(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/003689 A1

(51) International Patent Classification:
G01N 15/10 (2006.01) *G21K 1/00* (2006.01)
G01N 21/53 (2006.01)

(21) International Application Number:
PCT/SG2013/000270

(22) International Filing Date:
28 June 2013 (28.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/665,511 28 June 2012 (28.06.2012) US

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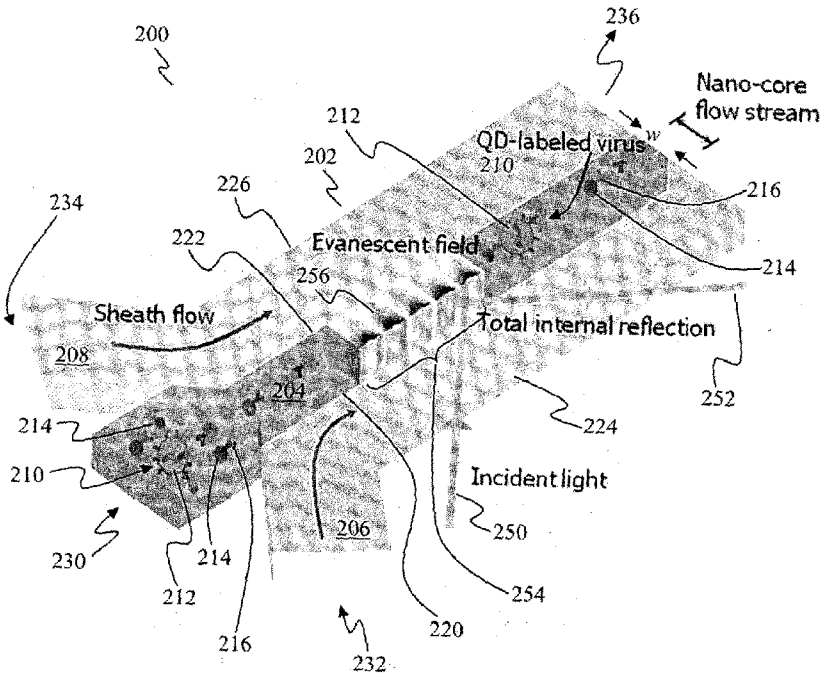
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

[Continued on next page]

(54) Title: DETECTION DEVICE AND METHOD FOR DETECTION OF PARTICLES



(57) Abstract: According to embodiments of the present invention, a detection device for detection of particles is provided. The detection device includes a flow channel adapted to guide a sample flow containing the particles to be detected and a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween, and an optical arrangement configured to direct an optical signal to within the flow channel at the interface to generate an evanescent wave into the sample flow for detection of the particles. According to further embodiments of the present invention, a method for detection of particles is also provided.

WO 2014/003689 A1

Published:

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

DETECTION DEVICE AND METHOD FOR DETECTION OF PARTICLES

Cross-Reference To Related Application

[0001] This application claims the benefit of priority of US provisional application No. 61/665,511, filed 28 June 2012, the content of it being hereby incorporated by reference in its entirety for all purposes.

Technical Field

[0002] Various embodiments relate to a detection device and a method for detection of particles.

Background

[0003] Detection and manipulation of a single molecule/nanoparticle with light have great potential in applications of biological and chemical sciences. Nevertheless, only average characteristic can be measured for bulk collection of molecules. However, the measurement of individual behavior for single molecules is an urge for today's research, which is still a big challenge in traditional optics method. For example, the diffraction limit makes it very difficult to detect particles of 100s of nanometers.

[0004] From a quantum point of view, light consists of photons that carry angular momentum, which can be transferred to objects of finite mass by the pressure of the photons, namely optical force. Many optical devices such as optical tweezers, optical lattice filters and waveguides are utilized to manipulate microscopic bio-samples and particles ranging in size from atom level to hundreds of micrometers. As a result, optical force has become a significant tool for research in the field of biology, chemistry and physics. Among them, the near-field optical manipulation has become a research forefront with prime interests on detection and sorting of single molecules/nanoparticles via evanescent field whose size is sufficiently smaller than the wavelength of the light.

[0005] A total internal reflection (TIR) microscopy is based on the principle of evanescent field illumination, which is created by the TIR between two media with different refractive indices, such as glass and water. A TIR microscopy has a higher sensitivity and signals-to-noise ratio than conventional microscopy. Therefore, it is one of the most widely used technologies in the detection of single molecules. Besides, the evanescent electromagnetic field decays exponentially, which makes the optical gradient field strong enough to hold and sort a single molecule/nanoparticle at the interface of two mediums. However, TIR needs several improvements to meet the needs of today's research and technology. Firstly, the penetration depth into the sample media is usually no more than 200 nm. Thus, only the samples near the interface of the two media can be detected. Secondly, compared to a pure microfluidic system, the solid-liquid interface cannot be fully exploited as the platform for complex chemical and biological processing and analysis. Finally, a pure liquid system is an advantage for real time detection and sorting which is difficult for the solid-liquid hybrid approach.

[0006] Hydrodynamic focusing is a pure microfluidic technology by building up the walls of the tunnel, through which a sample may flow, using the effects of fluid dynamics. The sample is injected into the middle of a sheath flow and the extreme core flow stream can be controlled down to 50 nm. The sheath flow and the core flow stream do not mix and form a two-layer stable flow when they differ enough in their velocity or density.

Summary

[0007] According to an embodiment, a detection device for detection of particles is provided. The detection device may include a flow channel adapted to guide a sample flow containing the particles to be detected and a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween, and an optical arrangement configured to direct an optical signal to within the flow channel at the interface to generate an evanescent wave into the sample flow for detection of the particles.

[0008] According to an embodiment, a method for detection of particles is provided. The method may include supplying a sample flow containing the particles to be detected through a flow channel, supplying a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween, and directing an optical signal at the interface to generate an evanescent wave into the sample flow for detection of the particles.

Brief Description of the Drawings

[0009] In the drawings, like reference characters generally refer to like parts throughout the different views. The drawings are not necessarily to scale, emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the invention are described with reference to the following drawings, in which:

[0010] FIG. 1A shows a schematic block diagram of a detection device for detection of particles, according to various embodiments.

[0011] FIG. 1B shows a flow chart illustrating a method for detection of particles, according to various embodiments.

[0012] FIG. 2A shows a schematic perspective view of a detection device, according to various embodiments.

[0013] FIG. 2B shows a schematic illustration of a generated evanescent wave in the core flow stream based on the embodiment of FIG. 2A.

[0014] FIG. 2C shows a simulated evanescent wave in a microchannel based on the embodiment of FIG. 2A.

[0015] FIG. 3A shows a plot illustrating the relationship between the penetration depth with the incident angle, according to various embodiments.

[0016] FIG. 3B shows a plot illustrating the relationship between the intensity of the evanescent field with incident angle, according to various embodiments.

[0017] FIG. 4A shows the simulation result of the optical force acting on a particle under an evanescent wave, according to various embodiments.

[0018] FIG. 4B shows a plot illustrating the relationship between the size of quantum dots (QDs) and the optical force acting on the QDs, according to various embodiments.

[0019] FIG. 4C shows a plot illustrating the acceleration of quantum dots (QDs) of different sizes in a flow channel, according to various embodiments.

[0020] FIG. 5A shows a microscopy image of a fabricated PDMS chip, according to various embodiments.

[0021] FIG. 5B shows a fluorescent microscopy image of total internal reflection occurring at a liquid-liquid interface between the sheath flow and the core flow of the embodiment of FIG. 5A.

[0022] FIG. 5C shows a three-dimensional (3D) confocal microscopy image of the flow streams in the microchannel of the embodiment of FIG 5A.

[0023] FIGS. 6A to 6C show EMCCD microscopy images of the detection of particles by evanescent field, according to various embodiments.

[0024] FIGS. 7A to 7E show microscopy images of the detection of micro/nano particles by evanescent wave illumination in the nano-optofluidic system of various embodiments.

Detailed Description

[0025] The following detailed description refers to the accompanying drawings that show, by way of illustration, specific details and embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, logical, and electrical changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

[0026] Embodiments described in the context of one of the methods or devices are analogously valid for the other method or device. Similarly, embodiments described in the context of a method are analogously valid for a device, and vice versa.

[0027] Features that are described in the context of an embodiment may correspondingly be applicable to the same or similar features in the other embodiments. Features that are

described in the context of an embodiment may correspondingly be applicable to the other embodiments, even if not explicitly described in these other embodiments. Furthermore, additions and/or combinations and/or alternatives as described for a feature in the context of an embodiment may correspondingly be applicable to the same or similar feature in the other embodiments.

[0028] In the context of various embodiments, the articles "a", "an" and "the" as used with regard to a feature or element includes a reference to one or more of the features or elements.

[0029] In the context of various embodiments, the phrase "at least substantially" may include "exactly" and a reasonable variance.

[0030] In the context of various embodiments, the term "about" or "approximately" as applied to a numeric value encompasses the exact value and a reasonable variance.

[0031] As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items.

[0032] As used herein, the phrase of the form of "at least one of A or B" may include A or B or both A and B. Correspondingly, the phrase of the form of "at least one of A or B or C", or including further listed items, may include any and all combinations of one or more of the associated listed items.

[0033] Various embodiments may relate to optofluidics, for example for detection of single molecules in a fluid using evanescent wave generated by way of total internal reflection (TIR) at a liquid-liquid interface. The evanescent wave may also exert an optical force on the single molecules for manipulating the single molecules.

[0034] Various embodiments may combine fluid dynamics technology with TIR microscopy for the detection and sorting of single molecules/nanoparticles.

[0035] Various embodiments may provide a nano-optofluidic device or system for single molecule detection and sorting. The nano-optofluidic device/system may employ total internal reflection (TIR) in or at a liquid-liquid interface for detection of single molecules or nanoparticles. The total internal reflection (TIR) occurring at the liquid-liquid interface may generate an evanescent wave for single molecule detection. The nano-optofluidic system may also allow sorting of single molecules or nanoparticles based on hydrodynamic focusing and optical force by an evanescent wave. In various

embodiments, nano-sized samples or particles in liquid may be measured and counted even if the size of the samples or particles is at least substantially smaller than the diffraction limit. For example, imaging of approximately 5 - 50 nm quantum dots (QDs) may be performed using the nano-optofluidic system of various embodiments.

[0036] As compared to conventional TIR microscopy which can only detect samples near a solid-liquid interface, all samples or particles may be focused in the extreme centre flow in the nano-optofluidic system of various embodiments and may be measured and manipulated in real time. Various embodiments may have a wide range of applications in areas including single molecule detection, imaging and counting.

[0037] FIG. 1A shows a schematic block diagram of a detection device 100 for detection of particles, according to various embodiments. The detection device 100 includes a flow channel 102 adapted to guide a sample flow containing the particles to be detected and a sheath flow through the flow channel 102, the sheath flow and the sample flow defining an interface therebetween, and an optical arrangement 104 configured to direct an optical signal to within the flow channel 102 at the interface to generate an evanescent wave into the sample flow for detection of the particles. The line represented as 106 is illustrated to show the relationship between the flow channel 102 and the optical arrangement 104, which may include optical coupling and/or mechanical coupling.

[0038] In other words, the detection device 100 may include a flow channel 102, for example a microchannel, within which a sample flow containing the particles to be detected and a sheath flow may flow. The sheath flow may flow adjacent to the sample flow. The sheath flow may flow in between a wall of the flow channel 102 and the sample flow such that the portion the sample flow adjacent the sheath flow may not abut the wall of the flow channel 102. This may minimise absorption or adsorption of the particles to be detected on the wall(s) of the flow channel 102.

[0039] The sheath flow may be in laminar flow with the sample flow. This may mean that the sample flow and the sheath flow do not at least substantially mix with each other, such that the sheath flow may flow in parallel to the sample flow. The sheath flow and the sample flow may form a two-layer stable flow. An interface may be defined between the sample flow and the sheath flow, as the sample flow and the sheath flow flow through

the flow channel 102. This may mean that a liquid-liquid interface or boundary may be defined between the sample flow and the sheath flow within the flow channel 102.

[0040] The detection device 100 may further include an optical arrangement 104 which may direct an optical signal (e.g. light) to the interior of the flow channel 102, at the liquid-liquid interface defined between the sample flow and the sheath flow, so as to generate an evanescent wave. The optical signal may be directed from the side of the sheath flow and through the sheath flow to the liquid-liquid interface. The evanescent wave that is generated may propagate or penetrate into the sample flow for detection of the particles that may be present in the sample flow. For example, the evanescent wave may illuminate the particles for detection of the particles.

[0041] In various embodiments, the sheath flow may be supplied on one side of the sample flow. This may mean that the sheath flow and the sample flow may flow side by side.

[0042] In various embodiments, the sample flow may be provided or injected into and through the sheath flow, for example into the middle of the sheath flow, such that the sample flow may be flanked by the sheath flow on opposite sides of the sample flow or may be at least substantially surrounded by the sheath flow, for example on all sides or around the sample flow.

[0043] In the context of various embodiments, the term "evanescent wave" may mean a wave or a near-field wave having an intensity which may decay (e.g. exponential decay) with distance from the point or plane at which the evanescent wave is generated. This may mean that the evanescent wave generated at the liquid-liquid interface defined between the sample flow and the sheath flow may have an optimal intensity near the interface, and whose intensity decays in the direction from the liquid-liquid interface into the sample flow. As the decay rate of the evanescent wave may be high, the evanescent wave may penetrate only a short distance (small penetration depth) into the sample flow such that portions of the sample flow beyond the reach of the evanescent wave may remain at least substantially unaffected by the evanescent wave. This may minimise any background properties or noise during any characterization activities as only particles in the sample flow that are within the reach of the evanescent wave may be characterised and/or detected and/or measured, with minimal interference from background noise.

[0044] In various embodiments, the width of the sample flow may be controllable by the sheath flow. The width of the sample flow may be controllable by the sheath flow such that a single particle flows through a cross section of the flow channel at a time. This means that single particle detection may be carried out.

[0045] In various embodiments, the width of the sample flow may be smaller than a wavelength of the optical signal.

[0046] In various embodiments, the width of the sample flow may be less than about 1 μm, for example less than about 0.8 μm, or less than about 0.5 μm.

[0047] The detection device 100 may include a first inlet and a second inlet, wherein the first inlet and the second inlet may be in fluid communication with the flow channel 102, wherein the first inlet may be configured for supplying the sample flow into the flow channel 102, and wherein the second inlet may be configured for supplying the sheath flow into the flow channel 102. Therefore, the sample flow may be supplied through the first inlet while the sheath flow may be supplied through the second inlet.

[0048] In various embodiments, the flow channel 102 may further be adapted to guide a second sheath flow through the flow channel 102, the second sheath flow and the sample flow defining a second interface therebetween.

[0049] The second sheath flow may flow adjacent to the sample flow. The second sheath flow may flow in between another wall of the flow channel 102 and the sample flow such that the portion the sample flow adjacent the second sheath flow may not abut that wall of the flow channel 102. This may minimise absorption or adsorption of the particles to be detected on the wall(s) of the flow channel 102. The second sheath flow may be in laminar flow with the sample flow. This may mean that the sample flow and the second sheath flow do not at least substantially mix with each other, such that the second sheath flow may flow in parallel to the sample flow. An interface may be defined between the sample flow and the second sheath flow, as the sample flow and the second sheath flow flow through the flow channel 102. This may mean that a liquid-liquid interface or boundary may be defined between the sample flow and the second sheath flow within the flow channel 102.

[0050] In various embodiments, the width of the sample flow may be controllable by the second sheath flow.

[0051] In various embodiments, the width of the sample flow may be controllable by the sheath flow and the second sheath flow. The width of the sample flow may be controllable by the sheath flow and the second sheath flow such that a single particle flows through a cross section of the flow channel at a time. This means that single particle detection may be carried out. In addition, the position of the sample flow within the flow channel 102 may be controllable by the sheath flow and the second sheath flow.

[0052] The detection device 100 may include a third inlet in fluid communication with the flow channel 102, wherein the third inlet may be configured for supplying the second sheath flow into the flow channel 102.

[0053] In various embodiments, the detection device 100 may further include flow rate adjustment means for adjusting a flow rate ratio between the sample flow and the sheath flow for controlling a width of the sample flow. The flow rate adjustment means may be used to control or change the flow rate of the sample flow or the sheath flow or both.

[0054] In various embodiments, the detection device 100 may further include flow rate adjustment means for adjusting at least one of a first flow rate ratio between the sample flow and the sheath flow, or a second flow rate ratio between the sample flow and the second sheath flow, for controlling a width of the sample flow. This means that for controlling the width of the sample flow, the first flow rate ratio and/or the second flow rate ratio may be adjusted by the flow rate adjustment means. The flow rate adjustment means may be used to control or change the flow rate of the sample flow or the sheath flow or the second sheath flow or any combination thereof. In addition, adjusting at least one of the first flow rate ratio between the sample flow and the sheath flow, or the second flow rate ratio between the sample flow and the second sheath flow may control the position of the sample flow within the flow channel 102, for example in the middle of the flow channel 102 or away from the central axis of the flow channel 102 towards one side of the flow channel 102.

[0055] In the context of various embodiments, the flow rate adjustment means may include at least one of a pump, a valve, a flow meter, a gauge or any delivery means or system.

[0056] In the context of various embodiments, at least one of the sheath flow or the second sheath flow may act as a buffer which may assist in guiding the flow of the sample flow through the flow channel 102.

[0057] In various embodiments, the optical arrangement 104 may be configured to generate the evanescent wave by way of total internal reflection (TIR) of the optical signal at the interface between the sample flow and the sheath flow. This may mean that the optical signal may be directed at the interface defined between the sheath flow and the sample flow at an incident angle that may be larger than a critical angle defined by the refractive indices of the respective solutions or media of the sample flow and the sheath flow, and subsequently total internally reflected at the interface, and in the process generating the evanescent wave.

[0058] In various embodiments, the optical arrangement 104 may include a waveguide integrally formed with the flow channel 102, the waveguide being configured to direct the optical signal at the interface between the sample flow and the sheath flow. The waveguide being integrally formed with the flow channel 102 may mean that the waveguide may be integrated with the flow channel 102 on the same substrate or chip, e.g. an on-chip waveguide. The waveguide may be an optical waveguide or an optical fiber.

[0059] In various embodiments, the optical arrangement 104 may include a lens integrally formed with the flow channel 102, the lens being configured to focus the optical signal at the interface between the sample flow and the sheath flow. The lens being integrally formed with the flow channel 102 may mean that the lens may be integrated with the flow channel 102 on the same substrate or chip, e.g. an on-chip lens. The lens may be arranged at the output side of the waveguide for focusing the optical signal guided by the waveguide at the interface defined between the sample flow and the sheath flow.

[0060] In various embodiments, the optical arrangement 104 may include a radiation source configured to provide the optical signal. The radiation source may be or may include a laser, e.g. a pulsed laser.

[0061] In various embodiments, the detection device 100 may further include a detector for detection of the particles.

[0062] In various embodiments, the detection device 100 may further include a labeling module configured for coupling each particle with an optical label, the optical label configured to provide a signal in response to the evanescent wave for detection of the particles.

[0063] In the context of various embodiments, the optical label may have a bead-like structure or shape.

[0064] In the context of various embodiments, the optical label may be or may include a quantum dot (QD) or a gold (Au) nanoparticle. The gold nanoparticle (Au NP) may be of any suitable shape (e.g. bead-like, rod-like, polygonal-shaped) and/or of any suitable size (e.g. about 5 to about 100 nm), for example depending on the desired signal to be produced in response to the evanescent wave.

[0065] In various embodiments, the optical label may be configured to fluoresce in response to the evanescent wave. This may mean that the optical label may be a fluorescent label.

[0066] In various embodiments, the optical label may be configured to reflect a portion of wavelength of the evanescent wave.

[0067] In the context of various embodiments, the flow channel may be made of a material selected from the group consisting of polydimethylsiloxane (PDMS), polymethyl methacrylate (PMMA), glass and silicon, such as for example a silicon-based wafer, e.g. silicon wafer, or silicon-on-insulator (SOI).

[0068] In the context of various embodiments, the detection device 100 may be adapted for detecting particles of a size smaller than a diffraction limit imposed by the optical arrangement 104.

[0069] In the context of various embodiments, the evanescent wave may exert at least one optical force on the particles for deflecting the particles away from the sample flow for sorting the particles. In exerting at least one optical force on the particles, the evanescent wave may be used for the purpose of optical trapping for trapping and/or manipulating the particles present in the sample flow.

[0070] In the context of various embodiments, the particles may be selected from the group consisting of quantum dots, gold nanoparticles, living cells, chromosomes, organelles, biomolecules, proteins, viruses, bacteria and any combination thereof.

[0071] In the context of various embodiments, each particle may have a size of between about 5 nm and about 5 μm, for example between about 5 nm and about 3 μm, between about 5 nm and about 1 μm, between about 5 nm and about 500 nm, between about 5 nm and about 200 nm, between about 100 nm and about 500 nm, between about 500 nm and about 2 μm, or between about 50 nm and about 200 nm.

[0072] FIG. 1B shows a flow chart 120 illustrating a method for detection of particles, according to various embodiments.

[0073] At 122, a sample flow containing the particles to be detected is supplied through a flow channel. Therefore, the sample flow containing the particles may be flowed through the flow channel.

[0074] At 124, a sheath flow is supplied through the flow channel, the sheath flow and the sample flow defining an interface therebetween. Therefore, the sheath flow may be flowed through the flow channel. The sheath flow may be in laminar flow with the sample flow. The sheath flow and the sample flow may form a two-layer stable flow.

[0075] At 126, an optical signal is directed at the interface to generate an evanescent wave into the sample flow for detection of the particles.

[0076] It should be appreciated that the sample flow and the sheath flow may be supplied at least substantially simultaneously or in any order of sequence.

[0077] In various embodiments, the sheath flow may be supplied on one side of the sample flow. This may mean that the sheath flow and the sample flow may flow side by side.

[0078] In various embodiments, the sample flow may be provided or injected into and through the sheath flow, for example into the middle of the sheath flow, such that the sample flow may be flanked by the sheath flow on opposite sides of the sample flow or may be at least substantially surrounded by the sheath flow, for example on all sides or around the sample flow.

[0079] In various embodiments, at 124, the sheath flow may be supplied at a flow rate that is higher than a flow rate of the sample flow.

[0080] In various embodiments, at 126, the evanescent wave may be generated across a width of the sample flow. This may mean that the evanescent wave may propagate through the entire width of the sample flow.

[0081] In various embodiments, at 126, the optical signal may be directed at the interface between the sample flow and the sheath flow to generate the evanescent wave by way of total internal reflection (TIR) of the optical signal at the interface.

[0082] The method may further include focusing the optical signal at the interface between the sample flow and the sheath flow.

[0083] The method may further include varying a flow rate ratio between the sample flow and the sheath flow for controlling a width of the sample flow. This may mean controlling or changing the flow rate of the sample flow or the flow rate of the sheath flow relative or both.

[0084] In the context of various embodiments, the width of the sample flow may be less than about 1 μm, for example less than about 0.8 μm, or less than about 0.5 μm.

[0085] In the context of various embodiments, the width of the sample flow may be smaller than a wavelength of the optical signal.

[0086] In the context of various embodiments, the width of the sample flow may be controlled by the sheath flow such that a single particle flows through a cross section of the flow channel at a time.

[0087] In the context of various embodiments, the sample flow may include a solution or medium having a refractive index that is lower than a refractive index of a solution or medium of the sheath flow. In various embodiments, the refractive index of the solution of the sample flow may be between about 1.332 and about 1.432. In various embodiments, the refractive index of the solution of the sheath flow may be between about 1.333 and about 1.433.

[0088] In various embodiments, the refractive index of the solution of the sheath flow may be at least substantially equal to a refractive index of a material of the flow channel. This may provide a substantially smooth transition at the solid-liquid interface defined between the material of the flow channel and the sheath flow as the optical signal propagates through the material of the flow channel and into the sheath flow so as to minimise any distortion or scattering of the optical signal.

[0089] The method may further include supplying a second sheath flow through the flow channel, the second sheath flow and the sample flow defining a second interface therebetween. The second sheath flow may be in laminar flow with the sample flow.

[0090] In various embodiments, the second sheath flow may be supplied at a flow rate that is higher than a flow rate of the sample flow.

[0091] In various embodiments, the flow rate of the sheath flow and the flow rate of the second sheath flow may be at least substantially the same.

[0092] The method may further include varying a flow rate ratio between the sample flow and the second sheath flow for controlling a width of the sample flow. This may mean controlling or changing the flow rate of the sample flow or the flow rate of the second sheath flow or both.

[0093] In various embodiments, varying or adjusting the flow rate ratio between the sample flow and the sheath flow and the flow rate ratio between the sample flow and the second sheath flow may also control the position of the sample flow within the flow channel, for example the sample flow may be in the middle of the flow channel along the central axis of the flow channel or away from the central axis of the flow channel towards one side of the flow channel. As a non-limiting example, by providing a flow rate ratio between the sample flow and the sheath flow that is higher than the flow rate ratio between the sample flow and the second sheath flow may cause the sample flow to be pushed towards the second sheath flow, away from the central axis of the flow channel.

[0094] In various embodiments, the sheath flow may be supplied on a first side of the sample flow, while the second sheath flow may be supplied on a second side of the sample flow, wherein the first side and the second side are opposite sides. This may mean that the sample flow may be sandwiched in between the sheath flow and the second sheath flow.

[0095] In the context of various embodiments, the refractive index of the solution or medium of the second sheath flow may be between about 1.333 and about 1.433.

[0096] The method may further include coupling or labelling each particle to be detected with an optical label, the optical label configured to provide a signal in response to the evanescent wave for detection of the particles. In various embodiments, the optical label may be or may include a quantum dot (QD) or a gold nanoparticle (Au NP).

[0097] In various embodiments, at least one optical label may have a size (e.g. diameter) that may be different from the remaining optical labels.

[0098] In various embodiments, at least one optical label may have a refractive index that may be different from the remaining optical labels.

[0099] The method may further include sorting the particles by means of the evanescent wave. In various embodiments, for sorting the particles, the particles may be deflected away from the sample flow. The particles may be deflected away from the sample flow by means of at least one optical force exerted by the evanescent wave on the particles. The particles may be deflected into the sheath flow or the second sheath flow.

[0100] The method may further include varying a power of the optical signal. This may affect the intensity of the evanescent wave that is generated such that the evanescent wave may be used for optical trapping and/or manipulation of the particles. This may provide for sorting the particles by deflection as different power levels of the optical signal may deflect different types and/or sizes of particles, and/or may cause deflection of the particles through different deflection paths. Furthermore, changing the power of the optical signal may provide improved illumination of the particles for detection of the particles.

[0101] In various embodiments, at least one particle may have a size (e.g. diameter) that may be different from the remaining particles.

[0102] In various embodiments, at least one particle may have a refractive index that may be different from the remaining particles.

[0103] In the context of various embodiments, the solution or medium of the sample flow may include a first ethylene glycol mixture, wherein the solution or medium of the second sheath flow may include a second ethylene glycol mixture, and wherein the first ethylene glycol mixture and second ethylene glycol mixture may have different compositions, and therefore at least substantially different refractive indices.

[0104] In the context of various embodiments, the solution or medium of the second sheath flow may include the second ethylene glycol mixture.

[0105] Design of the detection device of various embodiments and the related theoretical analysis will now be described.

[0106] FIG. 2A shows a schematic perspective view of a detection device 200, according to various embodiments, illustrating a nano-fluidic system, for example in the form of a nano-optofluidic evanescent wave sensor. The nano-fluidic system 200 may include a

flow channel 202, for example a microchannel. The nano-fluidic system 200 may provide for three flow streams in the microchannel 202, for example a sample flow 204, for example in the form of a nano-core flow stream, a first sheath flow 206 and a second sheath flow 208. The refractive index of the solution of the nano-core flow stream 204 may be at least substantially lower than that of the first sheath flow 206 and the second sheath flow 208. The sample flow 204 may contain particles that are to be detected. As a non-limiting examples, the particles to be detected may be quantum dot (QD)-labeled viruses 210, where each virus 212 may be stained or coupled with one or more quantum dots (QDs) 214, for example via a binding molecule (e.g. antibody) 216.

[0107] Each of the first sheath flow 206 and the second sheath flow 208 may be in laminar flow with the sample flow 204. This may provide stable flows of the sample flow 204, the first sheath flow 206 and the second sheath flow 208 through the microchannel 202, where the sample flow 204 do not at least substantially mix with the first sheath flow 206 and the second sheath flow 208. This may mean that each of the the sample flow 204, the first sheath flow 206 and the second sheath flow 208 may be maintained as respective individual flows through the microchannel 202. The QD-labeled viruses 210 may therefore be confined within the sample flow 204.

[0108] A first interface 220 may be defined between the sample flow 204 and the first sheath flow 206, and a second interface 222 may be defined between the sample flow 204 and the second sheath flow 208. Therefore, two liquid-liquid interfaces (i.e. first interface 220 and second interface 222) may be defined within the microchannel 202.

[0109] The first sheath flow 206 and the second sheath flow 208 may flow on opposite sides of the sample flow 204. The sample flow 204 may be confined by the first sheath flow 206 and the second sheath flow 208, such that the sample flow 204 do not abut the walls (e.g. first wall 224 and second wall 226) of the microchannel 202. This may minimise absorption or adsorption of the QD-labeled viruses 210 on the walls of the microchannel 202.

[0110] The sample flow 204, the first sheath flow 206 and the second sheath flow 208 may be provided via respective inlets that may be in fluid communication with the microchannel 202. For example, the sample flow 204 may be supplied via a first inlet 230, the first sheath flow 206 may be supplied via a second inlet 232, while the

second sheath flow 208 may be supplied via a third inlet 234, into the microchannel 202. An outlet 236 may be provided at an end of the microchannel 202 for discharging the sample flow 204, the first sheath flow 206 and the second sheath flow 208. In alternative embodiments, three respective outlets may be provided, each outlet for discharging one of the sample flow 204, the first sheath flow 206 and the second sheath flow 208 respectively.

[0111] The detection device 200 may further include an optical arrangement (not shown) to generate an evanescent wave within the microchannel 202 for detection of the QD-labeled viruses 210. The optical arrangement for example may include a radiation source (e.g. laser) for providing an optical signal (e.g. light) from which the evanescent wave may be induced. The optical arrangement may also include an optical waveguide and/or a lens.

[0112] As illustrated in FIG. 2A as a non-limiting example, the optical arrangement may direct an incident light 250 to within the microchannel 202 at the first interface 220 defined between the sample flow 204 and the first sheath flow 206. The incident light 250 may be total internally reflected at the first interface 220 as the incident light 250 hits the first interface 220 defined between the sample flow 204 and the first sheath flow 206 of different refractive indices, resulting in a reflected light 252. An evanescent field 254 with an evanescent wave 256 therewithin may be generated as a result of the total internal reflection of the incident light 250. The evanescent field 254 and the evanescent wave 256 may extend into the sample flow 204. The evanescent wave 256 may decay with distance from the first interface 220 into the sample flow 204.

[0113] FIG. 2B shows a schematic illustration of a generated evanescent wave 256 in the core flow stream 204 in the microchannel 202 of the detection device 200. FIG. 2C shows a simulated evanescent wave 256 in the microchannel 202 based on the detection device 200 of FIG. 2A. As shown in FIG. 2C, the evanescent wave 256 that may be generated may decay along the vertical direction of the centre flow stream 204. The evanescent wave 256 may propagate into the core stream or sample flow 204 with a penetration depth of approximately 1 μm and its intensity may exponentially decay.

[0114] In various embodiments, the nano-core flow stream 204 may be compressed by the sheath flow streams (i.e. the first sheath flow 206 and the second sheath flow 208) by

using hydrodynamic technology. The centre flow stream or sample flow 204 may be controlled such that its width, *w*, may be at least substantially smaller than the wavelength of the incident light 250 to make the molecules/nanoparticles to be detected, such as the QD-labeled viruses 210, suspended in the centre flow stream 204 one by one, like a string of pearls, by controlling the respective flow rates of at least one of the sample flow 204, the first sheath flow 206 or the second sheath flow 208, or at least one of the flow rate ratio between the sample flow 204 and the first sheath flow 206 or the flow rate ratio between the sample flow 204 and the second sheath flow 208.

[0115] Compared to a solid-liquid interface, the liquid-liquid interface corresponding to the first interface 220 and/or the second interface 222 may be naturally smooth to avoid, or at least minimise, optical scattering, so as to prevent or minimise any disturbance of the evanescent field 254. Furthermore, the refractive index of the solution of at least one of the first sheath flow 206 or the second sheath flow 208 may be at least substantially the same as the material (e.g. polydimethylsiloxane; PDMS) of the microchannel 202 so as to build uniform media of at least substantially similar refractive index for light input by using a mixture solution, for example, of (75 % $(CH_2OH)_2$ 25 % (CH_3OH) in mass) having a refractive index of about 1.410, for at least one of the first sheath flow 206 or the second sheath flow 208. In this way, optical scattering may be minimised as the incident light 250 is directed, for example, through the material of the microchannel 202 and the first sheath flow 206 as a result of the substantially similar refractive index.

[0116] The light from the radiation source may be input towards the microchannel 202 at a liquid-liquid interface therewithin by integrating an optical fiber (see for example FIG. 5A), as part of the optical arrangement, in or with the microchannel 202. The input light may be focused and collimated by an on-chip lens (see for example FIG. 5A) to make sure that the incident angle of the incident light 250 at the first interface 220 may be just slightly larger than the critical angle for total internal reflection. As a result, small nanoparticles, such as QD-labeled viruses 210, may be kept in the nano-core flow stream 204 and measured when they are illuminated by the evanescent wave 256. The evanescent field 254 may be designed to cover the whole nano-core flow stream 204 to ensure that all nanoparticles may be illuminated efficiently.

[0117] As described, the detection device 200 may be a hydrodynamic total internal reflection (TIR) microscopy for nanoparticle detection. The nanoparticles may be kept in the core flow stream 204 with a width, w, of < 1 μm by hydrodynamic focusing. The nanoparticles may be detected by the evanescent field 254 formed by TIR at the liquid/liquid interface 220.

[0118] In various embodiments, the nanoparticles (e.g. QD-labeled viruses 210) may be sorted based on their sizes by controlling the intensity of the input laser light. As shown in FIG. 2C, the evanescent field 254 may have a strong local confinement. The light intensity at the interface 220 between the liquid media of the sample flow 204 and the first sheath flow 206 may be enhanced about 4.7 times and then decay exponentially to form a gradient field.

[0119] Total internal reflection (TIR)

[0120] In a TIR system, penetration depth refers to the distance of the electromagnetic radiation that may penetrate into a material. It may be defined as the depth at which the intensity of the radiation inside the material falls to approximately $1/e$. The relationship between the penetration depth, d, and the incident angle, θ_1, for TIR may be expressed as

$$d = \frac{\lambda_0}{4\pi n_1}[\sin^2\theta_1 - n_2^2]^{-1/2} \qquad \text{(Equation 1)},$$

where λ_0 refers to the wavelength of the incident light (e.g. about 514 nm), n_1 and n_2 refer to the refractive index of the sheath flow streams (e.g. 206, 208, FIG. 2A) and the centre flow stream (e.g. 204, FIG. 2A), respectively. As a non-limiting example, n_1 may be about 1.410 and n_2 may be about 1.404, and the penetration depth may be infinite for propagating waves with the angle of incidence, θ_1, slightly larger than the critical angle, θ_c, which may be about 84.7°, as calculated using Equation 2 below based on n_1 = 1.410 and n_2 = 1.404.

$$\theta_c = arcsin\left(\frac{n_2}{n_1}\right) \qquad \text{(Equation 2)}.$$

[0121] The penetration depth, d, may decrease as the angle, θ_1, increases. Consequently, the optical forces decrease as this angle increases. FIG. 3A shows a plot 300 illustrating the relationship between the penetration depth with the incident angle, according to

various embodiments. The plot 300 shows result (solid line) 302 for parallel-polarized incident light, and result (dashed line) 304 for perpendicular-polarized incident light. When the incident angle, θ_I, is near the critical angle, θ_c, the penetration depth, d, may reach several micrometers. The penetration depth may be nearly about 6 μm when the incident angle, θ_I, is about 84.7°. As a result, at least substantially all particles to be detected or the entire width of the sample flow 204 may be covered by the evanescent field, combined with hydrodynamic focusing technology.

[0122] The intensity of the evanescent field for both parallel ($I_0(P)$) and perpendicular ($I_0(S)$) polarizations as a function of the incident angle may be expressed as

$$I_0(P) = I_1(P)\frac{4\cos^2\theta_1(2\sin^2\theta_1 - n_2^2)}{n_2^4\cos^2\theta_1 - n_2^2} \qquad \text{(Equation 3)},$$

$$I_0(S) = I_1(S)\frac{4\cos^2\theta_1}{1 - n_2^2} \qquad \text{(Equation 4)},$$

where $I_1(P)$ refers to the intensity of the parallel-polarized incident light and $I_1(S)$ refers to the intensity of the perpendicular-polarized incident light.

[0123] FIG. 3B shows a plot 320 illustrating the relationship between the intensity of the evanescent field with incident angle, according to various embodiments. FIG. 3B shows the analytical solution of the evanescent wave intensity for both parallel (result (solid line) represented as 322) and perpendicular (result (dashed line) represented as 324) polarizations as a function of the incident angle, θ_I, when the refractive index contrast or difference is fixed at about 0.006. As may be seen from FIG. 3B, the type of polarization does not affect the intensity of the evanescent field when the incident angle, θ_I, is about 85°.

[0124] Optical force

[0125] At the quantum level, each light photon carries a momentum, p. When a photon interacts with an object, the momentum may be transferred and the object may be pushed forward in the direction of light propagation, where the momentum may be proportional to the light intensity.

[0126] For optical manipulation and sorting, the optical force may be decomposed into two components: one being the scattering force in the direction of propagation, and the

other one being the gradient force in the light gradient direction. The scattering force tends to push the object along the beam axis while the gradient force may push the object into the focus of the light (e.g. focus of the laser beam).

[0127] For an object or particle that is smaller than the wavelength of the optical signal (e.g. light) used, it may be suitable to consider the forces in terms of electric field, which is called the dipole model. The optical force may be derived from the Lorentz force, and when the conditions for Rayleigh scattering may be satisfied, the particle may be treated as a point dipole in an inhomogeneous electromagnetic field. The Lorentz force, F_L, may be expressed as

$$F_L = q(E + v \times B) \qquad \text{(Equation 5)},$$

where v is the velocity, q is the electrical charge, E and B are the electrical and magnetic fields respectively.

[0128] Combined with the Maxwell's equations, the optical force, F, may be expressed as:

$$\boldsymbol{F} = \alpha[(\boldsymbol{E}\cdot\nabla)\boldsymbol{E} + \frac{\partial \boldsymbol{E}}{\partial t} \times \boldsymbol{B}] = \alpha[\frac{1}{2}\nabla \boldsymbol{E}^2 + \frac{\partial}{\partial t}(\boldsymbol{E} \times \boldsymbol{B})] \qquad \text{(Equation 6)},$$

where t refers to time.

[0129] The response on the electrical field, E, may be assumed to be: $\boldsymbol{p} = \alpha\varepsilon\boldsymbol{E}$,where α is the polarizability and ε is the permittivity. Since the power of the radiation source (e.g. laser) may be at least substantially constant, the second term $(\frac{\partial}{\partial t}(E \times B))$ may be averaged to zero. The polarizability, α, may be defined as

$$\alpha = \frac{\alpha_0}{1 - \frac{2}{3}\frac{ik^3\alpha_0}{4\pi}} \qquad \text{(Equation 7)},$$

where

$$\alpha_0 = 4\pi a^3(\frac{m^2 - 1}{m^2 + 2}) \qquad \text{(Equation 8)},$$

$$k = \frac{2\pi n_1 \sin\theta}{\lambda_0} \qquad \text{(Equation 9)},$$

a is the radius of the particle(s), n_2 is the refractive index of the surrounding medium (e.g. sample flow), m is the ratio of the refractive index of the particle(s), n_p, to the refractive

index of the surrounding medium ($m = n_p / n_2$). Also, n_1 is the refractive index of the sheath flow, λ_0 is to the wavelength of the incident light, and θ is the light incident angle.

[0130] A scattering force, F_{scat}, may arise from the absorption and retardation of light by the dipole. The scattering force, F_{scat}, may be derived from the imaginary part of the optical force, F, and may be expressed as:

$$F_{scat} = \frac{8}{3}\pi(ka)^4 a^2 \left(\frac{m^2-1}{m^2+2}\right)^2 \frac{n_2}{c} I(r) \qquad \text{(Equation 10)},$$

where I(r) is the intensity of the light incident on the particle(s), being Rayleigh particle(s), a is the radius of the particle(s), n_2 is the refractive index of the surrounding medium (e.g. sample flow), m is the ratio of the refractive index of the particle(s), n_p, to the refractive index of the surrounding medium ($m = n_p / n_2$), c is the speed of light in vacuum, k may be as defined in Equation 9.

[0131] A gradient force, F_{grad}, may originate from the interaction between the induced dipole and the inhomogeneous field, and may be expressed as:

$$F_{grad} = \frac{2\pi n_2 a^3}{c}\left(\frac{m^2-1}{m^2+2}\right)\nabla I(r) \qquad \text{(Equation 11)}.$$

[0132] The particle(s) or Rayleigh particle(s) may experience an acceleration towards the region with a higher light intensity. As a non-limiting example, for quantum dots (QDs), their refractive index may be higher than that of the surrounding solution or medium, which may lead to $m > 1$ and consequently a positive F_{grad}. As a result, QDs may be pushed, for example, downwards. On the contrary, for Au nanoparticles, their refractive index may be lower than that of the surrounding solution or medium, which may lead to $m < 1$ and consequently a negative F_{grad}. As a result, Au nanoparticles may be pushed, for example, upwards. Therefore, in one embodiment, a particle may be pushed or deflected in a particular motion or direction depending on the refractive index of the particle.

[0133] Quantum dots (QDs) under optical force and liquid drag force

[0134] Colloidal quantum dots (QDs) are nanosized fluorescent semiconductor crystals. QDs are different from the traditional fluorescent based organic molecules. The unique optical properties of QDs may provide long-term stability and simultaneous detection of

multiple signals, making QDs as promising applications in, for example, single molecule imaging, labeling and sensing.

[0135] In various embodiments, as a non-limiting example, water-soluble cadmium selenide (CdSe) core - zinc-sulfide (ZnS) shell QDs with an emission wavelength of 630 nm may be used. Each QD may have a CdSe core that is at least substantially surrounded by a ZnS shell. The CdSe-ZnS core-shell QDs may be obtained by way of a self-assembling process, where the self-assembled QDs may be about 5 nm in diameter. The molar mass of CdSe may be approximately 191.37 g/mol, with a density of approximately 5.819 g/cm^3. The molar mass of ZnS may be approximately 97.47 g/mol, with a density of approximately 4.090 g/cm^3. For the purpose of analysis, the CdSe core of the QDs may be assumed to be spherical with a refractive index, n_p, of about 2.56.

[0136] In an evanescent field, the intensity, I(r), of the evanescent field may be expressed as:

$$I(r) = I(y) = I_0 e^{(-\frac{y}{d})} \qquad \text{(Equation 12)},$$

where I(y) refers to the intensity of the evanescent field at position y, I_0 refers to the intensity of the evanescent field at the interface, y refers to the propagation direction of the evanescent field (perpendicular to the interface) and d refers to the penetration depth of the evanescent wave.

[0137] Combining Equation 12 with Equations 1, 3 and 4, the optical force acting on the QDs in microfluidic may be expressed by:

$$\boldsymbol{F}_{scat} = \frac{8}{3}\pi(ka)^4 a^2 (\frac{m^2-1}{m^2+2})^2 \frac{n_2}{c} I_1(P) \frac{4\cos^2\theta_1(2\sin^2\theta_1 - n_2^2)}{n_2^4\cos^2\theta_1 - n_2^2} e^{(-\frac{y}{d})} \qquad \text{(Equation 13)},$$

$$\boldsymbol{F}_{grad} = -\frac{1}{d}\frac{2\pi n_2 a^3}{c}(\frac{m^2-1}{m^2+2}) I_1(P) \frac{4\cos^2\theta_1(2\sin^2\theta_1 - n_2^2)}{n_2^4\cos^2\theta_1 - n_2^2} e^{(-\frac{y}{d})} \qquad \text{(Equation 14)}.$$

[0138] In additional to the optical force, the QDs in a liquid may also experience a liquid drag force, F_{drag}, which may be expressed by:

$$\boldsymbol{F}_{drag} = \frac{1}{2} C_d \rho_m \upsilon^2 A = 2\pi C_d \rho_m \upsilon^2 a^2 \qquad \text{(Equation 15)},$$

where C_d is the drag coefficient, ρ_m is the density of the centre flow stream, υ is the relative velocity of the QDs to the background flows, A is the reference areas of the QDs, and a is the radius of the QDs.

[0139] The liquid drag force, F_{drag}, and the optical scattering force, F_{scat}, may be both in the flow direction, and as a result, F_{drag} may be seen as a balance to the optical scattering force, F_{scat}. The gradient force, F_{grad}, may act on the QDs perpendicular to the flow direction and may direct the QDs and/or any molecule(s) or particle(s) coupled to the QDs to a sheath flow, from a core sample flow, for example when the QDs are flowed through the detection device 200 of FIG. 2A. The scattering force, F_{scat}, acting on the QDs in the flow direction, may cause the QDs to flow at different acceleration rates. The resultant of these two forces (F_{scat} and F_{grad}) may create specific parabolic flow paths for different samples or particles, which lays the foundation for molecule or particle sorting.

[0140] Both the scattering force, F_{scat}, and the gradient force, F_{grad}, may depend on the molecule's diameter and refractive index, e.g. $\boldsymbol{F}_{scat} \propto a^6\left(\frac{m^2-1}{m^2+2}\right)^2$ and $\boldsymbol{F}_{grad} \propto a^3\left(\frac{m^2-1}{m^2+2}\right)$, respectively, where a refers to the radius of the molecule, and m refers to the ratio of the refractive index of the molecule to the refractive index of the medium the molecule is in (e.g. the sample flow). Therefore, different molecules or particles, or particles with different labels (e.g. optical labels), or labelled and non-labelled particles may be sorted.

[0141] As a non-limiting example, free or unbound QDs (i.e. no particle or molecule coupled to the QDs) and QD-labeled viruses may be sorted based on their distinct biophysical properties. As unbound QDs (e.g. of approximately 5 nm in diameter) are several-fold smaller in size as compared to QD-labeled ones (e.g. of approximately 50 nm in diameter), the scattering force, F_{scat}, and the gradient force, F_{grad}, acting on the unbound QDs are relatively smaller, such that unbound QDs may be directed or deflected into a sheath flow, from a sample flow, with a shorter parabolic flow path (deflection path), while on the other hand, QD-labeled particles may be directed or deflected into a sheath flow with a longer parabolic flow path (deflection path). As a result, QD-labeled

samples or particles may be separated or sorted from other suspension species present in a fluid (e.g. a water sample) and may be effectively quantified.

[0142] FIG. 4A shows the simulation result 400 of the optical force acting on a particle 402 under an evanescent wave, according to various embodiments. The simulation is based on a flow channel or microchanel within which three flow streams of a core flow stream 404 in between two sheath flow streams 406, 408, flow. The optical force acting on the particle 402 may be divided into two parts: one is a scattering force, F_{scat}, represented by the arrow 410, along the flow direction, while the other is a gradient force, F_{grad}, represented by the solid line arrow 412a, or the dashed line arrow 412b, at least substantially perpendicular to the flow direction, for sorting the particle 402. A liquid drag force, F_{drag}, may additionally act on the particle 402 in the flow direction, and may generally be represented collectively with F_{scat} by the arrow 410.

[0143] Where the particle 402 is a quantum dot (QD), F_{scat} 410 may push the QD 402 along the flow direction, while F_{grad} 412a may pull the QD 402 downwards towards the sheath flow stream 406. As a result, the resultant force of F_{scat} 410 and F_{grad} 412a may cause the QD 402 to deflect into the sheath flow stream 406, for example via the parabolic flow path or deflection path as represented by the solid line arrow 414a. As described above in relation to Equation 11, this may be due, at least in part, to the higher refractive infex of QDs as compared to the refractive index of the core flow stream 404.

[0144] Where the particle 402 is a gold nanoparticle (Au NP), F_{scat} 410 may push the Au NP 402 along the flow direction, while F_{grad} 412b may push the Au NP 402 upwards towards the sheath flow stream 408. As a result, the resultant force of F_{scat} 410 and F_{grad} 412b may cause the Au NP 402 to deflect into the sheath flow stream 408, for example via the parabolic flow path or deflection path as represented by the dashed line arrow 414b. As described above in relation to Equation 11, this may be due, at least in part, to the lower refractive infex of Au NPs as compared to the refractive index of the core flow stream 404.

[0145] The deflection paths 414a, 414b may be of different lengths such that QDs and Au NPs may be deflected into the respective sheath flow streams 406, 408 at different deflection rates.

[0146] In various embodiments, two particles of different sizes (e.g. different radii; diameters) may be deflected into the same sheath flow via different deflection paths (e.g. different parabolic path dimension). The two particles may be of at least substantially similar refractive index.

[0147] In various embodiments, two particles of different refractive indices may be deflected into different sheath flows (e.g. opposite sheath flows). The two particles may be of at least substantially similar size (e.g. similar radius; diameter).

[0148] In various embodiments, two particles of different refractive indices and of different sizes (e.g. different radii; diameters) may be deflected into the same or different sheath flows and/or via different deflection paths.

[0149] FIG. 4B shows a plot 430 illustrating the relationship between the size of quantum dots (QDs) and the optical force acting on the QDs, according to various embodiments. The plot 430 illustrates the optical force (F_{scat} represented by result 432 and F_{grad} represented by result 434) acting on QDs of sizes, in terms of radius, between 5 nm and 50 nm, at a distance of about 200 nm above the interface (e.g. liquid-liquid interface) with a laser input power of about 80 mw and a focus area of approximately 40 μm × 40 μm. In FIG. 4B, the result line 432 representing F_{scat} and the result line 434 representing F_{grad} intersect at approximately a = 27 nm.

[0150] While not clearly shown in FIG. 4B, when the QDs are about 5 nm, the gradient force, F_{grad} (result 434), is much larger than the scattering force, F_{scat} (result 432) (larger by about 1000 folds), while for QDs larger than approximately 27 nm, the scattering force (result 432) becomes larger than the gradient force (result 434). For example, when a (radius) =30 nm, the gradient force acting in a vertical direction (perpendicular to flow direction) is approximately 6×10^{-5} pN, while the scattering force acting in the flow direction is approximately 8×10^{-5} pN. Based on this difference, the QDs and QD-labeled samples may be sorted downstream.

[0151] FIG. 4C shows a plot 450 illustrating the acceleration of quantum dots (QDs) of different sizes in a flow channel (e.g. microchannel), according to various embodiments. In FIG. 4C, the results are shown for acceleration of the QDs from a distance, d, of about 1 μm to the interface (i.e. d = 0) between the core flow stream 404 and the sheath flow stream 406.

[0152] In plot 450, the solid line result 452 and the solid line result 454 represent accelerations as a result of the gradient force and the scattering force respectively for QDs with a diameter of about 5 nm, while the dashed line result 456 and the dashed line result 458 represent accelerations as a result of the gradient force and the scattering force respectively for QDs with a diameter of about 50 nm. The accelerations by both optical forces in the form of the gradient force and the scattering force may become larger when close to the interface (d = 0). The acceleration (result 458) of the scattering force of the 50 nm QDs is significantly larger than that of the 5 nm ones (result 454). These results show that different QDs may be sorted at different parabolic flow paths, for example when the QDs are of differents sizes.

[0153] Experimental results and discussions

[0154] For the experimental study, the microchannel system was fabricated using soft photolithography processes. First, photoresist-on-silicon mold was prepared in a clean room facility with photolithography (Micro-Chem, SU-8) using transparent glass masks (CAD/Art Services, Inc. Poway, CA). Next, microchannels were molded using polydimethylsiloxane (PDMS) and sealed against flat PDMS sheets after plasma oxidation. After fabrication, the microchannel may have a width, W, of about 30 μm and a height, H, of about 50 μm.

[0155] The flow streams may be pumped into the microchannel (or flow channel) from a centre inlet, for the sample flow, and the outer inlets, for the two sheath flows, using syringe pumps (Genie, Kent Scientific Corporation, CT). As a non-limiting example, the chosen liquids used may be ethylene glycol mixtures as they do not substantially swell the PDMS material. The refractive index, n_1, of the solution of the sheath flow streams may be about 1.410 (75 % $(CH_2OH)_2$ 25 % (CH_3OH) in mass), which is at least substantially equal to the refractive index of PDMS. The refractive index, n_2, of the solution of the inner core sample flow stream may be about 1.404 (60 % $(CH_2OH)_2$ 40 % (CH_3OH) in mass). The refractive index of the liquids or solutions and PDMS may be measured by a refractometer (Reichert, AR200 digital hand-held). The low refractive index contrast between the core flow stream and the sheath flow streams may reduce smearing and/or maintain a smooth liquid-liquid interface.

[0156] FIG. 5A shows a microscopy image 500 of the fabricated PDMS chip 502, according to various embodiments, illustrating the detection device having a microchannel 504. The detection device includes a centre inlet 506 for the supply of a sample flow (core flow) 508 into the microchannel 504, a first side inlet 510 for the supply of a first sheath flow 512 into the microchannel 504, a second side inlet 514 for the supply of a second sheath flow 516 into the microchannel 504, and an outlet 515 for discharging or outflow of the sample flow 508, the first sheath flow 512 and the second sheath flow 516.

[0157] The first sheath flow 512 may be provided on one side of the sample flow 508, between the sample flow 508 and a wall 518 of the microchannel 504. The second sheath flow 516 may be provided on an opposite side of the sample flow 508, between the sample flow 508 and a wall 520 of the microchannel 504. The sample flow 508 and the first sheath flow 512 may define a liquid-liquid interface 522 therebetween while the sample flow 508 and the second sheath flow 516 may define a liquid-liquid interface 524 therebetween. The sample flow 508, the first sheath flow 512 and the second sheath flow 516 may be in laminar flow with each other in the microchannel 504.

[0158] The detection device may include an integral or on-chip collimation lens 530 and an integral or on-chip optical waveguide (e.g. fiber) 532. An incident light 540 may be coupled from the fiber 532 with the collimation lens 530 and directed to the liquid-liquid interface 522 at an incident angle, θ, of about 85°, which is slightly larger than the critical angle of about 84.7° resulting from n_1 = 1.410 and n_2 = 1.404. As a result, the incident light 540 may undergo total internal reflection at the interface 522, resulting in a reflected light 542 and the generation of an evanescent wave at the interface 522, which may propagate into the sample flow 508.

[0159] The nano-core flow stream 508, which hold the samples or particles to be detected, may be focused by the two sheath flows 512, 516, with the width of the nano-core flow stream 508 controlled to be less than 1 μm.

[0160] FIG. 5B shows a fluorescent microscopy image 550 of the total internal reflection occurring at the liquid-liquid interface 522 between the sheath flow 512 and the core flow 508 of the embodiment of FIG. 5A. The vertical direction across the core flow 508 and the sheath flows 512, 516 is amplified two times.

[0161] As shown in FIG. 5B, an evanescent field 552 may be induced where a generated evanescent wave may propagate. The evanescent wave may propagate into the core flow 508 with a penetration depth of approximately 1 μm and its intensity may be exponentially decayed into the sample flow 508.

[0162] FIG. 5C shows a three-dimensional (3D) confocal microscopy image 560 of the flow streams in the microchannel 504 of the embodiment of FIG 5A. The microscopy image 560, obtained experimentally, illustrate that the three laminar flow streams of the sample flow 508, the first sheath flow 512 and the second sheath flow 516 are steady in the microchannel, and may be maintained as stable flows.

[0163] In order to observe the illumination signals of the QDs by the evanescent wave, an electron multiplying charge-coupled device (EMCCD; Andor) may be employed as the detector for dynamic single molecule imaging. The signal-to-noise ratio (S/N) of the EMCCD is significantly greater than that of conventional CCD cameras even when operated at fast readout speed. The exposure time may be lowered down to about 10 μs, exhibiting frame rates that may be suitable for dynamic acquisition of transient single molecules and their interactions.

[0164] FIGS. 6A to 6C show EMCCD microscopy images 600a, 600b, 600c, of the detection of particles by evanescent field, according to various embodiments, illustrating evanescent wave illumination of the particles in the nano-core flow stream 602 from a Nd:YAG laser with a wavelength of about 514 nm. The focus area is approximately 40 μm × 40 μm.

[0165] Referring to FIG. 6A, using QDs, e.g. 610, 612, as the particles, when the input power from the laser is about 20 mW, the QDs 610, 612 may be illuminated clearly by the evanescent field and the QDs 610, 612 may flow in the nano-core flow stream 602 in the flow direction as represented by the arrow 620, one by one like a string of pearls, by hydrodynamic focusing resulting from the first sheath flow 604 and the second sheath flow 606.

[0166] When the laser input power is increased, for example to about 60 – 80 mW, manipulation of the particles from the core flow stream 602 into side flow streams 604, 606, by optical gradient force may be carried out. For example, referring to FIG. 6B, when the input laser power is increased to about 80 mW, the optical gradient force may

be sufficiently strong to pull the different QDs 630, 632, 634 down to the sheath flow 604 from the core flow 602 along a deflection path represented by the dashed arrow 636.

[0167] Referring to FIG. 6C, when the suspending particles are Au nanoparticles and the input laser power is about 80 mW, the optical gradient force may push the different Au nanoparticles 650, 652, 654, 656 upwards to the sheath flow 606 from the core flow 602 along a deflection path represented by the dashed arrow 660.

[0168] FIGS. 7A to 7E show microscopy images 700a, 700b, 700c, 700d, 700e of the detection of micro/nano particles by evanescent wave illumination in the nano-optofluidic system of various embodiments, illustrating the total internal reflection fluorescence (TIRF) illumination of micro/nanoparticles in core flow streams from a Nd : YAG laser with a wavelength of about 514 nm and at a power of about 80 mW for particles ranging from about 5 μm to about 200 nm in diameter.

[0169] FIG. 7A shows the image 700a for particle G0500B 702 of diameter of about 5 μm, FIG. 7B shows the image 700b for particle R0200B 704 of diameter of about 2 μm, FIG. 7C shows the image 700c for particle F13081 706 of diameter of about 1 μm, FIG. 7D shows the image 700d for particle F8813 708 of diameter of about 500 nm, while FIG. 7E shows the image 700e for particle F8811 710 of diameter of about 200nm. Each of the particles (from Invitrogen) G0500B, R0200B, F13081, F8813 and F8811 is a fluorescent bead.

[0170] In various embodiments, all samples or particles may be focused in the core flow stream by tuning the flow rates ratio between the core flow and one or more of the sheath flow streams. All samples may be detected and measured in the central flow (core flow) to ensure a more accurate data acquisition for research in biological and chemical sciences. The conditions may be dynamically controlled by tuning the flow rates and flow rates ratio to suit different samples with size ranging, for example, from about 200 nm to about 5 μm, as shown in FIGS. 7A to 7E. The range of the size of the particles as mentioned above may cover from viruses (100s nm) to cells (several micrometers). This shows the flexiability of the nano-optofluidic system of various embodiments for single cell/molecule detection and manipulation. As described above, the detection device (e.g. a nano-optofluidic device) of various embodiments may employ evanescent wave sensing

for single molecule detection, and sorting (manipulation) based on hydrodynamic focusing and total internal reflection (TIR).

[0171] While the invention has been particularly shown and described with reference to specific embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. The scope of the invention is thus indicated by the appended claims and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

CLAIMS

1. A detection device for detection of particles, the detection device comprising:

a flow channel adapted to guide a sample flow containing the particles to be detected and a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween; and

an optical arrangement configured to direct an optical signal to within the flow channel at the interface to generate an evanescent wave into the sample flow for detection of the particles.

2. The detection device as claimed in claim 1, further comprising:

a first inlet and a second inlet, wherein the first inlet and the second inlet are in fluid communication with the flow channel,

wherein the first inlet is configured for supplying the sample flow into the flow channel, and

wherein the second inlet is configured for supplying the sheath flow into the flow channel.

3. The detection device as claimed in claim 1 or 2, wherein the flow channel is further adapted to guide a second sheath flow through the flow channel, the second sheath flow and the sample flow defining a second interface therebetween.

4. The detection device as claimed in claim 3, further comprising a third inlet in fluid communication with the flow channel, wherein the third inlet is configured for supplying the second sheath flow into the flow channel.

5. The detection device as claimed in any one of claims 1 to 4, further comprising flow rate adjustment means for adjusting a flow rate ratio between the sample flow and the sheath flow for controlling a width of the sample flow.

6. The detection device as claimed in claim 3 or 4, further comprising flow rate adjustment means for adjusting at least one of a first flow rate ratio between the sample flow and the sheath flow or a second flow rate ratio between the sample flow and the second sheath flow, for controlling a width of the sample flow.

7. The detection device as claimed in any one of claims 1 to 6, wherein the optical arrangement is configured to generate the evanescent wave by way of total internal reflection of the optical signal at the interface between the sample flow and the sheath flow.

8. The detection device as claimed in any one of claims 1 to 7, wherein the optical arrangement comprises a waveguide integrally formed with the flow channel, the waveguide being configured to direct the optical signal at the interface between the sample flow and the sheath flow.

9. The detection device as claimed in any one of claims 1 to 8, wherein the optical arrangement comprises a lens integrally formed with the flow channel, the lens being configured to focus the optical signal at the interface between the sample flow and the sheath flow.

10. The detection device as claimed in any one of claims 1 to 9, wherein the optical arrangement comprises a radiation source configured to provide the optical signal.

11. The detection device as claimed in any one of claims 1 to 10, further comprising a detector.

12. The detection device as claimed in any one of claims 1 to 11, further comprising a labeling module configured for coupling each particle with an optical label, the optical label configured to provide a signal in response to the evanescent wave for detection of the particles.

13. The detection device as claimed in claim 12, wherein the optical label comprises a quantum dot or a gold nanoparticle.

14. The detection device as claimed in any one of claims 1 to 13, wherein the flow channel is made of a material selected from the group consisting of polydimethylsiloxane, polymethyl methacrylate, glass and silicon.

15. The detection device as claimed in any one of claims 1 to 14, wherein the detection device is adapted for detecting particles of a size smaller than a diffraction limit imposed by the optical arrangement.

16. The detection device as claimed in any one of claims 1 to 15, wherein the evanescent wave exerts at least one optical force on the particles for deflecting the particles away from the sample flow for sorting the particles.

17. The detection device as claimed in any one of claims 1 to 16, wherein the particles are selected from the group consisting of quantum dots, gold nanoparticles, living cells, chromosomes, organelles, biomolecules, proteins, viruses, bacteria and any combination thereof.

18. The detection device as claimed in any one of claims 1 to 17, wherein each particle has a size of between about 5 nm and about 5 μm.

19. A method for detection of particles, the method comprising:

supplying a sample flow containing the particles to be detected through a flow channel;

supplying a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween; and

directing an optical signal at the interface to generate an evanescent wave into the sample flow for detection of the particles.

20. The method as claimed in claim 19, wherein directing an optical signal at the interface comprises directing the optical signal at the interface between the sample flow and the sheath flow to generate the evanescent wave by way of total internal reflection of the optical signal at the interface.

21. The method as claimed in claim 19 or 20, further comprising focusing the optical signal at the interface between the sample flow and the sheath flow.

22. The method as claimed in any one of claims 19 to 21, wherein supplying a sheath flow comprises supplying the sheath flow at a flow rate that is higher than a flow rate of the sample flow.

23. The method as claimed in any one of claims 19 to 22, further comprising varying a flow rate ratio between the sample flow and the sheath flow for controlling a width of the sample flow.

24. The method as claimed in any one of claims 19 to 23, wherein a width of the sample flow is less than about 1 μm.

25. The method as claimed in any one of claims 19 to 24, wherein a width of the sample flow is smaller than a wavelength of the optical signal.

26. The method as claimed in any one of claims 19 to 25, wherein a width of the sample flow is controlled by the sheath flow such that a single particle flows through a cross section of the flow channel at a time.

27. The method as claimed in any one of claims 19 to 26, wherein the sample flow comprises a solution having a refractive index that is lower than a refractive index of a solution of the sheath flow.

28. The method as claimed in claim 27, wherein the refractive index of the solution of the sample flow is between about 1.332 and about 1.432.

29. The method as claimed in claim 27 or 28, wherein the refractive index of the solution of the sheath flow is between about 1.333 and about 1.433.

30. The method as claimed in any one of claims 27 to 29, wherein the refractive index of the solution of the sheath flow is at least substantially equal to a refractive index of a material of the flow channel.

31. The method as claimed in any one of claims 19 to 30, wherein the evanescent wave is generated across a width of the sample flow.

32. The method as claimed in any one of claims 19 to 31, further comprising supplying a second sheath flow through the flow channel, the second sheath flow and the sample flow defining a second interface therebetween.

33. The method as claimed in claim 32, wherein supplying a second sheath flow comprises supplying the second sheath flow at a flow rate that is higher than a flow rate of the sample flow.

34. The method as claimed in claim 32 or 33, further comprising varying a flow rate ratio between the sample flow and the second sheath flow for controlling a width of the sample flow.

35. The method as claimed in any one of claims 32 to 34, wherein supplying a sheath flow comprises supplying the sheath flow on a first side of the sample flow, wherein supplying a second sheath flow comprises supplying the second sheath flow on a second side of the sample flow, and wherein the first side and the second side are opposite sides.

36. The method as claimed in any one of claims 32 to 35, wherein the refractive index of the solution of the second sheath flow is between about 1.333 and about 1.433.

37. The method as claimed in any one of claims 19 to 36, further comprising coupling each particle with an optical label, the optical label configured to provide a signal in response to the evanescent wave for detection of the particles.

38. The method as claimed in claim 37, wherein at least one optical label has a size that is different from the remaining optical labels.

39. The method as claimed in claim 37 or 38, wherein at least one optical label has a refractive index that is different from the remaining optical labels.

40. The method as claimed in any one of claims 37 to 39, wherein the optical label comprises a quantum dot or a gold nanoparticle.

41. The method as claimed in any one of claims 19 to 40, further comprising sorting the particles by means of the evanescent wave.

42. The method as claimed in claim 41, wherein sorting the particles comprises deflecting the particles away from the sample flow.

43. The method as claimed in any one of claims 19 to 42, further comprising varying a power of the optical signal.

44. The method as claimed in any one of claims 19 to 43, wherein at least one particle has a size that is different from the remaining particles.

45. The method as claimed in any one of claims 19 to 44, wherein at least one particle has a refractive index that is different from the remaining particles.

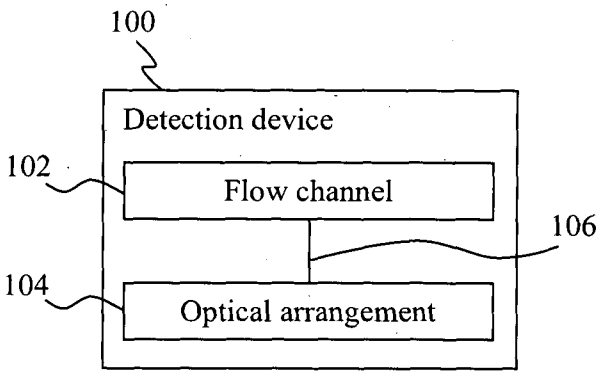

100
Detection device
102
Flow channel
106
104
Optical arrangement

FIG. 1A

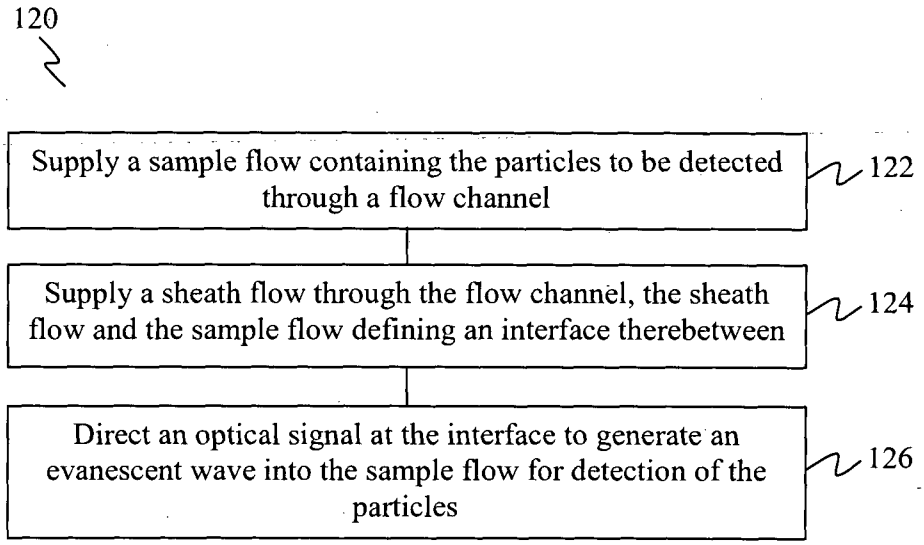

120
Supply a sample flow containing the particles to be detected through a flow channel
122
Supply a sheath flow through the flow channel, the sheath flow and the sample flow defining an interface therebetween
124
Direct an optical signal at the interface to generate an evanescent wave into the sample flow for detection of the particles
126

FIG. 1B

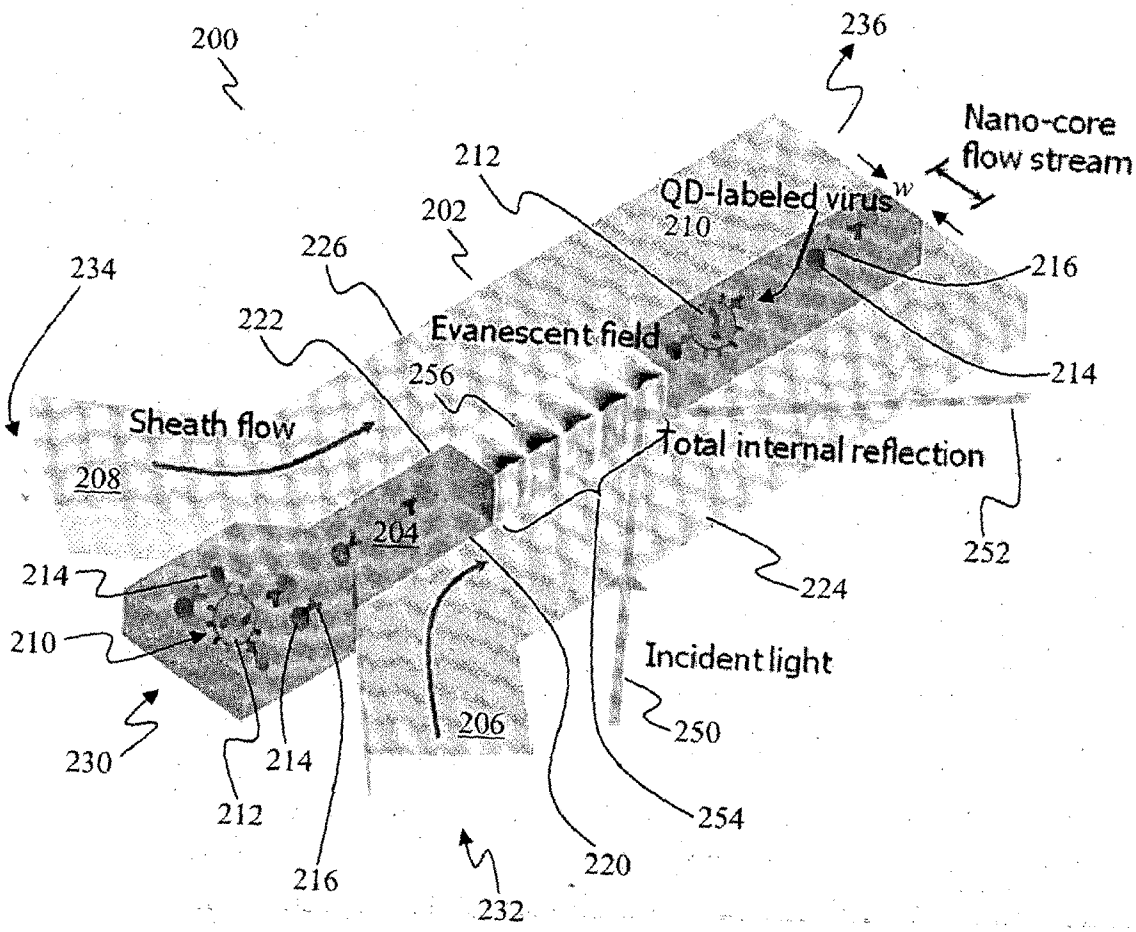

200
236
Nano-core
flow stream
212
QD-labeled virus
210
w
202
226
234
216
222
Evanescent field
214
256
Sheath flow
Total internal reflection
208
204
252
214
224
210
Incident light
250
206
230
214
212
254
216
220
232

FIG. 2A

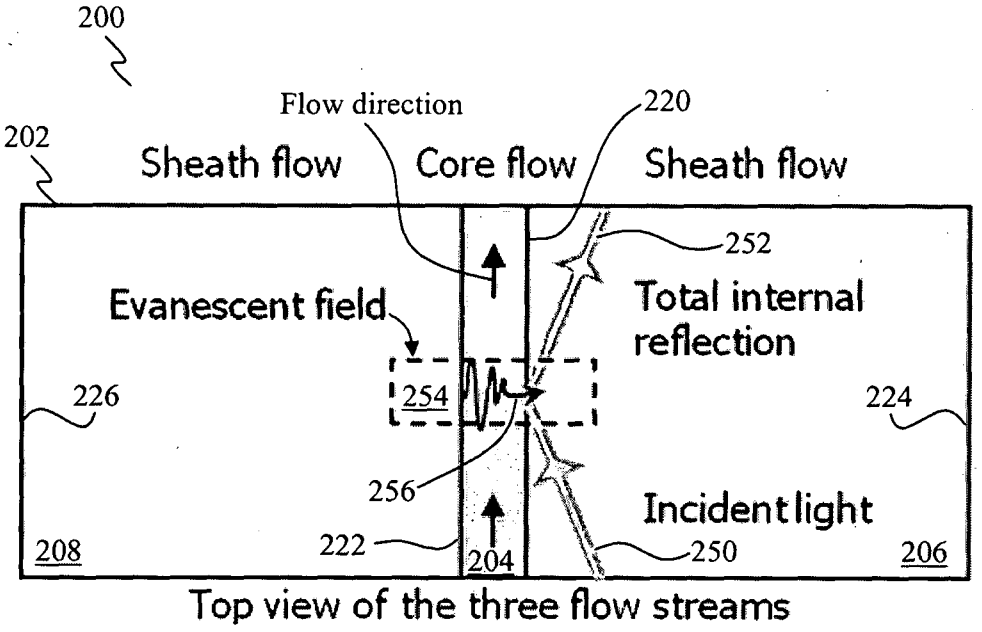

200
Flow direction
220
202
Sheath flow
Core flow
Sheath flow
252
Evanescent field
Total internal reflection
226
254
224
256
Incident light
208
222
204
250
206
Top view of the three flow streams

FIG. 2B

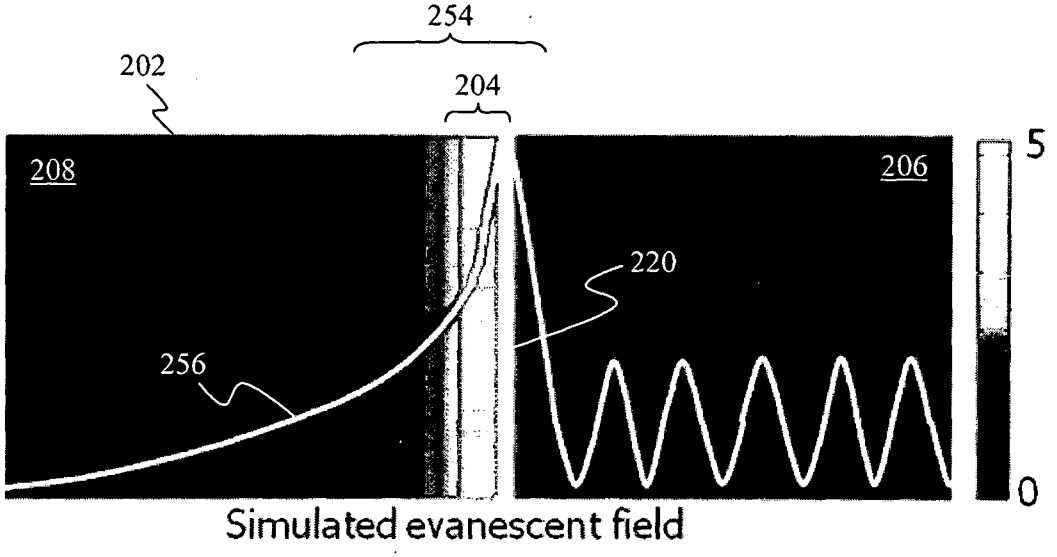

254
202
204
208
206
5
220
256
0
Simulated evanescent field

FIG. 2C

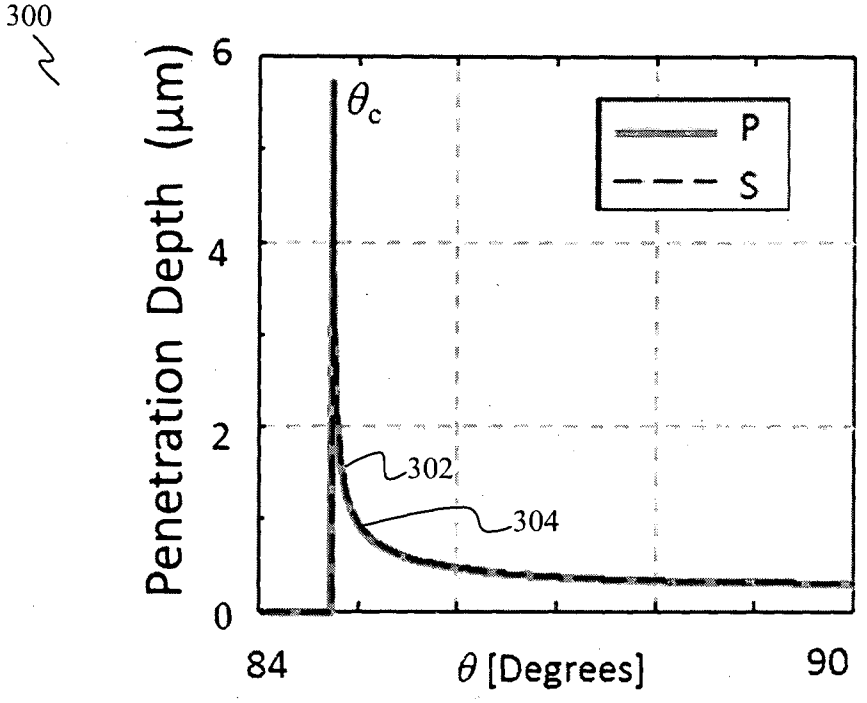

300
Penetration Depth (μm)
6
4
2
0
θ_c
P
S
302
304
84
θ [Degrees]
90

FIG. 3A

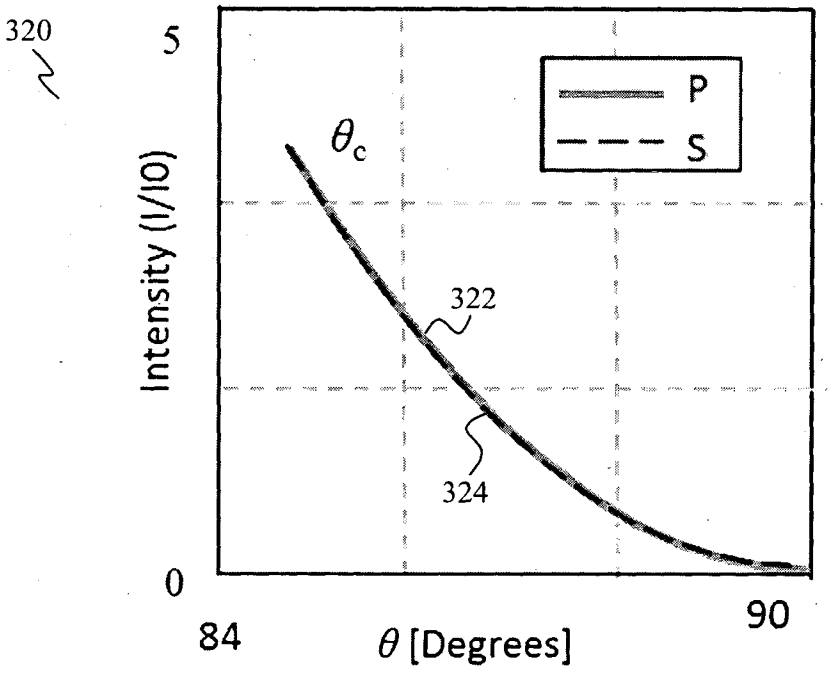

320
Intensity (I/I0)
5
0
θ_c
P
S
322
324
84
θ [Degrees]
90

FIG. 3B

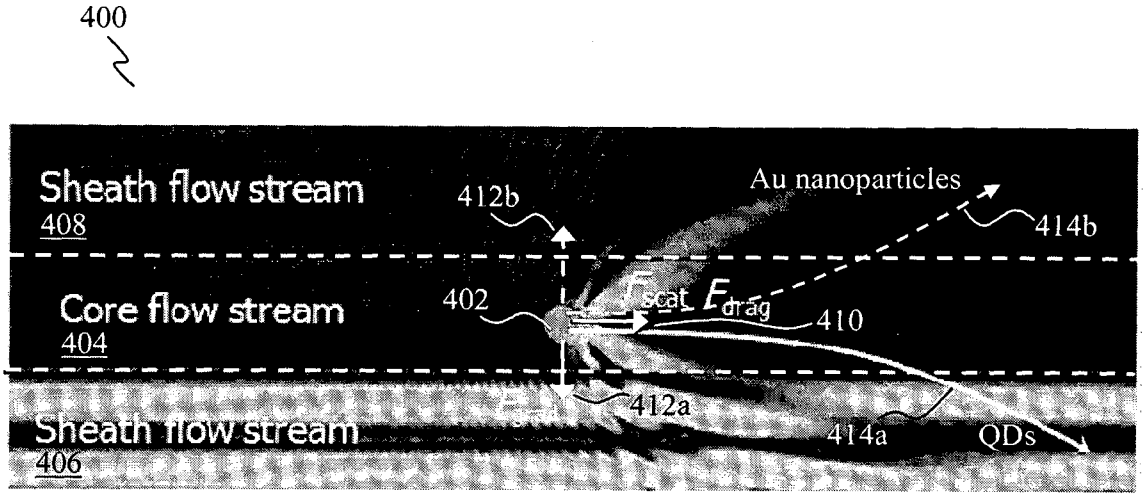

400
Sheath flow stream
408
412b
Au nanoparticles
414b
Core flow stream
404
402
F_{scat} F_{drag}
410
412a
Sheath flow stream
406
414a
QDs

FIG. 4A

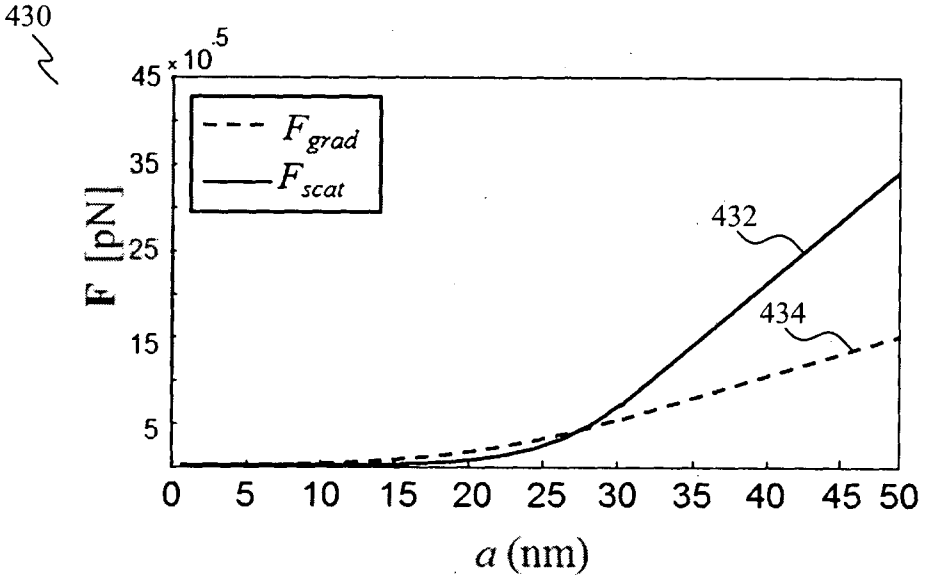

430
$\times 10^{-5}$
45
35
25
15
5
F [pN]
F_{grad}
F_{scat}
432
434
0 5 10 15 20 25 30 35 40 45 50
a (nm)

FIG. 4B

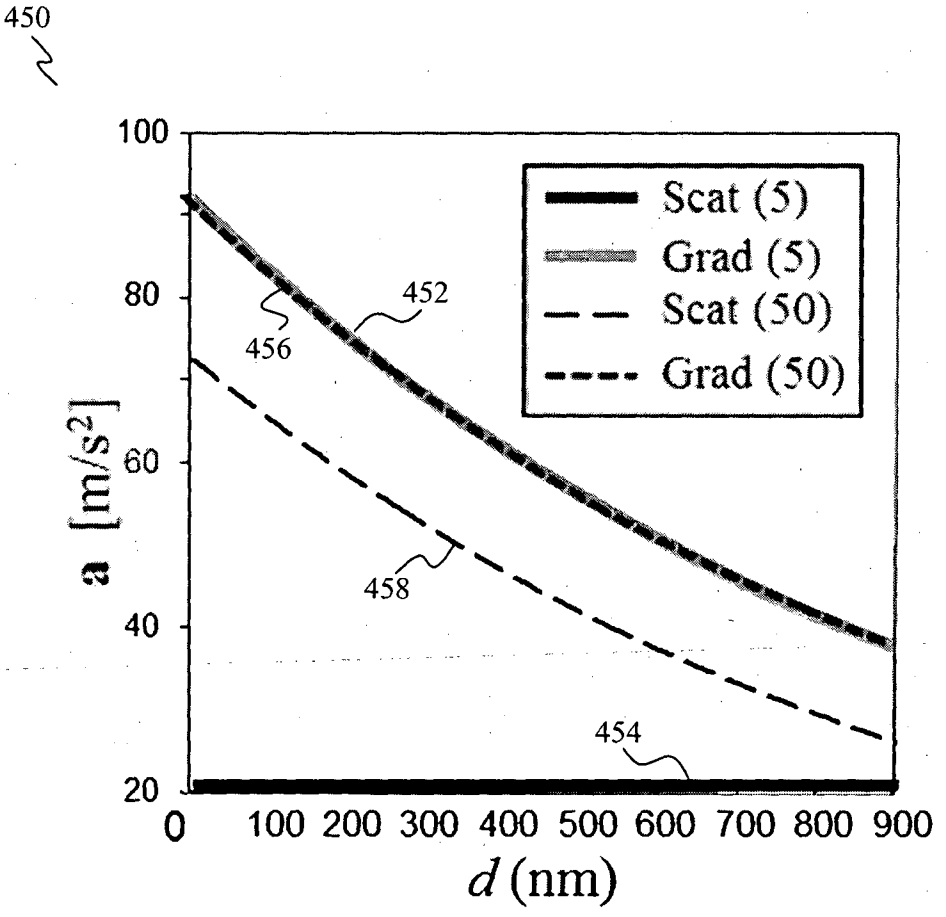
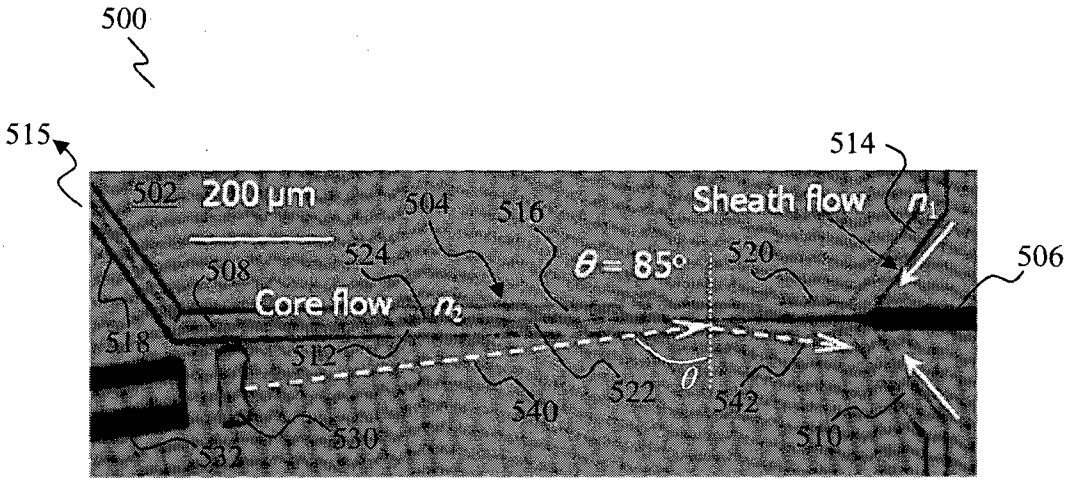
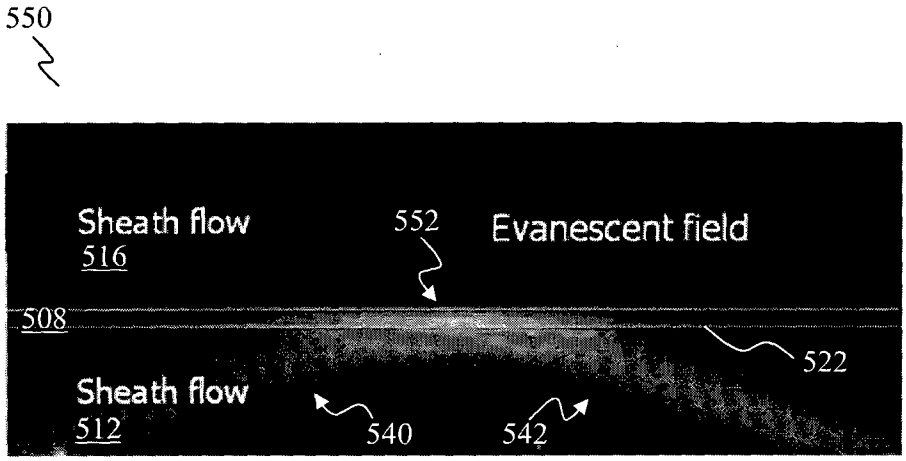

450
100
80
60
40
20
0
100 200 300 400 500 600 700 800 900
a [m/s²]
d (nm)
Scat (5)
Grad (5)
Scat (50)
Grad (50)
452
456
458
454

FIG. 4C



Microscopy images of the microchannnel

FIG. 5A



Microscopy images of the TIR in microchannel

FIG. 5B

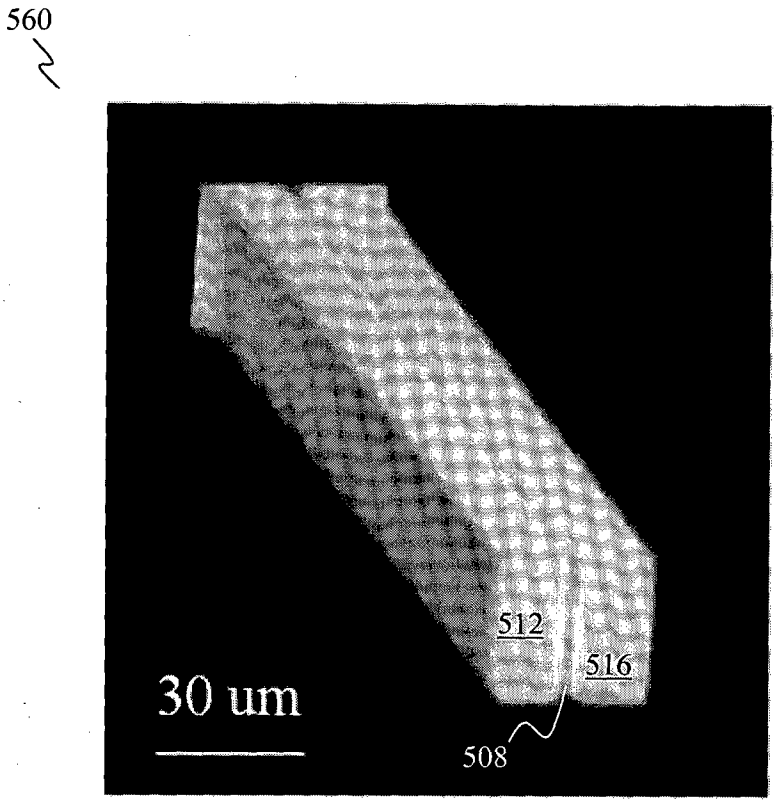


FIG. 5C

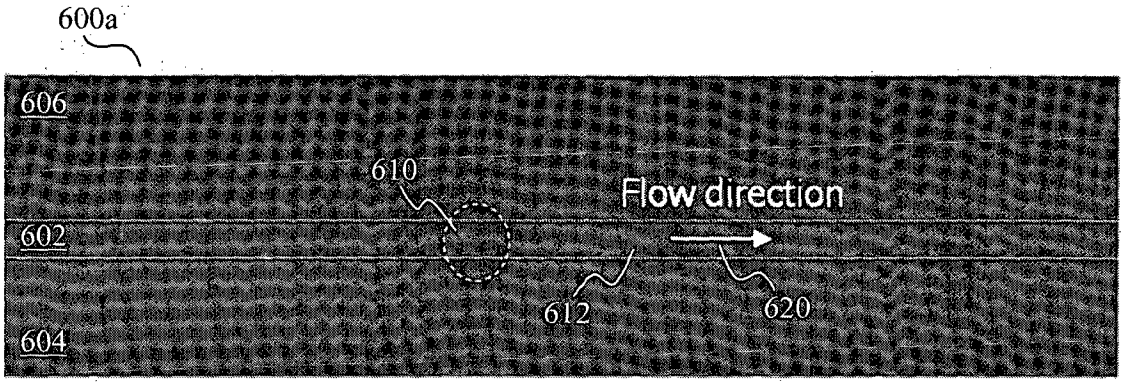


FIG. 6A

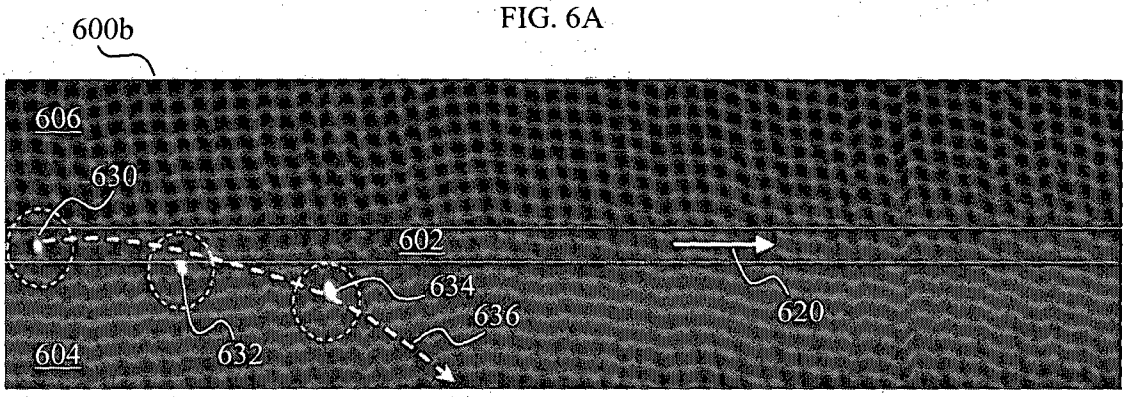


FIG. 6B

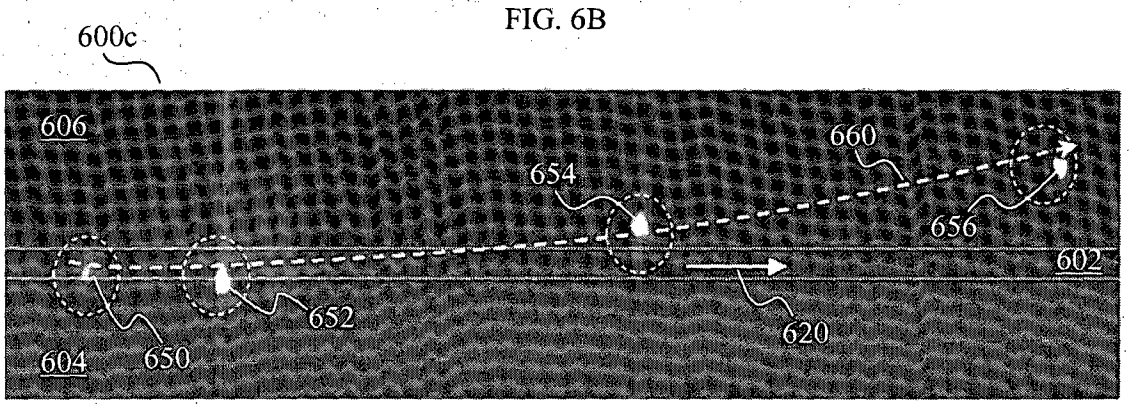


FIG. 6C

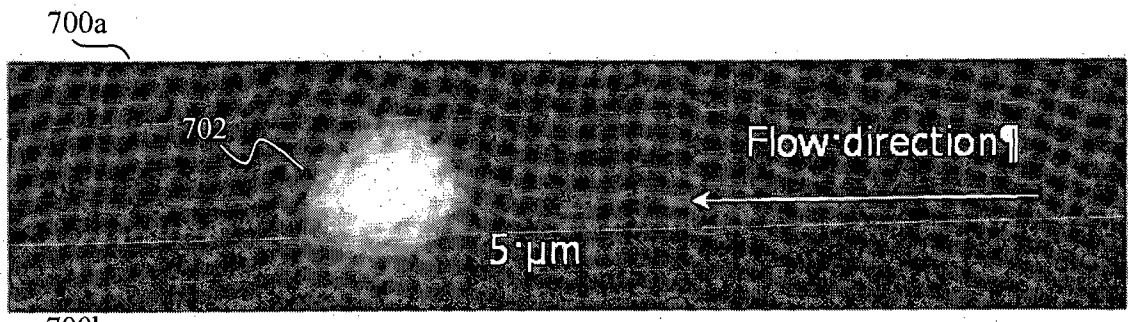


FIG. 7A

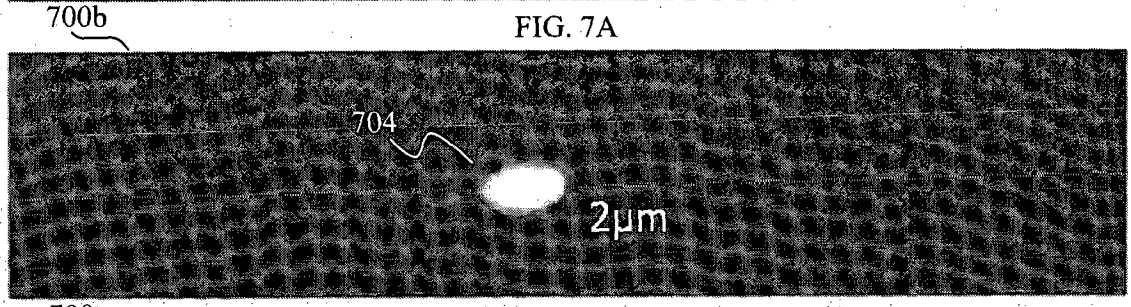


FIG. 7B

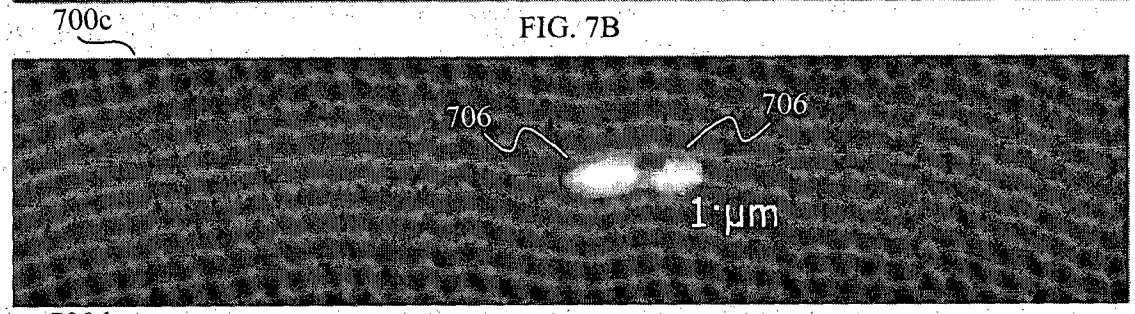


FIG. 7C

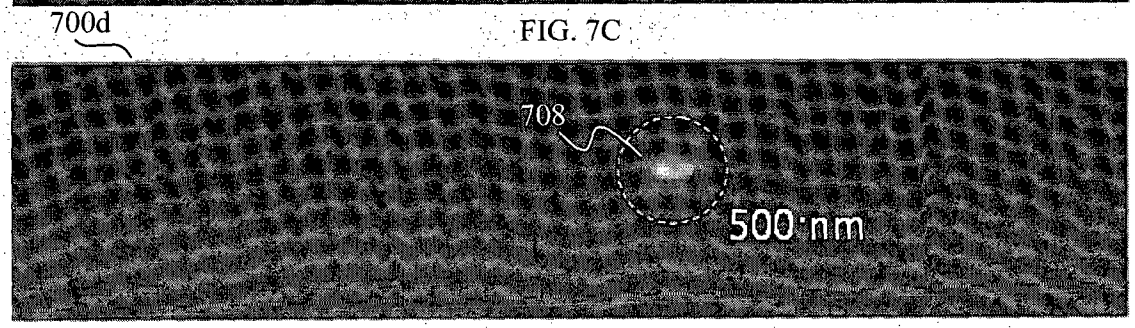


FIG. 7D

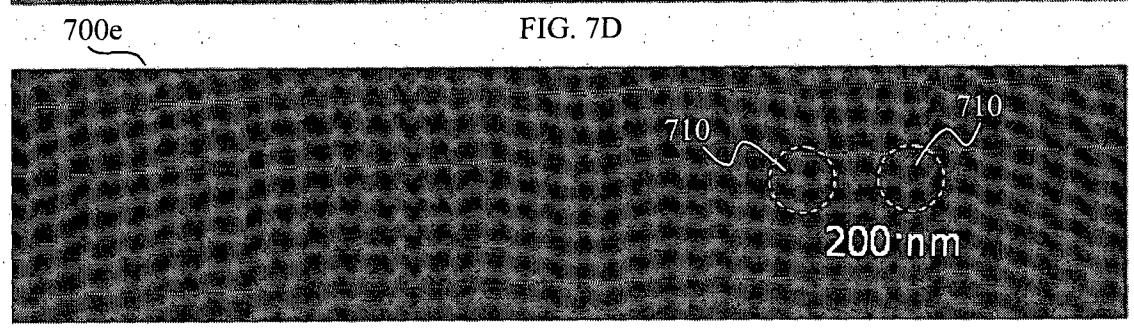


FIG. 7E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2013/000270

A. CLASSIFICATION OF SUBJECT MATTER

G01N 15/10 (2006.01) G01N 21/53 (2006.01) G21K 1/00 (2006.01)

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)

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)

Google Patent, Google Scholar and Espacenet:
hydrodynamic, laminar flow, particle, detector, laser, evanescent, optofluidic, separate and similar terms.

EPODOC, WPI and INSPEC:
particle, detector, optofluidic, evanescent, sheath and similar terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

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

[X] 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	Date of mailing of the international search report
1 August 2013	01 August 2013

Name and mailing address of the ISA/AU

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Authorised officer

Leo Lai
AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No. 0262832769

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/SG2013/000270**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YANG Y. et al., "Nano-Optofluidic For Single Molecule Detection and Sorting", MEMS 2012, pages 156-159, 2 Feb 2012: DOI: 10.1109/MEMSYS.2012.6170117 Abstract, Introduction, Deign and Theory, Results and Discussions Figures	1-45
A	PSALTIS D. et al., "Developing Optofluidic Technology through the fusion of microfluidics and optics", Nature, Vol. 442, pages 381-386, 27 Jul 2006: DOI: 10.1038/nature05060	
P,A	KAYANI A. A. et al., "Optofluidics Incorporating Actively Controlled Micro and Nano-Particles", Biomicrofluidics, Vol. 6, pages 031501-1 - 32, 18 Jul 2012: DOI: 10.1063/1.4736796	
A	US 6200814 B1 (MALMQVIST et al.) 13 March 2001	
A	US 2011/0003303 A1 (PAGANO et al.) 06 January 2011	
A	KR 1020090073650 A (SEOUL NATIONAL UNIVERSITY INDUSTRY FOUNDATION) 03 July 2009	

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/SG2013/000270**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
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		JP 2012530246 A	29 Nov 2012
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End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.