



(51) International Patent Classification:

G01N 15/14 (2006.01) G01N 15/00 (2006.01)
B01L 3/00 (2006.01) G01N 15/10 (2006.01)

(21) International Application Number:

PCT/EP2015/071085

(22) International Filing Date:

15 September 2015 (15.09.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(71) Applicant: SIEMENS HEALTHCARE GMBH
[DE/DE]; Henkestr. 127, 91052 Erlangen (DE).

(72) Inventors: HAYDEN, Oliver; Dachsweg 4 a, 91074 Herzogenaurach (DE). RICHTER, Lukas; Bügstraße 14, 96114 Hirschaid (DE). UGELE, Matthias; Kiefernweg 6, 92318 Neumarkt (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

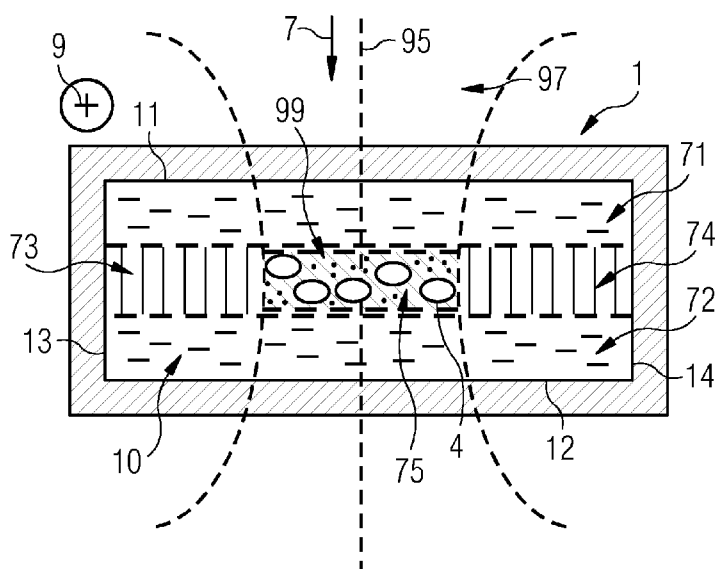
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: A TECHNIQUE FOR FOCUSING A SAMPLE IN A FLOW

FIG 7



(57) Abstract: A technique for focusing a sample into a desired region in a flow cell is presented. The flow cell includes a bottom flow input module, a sample input module, a top flow input module and a flow chamber having a rectangular cross-section. The desired region is in the flow chamber. The bottom flow, the top flow and the sample input modules receive and provide a first fluid, a second fluid, and the sample respectively, to the flow chamber. The first and the second fluids laminarly flow along the bottom and the top wall from one end towards another end of the flow chamber. The sample laminarly flows sandwiched between the top and the bottom laminar flows. The bottom and the top flow input modules respectively control a rate of flow of the first fluid and a rate of flow of the second fluid in the flow chamber.

Description

A technique for focusing a sample in a flow

- 5 The present invention relates to techniques for focusing a flowing sample that is to be inspected by an imaging device.

Medical technology in recent times has witnessed advent of numerous medical devices and microscopy techniques. A lot of
10 these microscopy techniques are used for imaging microscopic specimens or samples for analyzing one or more characteristics of the sample, or more precisely for determining one or more characteristics of a component, for example red blood cell (RBC), in the sample, for example
15 blood sample. Examples of characteristics of the component, say RBC, that may be determined may include a volumetric measurement of the RBC, a morphological study of the RBC, and so on and so forth. In general for any imaging dependant analysis, an 'in-focus' image or output from the imaging
20 device is essential for carrying out specific and detailed analysis of the component of the sample.

For example, a sample may be studied or inspected by detecting and analyzing interference patterns formed in
25 interferometric microscopy, also referred to as digital holographic microscopy (DHM). However, throughput of DHM device or any other imaging device, i.e. rate of number of images or interference patterns provided by the device, is highly dependent on providing the sample to a field of view,
30 hereinafter the FOV, of the imaging device, as the sample should be provided with in depth of field at a focus of the device to obtain 'in-focus' or sharp images or interference patterns as output of the imaging device. Providing sample as flowing in a flow cell, for example similar to the way sample
35 is provided in flow cytometry, is an efficient way of providing sample to the imaging device. It has several advantages for example it is easier to maintain the components of the sample, for example RBCs in the blood, in

their native morphology in a fluid flow as compared to placing such component on a slide. Furthermore, by providing the sample in a flow, the sample may be provided continuously for a time period of imaging and thus a larger amount of sample may be imaged which is beneficial for statistical means as compared to scanning or imaging a smaller amount of the sample.

However, providing the sample as flowing in a flow cell has also certain disadvantages. One disadvantage is focusing of the sample in the flow cell. The components of the sample for example RBCs in a diluted or whole blood sample flowing through the flow cell migrate to different sections of the flow cell and are not arranged in a desired region of the flow cell. Thus some of the components of the sample in the flow cell may be either completely out of the FOV or may be in the FOV but out of focus. The components of the sample that are completely out of the FOV are not represented in the image of the interference pattern. The components of the sample that are in the FOV but not in focus are imaged but parts or segments of the image or the interference pattern that represent such components lack sharpness i.e. are out of focus or to say that the sharpness of segments of the interference pattern or the image representing such components are either low or not of acceptable quality or blurred.

Such components flowing as part of the sample in the flow cell or flow channel may be brought in focus by readjusting the focus of the interferometric microscopic device or the imaging device but the components of the flowing samples are dynamic so there is no time to adjust the focus of the imaging device. Another approach may be to provide the sample in such a way in the flow cell that the sample flows within a desired region of the flow cell, and then the imaging device can be statically focused at the desired region with the depth of field of the imaging device aligned with the desired region and subsequently in-focus imaging of the components of

the sample may be achieved. However, it is a challenge to control the flow of sample in such flow cells, more particularly to control the components of the sample in the flow cell, so that the samples, or the components of the sample, are positioned or focused in a desired region of the flow cell.

Thus the object of the present disclosure is to provide a technique for focusing a sample into a desired region in a flow cell.

The above object is achieved by flow cell for focusing a sample into a desired region in the flow cell according to claim 1, a method for focusing a sample into a desired region in a flow cell according to claim 6, and a system for focusing a sample into a desired region according to claim 9. Advantageous embodiments of the present technique are provided in dependent claims. Features of independent can be combined with features of dependent claims, and features of dependent claims can be combined together.

A first aspect of the present technique provides a flow cell for focusing a sample into a desired region in the flow cell. The sample is to be inspected by an imaging device. The flow cell includes a flow chamber, a bottom flow input module and a top flow input module. The flow chamber has a rectangular cross-section, a top wall, a bottom wall opposite to the top wall, a first side wall, a second side wall opposite to the first side wall, and the desired region. The bottom flow input module receives a first fluid and provides the first fluid to the flow chamber such that the first fluid laminarly flows along the bottom wall in the flow chamber from one end of the flow chamber towards another end of the flow chamber. The laminarly flowing first fluid forms a bottom laminar flow. The bottom flow input module controls a rate of flow of the first fluid in the flow chamber. The top flow input module receives a second fluid and provides the second fluid to the flow chamber such that the second fluid laminarly

flows along the top wall in the flow chamber from the one end of the flow chamber towards the another end of the flow chamber. The laminarly flowing second fluid forms a top laminar flow.

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The sample input module receives the sample and provides the sample to the flow chamber such that the sample laminarly flows on top of the bottom laminar flow in the flow chamber from the one end of the flow chamber towards the another end of the flow chamber. The laminarly flowing sample forms a sample laminar flow. The sample laminar flow is sandwiched between the top laminar flow and the bottom laminar flow. The top flow input module controls a rate of flow of the second fluid in the flow chamber. Hereinafter, the 'rate of flow' has also been referred to as the flow rate. In the flow cell, by defining or by increasing or by decreasing the flow rate of the first fluid, a height of the bottom laminar flow is controlled or varied. Similarly, by defining or by increasing or by decreasing the flow rate of the second fluid, a height of the top laminar flow is controlled or varied.

In the present technique, 'width' or 'height' have been interchangeably used for any laminar flow, not including the sample laminar flow, and mean an extension of that laminar flow along the rectangular cross-section of the flow chamber from a wall of the flow chamber along which the laminar flow is aligned towards the opposite wall, for example 'width' or 'height' of the bottom laminar flow means an extension of the bottom laminar flow along the rectangular cross-section of the flow chamber from the bottom wall of the flow chamber towards the top wall of the flow chamber. Similarly 'width' or 'height' of the top laminar flow means an extension of the top laminar flow along the rectangular cross-section of the flow chamber from the top wall of the flow chamber towards the bottom wall of the flow chamber.

For the sample laminar flow, width means an extension of the sample laminar flow along the rectangular cross-section of

the flow chamber between the first and the second side walls. For the sample laminar flow, height means an extension of the sample laminar flow along the rectangular cross-section of the flow chamber between the top and the bottom walls. For the sample laminar flow, 'lateral position' means a location of a cross-section of the sample laminar flow along the rectangular cross-section of the flow chamber between the first and the second side walls, and 'longitudinal position' means a location of the cross-section of the sample laminar flow along the rectangular cross-section of the flow chamber between the top and the bottom walls.

In the flow cell, by controlling or varying the height of the bottom laminar flow and/or the top laminar flow, the width and/or the height and/or the longitudinal position of the sample laminar flow is controlled or varied. By defining the width and/or the height and/or the longitudinal position of the sample laminar flow, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the flow cell.

In an embodiment of the flow cell a first side flow input module is included. The first side flow input module receives a first side fluid and provides the first side fluid to the flow chamber such that the first side fluid laminarly flows along the first side wall in the flow chamber from the one end of the flow chamber towards the another end of the flow chamber. The laminarly flowing first side fluid forms a first side laminar flow. The first side laminar flow is sandwiched between the top and the bottom laminar flows and between the first side wall and the sample laminar flow. The first side flow input module controls a rate of flow of the first side fluid in the flow chamber. In the flow cell, by defining or by increasing or by decreasing the flow rate of the first side fluid, a width of the first side laminar flow is controlled or varied.

The 'width' of the first side laminar flow means an extension of the first side laminar flow along the rectangular cross-section of the flow chamber from the first side wall of the flow chamber towards the second side wall of the flow chamber. In the flow cell, by controlling or varying the width of the first side laminar flow, the width and/or the height and/or the lateral position of the sample laminar flow is controlled or varied. By defining the width and/or the height and/or the lateral position of the sample laminar flow, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the flow cell.

In another embodiment of the flow cell a second side flow input module is included. The second side flow input module receives a second side fluid and provides the second side fluid to the flow chamber such that the second side fluid laminarly flows along the second side wall in the flow chamber from the one end of the flow chamber towards the another end of the flow chamber. The laminarly flowing second side fluid forms a second side laminar flow. The second side laminar flow is sandwiched between the top and the bottom laminar flows and between the second side wall and the sample laminar flow. The second side flow input module controls a rate of flow of the second side fluid in the flow chamber. In the flow cell, by defining or by increasing or by decreasing the flow rate of the second side fluid, a width of the second side laminar flow is controlled or varied.

The 'width' of the second side laminar flow means an extension of the second side laminar flow along the rectangular cross-section of the flow chamber from the second side wall of the flow chamber towards the first side wall of the flow chamber. In the flow cell, by controlling or varying the width of the second side laminar flow, the width and/or the height and/or the lateral position of the sample laminar flow is controlled or varied. By defining the width and/or the height and/or the lateral position of the sample laminar

flow, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the flow cell.

In another embodiment of the flow cell, the sample input
5 module controls a rate of flow of the sample in the flow chamber. Thus amount of sample forming the sample laminar flow is controlled, which in turn contributes to the width and/or the height of the sample laminar flow.

10 In another embodiment of the flow cell, the flow chamber is a microfluidic channel. Thus the flow cell is compact.

A second aspect of the present technique presents a method for focusing a sample into a desired region in a flow cell.
15 The sample is to be inspected by an imaging device. The flow cell includes a flow chamber having a rectangular cross-section, a top wall, a bottom wall opposite to the top wall, a first side wall, a second side wall opposite to the first side wall and the desired region. In the method, a first
20 fluid, a second fluid and the sample are provided to the flow chamber. The first fluid, the second fluid and the sample may be provided either simultaneously or sequentially in any order. The first fluid is provided to the flow chamber such that the first fluid laminarly flows along the bottom wall in
25 the flow chamber from one end of the flow chamber towards another end of the flow chamber. The laminarly flowing first fluid forms a bottom laminar flow. The second fluid is provided to the flow chamber such that the second fluid laminarly flows along the top wall in the flow chamber from
30 the one end of the flow chamber towards the another end of the flow chamber. The laminarly flowing second fluid forms a top laminar flow. The sample is provided to the flow chamber such that the sample laminarly flows in the flow chamber in form of a sample laminar flow from the one end of the flow
35 chamber towards the another end of the flow chamber. The laminarly flowing sample forms a sample laminar flow. The sample laminar flow is sandwiched between the top and the bottom laminar flows. In the method, a rate of flow of the

first fluid and a rate of flow of the second fluid in the flow chamber are controlled.

In the method, by defining or by increasing or by decreasing
5 the flow rate of the first fluid, the height of the bottom laminar flow in the flow cell is controlled or varied.

Similarly, by defining or by increasing or by decreasing the flow rate of the second fluid, the height of the top laminar flow in the flow cell is controlled or varied. By controlling
10 or varying the height of the bottom and the top laminar flow, the width and/or the height and/or the longitudinal position of the sample laminar flow is controlled or varied. By defining the width and/or the height and/or the longitudinal position of the sample laminar flow, the sample laminar flow
15 is focused i.e. moved into or positioned into the desired region of the flow cell.

In an exemplary embodiment of the method, a first side fluid is provided to the flow chamber such that the first side
20 fluid laminarly flows in the flow chamber from the one end to the another end of the flow chamber. The laminarly flowing first side fluid forms a first side laminar flow sandwiched between the top laminar flow and the bottom laminar flow and between the first side wall and the sample laminar flow.

Thereafter in the method, a rate of flow of the first side fluid in the flow chamber is controlled. In the method, by defining or by increasing or by decreasing the flow rate of the first side fluid, the width of the first side laminar flow in the flow chamber is controlled or varied. By
30 controlling or varying the width of the first side laminar flow, the width and/or the height and/or the lateral position of the sample laminar flow in the flow chamber is controlled or varied. By defining the width and/or the height and/or the lateral position of the sample laminar flow in the flow
35 chamber, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the flow cell.

In another exemplary embodiment of the method, a second side fluid is provided to the flow chamber such that the second side fluid laminarly flows in the flow chamber from the one end to the another end of the flow chamber. The laminarly
5 flowing second side fluid forms a second side laminar flow sandwiched between the top laminar flow and the bottom laminar flow and between the second side wall and the sample laminar flow. Thereafter in the method, a rate of flow of the second side fluid in the flow chamber is controlled. In the
10 method, by defining or by increasing or by decreasing the flow rate of the second side fluid, the width of the second side laminar flow in the flow chamber is controlled or varied. By controlling or varying the width of the second side laminar flow, the width and/or the height and/or the
15 lateral position of the sample laminar flow in the flow chamber is controlled or varied. By defining the width and/or the height and/or the lateral position of the sample laminar flow in the flow chamber, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the
20 flow cell.

The first and the second side fluids may be provided either simultaneously or sequentially in any order.

25 In a third aspect of the present technique, a system for focusing a sample into a desired region is presented. The system includes an imaging device and a flow cell. The imaging device has a field of view which in turn has a depth of field. The flow cell is same as mentioned hereinabove in
30 reference to the first aspect of the present technique. The depth of field of the imaging device is aligned with the desired region. Thus, when by defining the width and/or the height and/or the lateral position and/or the longitudinal position of the sample laminar flow in the flow chamber, as
35 described hereinabove in reference to the first aspect of the present technique, the sample laminar flow is focused i.e. moved into or positioned into the desired region of the flow cell, and since the desired region of the flow cell is

aligned with or overlaps the depth of field of the imaging device, the sample is focused in the depth of field of the imaging device.

5 In an embodiment of the system, the imaging device is a digital holographic microscopy device. Thus the focusing of the sample in the depth of field of the digital holographic microscopy device is achieved and this in turn leads to obtaining of high quality or focused images of the sample
10 which then may be used for post imaging analysis for example volumetric measurements of components of the sample, morphological studies of the contents of the sample, and so and so forth.

15 The present technique is further described hereinafter with reference to illustrated embodiments shown in the accompanying drawing, in which:

FIG 1 schematically illustrates an exemplary embodiment
20 of a system of the present technique;

FIG 2 schematically illustrates an exemplary embodiment of a flow cell;

25 FIG 3 schematically illustrates the exemplary embodiment of the flow cell of FIG 2 with a sample flowing;

FIG 4 schematically illustrates an exemplary embodiment of the flow cell of the present technique;
30

FIG 5 schematically illustrates an exemplary embodiment of the flow cell depicting a bottom laminar flow and a top laminar flow;

35 FIG 6 schematically illustrates the embodiment of the flow cell of FIG 5 depicting an exemplary scheme for working of the flow cell;

FIG 7 schematically illustrates an exemplary embodiment of the flow cell depicting a first side laminar flow and a second side laminar flow; and

5 FIG 8 schematically illustrates the embodiment of the flow cell of FIG 7 depicting an exemplary scheme for working of the flow cell; in accordance with aspects of the present technique.

10 Hereinafter, above-mentioned and other features of the present technique are described in details. Various embodiments are described with reference to the drawing, wherein like reference numerals are used to refer to like elements throughout. In the following description, for
15 purpose of explanation, numerous specific details are set forth in order to provide a thorough understanding of one or more embodiments. It may be noted that the illustrated embodiments are intended to explain, and not to limit the invention. It may be evident that such embodiments may be
20 practiced without these specific details.

It may be noted that in the present disclosure, the terms "first", "second", "third", etc. are used herein only to facilitate discussion, and carry no particular temporal or
25 chronological significance unless otherwise indicated.

The basic idea of the present technique is to provide a flow cell with a flow chamber having a rectangular cross-section. In the flow chamber of such flow cell, the sample with its
30 components is flowed in a laminar flow. The laminarly flowing sample is sandwiched at least between two laminar flows, for example a top and a bottom flow. By regulating a flow rate of one or both of these laminar flows, dimensions of these laminar flows may be influenced and since the sample laminar
35 flow is sandwiched between these laminar flows, dimensions and position of the sample laminar flow are controlled within the flow chamber and thus the sample, along with the components of the sample, is made to flow within a desired

region of the flow chamber. Additionally, the laminarly flowing sample may also be sandwiched between two laminar flows, say side flows that are perpendicularly aligned to the top and the bottom flows. By regulating a flow rate of one or both of these side flows, dimensions of the side flows may be influenced and since the sample laminar flow is sandwiched between the side flows in addition to the top and the bottom flows, dimensions and position of the sample laminar flow are controlled within the flow chamber and thus the sample, along with the components of the sample, is made to flow within the desired region of the flow chamber.

FIG 1 schematically presents a system 100 of the present technique. The system 100 includes an imaging device 90 for inspecting the sample (not shown in FIG 1) and a flow cell 1 with a flow chamber 10. The imaging device 90 may have, but not limited to, a first part 92 for example an illumination source 92, and a second part 94 for example a detector with or without an interferometric unit. The imaging device 90 has a field of view 97, hereinafter the FOV 97 which represents an observable range of the imaging device 90 i.e. an object (not shown) is imaged by the imaging device 90 only when the object is positioned in the FOV 97. The imaging device 90 also has a focus within the FOV 97. The imaging device 90 has an axis 95 along which the imaging is performed by shining a probing radiation on the object for example a Laser or a lower-coherent light source, such as a superluminescent diode, from a direction 7 onto the object or specimen to be inspected by the imaging device 90.

The focus is extended according to a depth of field of the imaging device 90. Thus when the object is positioned in the depth of field around the focus of the imaging device 90, an 'in-focus' image of the object is obtainable. The focus and the depth of field of the imaging device 90 in the system 1 are arranged such that the focus and the depth of field around the focus of the imaging device 90 lie or fall within the flow chamber 10. The region within the depth of field

around the focus of the imaging device 90 is a region (not shown) in which the object should be ideally positioned or focused or concentrated within the flow chamber 10 for obtaining in-focus images or interference patterns of the object.

The flow cell 1 has an extended channel or cavity forming the flow chamber 10 through which a specimen to be imaged or inspected by the imaging device 90 is passed or flowed in a direction 9, generally perpendicular to the direction 7. The specimen or the sample to be inspected flows in the flow chamber 10 from one end 17 to another end 19 of the flow chamber 10 and the FOV 97 of the imaging device 90 is arranged such that at least a part of the flow chamber 10 between the one end 17 and the another end 19 is positioned in the FOV 97 of the imaging device 90.

Referring to FIG 2 in combination with FIG 1, the flow chamber 10 has been explained further. As depicted in FIG 2, the flow chamber 10 has a rectangular cross-section when viewed from a direction (not shown) opposite to the direction 9. The flow chamber 10 includes a top wall 11, a bottom wall 12 opposite to the top wall 11, a first side wall 13 and a second side wall 14 opposite to the first side wall 13. The flow chamber 10 has a desired region 99 within the flow chamber 10. If the sample (not shown in FIG 1 and 2) is passed or flowed through the desired region 99 and if the FOV 97 and the depth of field around the focus of the imaging device 90 are arranged such that the depth of field around the focus of the imaging device 90 overlaps or aligns with the desired region 99, then in-focus images or interference patterns are obtainable for part of the sample in the desired region 99 of the flow chamber 10 when imaging or inspecting of the sample is performed with the imaging device 90. It may be noted that the desired region 99, hereinafter the region 99, has been schematically depicted in FIG 2 to be positioned in a center location of the cross-section of the flow chamber 10, however, it is well within the scope of the present

technique that the region 99 may be present in a non-central location of the cross-section of the flow chamber 10.

FIG 3, in contrast to FIG 2, schematically presents a sample 5 flowing through the flow chamber 10. The sample 5 has components 4, for example corpuscles such as RBCs, and a fluidic carrier 6 for the component 4. For example, the fluidic carrier 6 may be diluted or undiluted blood plasma, a buffer, and so on and so forth. When the sample 5 flows through the flow chamber 10, as depicted in FIG 3, some of the components 4, hereinafter referred to as the cells 4, are in the desired region 99 and some are outside the desired region 99. If the FOV 97 and the depth of field around the focus of the imaging device 90 are arranged such that the depth of field around the focus of the imaging device 90 overlaps or aligns with the desired region 99, then some cells 4 are in the FOV 97, while some of the cells 4 are outside the FOV 97. Furthermore, some of the cells 4 are in the FOV 97 but either completely or partially outside the region 99.

Referring to FIG 4, 5 and 6 in combination of FIGs 1 and 2, the flow cell 1 of the present technique is explained hereinafter. As shown in FIG 4, the flow cell 1, besides having the flow chamber 10 as explained in reference to FIG 2, also includes a bottom flow input module 20, a sample input module 30 and a top flow input module 40. In an exemplary embodiment of the flow cell 1, the flow chamber 10 is a microfluidic channel.

AS shown in FIG 5 in combination with FIG 4, the bottom flow input module 20 receives a first fluid (not shown) and provides the first fluid to the flow chamber 10. The bottom flow input module 20, hereinafter also referred to as the module 20, provides the first fluid to the flow chamber 10 in such a way that the first fluid laminarly flows along the bottom wall 12 in the flow chamber 10 from the one end 17 (shown in FIG 1) of the flow chamber 10 towards the another

end 19 (shown in FIG 1) of the flow chamber 10. The laminarly flowing first fluid forms a bottom laminar flow 72. The bottom flow input module 20 controls a rate of flow of the first fluid in the flow chamber 10. The term 'control' as
5 used herein includes defines or decides, restricts, sets up, increases and/or decreases the rate of flow of the first fluid in the flow chamber 10 forming the bottom laminar flow 72, hereinafter also referred to as the flow 72. Forming laminar flow of fluids in a flow chamber is a well known
10 technique in the field of hydrodynamics or fluid dynamics and has not been described herein in details for sake of brevity. The module 20 may include, but not limited to, flow channels, valves, pumps, flow meters, etc. The flow 72 may be understood as a rectangular parallelepiped shaped flow
15 extending along the direction 9 in the flow chamber 10 and contiguous with the bottom wall 12.

The top flow input module 40 receives a second fluid (not shown) and provides the second fluid to the flow chamber 10.
20 The top flow input module 40, hereinafter also referred to as the module 40, provides the second fluid to the flow chamber 10 in such a way that the second fluid laminarly flows along the top wall 11 in the flow chamber 10 from the one end 17 (shown in FIG 1) of the flow chamber 10 towards the another
25 end 19 (shown in FIG 1) of the flow chamber 10. The laminarly flowing second fluid forms a top laminar flow 71. The top flow input module 20 controls a rate of flow of the second fluid in the flow chamber 10. The term 'control' as used herein includes defines or decides, restricts, sets up,
30 increases and/or decreases the rate of flow of the second fluid in the flow chamber 10 forming the top laminar flow 71, hereinafter also referred to as the flow 71. The module 40 may include, but not limited to, flow channels, valves, pumps, flow meters, etc. The flow 71 may be understood as a
35 rectangular parallelepiped shaped flow extending along the direction 9 in the flow chamber 10 and contiguous with the top wall 11.

The sample input module 30 receives the sample 5 and provides the sample 5 to the flow chamber 10. The sample input module 30, hereinafter also referred to as the module 30, provides the sample 5 to the flow chamber 10 in such a way that the sample 5 laminarly flows sandwiched between the flow 71 and the flow 72 from the one end 17 (shown in FIG 1) of the flow chamber 10 towards the another end 19 (shown in FIG 1) of the flow chamber 10. The laminarly flowing sample 5 forms a sample laminar flow 75. The sample input module 30 controls a rate of flow of the sample 5 in the flow chamber 10. The term 'control' as used herein includes defines or decides, restricts, sets up, increases and/or decreases the rate of flow of the sample 5 in the flow chamber 10 forming the sample laminar flow 75, hereinafter also referred to as the flow 75. The module 30 may include, but not limited to, flow channels, valves, pumps, flow meters, etc. The flow 75 may be understood as a rectangular parallelepiped shaped flow extending along the direction 9 in the flow chamber 10 and sandwiched between the flow 71 and the flow 72.

In the flow chamber 10, by defining or setting up or by increasing or by decreasing the flow rate of the first fluid, the height of the flow 72 is fixed or controlled or varied. Similarly, by defining or setting up or by increasing or by decreasing the flow rate of the second fluid, the height of the flow 71 is fixed or controlled or varied.

In the flow cell 1, by controlling or varying the height of the flow 71 and/or the flow 72, the width and/or the height and/or the longitudinal position of the flow 75 is controlled or varied. For example as schematically depicted in FIG 5, the flow 75 is now restricted to or concentrated in or focused at least partly in the region 99. In an exemplary embodiment (not shown) of the flow cell 1, the desired 99 extends from the first side wall 13 to the second side wall 14 and then the flow 75 is substantially positioned in the desired region 99.

As depicted in FIG 6, an exemplary working of the flow cell 1 has been schematically depicted. If relative heights of the flow 71 and the flow 72 are such that the flow 75 is below or beneath the desired region 99, as shown in FIG 6, then by
5 controlling the flow rates of the first and the second fluids for example by increasing the flow rate of the first fluid via the module 20 and/or decreasing the flow rate of the second fluid via module 40 the relative heights of the flow 72 and the flow 71 are altered thereby bringing the flow 75
10 at least partly in the region 99, as shown in FIG 5.

Alternatively, if relative heights of the flow 71 and the flow 72 are such that the flow 75 is above (not shown) the desired region 99 then by controlling the flow rates of the first and the second fluids for example by decreasing the
15 flow rate of the first fluid via the module 20 and/or increasing the flow rate of the second fluid via module 40 the relative heights of the flow 72 and the flow 71 are altered thereby bringing the flow 75 at least partly in the region 99. In short the height of the sample laminar flow 75
20 and/or the longitudinal position of the sample laminar flow 75 is decided or fixed or adjusted by altering the flow rates of the first and/or the second fluids via the modules 20 and/or 40.

25 Referring to FIG 4 in combination with FIGs 7 and 8, other exemplary embodiments of the flow cell 1 have been explained hereinafter. In an embodiment of the flow cell 1 a first side flow input module 50, hereinafter the module 50, is included. The module 50 receives a first side fluid (not shown) and
30 provides the first side fluid to the flow chamber 10. The first side fluid is provided by the module 50 in such a way that the first side fluid laminarly flows along the first side wall 13 in the flow chamber 10 from the one end 17 (shown in FIG 1) of the flow chamber 10 towards the another
35 end 19 (shown in FIG 1) of the flow chamber 10. The laminarly flowing first side fluid forms a first side laminar flow 73, hereinafter also referred to as the flow 73. The flow 73 is

sandwiched between the flow 71 and the flow 72 and between the first side wall 13 and the flow 75, as shown in FIG 7.

5 The module 50 controls a rate of flow of the first side fluid in the flow chamber 10. The term 'control' as used herein includes defines or decides, restricts, sets up, increases and/or decreases the rate of flow of the first side fluid in the flow chamber 10 forming the flow 73. The module 50 may include, but not limited to, flow channels, valves, pumps,
10 flow meters, etc. The flow 73 may be understood as a rectangular parallelepiped shaped flow extending along the direction 9 in the flow chamber 10 and contiguous with a part of the first side wall 13 on one face and the flow 75 on the opposite face, and also contiguous on another face with flow
15 71 and on a face opposite to the another face with the flow 72.

In another embodiment of the flow cell 1 a second side flow input module 60, hereinafter also referred to as the module
20 60, is included. The module 60 receives a second side fluid (not shown) and provides the second side fluid to the flow chamber 10. The second side fluid is provided by the module 60 in such a way that the second side fluid laminarly flows along the second side wall 14 in the flow chamber 10 from the
25 one end 17 (shown in FIG 1) of the flow chamber 10 towards the another end 19 (shown in FIG 1) of the flow chamber 10. The laminarly flowing second side fluid forms a second side laminar flow 74, hereinafter also referred to as the flow 74. The flow 74 is sandwiched between the flow 71 and the flow 72
30 and between the second side wall 14 and the flow 75, as shown in FIG 7.

The module 60 controls a rate of flow of the second side fluid in the flow chamber 10. The term 'control' as used
35 herein includes defines or decides, restricts, sets up, increases and/or decreases the rate of flow of the second side fluid in the flow chamber 10 forming the flow 74. The module 60 may include, but not limited to, flow channels,

valves, pumps, flow meters, etc. The flow 74 may be understood as a rectangular parallelepiped shaped flow extending along the direction 9 in the flow chamber 10 and contiguous with a part of the second side wall 14 on one face and the flow 75 on the opposite face, and also contiguous on another face with flow 71 and on a face opposite to the another face with the flow 72.

In the flow chamber 10, by defining or setting up or by increasing or by decreasing the flow rate of the first side fluid, the width of the flow 73 is fixed or controlled or varied. Similarly, by defining or setting up or by increasing or by decreasing the flow rate of the second side fluid, the width of the flow 74 is fixed or controlled or varied. In the flow cell 1, by controlling or varying the width of the flow 73 and/or the flow 74, the width and/or the height and/or the lateral position of the flow 75 is controlled or varied. For example as schematically depicted in FIG 7, the flow 75 is now restricted to or concentrated in or focused in the region 99.

As depicted in FIG 8, an exemplary working of the flow cell 1 has been schematically depicted. If relative widths of the flow 73 and the flow 74 are such that the flow 75 is at least partly shifted from the desired region 99 towards the second side wall 14, as shown in FIG 8, then by controlling the flow rates of the first side and the second side fluids for example by increasing the flow rate of the second side fluid via the module 60 and/or decreasing the flow rate of the first side fluid via module 50 the relative widths of the flow 74 and the flow 73 are altered thereby bringing the flow 75 in the region 99, as shown in FIG 7. Alternatively, if relative widths of the flow 73 and the flow 74 are such that the flow 75 is shifted (not shown) to the other side of the the desired region 99 i.e. towards the first side wall 13, then by controlling the flow rates of the first side and the second side fluids for example by increasing the flow rate of the first side fluid via the module 50 and/or decreasing the

flow rate of the second fluid via module 60 the relative widths of the flow 73 and the flow 74 are altered thereby bringing the flow 75 in the region 99, as shown in FIG 7. In short the width of the sample laminar flow 75 and/or the lateral position of the sample laminar flow 75 is decided or fixed or adjusted by altering the flow rates of the first side and/or the second side fluids via the modules 50 and/or 60.

10 As shown in FIG 4, in another embodiment of the flow cell 1, an exit 80 is present for allowing the flows 71, 72, 73, 74 and 75 to exit the flow chamber 10.

As shown in FIG 1, the system 100 includes the imaging device 90. In one embodiment of the system 100, the second part 94 of the imaging device 90 includes an interferometry unit (not shown) and a detector (not shown). The interferometry unit may be a common path interferometry unit or different path interferometry unit. In common path interferometry unit, a light beam is shone or impinged on the sample 5 from the first part 92 of the imaging device 90 and then the light beam emerging after interacting with the sample 5 is split into a reference beam (not shown) and an object beam (not shown). Subsequently, object information is filtered out or deleted from the reference beam and then the filtered reference beam is superimposed with the object beam to detect the interference pattern at the detector. In different path interferometry unit, a light beam to be incident on the sample 5 is first split into an object beam (not shown) and a reference beam (not shown) i.e. the light beam is split into the reference beam and the object beam before interacting with the sample 5. The object beam is then shone or impinged upon the sample 5 but the reference beam is directed to another optical path (not shown) within the different path interferometric unit and is not shone or impinged upon the sample 5. Subsequently, the object beam carrying object information is superimposed with the reference beam to obtain interference pattern at the detector. The interference

pattern obtained as an output of the common path or different path interferometry is analyzed. The interference pattern also referred to as image of the cells 4 represents characteristics of the cells 4 such as physical structures in the cells 4, morphology of the cells 4, and so on and so forth. Designs, setups and principle of working of the common path interferometry and the different path interferometry are known in the field of interferometric microscopy and not described herein in details for sake of brevity.

The present technique also encompasses a method focusing a sample 5 into a desired region 99 in a flow cell 1. The flow cell 1 is same as the flow cell 1 described in reference to FIGs 1 to 8 and presented in accordance with the first and the second aspects of the present technique. In the method, a first fluid, a second fluid and the sample 5 are provided to the flow chamber 10. The first fluid, the second fluid and the sample 5 may be provided either simultaneously or sequentially in any order. The first fluid is provided to the flow chamber 10 such that the first fluid laminarly flows along the bottom wall 12 in the flow chamber 10 from one end 17 of the flow chamber towards another end 19 of the flow chamber 10. The laminarly flowing first fluid forms a bottom laminar flow 72, which is same as the flow 72 described hereinabove with reference to FIGs 1 to 8. The second fluid is provided to the flow chamber 10 such that the second fluid laminarly flows along the top wall 11 in the flow chamber 10 from the one end 17 of the flow chamber 10 towards the another end 19 of the flow chamber 10. The laminarly flowing second fluid forms a top laminar flow 71, which is same as the flow 71 described hereinabove with reference to FIGs 1 to 8. The sample 5 is provided to the flow chamber 10 such that the sample 5 laminarly flows in the flow chamber 10 in form of a sample laminar flow 75 from the one end 17 of the flow chamber 10 towards the another end 19 of the flow chamber 10.

The laminarly flowing sample 5 forms a sample laminar flow 75, which is same as the flow 75 described hereinabove with

reference to FIGs 1 to 8. The flow 75 is sandwiched between the flow 71 and the flow 72. In the method, a rate of flow of the first fluid and a rate of flow of the second fluid in the flow chamber 10 are controlled. In the method, by defining or setting or fixing or by increasing or by decreasing the flow rate of the first and/or the second fluid, the height of the flow 72 and/or the flow 71 in the flow cell 10 is controlled or varied which in turn effects the width and/or the height and/or the longitudinal position of the flow 75 which is thereby controlled or varied by controlling the flow rates of the first and the second fluids. By defining the width and/or the height and/or the longitudinal position of the flow 75, the flow 75 is focused i.e. moved into or positioned into the desired region 99 of the flow cell 1.

In an exemplary embodiment of the method, a first side fluid is provided to the flow chamber 10 to form the flow 73, and a rate of flow of the first side fluid in the flow chamber 10 is controlled. The providing of the first side laminar flow 73 and controlling the rate of flow of the first side laminar flow 73 is same as described hereinabove with reference to FIGs 1 to 8. In another exemplary embodiment of the method, a second side fluid is provided to the flow chamber 10 to form the flow 74, and a rate of flow of the second side fluid in the flow chamber 10 is controlled. The providing of the second side laminar flow 74 and controlling the rate of flow of the second side laminar flow 74 is same as described hereinabove with reference to FIGs 1 to 8.

By controlling or varying the width of the flow 73 and/or the flow 74, the width and/or the height and/or the lateral position of the flow 75 in the flow chamber 10 is controlled or varied, and thus the flow 75 is focused i.e. moved into or positioned into the desired region 99 of the flow cell 1.

While the present technique has been described in detail with reference to certain embodiments, it should be appreciated that the present technique is not limited to those precise

embodiments. Rather, in view of the present disclosure which describes exemplary modes for practicing the invention, many modifications and variations would present themselves, to those skilled in the art without departing from the scope and spirit of this invention. The scope of the invention is, therefore, indicated by the following claims rather than by the foregoing description. All changes, modifications, and variations coming within the meaning and range of equivalency of the claims are to be considered within their scope.

Patent claims

1. A flow cell (1) for focusing a sample (5) into a desired region (99) in the flow cell (1), the sample (5) to be
5 inspected by an imaging device (90), the flow cell (1) comprising:
- a flow chamber (10) having a rectangular cross-section, a top wall (11), a bottom wall (12) opposite to the top wall (11), a first side wall (13), a second side wall (14)
10 opposite to the first side wall (13) and the desired region (99);
 - a bottom flow input module (20) configured to receive a first fluid and to provide the first fluid to the flow chamber (10) such that the first fluid laminarly flows in the
15 flow chamber (10) in form of a bottom laminar flow (72) along the bottom wall (12), wherein the bottom flow input module (20) is further configured to control a rate of flow of the first fluid in the flow chamber (10);
 - a sample input module (30) configured to receive the sample (5) and to provide the sample (5) to the flow chamber (10)
20 such that the sample (5) laminarly flows in the flow chamber (10) in form of a sample laminar flow (75) on top of the bottom laminar flow (72); and
 - a top flow input module (40) configured to receive a second
25 fluid and to provide the second fluid to the flow chamber (10) such that the second fluid laminarly flows in the flow chamber (10) in form of a top laminar flow (71) along the top wall (11) and the sample laminar flow (75) is sandwiched
between the top laminar flow (71) and the bottom laminar flow
30 (72), wherein the top flow input module (40) is further configured to control a rate of flow of the second fluid in the flow chamber (10);
- wherein the top laminar flow (71), the sample laminar flow (75) and the bottom laminar flow (72) move from one end (17)
35 of the flow chamber (10) towards another end (19) of the flow chamber (10).

2. The flow cell (1) according to claim 1, comprising:

- a first side flow input module (50) configured to receive a first side fluid and to provide the first side fluid to the flow chamber (10) such that the first side fluid laminarly flows in the flow chamber (10) in form of a first side laminar flow (73) sandwiched between the top laminar flow (71) and the bottom laminar flow (72) and between the first side wall (13) and the sample laminar flow (75), wherein the first side flow input module (50) is further configured to control a rate of flow of the first side fluid in the flow chamber (10) and wherein the first side laminar flow (73) moves from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10).

3. The flow cell (1) according to claim 1 or 2, further comprising:

- a second side flow input module (60) configured to receive a second side fluid and to provide the second side fluid to the flow chamber (10) such that the second side fluid

laminarly flows in the flow chamber (10) in form of a second side laminar flow (74) sandwiched between the top laminar flow (71) and the bottom laminar flow (72) and between the second side wall (14) and the sample laminar flow (75),

wherein the second side flow input module (60) is further configured to control a rate of flow of the second side fluid in the flow chamber (10) and wherein the second side laminar flow (74) moves from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10).

4. The flow cell according to any of claims 1 to 3, wherein the sample input module (30) is configured to control a rate of flow of the sample (5) in the flow chamber (10).

5. The flow cell according to any of claims 1 to 4, wherein the flow chamber (10) is a microfluidic channel.

6. A method for focusing a sample (5) into a desired region (99) in a flow cell (1), the sample (5) to be inspected by an

imaging device (90), the flow cell (1) comprising a flow chamber (10) having a rectangular cross-section, a top wall (11), a bottom wall (12) opposite to the top wall (11), a first side wall (13), a second side wall (14) opposite to the first side wall (13) and the desired region (99); the method comprising:

- providing a first fluid to the flow chamber (10) such that the first fluid laminarly flows in the flow chamber (10) in form of a bottom laminar flow (72) along the bottom wall (12) from one end (17) of the flow chamber (10) towards another end (19) of the flow chamber (10);

- providing the sample (5) to the flow chamber (10) such that the sample (5) laminarly flows in the flow chamber (10) in form of a sample laminar flow (75) on top of the bottom laminar flow (72) from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10);

- providing the second fluid to the flow chamber (10) such that the second fluid laminarly flows in the flow chamber (10) in form of a top laminar flow (71) along the top wall (11) and the sample laminar flow (75) is sandwiched between the top laminar flow (71) and the bottom laminar flow (72) from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10);

- controlling a rate of flow of the first fluid in the flow chamber (10); and

- controlling a rate of flow of the second fluid in the flow chamber (10).

7. The method according to claim 6, comprising:

- providing a first side fluid to the flow chamber (10) such that the first side fluid laminarly flows in the flow chamber (10) in form of a first side laminar flow (73) sandwiched between the top laminar flow (71) and the bottom laminar flow (72) and between the first side wall (13) and the sample laminar flow (75) from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10); and

- controlling a rate of flow of the first side fluid in the flow chamber (10).

8. The method according to claim 6 or 7, comprising:

- 5 - providing a second side fluid to the flow chamber (10) such that the second side fluid laminarly flows in the flow chamber (10) in form of a second side laminar flow (74) sandwiched between the top laminar flow (71) and the bottom laminar flow (72) and between the second side wall (14) and
10 the sample laminar flow (75) from the one end (17) of the flow chamber (10) towards the another end (19) of the flow chamber (10); and
- controlling a rate of flow of the second side fluid in the flow chamber (10).

15

9. A system (100) for focusing a sample (5) into a desired region (99), the system (100) comprising:

- an imaging device (90) having a field of view (97), wherein the field of view (97) includes a depth of field; and
20 - a flow cell (1) according to any of claims 1 to 5, wherein the depth of field of the imaging device is aligned with the desired region (99).

10. The system (100) according to claim 9, wherein the
25 imaging device (90) is a digital holographic microscopy device.

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FIG 1

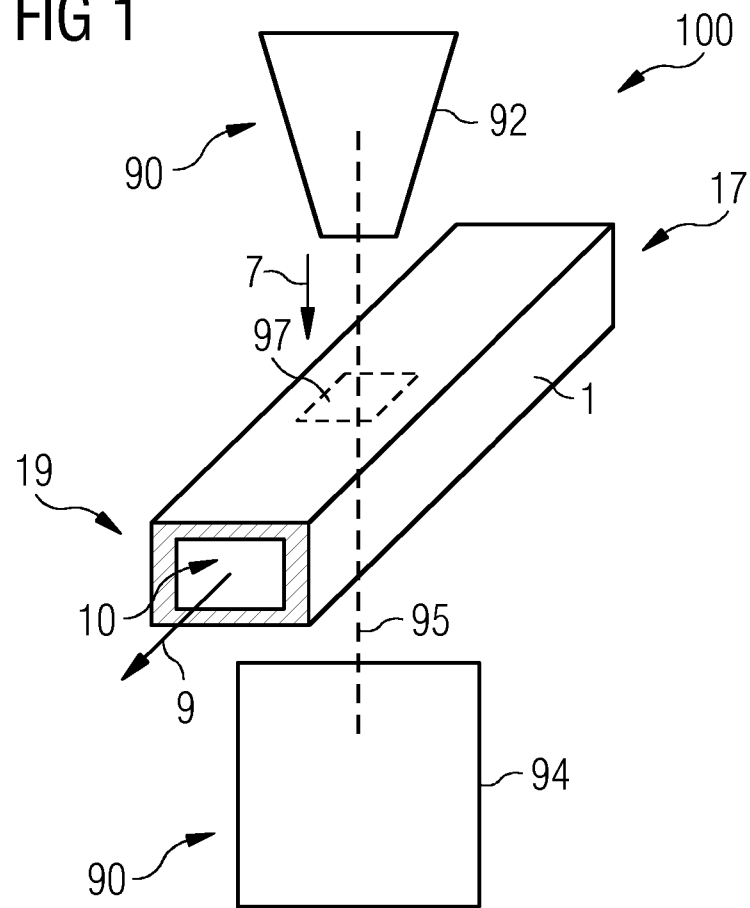


FIG 2

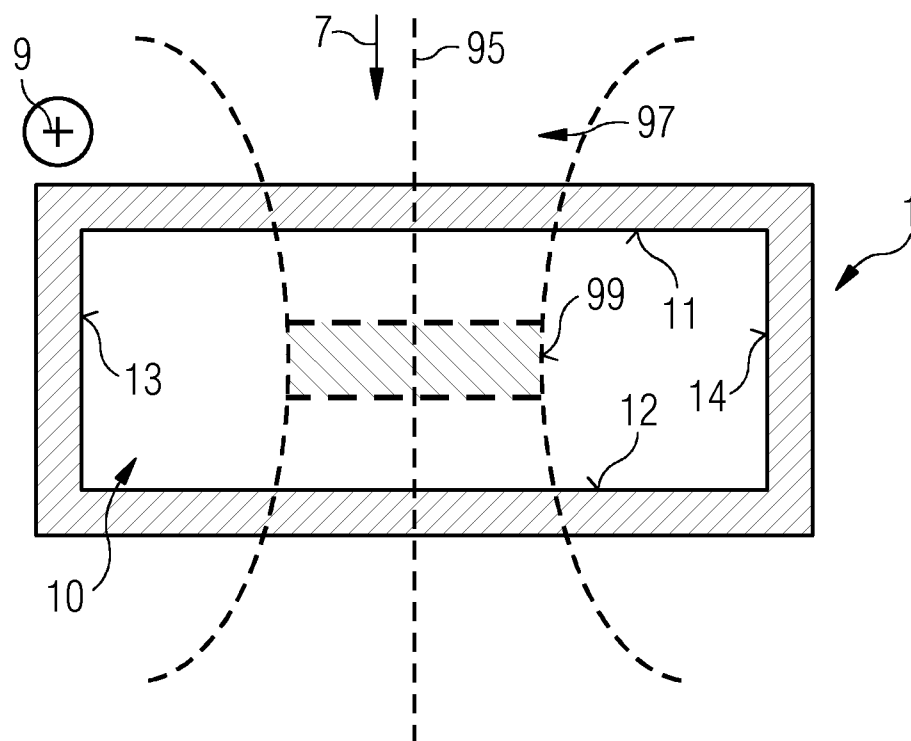


FIG 3

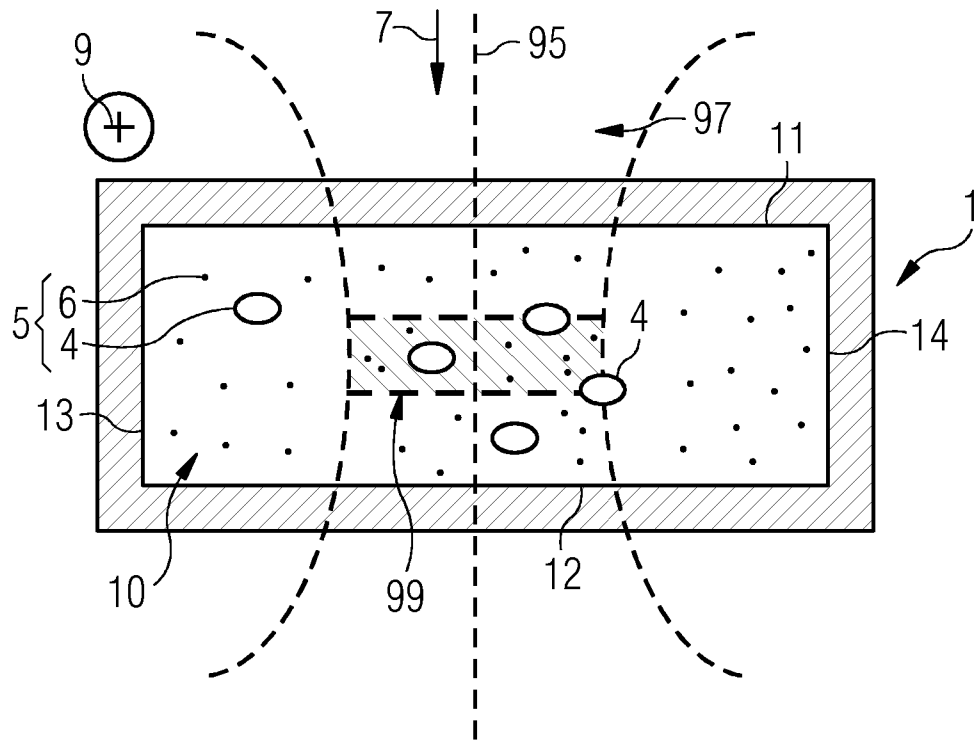


FIG 4

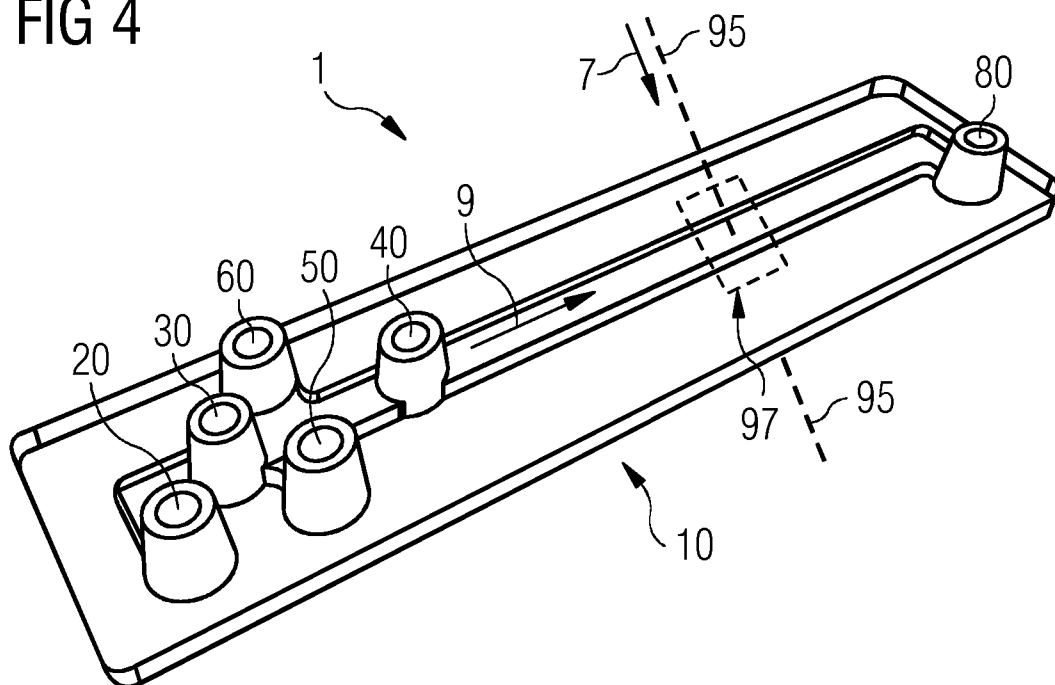


FIG 5

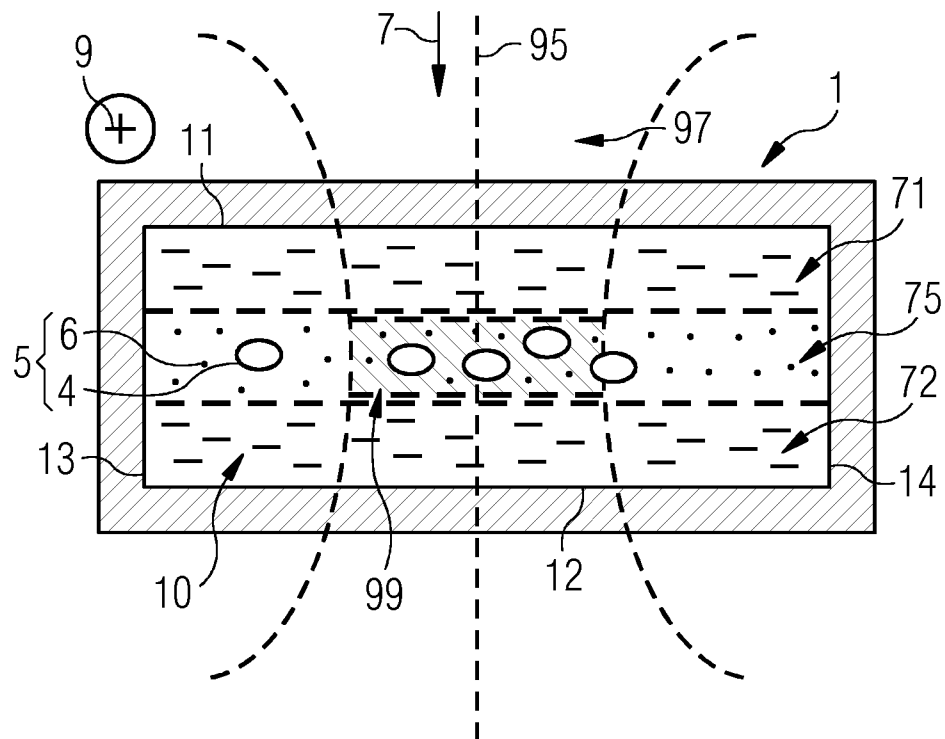


FIG 6

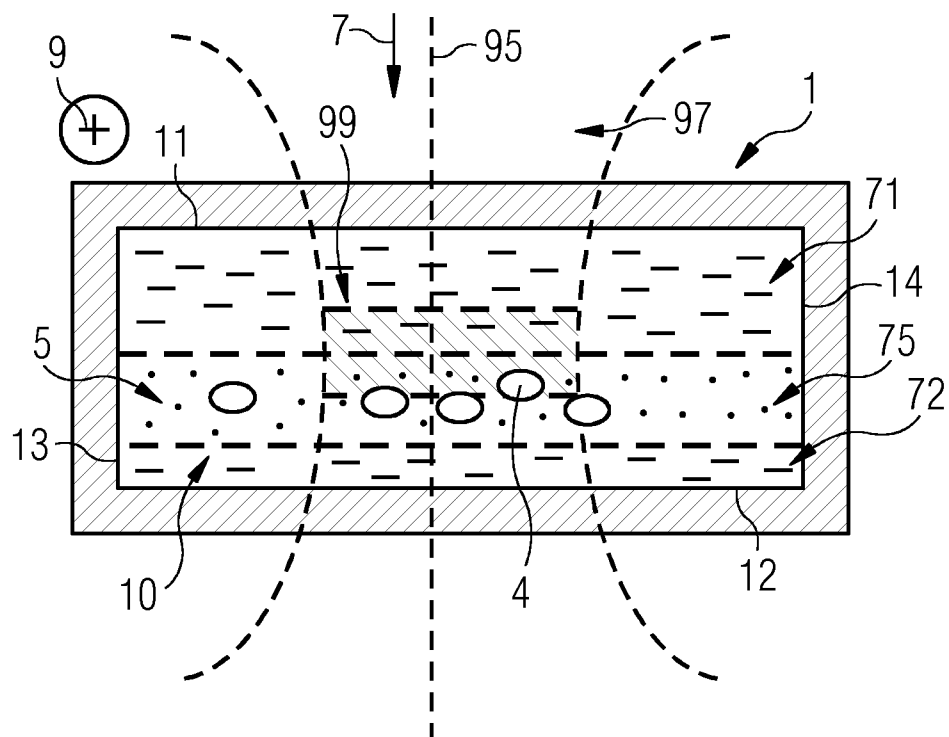


FIG 7

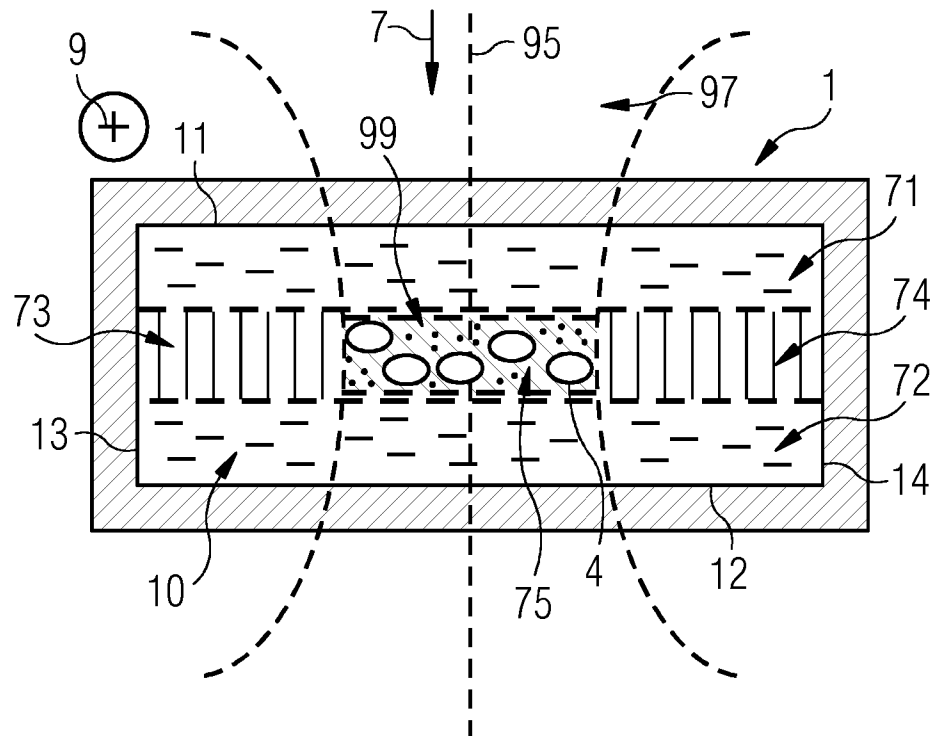
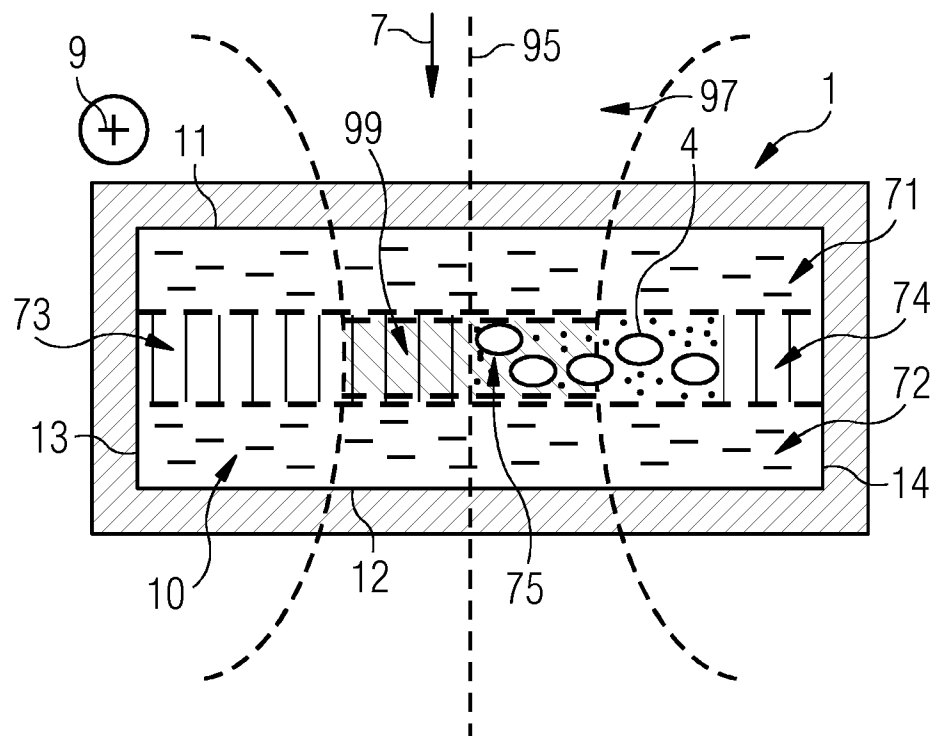


FIG 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/071085

A. CLASSIFICATION OF SUBJECT MATTER INV. G01N15/14 B01L3/00 G01N15/00 G01N15/10 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) G01N B01L 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 <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>US 2012/138152 A1 (VILLARRUEL CARL A [US] ET AL) 7 June 2012 (2012-06-07) par. 9, par. 19, par. 20, par. 21, par. 24, par. 26, par. 28, par. 29; figures 1,2 -----</td> <td>1-8</td> </tr> <tr> <td>X</td> <td>US 2015/114093 A1 (APPLEYARD DAVID [US] ET AL) 30 April 2015 (2015-04-30) paragraphs [0134], [0139], [0251] - paragraphs [0252], [0269] -----</td> <td>1,6,9,10</td> </tr> <tr> <td>X</td> <td>EP 0 614 077 A2 (HITACHI LTD [JP]) 7 September 1994 (1994-09-07) column 25, line 25-38; column 28, line 26-39; column 18, line 40-48,; figure 30 ----- -/-</td> <td>1,6</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2012/138152 A1 (VILLARRUEL CARL A [US] ET AL) 7 June 2012 (2012-06-07) par. 9, par. 19, par. 20, par. 21, par. 24, par. 26, par. 28, par. 29; figures 1,2 -----	1-8	X	US 2015/114093 A1 (APPLEYARD DAVID [US] ET AL) 30 April 2015 (2015-04-30) paragraphs [0134], [0139], [0251] - paragraphs [0252], [0269] -----	1,6,9,10	X	EP 0 614 077 A2 (HITACHI LTD [JP]) 7 September 1994 (1994-09-07) column 25, line 25-38; column 28, line 26-39; column 18, line 40-48,; figure 30 ----- -/-	1,6
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X	US 2012/138152 A1 (VILLARRUEL CARL A [US] ET AL) 7 June 2012 (2012-06-07) par. 9, par. 19, par. 20, par. 21, par. 24, par. 26, par. 28, par. 29; figures 1,2 -----	1-8												
X	US 2015/114093 A1 (APPLEYARD DAVID [US] ET AL) 30 April 2015 (2015-04-30) paragraphs [0134], [0139], [0251] - paragraphs [0252], [0269] -----	1,6,9,10												
X	EP 0 614 077 A2 (HITACHI LTD [JP]) 7 September 1994 (1994-09-07) column 25, line 25-38; column 28, line 26-39; column 18, line 40-48,; figure 30 ----- -/-	1,6												
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.														
* Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;"> "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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "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 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			"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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "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 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family										
"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 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "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 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family													
Date of the actual completion of the international search		Date of mailing of the international search report												
3 June 2016		14/06/2016												
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		Lokajova, Jana												

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/071085

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

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