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Beckwith et al.

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(54) **MICROFLUIDIC TISSUE BIOPSY AND IMMUNE RESPONSE DRUG EVALUATION DEVICES AND SYSTEMS**

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C12M 1/32 (2006.01)
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CPC ***G01N 33/5008*** (2013.01); ***B01L 3/502761*** (2013.01); ***C12M 23/12*** (2013.01);
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(58) **Field of Classification Search**
CPC . C12M 23/16; C12M 23/12; B01L 3/502761; B01L 2300/0816;
(Continued)

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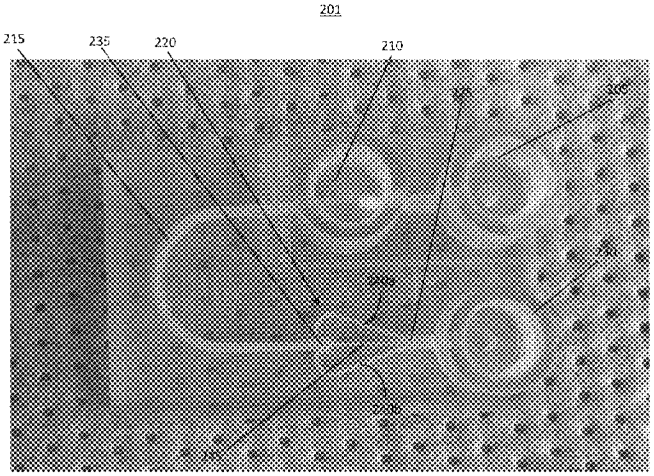
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

This disclosure describes microfluidic tissue biopsy and immune response drug evaluation devices and systems. A microfluidic device can include an inlet channel having a first end configured to receive a fluid sample optionally containing a tissue sample. The microfluidic device can also include a tissue trapping region at the second end of the inlet channel downstream from the first end. The tissue trapping region can include one or more tissue traps configured to catch a tissue sample flowing through the inlet channel such that the fluid sample contacts the tissue trap. The microfluidic device can also include one or more channels providing an outlet.

29 Claims, 17 Drawing Sheets



(51) **Int. Cl.**

B01L 3/00	(2006.01)
C12M 3/06	(2006.01)

(52) **U.S. Cl.**
CPC ***G01N 33/5082*** (2013.01); *B01L 2200/027* (2013.01); *B01L 2200/0668* (2013.01); *B01L 2200/0684* (2013.01); *B01L 2300/0816* (2013.01); *B01L 2300/0864* (2013.01); *B01L 2300/0877* (2013.01); *B01L 2300/0883* (2013.01); *B01L 2400/0463* (2013.01); *B01L 2400/0487* (2013.01); *B01L 2400/086* (2013.01); *C12M 23/16* (2013.01)

(58) **Field of Classification Search**
CPC B01L 2300/0864; B01L 2300/0883; B01L 2300/0877; B01L 2200/0668; B01L 2200/0684; B01L 2400/0463; B01L 2400/0487; B01L 2400/086; G01N 33/5008; G01N 33/5082
See application file for complete search history.

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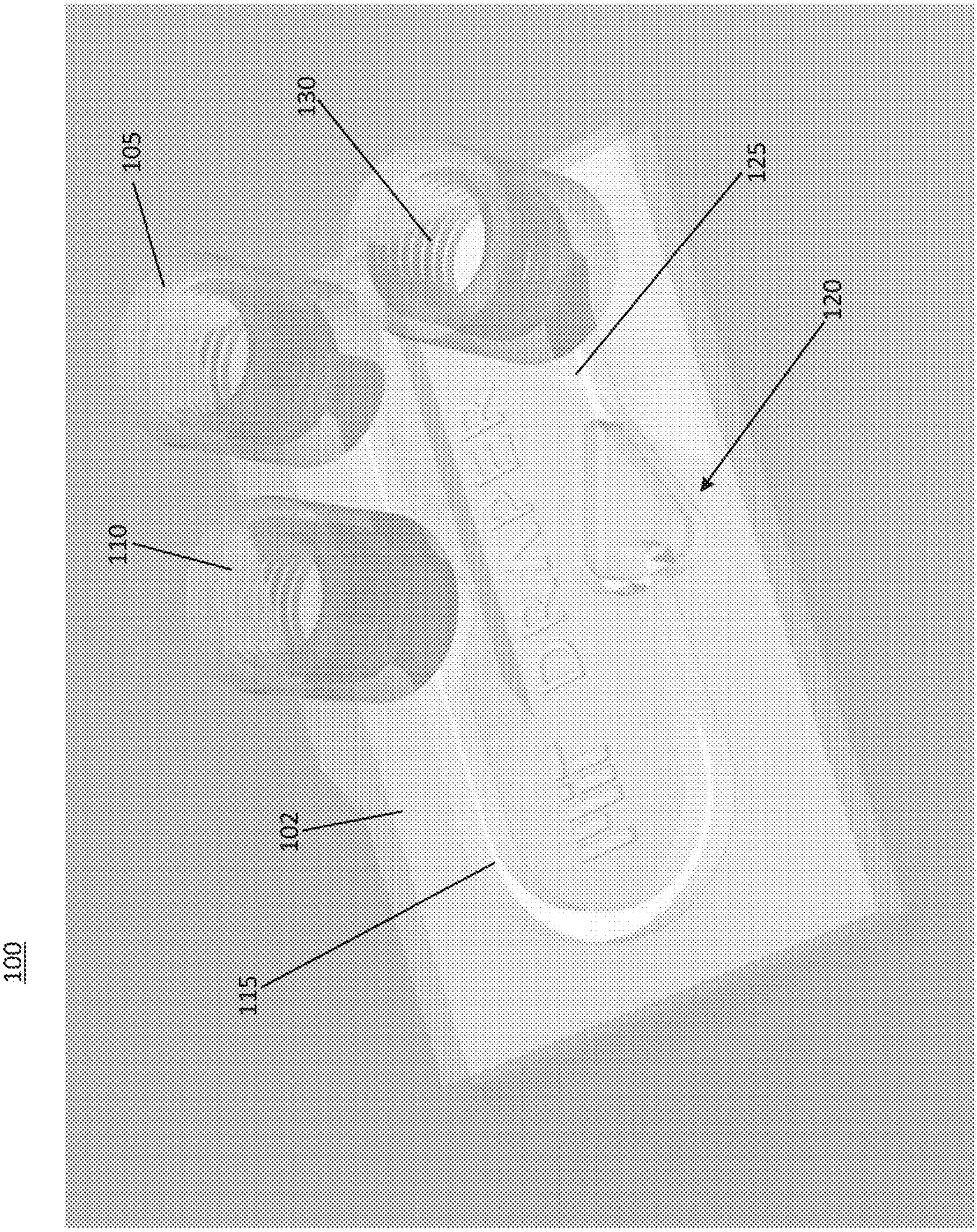

FIG. 1A

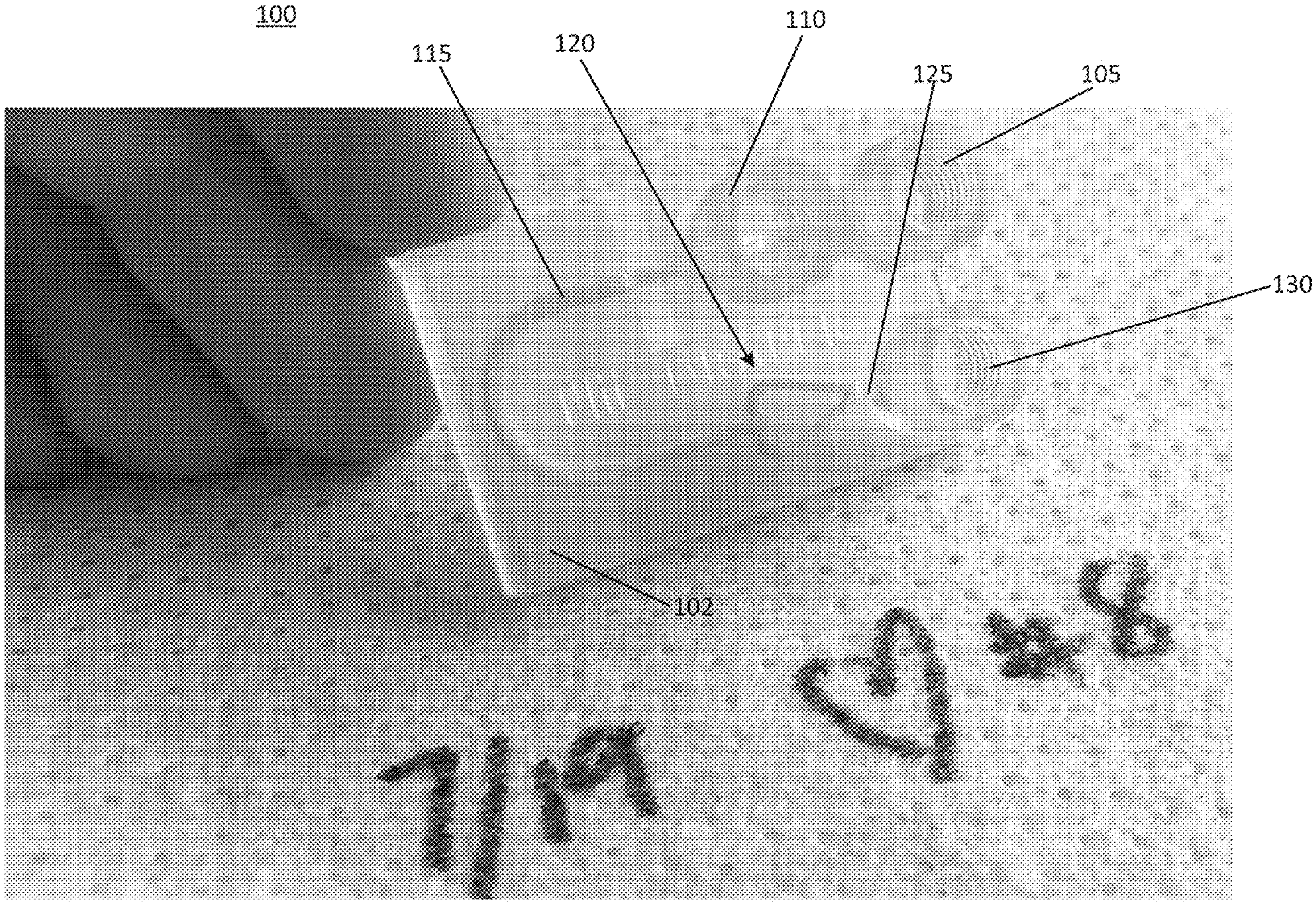

FIG. 1B

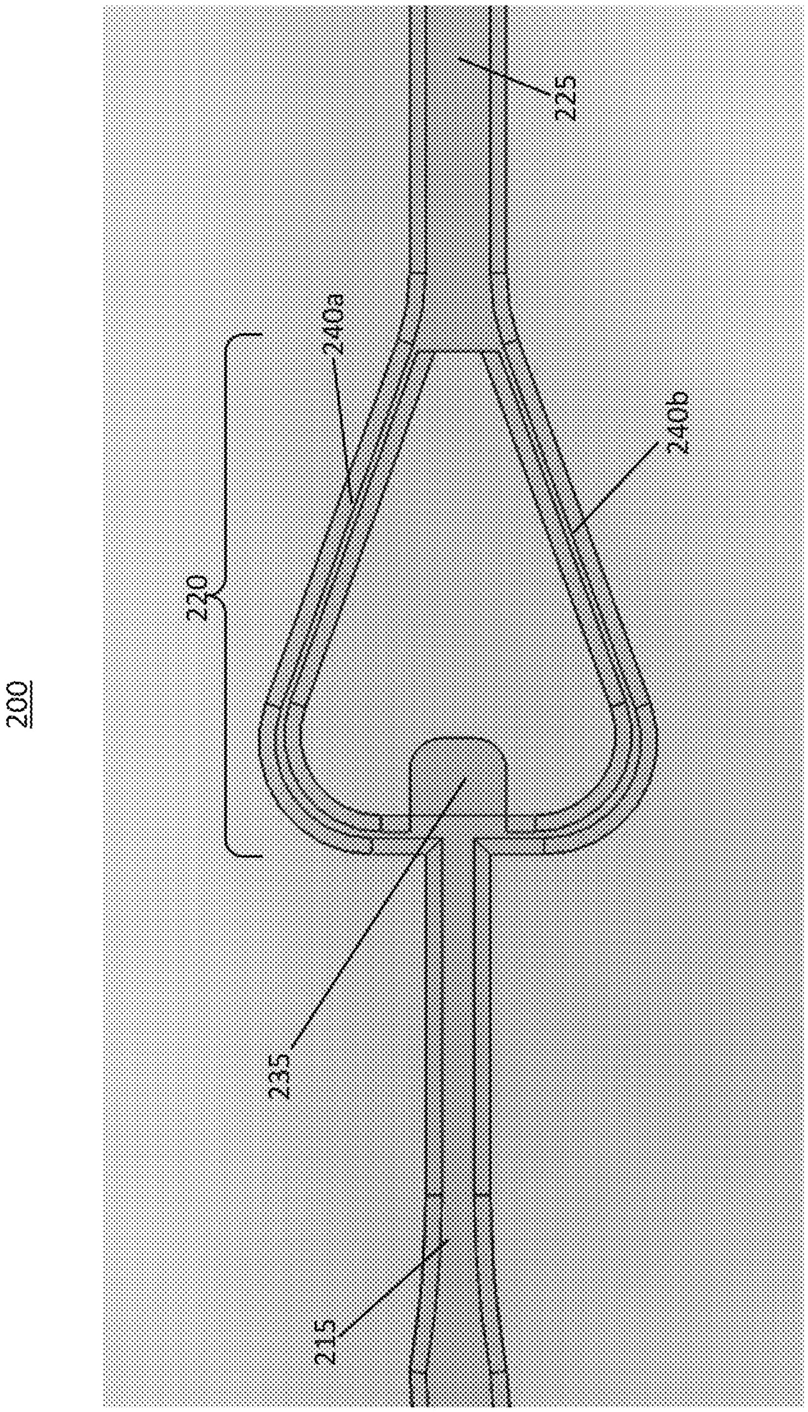

FIG. 2A

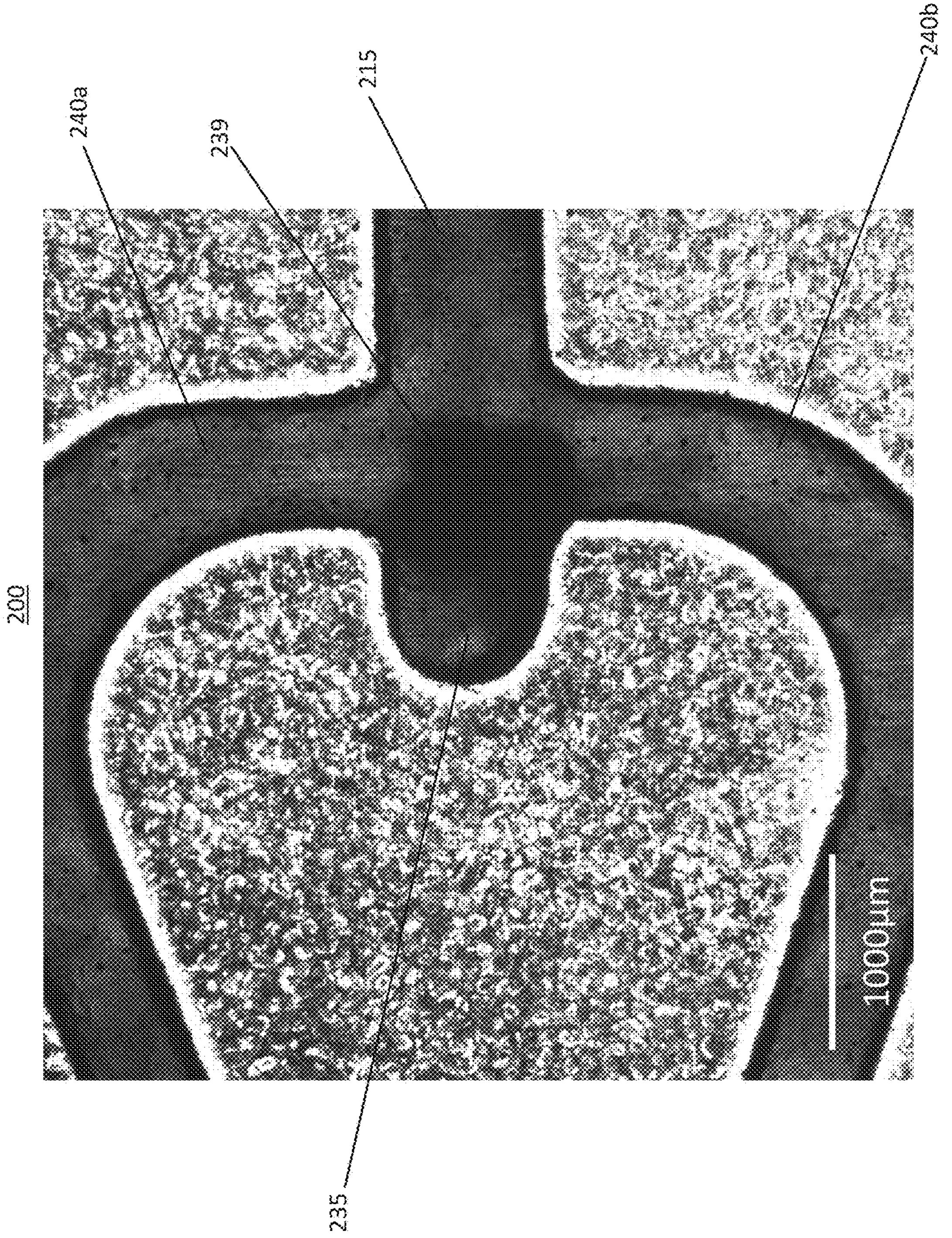

FIG. 2B

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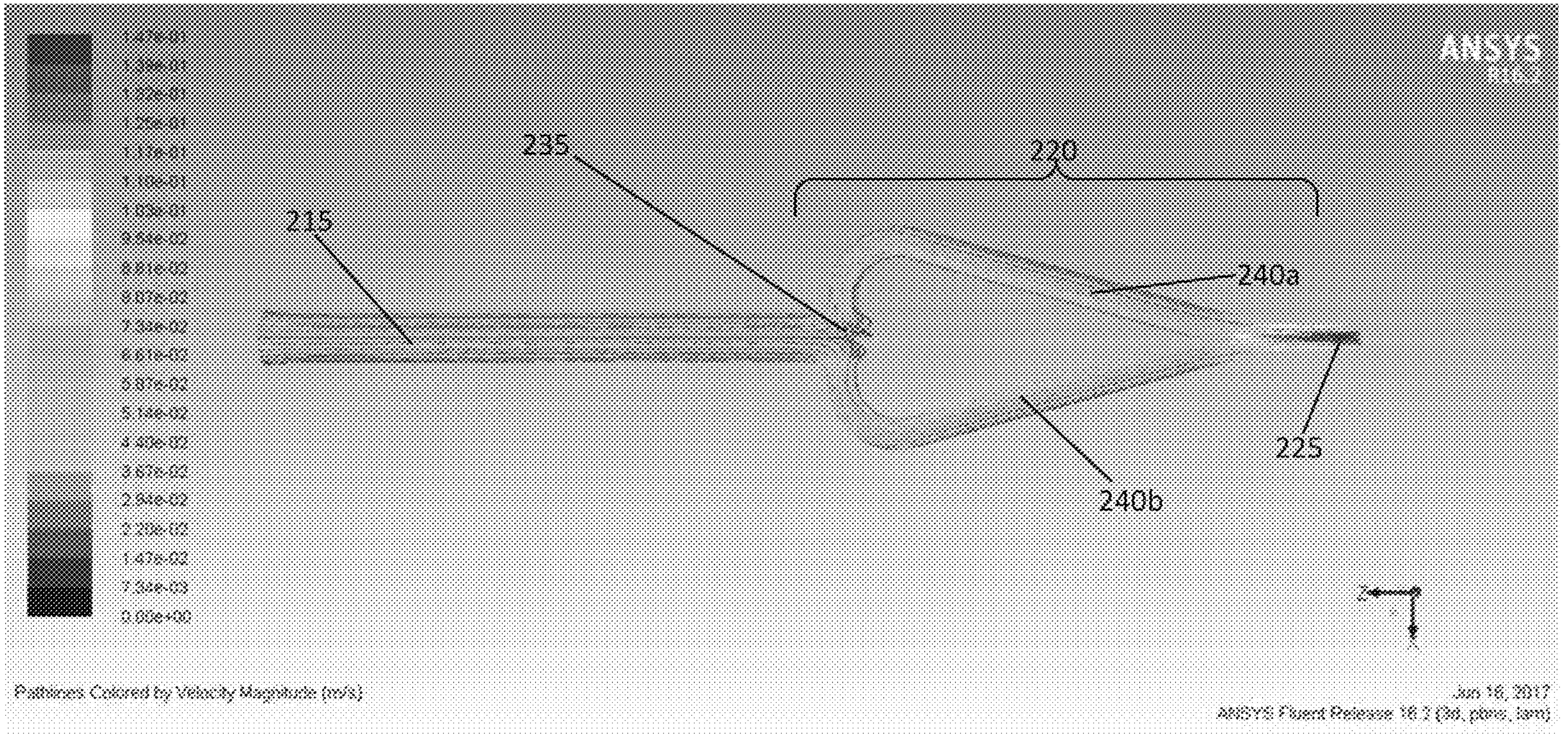
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FIG. 2C

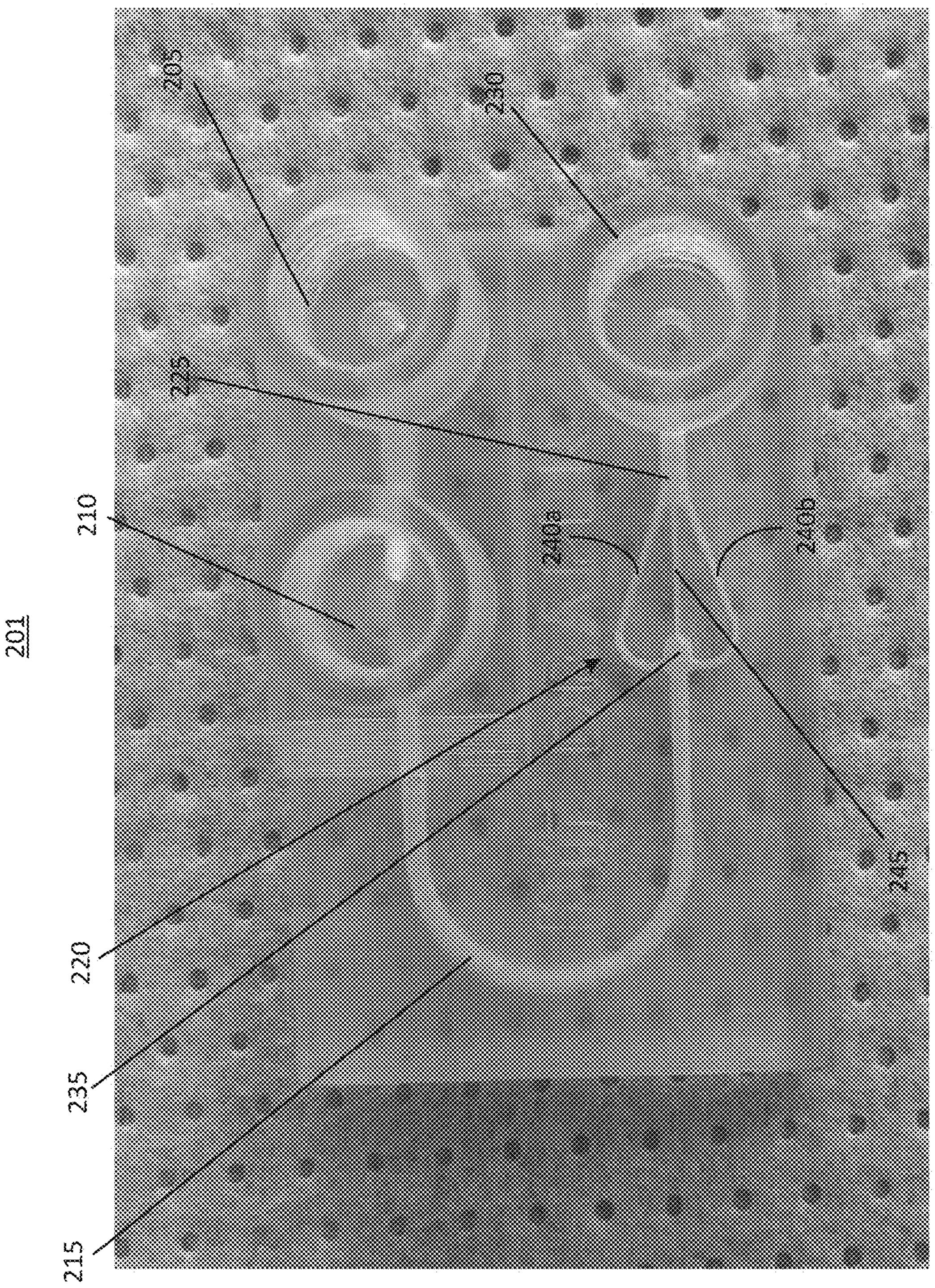
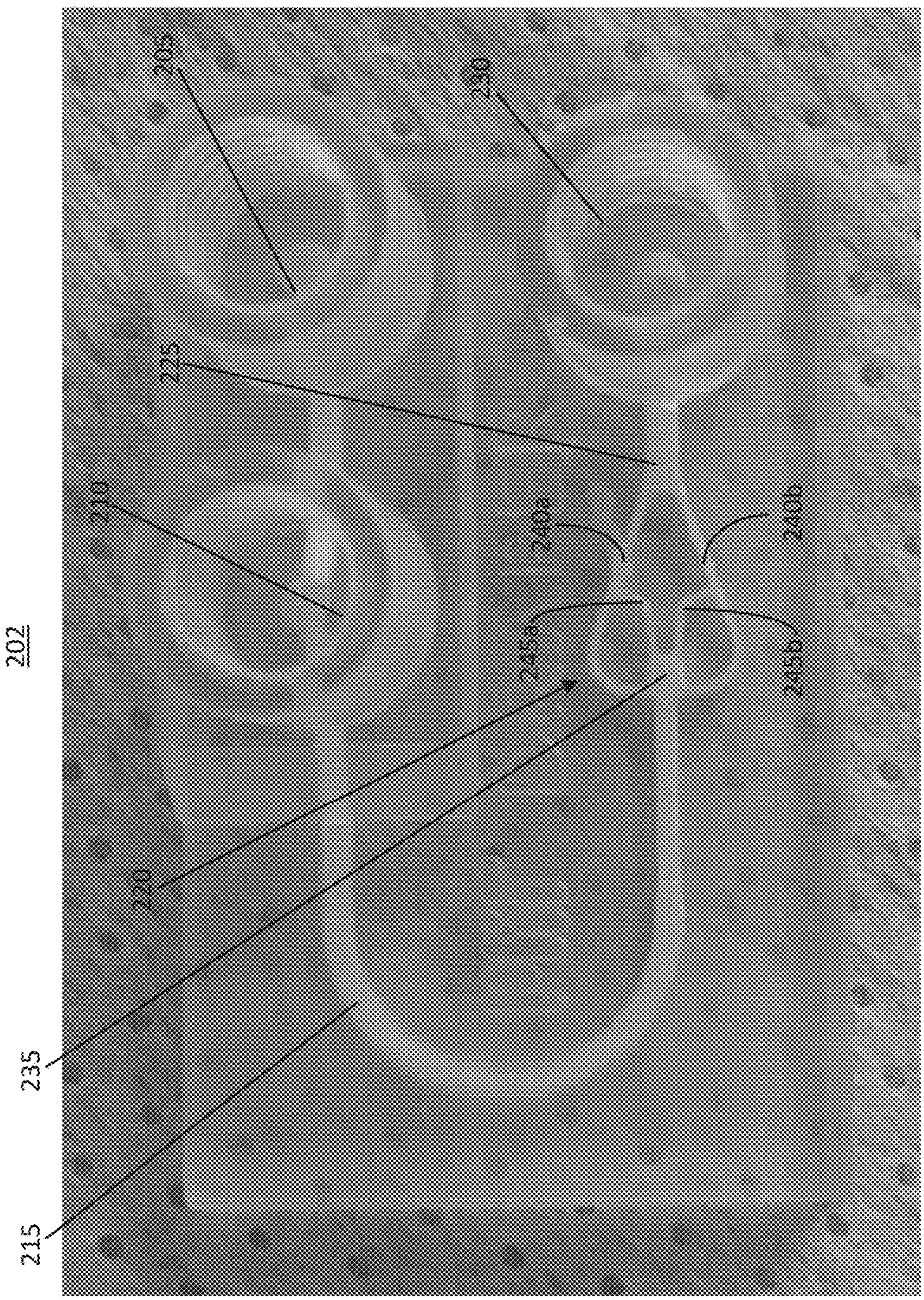


FIG. 2D



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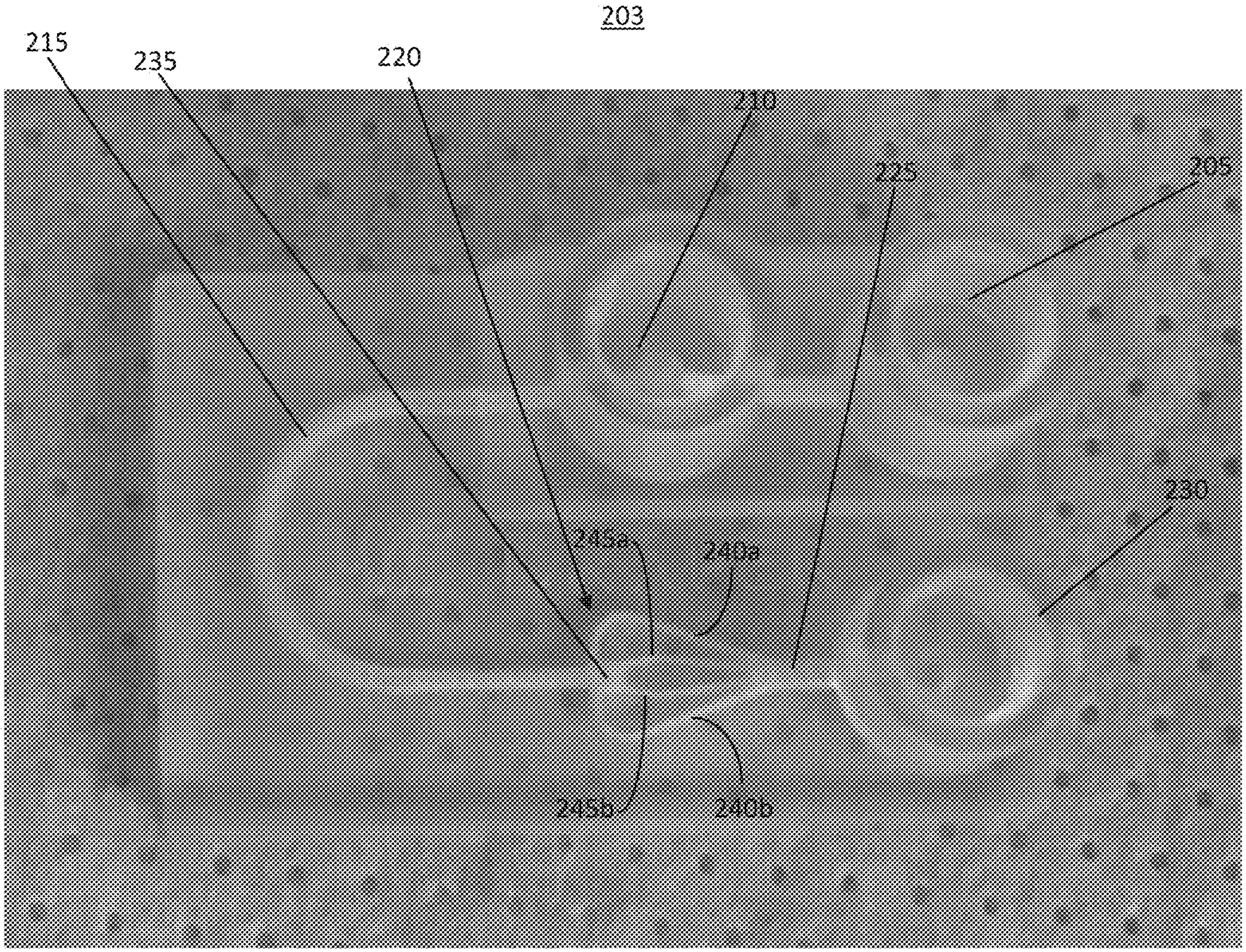

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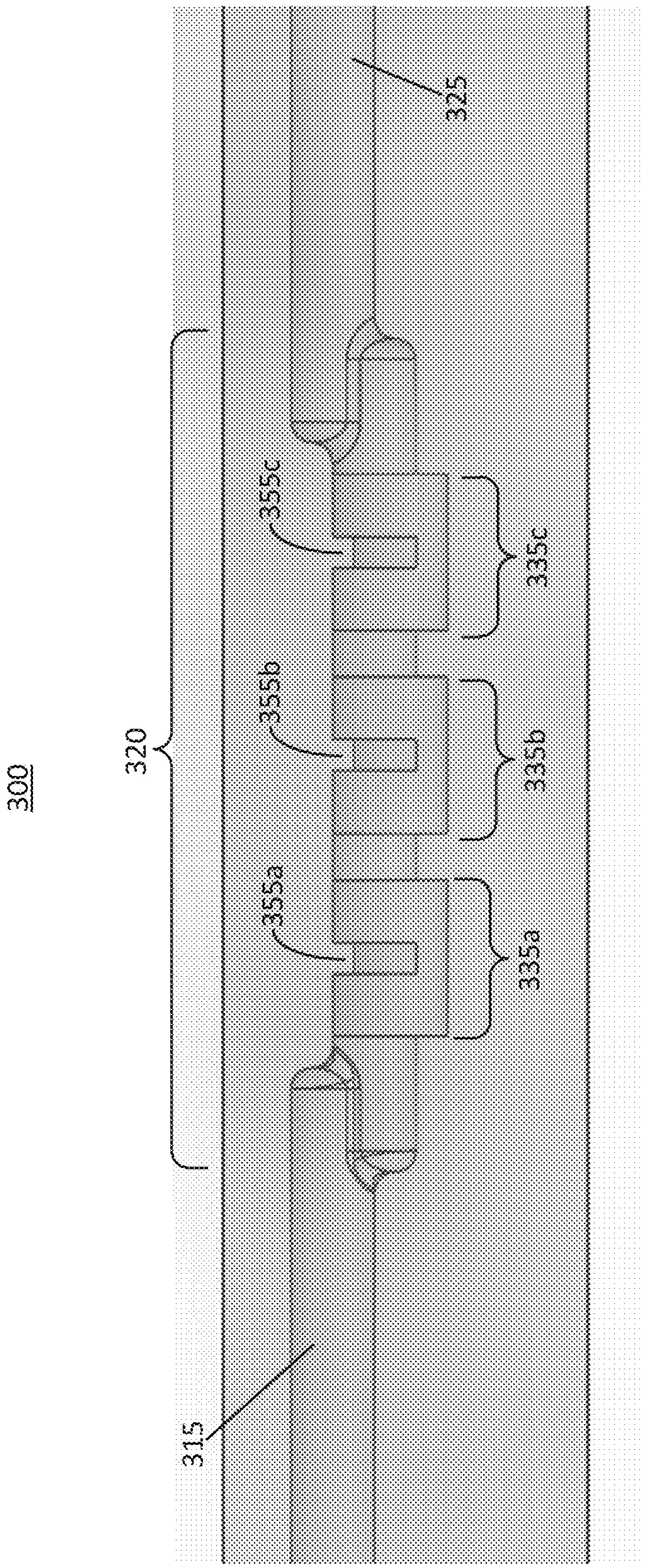

FIG. 3A

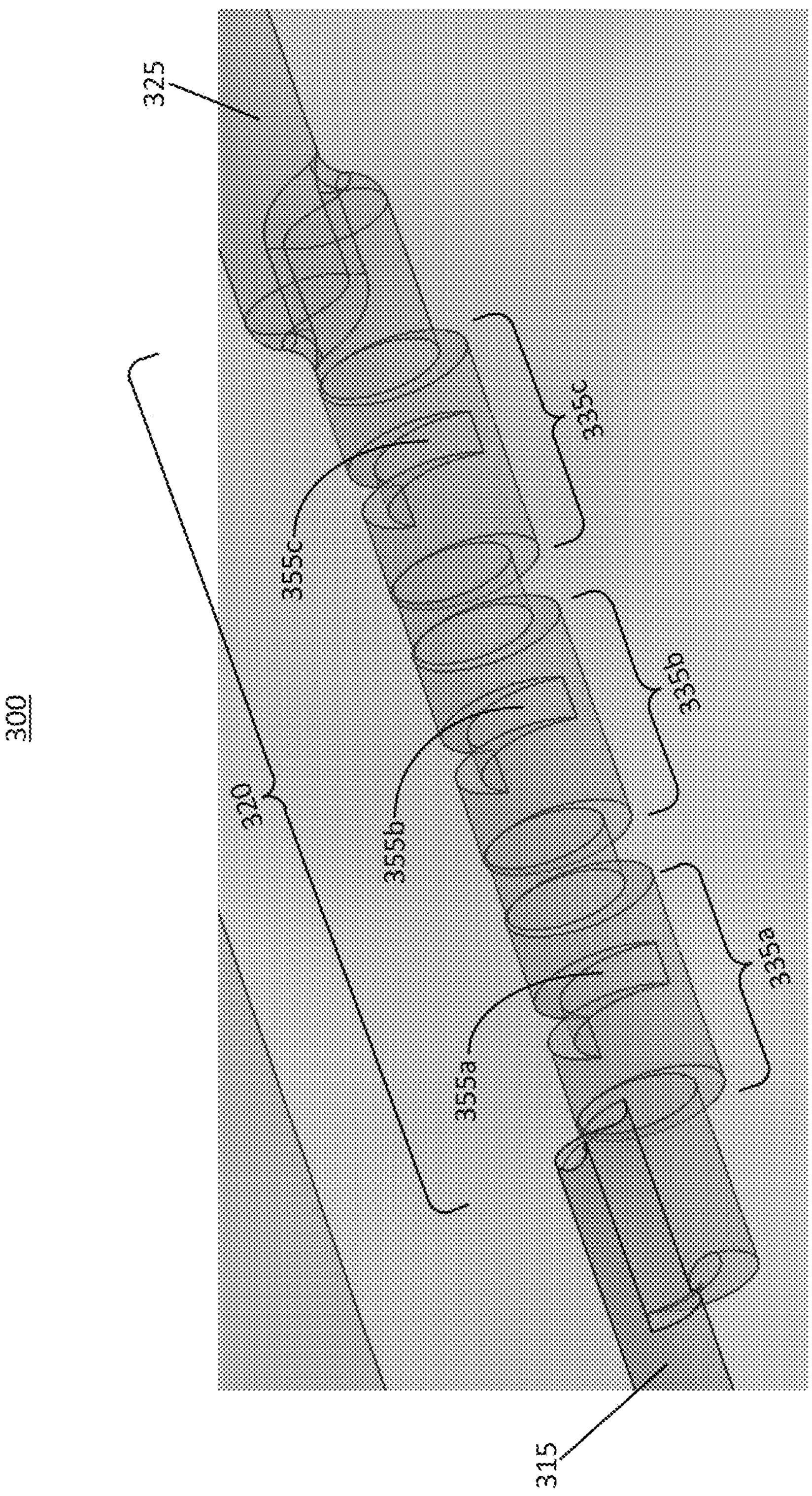

FIG. 3B

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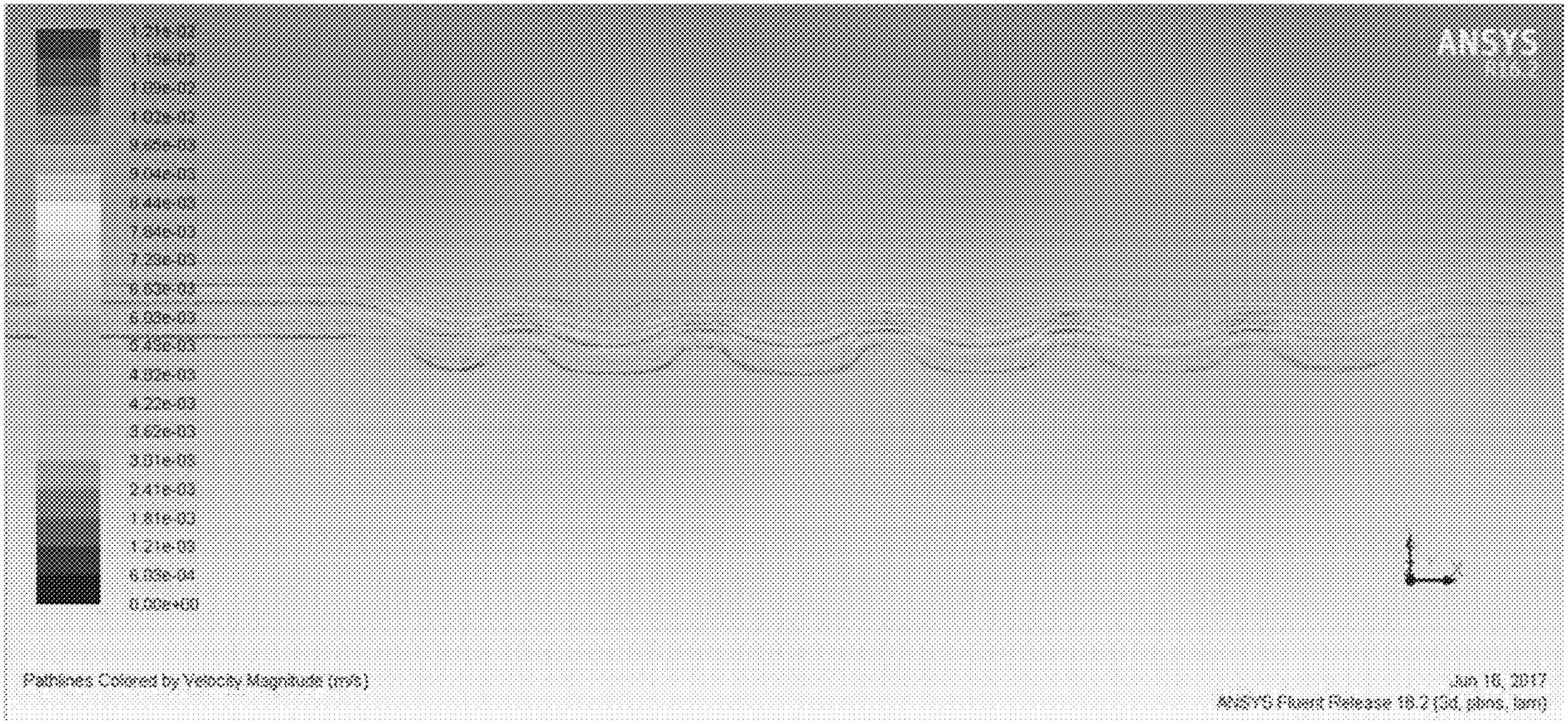
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FIG. 3C

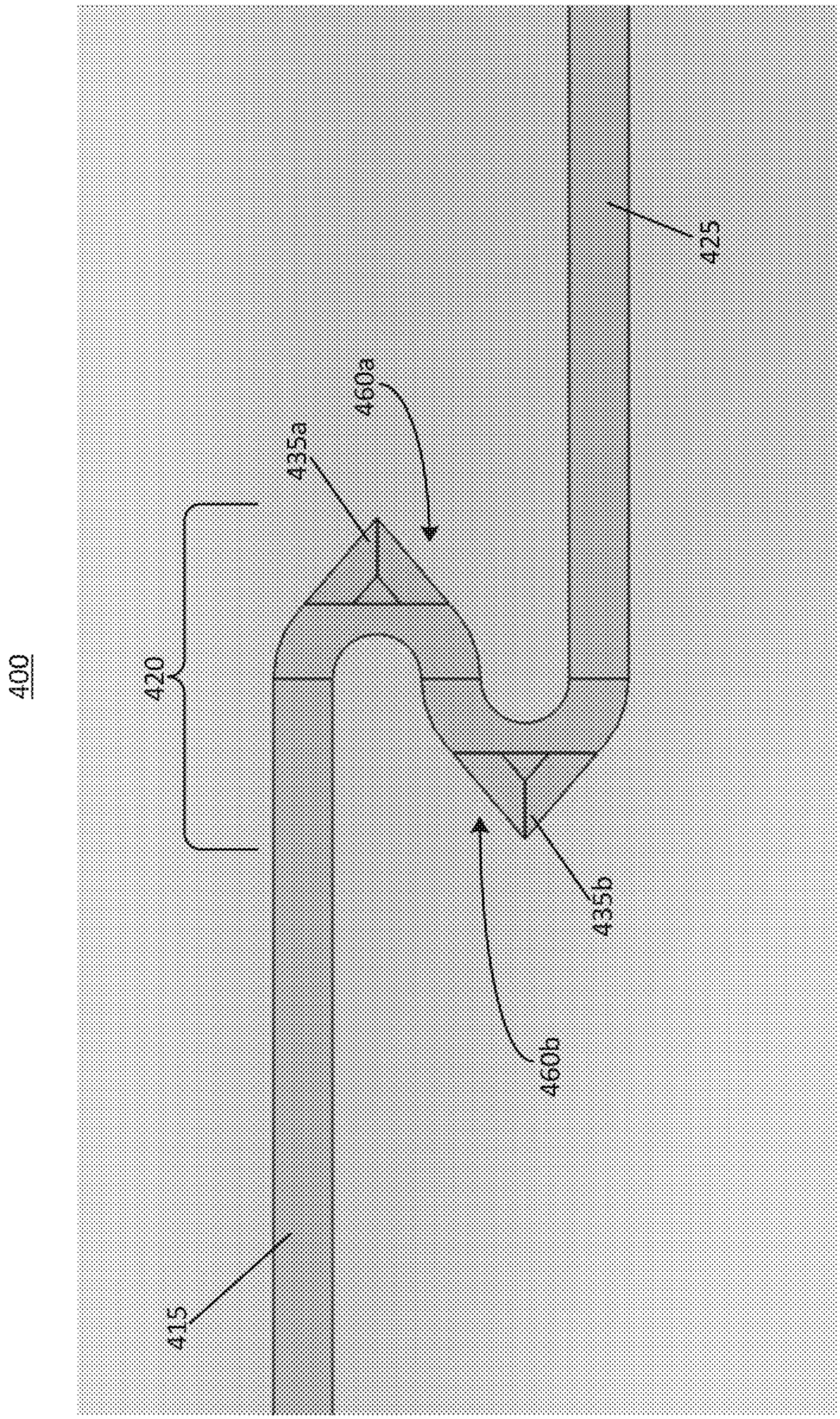

FIG. 4A

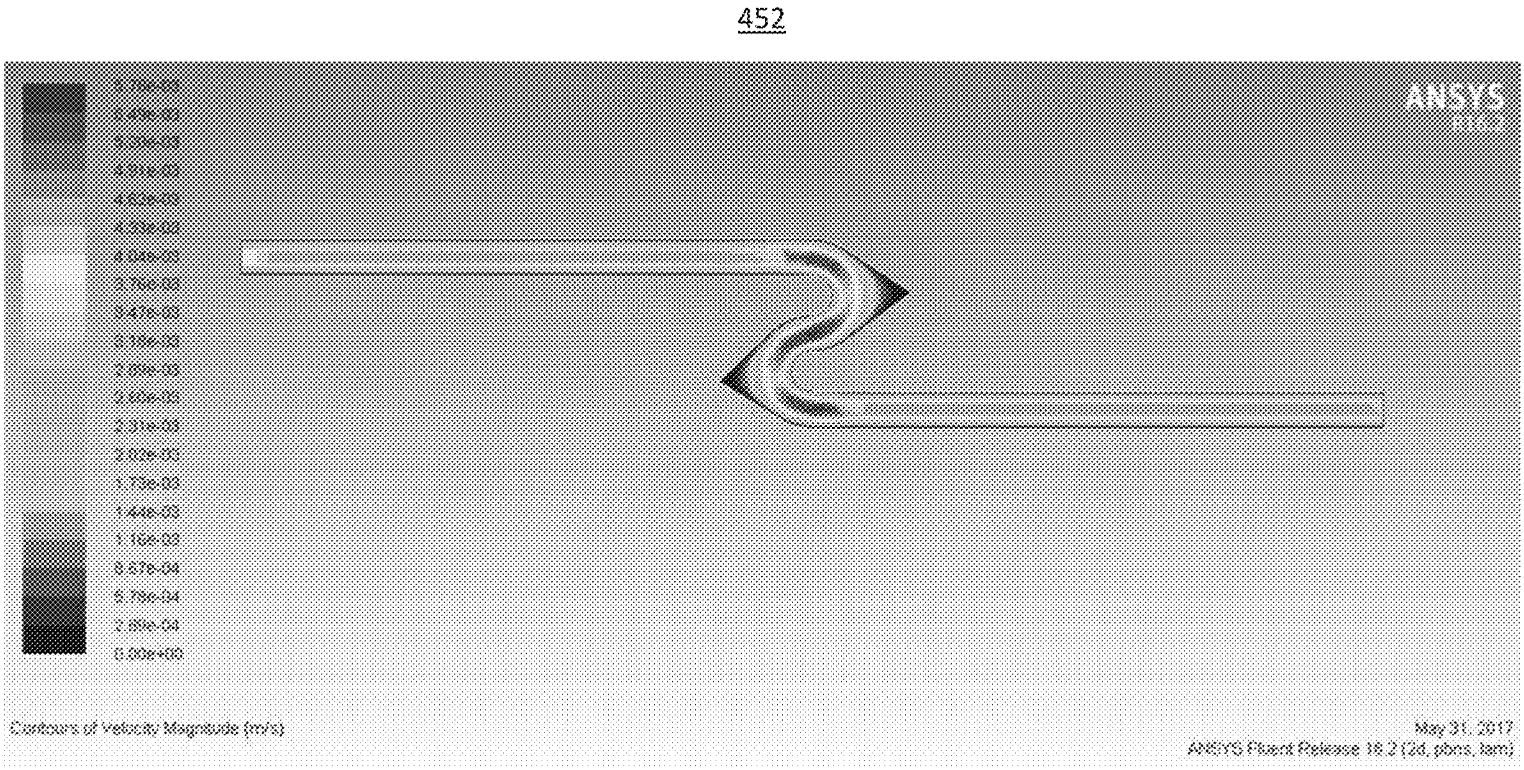
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FIG. 4B

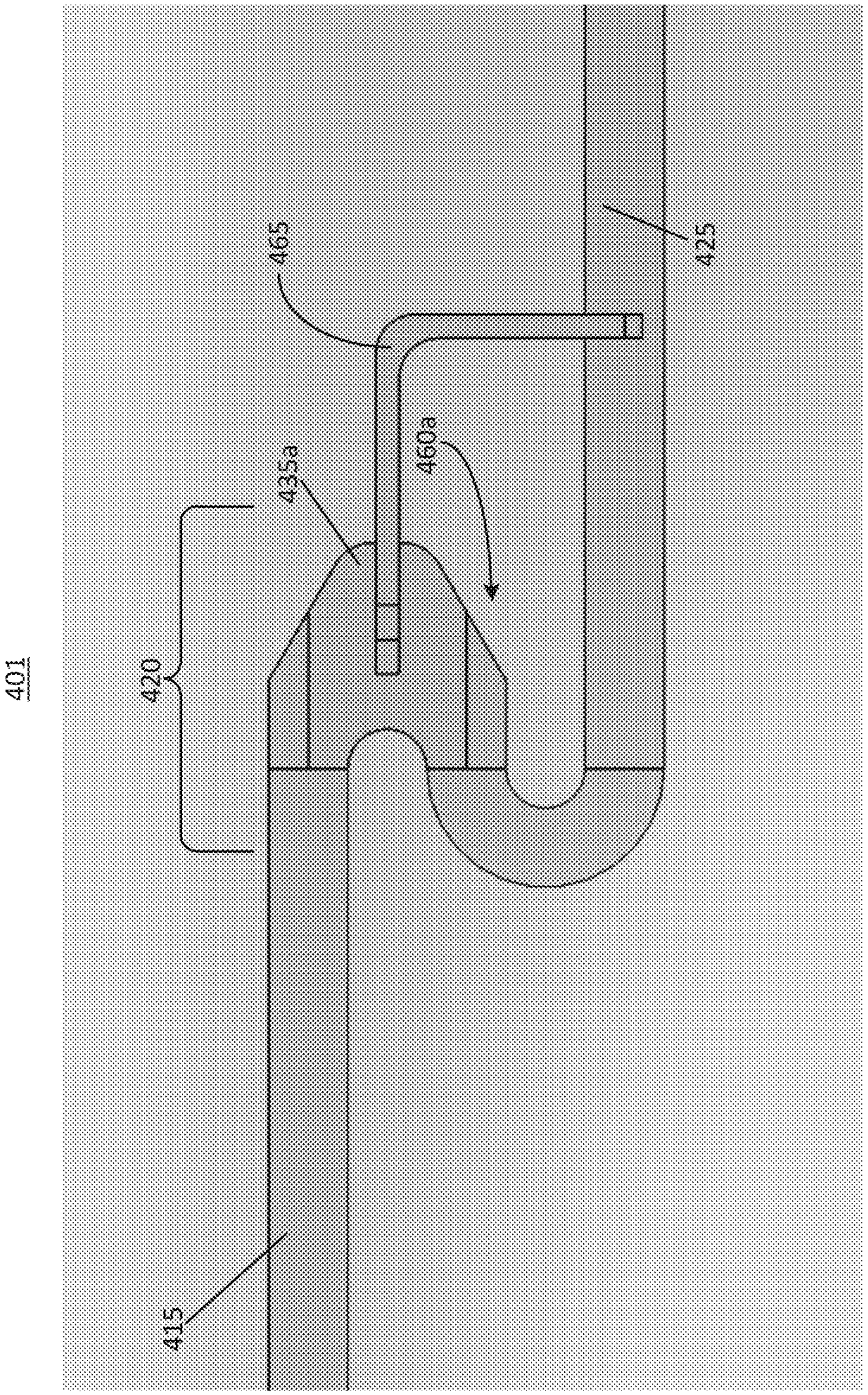

FIG. 4C

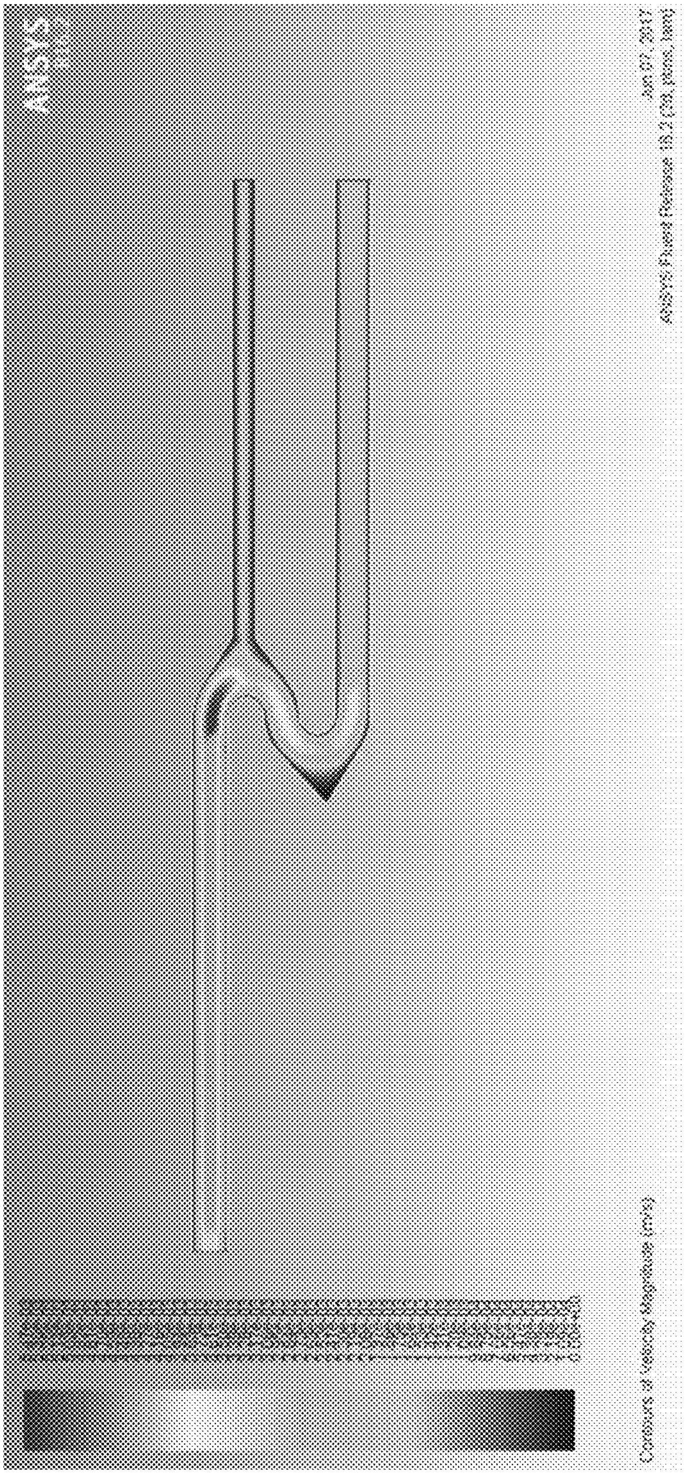
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FIG. 4D

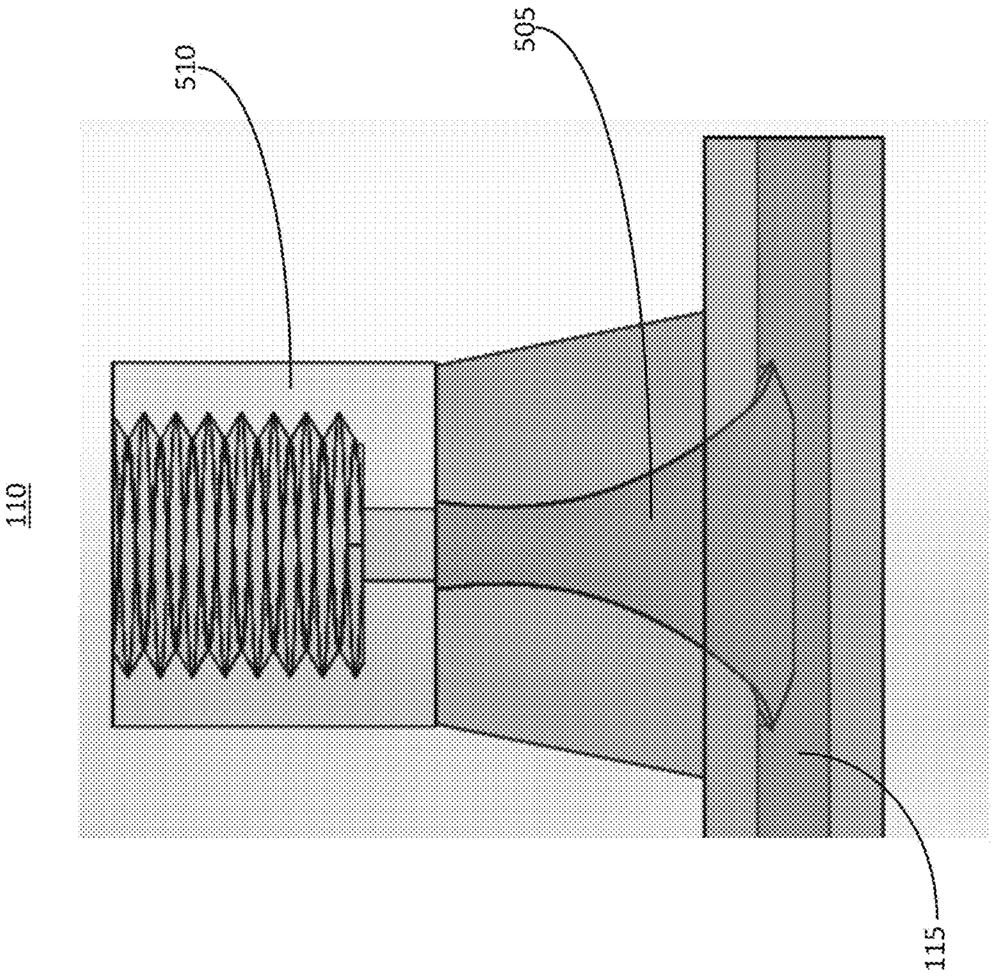

FIG. 5

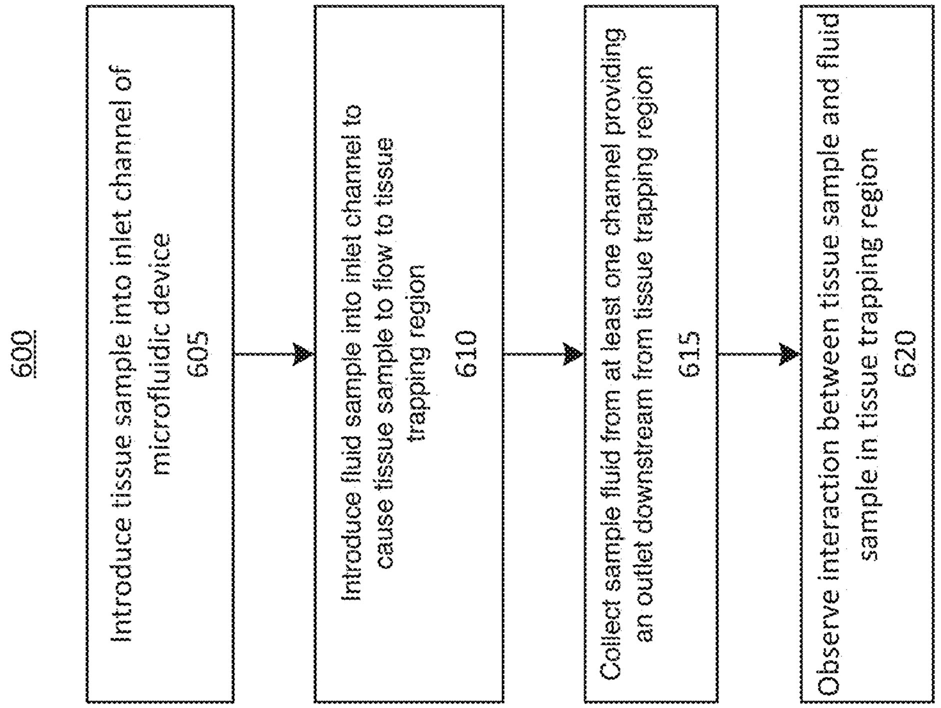
600
Introduce tissue sample into inlet channel of microfluidic device
605
Introduce fluid sample into inlet channel to cause tissue sample to flow to tissue trapping region
610
Collect sample fluid from at least one channel providing an outlet downstream from tissue trapping region
615
Observe interaction between tissue sample and fluid sample in tissue trapping region
620

FIG. 6

MICROFLUIDIC TISSUE BIOPSY AND IMMUNE RESPONSE DRUG EVALUATION DEVICES AND SYSTEMS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent Application 62/552,264, filed Aug. 30, 2017 and titled "MICROFLUIDIC TISSUE BIOPSY AND IMMUNE RESPONSE DRUG EVALUATION DEVICES AND SYSTEMS," and to U.S. Provisional Patent Application 62/581,667, filed Nov. 4, 2017 and titled "MICROFLUIDIC TISSUE BIOPSY AND IMMUNE RESPONSE DRUG EVALUATION DEVICES AND SYSTEMS," each of which is incorporated herein by reference in its entirety.

BACKGROUND

Current technology for simulating dynamic processes involving interactions between mammalian tissue samples and cells is gated by the inability to recapitulate the tissue microenvironment and interactions between tissues, therapeutic compounds and the host immune system.

SUMMARY

One aspect of this disclosure is directed to microfluidic device comprising including a substrate. The substrate defines an inlet channel having a first end configured to receive a fluid sample optionally containing a tissue sample. The substrate defines a tissue trapping region at the second end of the inlet channel downstream from the first end. The tissue trapping region includes one or more tissue traps configured to catch a tissue sample flowing through the inlet channel such that the fluid sample contacts the tissue trap. The substrate also defines one or more channels providing an outlet.

In some implementations, at least one of the one or more tissue traps comprises an arrangement of one or more walls. In some implementations, the one or more channels providing the outlet include one or more branch channels connecting to the second end of the inlet channel where the second end of the inlet channel and the tissue trapping region converge. In some implementations, the convergence of the second end of the inlet channel and the tissue trapping region further includes a first branch channel coupled to the second end of the inlet channel at a first junction and configured to direct a first portion of the fluid sample in a first direction, and a second branch channel coupled to the second end of the inlet channel at the first junction and configured to direct a second portion of the fluid sample in a second direction, different form the first direction, wherein the tissue trap is positioned at the first junction.

In some implementations, the one or more channels providing the outlet further include one or more suction channels downstream of the one or more tissue traps and configured to hold the tissue sample in place within the one or more tissue traps. In some implementations, at least one of the one or more tissue traps includes a bottom surface positioned at a lower depth than a bottom surface of the inlet channel. In some implementations, the first branch channel and the second branch channel converge at a second junction downstream from the one or more tissue traps.

In some implementations, the microfluidic device further includes a first suction channel coupling at least one of the one or more tissue traps to the first branch channel at a third junction downstream from the second end of the inlet channel. The microfluidic device can also include a second suction channel coupling the at least one of the one or more tissue traps to the second branch channel at a fourth junction downstream from the second end of the inlet channel. In some implementations, a diameter of at least one of the one or more the tissue traps is about twice that of the inlet channel.

In some implementations, the tissue trapping region includes a ribbed channel coupling the inlet channel to the one or more channels providing the outlet. In some implementations, at least one of the one or more tissue traps can be defined by sidewalls of ribs of the ribbed channel and a bottom wall positioned at a lowest depth of the ribbed channel. In some implementations, the at least one tissue trap can further include at least a second tissue trap and a third tissue trap.

In some implementations, the tissue trapping region can include a circuitous channel having a first curved portion coupled to the second end of the inlet channel. The microfluidic device can also include at least one of the one or more tissue traps positioned at a center of the first curved portion such that the fluid sample flows along the first curved portion past the tissue trap. In some implementations, the one or more channels providing the outlet channel can include a suction channel coupling to the at least one of the one or more tissue traps and configured to carry the fluid sample downstream from the at least one of the one or more tissue traps. In some implementations, the circuitous channel can further include a second curved portion coupled to a downstream end of the first curved portion and a second tissue trap positioned at a center of the second curved portion such that the fluid sample flows along the second curved portion past the second tissue trap. In some implementations, a downstream end of the second curved portion is coupled to the one or more channels providing the outlet.

In some implementations, the microfluidic device can also include an inlet port coupled to the first end of the inlet channel and configured to deliver the fluid sample to the inlet channel. In some implementations, the inlet port can include a first threaded connector configured for attachment to a fluid line.

In some implementations, the microfluidic device can also include a bubble trapping structure coupled to the inlet channel downstream from the inlet port. The bubble trapping structure can be configured to facilitate evacuation of air bubbles from the fluid sample. In some implementations, a surface of the bubble trapping structure can have a shape defined by a parabolic function. In some implementations, the bubble trapping structure can further include a second threaded connector configured for attachment to an air release line.

In some implementations, the microfluidic device can also include an outlet port coupled to the at least one of the one or more channels providing the outlet and configured to remove the fluid sample from the microfluidic device. In some implementations, the substrate can be formed from a biocompatible material. In some implementations, the substrate can be formed from an optically transparent material, and the microfluidic device can further include an optical interface providing optical access to the tissue sample positioned within the tissue trapping region. In some implementations, the one or more tissue traps can be configured to entrain the tissue sample in place within the one or more tissue traps.

Another aspect of this disclosure is directed to a method for evaluating an interaction between a tissue sample and a fluid sample. The method can include introducing a tissue sample into a first end of an inlet channel of a microfluidic device. The method can include introducing a fluid sample into the first end of the inlet channel to cause the tissue sample to flow to a tissue trapping region at a second end of the inlet channel downstream from the first end. The tissue trapping region can include a tissue trap configured to catch the tissue sample such that at least a portion of the fluid sample contacts the tissue sample. The method can include collecting the sample fluid from at least one channel providing an outlet downstream from the tissue trapping region.

In some implementations, the method can include priming the inlet channel with fluid prior to introducing the tissue sample into the first end of the inlet channel. In some implementations, the method can include observing an interaction between the tissue sample and the fluid sample in the tissue trapping region. In some implementations, the microfluidic device can be formed from a transparent material, and observing the interaction between the tissue sample and the fluid sample can further include positioning a lens of a microscope in proximity to the microfluidic device.

In some implementations, the tissue trap can be configured to secure the tissue sample without damaging the tissue sample. In some implementations, the method can include introducing the tissue sample via a bubble trapping structure coupled to the inlet channel, and introducing the fluid sample via an inlet port coupled to the inlet channel. The inlet port can be upstream from the bubble trapping structure. In some implementations, the method can include removing air from the fluid sample via the bubble trapping structure.

In some implementations, the method can include releasing the tissue sample from the tissue trap by introducing a second fluid sample into at least one of the one or more channels configured to provide the outlet such that the second fluid sample flows towards the inlet channel.

In some implementations, after collecting the sample fluid at least one of the one or more channels configured to provide the outlet downstream from the tissue trapping region, the method can include reintroducing the collected sample fluid into the inlet channel of the microfluidic device.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are not intended to be drawn to scale. Like reference numbers and designations in the various drawings indicate like elements. For purposes of clarity, not every component may be labeled in every drawing.

FIG. **1**A illustrates a perspective view of an example microfluidic device, according to an illustrative implementation.

FIG. **1**B illustrates a second perspective view of the example microfluidic device of FIG. **1**A, according to an illustrative implementation.

FIG. **2**A illustrates a cross-sectional view of a portion of an example microfluidic device that can be used to implement the microfluidic device of FIG. **1**A, according to an illustrative implementation.

FIG. **2**B illustrates a tissue sample within the microfluidic device of FIG. **2**A, according to an illustrative implementation.

FIG. **2**C is a visual depiction of the flow characteristics of the microfluidic device of FIG. **2**A, according to an illustrative implementation.

FIG. **2**D illustrates a first arrangement of the microfluidic device of FIG. **2**A having suction channels, according to an illustrative implementation.

FIG. **2**E illustrates a second arrangement of the microfluidic device of FIG. **2**A having suction channels, according to an illustrative implementation.

FIG. **2**F illustrates a third arrangement of the microfluidic device of FIG. **2**A having suction channels, according to an illustrative implementation.

FIG. **3**A illustrates a cross-sectional view of a portion of an example microfluidic device that can be used to implement the microfluidic device of FIG. **1**A, according to an illustrative implementation.

FIG. **3**B illustrates a perspective view of the portion of the microfluidic device shown in FIG. **3**A, according to an illustrative implementation.

FIG. **3**C is a visual depiction of the flow characteristics of the microfluidic device of FIG. **3**A, according to an illustrative implementation.

FIG. **4**A illustrates a cross-sectional view of a portion of an example microfluidic device that can be used to implement the microfluidic device of FIG. **1**A, according to an illustrative implementation.

FIG. **4**B is a visual depiction of the flow characteristics of the microfluidic device of FIG. **4**A, according to an illustrative implementation.

FIG. **4**C illustrates a first arrangement of the microfluidic device of FIG. **4**A having suction channels, according to an illustrative implementation.

FIG. **4**D is a visual depiction of the flow characteristics of the microfluidic device of FIG. **4**C, according to an illustrative implementation.

FIG. **5** illustrates a bubble trapping structure that can be included in the microfluidic device of FIG. **1**A, according to an illustrative implementation.

FIG. **6** illustrates a flowchart of a method for evaluating an interaction between a tissue sample and a fluid sample, according to an illustrative implementation.

DETAILED DESCRIPTION

This disclosure aims to establish a robust platform to recapitulate the tissue microenvironment and interactions with host immune cells.

This disclosure describes devices and systems capable of recapitulating the tissue microenvironment and tissue interactions with fluid which may contain cells (such as circulating immune cells), medications, therapeutic compounds, or other components. As used herein, "fluid" can refer to fluid containing components that are intended to interact with a tissue sample (such as cells, medications, therapeutic compounds, or other substances) in order to observe a response, or can refer to fluid devoid of such components. A key challenge in this regard is the ability to maintain a tissue sample, such as a tumor biopsy, in a configuration that permits real-time observation of tumor viability and responses to therapeutic compounds, such as dynamic interactions between circulating immune cells and the tissue biopsy sample. This disclosure describes multiple novel designs capable of capturing and maintaining the position of a tissue sample in a flow field that presents cells, medications, therapeutic compounds, or other components to the tissue in a physiologically relevant manner, permitting control over perfusion rates and shear forces to ensure that results are relevant to human in vivo conditions.

Beyond the tissue trapping and flow field device, in order to fully recapitulate the dynamics of tissue interactions with cells such as immune cells, medications, therapeutic compounds, or other components, and to do so in a high throughput manner, it can be useful to integrate the device with a system capable of sustaining the tissue, maintaining control over the flow rate, viability of cells and density of circulating components, and to avoid problems common to microfluidic systems such as bubbles, debris, blockages or variability in flow rates. A key challenge is the ability to integrate these features in a manner that provides robust control over system dynamics for periods of up to one week or more.

In some implementations, the devices of this disclosure are capable of ex vivo simulation of the dynamics of tissue interactions with various fluid components, such as cells, medications, or therapeutic compounds. The devices can integrate capture regions, cell flow channels, resistance lines and fluidic connections, and bubble trapping structures. The devices described herein can permit observation and control over interactions between various types of fluid components and excised tissues such as tumor biopsy samples, skin biopsies, epithelial tissues such as gut, airway, renal or reproductive tract tissues. The figures and corresponding description below provide further detailed information regarding the design of such devices and systems. In brief, this disclosure includes various aspects, including specific designs for tissue traps, including a heart-shaped branching structure, ribbed channel bottom structure, S-curve structure, and suction port structure. Each serves as a means to precisely control and freeze the position of a tissue biopsy sample in a flow stream, and to expose the fixed tissue sample to a precisely controlled flow of fluid containing components such as cells, medications, or therapeutic compounds in order to observe interactions between the fluid components and tissue samples. This disclosure also includes aspects relating to integration of these trapping devices with other fluidic components. These additional components can include resistance channels, fluidic connectors and branch points, tissue sample loading ports, bubble trapping structures, drug dosing and media sampling ports, cell containment vessels, and manifolds that serve as distribution branches for cells and gas pressure lines.

For tissue trapping regions, other ways to address the problem include the use of V-shaped posts to trap tissues, side chamber regions, or side-to-side channels with cells flowing through one lane and tissues held in another, with a gel region in between. Additional potential designs for these systems include methods where the biopsied tissue sample is contained within a side channel or side compartment that indirectly receives flow from the main dynamic perfusion channel, methods where excised biopsy samples are contained within larger excised tissues or organs, or methods where biopsy samples are contained within constructs that are molded from mammalian tissues.

In other implementations, interactions between fluid and tissues can be mimicked by generating tissue constructs contained within gel or matrix regions. Fluid can flow through adjacent channels in which they are permitted to migrate toward the matrix-embedded tissue constructs. Some such devices and systems can utilize conventional microwell plates or transwells to contain excised tissues, as a static representation of the cell-tissue interaction.

The devices of this disclosure include innovative aspects in the nature of the tissue trapping geometry as compared to other approaches that may use V-shaped posts, side chambers, or side-to-side channels with intervening gel regions. The disadvantages of these approaches relate to the inability to precisely control the rate at which circulating fluid are presented to the tissue biopsy sample, because V-shaped post regions require dealing with a tradeoff between allowing flow around the tissue and raising the hydrostatic pressure of flow against the tissue sample. For side chambers or side-to-side channels, tissue interactions with fluid can occur via migration phenomena, which may be difficult to control in the microenvironment, or by random “strikes” of fluid traveling obliquely through the flow stream. This disclosure provides novel designs that can be used to contain tissue biopsy samples and channels for flowing fluid.

Other approaches to solving the tissue-cell interaction problem include using conventional means to contain tissues and fluid (e.g., static wells or transwells) and/or gel-matrix systems in which tissue samples are disaggregated and seeded into microfluidic devices in compartments adjacent to blood/cell-flow channels. Technical obstacles to the innovations described herein include developing designs capable of capturing tissue biopsy samples and effectively causing interaction of these captured samples with flowing media. These innovative concepts are not obvious because they include new tissue biopsy sample containment designs that overcome previous limitations. Key advantages of the devices and systems of this disclosure include designs that effectively entrain tissue biopsy samples and expose them to flowing fluid in a manner that optimizes the cross-section of interaction between the two.

FIG. **1**A illustrates a perspective view of an example microfluidic device **100**, according to an illustrative implementation. FIG. **1**B illustrates a second perspective view of the example microfluidic device **100** of FIG. **1**A. Similar reference numerals in FIGS. **1**A and **1**B refer to similar elements. Referring to both FIG. **1**A and FIG. **1**B, the microfluidic device **100** can be used to simulate interactions between tumors or other tissue samples and the immune system, for example by providing a microenvironment for testing the effectiveness of immunotherapy treatments on lymphocytes and tumor biopsies taken directly from a patient. As a result, the microfluidic device **100** can be used to model the in vivo environment and analyze the prolonged response of a tumor and circulating lymphocytes to the controlled introduction of immunotherapy pharmaceuticals. Thus, the microfluidic device **100** can enables judicious administration of immunotherapy treatments by allowing medical professionals to make informed decisions regarding course of treatment for a patient based on experiments conducted using the microfluidic device **100**.

The microfluidic device **100** is formed from a substrate **102**. The substrate **102** defines a variety of structural features, including an inlet port **105** leading to an inlet channel **115**. Downstream from the inlet port **105** and coupled to the inlet channel **115** is a bubble trapping structure **110**. Farther downstream from the inlet channel **115** is a tissue trapping region **120**, which leads to an outlet channel **125**. An outlet port **130** is positioned at a downstream end of the outlet channel **125**. While only a single microfluidic device **100** is depicted in FIGS. **1**A and **1**B, it should be understood that in some implementations, multiple devices similar to the microfluidic device **100** can be incorporated into a single chip without departing from the scope of this disclosure.

In use, the microfluidic device **100** can capture a tissue sample and allow testing of the interaction of the tissue sample with various cells, medications, therapeutic compounds, or other agents or components included within a fluid sample flowing within the microfluidic device **100**. For example, a tissue sample, such as a portion of a tumor, can be loaded into the device via the inlet port **105** or via the bubble trapping structure **110**. After the tissue sample flows through the inlet channel **115**, the structural characteristics of the tissue trapping region **120** cause the tissue sample to become trapped. A fluid sample can then be introduced into the inlet port **105** and flowed through the inlet channel **115**, while the tissue sample remains held in place in the tissue trapping region **120**. At least a portion of the fluid sample (and the cells, medications, therapeutic compounds, or other components within the sample) can contact the trapped tissue sample as it flows from the inlet channel **115** to the outlet channel **125** and finally exits the microfluidic device **100** via the outlet port **130**. In some implementations, air bubbles that may be present in the fluid sample, and which may cause damage to the tissue sample or may otherwise interfere with the results of the experiment, can be removed from the microfluidic device **100** via the bubble trapping structure **110**.

It should be understood that, in the implementation shown in FIG. **1**A, the outlet channel **125** serves as an outlet for the microfluidic device **100** as a whole, but not for the tissue trapping region **120**. Thus, in some implementations, the outlet channel **125** may not be an outlet channel relative to the tissue trapping region **120**, and therefore may be referred to by a different name. In some implementations, one or more channels may provide an outlet for fluid at or near the tissue trapping region **120**. For example, branching channels, suction channels, and other channels further described below may provide such an outlet. Thus, in some implementations, these channels also may be referred to as outlet channels. Various types of channels that may provide an outlet for fluid at or near the tissue trapping region **120** are described further below.

In some implementations, the microfluidic device **100** can be further configured to provide an optical interface for viewing the interaction site where the tissue sample interacts with the fluid sample. To facilitate optical access, the channels within the microfluidic device **100** can be configured to substantially avoid optical distortion. In some implementations, the channels can have a rounded rectangular cross-sectional shape. Such a shape exhibits smaller surface area to volume ratio than a purely rectangular channel, which can help to preserve pumping efficiency by reducing resistance in the channels. In addition, rounded rectangular channels may not produce image distortion that is characteristic of channels having circular cross-sectional shapes.

These and other aspects of this disclosure are described further below. In particular, a variety of different geometries and structural shapes can be used to implement the tissue trapping region **120**, and several examples of such geometries are shown in the figures. In particular, FIGS. **2**A-**2**F generally relate to a first geometry for the tissue trapping region **120**, FIGS. **3**A and **3**B generally relate to a second geometry for the tissue trapping region **120**, and FIGS. **4**A-**4**D generally relate to a third geometry for the tissue trapping region **120**.

FIG. **2**A illustrates a cross-sectional view of a portion of an example microfluidic device **200** that can be used to implement the microfluidic device **100** of FIG. **1**A, according to an illustrative implementation. The features of the microfluidic device **200** generally correspond to the features of the microfluidic device **100**, and like reference numerals refer to like elements. For example, the microfluidic device **200** includes an inlet channel **215**, a tissue trapping region **220**, and an outlet channel **225** that can carry fluid out of the microfluidic device **200**. FIG. **2** shows the structural details of the tissue trapping region **220**, which in this example includes a tissue trap (also referred to as a tissue trapping zone or trapping zone) **235** positioned at a downstream end of the inlet channel **215**, as well as two branch channels **240***a* and **240***b* branching off from the inlet channel **215** in opposing directions at a junction near the tissue trap **235**.

As described above, the tissue trapping region **220** is configured to trap a tissue sample in a fixed location while a fluid sample is flowed through the microfluidic device **200**. For example, in some implementations, the tissue trapping region **220** is shaped such that, when the fluid sample flows through the microfluidic device **200**, a stagnation zone exists in at least a portion of the area of the tissue trap **235**, causing the tissue sample to become trapped in the tissue trap **235**. FIG. **2**B illustrates a tissue sample **239** within the microfluidic device **200** of FIG. **2**A, according to an illustrative implementation. It should be noted that FIG. **2**B shows the microfluidic device **200** in a reversed orientation relative to that shown in FIG. **2**A, such that fluid flows from right to left in the depiction of the microfluidic device **200** of FIG. **2**B. As shown, the tissue sample **239** becomes trapped in the tissue trap **235** in a manner that allows the fluid sample to continue flowing through the inlet channel **215** to the branch channels **240***a* and **240***b*, while a portion of the fluid sample contacts the tissue sample **239** as it flows.

In some implementations, the tissue trap or trapping zone **235** can have a bottom wall that is positioned at a lower depth than the bottom of the inlet channel **215** that leads up to it. That is, the tissue trap **235** can be stepped down relative to the bottom surface of the inlet channel **215**. Thus, the tissue trap **235** can serve as a pocket for catching, trapping, holding, immobilizing, or securing the tissue sample **239**. In some implementations, the shape of the tissue trapping region **220**, including the tissue trap **235**, is selected to catch or otherwise facilitate trapping of the tissue sample **239** while the fluid sample passes through the microfluidic device **200**. For example, the tissue trap **235** can have a diameter that is larger than that of the inlet channel **215**. In some implementations, the tissue trap **235** can have a diameter that is about twice that of the inlet channel **215**. FIG. **2**C is a visual depiction **252** of the flow characteristics of the microfluidic device **200** of FIG. **2**A, according to an illustrative implementation. The shading within the channels shows the velocity of the streamlines within the device. When the streamlines bend at the branch channels **240***a* and **240***b*, the inertia of the tissue sample can overcome the viscous forces and can become lodged in the tissue trap **235**.

Referring again to FIG. **2**B, the trapping of the tissue sample **239** in a manner that allows the fluid sample to continue flowing through the device while contacting the tissue sample **239** can allow the interactions between the tissue sample **239** and agents within the fluid sample. For example, in some implementations fluorescent materials can be added to either the fluid sample or the tissue sample **239**, and the visual characteristics of the tissue sample **239** and the fluid sample can be observed over time. To facilitate such observation, the microfluidic device **200** can be formed from a material that is transparent and optically clear, at least in the region of the device near the tissue trap **235**. This area can serve as an optical interface that can be examined by an optical instrument, such as a camera or a microscope, that is brought into proximity with the microfluidic device **200**.

FIG. **2**D illustrates a first arrangement **201** of the microfluidic device of FIG. **2**A having suction channels, according to an illustrative implementation. Components shown in the arrangement **201** are substantially similar to the components shown in FIG. **2**A, and like reference numerals refer to like elements. However, the arrangement **201** of FIG. **2**D differs from that shown in FIG. **2**A in that the arrangement **201** includes a suction channel **245**. The suction channel **245** is coupled between a downstream end of the tissue trap **235** and the outlet channel **225**. Thus, the suction channel **245** can provide an outlet for fluid in the tissue trap **235**, and therefore may sometimes itself be referred to as an outlet channel. Similarly, the microfluidic device **201** also includes branch channels **240***a* and **240***b* that can provide an outlet for fluid near the tissue trap **235**, and therefore the branch channels **240***a* and **240***b* may also be referred to as outlet channels **240***a* and **240***b*. Furthermore, it should be understood that the outlet channel provides an outlet of the microfluidic device **201** (i.e., it is configured to carry fluid out of the microfluidic device **201**), but does not couple to the tissue trap **235** and therefore does not serve as an outlet for fluid from the tissue trap **235**. In some implementations, the suction channel **245** can be configured to facilitate trapping of the tissue sample within the tissue trap **235**. For example, as the fluid sample flows from left to right in the depiction of FIG. 2D, through the branch channels **240***a* and **240***b* and into the outlet channel **225**, the suction channel **245** can create a pressure drop or suction effect that tends to cause the tissue sample to be forced towards the right-hand side of the tissue trap **235**, thereby becoming lodged within the tissue trap **235** more forcefully.

FIG. **2**E illustrates a second arrangement **202** of the microfluidic device of FIG. **2**A having suction channels, according to an illustrative implementation. Components shown in the arrangement **202** are substantially similar to the components shown in FIG. 2A, and like reference numerals refer to like elements. However, the arrangement **202** of FIG. **2**E differs from that shown in FIG. **2**A in that the arrangement **202** includes two suction channels **245***a* and **245***b*. The suction channels **245***a* and **245***b* are coupled between a downstream end of the tissue trap **235** and the branch channels **240***a* and **240***b*, respectively. In some implementations, the suction channels **245***a* and **245***b* can be configured to facilitate trapping of the tissue sample within the tissue trap **235**, in a manner similar to that of the suction channel **245** shown in FIG. **2**D. For example, as the fluid sample flows from left to right in the depiction of FIG. **2**E, through the branch channels **240***a* and **240***b*, the suction channels **245***a* and **245***b* can create a pressure drop or suction effect that tends to cause the tissue sample to be forced towards the right-hand side of the tissue trap **235**, thereby becoming lodged within the tissue trap **235** more forcefully. In addition, because the suction channels **245***a* and **245***b* couple directly to a downstream end of the tissue trap **235**, the suction channels **245***a* and **245***b* can provide an outlet for fluid in the tissue trap **235**. Therefore, in some implementations the suction channels **245***a* and **245***b* may sometimes be referred to as outlet channels.

Similarly, FIG. **2**F illustrates a third arrangement **203** of the microfluidic device of FIG. **2**A having suction channels **245***a* and **245***b*, according to an illustrative implementation. The arrangement **203** of FIG. **2**F is similar to the arrangement **202** of FIG. **2**E, with the exception that the suction channels **245***a* and **245***b* in the arrangement **203** couple to a junction of the branch channels **240***a*, **240***b*, and the outlet channel **225**. However, the suction channels **245***a* and **245***b* in the arrangement **203** serve a similar purpose to that described above in connection with FIG. **2**E. That is, as the fluid sample flows from left to right in the depiction of FIG. **2**F, through the branch channels **240***a* and **240***b* and into the outlet channel **225**, the suction channels **245***a* and **245***b* can create a pressure drop or suction effect that tends to cause the tissue sample to be forced towards the right-hand side of the tissue trap **235**, thereby becoming lodged within the tissue trap **235** more forcefully. The suction channels **245***a* and **245***b* couple directly to a downstream end of the tissue trap **235**, thereby providing an outlet for fluid in the tissue trap **235**. Therefore, in some implementations the suction channels **245***a* and **245***b* may sometimes be referred to as outlet channels.

FIG. **3**A illustrates a cross-sectional view of a portion of an example microfluidic device **300** that can be used to implement the microfluidic device of FIG. **1**A, according to an illustrative implementation. FIG. **3**B illustrates a perspective view of the portion of the microfluidic device **300** shown in FIG. **3**A. The features of the microfluidic device **300** generally correspond to the features of the microfluidic device **100**, and like reference numerals refer to like elements. For example, the microfluidic device **300** includes an inlet channel **315**, a tissue trapping region **320**, and an outlet channel **325**. FIGS. **3**A and **3**B show the structural details of the tissue trapping region **320**, which in this example includes a ribbed channel coupled between the inlet channel **315** and the outlet channel **325**. The ribbed channel includes ribs, such as the ribs **355***a*-**355***c* (generally referred to as ribs **355**), that project into the ribbed channel. The ribbed channel also defines tissue traps **335***a*-**335***c* (generally referred to as tissue traps **335**).

In general, each of the tissue traps **335** has sidewalls defined by a subset of the ribs **355**. As shown, the bottom wall of each tissue trap **335** is positioned at a lowest depth of the ribbed channel, which is lower than the bottom wall of the inlet channel **315** and the outlet channel **325**. While the depiction of FIG. **3**A shows the ribbed channel defining three tissue traps **355**, it should be understood that, in other implementations, the ribbed channel may include any number of ribs **355** defining any number of tissue traps **335** without departing from the scope of this disclosure.

Similar to the tissue trapping region **220** shown in FIG. **2**A, the tissue trapping region **320** (including the tissue traps **335**) can be configured to trap a tissue sample in a fixed location while a fluid sample is flowed through the microfluidic device **300**. For example, the tissue trapping region **320** is shaped such that, when the fluid sample flows through the microfluidic device **300**, the tissue sample becomes trapped in the tissue traps **335**. In some implementations, a separate tissue sample can become trapped in each of the tissue traps **335**. In some other implementations, one or more of the tissue traps **335** may remain unused for a given experiment.

In some implementations, the ribbed shape of the tissue trapping region **320**, including the tissue traps **335**, is selected to facilitate trapping of a tissue sample while the fluid sample passes through the microfluidic device **300**. FIG. **3**C is a visual depiction **352** of the flow characteristics of the microfluidic device **300** of FIG. **3**A, according to an illustrative implementation. The shading within the channels shows the velocity of the streamlines within the microfluidic device **300**. Generally, a tissue sample will be larger and heavier than other particles that flow through the device **300** within the fluid sample. As a result, the tissue sample will tend to sink within the flow due to gravity. Thus, positioning the tissue traps **335** at the lowest depth of the ribbed channel, which includes small obstructing ribs **355**, can help to cause the tissue sample to become trapped within one of the tissue traps **335**.

It should be understood that the microfluidic device **300** can include any of the features and functionality described above with respect to the microfluidic device **100** and the microfluidic device **200** shown in FIGS. **1**A and **2**A, respectively. For example, the microfluidic device **300** can be formed from a material that is transparent and optically clear in the region of the device near the tissue traps **335**, which can serve as an optical interface that can be examined by an optical instrument brought into proximity with the microfluidic device **300**. As a result, the tissue samples and the fluid sample in the tissue traps **335** can be observed optically over time.

It should be understood that, in the implementation shown in FIG. **3**A, the outlet channel **325** serves as an outlet for the microfluidic device **100** as a whole, and also for the tissue trapping region **120**. In some implementations, although not illustrated in FIG. **3**A, the microfluidic device **300** also may include one or more additional channels that serve as outlets for fluid at or near the tissue trapping region **320**, which may also be referred to as outlet channels. For example, such channels may be branch channels or suction channels similar to those described above in connection with FIGS. **2**D-**2**F.

FIG. **4**A illustrates a cross-sectional view of a portion of an example microfluidic device **400** that can be used to implement the microfluidic device **100** of FIG. **1**A, according to an illustrative implementation. The features of the microfluidic device **400** generally correspond to the features of the microfluidic device **100**, and like reference numerals refer to like elements. For example, the microfluidic device **400** includes an inlet channel **415**, a tissue trapping region **420**, and an outlet channel **425**. FIG. **4**A shows the structural details of the tissue trapping region **420**, which in this example includes a circuitous channel coupled between the inlet channel **415** and the outlet channel **425**. The circuitous channel includes a first curved portion **460***a* and a second curved portion **460***b* (generally referred to as curved portions **460**). The curvature of the first curved portion **460***a* is opposed to the curvature of the second curved portion **460***b*. The first curved portion **460***a* includes a first tissue trap **435***a* positioned at its center. The second curved portion **460***b* is coupled to a downstream end of the first curved portion **460***a*, and includes a second tissue trap **435***b* positioned at its center. The first tissue trap **435***a* and the second tissue trap **435***b* are generally referred to as tissue traps **435** in this disclosure. The downstream end of the second curved portion **460***b* is coupled to the outlet channel **425**.

While the depiction of FIG. **4**A shows the circuitous channel as including two curved portions **460***a* and **460***b*, it should be understood that, in other implementations, the circuitous channel may include any number of curved portions each defining a respective tissue trap **435** without departing from the scope of this disclosure. For example, the circuitous channel may include only a single curved portion (i.e., the first curved portion **460***a*), or may include three or more curved portions.

Similar to the tissue trapping regions **220** shown in FIG. **2**A and **320** shown in FIG. **3**A, the tissue trapping region **420** (including the tissue traps **435**) can be configured to trap a tissue sample in a fixed location while a fluid sample is flowed through the microfluidic device **400**. For example, the tissue trapping region **420** is shaped such that, when the fluid sample flows through the microfluidic device **400**, a respective tissue sample can become trapped in the tissue traps **435**. In some implementations, a separate tissue sample can become trapped in each of the tissue traps **435**. In some other implementations, one or more of the tissue traps **435** may remain empty.

In some implementations, the circuitous shape of the tissue trapping region **420**, including the tissue traps **435**, is selected to facilitate trapping of a tissue sample while the fluid sample passes through the microfluidic device **300**. FIG. **4**B is a visual depiction **452** of the flow characteristics of the microfluidic device **400** of FIG. **4**A, according to an illustrative implementation. The shading within the channels shows the velocity of the streamlines within the microfluidic device **400**. Generally, a particle (such as a tissue sample) in the fluid sample will tend to follow the streamline located at its center of mass. If the Reynolds number of the tissue sample is sufficiently large, the inertia of the particle will overcome the viscous forces when the streamlines bend along the circuitous path including the curved portions **460** of the tissue trapping region **420**. As a result, the tissue sample will tend to become secured within the one of the tissue traps **435**.

FIG. **4**C illustrates a first arrangement **401** of the microfluidic device **400** of FIG. **4**A having a suction channel, according to an illustrative implementation. Components shown in the arrangement **401** are substantially similar to the components shown in FIG. **4**A, and like reference numerals refer to like elements. However, the arrangement **401** of FIG. **4**C differs from that shown in FIG. **4**A in that the arrangement **401** includes only a single tissue trap **435***a*, as well as a suction channel **465**. The suction channel **465** is coupled between the tissue trap **435***a* and the outlet channel **425**. In some implementations, the suction channel **465** can be configured to facilitate trapping of the tissue sample within the tissue trap **435***a*. For example, as the fluid sample flows from left to right in the depiction of FIG. **4**D, into the outlet channel **425**, the suction channel **465** can create a pressure drop or suction effect that tends to cause the tissue sample to be forced towards the right-hand side of the tissue trap **435***a*, thereby becoming lodged within the tissue trap **435***a* more forcefully. FIG. **4**D illustrates the flow characteristics of the microfluidic device **401** of FIG. **4**C, according to an illustrative implementation. As described in the flow characteristic figures above, the shading in FIG. **4**C shows the velocity of the streamlines within the microfluidic device **401**. In addition, because the suction channel **465** couples directly to a downstream end of the tissue trap **435***a*, the suction channel **465** can provide an outlet for fluid in the tissue trap **435***a*. Therefore, in some implementations the suction channel **465** may sometimes also be referred to as an outlet channel.

FIG. **5** illustrates a bubble trapping structure **110** that can be included in the microfluidic device **100** of FIG. **1**A, according to an illustrative implementation. Generally, the bubble trapping structure **110** can help to facilitate the capture of air bubbles from within the fluid sample that flows through the microfluidic device **100**, whose presence may be undesirable. Bubbles can be introduced into the microfluidic device **100**, for example, during the tissue loading process or via the incoming flow of the fluid sample. In some implementations, bubbles can negatively impact experimental outcomes. Therefore, it may be desirable to prevent air bubbles from entering the system, or to remove them before they reach the tissue sample downstream. Incorporation of an in-line bubble trapping structure **110** into the microfluidic device **100** allows for easy removal of air introduced by either mechanism

As shown, the microfluidic device **100** is coupled to a ceiling of the inlet channel **115**. The bubble trapping structure **110** includes sidewalls that curve inwards toward each other in a direction away from the inlet channel **115**. As shown in FIG. **1**A, the bubble trapping structure **110** can be positioned downstream from the inlet port **105**, such that air bubbles introduced through the inlet port **105** can be removed via the bubble trapping structure **110** before they reach the tissue trapping region **120**. In some implementations, the shape of the sidewalls of the bubble trapping structure **110** can be defined by a parabolic function. The microfluidic device **100** also includes a threaded connector **510**. The threaded connector **510** can be configured for attachment to an air line, through which air bubbles can be removed from the device after being captured by the bubble trapping structure **110**.

The bubble trapping structure **110** is incorporated directly into the microfluidic device **100**. This design eliminates the need for an external air removal device, thereby reducing the number of required connections. Additionally, inclusion of the bubble trapping structure **110** within the microfluidic device **100** can reduce the overall fluid volume requirement. In some implementations, the bubble trapping structure **110** can be configured to produce limited disruption of the primary flow path of the fluid sample through the inlet channel **115**. For example, the parabolic curvature of the bubble trapping structure **110** can encourage the gentle removal of bubbles from the flow, and the threaded connector **510**, which can couple to an air line or a syringe, allows evacuation of air from the chimney as needed.

In some implementations, the bubble trapping structure **110** also can be configured to serve as the loading port for the tissue sample. For example, the opening of the bubble trapping structure **110** can be configured to accommodate a pipette tip through which the tissue sample is introduced into the microfluidic device **100**. In some implementations, the tissue sample can be injected through the bubble trapping structure **110**, which may include a valve that can be closed after that tissue sample is injected. Flow of the fluid sample from the inlet port **105** can then cause the tissue sample to flow towards the tissue trapping region **120**, where it becomes secured in place as described above.

FIG. **6** illustrates a flowchart of a method **600** for evaluating an interaction between a tissue sample and a fluid sample, according to an illustrative implementation. In some implementations, the method **600** can be carried out using a microfluidic device such as the microfluidic device **100** shown in FIG. **1**A. In brief overview, the method **600** can include introducing a tissue sample into an inlet channel of a microfluidic device (step **605**), introducing a fluid sample into the inlet channel to cause the tissue sample to flow to a tissue trapping region of the microfluidic device (step **610**), collecting the sample fluid from one or more channels providing an outlet downstream from the tissue trapping region (step **615**), and observing an interaction between the tissue sample and the fluid sample in the tissue trapping region (step **620**).

Referring again to FIG. **6**, the method **600** can include introducing a tissue sample into an inlet channel of a microfluidic device (step **605**). In some implementations, the tissue sample can be or can include a portion of a tumor or other cancerous cells whose reaction to an immunotherapy is of interest. The tissue sample can be injected into the microfluidic device, for example via a port configured to serve as a bubble trapping structure similar to that shown in FIG. **5**. In some implementations, the inlet channel can first be primed with a fluid before the tissue sample is introduced. This can allow the tissue sample to be introduced directly into a fluid, which may help to better preserve the tissue sample for experimentation.

The method **600** also can include introducing a fluid sample into the inlet channel to cause the tissue sample to flow to a tissue trapping region of the microfluidic device (step **610**). In some implementations, the fluid sample can include cells, medications, therapeutic compounds, or other components. In some implementations, the fluid sample can be introduced at an area of the inlet channel upstream from the area where the tissue sample was introduced. For example, referring to the microfluidic device **100** of FIG. **1**A, the tissue sample can be introduced via the bubble trapping structure **110**, and the fluid sample can be introduced at the inlet port **105**, upstream from the bubble trapping structure **110**. This tissue sample and fluid sample introduction technique can help to ensure that the fluid sample is able to carry the tissue towards the tissue trapping region, which can be downstream from the areas in which both the fluid sample and the tissue sample are introduced.

In some implementations, the tissue trapping region can include at least one tissue trap configured to trap the tissue sample. The tissue trap can include an intersection or junction of one or more fluidly connected channels, cavities, spaces, or chambers. In some implementations, the geometry of the tissue trap can result in a stagnation zone configured such that the fluid flow characteristics in the stagnation zone are relatively stagnant (i.e., fluid velocity is lower, and in some cases may be zero) as compared with the fluid flow characteristics of other portions of the microfluidic device.

In some implementations, the tissue trap can be positioned at an intersection of a relatively large inlet channel and one or more relatively smaller branching channels that carry fluid away from the tissue trap to an outlet channel, for example as illustrated by the tissue trap **235** shown in FIG. **2**A. Other structural features also may contribute to the functionality of the tissue trap. For example, in some implementations the tissue trap can include an elevation change relative to the channels that couple to it, such that tissue trap serves as a sunken pocket for receiving and securing the tissue sample. As a result, in some implementations, the tissue trap may sometimes be referred to as a tissue trapping pocket. In some implementations, other walls of the tissue trap also may be stepped away, stepped up or stepped down from the walls of channels that lead to them. For example, a ceiling of the tissue trap may be positioned at an elevated height relative to the ceiling of the inlet channel, and the sidewalls of the tissue trap may be farther apart from one another than the sidewalls of the inlet channel.

In addition, the branching channels carrying fluid away from the tissue trap, as well as the outlet channel, can have a size that helps to trap the tissue sample within the tissue trap. For example, the branching channels and the outlet channel can be sized such that tissue samples larger than about 300 microns cannot progress to the outlet of the microfluidic device from the tissue trap. Thus, the tissue sample can become secured within the tissue trap, such that the cells in the fluid sample can contact the tissue sample as the fluid sample flows through the microfluidic device.

In some implementations, the tissue trap or trapping zone can have a geometry that is selected and/or arranged to trap the tissue sample without damaging the tissue sample. The tissue trap or trapping zone may be formed in any geometrical shape or combination of geometries. The tissue trap may be formed as a chamber or portion of a chamber and in some implementations may be referred to as a trapping chamber. The tissue trap may be formed as any type of pocket, such as a partial pocket or a covered pocket, and in some implementations may be referred to as a trapping pocket. The tissue trap may be formed as any type of cavity and may be referred to as a trapping cavity in some implementations. The tissue trap may be designed, configured and formed such as to provide a pressure drop or suction effect with respect to fluid sample flows traversing an opening of the tissue trap and in some implementations, may be referred to as a pressure drop trap, suction trap or tissue pressure drop zone or tissue suction zone.

The tissue trap may be formed as an arrangement of one or more walls. The one or more walls may be selected designed or configured with predetermined heights and/or lengths and/or widths, such as in relation to any of the dimensions of the device comprising the tissue trap. The one or more walls may be formed to meet at predetermined angles and/or predetermined points, such as in relation to any of the dimensions or geometries of the device comprising the tissue trap. The one or walls may be formed to be at predetermined orientations with respect to other walls and/or other walls of the device comprising the tissue trap. For example, the tissue trap can include one or more walls configured to secure the tissue sample. The walls may be formed from the edges of channels that are in fluid communication with the tissue trap, or may be formed from the edges of the tissue trap itself. In some implementations, a wall included in a tissue trap can be a sidewall, a bottom surface, or a ceiling. In some implementations, the tissue trap may include a curved wall, or may include two or more substantially flat walls that couple to one another at an edge. A wall included in a tissue trap can be configured to restrict the motion of a tissue sample without shearing, tearing, or otherwise damaging the tissue sample, in contrast to other types of structures that may be designed to trap a tissue sample. For example, while a series of narrow posts may be used to secure a tissue sample at a particular point within a microfluidic device, the relatively small width of such posts relative to the width of the tissue sample can cause the tissue sample to become torn by the posts as fluid pressure is exerted on the tissue sample by the fluid flowing through the device. Because a wall has a larger surface area than such a post, the tissue traps described in this disclosure can secure a tissue sample while substantially reducing the risk that the tissue sample will become torn or damaged.

In some implementations, a tissue trap also may include one or more channels, such as suction channels, that exit from a rear surface of the tissue trap and join with branching channels and or an outlet channel downstream from the tissue trap. Examples of such suction channels are illustrated in by the suction channels **240***a* and **240***b* of FIGS. **2**D-**2**F and the suction channel **465** of FIG. **4**C. As fluid flows through the microfluidic device, such suction channels can cause a pressure drop or other suction force to more securely trap a tissue sample within the tissue trap. Thus, in some implementations, the tissue trap may be referred to as a suction trap. Examples of suitable geometries for such a tissue trap have been described above, for example in connection with FIGS. **1**A, **2**A, **3**A, and **4**A.

The method **600** also can include collecting the sample fluid from one or more channels providing an outlet downstream from the tissue trapping region (step **615**). In some implementations, the microfluidic device can include an outlet port coupled to an outlet channel and configured to allow the fluid sample to be collected. For example, the outlet port can include a threaded connector, which can be coupled to a fluid line or a syringe to extract the fluid sample. In some implementations, the air bubbles also can be extracted from the fluid sample. For example, air bubbles can be extracted via a bubble trapping structure such as the bubble trapping structure **110** shown in FIG. **5**. In some implementations, the bubble trapping structure can be positioned upstream from the tissue trapping region, such that air bubbles can be extracted from the fluid sample before they reach the tissue trapping region.

In some implementations, the method **600** also can include reintroducing the collected sample fluid into the inlet channel of the microfluidic device. That is, the fluid sample can be recirculated one or more times through the microfluidic device. For example, the fluid sample can be introduced into the microfluidic device at step **610** and can be collected at step **615**. Then, the same fluid sample can be recirculated through the microfluidic device by reintroducing the fluid sample back into the inlet channel of the microfluidic device, and again collecting the fluid sample from the one or more channels providing the outlet. In some implementations, steps **610** and **615** of the method **600** can be iterated any number of times.

The method **600** also can also include observing an interaction between the tissue sample and the fluid sample in the tissue trapping region (step **620**). Because the microfluidic device as described in this disclosure can be configured to simulate the dynamics of tissue-cell interactions that occur in vivo, the observation of the interaction between the tissue sample and the fluid sample can provide valuable insights into the way in which a patient will respond to a particular immunotherapy. In some implementations, the microfluidic device can be formed form a transparent and/or optically clear material, and can be sufficiently thin to permit observation of the interaction between the tissue sample and the fluid sample by external equipment. For example, the microfluidic device can include an optical interface positioned near the tissue trapping region, to allow a microscope, camera, or other optical equipment to be used to observe the interaction that takes place in the tissue trapping region from outside of the microfluidic device. In some implementations, at least one the tissue sample and the fluid sample can include fluorescent particles that may be observed by such optical equipment.

In some implementations, the method **600** also can include releasing the tissue sample from the tissue trap. To release the tissue sample, in some implementations a second fluid sample can be introduced into the one or more channels providing the outlet. This can cause the second fluid sample to flow towards the inlet channel. This reverse flow of fluid can exert fluid forces on the tissue sample within the tissue trap that tend to dislodge the tissue sample from the tissue trap. In some implementations, the tissue sample may be brought to an inlet port of the microfluidic device in this manner, and may be collected and removed from the device at the inlet port.

Having now described some illustrative implementations, it is apparent that the foregoing is illustrative and not limiting, having been presented by way of example. In particular, although many of the examples presented herein involve specific combinations of method acts or system elements, those acts and those elements may be combined in other ways to accomplish the same objectives. Acts, elements and features discussed only in connection with one implementation are not intended to be excluded from a similar role in other implementations.

The systems and methods described herein may be embodied in other specific forms without departing from the characteristics thereof. The foregoing implementations are illustrative rather than limiting of the described systems and methods. Scope of the systems and methods described herein is thus indicated by the appended claims, rather than the foregoing description, and changes that come within the meaning and range of equivalency of the claims are embraced therein.

The invention claimed is:

1. A microfluidic device comprising:

a substrate defining:

an inlet channel having a first end configured to receive a fluid sample optionally containing a tissue sample;

- a tissue trapping region at a second end of the inlet channel downstream from the first end, the tissue trapping region including one or more tissue traps configured to catch the tissue sample flowing through the inlet channel such that the fluid sample contacts the one or more tissue traps;
- a first branch channel coupled to the second end of the inlet channel at a first junction and configured to direct a first portion of the fluid sample in a first direction;
- a second branch channel coupled to the second end of the inlet channel at the first junction and configured to direct a second portion of the fluid sample in a second direction, different from the first direction, wherein at least one of the one or more tissue traps is positioned at the first junction;
- a first suction channel coupling at least one of the one or more tissue traps to the first branch channel at a third junction downstream from the second end of the inlet channel; and
- a second suction channel coupling at least one of the one or more tissue traps to the second branch channel at a fourth junction downstream from the second end of the inlet channel.

2. The microfluidic device of claim **1**, wherein at least one of the one or more tissue traps comprises an arrangement of one or more walls.

3. The microfluidic device of claim **1**, wherein at least one of the one or more tissue traps includes a bottom surface positioned at a lower depth than a bottom surface of the inlet channel.

4. The microfluidic device of claim **1**, wherein the first branch channel and the second branch channel converge at a second junction downstream from the one or more tissue traps.

5. The microfluidic device of claim **1**, wherein a diameter of at least one of the one or more tissue traps is about twice that of the inlet channel.

6. The microfluidic device of claim **1**, further comprising an inlet port coupled to the first end of the inlet channel and configured to deliver the fluid sample to the inlet channel.

7. The microfluidic device of claim **6**, wherein the inlet port comprises a first threaded connector configured for attachment to a fluid line.

8. The microfluidic device of claim **6**, further comprising a bubble trapping structure coupled to the inlet channel downstream from the inlet port, the bubble trapping structure configured to facilitate evacuation of air bubbles from the fluid sample.

9. The microfluidic device of claim **8**, wherein a surface of the bubble trapping structure has a shape defined by a parabolic function.

10. The microfluidic device of claim **8**, wherein the bubble trapping structure further comprises a second threaded connector configured for attachment to an air release line.

11. The microfluidic device of claim **1**, further comprising an outlet port coupled to at least one of the first branch channel or the second branch channel providing an outlet and configured to remove the fluid sample from the microfluidic device.

12. The microfluidic device of claim **1**, wherein the substrate is formed from a biocompatible material.

13. The microfluidic device of claim **1**, wherein the substrate is formed from an optically transparent material, the microfluidic device further comprising:

- an optical interface providing optical access to the tissue sample positioned within the tissue trapping region.

14. The microfluidic device of claim **1**, wherein the one or more tissue traps are configured to entrain the tissue sample in place within the one or more tissue traps.

15. A microfluidic device, comprising:

- a substrate defining:
  - an inlet channel having a first end configured to receive a fluid sample;
  - a tissue trapping region at a second end of the inlet channel downstream from the first end, the tissue trapping region including one or more tissue traps configured to catch a tissue sample flowing through the inlet channel such that the fluid sample contacts the one or more tissue traps;
  - wherein at least one of the one or more tissue traps comprises a bottom surface defined at a lower depth in the substrate than a bottom surface of the inlet channel defined in the substrate; and
  - one or more channels providing an outlet, the one or more channels comprising one or more suction channels downstream from the one or more tissue traps and configured to hold the tissue sample in place within the lower depth of the one or more tissue traps.

16. The microfluidic device of claim **15**, wherein at least one of the one or more tissue traps comprises an arrangement of one or more walls.

17. The microfluidic device of claim **15**, wherein the one or more channels providing the outlet comprise one or more branch channels connecting to the second end of the inlet channel where the second end of the inlet channel and the tissue trapping region converge.

18. The microfluidic device of claim **17**, wherein the convergence of the second end of the inlet channel and the tissue trapping region further comprises:

- a first branch channel coupled to the second end of the inlet channel at a first junction and configured to direct a first portion of the fluid sample in a first direction; and
- a second branch channel coupled to the second end of the inlet channel at the first junction and configured to direct a second portion of the fluid sample in a second direction, different from the first direction, wherein at least one of the one or more tissue traps is positioned at the first junction.

19. The microfluidic device of claim **18**, wherein the first branch channel and the second branch channel converge at a second junction downstream from the one or more tissue traps.

20. The microfluidic device of claim **18**, further comprising:

- a first suction channel coupling at least one of the one or more tissue traps to the first branch channel at a third junction downstream from the second end of the inlet channel; and
- a second suction channel coupling the at least one of the one or more tissue traps to the second branch channel at a fourth junction downstream from the second end of the inlet channel.

21. The microfluidic device of claim **18**, wherein a diameter of at least one of the one or more tissue traps is about twice that of the inlet channel.

22. The microfluidic device of claim **15**, further comprising an inlet port coupled to the first end of the inlet channel and configured to deliver the fluid sample to the inlet channel.

23. The microfluidic device of claim **22**, further comprising a bubble trapping structure coupled to the inlet channel downstream from the inlet port, the bubble trapping structure configured to facilitate evacuation of air bubbles from the fluid sample.

24. The microfluidic device of claim **22**, wherein the inlet port comprises a first threaded connector configured for attachment to a fluid line.

25. The microfluidic device of claim **23**, wherein a surface of the bubble trapping structure has a shape defined in part by a parabolic function.

26. The microfluidic device of claim **23**, wherein the bubble trapping structure further comprises a second threaded connector configured for attachment to an air release line.

27. The microfluidic device of claim **15**, wherein the substrate is formed from a biocompatible material.

28. The microfluidic device of claim **15**, wherein the substrate is formed from an optically transparent material, and the microfluidic device further comprises an optical interface providing optical access to the tissue sample positioned within the tissue trapping region.

29. The microfluidic device of claim **15**, wherein the one or more tissue traps are configured to entrain the tissue sample in place within the one or more tissue traps.

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