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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 November 2014 (27.11.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/190331 A2

(51) International Patent Classification:
A61B 5/1455 (2006.01)

(21) International Application Number:
PCT/US2014/039457

(22) International Filing Date:
23 May 2014 (23.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/826,978 23 May 2013 (23.05.2013) US

(71) Applicant: **CORNELL UNIVERSITY** [US/US]; 395 Pine Tree Road, Suite 310, Ithaca, NY 14850 (US).

(72) Inventors: **LIPSON, Michal**; 1 Millcroft Way, Ithaca, NY 14850 (US). **PHARE, Christopher**; 130 Simsbury Drive, Ithaca, NY 14850 (US).

(74) Agent: **AI, Bing**; Perkins Coie LLP, P.O. Box 1247, Seattle, WA 98111-1247 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, 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, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, 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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: NANOPHOTONIC RAMAN SPECTROSCOPY BIOSENSORS

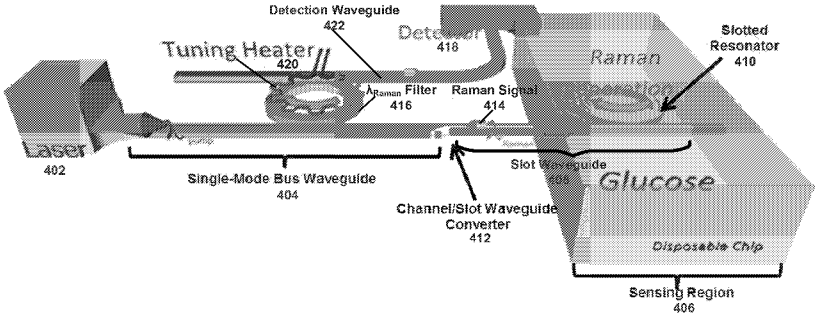

FIG. 4

(57) Abstract: Methods, systems, and devices are disclosed for implementing an ultra-sensitive micro-Raman spectrometer based on high confinement nanometer-scale photonic structures, which can enhance the sensitivity while maintaining an extremely compact size. In one aspect, a portable, ultra-sensitive, chip-scale system for performing sensing and identification on liquid and gaseous samples based on Raman spectroscopy is disclosed. The disclosed chip-scale system can be especially useful for biosensing including glucose sensing and monitoring (e.g., finding concentrations of glucose in complex body fluids like blood, urine, or saliva). For example, in implementations for glucose monitoring, the disclosed technology can make an impact that not only provides relief from the typical required "finger prick" for blood sampling, but also provides an easy-to-use device that diabetics and other people in need of glucose monitoring (and eventually other types of monitoring) can use.

WO 2014/190331 A2

NANOPHOTONIC RAMAN SPECTROSCOPY BIOSENSORS

PRIORITY CLAIM AND RELATED PATENT APPLICATIONS

[0001] This patent document claims the benefit of U.S. Provisional Application No. 61/826,978 entitled "NANOPHOTONIC RAMAN SPECTROSCOPY BIOSENSORS" and filed May 23, 2013, the disclosure of which is incorporated by reference as part of the specification of this document.

TECHNICAL FIELD

[0002] This patent document generally relates to biosensor technologies based on optical sensing.

BACKGROUND

[0003] A biosensor is an analytical tool that can detect a chemical, substance, or organism using a biologically sensitive component coupled with a transducing element to convert a detection event into a signal for processing and/or display. Biosensors can use biological materials as the biologically sensitive component, e.g., such as biomolecules including enzymes, antibodies, nucleic acids, etc., as well as living cells. For example, molecular biosensors can be configured to use specific chemical properties or molecular recognition mechanisms to identify target agents. Biosensors can use the transducer element to transform a signal resulting from the detection of an analyte by the biologically sensitive component into a different signal that can be addressed by optical, electronic or other means. For example, the transduction mechanisms can include physicochemical, electrochemical, optical, piezoelectric, as well as other transduction means.

[0004] Analyte testing and monitoring devices play a highly important role in modern diagnosis and management of health-related issues. An analyte, or component (in clinical chemistry), is a substance or chemical constituent that is of interest in an analytical procedure. For example, a sample of human blood, urine, and/or saliva can be tested for glucose, fructosamine, hematocrit, hemoglobin blood oxygen saturation, lactates, iron, pH, cholesterol, liver enzymes (e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) / gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, etc.), hormones, and other compounds.

SUMMARY

[0005] Techniques, systems, and devices are disclosed for optically detecting or sensing a fluid to obtain Raman scattering signals from one or more substances in the fluid. The disclosed technology can be implemented for various biosensing applications, devices or systems, including an ultra-sensitive chip-scale Raman spectrometer based on high confinement nanometer-scale photonic structures, e.g., which enhances the sensitivity while maintaining an extremely compact size.

[0006] In one aspect, a biosensor system for optically detecting a fluid is provided to include a base unit including a substrate, and a waveguide for guiding light, an optical filter coupled to the waveguide to receive light from the waveguide, and an optical detector coupled to receive light from the optical filter; a sensing unit coupled to the base unit and structured to include a containment region capable of containing a fluid and including a waveguide resonator optically coupled to the waveguide of the base unit at an interface and to direct light from the waveguide into the containment region to interact with the fluid; and a coherent light source optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the fluid including the substance. The waveguide is optically coupled to receive the emitted light beam from the coherent light source to carry the emitted light beam to an interface with the sensing unit to collect Raman scattered light travelling in the opposite direction from the interface, the optical filter is coupled to the waveguide to receive and filter the collected Raman scattered light, and the optical detector is coupled to the optical filter to detect a Raman spectrum of the collected Raman scattered light. In some implementations, the waveguide resonator is structured as a slot waveguide resonator to increase an optical field of the emitted light beam interacting with the fluid to enhance the Raman scattered light.

[0007] In another aspect, an optical-fluid biosensor system to detect an analyte in a fluid includes a fixed unit formed of a substrate material and structured to include a recessed region, a detachable unit capable of attaching to the fixed unit at the recessed region and structured to include a detection region capable of containing a fluid including a substance, and a coherent light source optically coupled to the fixed unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the substance. The fixed unit includes a waveguide optically coupled to the coherent light source to carry the emitted light beam to an interface with the recessed region and collect Raman scattered light travelling in the opposite direction the interface, an optical filter coupled to the waveguide to

filter the collected Raman scattered light, and an optical detector coupled to the optical filter to detect a Raman spectrum of the collected Raman scattered light. The detachable unit includes a second substrate material including a second recessed region forming the detection region to contain the fluid, and a slot waveguide resonator to enhance the Raman scattered light generated based on the presence of the substance in the fluid.

[0008] In another aspect, a biosensor system for optically sensing a fluidic sample is provided to include a fixed unit including a substrate that includes a first region for detecting an optical signal containing Raman fingerprint of the fluidic sample and a second region including a recessed area for receiving a disposable unit, a coherent light source configured to emit a probe light at a wavelength capable of causing Raman scattering when incident on the fluidic sample, and a waveguide optically coupled to receive the probe light from the coherent light source to carry the probe light to a coupling interface; and a disposable chip unit structured to be removeably attached to the fixed unit by fitting into the recessed area of the fixed unit, the disposable chip including a sensing unit optically coupled to the fixed unit to receive the probe light and capable of receiving a fluidic sample including the analyte. The sensing unit includes a waveguide structure configured to confine and guide the probe light to cause Raman scattering interaction between the confined probe light and the analyte through either evanescent coupling or directly contact and to collect Raman scattered light from the analyte; an optical coupler coupled between the waveguide structure and the coupling interface in the fixed unit to couple the probe light to the waveguide structure through the coupling interface; and collect the collected Raman scattered light from the waveguide structure.

[0009] In another aspect, an optical-fluid biosensor system to detect an analyte in a fluid includes a base unit formed of a substrate, a sensing unit coupled to the base unit and structured to include a containment region capable of containing a fluid including a substance, and a coherent light source optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the substance. The base unit includes a waveguide optically coupled to the coherent light source to carry the emitted light beam to an interface with the sensing unit and collect Raman scattered light travelling in the opposite direction from the interface, an optical filter coupled to the waveguide to filter the collected Raman scattered light, and an optical detector coupled to the optical filter to detect a Raman spectrum of the collected Raman scattered light. The sensing unit includes a slot waveguide resonator optically coupled to the waveguide at the

interface and to enhance the Raman scattered light generated based on the presence of the substance in the fluid.

[0010] In yet another aspect, a biosensor system for optically detecting a fluidic sample includes a sensing unit formed on a substrate to receive a probe light and structured to include a containment region capable of receiving and containing the fluidic sample including a substance. This sensing unit also includes: a waveguide structure configured to confine and guide the probe light to cause Raman scattering interaction between the confined probe light and the fluidic sample through either evanescent coupling or direct contact and to collect Raman scattered light generated from the fluidic sample. The waveguide structure is optically coupled to an interface to guide the collected Raman scattered light from the fluidic sample to the interface. The biosensor system further includes a base unit formed on the substrate and coupled to the sensing unit. This base unit also includes: a waveguide optically coupled to a coherent light source to carry an emitted probe light from the coherent light source to the interface with the sensing unit and to receive the collected Raman scattered light travelling in the opposite direction to the emitted probe light from the sensing unit at the interface; an optical filter coupled to the waveguide and tunable to select and filter out the received Raman scattered light; and an optical detector coupled to the optical filter to generate a Raman spectrum of the substance based on the outputs of the optical filter.

[0011] In some implementations, the coherent light source is a laser external to the biosensor system and configured to emit the probe light at a wavelength capable of Raman scattering when incident on the fluidic sample including the substance.

[0012] In some implementations, the coherent light source is a pump laser formed on the substrate and configured to emit the probe light at a wavelength capable of Raman scattering when incident on the fluidic sample including the substance.

[0013] In some implementations, the coherent light source is a pump laser generating the probe light of a first wavelength.

[0014] In some implementations, the biosensor system includes one or more additional lasers, each of which is tuned to a specific Raman wavelength of interest to cause stimulated Raman emission from the substance at the specific Raman wavelength of interest.

[0015] In some implementations, the biosensor system includes a coherent anti-Stokes Raman spectroscopy (CARS) that further includes a second laser to generate a Stokes

beam of a second wavelength and a third laser to generate a probe beam at a third wavelength, wherein the pump laser.

[0016] In some implementations, the waveguide structure includes a slot waveguide configured to enhance the Raman scattering interaction by focusing the probe light strongly inside and in close proximity of the slot region of the slot waveguide.

[0017] In some implementations, the waveguide structure further includes a ring resonator optically coupled to the slot waveguide to enhance the Raman scattering interaction by enabling a long interaction length between the probe light and the analyte while maintaining the compact size of the sensing unit.

[0018] In some implementations, the ring resonator is a slotted ring resonator configured to further enhance the Raman scattering interaction by focusing the probe light strongly inside and in close proximity of the slot region of the slotted ring resonator.

[0019] In some implementations, the fixed unit further includes one or both of CMOS electronics and a display.

[0020] In some implementations, the fixed unit further includes a processing unit to process the collected Raman scattered light to determine the Raman spectrum of the analyte. This processing unit can include: (1) an optical filter coupled to the waveguide and configured to filter out the collected Raman scattered light; (2) a tuning mechanism thermally coupled to the optical filter to tune the optical response of the optical filter to match a set of targeted Raman wavelengths; and (3) an optical detector coupled to the optical filter to generate a Raman spectrum of the analyte based on the outputs of the optical filter.

[0021] In some implementations, the optical filter includes a ring resonator, the tuning mechanism includes a micro-heater, and the optical detector includes a photodiode.

[0022] In some implementations, the substrate includes at least one of silicon, silicon oxide, silicon oxynitride (SiON), aluminum oxide (Al_2O_3), titanium dioxide (TiO_2), or silicon nitride (SiN).

[0023] In some implementations, the waveguide structure includes a high-index material of at least one of: silicon nitride (SiN), silicon carbide (SiC), titanium oxide (TiO_2), aluminum oxide (Al_2O_3), silicon, and diamond.

[0024] In some implementations, the disposable chip unit is capable of detaching from the fixed unit after used for detecting the analyte, and the fixed unit is reconfigured to receive a new disposable chip after the used disposable chip has been removed.

[0025] In some implementations, the analyte is glucose.

[0026] In some implementations, the fluidic sample includes one of: tears, saliva, urine, and blood.

[0027] In yet another aspect, a biosensor system for optically detecting a fluidic includes: a base unit including a substrate, and a waveguide for guiding light; a sensing unit coupled to the base unit and structured to include a containment region capable of containing a fluid and including a slot waveguide optically coupled to the waveguide of the base unit at an interface and to direct light from the waveguide into the containment region to interact with the fluid; and a coherent light source optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the fluid including a substance. The slot waveguide is configured to collect Raman scattered light generated in and around the slot waveguide. The waveguide is optically coupled to receive the emitted light beam from the coherent light source to carry the emitted light beam to an interface with the sensing unit and to receive a portion of the collected Raman scattered light which travels in the opposite direction to the emitted light beam from the interface. The slot waveguide resonator is structured to increase an optical field of the emitted light beam interacting with the fluid to enhance the Raman scattered light.

[0028] In yet another aspect, an opto-fluidic biosensor system for detecting an analyte in a fluidic sample is disclosed. This opto-fluidic biosensor system includes: a base unit formed on a substrate; a coherent light source optically coupled to the base unit and configured to emit a probe light at a wavelength capable of Raman scattering when incident on the analyte; and a sensing unit coupled to the base unit to receive the probe light and structured to include a containment region capable of receiving and containing a fluidic sample including an analyte. The base unit includes the following components: (1) waveguide optically coupled to the coherent light source to carry the emitted probe light to an interface at the sensing unit and collect Raman scattered light travelling in the opposite direction from the interface; (2) an optical filter coupled to the waveguide and is tunable to select and filter out the collected Raman scattered light; and (3) an optical detector coupled to the optical filter to generate a Raman spectrum of the analyte based on the outputs of the

optical filter. Separately, the sensing unit includes a waveguide structure configured to confine and guide the probe light to cause Raman scattering interaction between the confined probe light and the analyte through either evanescent coupling or directly contact and to collect Raman scattered light from the analyte. The waveguide structure is optically coupled to interface to guide the collected Raman scattered light from the waveguide structure to the waveguide through the interface.

[0029] In some implementations, the coherent light source is built onto the base unit.

[0030] In some implementations, the sensing unit further includes a microfluidic channel structured to carry the fluidic sample to the containment region.

[0031] The above and other aspects of the disclosed technology and their implementations are described in greater detail in the drawings, the description and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIG. 1 shows a schematic of an exemplary high-index waveguide surrounded by low-index cladding.

[0033] FIG. 2A shows a schematic of an exemplary slot waveguide.

[0034] FIG. 2B shows an exemplary cross-section computer simulation of the electromagnetic field intensity distribution in the slot waveguide.

[0035] FIG. 3A shows a scanning electron microscopy (SEM) image of an exemplary silicon slotted micro-ring resonator used in the exemplary chip-scale sensing systems and techniques, and the inset image showing the zoom-in view of a section of the exemplary slot waveguide.

[0036] FIG. 3B shows a cross-sectional SEM image of the exemplary slot waveguide.

[0037] FIG. 3C shows an illustrative plot of a simulated and calculated optical mode profile for the exemplary slot waveguide in FIG. 3B with analyte present around and inside the slot.

[0038] FIG. 4 shows a schematic of an exemplary integrated sensing platform of the disclosed technology.

[0039] FIG. 5 shows a schematic of an exemplary fully integrated biosensing system comprising a fixed unit and a disposable chip.

[0040] FIG. 6A shows a schematic of an exemplary chip-to-chip waveguide coupling scheme between a fixed chip and a disposable chip.

[0041] FIG. 6B shows a plot of the misalignment tolerance between the exemplary coupled waveguides in FIG. 6A, wherein the coupling loss is plotted as a function of the misalignment between the two chips.

[0042] FIG. 7A shows a schematic of an exemplary slot waveguide capable of optical trapping of nanoparticles within the slot waveguide.

[0043] FIG. 7B shows an SEM image of an exemplary 100 nm slot waveguide used in exemplary opto-fluidic implementations.

[0044] FIG. 8 shows a photo image of an exemplary gas cell affixed to the silicon photonic chip and an associated SEM image of an exemplary silicon slotted micro-ring resonator used in the gas sensing region.

[0045] Like reference symbols and designations in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0046] Techniques, systems, and devices are disclosed for optically detecting or sensing one or more biological, chemical, biochemical or other substances to obtain Raman scattering signals from such one or more substances. The specific examples provided use a fluid as a sample that contains the one or more substances to be detected. The disclosed technology can be implemented in various configurations including a biosensor system for optically detecting a fluid that is configured to include a base unit to direct probe light to the target sample and to detect signal light from the target sample and a sensing unit that holds the target sample and to provide the optical interaction between the probe light and the target sample. In some implementations, the base unit includes a substrate, and a waveguide for guiding light, an optical filter coupled to the waveguide to receive light from the waveguide, and an optical detector coupled to receive light from the optical filter. The sensing unit is coupled to the base unit and is structured to include a containment region capable of containing a fluid and including a waveguide resonator optically coupled to the waveguide of the base unit at an interface and to direct light from the waveguide into the containment region to interact with the fluid. A light source, such as a coherent light source (e.g., a laser), is optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the fluid including the substance. The

waveguide is optically coupled to receive the emitted light beam from the light source to carry the emitted light beam to an interface with the sensing unit to collect Raman scattered light travelling in the opposite direction from the interface. The optical filter is coupled to the waveguide to receive and filter the collected Raman scattered light, and the optical detector is coupled to the optical filter to detect a Raman spectrum of the collected Raman scattered light. As disclosed below, the waveguide resonator may be a slot waveguide resonator to increase an optical field of the emitted light beam interacting with the fluid to enhance the Raman scattered light. Such and other structures can be designed to provide a sensitive micro-Raman spectrometer based on high confinement nanometer-scale photonic structures, e.g., which enhances the sensitivity while maintaining a compact size.

[0047] Compact and sensitive Raman spectrometers can be used to provide optical detection of minute amounts or traces of substances in a wide range applications, including medical diagnostics devices and uses. Consider the example of glucose testing for diabetes patients where the data of patent blood glucose levels is important to treatment and health maintenance of diabetes patients. The consequences of inadequately monitoring diabetes resulted in 4.8 million deaths in 2012 alone. It is also projected that the global prevalence will increase from 366 million people affected with diabetes (2011) to 552 million by 2030. The accurate monitoring of blood glucose levels is necessary to ensure that it is within the normal range of 80-120 mg/dL (e.g., 4.4-6.6 mM), otherwise variations of blood glucose levels can result in and expedite the onset of major health problems such as heart and kidney problems and blindness. Diabetics need an accurate, quick and reliable test platform that is as minimally invasive and low cost as possible.

[0048] Given the widespread of diabetes, glucose monitoring devices account for about 85% of the entire biosensor market, significant research has been undertaken to demonstrate innovative approaches in glucose monitoring. Among the most prevalent monitoring devices, many commercial devices involve "finger prick" to extract a small amount of blood from a finger to monitor the evolution of H_2O_2 resulting from the oxidation of glucose with glucose oxidase. However, this approach has inconveniences such as deterring patients from regular monitoring and those factors tend to reduce the frequency of tests of patient blood glucose levels. This lack of proper monitoring of the blood glucose levels can lead to poor or lack of patient blood glucose levels that would adversely affect patient health or well-being.

[0049] Raman spectroscopy is a molecular spectroscopy technique that is sensitive to analyte composition. Molecules have individual Raman fingerprints, so their composition and concentration can be measured even in complex mixtures, without separate chemical markers. The Raman signature of glucose, and any other molecule of interest, is unique and can easily be isolated from the environment. The Raman spectroscopy based detection technique is extremely promising for the detection of analytes in general in a "dirty" medium (e.g., such as body fluids) without the need for pre-filtering. While Raman signals have the ability to identify uniquely analytes from which they are emitted, they are typically weak and their detection suffers from a fundamental tradeoff between the size of the sensing platform and the associated detection sensitivity. The weak Raman signals typically require a sensor to have long interaction lengths.

[0050] Generally in Raman spectroscopy, a sample is excited by a powerful laser, and generated Raman light is collected, filtered from the pump laser, and routed to a spectrometer (in free-space optics) to collect the Raman signal at several wavelengths. Raman scattering can be an extremely weak signal (e.g., less than 1 in 10^6 pump photons are converted to a Raman photon) if the Raman measurements are not conducted under desired conditions. Raman detection tends to be performed by using powerful lasers, long integration times, cooled detectors, and bulky and expensive optics in various existing Raman measurement systems. Surface-enhanced Raman spectroscopy (SERS) can enhance the Raman signal but has its own limitations for practical diagnostic instrumentation or applications.

[0051] Some implementations of existing glucose biosensing technologies use Raman spectroscopy in a photonic crystal ("hollow core") fiber and have shown capabilities of detecting glucose concentrations from 50 mg/dL with ~25% error. This technique usually uses a high numerical aperture (NA) lens to couple laser light into the fiber and collect the Raman signal. The detection sensitivity can be limited due to this lens coupling feature and other factors.

[0052] Hence, there is a need for achieving a Raman signal based testing platform that is sensitive, flexible, reliable, and affordable while being easy-to-use. The disclosed technology can be implemented for a range of applications including providing the capabilities of meeting this need.

[0053] In one aspect, a portable, ultra-sensitive, chip-scale system for performing sensing and identification on liquid and gaseous samples based on Raman spectroscopy is

disclosed. The disclosed chip-scale system can be especially useful for biosensing including glucose sensing and monitoring (e.g., finding concentrations of glucose in complex body fluids like blood, urine, or saliva). For example, in implementations for glucose monitoring, the disclosed technology can make an impact that not only provides relief from the typical required "finger prick" for blood sampling, but also provides an easy-to-use device that diabetics and other people in need of glucose monitoring (and eventually other types of monitoring) can use. While the following discussion tends to be described in the context of biosensing such as glucose monitoring, the disclosed ultra-sensitive chip-scale Raman spectroscopy can be conveniently applied for gas sensing, general chemical identification, and quality control (e.g., Raman spectroscopy has been able to demonstrate the difference between brand-name and generic acetaminophen).

[0054] In some implementations, the disclosed chip-scale sensing system/platform is based on photonic resonator devices that enhance the Raman signals and the associated detection sensitivities by orders of magnitude. More specifically, the disclosed technology includes an ultra-sensitive micro Raman spectrometer that is based on high confinement nanometer-scale photonic structures that are configured to enhance the Raman signals and the associated detection sensitivity while maintaining an extremely compact size.

[0055] In some implementations, the disclosed chip-scale sensing system/platform uses a special type of waveguide, a "slot waveguide," to enhance the sensitivity of detection. In the example of a glucose sensor, a slot waveguide can focus light extremely strongly and precisely at the location of the glucose sample. In some implementations, the disclosed chip-scale sensing system/platform also incorporates a ring resonator waveguide to decrease the size of the sensing platform based on Raman spectrometer while maintaining the interaction length between probe light and the analytes, such as glucose sample, by recycling the probe light. In some embodiments, the ring resonator is configured as a slotted waveguide to enhance the sensitivity of the biosensing system/platform and to enable long interaction lengths while keeping the device compact. Hence, the disclosed technology provides solutions to overcome the tradeoff between size and sensitivity in Raman spectrometer.

[0056] In some implementations, the disclosed chip-scale sensing system/platform can be fully portable (e.g., size of fully packaged device can be configured to be < 3 cm × 3 cm) and can include both a fixed analysis unit (e.g., containing a fixed chip, electronics and display) and one or more disposable sensing "chips" or "strips" receiving biological fluid samples, including but not limited to blood, saliva, and urine. Some exemplary advantages of

the disclosed biosensing system/platform include low cost. For example, the cost of the fixed chip can be estimated to be of a few dollars and the cost of the disposable chip to be less than a dollar. Additionally, the disclosed biosensing system/platform can be configured to be compact, e.g., on the order of a few mm^2, and with little power consumption (~1 mW).

[0057] Exemplary implementations of the disclosed chip-scale sensing system/platform are described below, e.g., based on integrated waveguide structures and resonators. The disclosed technology demonstrates the high sensitivity of exemplary slot waveguide structures, the ability to use the exemplary slot waveguides for fluidic sensing, and the ability to obtain spectra with high resolution and sensitivity using the disclosed nano-photonic ring resonator structures.

[0058] In some embodiments, the disclosed chip-scale sensing system/platform is based on nanometer-size waveguides. These waveguides, similarly to optical fibers, confine and guide light, but are configured and operate at chip scales. For example, the disclosed waveguides can have cross-sectional dimensions typically of 500 nm wide by 500 nm high, and can have lengths of a few tens of microns or longer. These waveguides have a higher index of refraction than their surroundings, allowing the confinement of light inside the waveguide.

[0059] One implementation of the disclosed chip-scale sensing platform is based on a special type of waveguide, a "slot waveguide," that is configured to enhance the sensitivity of detection by focusing probe light extremely strongly and precisely at the location of the analyte (e.g., glucose sample). FIG. 1 shows a schematic of an exemplary high-index of refraction (or "high-index") waveguide 102 surrounded by low-index of refraction (or "low-index") cladding 104. The waveguide structure is defined on a silicon substrate 106. A slot waveguide is similar to a regular waveguide except that a "slot" is defined in the middle of the high-index waveguide and through the entire length of the waveguide by removing the corresponding portion of the high-index material from the high-index waveguide.

[0060] FIG. 2A shows a schematic of an exemplary slot waveguide. As shown in FIG. 2A, the slot waveguide is composed of two regions 202 of high-index material (n_H) separated by a narrow gap ("the slot") 204 of low-index material (n_L). Some typical values of the slot waveguide dimensions w_h, w_s and h are ~200 nm, 100 nm and 500 nm, respectively. In some embodiments, the slot width w_s is ~50 nm or smaller but are greater than the size of the analytes to be studied. The illustrated slotted waveguide can confine light extremely

strongly in the low index region 204, thereby creating high optical field intensities in the slotted region. In some implementations, the high-index material of the slot waveguide can include but is not limited to: silicon nitride (SiN), silicon carbide (SiC), titanium oxide (TiO_2), aluminum oxide (Al_2O_3), silicon, and diamond.

[0061] FIG. 2B shows an exemplary cross-section computer simulation of the electromagnetic field intensity distribution in the slot waveguide. As can be seen in FIG. 2B, high field intensities (red) are confined within the low index of refraction slot region 206 where sensing takes place.

[0062] As described above, other Raman spectrometers typically require a sensor to have long interaction lengths to mitigate the weak Raman signal, thereby leading to large sensor dimensions. In some implementations, the disclosed chip-scale sensing platform uses a ring resonator waveguide to decrease the size of the Raman spectrometer while maintaining the interaction length between probe light and the analytes, such as glucose, by recirculating/recycling the light. A ring resonator is a waveguide that is wrapped around itself to form a ring. In some embodiments, the proposed ring resonator is also slotted in a manner similar to the slotted waveguide described in conjunction with FIGs. 2A and 2B. In such designs, the high field intensities can be created and confined within the slotted region of the slotted ring resonator.

[0063] FIG. 3A shows a scanning electron microscopy (SEM) image of an exemplary silicon slotted micro-ring resonator 302 used in the exemplary chip-scale sensing systems and techniques. The inset image of FIG. 3A shows a zoom-in view of a section of the exemplary slot waveguide 302, wherein the low-index slot region is clearly shown through the middle of the waveguide. Note that FIG. 3A also shows a straight waveguide 304 in close proximity to slotted ring resonator 302, in which red arrows show direction of light propagation. Light traveling inside waveguide 304, which can also be a slotted waveguide, will couple to the ring resonator 302 for certain wavelengths (e.g., those resonant wavelengths of the ring resonator), and this coupled light will circulate in the resonator 302 when the wavelength λ_0 of the light satisfies the relation $m\lambda_0 = 2\pi R n_{eff}$, where m is an integer, R is the ring radius, and n_{eff} is the effective index of refraction of the resonator 302. The number of times light circulates typically depends on the quality factor Q of the ring resonator. Hence, a ring resonator results in an effective interaction "length" over which light-matter interactions can take place that is much longer than the actual circumference of the resonator. For example, an effective interaction length of 1 cm can be achieved using a 10 μm radius ring resonator

that has a quality factor (Q) of 10,000. The slotted ring resonator 302 combined with a slot waveguide 304 (as shown in FIG. 3A) forms a nano-photonic sensing structure which enhances the sensitivity and enables long interaction lengths while keeping the sensing device compact. FIG. 3B shows a cross-sectional SEM image of the exemplary slot waveguide, i.e., the ring resonator 302. In this example, the average width of the slot 306 is less than 50 nm. FIG. 3C shows an illustrative plot of a simulated and calculated optical mode profile for the exemplary slot waveguide in FIG. 3B with analyte present around and inside the slot. The illustrative plot of FIG. 3C shows that there is a high concentration of electromagnetic field in the slot region due to the slot confinement effect.

[0064] The disclosed nano-photonic sensor can be developed on a material platform that (1) is transparent (e.g., lossless) at visible wavelengths, for example, near wavelengths of 500 nm and 800nm (e.g., for achieving high sensitivity); and (2) exhibits low luminescence (e.g., so as not to drown the Raman signal and render the latter undetectable). The disclosed nano-photonic sensor can employ a wide range of materials for the platform. In some examples, the materials can include silicon oxynitride (SiON), silicon carbide (SiC), titanium dioxide (TiO_2), and silicon nitride (SiN), aluminum oxide (Al_2O_3), silicon, and diamond.

[0065] FIG. 4 shows a schematic of an exemplary integrated sensing platform of the disclosed technology. As can be seen in FIG. 4, the exemplary integrated sensing platform includes an optical pump signal (e.g., laser light) of wavelength λ_{pump} generated from an on-chip laser 404 (e.g., a laser diode lasing at a wavelength of around 450 nm). The pump signal λ_{pump} propagates from left to right in a single-mode bus waveguide 404 and travels to the sensing region 406 of the exemplary sensing platform. The sensing region 406 includes a slot waveguide 408 coupled to a slotted ring resonator 410. Slot waveguide 408 and slotted ring resonator 410 have been described in conjunction with FIGs. 2A-2B and 3A-3C. As described above, the slotted ring resonator 410 can significantly increase the effective interaction length between the pump signal λ_{pump} and the analyte in the sensing region 406 while maintaining the small size of the sensing region and the overall sensing platform. In particular, when sensing function is based on Raman signals, a small size Raman spectrometer is realized. In the embodiment shown, slot waveguide 408 is extended beyond sensing region 406 and coupled with the single-mode bus waveguide 404 through a waveguide converter 412. In certain implementations, slot waveguide 408 may be entirely situated within the sensing region 406. Also, both the slot region in slot waveguide 408 and the slot region in slotted ring resonator 410 may be in direct contact with the sample so that

the analytes can interact with the confined pump signal in these slots either through evanescent coupling (e.g., the analytes located in close proximity slightly above the slots) or in directly contact with the confined pump signal by penetrating inside the slots.

[0066] For the sensing function, the pump signal λ_{pump}, amplified by the slotted resonator 410, interacts with the analyte (e.g., cyclohexane, glucose) surrounding the slot waveguide 408 and slotted ring resonator 410 in the sensing region 406, and Raman signal is generated through the Raman scattering interaction (e.g., shown in orange and labelled as "Raman generation"). The Raman signal can include Raman fingerprint of the analyte, which includes multiple Raman shifted wavelengths $\lambda_{Raman} = \lambda_{pump} + \Delta\lambda$. Some of this Raman optical signal can in turn be captured by the slotted resonator 410, and subsequently coupled into the slot waveguide 408. Some of the captured Raman optical signal 414 (shown as a small yellow arrow pointing to the left) propagates down the slot waveguide 408 and the single-mode bus waveguide 404 from right to left in the opposite direction to the pump signal λ_{Raman} (shown as a large blue arrow pointing to the right).

[0067] For the detection function, the exemplary integrated sensing platform further includes a ring resonator filter (or the "λ_{Raman} filter") 416 coupled in close proximity to single-mode bus waveguide 404. Raman signal 414 can be filtered out (e.g., selected) from multiple optical signals propagating out of the sensing area 406 from right to left using ring resonator filter 416 and routed to an optical detector 418 such as a photodiode. In some implementations, the ring resonator filter 416 may be based on standard channel waveguide and not as a slot waveguide where the primary function of the ring resonator filter 416 may be for selecting the Raman signal 414. The exemplary integrated sensing platform may further include an integrated tuning micro-heater 420 integrated above the ring resonator filter 416 to tune the optical response of the ring resonator filter 416 to match different Raman wavelengths $\lambda_{pump} + \Delta\lambda$. This approach is used for optical tuning ring resonator filter 416 to select and thus couple out multiple Raman wavelengths $\lambda_{pump} + \Delta\lambda$. This ring resonator filter 416 can re-route the Raman signal 414 into the detection waveguide 422 which guides the Raman signal 414 towards the optical detector 418. Hence, a spectrum including Raman fingerprint of a given analyte, such as glucose can be obtained using a single-point detector and thermal tuning of the ring resonance.

[0068] While the exemplary integrated sensing platform in FIG. 4 uses both a slot waveguide (408) and a slotted ring resonator (410) in the sensing structure to achieve high sensitivity, other implementations of the exemplary integrated sensing platform can use

different sensing structures. In one implementation, the sensing structure in the sensing platform uses a slot waveguide combined with a solid (un-slotted) ring resonator. In another implementation, the sensing structure in the sensing platform uses a slot waveguide without using a ring resonator. In yet another implementation, the sensing structure in the sensing platform uses a solid waveguide and a solid ring resonator (i.e., no slotting used in the sensing structure). Still other variations to the above described implementations may be used in the sensing structure.

[0069] Lab-on-a-chip devices are able to integrate fluidic, electrical, and optical capabilities onto a planar platform and perform high throughput measurements. One of the main challenges for transitioning to commercial products, however, is that many such demonstrations are not easily separated from the lab environment. For example, some existing lab-on-a-chip devices still require macroscale laboratory equipment or the attention of skilled laboratory technicians to operate such as expensive microscopes to perform the measurements or act as a detector.

[0070] The disclosed biosensing platform can be configured into a fully portable lab-on-a-chip device, e.g., a size of fully packaged device based on the disclosed technology can be configured to be < 3 cm × 3 cm. More specifically, a disclosed fully integrated sensing system can include a fixed analysis unit (also referred to as a "fixed unit") and disposable sensing "chips" or "strips" for receiving biological fluids, such as blood, saliva, and/or urine (each of which is also referred to as a "disposable chip"). The fixed unit can be configured to contain a display, CMOS electronics, and a fixed chip comprising the above-described ring resonator filter, the optical detector and the on-chip laser. The disposable chip can be configured to contain the above-described sensor unit. FIG. 5 shows a schematic of an exemplary full integrated biosensing system comprising a fixed unit 502 and a disposable chip 504. In particular, FIG. 5 illustrates how the disclosed disposable chip fits in the fixed unit.

[0071] In the example in FIG. 5, fixed unit 502 includes a fixed chip 506 wherein individual components on fixed chip 506 such as the laser, the filter and the detector have been described above in conjunction with FIG. 4. Fixed unit 502 also includes a display 508, for example, for showing the measured glucose levels, and a CMOS controller 510 for processing the measured Raman signals and controlling the display 508, as well as other electronic components on the device. Fixed unit 502 also has a recessed chip receiving area 512 configured with dimensions substantially the same as disposable chip 504. Disposable

chip 504 includes a straight waveguide and a slotted ring resonator which have been described above in conjunction with FIG. 4.

[0072] The top schematic in FIG. 5 shows the fixed unit 502 and disposable chip 504 prior to the latter being "snapped" onto the fixed unit 502. The bottom schematic in FIG. 5 shows the fixed unit 502 and disposable chip 504 after the latter is snapped onto the fixed unit 502. Both fixed unit 502 and disposable chip 504 can include an optical coupler, such as optical coupler 514. After the disposable chip is snapped onto the fixed unit, a fully integrated biosensing system is realized. A fluidic sample, such as glucose sample 516 (or other fluidic samples in other implementations) can be dropped onto the sensing region of the disposable chip 504 before or after the "snapping" action. Note that the sample is confined within the disposable chip 504, therefore does not contaminate the fixed unit 502. Hence, after the current disposable chip 504 is used and discarded, the fixed unit 502 is ready to receive a new disposable chip 504.

[0073] After integration of the detection and sensing units, laser light generated from the fixed unit 502 is coupled to the disposable chip 504 using the optical couplers present on both chips that have high tolerance to mismatch of the coupling facets. This coupling can be enabled by placing two waveguides (i.e., one coupler from the fixed chip and the other coupler from the disposable chip) with strong evanescent field in close proximity. The evanescent field from one waveguide to another can be configured to be efficiently coupled. Exemplary simulations on the coupling mechanism demonstrates that this evanescent coupling is extremely robust to misalignments as discussed below.

[0074] The disclosed integrated biosensing platform can include efficient coupling between the waveguide in the fixed chip 506 and the waveguide in the disposable chip 504 with extremely high tolerance to misalignment (e.g., up to a few mm). This property can enable snapping the disposable chip onto the fixed unit in the exemplary system shown in FIG. 5. The disclosed techniques can be based on evanescent coupling between the two waveguides.

[0075] FIG. 6A shows a schematic of an exemplary chip-to-chip waveguide coupling scheme between a fixed chip and a disposable chip similar to those shown in FIG. 5. In the example of FIG. 6A, both the waveguide 602 on the fixed chip unit and the waveguide 604 on the disposable chip can be made of SiN, each can have dimensions measuring 400 nm × 200 nm in the cross-section and surrounded by silicon dioxide. The separation between the

two chips can determine the degree of misalignment. FIG. 6B shows a plot of the misalignment tolerance between the exemplary coupled waveguides in FIG. 6A, wherein the coupling loss is plotted as a function of the misalignment between the two chips. As illustrated in FIG. 6B, if the chips are misaligned by over 5 mm, a small loss less than 2 dB is expected.

[0076] The disclosed biosensing system (e.g., the fixed chip 506 and the disposable chip 504) can be configured to be extremely compact, e.g., on the order of a few mm^2, and with very little power consumption (~1 mW). In some implementations, the size of the fully integrated biosensing system shown in FIG. 5, can be less than 3 cm × 3 cm. This size of the system allows ease of insertion and removal of the disposable chip. In other implementations, the size of the fully integrated biosensing system in FIG. 5 can be much smaller than 3 cm × 3 cm.

[0077] The disclosed chip-scale sensing platform when implemented as a glucose sensing system provides significantly smaller dimensions and better sensitivity in glucose sensing (e.g., ~20 mg/dL) and with less than 10% error (see Table 1). The enhanced sensitivity in such biosensors is at least due to the high optical confinement in the employed slot waveguides, which have cross-sectional areas orders of magnitude smaller than optical fiber. The size of the sensing area of the exemplary biosensors can be significantly smaller than existing Raman spectroscopy at least due to the use of the ring resonators. It is noted that while the disclosed integrated waveguide system may have higher optical losses than optical fibers in some examples, the high optical confinement of the waveguides results in greater sensitivity. Table 1 shows expected performances of the disclosed chip-scale glucose system as compared to other glucose sensing approaches.

Table 1. Expected performance of the exemplary chip-scale approach, e.g., as compared to other approaches.

	Cross-Sectional Sensing Area	Losses	Length	Sensitivity	Error	Laser Power Needs
Free Space Optics	3 μm × 3 μm	~ 10^{-7} dB/cm	~3 cm	~300 mg/dL	~10%	~1 W
Hollow Core Fiber*	10 μm × 10 μm	~0.004 dB/cm	~10 cm	~50 mg/dL	~25%	2 mW
Our Chip-Scale Approach	**50 nm × 250 nm**	**~0.2 dB/cm**	**100 μm**	**< 20 mg/dL**	**< 10%**	**2 mW**

*In estimating the error (error = # counts/noise level), considered was the noise level of a standard CCD operating at room to be 100 counts. For example, in the disclosed system (FIGS. 4 and 5) a CCD is not utilized (e.g., a single point detector can be sufficient), since individual spectral lines are monitored.

Modeling of the Disclosed Chip-Scale Raman Spectrometer

[0078] The disclosed chip-scale sensing system described in FIG. 4 can be modeled using modeling parameters which can include the dimensions of the slot waveguides and the ring resonators under the consideration of the optical field interaction and device size tradeoff, sensing area dimensions, among other. Exemplary implementations of the chip-scale sensing system modeling include analytical modeling and computer simulations, and design of an optical coupler to enable high tolerance to mismatch of the fixed and disposable chip facets. In one embodiment, the system modeling includes analysis and determination of material choices for the sensing platform for the wavelength range of interest (e.g., visible wavelengths generated by the pump laser and near infrared wavelengths generated by Raman signals), so that optical losses (e.g., intrinsic material losses and other losses resulting from fabrication) in the system are minimal. In one implementation, the system modeling includes analysis of the fabrication and calibration of an exemplary biosensing platform using a relatively high power (e.g., 10 -100 mW) and measuring the Raman signature with cyclohexane and glucose. The modeling can also include analysis of the optical coupler for maximum tolerance to misalignments between the fixed and disposable chip facets.

[0079] The exemplary sensing system based on Raman spectrometer shown in FIG. 4 can be modeled using analytical tools and computer simulations to guide the designs of the system that when fabricated, is able to achieve desired performances, such as low optical losses and zero to low luminescence in the target material platforms (e.g., SiC, SiN, SiON or TiO_2). The exemplary sensing system based on Raman spectrometer can cover an approximate area of a few mm^2 and can be used to detect multiple analytes, such as cyclohexane and glucose fluidic concentrations.

[0080] In some embodiments, the modeling attempts to find an optimal balance between the amount of sensitivity, throughput, and size and is based on the expected Raman signal discussed below. For example, an exemplary device with a larger amount of evanescent field in the fluidic channel facilitated by smaller waveguide dimensions can give rise to a higher sensitivity but may also lead to a larger footprint. This exemplary design can enable the coverage of the entire surface of a few mm^2 platform with the waveguide structures. Modeling of the exemplary platform (e.g., waveguide dimensions, coupling gaps) at the pump light and Raman wavelengths can be performed.

Theory of Raman Signal Generation in the Exemplary Platform

[0081] Spontaneous Raman spectroscopy in a waveguide can be considered as an automatically phase-matched χ^3 process which depends on pump light intensity. The generated Raman (also referred to as "Stokes signal") power P_s is proportional to both the laser pump intensity I_{pump} and the Raman cross-section of the excited molecule such that:

$$P_S \propto \sigma' I_{Pump}. \quad (1)$$

Note that the cross-section parameter is denoted by σ' to indicate that it is a "lumped" factor to include, among others, the density of molecules and the scattering solid angle. Given that in the exemplary sensing region, interactions between the pump laser and the analytes (e.g., glucose) occurs over some length L and over a cross-sectional area A, and assuming that the exemplary waveguiding system has linear optical losses α, P_s can be written as:

$$P_S \approx \frac{\sigma'}{2\alpha A\Gamma} P_{Pump}, \quad (2)$$

where Γ is the optical confinement factor which measures how much the optical field overlaps the sensing region, and P_{pump} is the laser pump power. The Γ factor can reflect the fact that using slot waveguides increases light-matter interactions. The use of a ring resonator can further enhance the generation of the Raman signal by a factor F/π, where F is the finesse of the resonator.

Fabrication of the Raman Glucose Sensor

[0082] In some implementations, a microlithography fabrication process can be used to define all of the components of the sensing platform. For example, after determining the optimal material to use, a thin film of this material can be deposited on top of a thermally oxidized Si wafer which can then be patterned into the waveguides and sensing areas (including the ring resonators) using, for example, deep ultraviolet (DUV) lithography and reactive ion plasma etching. In some implementations, both the regular waveguides and the slot waveguides can be patterned at the same time.

Exemplary Implementations of the Raman Glucose Sensor

[0083] In some implementations, cyclohexane and varied concentrations of glucose in water can be characterized. For example, the on-chip Raman generation structure can be pumped with a frequency-doubled Ytterbium fiber amplifier seeded with an external cavity diode laser, providing a tunable laser operating near the traditional Raman pump wavelength of 532 nm. The short wavelength enhances Raman scattering interaction, while the tunable laser allows for easy tuning directly onto the ring resonance. Light backscattered from the Raman generation structure can be separated from the pump light with a dichroic beamsplitter and coupled into a spectrometer, where the full Raman spectrum can be collected. In some embodiments of the disclosed biosensing system, the laser can be a 645 nm, 1 mW diode laser. In some exemplary biosensing systems, a spectrometer is not needed. Instead, the exemplary systems can contain a single point detector, and the spectra can be obtained using integrated thermal tuning of the filtering ring resonance position as described in conjunction with FIG. 4.

[0084] In some implementations, several analytes can be pipetted directly onto the sensing chip. Cyclohexane has a large Raman cross-section and well-defined Raman peaks, making it a useful calibration sample for the exemplary biosensing systems. Glucose, while physiologically relevant, typically has a much smaller Raman signal. Thus, dilutions of glucose (e.g., in water) can be used to test for the sensitivity of the exemplary system. The exemplary system can also be implemented in "dirty" environments, for example, by introducing small amounts of fructose into the glucose dilutions or spiking blood serum with glucose, and detecting only the peaks corresponding to glucose in the resulting spectra.

[0085] In some implementations of the disclosed biosensing system, calibrations can be performed using prepared glucose solutions with known concentrations (e.g., ranging from a low concentration less than 20 mg/dL to a high concentration higher than 600 mg/dL) so as to achieve an error less than 15%. The disclosed technology can be implemented using a variety of biological fluids, e.g., including tears, saliva, urine and/or blood, e.g. which can also be used to calibrate target measurement range and error.

[0086] In some implementations, fluidic samples can be integrated with slot waveguides in a disclosed integrated biosensing system. For example, fluidic sample can penetrate into the slot and interact strongly with the spatially confined optical field in the proposed sensor. Sub-micron sized nanoparticles (e.g., ~75 nm) as well as DNA may be

optically trapped and transported using the proposed slot waveguides. In some implementations, for example, fluidic solutions containing the nanoparticles (and DNA) were flowed through a microfluidic channel onto the slot waveguide structures where the successful optical trapping was observed, thereby confirming the presence of the nanoparticles (and DNA) in the ~100 nm slot. FIG. 7A shows a schematic of an exemplary slot waveguide capable of optical trapping of nanoparticles within the slot waveguide. FIG. 7B shows an SEM image of an exemplary 100 nm slot waveguide used in exemplary opto-fluidic implementations.

[0087] Slot waveguides exhibit high sensitivity for sensing, which can provide enhanced Raman signal in the disclosed devices. Exemplary implementations were performed which showed the use of slot waveguides with a slotted ring resonator as a high sensitivity gas sensing platform, as exemplified in FIG. 8. FIG. 8 shows a photo image of an exemplary gas cell affixed to the silicon photonic chip (e.g., in which the dotted line shows the path of the light through the waveguide and the circle denotes the approximate location of the slotted ring resonator) and an associated SEM image of an exemplary silicon slotted micro-ring resonator used in the gas sensing region. The SEM image also includes an inset image showing a zoom-in view of a small section of the slotted ring resonator, with the red arrows showing direction of light propagation along the straight bus waveguide. The exemplary device showed high sensitivity based on measuring small (e.g., 10^{-4}) index of refraction changes in the slotted ring region caused by the presence of gases. As described above, the slot waveguide geometry combined with a slotted ring resonator increased the interaction between the optical field and the gas due to the high optical field intensities resulting from the slotted waveguide structures.

[0088] As mentioned above, a single point detector combined with thermal tuning of the ring resonance has the ability to obtain a spectrum without using a separate spectrometer. Exemplary implementations of an on-chip spectrophotometry for bio-analysis can be performed to measure the response of a single ring resonator and are able to demonstrate the ability to extract absorption of the surrounding fluid through spectral measurement. For example, the presence of fluid does not deteriorate the optical response of the ring.

[0089] The disclosed technology uses microfabricated waveguides and slot waveguides to enhance the generated Raman signal from a liquid or gas surrounding the waveguides. A filter or spectrometer can also be integrated monolithically with the Raman enhancement structures, such as slot waveguide and slotted ring resonator to create a Raman

spectroscopy platform completely on-chip. Additional information on slot waveguides is described in the US Patent 7,519,257, entitled "Waveguide Structure for Guiding Light in Low-Index Material," by inventors Michal Lipson, et al., the disclosure of which is incorporated by reference.

[0090] In the disclosed integrated sensing systems, waveguides and associated structures can be made with microfabrication technology. Exemplary waveguide materials can include, but are not limited to, silicon carbide epitaxially grown on silicon or silicon carbide, titanium dioxide, aluminum nitride, or aluminum oxide deposited in thin films on silicon dioxide via sputtering or plasma-enhanced chemical vapor deposition (PECVD). Waveguides can be exposed to the analyte on top of the waveguides or can be undercut by etching the buried silicon or silicon dioxide layer. Raman signal enhancement can occur in the exemplary systems in either a slot waveguide or a slotted ring resonator. An exemplary sensing device can be pumped from one end of the device with a laser source and Raman light is collected while travelling in the opposite direction to the pump light. In other exemplary embodiments of the device, other photonic devices may be included, such as a ring resonator to filter the Raman signal from the pump light, integrated detectors, and laser sources. Fluidic samples to be analyzed may be introduced to the waveguide sensing structure using either microfluidic channels or simply by dropping the liquid onto the waveguide sensing structure.

[0091] Some exemplary advantages of the disclosed biosensing systems include low cost of manufacturing. It is estimated that the cost of fabrication of the disposable chip containing the sensor can be negligible. For example, assuming mass production, the cost could be on the order of a few cents. This low cost is due to the number of chips fabricated per wafer can be over tens of thousands, the materials and fabrication (single mask) required for the disposable chip can be compatible with standard microfabrication processes, and the minimum feature size on the disposable chip is approximately 80 nm (e.g., slot waveguide), compatible with current DUV lithography. Moreover, the cost of the fixed chip can be estimated to be of a few dollars. For example, this exemplary estimated cost includes the packaging (e.g., estimated to be approximately 40-60% of the component). The laser and the single point detector can be bonded on the chip and can be expected to have extremely low cost, e.g., of less than $1 per die. Both a highly sensitive detector and a 1 mW laser at a wavelength of 645 nm are widely available on the market at a few dollars per fully packaged part.

[0092] The disclosed technology addresses the need for rapid, specific and sensitive detection of glucose levels using on-chip Raman spectroscopic analysis. This transformative platform can revolutionize glucose detection by enabling its rapid, low-cost and simple measurement. For example, the disclosed technology can have impact on diabetic patients through quick, accurate and pain-free monitoring of their blood glucose levels and will significantly and positively affect their quality of life. The impact of the disclosed sensing platforms can also have applications beyond the sensitive, reliable and rapid detection of glucose. For example, the disclosed sensing platforms can be easily modified and calibrated for other sensing applications such as the detection of nucleic acids, proteins, lipids, carbohydrates, toxins, among others.

[0093] The present technology disclosed in this patent document identifies a material platform (e.g., using transparent dielectric waveguide) that will have minimal background luminescence and optical propagation losses. The disclosed technology also describes design and engineering processes to produce and implement the nano-photonic structures, including analytical calculations and computer simulations to determine optimal parameters (e.g., waveguide dimensions, slot width, etc.) for guiding and detecting optical signals, and for the generation of the Raman signal. Moreover, the disclosed technology describes implementations of the photonic structures and the sensing device, e.g., using pump powers of 10-100 mW, and measure and calibrate the Raman signature in samples (e.g., cyclohexane (C_6H_{12}) and glucose) of different concentrations using the proposed slot waveguides.

[0094] While the disclosed embodiments described herein are primarily based on glucose monitoring to facilitate understanding of the underlying concepts, it is understood that the disclosed embodiments can also include monitoring of other analytes.

[0095] While this patent document and attached appendix contain many specifics, these should not be construed as limitations on the scope of any invention or of what may be claimed, but rather as descriptions of features that may be specific to particular embodiments of particular inventions. Certain features that are described in this patent document and attached appendix in the context of separate embodiments can also be implemented in combination in a single embodiment. Conversely, various features that are described in the context of a single embodiment can also be implemented in multiple embodiments separately or in any suitable subcombination. Moreover, although features may be described above as acting in certain combinations and even initially claimed as such, one or more features from a

claimed combination can in some cases be excised from the combination, and the claimed combination may be directed to a subcombination or variation of a subcombination.

[0096] Similarly, while operations are depicted in the drawings in a particular order, this should not be understood as requiring that such operations be performed in the particular order shown or in sequential order, or that all illustrated operations be performed, to achieve desirable results. Moreover, the separation of various system components in the embodiments described in this patent document and attached appendix should not be understood as requiring such separation in all embodiments.

[0097] Only a few implementations and examples are described and other implementations, enhancements and variations can be made based on what is described and illustrated in this patent document and attached appendix.

CLAIMS

What is claimed is:

1. A biosensor system for optically detecting a fluid, comprising:

a base unit including a substrate, and a waveguide for guiding light, an optical filter coupled to the waveguide to receive light from the waveguide, and an optical detector coupled to receive light from the optical filter;

a sensing unit coupled to the base unit and structured to include a containment region capable of containing a fluid and including a slot waveguide resonator optically coupled to the waveguide of the base unit at an interface and to direct light from the waveguide into the containment region to interact with the fluid; and

a coherent light source optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the fluid including the substance,

wherein the waveguide is optically coupled to receive the emitted light beam from the coherent light source to carry the emitted light beam to an interface with the sensing unit to collect Raman scattered light travelling in the opposite direction from the interface, the optical filter is coupled to the waveguide to receive and filter the collected Raman scattered light, and the optical detector is coupled to the optical filter to detect a Raman spectrum of the collected Raman scattered light, and

wherein the slot waveguide resonator is structured to increase an optical field of the emitted light beam interacting with the fluid to enhance the Raman scattered light.

2. The system of claim 1, wherein the base unit further includes one or both of CMOS electronics and a display.

3. The system of claim 1, further comprising a processing unit to process detected Raman spectra obtained from the optical detector to determine at least one parameter of the substance in the fluid.

4. The system of claim 1, wherein the system is configured to have a portable size including 3 cm × 3 cm or smaller.

5. The system of claim 1, wherein the substrate includes at least one of silicon, silicon oxide, silicon oxynitride (SiON), aluminum oxide (Al_2O_3), titanium dioxide (TiO_2), or silicon nitride (SiN).

6. The system of claim 1, wherein at least one of the waveguide or the slot waveguide resonator includes at least one of silicon carbide epitaxially grown on silicon (Si) or silicon carbide (SiC), titanium dioxide (TiO_2), aluminum nitride (AlN), or aluminum oxide (Al_2O_3) deposited in thin films on silicon dioxide (SiO_2).

7. The system of claim 1, wherein the base unit and the sensing unit further include an optical coupler to couple the evanescent field of light at the interface between the waveguide and the slot waveguide resonator.

8. The system of claim 1, wherein the coherent light source is in the base unit.

9. The system of claim 1, wherein the sensing unit further includes a microfluidic channel structured to carry the fluid to the containment region.

10. The system of claim 1, wherein the containment region is in a cavity of the sensing unit.

11. The system of claim 1, wherein the base unit is structured to include a recessed region, and the sensing unit is configured as a detachable unit capable of attaching to the base unit at the recessed region.

12. The system of claim 1, wherein the optical filter is tunable to selectively couple different Raman spectral components at different Raman signal wavelengths within the collected Raman scattered light to the optical detector.

13. The system of claim 12, wherein the optical filter is a tunable optical resonator filter.

14. The system of claim 12, wherein the optical filter is a tunable optical ring resonator filter.

15. The system of claim 12, further including a heater coupled to the optical filter to tune the optical filter.

16. The system of claim 12, wherein the waveguide in the base unit and the slot waveguide resonator in the sensing unit are transparent at visible wavelengths.

17. A biosensor system for optically sensing a fluidic sample, comprising:

a fixed unit including a substrate that includes a first region for detecting an optical signal containing Raman fingerprint of the fluidic sample and a second region configured to receive a disposable unit, a coherent light source configured to emit a probe light at a wavelength capable of causing Raman scattering when incident on the fluidic sample, and a

waveguide optically coupled to receive the probe light from the coherent light source to carry the probe light to a coupling interface; and

a disposable chip unit structured to be removeably attached to the fixed unit by fitting into the second region of the fixed unit, the disposable chip including a sensing unit optically coupled to the fixed unit to receive the probe light and capable of receiving a fluidic sample including the analyte, the sensing unit including:

a waveguide structure configured to confine and guide the probe light to cause Raman scattering interaction between the confined probe light and the analyte through either evanescent coupling or direct contact and to collect Raman scattered light from the analyte; and

an optical coupler coupled between the waveguide structure and the coupling interface in the fixed unit to couple the probe light to the waveguide structure through the coupling interface and to collect the collected Raman scattered light from the waveguide structure.

18. The system of claim 22, wherein the waveguide structure includes a slot waveguide configured to enhance the Raman scattering interaction by focusing the probe light inside and in close proximity of the slot region of the slot waveguide.

19. The system of claim 23, wherein the waveguide structure further includes a ring resonator optically coupled to the slot waveguide to enhance the Raman scattering interaction by enabling a long interaction length between the probe light and the analyte while maintaining the compact size of the sensing unit.

20. The system of claim 24, wherein the ring resonator is a slotted ring resonator configured to further enhance the Raman scattering interaction by focusing the probe light strongly inside and in close proximity of the slot region of the slotted ring resonator.

21. The system of claim 22, wherein the fixed unit further includes one or both of CMOS electronics and a display.

22. The system of claim 22, wherein the fixed unit further includes a processing unit to process the collected Raman scattered light to determine a Raman spectrum of the collected Raman scattered light.

23. The system of claim 22, wherein the processing unit includes:

an optical filter coupled to the waveguide and configured to filter out the collected Raman scattered light; and

an optical detector coupled to the optical filter to generate a Raman spectrum of the analyte based on the outputs of the optical filter.

24. The system of claim 23, wherein the optical filter includes a ring resonator.

25. The system of claim 23, wherein the processing unit further includes a tuning mechanism coupled to the optical filter to tune the optical response of the optical filter to match a set of targeted Raman wavelengths.

26. The system of claim 25, wherein the tuning mechanism includes a micro-heater.

27. The system of claim 23, wherein the optical detector includes a photodiode.

28. The system of claim 22, wherein the substrate includes at least one of silicon, silicon oxide, silicon oxynitride (SiON), aluminum oxide (Al_2O_3), titanium dioxide (TiO_2), or silicon nitride (SiN).

29. The system of claim 22, wherein the waveguide structure includes a high-index material which includes at least one of: silicon nitride (SiN), silicon carbide (SiC), titanium oxide (TiO_2), aluminum oxide (Al_2O_3), silicon, and diamond.

30. The system of claim 22, wherein the disposable chip unit is capable of detaching from the fixed unit after used for detecting the fluidic sample, and wherein the fixed unit is reconfigured to receive a new disposable chip after the used disposable chip has been removed.

31. The system of claim 22, wherein the analyte is glucose.

32. The system of claim 22, wherein the fluidic sample includes a sample of tears, saliva, urine, or blood.

33. A biosensor system for optically detecting a fluidic sample, comprising:

a sensing unit formed on a substrate to receive a probe light and structured to include a containment region capable of receiving and containing the fluidic sample including a substance, the sensing unit including:

a waveguide structure configured to confine and guide the probe light to cause Raman scattering interaction between the confined probe light and the fluidic sample through either evanescent coupling or direct contact and to collect Raman scattered light generated from the fluidic sample,

wherein the waveguide structure is optically coupled to an interface to guide the collected Raman scattered light from the fluidic sample to the interface; and

a base unit formed on the substrate and coupled to the sensing unit, the base unit including:

a waveguide optically coupled to a coherent light source to carry an emitted probe light from the coherent light source to the interface with the sensing unit and to receive the collected Raman scattered light travelling in the opposite direction to the emitted probe light from the sensing unit at the interface;

an optical filter coupled to the waveguide and tunable to select and filter out the received Raman scattered light; and

an optical detector coupled to the optical filter to generate a Raman spectrum of the substance based on the outputs of the optical filter.

34. The system of claim 33, wherein the waveguide structure includes a slot waveguide configured to enhance the Raman scattering interaction by focusing the probe light strongly inside and in close proximity of the slot region of the slot waveguide.

35. The system of claim 34, wherein the waveguide structure further includes a ring resonator optically coupled to the slot waveguide to enhance the Raman scattering interaction by enabling a long interaction length between the probe light and the analyte while maintaining the compact size of the sensing unit.

36. The system of claim 35, wherein the ring resonator is a slotted ring resonator configured to further enhance the Raman scattering interaction by focusing the probe light strongly inside and in close proximity of the slot region of the slotted ring resonator.

37. The system of claim 33, wherein the base unit further includes one or both of CMOS electronics and a display.

38. The system of claim 33, wherein the optical filter includes a ring resonator.

39. The system of claim 33, wherein the base unit further includes a tuning mechanism thermally coupled to the optical filter to tune the optical response of the optical filter to match a set of targeted Raman wavelengths.

40. The system of claim 39, wherein the tuning mechanism includes a micro-heater.

41. The system of claim 33, wherein the optical detector includes a photodiode.

42. The system of claim 33, wherein the substrate includes at least one of silicon, silicon oxide, silicon oxynitride (SiON), aluminum oxide (Al_2O_3), titanium dioxide (TiO_2), or silicon nitride (SiN).

43. The system of claim 33, wherein the waveguide structure includes a high-index material which includes at least one of: silicon nitride (SiN), silicon carbide (SiC), titanium oxide (TiO_2), aluminum oxide (Al_2O_3), silicon, and diamond.

44. The system of claim 33, wherein the base unit and the sensing unit further include an optical coupler to couple the evanescent field of light at the interface between the waveguide structure and the waveguide.

45. The system of claim 33, wherein the coherent light source is configured in the base unit.

46. The system of claim 33, wherein the sensing unit further includes a microfluidic channel structured to carry the fluidic sample to the containment region.

47. The system of claim 33, wherein the base unit is structured to include a recessed region, and the sensing unit is configured as a detachable unit capable of attaching to the base unit at the recessed region.

48. The system of claim 33, wherein the coherent light source is a laser external to the biosensor system and configured to emit the probe light at a wavelength capable of Raman scattering when incident on the fluidic sample including the substance.

49. The system of claim 33, wherein the coherent light source is a pump laser formed on the substrate and configured to emit the probe light at a wavelength capable of Raman scattering when incident on the fluidic sample including the substance.

50. The system of claim 33, wherein the coherent light source is a pump laser generating the probe light of a first wavelength.

51. The system of claim 50, further comprising one or more additional lasers, each of which is tuned to a specific Raman wavelength of interest to cause stimulated Raman emission from the substance at the specific Raman wavelength of interest.

52. The system of claim 50, wherein the biosensor system includes a coherent anti-Stokes Raman spectroscopy (CARS) that further comprises a second laser to generate a Stokes beam of a second wavelength and a third laser to generate a probe beam of a third wavelength,

53. A biosensor system for optically detecting a fluid, comprising:

a base unit including a substrate, and a waveguide for guiding light;

a sensing unit coupled to the base unit and structured to include a containment region capable of containing a fluid and including a slot waveguide optically coupled to the

waveguide of the base unit at an interface and to direct light from the waveguide into the containment region to interact with the fluid; and

a coherent light source optically coupled to the base unit and configured to emit a light beam at a wavelength capable of Raman scattering when incident on the fluid including a substance,

wherein the slot waveguide is configured to collect Raman scattered light generated in and around the slot waveguide;

wherein the waveguide is optically coupled to receive the emitted light beam from the coherent light source to carry the emitted light beam to an interface with the sensing unit and to receive a portion of the collected Raman scattered light which travels in the opposite direction to the emitted light beam from the interface; and

wherein the slot waveguide resonator is structured to increase an optical field of the emitted light beam interacting with the fluid to enhance the Raman scattered light.

54. The system of claim 53, wherein the biosensor system further comprises: an optical filter coupled to the waveguide to receive and filter the portion of the collected Raman scattered light; and an optical detector coupled to the optical filter to receive the filtered Raman scattered light and detect a Raman spectrum within the filtered Raman scattered light.

55. The system of claim 53, wherein the coherent light source is a pump laser to generate a first wavelength.

56. The system of claim 55, further comprising one or more additional lasers, each of which is tuned to a specific Raman wavelength of interest to cause stimulated Raman emission from the substance at the specific Raman wavelength of interest.

57. The system of claim 55, wherein the biosensor system includes a coherent anti-Stokes Raman spectroscopy (CARS) that further comprises a second laser to generate a Stokes beam of a second wavelength and a third laser to generate a probe beam of a third wavelength, wherein the pump laser.

58. The system of claim 53, wherein the slot waveguide includes a straight slot waveguide and a slotted ring resonator coupled to the straight slot waveguide.

59. The system of claim 53, wherein the base unit and the sensing unit further include an optical coupler to couple the evanescent field of light at the interface between the waveguide and the slot waveguide resonator.

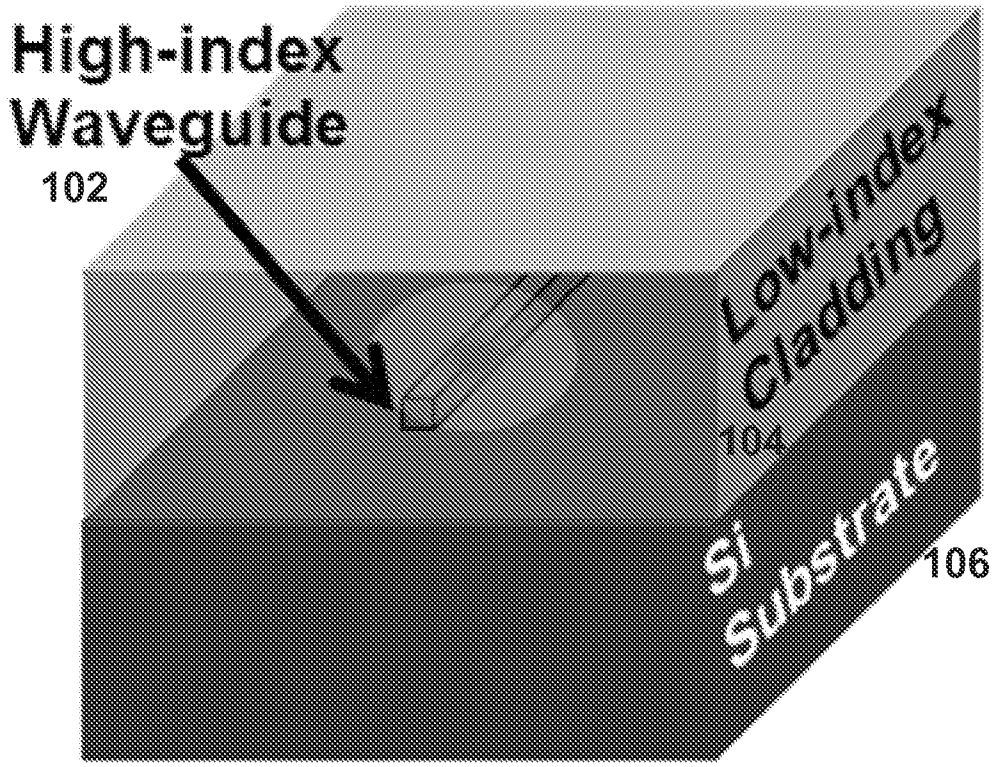
High-index
Waveguide
102
Low-index
Cladding
104
Si
Substrate
106

FIG. 1

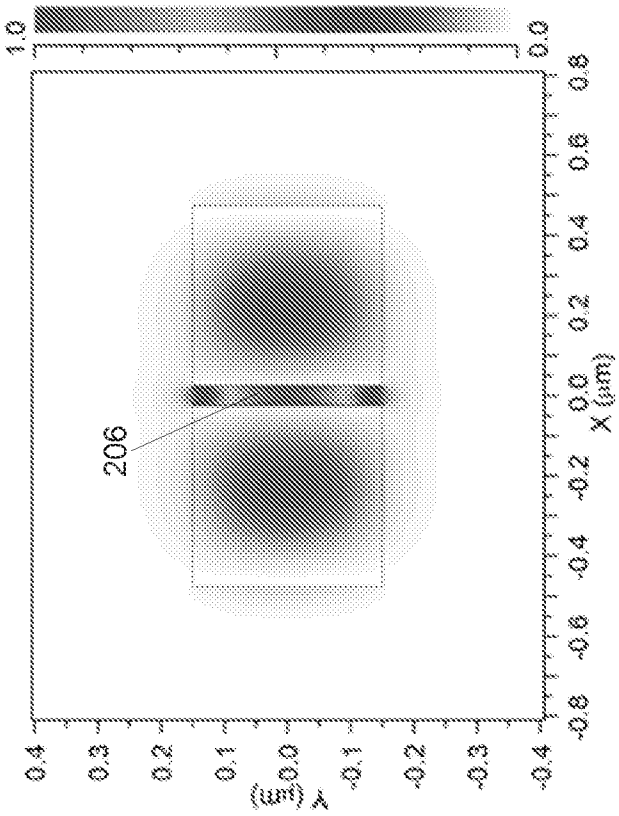

FIG. 2B

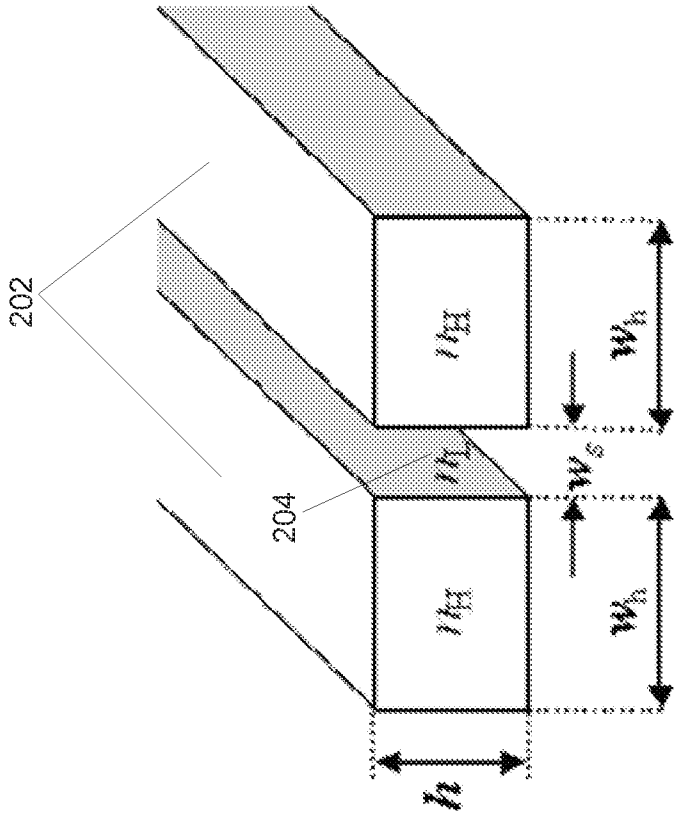

FIG. 2A

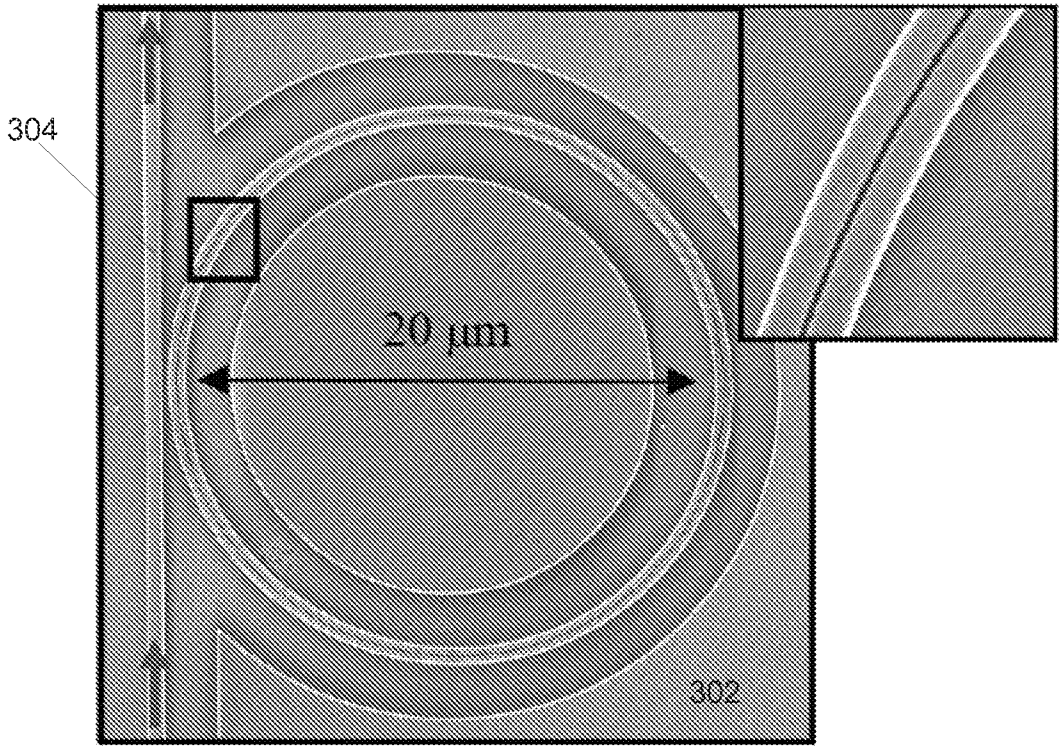

FIG. 3A

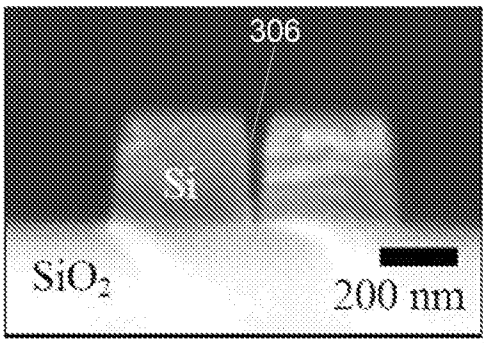

FIG. 3B

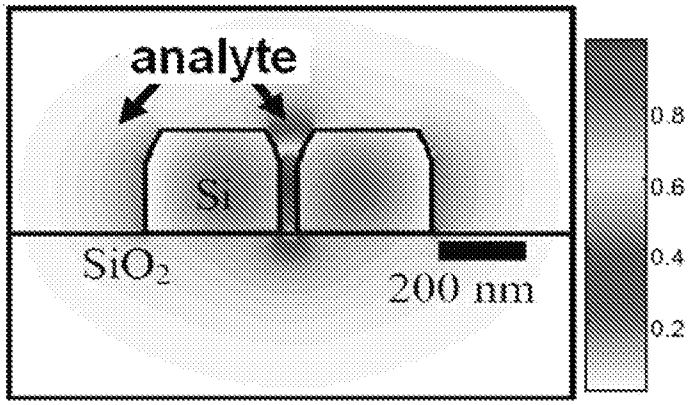

FIG. 3C

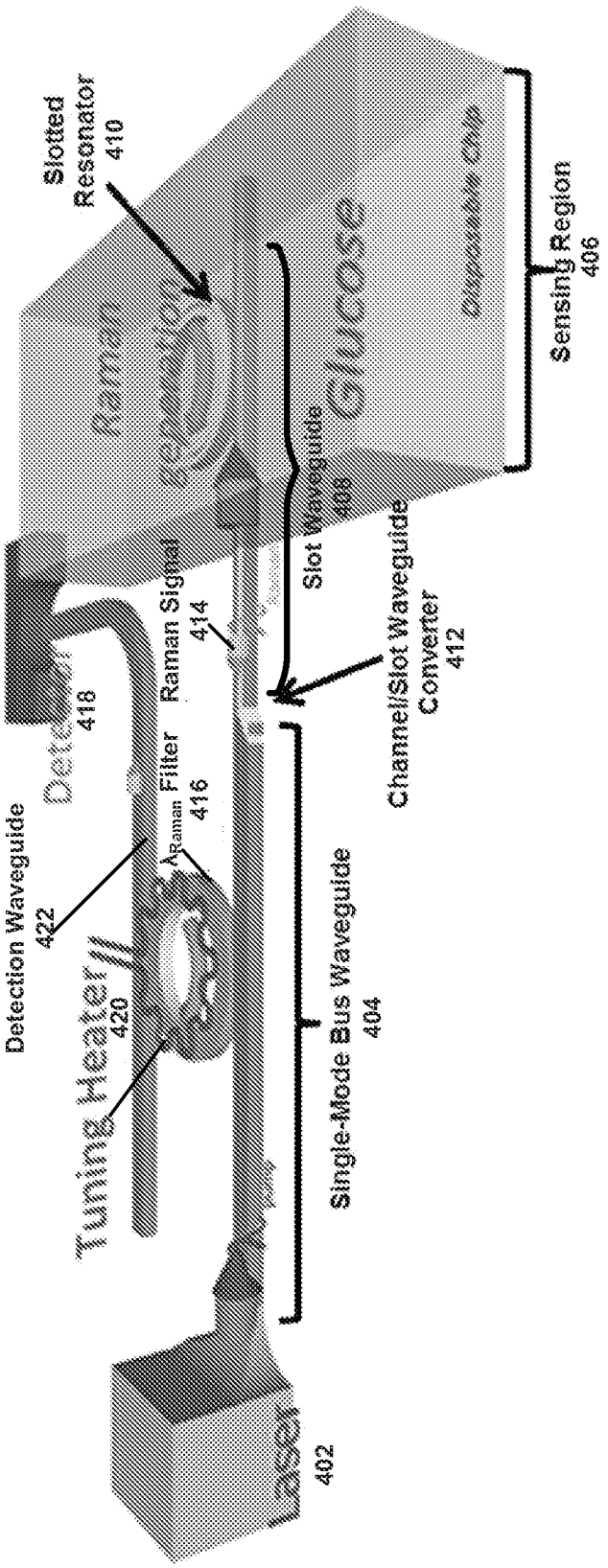
Slotted Resonator 410
Sensing Region 406
Slot Waveguide 408
Channel/Slot Waveguide Converter 412
Raman Signal 414
Raman Filter 416
Detector 418
Tuning Heater 420
Detection Waveguide 422
Single-Mode Bus Waveguide 404
Laser 402

FIG. 4

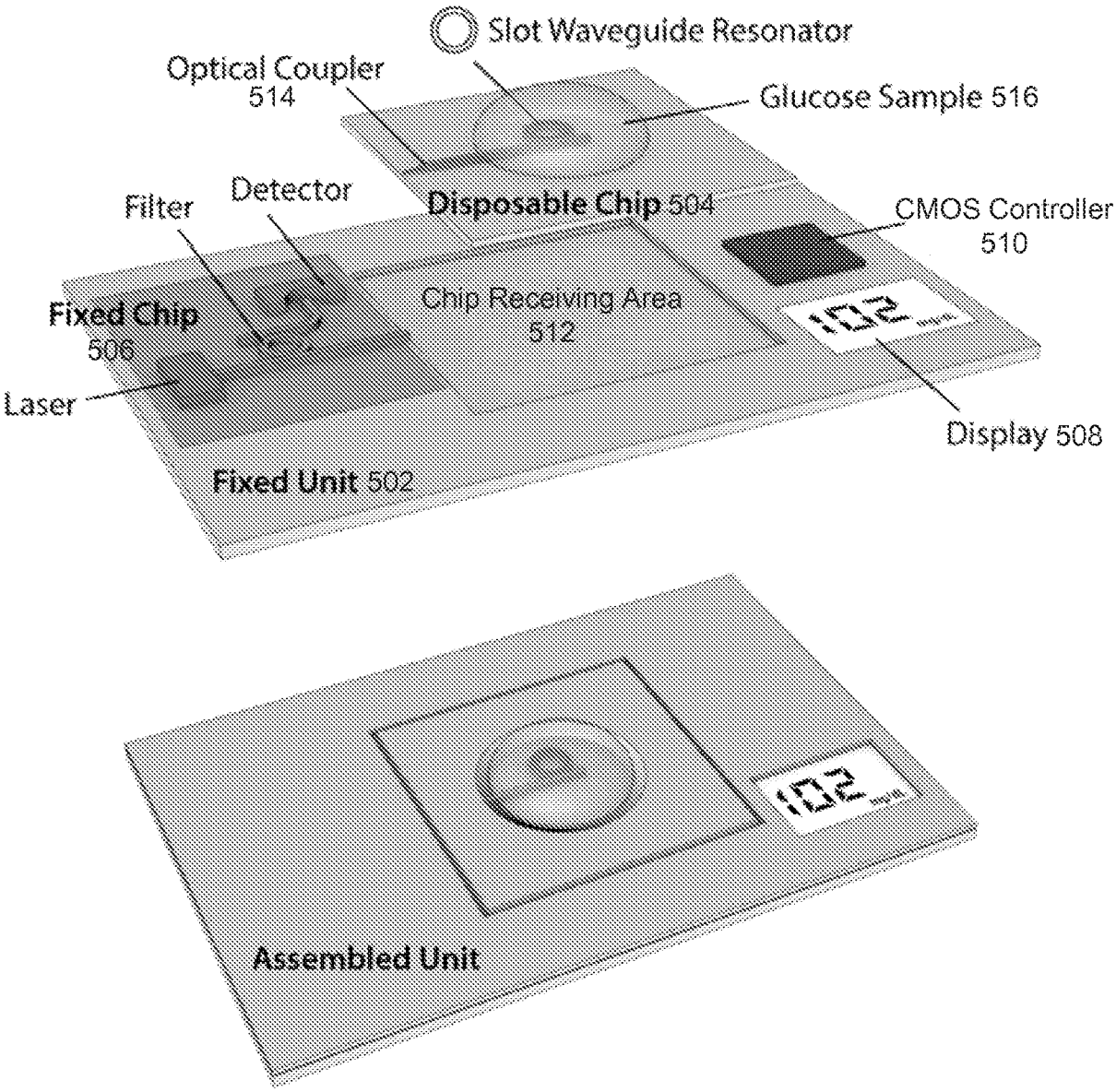
Slot Waveguide Resonator
Optical Coupler
514
Glucose Sample 516
Filter
Detector
Disposable Chip 504
CMOS Controller
510
Fixed Chip
506
Chip Receiving Area
512
Laser
Display 508
Fixed Unit 502
Assembled Unit

FIG. 5

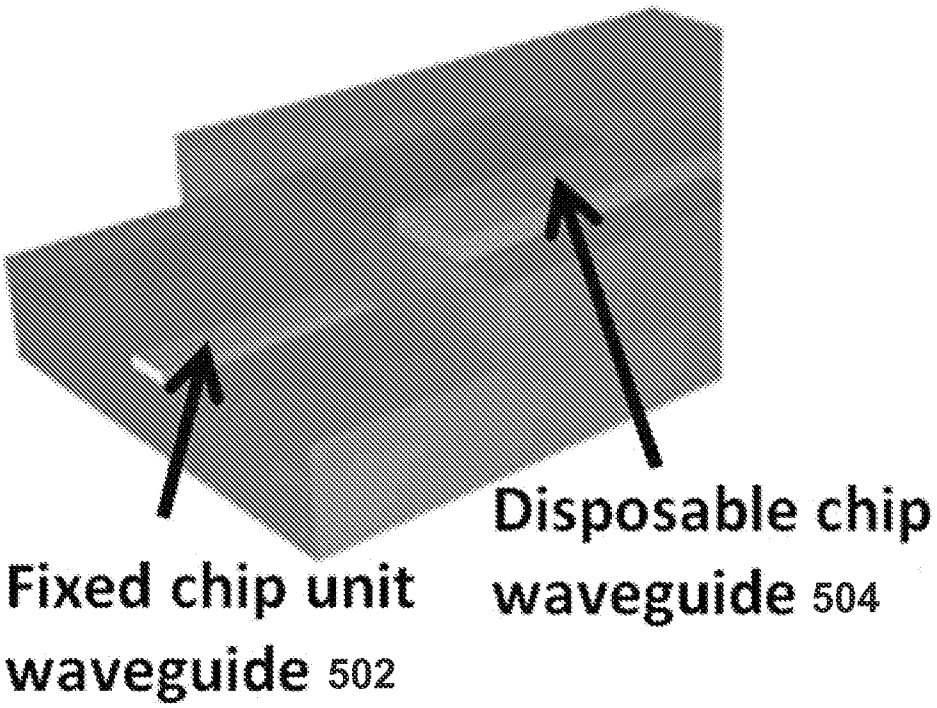
Disposable chip waveguide 504
Fixed chip unit waveguide 502

FIG. 6A

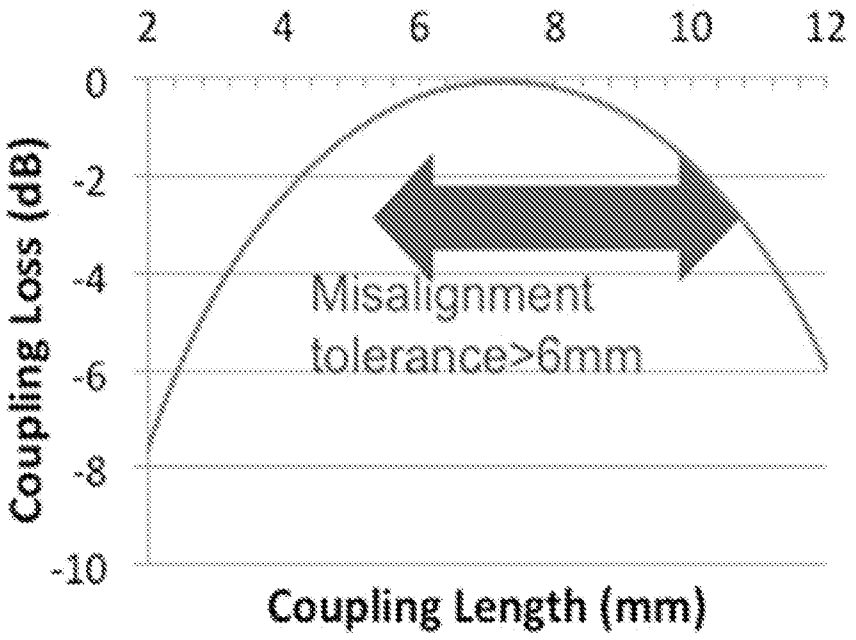
2
4
6
8
10
12
0
-2
-4
-6
-8
-10
Coupling Loss (dB)
Misalignment tolerance>6mm
Coupling Length (mm)

FIG. 6B

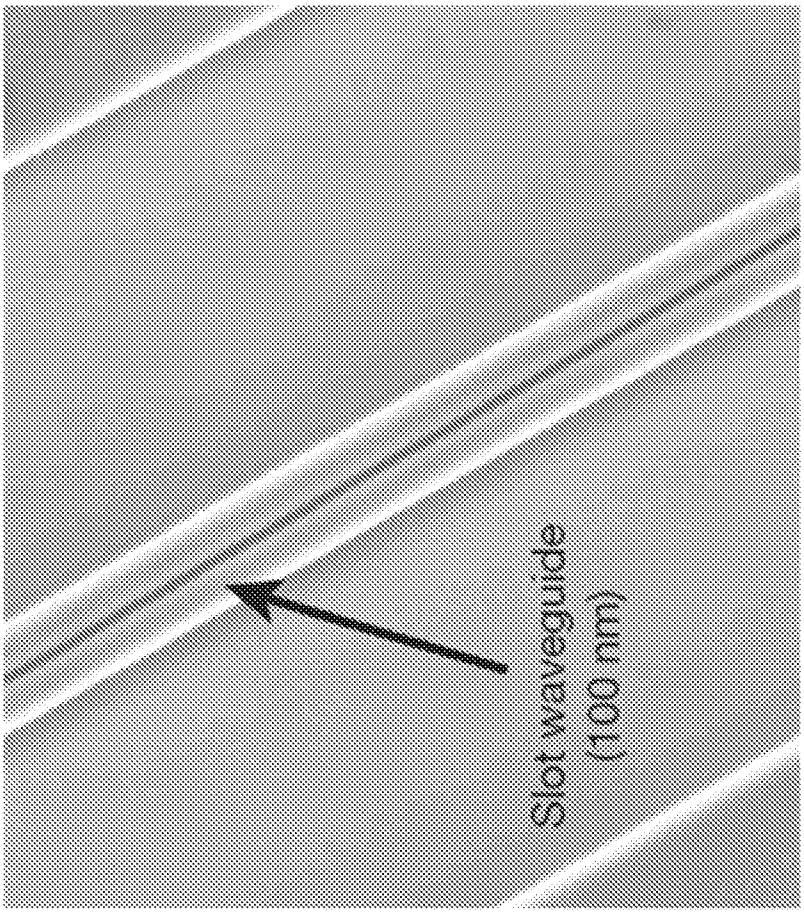
Slot waveguide
(100 nm)

FIG. 7B

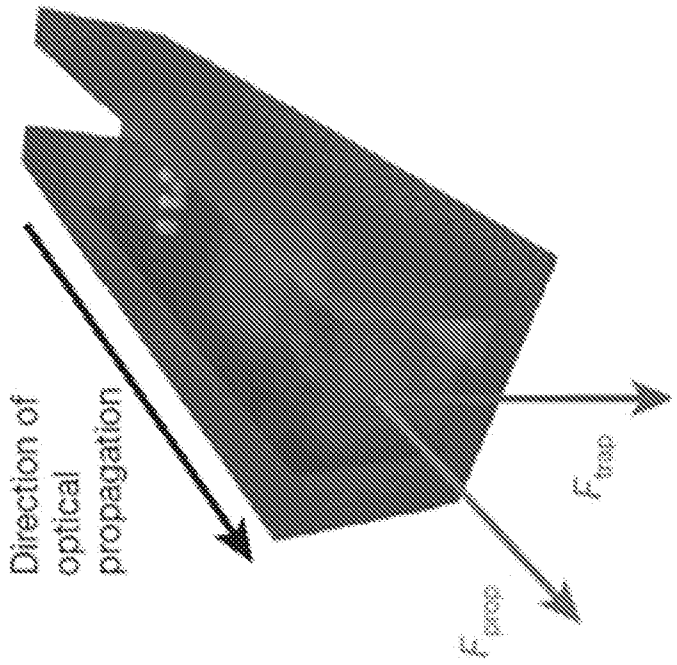
Direction of
optical
propagation
F_{drop}
F_{drop}

FIG. 7A

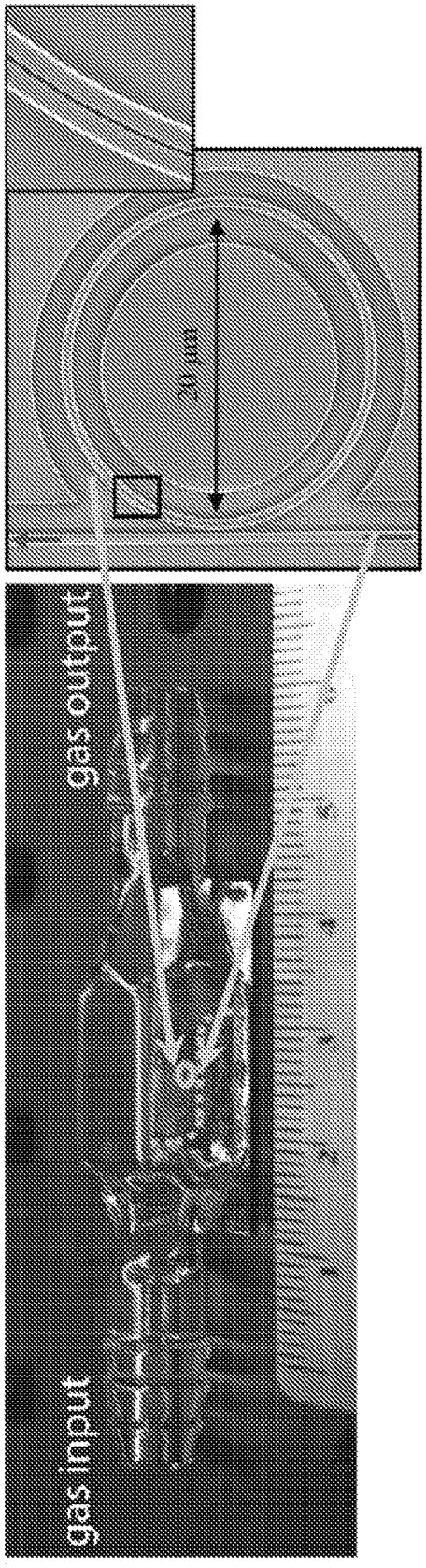

FIG. 8