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(54) **Title:** FLUID HANDLING METHOD, AND FLUID HANDLING DEVICE AND FLUID HANDLING SYSTEM USED FOR THE METHOD

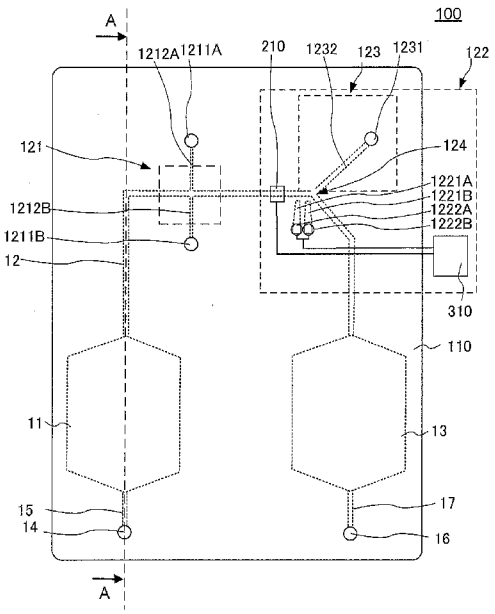


FIG. 1

(57) **Abstract:** A fluid handling method includes a step of generating a plurality of first droplets each including a plurality of separation objects by dividing first fluid containing a large number of separation objects by a droplet generation part; a step of separating a first particular droplet containing at least one particular separation object from a plurality of first droplets by an electric field generation part, to move it into a second chamber; a step of generating second fluid in which a plurality of the first particular droplets are united to one another by moving the first particular droplet to the electric field generation part side and by generating an electric field; a step of injecting liquid from an injection part so as to join the liquid to the second fluid; a step of generating a second droplet containing at most one separation object by dividing the second fluid by the droplet generation part; and a step of separating a second particular droplet containing a particular separation object from a plurality of second droplets and moving it to the second chamber.

Description

Title of Invention: FLUID HANDLING METHOD, AND FLUID HANDLING DEVICE AND FLUID HANDLING SYSTEM USED FOR THE METHOD

Technical Field

[0001] The present invention relates to a fluid handling method, and a fluid handling device and a fluid handling system that are used for the fluid handling method.

Background Art

[0002] In laboratory tests, food tests, environment tests and the like, highly accurate analysis of a trace substance such as cell, protein and nucleic acid is required in some situation. A method for analyzing a trace substance is known in which a micro liquid droplet (hereinafter referred to also as "droplet") is generated from liquid containing the analysis object so as to observe and analyze the droplet.

[0003] Normally, each droplet contains at most one material (analysis object) that is subjected to the analysis. The number of the analysis objects contained in the droplet depends on a probability distribution called Poisson distribution. In the case where multiple droplets are generated such that each includes at most one analysis object, about 90% of the generated droplets are empty droplets containing no analysis object. As such separation of droplets containing a particular analysis object from multiple droplets takes long time.

[0004] In view of this, PTL 1 discloses the following method. First, a plurality of first droplets containing a plurality of separation objects are generated. Then droplets each of which contains a particular separation object are separated from the first droplets. Thereafter, the separated first droplets are divided such that each contains at most one separation object. Then, droplets containing the particular separation object are separated from the divided droplets.

Citation List

Patent Literature

[0005] PTL 1: WO2018/173611

Summary of Invention

Technical Problem

[0006] In comparison with the conventional method, the method disclosed in PTL 1 can separate droplets each of which contains a particular separation object in a far shorter period of time. Note that the above-described method is performed by using a fluid handling system including a plurality of separating units. Therefore, the configuration

of the fluid handling system tends to be complicated, and downsizing of the fluid handling device is difficult.

[0007] An object of the present invention is to provide a fluid handling method that can readily separate a droplet containing a desired separation object with a simple and small apparatus. Another object of the present invention is to provide a fluid handling device and a fluid handling system intended for the above-mentioned method.

Solution to Problem

[0008] The present invention provides the following fluid handling method.

A fluid handling method that uses a fluid handling system, the fluid handling system including a first chamber configured to house fluid and/or droplets, a droplet generation part connected with the first chamber and configured to divide fluid to generate a plurality of droplets, an electric field generation part including a pair of electrodes, the electric field generation part being configured to separate a particular droplet from the plurality of droplets generated at the droplet generation part, and a second chamber connected with the electric field generation part and configured to house the particular droplet, and an injection part disposed between the first chamber and the second chamber and configured to inject liquid, the method including: housing first fluid containing a large number of separation objects in the first chamber; generating a plurality of first droplets by dividing the first fluid by the droplet generation part, each of the plurality of first droplets containing a plurality of separation objects; separating a first particular droplet containing at least one particular separation object from the plurality of first droplets by generating an electric field by the pair of electrodes, so as to move the first particular droplet into the second chamber; generating second fluid in which a plurality of the first particular droplets are united to one another by moving the plurality of the first particular droplets from the second chamber to the electric field generation part while generating an electric field by the pair of electrodes; injecting liquid from the injection part so as to join the liquid to the second fluid; dividing the second fluid by the droplet generation part to generate a second droplet containing at most one separation object; and separating a second particular droplet containing the particular separation object from a plurality of the second droplets by the electric field generation part, so as to move the second particular droplet to the second chamber.

[0009] The present invention provides the following fluid handling device.

A fluid handling device including: a first chamber and a second chamber configured to house fluid and/or droplets, a channel connecting the first chamber and the second chamber; an injection channel connected with the channel and configured to inject liquid; and a pair of electrodes. The channel includes a droplet generation part

configured to divide fluid containing a predetermined separation object to generate droplets, and a branch disposed closer to the second chamber than the droplet generation part, and configured to separate a particular droplet. The pair of electrodes generates an electric field at the branch.

[0010] The present invention provides the following fluid handling system.

A fluid handling system including: the above-mentioned fluid handling device; a detection part configured to detect the particular droplet in the channel; and a control part configured to perform a control of carrying the particular droplet toward the second chamber at the branch.

Advantageous Effects of Invention

[0011] According to the fluid handling method of an embodiment of the present invention, a droplet containing a particular separation object can be readily separated with a small and simple apparatus.

Brief Description of Drawings

[0012] [fig.1]FIG. 1 is a plan view illustrating a configuration of a fluid handling system according to an embodiment of the present invention.

[fig.2]FIG. 2 is a sectional view taken along line A-A of a fluid handling device illustrated in FIG. 1 according to the embodiment of the present invention.

[fig.3]FIG. 3 is a bottom view of a substrate of the fluid handling device according to the embodiment of the present invention.

[fig.4]FIG. 4 schematically illustrates a first droplet generation step in a fluid handling method according to the embodiment of the present invention.

[fig.5]FIG. 5 schematically illustrates a first separation step in the fluid handling method according to the embodiment of the present invention.

[fig.6]FIG. 6 is a plan view illustrating a configuration of a fluid handling system according to another embodiment of the present invention.

Description of Embodiments

[0013] An embodiment of the present invention is elaborated below with reference to the accompanying drawings. For simplicity and clarity, elements in the figures may not be drawn to scale.

[0014] The fluid handling method of the embodiment of the present invention is a method for generating and separating a particular droplet containing a particular separation object from fluid containing a large number of separation objects. First, a fluid handling system and a fluid handling device for the fluid handling method are described, and thereafter the fluid handling method is described.

[0015] A. Fluid Handling System

FIG. 1 is a plan view of fluid handling system 100 according to the embodiment of

the present invention. Fluid handling system 100 of the present embodiment includes fluid handling device 110, detection part 210, and control part 310. In addition, fluid handling system 100 includes first chamber 11 for housing fluid and/or droplets, droplet generation part 121 for generating droplets, electric field generation part 122 for separating and uniting particular droplets, injection part 123 for injecting liquid, and second chamber 13 for housing the particular droplets. Note that, in the present embodiment, first chamber 11, droplet generation part 121, second chamber 13 and injection part 123 are disposed in fluid handling device 110. Electric field generation part 122 is configured to include a part of fluid handling device 110, detection part 210 and control part 310.

[0016] Fluid Handling Device

FIG. 2 is a sectional view (taken along line A-A of FIG. 1) of fluid handling device 110 of the present embodiment. As illustrated in FIG. 2, fluid handling device 110 of the present embodiment includes substrate 111 including a groove, a recess, a through hole and the like, film 112 configured to cover the groove, the recess, the through hole and the like of substrate 111, and a pair of electrodes 1221A and 1221B disposed between substrate 111 and film 112. FIG. 3 is a bottom view of substrate 111 in the state where film 112 is removed from fluid handling device 110.

[0017] As illustrated in FIG. 3, fluid inlet 14 (through hole), first groove 15a, first chamber recess 11a, second groove 12a, second chamber recess 13a, third groove 17a, outlet 16 (through hole), a pair of fourth grooves 1212a and 1212b, a pair of solvent inlets (through holes) 1211A and 1211B, fifth groove 1232a, inlet/outlet 1231 (through hole), and a pair of electrode connection ports 1222A and 1222B are formed in substrate 111 of fluid handling device 110.

[0018] In the present embodiment, the region surrounded by first groove 15a and film 112 serves as fluid introduction channel 15, and the region surrounded by first chamber recess 11a and film 112 serves as first chamber 11. The region surrounded by second groove 12a and film 112 serves as main channel 12, and the region surrounded by second chamber recess 13a and film 112 serves as second chamber 13. Further, the region surrounded by third groove 17a and film 112 serves as discharging channel 17, the region surrounded by the pair of fourth grooves 1212a and 1212b and film serves as solvent introduction channels 1212A and 1212B, and the region surrounded by fifth groove 1232a and film 112 serves as injection channel 1232.

[0019] First chamber 11 is a region for housing fluid, droplets and the like. In addition, second chamber 13 is a region for housing a particular droplet. The depth and/or the width of first chamber 11 and second chamber 13 is appropriately selected in accordance with the size of the droplets, the number of droplets, and/or the fluid. In the present embodiment, each of first chamber 11 and second chamber 13 has a hexagonal

prism shape; however, first chamber 11 and second chamber 13 may have other shapes such as a square columnar shape, a columnar shape, an elliptic cylinder shape, a truncated cone shape and a truncated pyramid shape. While first chamber 11 and second chamber 13 have substantially the same shape in the present embodiment, the sizes and/or shapes of first chamber 11 and second chamber 13 may differ from each other.

[0020] First chamber 11 is connected with fluid introduction channel 15 and main channel 12. One end of fluid introduction channel 15 is open to first chamber 11, and the other end of fluid introduction channel 15 is open to fluid inlet 14. The width and/or the depth of fluid introduction channel 15 is not limited as long as fluid injected from fluid inlet 14 can flow to first chamber 11 side. The width and the depth of fluid introduction channel 15 is appropriately selected in accordance with the type of fluid (in particular, separation object) and the like.

[0021] In addition, fluid inlet 14 connected with fluid introduction channel 15 is a structure for injecting fluid into first chamber 11. While fluid inlet 14 is a columnar through hole provided in substrate 111 in the present embodiment, fluid inlet 14 is not limited to this shape, and fluid inlet 14 may have a structure for connecting a tube, a syringe and/or the like, for example. In addition, the opening diameter of fluid inlet 14 is not limited as long as fluid can be injected.

[0022] On the other hand, second chamber 13 is connected with discharging channel 17 and main channel 12. One end of discharging channel 17 is open to second chamber 13, and the other end of discharging channel 17 is open to outlet 16. The width and/or the depth of discharging channel 17 is not limited as long as particular droplets housed in second chamber 13 can flow to outlet 16 side. The width and/or the depth of discharging channel 17 is appropriately selected in accordance with the size of the particular droplet and the like.

[0023] In addition, outlet 16 connected with discharging channel 17 is a structure for discharging particular droplets (second particular droplets described later) and the like housed in second chamber 13. While outlet 16 is a columnar through hole provided in substrate 111 in the present embodiment, the shape of outlet 16 is not limited to this, and outlet 16 may have a structure for connecting a tube, a syringe and/or the like, for example. Also, the opening diameter of outlet 16 is not limited as long as droplets and the like can be discharged.

[0024] One end of main channel 12 is open to first chamber 11, and the other end of main channel 12 is open to second chamber 13. In addition, a pair of solvent introduction channels 1212A and 1212B, and injection channel 1232 are connected with main channel 12. In the present embodiment, the joining part of main channel 12 and the pair of solvent introduction channels 1212A and 1212B serves as droplet generation

part 121 for generating droplets. In addition, the joining part of main channel 12 and injection channel 1232 serves as branch 124 (a part of electric field generation part 122) for separating particular droplets.

[0025] Here, in the present embodiment, main channel 12 has a crank shape in the bottom view. Note that the shape of main channel 12 in the bottom view is not limited to the above-mentioned shape. Main channel 12 may have any shape in accordance with the size of fluid handling device 110 (fluid handling system 100), the positions of first chamber 11 and second chamber 13 and the like.

[0026] In addition, while the depth and the width of main channel 12 from first chamber 11 side to second chamber 13 side are constant in the present embodiment, the depth and the width may be continuously or intermittently varied. Note that in the fluid handling method described later, it is preferable to confirm the droplets one by one by electric field generation part 122 (in particular, detection part 210) so as to surely separate particular droplets. In view of this, it is preferable to set the width and the depth of main channel 12 at and near electric field generation part 122 to a width and a depth with which droplets are not allowed to overlap each other.

[0027] On the other hand, one end of each of solvent introduction channels 1212A and 1212B connected with main channel 12 is open at main channel 12, and the other end of each of solvent introduction channels 1212A and 1212B is open at solvent inlets 1211A and 1211B. The pair of solvent introduction channels 1212A and 1212B are channels for injecting a solvent that is incompatible with the fluid flowing in main channel 12 from the both sides so as to divide the fluid (produce droplets). Here, the opening of solvent introduction channel 1212A on main channel 12 side and the opening of solvent introduction channel 1212B on main channel 12 side face each other with main channel 12 there between. More specifically, each opening is disposed such that a straight line connecting the center of the opening of solvent introduction channel 1212A on main channel 12 side and the center of the opening solvent introduction channel 1212B on main channel 12 side is substantially orthogonal to the fluid flowing in main channel 12. With the straight line and the channels substantially orthogonal to each other, the fluid flowing in main channel 12 can be surely divided by the shearing force of the solvent injected from the pair of solvent introduction channels 1212A and 1212B.

[0028] In addition, in the present embodiment, the pair of solvent introduction channels 1212A and 1212B and main channel 12 are disposed at a substantially right angle. With solvent introduction channels 1212A and 1212B disposed in the above-mentioned manner, not only the fluid flowing from first chamber 11 side toward second chamber 13 side, but also fluid flowing from second chamber 13 side toward first chamber 11 side can be divided to produce droplets. Note that the angle between

the pair of solvent introduction channels 1212A and 1212B and main channel 12 may not be a right angle.

[0029] Note that the depth and the width of the pair of solvent introduction channels 1212A and 1212B are appropriately selected in accordance with the type of the solvent injected from solvent inlets 1211A and 1211B. Further, the lengths, the widths, and the depths of the pair of solvent introduction channels 1212A and 1212B are equal to each other in the present embodiment, the length, the width, and the depth may be different from each other.

[0030] The pair of solvent inlets 1211A and 1211B connected with the pair of solvent introduction channels 1212A and 1212B are structures for injecting solvent. While solvent inlets 1211A and 1211B are columnar through holes provided in substrate 111 in the present embodiment, the shapes of the inlets are not limited to this, and the inlets may have a structure for connecting a tube, a syringe and/or the like, for example. In addition, the opening diameters of solvent inlets 1211A and 1211B are not limited as long as solvent can be injected.

[0031] In addition, one end of injection channel 1232 connected with main channel 12 is open to main channel 12, and the other end of injection channel 1232 is open to inlet/outlet 1231. In the present embodiment, injection channel 1232 is used as a channel for discharging, from main channel 12, droplets that are determined to be unnecessary (droplets that do not contain a particular separation object) at electric field generation part 122. Further, the injection channel 1232 is also used as a channel (injection part 123 of fluid handling system 100) for injecting liquid to main channel 12.

[0032] The width and the depth of injection channel 1232 are not limited as long as droplets and desired liquid can flow through injection channel 1232. While the width and the depth are substantially equal to those of main channel 12 in the present embodiment, the width and the depth may be different from those of main channel 12. In addition, the branching angle between injection channel 1232 and main channel 12 at branch 124 is a substantially right angle in the present embodiment. Note that the angle is not limited to a right angle.

[0033] In addition, inlet/outlet 1231 connected with injection channel 1232 is a structure for discharging droplets determined to be unnecessary at electric field generation part 122 (droplets that do not contain a particular separation object), and for injecting desired liquid to main channel 12 side. While inlet/outlet 1231 is a columnar through hole provided in substrate 111 in the present embodiment, the shape of inlet/outlet 1231 is not limited to this, and inlet/outlet 1231 may have a structure for connecting a tube, a syringe and/or the like, for example. In addition, the opening diameter of inlet/outlet 1231 is not limited as long as discharge of droplets, introduction of liquid and the like can be achieved.

[0034] In addition, the pair of electrode connection ports 1222A and 1222B are through holes for electrically connecting an external circuit and the pair of electrodes 1221A and 1221B disposed between substrate 111 and film 112. While electrode connection ports 1222A and 1222B are columnar through holes provided in substrate 111 in the present embodiment, electrode connection ports 1222A and 1222B are not limited to this structure as long as the pair of electrodes 1221A and 1221B and the circuit can be electrically conducted.

[0035] In addition, the pair of electrodes 1221A and 1221B, which are composed of a positive electrode and a negative electrode disposed between substrate 111 and film 112, are structures for generating an electric field at branch 124. The pair of electrodes 1221A and 1221B are separated from each other. In addition, the distance between main channel 12 and the end of each of the pair of electrodes 1221A and 1221B is not limited as long as an electric field can be generated at branch 124 so as to guide particular droplets to second chamber 13 side. Note that the other ends of the pair of electrodes 1221A and 1221B are exposed to the inside of electrode connection ports 1222A and 1222B.

[0036] While the pair of electrodes 1221A and 1221B is disposed on film 112 in the present embodiment, the pair of electrodes 1221A and 1221B may be disposed on substrate 111. Examples of the method of forming electrodes 1221A and 1221B on film 112 or substrate 111 include a vacuum deposition method and a sputtering method. In addition, electrodes 1221A and 1221B may be formed by a method in which conductive ink is injected to a recess formed in substrate 111 or film 112 and then the ink is solidified.

[0037] In addition, the method of forming substrate 111 including the through hole, the groove, and/or the recess is not limited, and may be a metal molding method, a lithography method or the like. Note that substrate 111 may be integrally shaped, or may be composed of a combination of a plurality of members. In addition, the thickness, the size and the like of substrate 111 are appropriately selected in accordance with the use of fluid handling system 100.

[0038] The material of substrate 111 is not limited as long as the material is conductive and is not eroded by fluid, droplets and the like injected to the fluid handling system 100. Examples of the material of substrate 111 include resin materials such as polyester such as polyethylene terephthalate; polycarbonate; acrylic resins such as polymethylmethacrylate; polyvinyl chloride; polyolefin such as polyethylene, polypropylene, and cycloolefin resin; polyether; polystyrene; silicone resins such as polydimethyl siloxane; and elastomers.

[0039] Note that, in the case where a fluorescence detection of a particular droplet is performed by the fluid handling method described later, it is preferable that substrate

111 be formed of a material whose autofluorescence is small. In addition, substrate 111 may or may not be optically transparent. In the case where a particular droplet is optically detected from substrate 111 side by the fluid handling method described later, it is preferable that substrate 111 have optical transparency.

[0040] On the other hand, film 112 for covering the recess, the through hole, and/or the groove of substrate 111 is a flat film or a plate-shaped member. The material of film 112 is not limited as long as the material is conductive and is not eroded by fluid, droplets or the like injected to the fluid handling system 100. The thickness and the like of film 112 are appropriately selected.

[0041] The material of film 112 may be an inorganic material such as glass; or a resin material such as polyester such as polyethylene terephthalate; polycarbonate; acrylic resin such as polymethylmethacrylate; polyvinyl chloride; polyolefin such as polyethylene, polypropylene, and cycloolefin resin; polyether; polystyrene; silicone resin; and elastomers.

[0042] In addition, in the case where a fluorescence detection of a particular droplet is performed by the fluid handling method described later, it is preferable that film 112 be formed of a material whose autofluorescence is small. Film 112 may or may not be optically transparent. In the case where a particular droplet is optically detected from film 112 side by the fluid handling method described later, it is preferable that film 112 be optically transparent.

[0043] In addition, substrate 111 and film 112 may be joined by a publicly known method such as heat fusing and bonding with an adhesive agent.

[0044] Detection Part

Detection part 210 is a configuration for detecting a particular separation object included in a plurality of droplets. Detection part 210 functions as a unit that detects a droplet (particular droplet) including a particular separation object and transmits the detection result to control part 310 in electric field generation part 122 of fluid handling system 100.

[0045] In fluid handling system 100 of the present embodiment, the detection part 210 is disposed between branch 124 and droplet generation part 121 of fluid handling device 100. In addition, detection part 210 may be disposed on the rear side of fluid handling system 100, or in other words on film 112 side. Alternatively, detection part 210 may be disposed on the front side of fluid handling system 100, or in other words on substrate 111 side.

[0046] The type of detection part 210 is appropriately selected in accordance with the type of the separation object. A particular separation object may be detected by an optical method such as a fluorescence detection method, an ultraviolet spectroscopic method, and an infrared spectroscopic method, or by an electric method such as an electric re-

sistance measurement method. In the case where a particular separation object is detected by a fluorescence detection method, detection part 210 may detect the autofluorescence of the particular separation object, or may detect fluorescence from the fluorescence material labelling the predetermined separation object.

[0047] For example, in the case where detection part 210 detects a particular separation object by means of an optical unit, detection part 210 includes a light source for irradiating droplets with desired light, and a light receiving sensor for detecting response light from the droplets. In addition, in the case where a particular separation object is detected by means of the electric unit, detection part 210 includes a power source and an ammeter.

[0048] Control Part

Control part 310 is composed of a publicly known computer, microcomputer, or the like including a computation device, a control device, a storage device, and an inputting device, for example. In electric field generation part 122 of fluid handling system 100, control part 310 functions as a unit for receiving a detection result of detection part 210 and for applying a voltage to the pair of electrodes 1221A and 1221B of fluid handling device 110.

[0049] B. Liquid Handling Method

Next, how fluid handling system 100 is used (the liquid handling method according to the present embodiment) is described.

[0050] In the fluid handling method of the present embodiment, fluid and droplets are carried three times between first chamber 11 and second chamber 13 of fluid handling device 110, and thus a particular droplet containing only a particular separation object can be produced and separated.

[0051] Specifically, the fluid handling method of the present embodiment includes a housing step of housing first fluid containing a large number of separation objects in the first chamber 11; a first droplet generation step of dividing the first fluid by droplet generation part 121 and generating a plurality of first droplets including a plurality of separation objects; a first separation step of generating an electric field by electric field generation part 122 and separating a first particular droplet containing a particular separation object from a plurality of first droplets to move it into second chamber 13; a uniting step of moving the first particular droplet from second chamber 13 to electric field generation part 122, generating an electric field by the pair of electrodes 1221A and 1221B, and generating second fluid composed of a plurality of first particular droplets united to one another; a liquid injection step of injecting liquid from injection part 123 such that the liquid joins the second fluid; a second droplet generation step of dividing the second fluid by droplet generation part 121 and generating a second droplet containing at most one separation object; and a second separation step of

separating a second particular droplet containing a particular separation object from the plurality of second droplets by electric field generation part 122 so as to move it to second chamber 13. Each step is elaborated below.

[0052] Housing Step

In the housing step, first fluid containing a large number of separation objects is housed in the first chamber 11. More specifically, the first fluid is introduced from fluid inlet 14 of fluid handling system 100 through fluid introduction channel 15, and housed in first chamber 11. At this time, a pressure may be applied from fluid inlet 14 side to facilitate the flow of the first fluid. Note that it is preferable to fill main channel 12 and/or second chamber 13 with solvent in advance before injection of the first fluid into first chamber 11.

[0053] Here, in the specification, the separation object is various types of components subjected to various types of inspections such as laboratory tests, food tests, and/or environment tests. Examples of the separation object include a cell, a protein, a nucleic acid and the like. In addition, the particular separation object is a component that should be separated from among the separation objects. For example, in the case where the separation object is cells, examples of the particular separation object include cancer cells and the like.

[0054] In addition, in the specification, the fluid typically contains the separation object and dispersion solvent for dissolving and dispersing the separation object. Further, the fluid may include solvent for dispersing droplets, or more specifically, solvent whose compatibility with the separation object and/or the dispersion solvent is low (hereinafter referred to also as "host solvent").

[0055] First Droplet Generation Step

In the first droplet generation step, the first fluid is divided at droplet generation part 121 to produce first droplets containing a plurality of separation objects. FIG. 4 is a schematic view for describing this step (a schematic view of droplet generation part 121). In this step, the first fluid containing separation object 40 and dispersion solvent 41 housed in first chamber 11 in the housing step is carried in main channel 12 toward second chamber 13 side. For the purpose of adjusting the movement rate of the first fluid in main channel 12, a pressure may be applied or solvent may be injected from fluid inlet 14. In addition, suction or the like from outlet 16 may be performed.

[0056] Then, when the first fluid passes through droplet generation part 121, host solvent 42 is injected into main channel 12 from the pair of solvent introduction channels 1212A and 1212B (inlets 1211A and 1211B). In FIG. 4, the dashed line arrow indicates the flow direction of host solvent 42, the white arrow indicates the flow direction of the first fluid. When host solvent 42 is injected into main channel 12 from the pair of solvent introduction channels 1212A and 1212B, the first fluid is divided and shaped

into a spherical shape (first droplet 43) by the shearing force of host solvent 42. Then, first droplet 43 thus generated moves to second chamber 13 side together with host solvent 42. Note that the injection of host solvent 42 may be performed continuously or intermittently. Further, the type of host solvent 42 is not limited as long as the compatibility of the liquid with the first fluid is low, and surfactant and the like may be contained as necessary.

[0057] Here, the number of separation objects contained in first droplet 43 may be adjusted by the concentration of the separation object in the first fluid, the flow rate of the first fluid, and the flow rate of host solvent 42. Preferably, the number of the separation objects in first droplet 43 is 10 to 140 although the number of the separation objects in first droplet 43 is appropriately selected in accordance with the type of the separation object.

[0058] First Separation Step

In the first separation step, electric field generation part 122 identifies a first particular droplet containing at least one particular separation object from among a plurality of first droplets 43 generated by droplet generation part 121. Then, the pair of electrodes 1221A and 1221B generates an electric field at branch 124 so as to move the first particular droplet to second chamber 13 side. FIG. 5 is a schematic view (of electric field generation part 122) for illustrating this step.

[0059] In this step, detection part 210 detects first particular droplet 431 containing particular separation object 40a (indicated with white circles in FIG. 5) from among first droplets 43 flowing in main channel 12. Then, detection part 210 transmits a detection result to control part 310. When receiving a result from detection part 210, control part 310 applies a voltage to the pair of electrodes 1221A and 1221B at a timing when first particular droplet 431 reaches branch 124 (a part where main channel 12 and injection channel 1232 joins together). As a result, an electric field is generated at branch 124, and first particular droplet 431 flows to second chamber 13 side. Meanwhile, control part 310 does not apply the voltage to the pair of electrodes 1221A and 1221B when unnecessary first droplet 432 containing only unnecessary separation object 40b (indicated with black circles in FIG. 5) passes through branch 124. As a result, no electric field is generated at branch 124, and unnecessary first droplet 432 flows to injection channel 1232 side. Then, unnecessary first droplet 432 is discharged out of the fluid handling system 100 from inlet/outlet 1231.

[0060] Note that for the purpose of surely carrying first particular droplet 431 to second chamber 13 side, and/or surely carrying unnecessary first droplet 432 to injection channel 1232 side, suction and the like may be performed from outlet 16 and/or inlet/outlet 1231 as necessary.

[0061] Through this step, only first particular droplet 431 containing the particular

separation object is housed in second chamber 13, and unnecessary first droplet 432 that does not contain the particular separation object is removed.

[0062] Uniting Step

In the uniting step, first particular droplet 431 housed in second chamber 13 is carried inside main channel 12 toward electric field generation part 122 side. At this time, as necessary, a pressure may be applied and/or solvent may be injected from outlet 16 side, and suction may be performed from fluid inlet 14 side.

[0063] When first particular droplet 431 passes through electric field generation part 122, the pair of electrodes 1221A and 1221B generates an electric field. With this configuration, first particular droplets 431 are united to become second fluid containing a large number of separation objects.

[0064] Liquid Injection Step

In the liquid injection step, liquid is injected from inlet/outlet 1231 to join the liquid to the second fluid before the uniting step, or during the uniting step, or, after the uniting step. The type of the liquid injected here is not limited as long as the liquid can be united with the second fluid. The liquid injected here may be identical to the dispersion solvent contained in the first particular droplet, for example. With the injected liquid, the concentration of the separation object in the second fluid is reduced, and a second droplet containing at most one separation object can be easily generated in the second droplet generation step described later. Note that the liquid may be injected continuously or intermittently.

[0065] Second Droplet Generation Step

In the second droplet generation step, the second fluid droplet generated in the electric field generation part 122 is divided by droplet generation part 121 to produce a second droplet containing at most one separation object. More specifically, when the second fluid passes through droplet generation part 121, host solvent is injected into main channel 12 from the pair of solvent introduction channels 1212A and 1212B (solvent inlets 1211A and 1211B) so as to divide the second fluid. The second droplets generated by the division of the second fluid move to first chamber 11 side together with the host solvent, and are housed in first chamber 11. Note that the host solvent may be injected continuously or intermittently. In addition, the host solvent used in the second droplet generation step may be identical to or different from the host solvent used in the first droplet generation step. In addition, surfactant and the like may be contained as necessary.

[0066] Here, the number of separation objects contained in the second droplets generated in this step is adjusted by the concentration of the separation objects in the second fluid, the flow rate of the second fluid, and the flow rate of the host solvent. The number of the separation object in the second droplet is dictated by Poisson statistics and

expected to be 0 or 1.

[0067] Second Separation Step

In the second separation step, the second droplets housed in first chamber 11 are carried in main channel 12 toward second chamber 13. At this time, as necessary, a pressure may be applied and/or solvent may be injected from fluid inlet 14 side, and suction may be performed from outlet 16 side.

[0068] Then, the second droplets are moved to electric field generation part 122, and a second particular droplet containing a particular separation object is separated from the second droplets, and, an electric field is generated at branch 124 to move it to second chamber 13 side. More specifically, detection part 210 detects a second particular droplet containing a particular separation object from second droplets flowing in main channel 12. Then, detection part 210 transmits a detection result to control part 310. When receiving a result from detection part 210, control part 310 applies a voltage to the pair of electrodes 1221A and 1221B at the timing when the second particular droplet reaches branch 124. As a result, an electric field is generated at branch 124 and the second particular droplet flows to second chamber 13 side. Meanwhile, control part 310 does not apply a voltage to the pair of electrodes 1221A and 1221B when second droplets that contain an unnecessary separation object, or second droplets that contain no separation object pass through branch 124. As a result, no electric field is generated at branch 124, and the unnecessary second droplet flows to injection channel 1232 side. Then, the unnecessary second droplet is discharged out of fluid handling system 100 from inlet/outlet 1231.

[0069] Note that, for the purpose of surely carrying the second particular droplet to second chamber 13 side, and/or surely carrying the unnecessary second droplet to inlet/outlet 1231 side, suction and the like may be performed from outlet 16 side and/or inlet/outlet 1231 side as necessary.

[0070] Through this step, the second particular droplet containing only a particular separation object is housed in second chamber 13, the second droplet that does not contain the particular separation object is removed. The second particular droplet housed in second chamber 13 can be removed from outlet 16, and can be used for various inspections and the like as necessary.

[0071] Other Embodiments

In the embodiment, the second droplet generation step is performed when moving the second fluid from the branched channel to the first chamber side. However, after the second fluid is generated, the second fluid may be carried through the droplet generation part without change so as to house the second fluid in first chamber. In this case, while the second fluid housed in the first chamber is carried toward the second chamber, droplets are generated at the droplet generation part (second drop generation

step), and thereafter, the second particular droplets are separated at the electric field generation part (second separation step).

[0072] In the embodiment, the injection channel serves as a channel for discharging a droplet (droplets that do not contain a particular separation object) that is determined to be unnecessary by the detection part of the electric field generation part from the main channel, and as a channel for injecting liquid to the main channel. Note that, as illustrated in FIG. 6, injection channel 2232 may be branched into droplet discharging channel 2234 for discharging droplets, and liquid injection channel 2236 for injecting liquid. In this case, in the first separation step and/or the second separation step, unnecessary droplets are discharged from droplet outlet 2233 through droplet discharging channel 2234. In addition, in the liquid injection step, liquid is injected into liquid inlet 2235. Then, the liquid is introduced into main channel 12 through liquid injection channel 2236 and injection channel 2232. Note that fluid handling system 200 illustrated in FIG. 6 is identical to fluid handling system 100 of the embodiment except for injection part 223 (injection channel). In view of this, the same configurations are denoted with the same reference numerals, and detailed description thereof is omitted.

[0073] In addition, the position of the injection part (injection channel) for injecting liquid is not limited to that of injection part 123 or 223 of fluid handling system 100 or 200 illustrated in FIG. 1 or FIG. 6. For example, the joining part of the injection channel and the main channel may be disposed at a position between the branch and the second chamber, a position between the droplet generation part and the electric field generation part, a position between the first chamber and the droplet generation part and the like.

[0074] While the droplets are separated in two steps in the embodiment, droplets may be separated in three or more steps in the liquid handling method according to embodiments of the present invention.

[0075] Further, in the embodiment, in the first separation step and the second separation step, a voltage is applied to a pair of electrodes of the electric field generation part so as to generate an electric field at a branch, and thus the droplets are guided to the second chamber side. Note that the droplets may be guided to the second chamber side by other methods. For example, the droplets may be physically separated by a cantilever disposed at the branch, electro-osmosis of a direct current, or an optical tweezer.

[0076] Effect

In the fluid handling method of the present embodiment, a plurality of first particular droplets containing a predetermined separation object are separated from first fluid containing a plurality of separation objects. Then, the separated first particular droplets are united to produce second fluid, and a plurality of second droplets each of which

contains at most one separation object are generated from the second fluid. Thereafter, only second particular droplets containing a particular separation object are separated from the plurality of second droplets. In this manner, by separating droplets stepwise, droplets containing only a particular separation object can be separated in a very short time.

[0077] In addition, the liquid handling method according to the present embodiment can be performed with a simple fluid handling system including a first chamber for housing fluid and/or droplets; a droplet generation part connected with the first chamber, and configured to divide fluid and generate a plurality of droplets; an electric field generation part for separating a particular droplets from the plurality of droplets generated at the droplet generation part; a second chamber connected with the electric field generation part and configured to house a particular droplet; and an injection part disposed between the first chamber and the second chamber and configured to inject liquid. The fluid handling system does not require complicated wiring, structure or the like, and can separate droplets stepwise by only carrying liquid between the first chamber and the second chamber multiple times.

Industrial Applicability

[0078] The fluid handling method, the fluid handling device, and the fluid handling system of the embodiments of the present invention are applicable to laboratory tests, food tests, environment tests and the like, for example.

Reference Signs List

[0079] 11 First chamber
11a First chamber recess
12 Main channel
12a Second groove
13 Second chamber
13a Second chamber recess
14 Fluid inlet
15 Fluid introduction channel
15a First groove
16 Outlet
17 Discharging channel
17a Third groove
100, 200 Fluid handling system
110 Fluid handling device
111 Substrate
112 Film

121 Droplet generation part
122 Electric field generation part
123, 223 Injection part
124 Branch
210 Detection part
310 Control part
1211A and 1211B Solvent inlet
1212A, 1212B Solvent introduction channel
1212a, 1212b Fourth groove
1221A, 1221B Electrode
1222A and 1222B Electrode connection port
1231 Inlet/outlet
1232, 2232 Injection channel
1232a Fifth groove
2233 Droplet outlet
2234 Droplet discharging channel
2235 Liquid inlet
2236 Liquid injection channel

Claims

[Claim 1] A fluid handling method that uses a fluid handling system, the fluid handling system including
a first chamber configured to house fluid and/or droplets,
a droplet generation part connected with the first chamber and configured to divide fluid to generate a plurality of droplets,
an electric field generation part including a pair of electrodes, the electric field generation part being configured to separate a particular droplet from the plurality of droplets generated at the droplet generation part, and
a second chamber connected with the electric field generation part and configured to house the particular droplet, and
an injection part disposed between the first chamber and the second chamber and configured to inject liquid, the method comprising:
housing first fluid containing a large number of separation objects in the first chamber;
generating a plurality of first droplets by dividing the first fluid by the droplet generation part, each of the plurality of first droplets containing a plurality of separation objects;
separating a first particular droplet containing at least one particular separation object from the plurality of first droplets by generating an electric field by the pair of electrodes, so as to move the first particular droplet into the second chamber;
generating second fluid in which a plurality of the first particular droplets are united to one another by moving the plurality of the first particular droplets from the second chamber to the electric field generation part while generating an electric field by the pair of electrodes;
injecting liquid from the injection part so as to join the liquid to the second fluid;
dividing the second fluid by the droplet generation part to generate a second droplet containing at most one separation object; and
separating a second particular droplet containing the particular separation object from a plurality of the second droplets by the electric field generation part, so as to move the second particular droplet to the second chamber.

[Claim 2] The fluid handling method according to claim 1, wherein the injecting

of the liquid is performed by the electric field generation part.

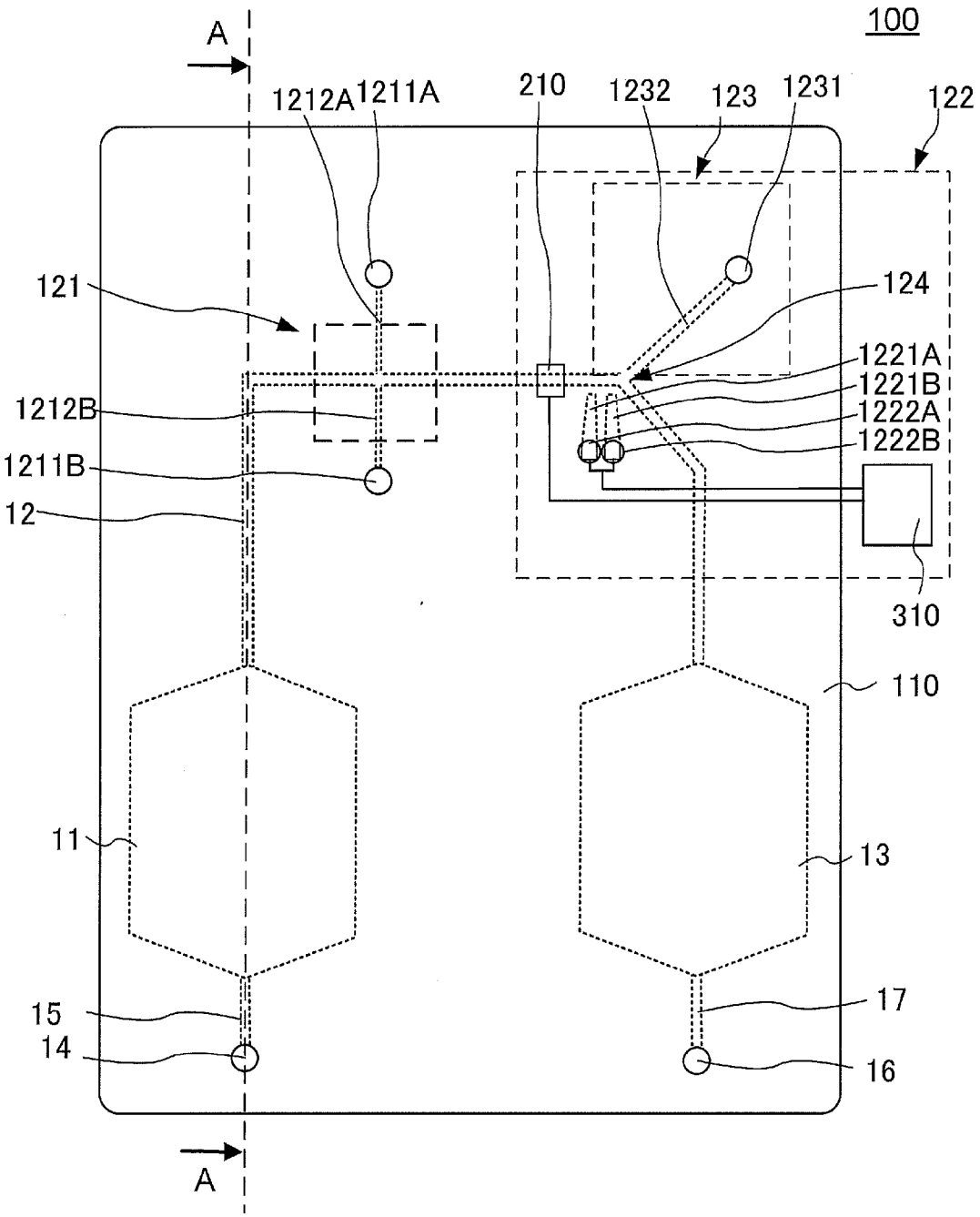
[Claim 3] A fluid handling device, comprising:
a first chamber and a second chamber configured to house fluid and/or droplets,
a channel connecting the first chamber and the second chamber;
an injection channel connected with the channel and configured to inject liquid; and
a pair of electrodes, wherein
the channel includes:
a droplet generation part configured to divide fluid containing a predetermined separation object to generate droplets, and
a branch disposed closer to the second chamber than the droplet generation part, and configured to separate a particular droplet, and
wherein the pair of electrodes generates an electric field at the branch.

[Claim 4] The fluid handling device according to claim 3, wherein the branch is a joining part of the channel and the injection channel.

[Claim 5] The fluid handling device according to claim 3 or 4, wherein the droplet generation part is capable of generating a droplet from fluid flowing from the first chamber to the second chamber, and fluid flowing from the second chamber to the first chamber.

[Claim 6] A fluid handling system, comprising:
the fluid handling device according to any one of claims 3 to 5;
a detection part configured to detect the particular droplet in the channel; and
a control part configured to perform a control of carrying the particular droplet toward the second chamber at the branch.

[Fig. 1]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14
17
16
A

FIG. 1

[Fig. 2]

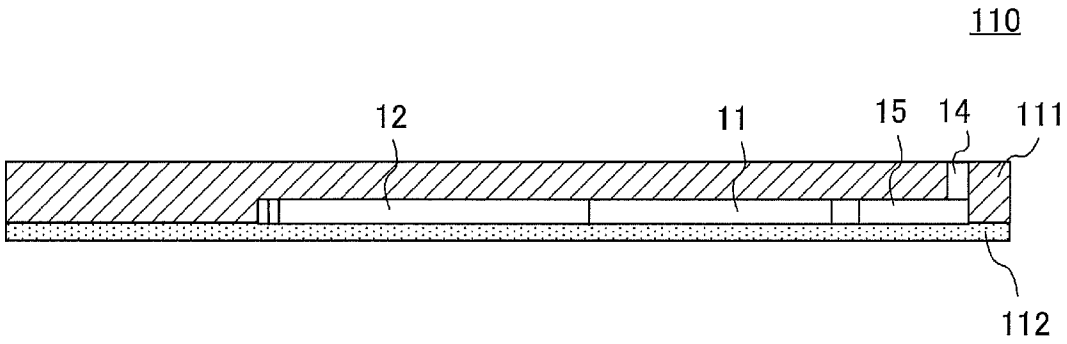
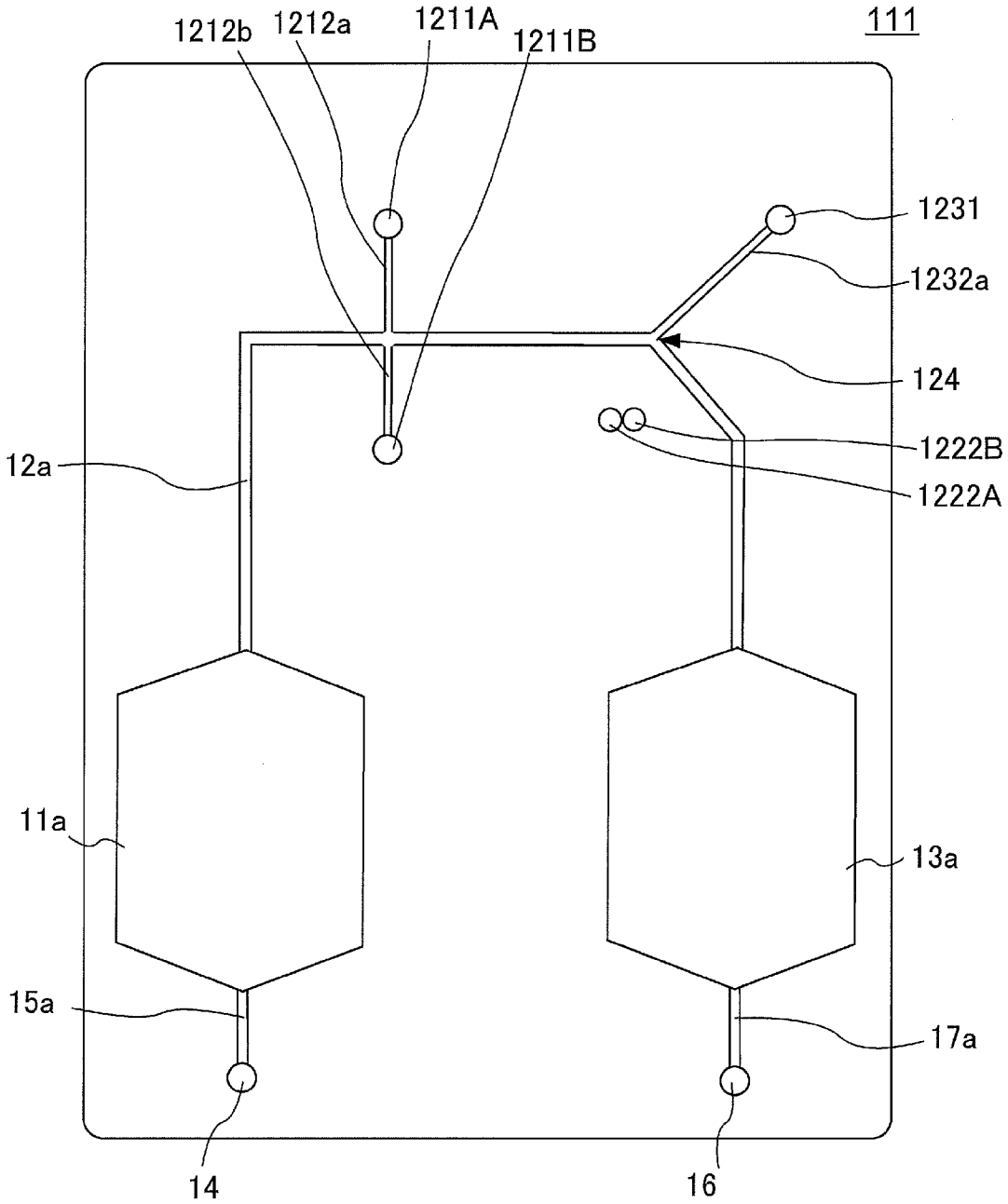


FIG. 2

[Fig. 3]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1211A
1211B
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16

FIG. 3

[Fig. 4]

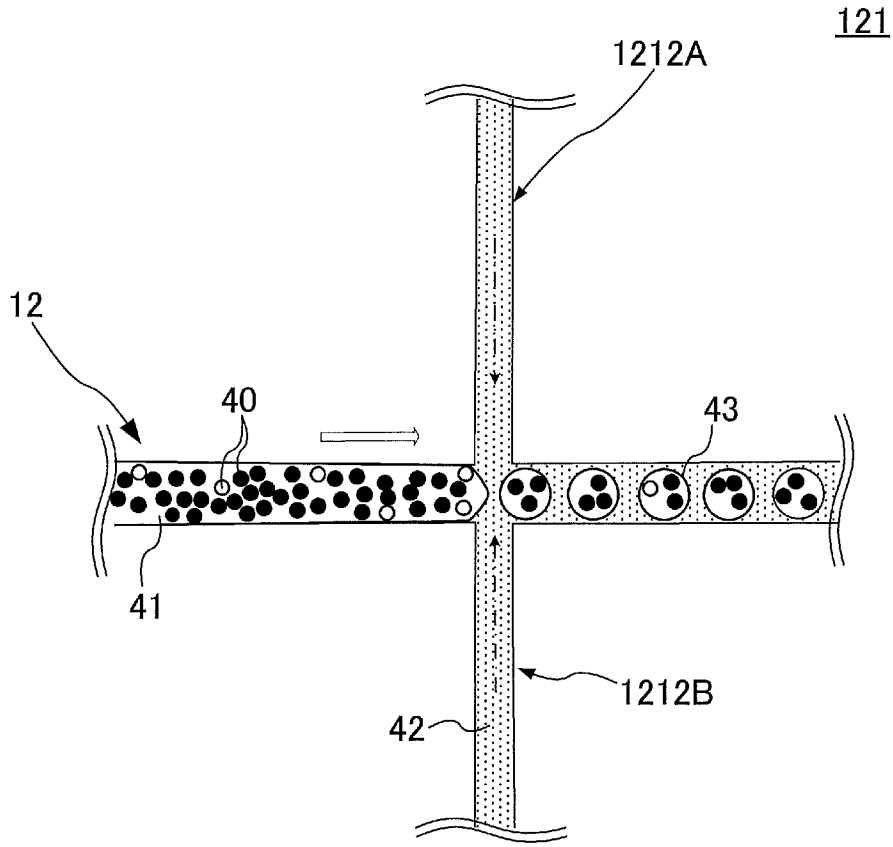


FIG. 4

[Fig. 5]

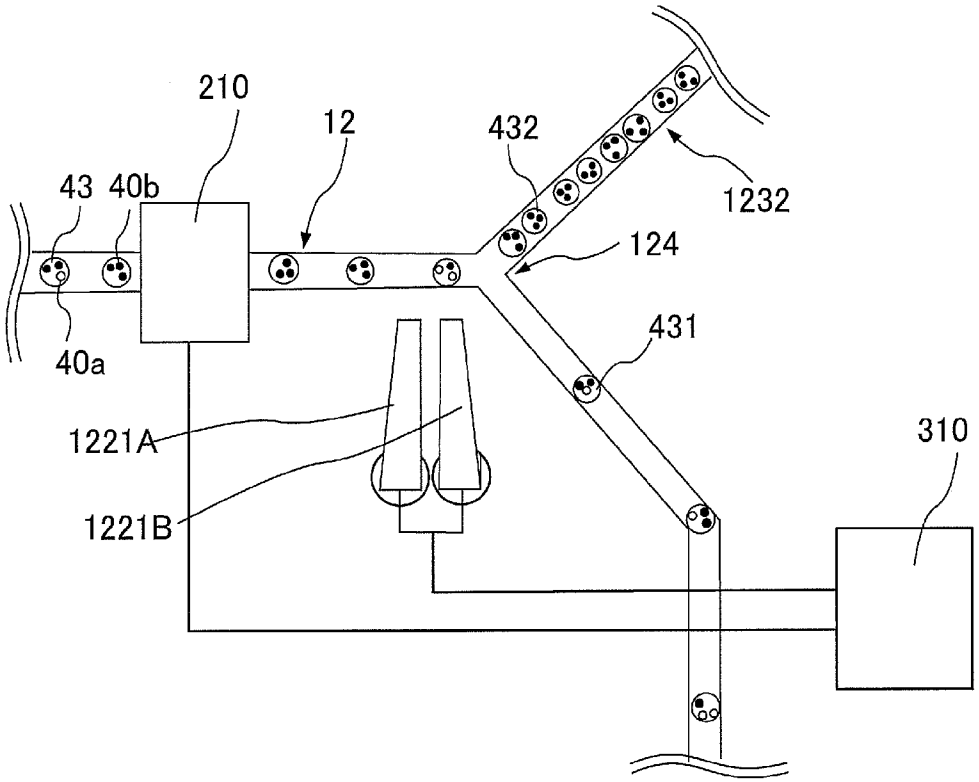
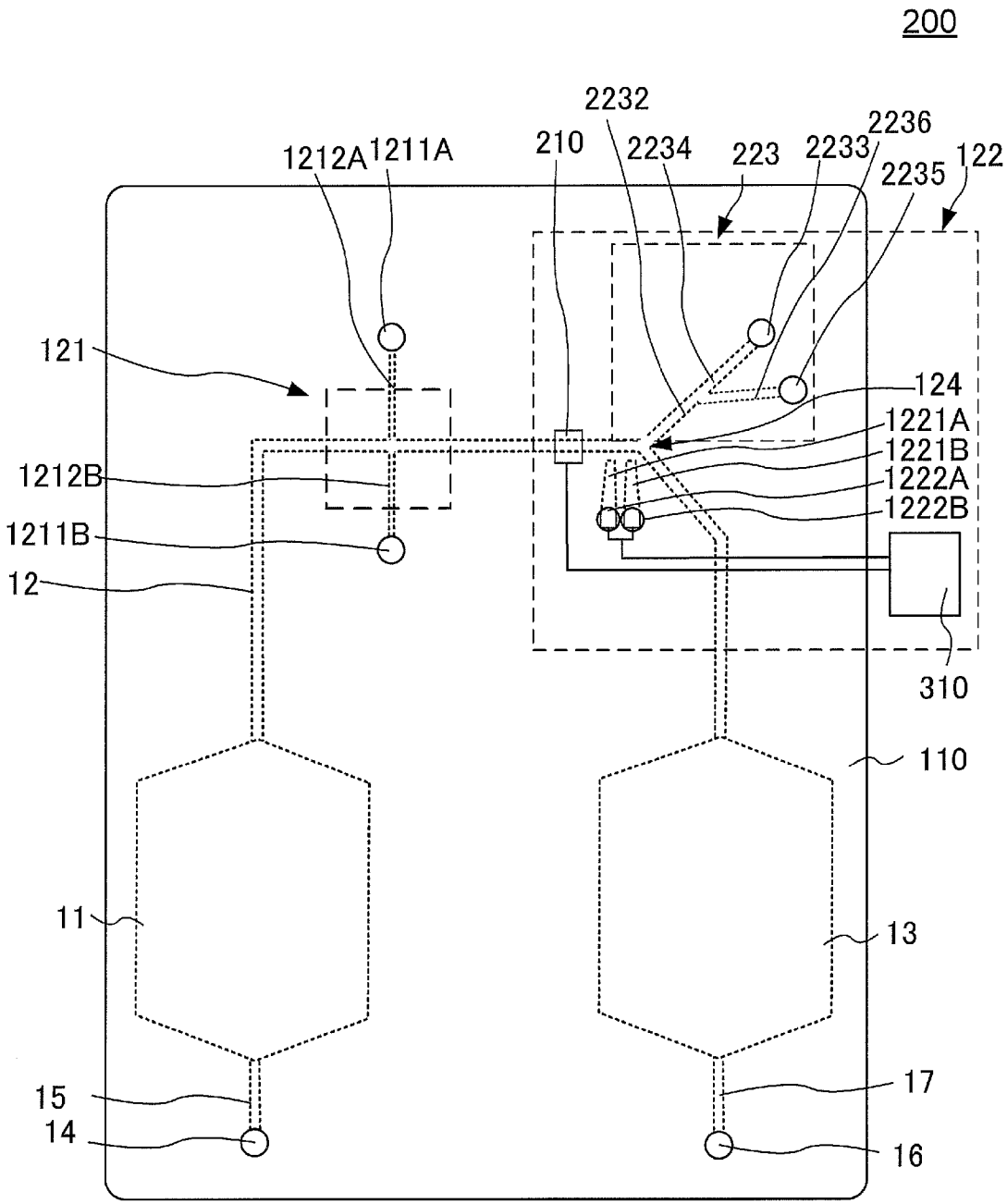


FIG. 5

[Fig. 6]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1212B
1211B
12
310
110
11
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14
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FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2019/009814

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L3/00
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

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

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Y	paragraphs [0006] - [0007], [0015] - [0039], [0043] - [0047], [0053] - [0060], [0064] - [0071], [0086]; figure 1A	1,2

X	US 2012/196288 A1 (BEER NEIL REGINALD [US]) 2 August 2012 (2012-08-02)	3,6
A	paragraphs [0022] - [0037]; figures 1-4, 5A-C	1

Y	US 2013/092539 A1 (POLLACK MICHAEL G [US] ET AL) 18 April 2013 (2013-04-18) paragraphs [0010], [0013] - [0023], [0045] - [0046], [0117], [0252], [0321], [0342] - [0371]; figures 6, 13-15	1,2

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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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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"&" 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 May 2019	10/05/2019

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Form PCT/ISA/210 (second sheet) (April 2005)

International application No
PCT/JP2019/009814

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
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