h to 100 mbar / μ l/h, or it may exceed 0.0001, 0.001, 0.01, 0.1, 1, 10 or 100 mbar / μ l/h. In some embodiments, the low resistance fluid pathway 10 may have a resistance less than 100, 50, 10, 1, 0.1, 0.01, 0.001 or 0.0001 mbar / μ l/h. Preferably, the low resistance fluid pathway has a resistance of 0.001 mbar / μ l/h.

The valve may be configured to close the low resistance fluid pathway only. By 15 closing the low resistance fluid pathway only, it may provide a means to prevent one or more fluids flowing through the low resistance fluid pathway and/or, it may direct one or more fluids to flow from the low resistance fluid pathway to the high resistance fluid pathway.

20 Preferably, the fluid flow controller disclosed in the present invention is provided as an interface to a microfluidic chip.

The invention will now be further and more particularly described, by way of example only, and with reference to the accompanying drawings, in which:

25 Figure 1A shows a fluid flow controller according to the present invention applied to a microfluidic chip with a closed valve on a low resistance fluid pathway;

Figure 1B shows the fluid flow controller according to Figure 1A, applied to the 30 microfluidic chip with a open valve on the low resistance fluid pathway;

Figure 2 shows a plurality of fluid pathways according to Figures 1A and 1B being

applied to the microfluidic chip;

Figure 3A shows a side view of the fluid flow controller of the present invention; and

5

Figure 3B shows a perspective view of the fluid flow controller.

Referring to Figure 1A, there is shown a fluid flow controller **10** used for

introducing fluids into a microfluidic device **22**. The fluid flow controller **10**

10 comprises at least one high resistance fluid pathway **12** provided between an inlet

port **16** and a connection port **18** which provides an outlet from the flow controller

together with connection into the microfluidic device **22**.

The fluid flow controller also comprises at least one low resistance fluid pathway

15 **14** between the inlet port **16** and connection port **18**; and at least one valve **20**

configured to enable a fluid flow through the high resistance fluid pathway **12**, the

low resistance fluid pathway **14** or both. Each high resistance fluid pathway has a

corresponding low resistance fluid pathway in order to enable the fluids to flow to

the same inlet port or connection port.

20

The microfluidic chip **22** as illustrated in Figures 1A, 1B and 2 is configured to

combine one or more high resistance fluid pathways **12** and one or more low

resistance fluid pathways **14** at one or more combination junctions **24**. The

combination junction **24** is situated at the end of at least one inlet port **16** or at

25 least one connection port **18** of the fluid pathways as shown in Figures 1A, 1B and

2. The combination junction **24** provides a means for combining the high

resistance fluid pathways **12** and the low resistance fluid pathways **14**.

In some embodiments, the configuration downstream of the chip **22** may differ

30 from the illustrated embodiments. For example, there may be no combination

junction **24**. In some embodiments, there may be more than one combination

junction **24**. In particular, there may be several low resistance fluid pathways and

valves **20** in parallel. It should be apparent, therefore, that the number of connection ports **18** does not need to match the number of inlet ports **16**.

In some embodiments, the combined fluids from the high resistance fluid pathway

5 **12** and the low resistance fluid pathway **14** continues to flow along a further fluid pathway **15** towards the microfluidic chip as illustrated in Figures 1A, 1B and 2.

The valve **20** is provided on the low resistance fluid pathway. When in use, the

valve is opened to enable the fluid to flow preferentially along the low resistance

10 fluid pathway **14** and towards the microfluidic chip **22**, as illustrated in Figure 1A.

In some instances, the opening of the valve can enable the fluid to flow along both

the high resistance fluid pathway and the low resistance fluid pathway. Therefore,

when in use, the valve **20** is configured to enable a fluid flow to partially or

completely bypass the high resistance fluid pathway **12**. In this context, a partial

15 bypass will be effected by enabling access to the low resistance fluid pathway, but

not actively blocking the high resistance fluid pathway. Under these

circumstances, the relative flow rates through the pathways will be related to the

relative resistance of the pathways. As a result, there will be very little flow

through the high resistance pathway as soon as access is enabled to the low

20 resistance pathway.

The flow rate of the fluids through the high resistance fluid pathway can often be

slow and as a result, the time taken for a volume to pass through the microfluidic

device can take minutes to hours. This can often be a time-consuming process. In

25 contrast, the time taken for fluids to flow along the low resistance fluid pathway is

significantly reduced, typically taking seconds to minutes for the fluids to flow

along the low resistance fluid pathway and into the microfluidic chip. This may be

desirable in situations where for instance, a fast flow rate of a fluid is required to

remove air bubbles quickly from the microfluidic chip.

30

Referring to Figure 1B, there is shown a closed valve **20** on the low resistance

fluid pathway **14**. The closed valve is configured to partially or completely obstruct

the flow of the fluids along the low resistance fluid pathway. As a result, the fluids are forced to flow along the high resistance fluid pathway towards the microfluidic chip.

5 In some embodiments, there can be several low resistance pathways provided in parallel, with a valve at each low resistance pathway, wherein the device is configured so that each of the low resistance pathways introduces a different fluid.

As shown in Figures 3A and 3B, the combination junction **24** may have a small 10 swept volume and virtually a zero dead volume. As disclosed herein, and unless otherwise stated, the term “dead volume” refers to a portion of the internal fluids that is out of a flow path for example, and the term “swept volume” refers to the additional volume the valve provides compared to the bare, valve-free fluid pathway. The dead volume of the combination junction **24** is substantially zero, 15 and the total swept volume is only the volume of the pathway itself. Therefore, the combination junction can be considered to have substantially zero swept volume.

Referring to Figure 2, there is shown a plurality of high resistance fluid pathways **12** and low resistance fluid pathways **14** in an array. The high resistance fluid 20 pathways **12** and low resistance fluid pathways **14** are applied to the microfluidic chip **22**, as shown in Figure 2, in order to introduce a plurality of fluids into the chip. Furthermore, the plurality of high resistance fluid pathways **12** and low resistance fluid pathways **14** may allow for a separation or analysis of biological components, such as proteins or nucleic acids, in the fluid flows.

25

As illustrated in Figure 2, the valve **20** is opened to enable the fluids to flow along the low resistance fluid pathways **12** in an array. As a result, the fluids partially or completely bypass the high resistance fluid pathways **14** within the array. The flow rate in each of the low resistance fluid pathways will be greater than the flow rate 30 in each of the high resistance fluid pathways.

The resistances **26** of the high resistance fluid pathways **12** and the low resistance fluid pathways **14**, as illustrated in Figures 1A, 1B, 2, 3A and 3B are provided in order to control the flow of the fluids along the fluid pathways. In particular, a combination of resistances **26** within the high resistance fluid pathways and the low resistance fluid pathways are used to control a flow rate within the high resistance fluid pathways **12**, the low resistance fluid pathways **14** or both. The combination of resistances **26** of the high resistance fluid pathways **12** and the low resistance fluid pathways **14** may also be used to control the overall flow rates. Furthermore, in configurations including more than one valve **20**, the valves can be switched at different times in order to increase control over the flow of fluids. Controlling the flow rate can be particularly valuable for performing and controlling biological or chemical reactions, or for separating and analysing components in a fluid for example.

Referring to Figures 3A and 3B, the low resistance fluid pathway has a rectangular cross section, which may have a diameter of between 0.1 mm to 10 mm. The length of the low resistance fluid pathway may be between 1 mm and 1000 mm. The diameter of the high resistance fluid pathway may be between 0.001 mm and 0.5 mm and its length may be within the range of 1 to 2500 mm. An example of a fluid pathway may be a capillary pathway or a tubing pathway. Alternatively, the fluid pathways may have a circular, a D-shaped or a square cross section.

As shown in Figure 3A and 3B, the connection port **18** of the high resistance fluid pathway is connected to the low resistance fluid pathway at a combination junction **24**. The flow of the fluids along the fluid pathways can be dictated by the resistances of the fluid pathways.

The value of the resistance **26** of the high resistance fluid pathway **12** is provided by the geometry of the high resistance fluid pathway. The value of the resistance **26** of the low resistance fluid pathway **14** is provided by the geometry of the low resistance fluid pathway.

As an example, the resistance **26** of the high resistance fluid pathway and the low resistance fluid pathway can be dictated by one or more of the following: the cross sectional area of the pathway, the length of the pathway and the surface roughness of the pathway. In some embodiments, the resistance of the low

5 resistance fluid pathway with a 1 mm diameter and 100 mm in length is 0.00001 mbar / (μl/h).

The resistance of the low resistance fluid pathway can be 3 times less than the resistance of the high resistance fluid pathway. Alternatively, the resistance of the

10 low resistance fluid pathway can be at least 10 times less than the resistance of the high resistance fluid pathway. The high resistance fluid pathway has a resistance of 10 mbar / μl/h, which is large in comparison to the resistance of 0.001 mbar / μl/h provided at the low resistance fluid pathway.

15 The fluid flow controller **10** may further comprise a manifold including a plurality of valves for controlling the array of fluid pathways.

It will be appreciated that the number of high resistance fluid pathways and low resistance fluid pathways within a microfluidic chip may vary substantially. The

20 resistances of the high resistance fluid pathways and low resistance fluid pathways allow for accurate and controlled flow rates in the microfluidic chips. The valves on the low resistance fluid pathways are configured to, when in use, permit one or more fluid flows to bypass the high resistance fluid pathways.

25 It will further be appreciated by those skilled in the art that although the invention has been described by way of example with reference to several embodiments. It is not limited to the disclosed embodiments and that alternative embodiments could be constructed without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. A fluid flow controller for introducing fluids into a microfluidic device, the controller comprising:

5 at least one high resistance fluid pathway provided between an inlet port and a connection port;

at least one low resistance fluid pathway between the inlet and connection port; and

at least one valve configured to enable fluid flow through the high resistance fluid

10 pathway, the low resistance fluid pathway or both.

2. The controller according to claim 1, wherein the resistance of the high and low resistance fluid pathway is dictated by one or more of the following: the cross sectional area of the pathway, the length of the pathway and the surface 15 roughness of the pathway.

3. The controller according to claim 1 or claim 2, wherein the high resistance fluid pathway is one pathway within a network of pathways linking one or more inlet ports to one or more connection ports.

20

4. The controller according to claim 1 or claim 2, wherein each high resistance fluid pathway has a corresponding low resistance fluid pathway.

5. The controller according to any one of the preceding claims, wherein a

25 plurality of high resistance fluid pathways and a plurality of low resistance pathways are provided in an array.

6. The controller according to claim 5, further comprising a manifold including a plurality of valves for controlling the array of fluid pathways.

30

7. The controller according to any one of the preceding claims, wherein the resistance of the low resistance fluid pathways is at least three times less than the resistance of the high resistance fluid pathway.

5 8. The controller according to any one of the preceding claims, wherein the resistance of the low resistance fluid pathway is at least 10 times less than the resistance of the high resistance fluid pathway.

9. The controller according to any one of the preceding claims, wherein the
10 high resistance fluid pathway has a resistance of between 1 mbar / μ l/h and 1000 mbar / μ l/h.

10. The controller according to any one of the preceding claims, wherein the low resistance fluid pathway has a resistance in the range of 1×10^{-5} mbar / μ l/hr
15 and 100 mbar / μ l/hr.

11. The controller according to any one of the preceding claims, wherein the valve is configured to close the low resistance fluid pathway only.

20 12. The controller according to any one of the preceding claims, provided as an interface to a chip.

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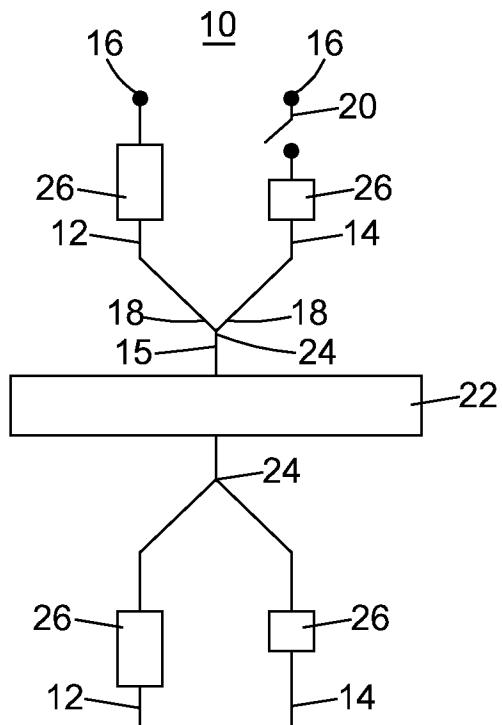


Fig. 1A

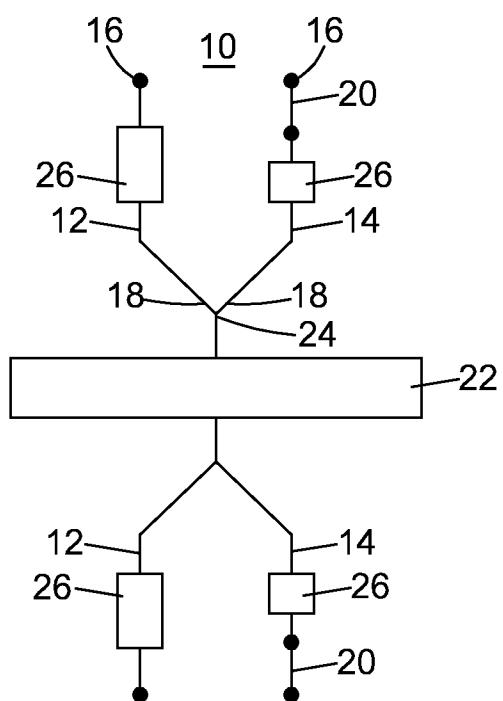


Fig. 1B

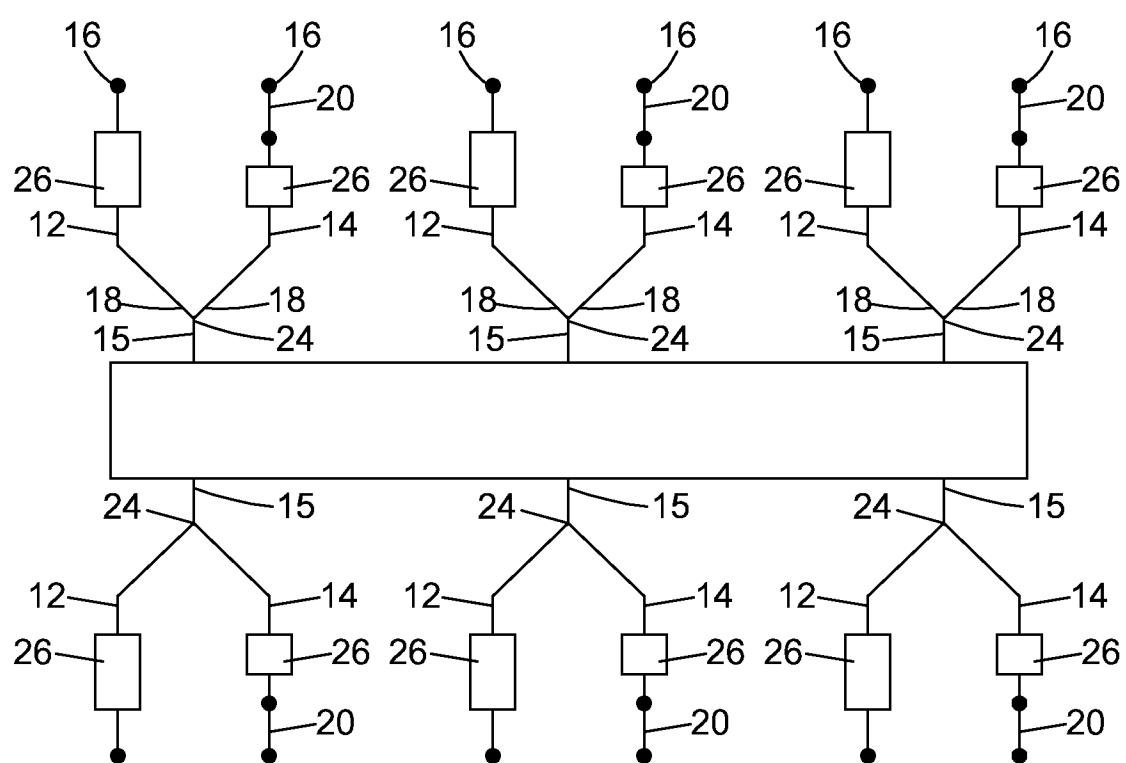


Fig. 2

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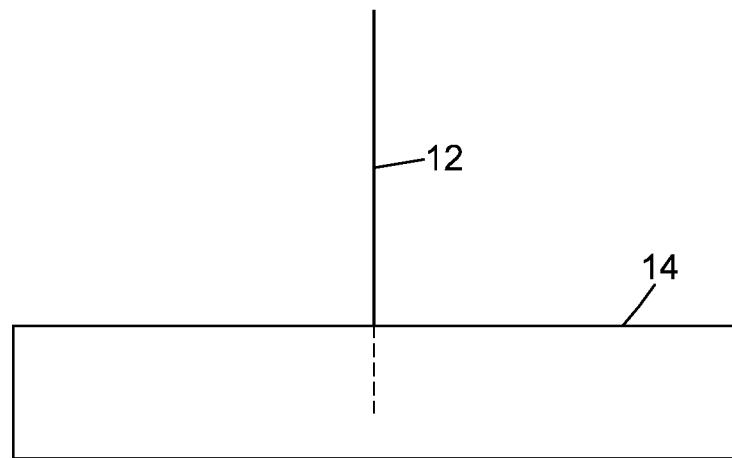


Fig. 3A

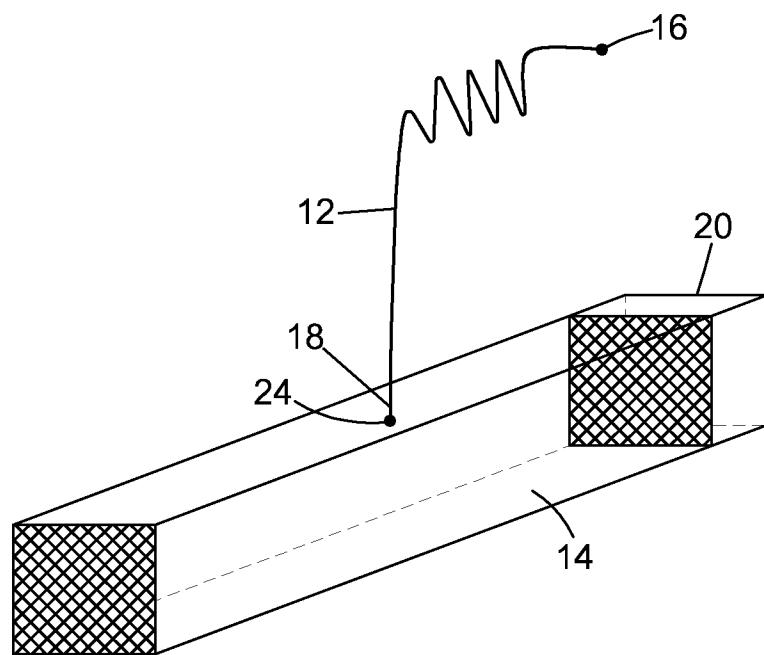


Fig. 3B

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/052552

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L3/00 B01J19/00
ADD.

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)
B01L B01J

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| E | WO 2017/174975 A1 (FLUIDIC ANALYTICS LTD [GB]) 12 October 2017 (2017-10-12) the whole document ----- | 1-12 |



Further documents are listed in the continuation of Box C.



See patent family annex.

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- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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| Date of the actual completion of the international search 20 October 2017 | Date of mailing of the international search report 02/11/2017 |
| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer Vlassis, Maria |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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