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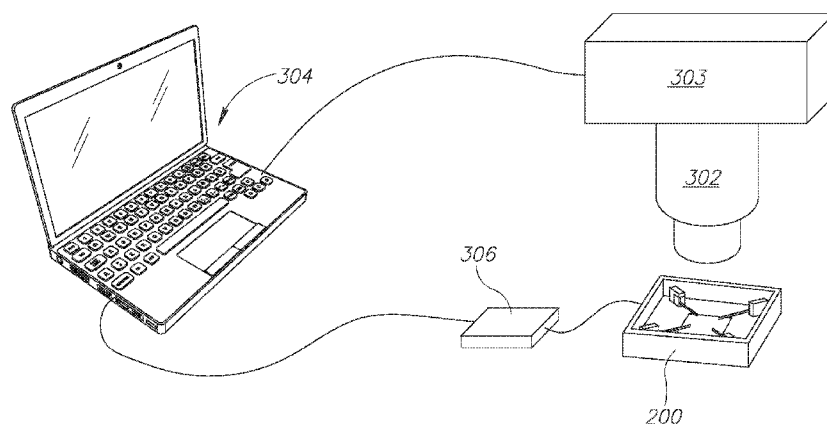


FIG. 4

(57) **Abstract:** Apparatus for controlling movement and/or location of a particle suspended in a fluid, the apparatus comprising: a container configured to contain a fluid in which the particle is suspended; at least one elastic body configured to be located in the fluid; an actuator controllable to generate vibrations in the at least one elastic body that produce a jet-like flow of fluid that to move the particle by advection along a direction of the jet-like fluid flow.

PARTICLE MANIPULATION SYSTEM (PMS)

RELATED APPLICATIONS

[0001] The present application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application 62/293,795, filed on February 11, 2016, the disclosure of which is incorporated herein by reference

BACKGROUND

[0002] Micromanipulation refers to the control of the location and/or orientation of microscopic bodies while being observed and/or manipulated, generally, in a field of view of a microscope. Typically the microscopic bodies are characterized by dimensions that range from as little as about half a micrometer (μm) to as many tens of micrometers, and are located in a fluid environment. Micromanipulation apparatuses or systems, “micromanipulators”, and technologies may employ direct physical contact and/or non-contact technologies, and different forces of nature to micro-manipulate particles. Contact micromanipulators include by way of example pipettes, atomic force microscopy, micro-robots. Non-contact micromanipulators typically configure energy potential wells in electric, magnetic, acoustic, and hydrodynamic fields to trap and/or manipulate microscopic particles. Non-contact micromanipulators include by way of example, optical, magnetic, dielectrophoretic, acoustic, and hydrodynamic tweezers.

[0003] Micromanipulators are used in the study of fundamental processes in physics, chemistry, and biology, and in the development and use of such applied disciplines as material science, cytometry, embryology, single cell transfection, and tissue engineering. By way of example, in in vitro fertilization, micromanipulation tools and technologies may be used to inject a sperm, which measures between 10-20 μm , into an oocyte which has a diameter of about 100 μm in diameter.

SUMMARY

[0004] An aspect of an embodiment of the invention relates to providing a micromanipulator, also referred to as a Particle Manipulation System (PMS), for manipulating a particle suspended in a fluid using at least one cantilever controllable to vibrate and generate flow in the fluid that operates to transport the particle in a desired direction. In an embodiment, for time independent forms of vibration the flow is substantially a time independent flow referred to as steady streaming (SS) flow. The SS flow is characterized by a region of enhanced jet-like fluid flow generated between vortices in a flow field created in the fluid by vibration of

the at least one cantilever. Optionally, the fluid is an incompressible fluid. In an embodiment of the disclosure a closed loop control system controls vibration of the at least one cantilever, hereinafter also referred to as a flow control beam or “flow-beam”, responsive to images of the particle acquired by an image processing system to control location of the particles.

[0005] This Summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

BRIEF DESCRIPTION OF FIGURES

[0006] Non-limiting examples of embodiments of the invention are described below with reference to figures attached hereto that are listed following this paragraph. Identical features that appear in more than one figure are generally labeled with a same label in all the figures in which they appear. A label labeling an icon representing a given feature of an embodiment of the invention in a figure may be used to reference the given feature. Dimensions of features shown in the figures are chosen for convenience and clarity of presentation and are not necessarily shown to scale.

[0007] Fig. 1A schematically shows a vibrating flow-beam having a fixed end mounted to a wall and a free, vibrating, end to generate SS flow in a fluid having a SS jet-flow advantageous for manipulating a particle in the fluid in accordance with an embodiment of the disclosure;

[0008] Fig. 1B schematically shows a flow field in the fluid shown in Fig. 1A having an SS flow characterized by an SS jet-flow generated by the vibrating flow-beam in a region of the fluid in a neighborhood of the beam’s vibrating end, in accordance with an embodiment of the disclosure;

[0009] Fig. 1C show a graph of velocity of the SS jet-flow as a function of distance from the vibrating end of the flow-beam shown in Figs. 1A and 1B, in accordance with an embodiment of the disclosure;

[0010] Fig. 1D show a graph of velocity of the SS jet-flow as a function of amplitude of vibration of the vibrating end of the flow-beam shown in Figs. 1A-1B, in accordance with an embodiment of the disclosure;

[0011] Fig. 2A schematically shows show a fluid flow field and SS jet-flow generated by a pair of vibrating flow-beams for manipulating a particle in the fluid, in accordance with an embodiment of the disclosure;

[0012] Fig. 2B schematically shows a particle manipulator fluid flow box for containing a fluid and comprising four flow-beams symmetrically arrayed in the fluid box, operable to

vibrate and generate SS jet-flows in the fluid for manipulating a particle in the fluid, in accordance with an embodiment of the disclosure;

[0013] Figs 3A-3B schematically shows activation of different flow-beams in the fluid flow box shown in Fig. 2B to generate SS jet-flows in different directions to manipulate a particle in a fluid in the fluid box, in accordance with an embodiment of the disclosure;

[0014] Fig. 4 schematically shows a particle manipulator system (PMS) comprising the fluid-flow box shown in Figs, 2B-3D in accordance with an embodiment of the disclosure; and

[0015] Figs. 5A and 5B schematically show flow-boxes comprising configurations of flow-beams different from that shown in Figs. 2B-3, in accordance with embodiments of the disclosure.

DETAILED DESCRIPTION

[0016] In the following detailed description, operation of a flow-beam vibrating to generate SS flow in a fluid in accordance with an embodiment is characterized and discussed with reference to Figs. 1A-1D. Linear superposition of SS flow fields generated by two flow-beams configured in accordance with an embodiment to provide two degree of freedom (DOF) micromanipulation of a particle is described and discussed with reference to Fig. 2A. Fig. 2B shows a flow-box comprising a configuration of four flow-beams operable to generate SS jet-flow in different directions in a fluid contained in the flow-box to control two DOF motion of a particle in the fluid. Operation of a PMS comprising the flow-box shown in Fig. 2D is discussed with reference to Fig. 4A and a trajectory travelled by a particle controlled by a PMS similar to that shown in Fig. 4A is shown in Fig. 4B. Figs. 5A and 5B show flow-boxes configured to generate SS flow to control particle motion in three dimensions.

[0017] In the discussion, unless otherwise stated, adjectives such as “substantially” and “about” modifying a condition or relationship characteristic of a feature or features of an embodiment of the disclosure, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended. Unless otherwise indicated, the word “or” in the description and claims is considered to be the inclusive “or” rather than the exclusive or, and indicates at least one of, or any combination of items it conjoins.

[0018] Fig. 1A schematically shows a flow-beam 20 extending along a y-axis of a coordinate system 80 and having an optionally rectangular cross section perpendicular to the y-axis. A long side of the rectangular cross section is perpendicular to the x-axis of the coordinate system, in accordance with an embodiment of the disclosure. Flow-beam 20 has a fixed end 22 mounted to a panel 23 and a free end 24. Flow-beam 20 is located in a fluid schematically

represented by a shaded ellipse 30 and is controllable to vibrate so that free end 24 exhibits oscillatory motion, optionally, in the x-direction as schematically indicated by arrows 26, to generate a desired SS flow field in fluid 30 advantageous for manipulating a particle in the fluid.

[0019] Flow-beam 20 may comprise any of various materials configured to provide a beam construction controllable to vibrate so that free end 24 oscillates. For example, flow-beam 20 may comprise a piezoelectric bar formed from polyvinylidene fluoride (PVDF), lead zirconate titanate (PZT), or a piezoelectric ceramic, having embedded, and/or surface, electrodes excitable to cause the beam to vibrate and generate oscillatory motion of free end 24. Flow-beam 20 may be configured by way of example, as a bimorph sandwich controllable to exhibit repetitive bending motion, or as a solid strip of piezoelectric material having a surface electrode configuration excitable to generate traveling waves in the strip. Advantageously, flow-beam 20 is excited to vibrate at a resonant frequency of its structure. Hereinafter for convenience of presentation flow-beam 20 is assumed to be a piezoelectric bimorph having thickness T, width W, and length L as shown in Fig. 1A.

[0020] In an embodiment, vibration of flow-beam 20 is controlled so that frequency, ω , and amplitude “A”, of oscillation of free end 24 generates a SS flow field in fluid 30 having a “jet-like”, SS flow extending away from free end 24, along a direction, optionally referred to as a “jet-flow axis”, substantially coincident with a direction of a longitudinal axis (not shown) of flow-beam 20, which in Fig. 1A lies along the y-axis of coordinate system 80. The SS jet-flow may advantageously be used in accordance with an embodiment to move a particle in fluid 30 by advection along the SS jet-flow. Direction of the SS jet-flow may be changed by physically changing location and/or orientation, that is, a “pose”, of the flow-beam in fluid 30. In an embodiment direction along which a particle in fluid 30 is moved may be determined by combining the SS flow field generated by vibration of flow-beam 20 with a SS flow field generated by another flow-beam.

[0021] Let ε represent a ratio of amplitude A of vibration of free end 24 to width W of flow beam 20. In symbols $\varepsilon = A/W$. A SS jet-flow in fluid 30 may be generated by oscillation of free end 24 by controlling frequency ω and amplitude A in accordance with an embodiment of the disclosure, so that ε has a value between about 10^{-3} and about 1 and that in a neighborhood of free end 24, a streaming Reynolds number, $Re_S = \varepsilon Re$, has a value between 10^{-5} and 1. In the expression for Re_S , Re is the oscillatory Reynolds number of fluid 30 in the neighborhood of free end 24. The oscillatory Reynolds number Re may be

defined by an expression $Re = \omega AW/\nu$, where ν is the kinematic viscosity of the fluid in the neighborhood of free end 24.

[0022] Fig. 1B shows a SS flow field 40 in the xy-plane of coordinate system 80 (Fig. 1A) generated by vibration of flow-beam 20 shown in Fig. 1A immersed in a silicone oil and configured as a PZT bimorph having thickness T , width W , and length L equal respectively to 0.8mm, 2mm, and 30mm, oriented as shown in Fig. 1A. Flow-beam 20 was excited to generate SS flow field 40 by a sinusoidal signal having amplitude of about 10 volts and a frequency ω substantially equal to a resonant frequency of the flow-beam equal to about 200 Hz. The silicone oil had a density of 970 kg/m^3 , viscosity 430 cSt (centistokes), and an oscillatory Reynolds number Re less than about 0.5

[0023] SS flow field 40 is characterized by counter rotating, substantially mirror image, vortexes 41 and 42 opposite each other on either side of the y-axis that cooperate to generate an SS jet-flow 43 having a jet-flow axis indicated by a block arrow 44 along the y-axis. Fluid flow velocity $\mathbf{v}$, in SS jet-flow 43 is substantially parallel to the y-axis, having a y-component, v_y , with, in comparison to v_y , little or no v_x or v_z components perpendicular to the y-axis.

[0024] A graph 50 in Fig. 1C shows dependence of an average magnitude of the y-component, v_y , of velocity of SS jet-flow 43 as a function of distance from free end 24 of flow-beam 20 for different amplitudes A of oscillation of the free end, and the conditions and numerical specifications noted above. The abscissa of graph 50 shows distance from free end 24 along the y-axis of coordinate system 80 normalized to the length L , 30 mm, of flow-beam 20. The average magnitude of v_y of SS jet-flow 43 is shown in mm/s (millimeters per second) along the ordinate of graph 50. Curves 51, 52, 53, and 54 show dependence of v_y on distance for oscillation amplitudes A normalized to flow-beam length L , respectively equal to about 0.054, 0.084, 0.09, and 0.13. The amplitudes correspond respectively to Reynolds numbers Re equal to 0.12, 0.19, 0.21, and 0.3. Each curve 51-53 peaks at about a same distance, $1.036L$, or about 1.1 mm ($0.03 \times 30\text{mm}$) from free end 24 of flow-beam 20. Curves 51-53 show that for the normalized amplitudes, 0.054, 0.084, 0.09 and 0.13, peak magnitudes of component v_y of SS jet-flow 43 along jet-flow axis 44 are 0.15, 0.28, 0.31, and 0.49 mm/s respectively.

[0025] A graph 60 shows a regression curve 62 that illustrates dependence on ε (oscillation amplitude A normalized to thickness T of flow-beam 20) of the average magnitude of v_y of SS jet-flow 43 along the y-axis, the. Curve 62 shows that the average magnitude of v_y along the y-axis and jet-flow axis 44, is substantially proportional to ε^2 . Since vibration amplitude

A for bimorph SS flow-beam 20 is substantially proportional to a driving voltage, “U”, that excites vibration in the flow-beam, magnitude of flow velocity v_y in SS jet-flow 43 along jet-flow axis 44 is substantially proportional to the square, U^2 , of the driving voltage.

[0026] It is noted that whereas graph shows a flow velocity range that extends from about 0.15 mm/s to about 0.5 mm/s, flow velocities provided by a flow-beam in accordance with an embodiment of the disclosure are not limited to the shown range. For example, flow velocities that may be provided by a flow-beam in accordance with an embodiment may have a submicron per second lower bound velocity. A practical submicron flow velocity may be achieved by lowering excitation voltage amplitude and/or frequency, and or exciting the flow-beam with an excitation voltage having a suitably time dependent amplitude. For example a flow beam may be excited for short periods of time using a pulsed excitation voltage. It is also noted that whereas in the above description an excitation voltage is characterized by a frequency of about 200 Hz an excitation voltage frequency range may extend from about 10 Hz to as high as 10,000 Hz. High frequency excitation may enable effecting practical changes in excitation voltage, and thereby in a flow velocity profile of a jet-flow in time scales of a few periods of the voltage. In practice a PMS similar to that shown in Fig. 4 having flow-beams in accordance with an embodiment of the disclosure and described below has been operated to provide flow velocities as low as about 0.2 $\mu\text{m/s}$ and spatial resolution for positioning a particle of about 0.2 μm .

[0027] In an embodiment, a region of SS flow field 40 advantageous for controlling motion of a particle in fluid 30 may be limited to a region, hereinafter also referred to as a “control region”, of fluid 30 for which v_y is greater than about 80 $\mu\text{m/s}$, and magnitude, $|v_x|$, is less than about 10 $\mu\text{m/s}$. A region of SS flow field 40 for which the noted limits on magnitudes of v_y and $|v_x|$ apply, are schematically indicated by a dashed rectangle 46 that extends along the y-axis from about 1.5 mm to 5.3 mm from free end 24 and lies between ± 1.25 mm parallel to the x-axis.

[0028] For the relatively low Reynolds number, Re , for which vibration of a flow beam, such as flow beam 20, generates a SS flow field having a SS jet-flow, SS flow fields generated by each of a plurality of flow-beams in a fluid combine substantially linearly to provide a “compound” SS flow field. The plurality of flow-beams may be configured in accordance with an embodiment of the disclosure so that the compound SS flow field exhibits a SS jet-flow

that is substantially a linear superposition of the SS jet flows generated by vibration of each of the plurality of flow-beams.

[0029] By way of example, Fig. 2A shows a compound SS flow field 140 which is a superposition of flow fields generated by vibration of two flow-beams 201 and 202 similar to flow-beam 20 immersed in a silicone oil similar to silicone oil 30 (Figs. 1A and 1B) in which flow-beam 20 shown in Fig. 1B is immersed. Flow beams 201 and 202 are oriented substantially at 90° to each other parallel to the x and y axes respectively with their respective free ends 221 and 222 about $\sqrt{50}$ mm apart. The flow-beams are excited by 200 Hz sinusoidal signals so that their respective free ends oscillate with amplitudes equal to about 0.13 mm. SS jet flow has a jet-flow axis 144 oriented at about 45° to the x and y axes.

[0030] SS flow field 140 exhibits two counter rotating mirror image vortexes 141 and 142 that generate a SS jet-flow 143 having a jet-flow axis 144. The SS flow field has a control area indicated by a dashed rectangle 146 for which fluid flow along jet-flow axis 144 has a magnitude greater than about 80 mm/s and fluid flow perpendicular to the jet-flow axis is less than about 10 mm/s. Control area 146 has length along jet-flow axis 144 equal to about 3.6 mm and width perpendicular to jet-flow axis 144 equal to about 5.5 mm. Control region 146 provided by vibration of flow-beams 201 and 202 is about twice the size of control region 46 provided by vibration of flow-beam 20 (Fig. 1B).

[0031] In an embodiment a PMS may use compound SS flow fields generated by controlling vibrations of different flow-beams and/or different combinations of a plurality of flow-beams to manipulate particles in accordance with an embodiment of the disclosure. By way of example, Fig. 2B shows a PMS fluid flow box 200 configured to contain a fluid in which particles may be suspended for micromanipulation and having a plurality of four flow-beams 201, 202, 203, and 204 for manipulating the particles.

[0032] Flow-beams 201-204 are, optionally, positioned substantially in a same plane, and are angularly located symmetrically at a same distance from a common center (not shown), with a 90° angle between any two adjacent flow-beams. Each flow beam 201-202 is mounted to a coupling block 230 having electrical connections (not shown) for connecting the flow-beam to a power source that provides electrical signals for exciting vibrations in the flow-beam, in accordance with an embodiment of the disclosure. Optionally a bottom 231 of flow box 200 has a transparent window 232 through which light may be directed to illuminate particles suspended in fluid in the flow box for viewing.

[0033] Flow-beams 201-204 may be excited to vibrate singly or in combinations of more than one flow-beam to generate SS flow fields having SS jet-flows in different directions and different magnitudes. By way of example, pairs of adjacent flow beams in flow box 200 may be excited to generate SS flow fields having SS jet flows in different directions. Figs. 3A -3D schematically show different adjacent pairs of flow-beams 201-204 excited so that oscillations in their free ends generate SS jet-flows in accordance with an embodiment of the disclosure. In each Fig. 3A-3D, free ends of flow-beams 201-204 that are excited are shown solid, and free ends of flow-beams 201-204 that are passive, unexcited, are shown in outline. Directions of a flow-jet axis of an SS flow-jet that oscillations of the free ends of the flow-beams generate are indicated by a solid arrow 144.

[0034] Fig. 3A shows flow-beams 201 and 202 excited and flow-beams 203 and 204 passive to generate an SS flow field 140 having a flow-jet axis 144 directed at a 45° angle relative to the x-axis shown in the figure. Fig. 3B shows flow-beams 202 and 203 excited and flow-beams 204 and 201 passive to generate an SS flow field 140 having a flow-jet axis 144 directed at a 135° angle relative to the x-axis. Fig. 3C shows flow-beams 203 and 204 excited and flow-beams 201 and 202 passive to generate an SS flow field 140 having a flow-jet axis 144 directed at a 225° angle relative to the x-axis. And Fig. 3D shows flow-beams 204 and 201 excited and flow-beams 202 and 203 passive to generate an SS flow field 140 having a flow-jet axis 144 directed at a 315° angle relative to the x-axis.

[0035] In general, since SS flow fields excited by different flow-beams, such as flow beams 201-204, superpose linearly to provide a compound SS flow field, and magnitude of velocity of a SS jet-flow generated by oscillation of a free end of a flow-beam is proportional to the square of its excitation voltage, velocity of a SS jet-flow in accordance with an embodiment of the disclosure may be expressed as a linear function of the square of excitation voltages. For a configuration of flow-beams such as flow-beams 201-204, dependence of velocity components v_x and v_y of fluid flow along a SS jet-flow axis 144 on excitation voltages applied to generate vibrations in flow-beams 201-204 may therefore be expressed by a matrix equation $\mathbf{v} = C\mathbf{u}^2$. In the equation, $\mathbf{u}$ represents an excitation vector having components that are amplitudes of excitation voltages applied to flow-beams 201-204 and C represents a “flow control” matrix that determines the velocity vector $\mathbf{v}$ for a given excitation vector $\mathbf{u}$. Explicitly writing out the components of the matrix equation that relates SS jet-flow velocity $\mathbf{v}$ to excitation voltages $\mathbf{u}$ of the four flow-beams 201-204 in flow box 200 provides an expression:

$$\begin{bmatrix} v_x \\ v_y \end{bmatrix} = \begin{bmatrix} c_{11} & c_{12} & c_{13} & c_{14} \\ c_{21} & c_{22} & c_{23} & c_{24} \end{bmatrix} \begin{bmatrix} u_1^2 \\ u_2^2 \\ u_3^2 \\ u_4^2 \end{bmatrix}, \text{ where } u_1, u_2, u_3, \text{ and } u_4 \text{ represent amplitudes of}$$

excitation voltages of flow-beams 201, 202, 203, and 204, respectively. In an embodiment the excitation voltages are harmonic functions of time and the excitation voltages driving flow-beams 201, 202, 203, and 204 may be written, $u_1 \sin(\omega_1 t)$, $u_2 \sin(\omega_2 t)$, $u_3 \sin(\omega_3 t)$, and $u_4 \sin(\omega_4 t)$ respectively where the frequencies ω_1 , ω_2 , ω_3 , and ω_4 , are, optionally, respective resonant frequencies of the flow-beams.

[0036] Representing the components of the location of a particle in a fluid contained in flow-box 200 by x_p and y_p , and remembering that a SS jet-flow in accordance with an embodiment of the disclosure moves the particle substantially by advection, components, $\dot{x}_p$ and $\dot{y}_p$, of the velocity of motion of the particle may be written $\dot{x}_p = v_x$ and $\dot{y}_p = v_y$ and

$$\begin{bmatrix} \dot{x}_p \\ \dot{y}_p \end{bmatrix} = \begin{bmatrix} c_{11} & c_{12} & c_{13} & c_{14} \\ c_{21} & c_{22} & c_{23} & c_{24} \end{bmatrix} \begin{bmatrix} u_1^2 \\ u_2^2 \\ u_3^2 \\ u_4^2 \end{bmatrix}.$$

[0037] A flow box comprising flow beams in accordance with an embodiment of the disclosure, such as, by way of example, flow box 200 comprising flow-beams 201-204, provides a simple, elegant, and relatively inexpensive tool that may be controlled by application of suitable voltages to the flow-beams to manipulate microscopic size particles.

[0038] By way of example, Fig. 4 schematically shows a PMS 300 comprising a flow box 200 located in a field of view (FOV) of a microscope 302. The microscope is coupled to a camera 303 operable to acquire images of a particle suspended in a fluid contained in flow box 200 and located in the FOV of the microscope. PMS 300 comprises a computer system 304 that receives and processes the images to determine locations of the particle as a function of time. The computer system may use the determined locations to generate a display of the particle to a user for use in providing input to the computer directing the computer to control movement and/or location of the particle in a desired manner. In response to the user input, computer system 304 may control a signal generator 306 to generate excitation voltages based on the flow control matrix C configured to control flow-beams 201-204 to generate SS jet-flows that manipulate the particle in the flow-box. For example, if the user uses a mouse or joystick to indicate that the particle should be moved a distance $\Delta \mathbf{d}$, where the bold type indicates a vector having x and/or y components, and a time available for moving the particle is limited to a

maximum Δt , by an upper bound on magnitude of excitation voltage computer system 306 may determine an excitation voltage in accordance with an expression $\mathbf{u} = \sqrt{(C^{-1} \Delta \mathbf{d} / \Delta t)}$.

[0039] In an embodiment, computer system 304 may control signal generator 306 responsive to the determined locations and a desired location of the particle in the FOV of microscope 302 in accordance with a closed loop control algorithm to excite configurations of flow-beams 201-204 and generate SS jet-flows that move the particle to the desired location. By way of a simplified example of closed loop control of particle location, computer system 304 may control camera 303 to acquire a sequence of images of a particle in flow box 200, optionally at fixed time intervals. The computer may process a k-th image to determine a location, $p(t_k)$, of the particle at a time t_k at which camera 303 acquired the image of the particle. Assuming an image acquisition and processing time, τ , computer system 304 may estimate a location of the particle $p(t_k + \tau)$ at a current time $(t_k + \tau)$ using an estimate of particle velocity at time t_k to how far the particle traveled in time τ . An estimate of velocity may be determined based on images of the particle at acquisition time t_k and at an acquisition time prior to t_k , and/or SS jet-flow in the fluid at time t_k determined from excitation voltage $\mathbf{u}$ at time t_k and flow control matrix C . Given $p(t_k + \tau)$ and a desired final location p_D computer system 304 may determine a new setting for excitation voltage $\mathbf{u}$ based on flow control matrix C responsive to $[p_D - p(t_k + \tau)]$.

[0040] To provide advantageous open or closed loop control of the location of a particle suspended in a fluid in flow box 200, PMS 300 may be calibrated to determine the components $c_{i,j}$ of flow control matrix C . In an embodiment of the disclosure a given component $c_{i,j}$ of the flow control matrix C may be determined by applying a known excitation voltage to only flow beam 20j (for example if $j=2$ applying excitation voltage only to flow beam 202, and if $j=3$ applying excitation voltage only to flow beam 203) and controlling camera 303 to acquire a time sequence of images of a particle in the fluid. Processing the images to determine distances traveled by the particle between times at which camera 303 acquires the images may be used to determine the velocity components v_i of the particle caused by a SS jet-flow generated by exciting flow-beam 20j. If the known excitation voltage has amplitude A , then $c_{i,j}$ may be determined from an expression $c_{i,j} = v_i / A^2$.

[0041] It is noted that in the above discussion a flow box and PMS are shown and described having a plurality of flow-beams that are substantially coplanar. However, practice of an

embodiment of the disclosure is not limited to coplanar flow-beams. By way of example, Figs. 5A and 5B schematically show cutaway images of flow boxes 401 and 402 respectively having configurations of flow-beams that are not coplanar. The flow boxes enable convenient three DOF control of particle motion and position. Flow box 401 comprises four vertical flow-beam stands 410 each comprising two flow beams 412, optionally oriented at right angles to each other. The four flow beam stands 410 are symmetrically positioned in flow box 401 with a 90° angle between adjacent flow beam stands 410 to exhibit substantially four fold rotational symmetry. Flow box 402 comprises three vertical flow-beam stands 410 symmetrically positioned in flow box 402 with a 120° angle between adjacent flow beam stands 410 to exhibit substantially three fold rotational symmetry.

[0042] It is also noted that whereas cantilever flow beams are discussed above to provide SS jet-flows, practice of an embodiment of the disclosure is not limited to flow-beams. For example a flexible whip-like body may be mechanically excited to cause a free end of the whip-like body to oscillate and generate SS flow characterized by SS jet-flow. In addition free ends of a vibrating body used to generate an SS jet-flow may have shape different from the square appearing ends shown above. For example, a free end may be configured having a point or being rounded. Nor is micromanipulation of a particle limited to controlling substantially linear motion of a particle. A fluid vortex generated by vibration of a flow-beam may be used to rotate a particle.

[0043] There is therefore provided in accordance with an embodiment of the disclosure, apparatus for controlling movement and location of a particle suspended in a fluid, the apparatus comprising: a container configured to contain a fluid in which the particle is suspended; at least one elastic body configured to be located in the fluid; an actuator controllable to generate vibrations in the at least one elastic body that produce a steady streaming (SS) jet-flow of fluid to move the particle by advection along a direction of the jet-flow. Optionally vibrations of an elastic body of the at least one elastic body generate the jet-like flow and a pair of vortices in the fluid. Optionally the apparatus is configured to use a vortex of the pair of vortices to rotate the particle in the fluid.

[0044] In an embodiment the apparatus is configured to use a jet-flow to rotate the particle in the fluid. In an embodiment the at least one elastic body comprises at least two elastic bodies and the actuator is configured to generate vibrations in different elastic bodies of the at least two elastic bodies to produce jet-like flows in different directions that move the particle in different directions. Optionally the at least two elastic bodies comprises at least three elastic

bodies. Additionally or alternatively the jet-like flows may be substantially coplanar. Additionally or alternatively at least one of the jet-like flows is not coplanar with another of the jet-like flows.

[0045] In an embodiment the flow of fluid in the jet-like flows is Stokes flow. In an embodiment flow of fluid generated in the fluid by the vibrations is not Stokes flow.

[0046] In an embodiment an elastic body of the at least one elastic body is a beam having a longitudinal axis and the vibrations generated in the beam are flexural vibrations of the beam that cause a free end of the beam to oscillate. Optionally a direction along which fluid in the jet-like flow generated by the vibrations in the beam is substantially parallel to the longitudinal axis of the beam.

[0047] In an embodiment an elastic body of the at least one elastic body comprises piezoelectric material that is excited to generate the vibrations.

[0048] There is further provided in accordance with an embodiment, a method of controlling motion of a particle, the method comprising: suspending the particle in a fluid; and generating at least one jet-like fluid flow in the fluid to move the particle by advection. Optionally the method comprises generating vortices in the fluid and rotating the particle. Additionally or alternatively the at least one jet-like flow comprises a plurality of jet-like flows that flow in different directions. Optionally, the flow directions are substantially coplanar and are controllable to move the particle in a plane. Optionally, at least one of the plurality of jet-like flow directions is not coplanar with another of the jet-like flow directions. Optionally the method comprises controlling the jet-like flows to move the particle along non-coplanar directions.

[0049] In the description and claims of the present application, each of the verbs, “comprise” “include” and “have”, and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb.

[0050] Descriptions of embodiments of the disclosure in the present application are provided by way of example and are not intended to limit the scope of the disclosure. The described embodiments comprise different features, not all of which are required in all embodiments. Some embodiments utilize only some of the features or possible combinations of the features. Variations of embodiments of the disclosure that are described, and embodiments comprising different combinations of features noted in the described embodiments, will occur to persons of the art. The scope of the invention is limited only by the claims.

CLAIMS

1. Apparatus for controlling movement and location of a particle suspended in a fluid, the apparatus comprising:
 - a container configured to contain a fluid in which the particle is suspended;
 - at least one elastic body configured to be located in the fluid;
 - an actuator controllable to generate vibrations in the at least one elastic body that produce a steady streaming (SS) jet-flow of fluid to move the particle by advection along a direction of the jet-flow.
2. The apparatus according to claim 1 wherein vibrations of an elastic body of the at least one elastic body generate the jet-like flow and a pair of vortices in the fluid.
3. The apparatus according to claim 2 wherein the apparatus is configured to use a vortex of the pair of vortices to rotate the particle in the fluid.
4. The apparatus according to any of claims 1-3 wherein the apparatus is configured to use a jet-flow to rotate the particle in the fluid.
5. The apparatus according to any of claims 1-4 wherein the at least one elastic body comprises at least two elastic bodies and the actuator is configured to generate vibrations in different elastic bodies of the at least two elastic bodies to produce jet-like flows in different directions that move the particle in different directions.
6. The apparatus according to claim 5 wherein the at least two elastic bodies comprises at least three elastic bodies.
7. The apparatus according to claim 5 or claim 6 wherein the jet-like flows are substantially coplanar.
8. The apparatus according to claim 5 or claim 6 wherein at least one of the jet-like flows is not coplanar with another of the jet-like flows.

9. The apparatus according to any of the preceding claims wherein the flow of fluid in the jet-like flows is Stokes flow.
10. The apparatus according to any of the preceding claims wherein flow of fluid generated in the fluid by the vibrations is not Stokes flow.
11. The apparatus according to any of the preceding claims wherein an elastic body of the at least one elastic body is a beam having a longitudinal axis and the vibrations generated in the beam are flexural vibrations of the beam that cause a free end of the beam to oscillate.
12. The apparatus according to claim 11 wherein a direction along which fluid in the jet-like flow generated by the vibrations in the beam is substantially parallel to the longitudinal axis of the beam.
13. The apparatus according to any of the preceding claims wherein an elastic body of the at least one elastic body comprises piezoelectric material that is excited to generate the vibrations.
14. A method of controlling motion of a particle, the method comprising:
suspending the particle in a fluid; and
generating at least one jet-like fluid flow in the fluid to move the particle by advection.
15. The method according to claim 14 and comprising generating vortices in the fluid and rotating the particle.
16. The method according to claim 14 or claim 15 wherein the at least one jet-like flow comprises a plurality of jet-like flows that flow in different directions.
17. The method according to claim 16 wherein the flow directions are substantially coplanar and are controllable to move the particle in a plane.
18. The method according to claim 16 wherein at least one of the plurality of jet-like flow directions is not coplanar with another of the jet-like flow directions.

19. The method according to claim 18 and comprising controlling the jet-like flows to move the particle along non-coplanar directions.

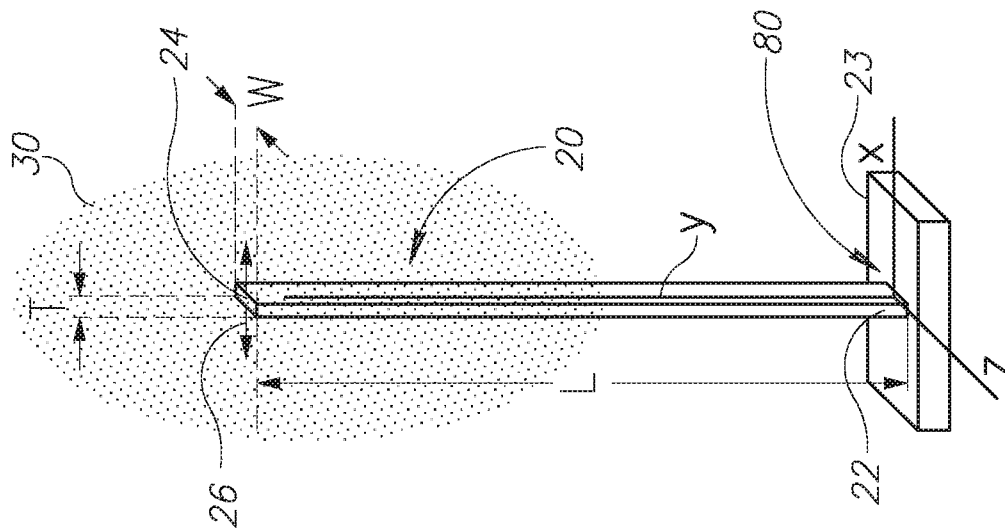


FIG. 1A

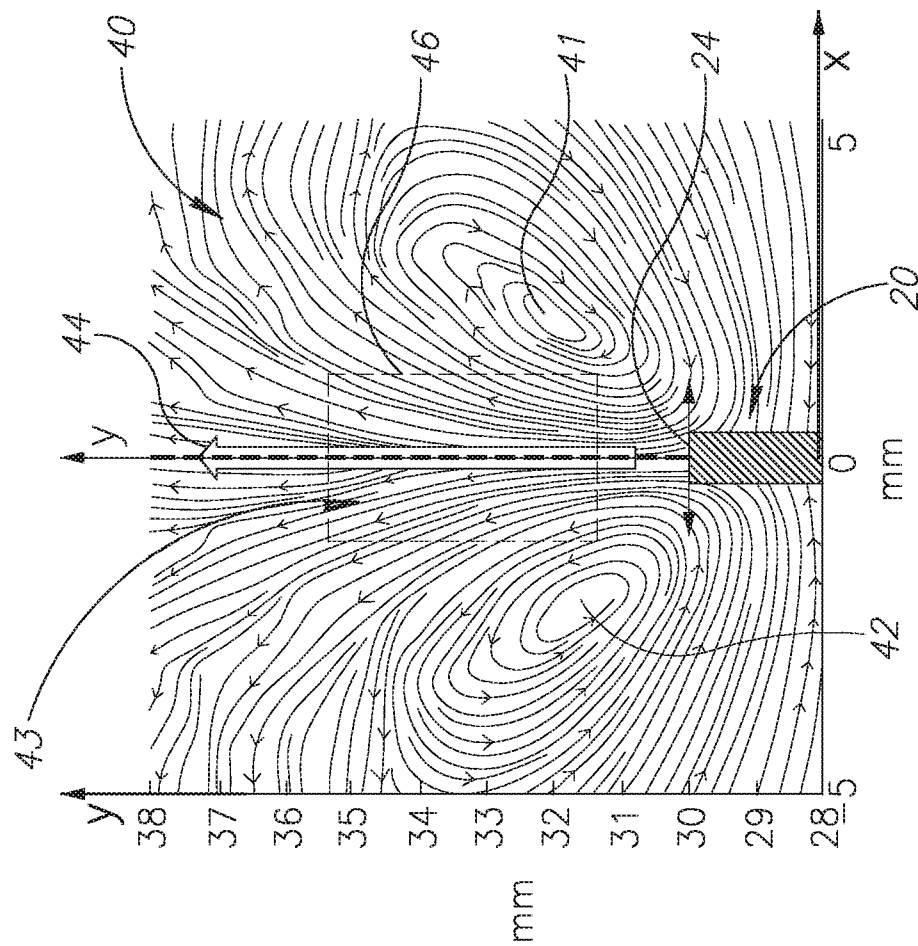


FIG. 1B

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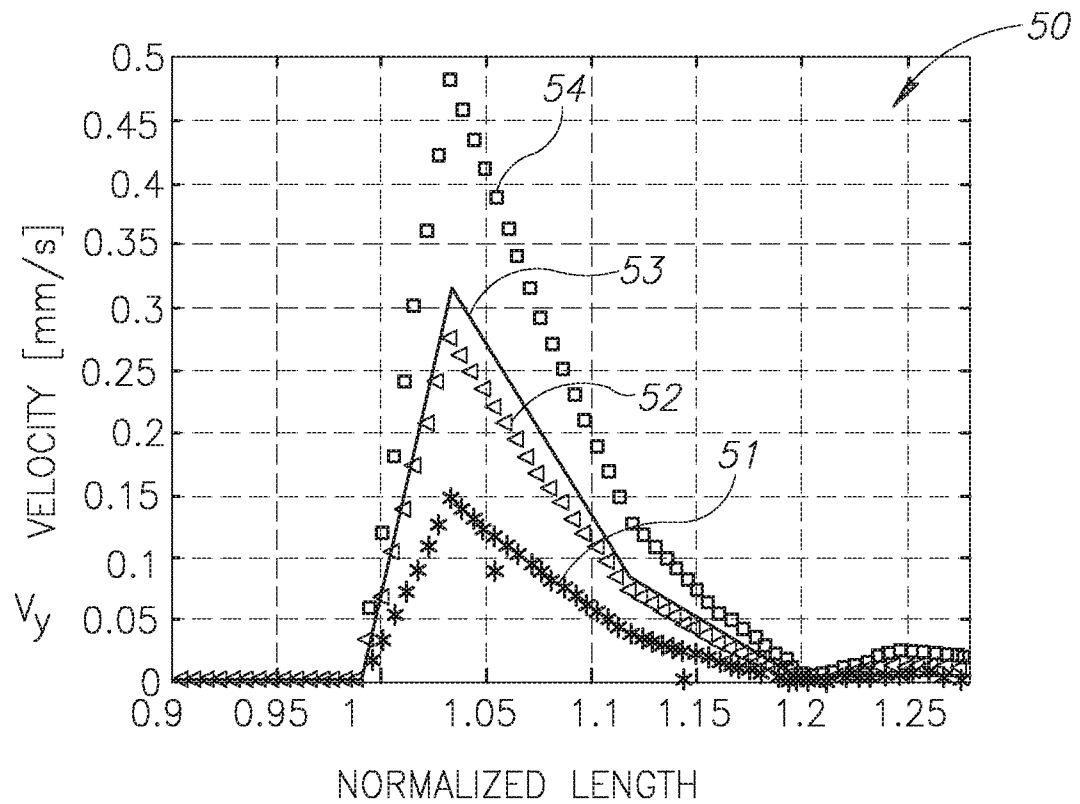


FIG.1C

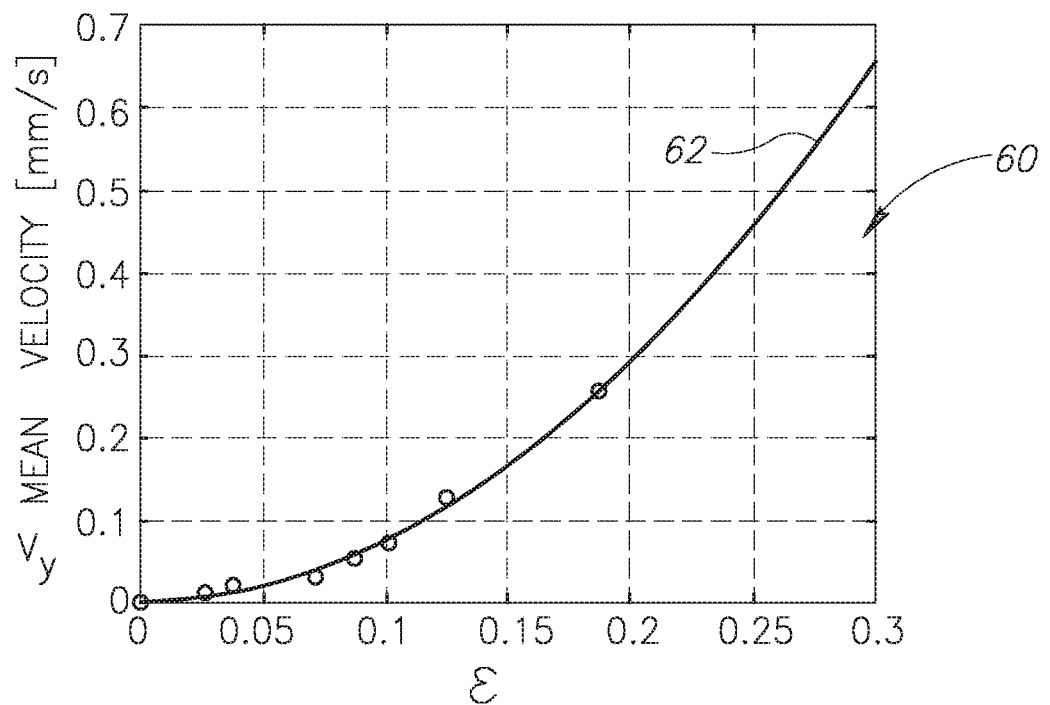


FIG.1D

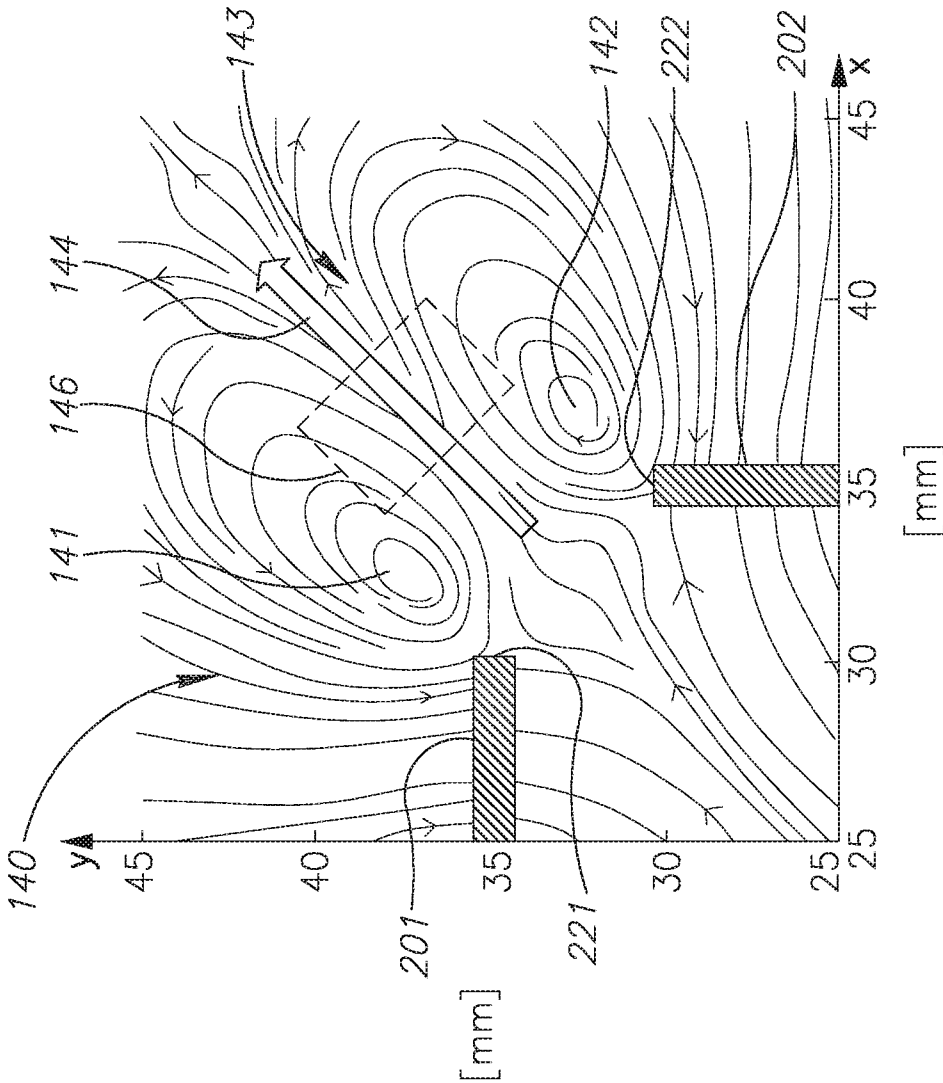


FIG. 2A

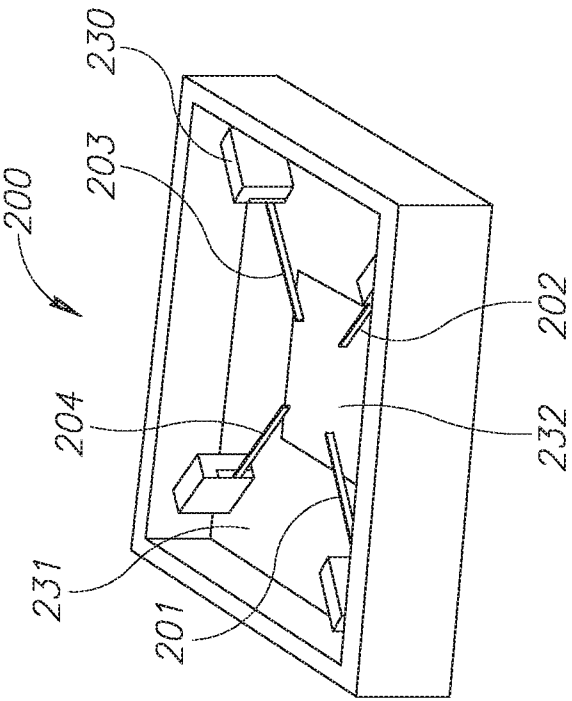


FIG. 2B

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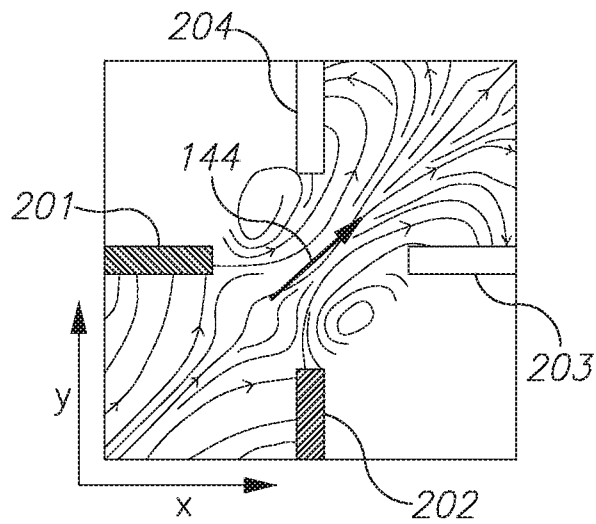


FIG. 3A

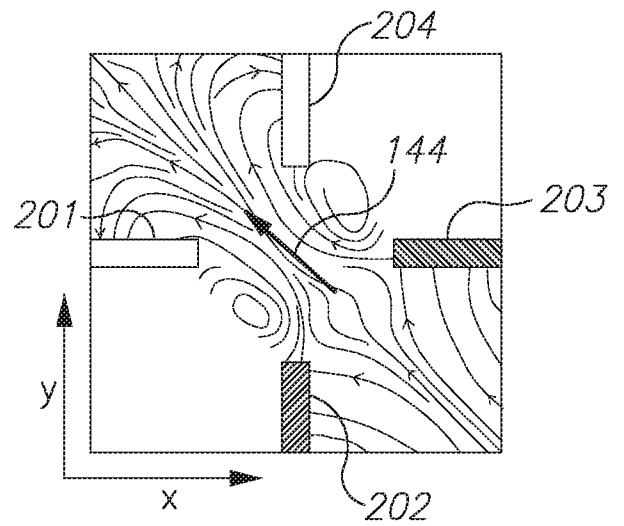


FIG. 3B

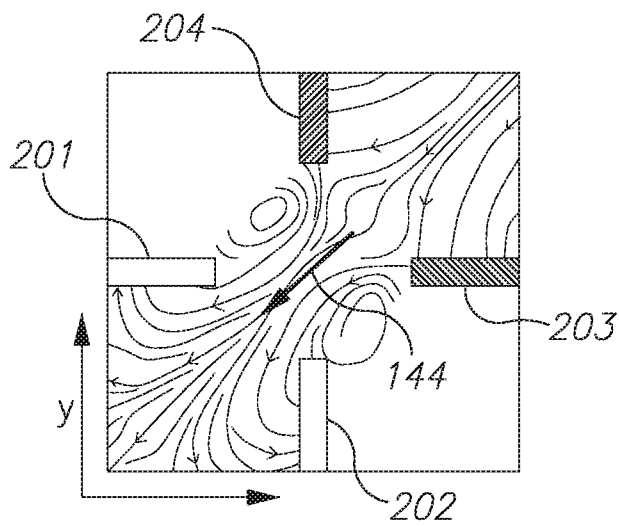


FIG. 3C

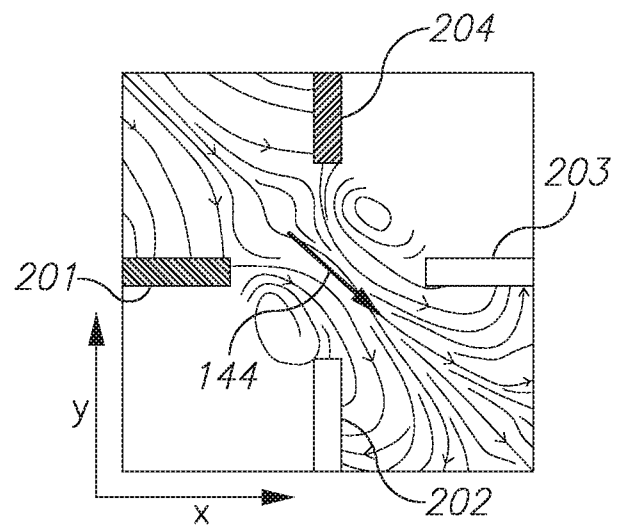


FIG. 3D

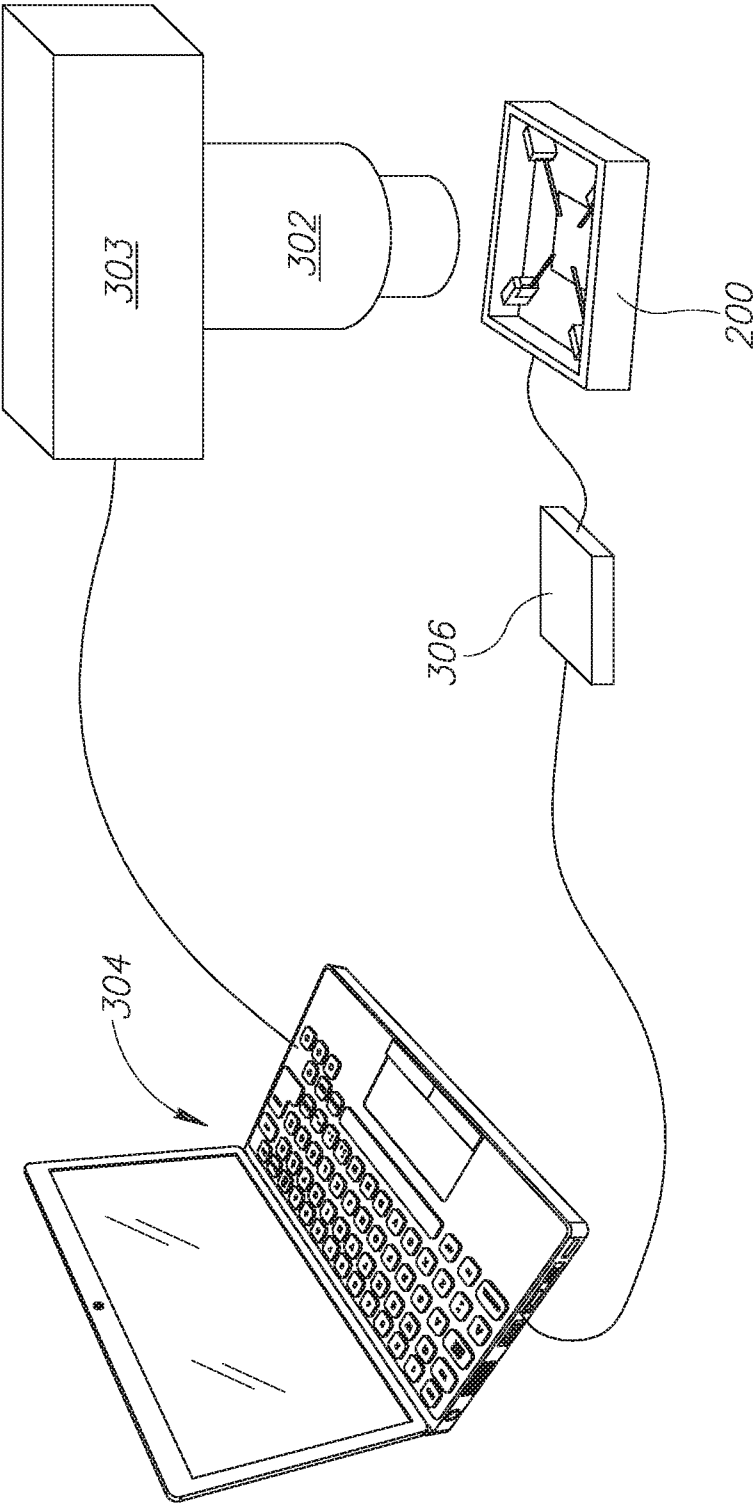


FIG.4

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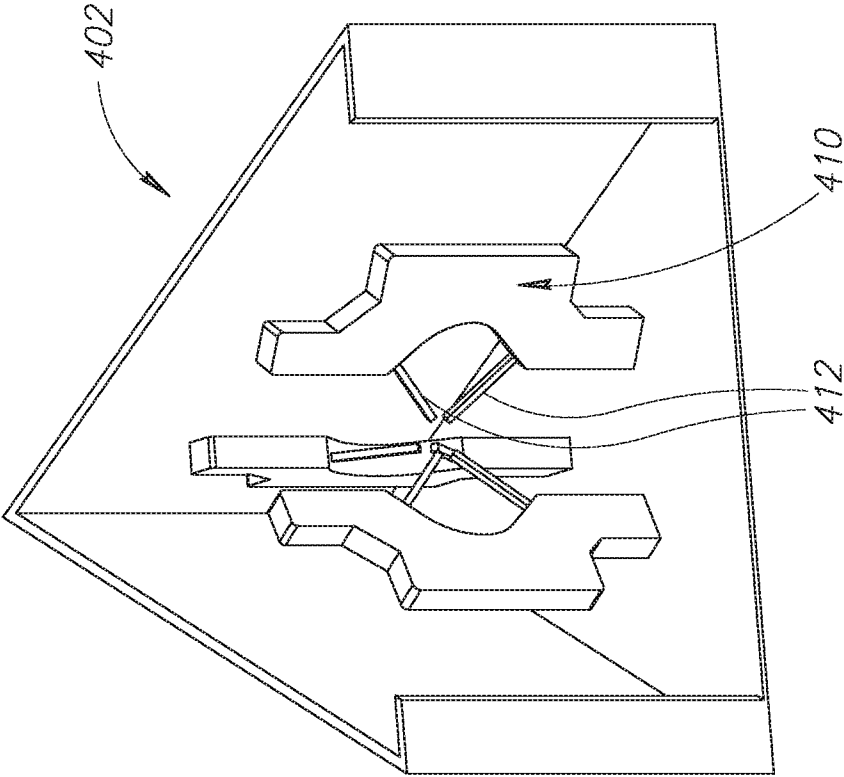


FIG. 5B

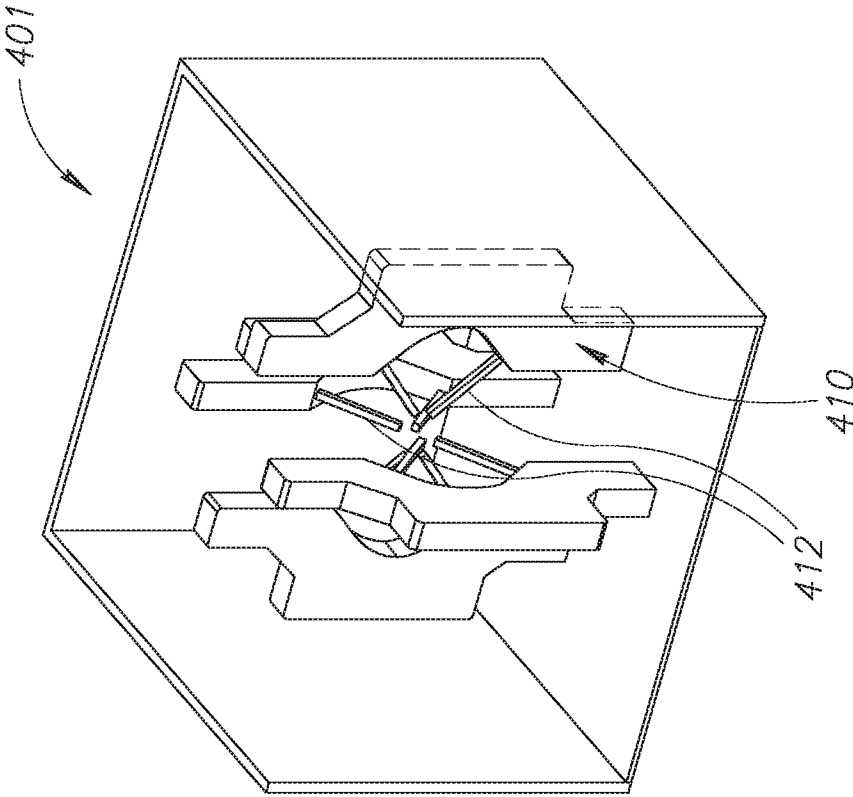


FIG. 5A

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2017/050165

A. CLASSIFICATION OF SUBJECT MATTER IPC (2017.01) G01N 1/28, G02B 21/32, B06B 1/06, H02N 2/02, B01L 3/00 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) IPC (2017.01) B01L, B06B 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) Databases consulted: Esp@cenet, Google Patents, Google Scholar, FamPat database Search terms used: Particle ,Jet flow, Mmanipulation, Eddies, Vortex, Trapping, Control, Vibration, Advection, Piezoelectric		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2009178784 A KYUSHU INSTITUTE OF TECHNOLOGY 13 Aug 2009 (2009/08/13) Para. [0001],[009],[0014]-[0021]; fig. 1&2 ---- based on machine translation provided by J-PlatPat	1,2,5-7,9,10,13
A		3,4,8,11,12
X	US 2014087412 A1 4DX PTY LTD. 27 Mar 2014 (2014/03/27) Abstract; fig. 1; para. [0027]-[0030], [0037]-[0038], [0132], [0135]	14-19
X	US 2006005634 A1 SCHROEDER C. M. et al. 12 Jan 2006 (2006/01/12) Abstract; fig. 1&3; para. [0009]- [0011], [0027], [0030], [0039]	14,16,17
X	TANYERI M. et al. "Manipulation and Confinement of Single Particles Using Fluid Flow" (2013) Nano letter, Vol. 13, No. 6, Pages 2357-2364, DOI:10.1021/nl4008437 (published on-line 17 May 2013). 17 May 2013 (2013/05/17) Abstract; fig. 1-4	14,16,17
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 22 May 2017		Date of mailing of the international search report 24 May 2017
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616		Authorized officer GUTMAN Ariel Telephone No. 972-2-5657816

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2017/050165

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	: LIEU V. H. et al. " Hydrodynamic Tweezers: Impact of Design Geometry on Flow and Microparticle Trapping" (2012) Analytical Chemistry, Vol. 84, No. 4, Pages 1963-1968, DOI: dx.doi.org/10.1021/ac203002z (published on-line 24 Jan. 2012). 24 Jan 2012 (2012/01/24) Abstract; "Materials and methods"	1-13
A	LUTZ B. R. et al. " Hydrodynamic Tweezers: 1. Noncontact Trapping of Single Cells Using Steady Streaming Microeddies" (2006) Vol. 78, No. 15, Pages 5429-5435, 10.1021/ac060555y (published on-line 7 Jul. 2006). 07 Jul 2000 (2000/07/07) Abstract; Fig. 1; "Methods"	1-13
P,X	AMIT R. et al. "Characterization of steady streaming for a particle manipulation system" (2014) Biomedical Microdevices, Vol. 18, No. 2, Article 39, Pages 1-20, DOI: 10.1007/s10544-016-0055-1 (published on line 23 Apr. 2016). 23 Apr 2016 (2016/04/23) The whole document	1-19

International application No.
PCT/IL2017/050165

Form PCT/ISA/210 (patent family annex) (January 2015)