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TRENDS

Optical ring resonators for biochemical and chemical sensing

Yuze Sun · Xudong Fan

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Abstract In the past few years optical ring resonators have emerged as a new sensing technology for highly sensitive detection of analytes in liquid or gas. This article introduces the ring resonator sensing principle, describes various ring resonator sensor designs, reviews the current state of the field, and presents an outlook of possible applications and related research and development directions.

Keywords Optical ring resonators · Biological sensors · Chemical sensors · Vapor sensors

Introduction

Starting from initial idealization and subsequent groundbreaking work [1–3], the optical ring resonator has quickly emerged in the past few years as a new sensing technology. Over 300 papers related to ring resonator bio/chemical sensing have been published in the last decade, most in the last five years. Intensive research in this field is motivated by broad applications of ring resonator sensors in healthcare, environmental monitoring, homeland security, the food industry, and pharmaceuticals, which require sensitive and rapid analytical tools.

The optical ring resonator sensor relies on a light–analyte interaction to convert the presence of chemical or biological analytes into quantitatively measurable optical signals. As illustrated in Fig. 1, an optical ring resonator can be regarded as a ring-shaped waveguide. Because of total internal reflection of light at the curved boundary, a resonant optical mode forms. The resonant wavelength, λ, is given by:

$$\lambda = 2\pi r n_{eff}/m \quad (1)$$

where r is the resonator radius, n_{eff} is the effective refractive index (RI) experienced by the optical resonant mode, and m is an integer number. The resonant light circulates along the ring resonator and has an evanescent field that reaches several hundred nanometers into the surrounding medium (e.g., liquid, gas, and polymer coatings) and interacts repeatedly with the analytes near the resonator surface.

As new sensing technology, the ring resonator has a number of distinctive advantages. In contrast to the traditional linear waveguide- or fiber-based sensor in which the light–analyte interaction length is essentially the physical length of the sensor, the circulating nature of the resonant mode creates an extremely long effective interaction length, which is determined by

$$L_{eff} = Q\lambda/(2\pi n),$$

where Q is the resonator quality factor (Q-factor), representing the number of round trips that circulating resonant light can make along the ring resonator. Depending on ring resonator configuration, as described later, the Q-factor usually ranges from 10^4 to 10^8. Therefore, despite a small physical size, the ring resonator has an effective interaction length of a few tens of centimeters or even longer, which renders the ring resonator better sensing performance, smaller footprint, and higher multiplexing capability while using less analyte. Another benefit of the ring resonator is significantly enhanced light intensity near its surface with the enhancement being proportional to the Q-factor, which is due once again to the circulating nature of the resonant light. This phenomenon can also be exploited for sensing applications.

To date, various optical properties have been used in ring resonator sensors to generate the sensing signal, including

Y. Sun · X. Fan (✉)
Biomedical Engineering Department, University of Michigan,
2158 Lurie Biomedical Engineering Building, 1101 Beal Ave,
Ann Arbor, MI 48109, USA
e-mail: xsfan@umich.edu

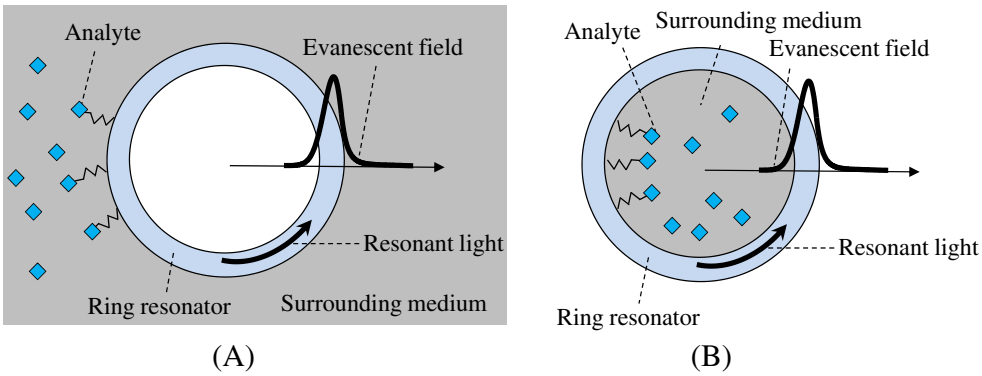

Fig. 1 Conceptual illustrations of an optical ring resonator sensor. The resonant light circulates along the resonator and its evanescent field is present in the surrounding medium outside (**a**) or inside (**b**) the ring resonator, interacting with the analyte on the ring resonator exterior surface (**a**) or interior surface (**b**) and in the surrounding medium

RI, fluorescence, Raman, and optical absorption. RI detection is also called label-free detection, because it does not involve any sample labeling or optical excitation of a sample. It is one of the most popular detection methods used in many miniaturized sensors. Given the limited space of this article, we will focus mainly on the RI detection-based ring resonator sensors.

Generally, there are two types of sensing that a ring resonator can perform, depending on where the sensing signal originates. Surface sensing signals come from analytes in close proximity to the ring resonator surface (much closer than the evanescent field decay length) whereas bulk sensing signals result from the optical change induced by the presence of the analytes in the whole region of the evanescent field [1]. Currently, an overwhelming portion of ring resonator sensor research is focused on surface sensing, although bulk sensing has its unique applications [4].

After nearly 10 years of investigation, a variety of chemical and biological species have been detected by use of ring resonators, including DNA, proteins, viruses, nanoparticles, bacteria, heavy metals, pesticides, and volatile organic compounds (VOCs) in liquid or gaseous phases [2–21]. Different types of ring resonators have been designed to achieve such detection. In the remainder of this article, we will briefly describe ring resonator structures and the corresponding sensing performance, followed by the outlook for future research and development in optical ring resonator sensing. For more technical details, readers are referred to review articles published in the last two years [22–28] and to publications on ring resonator design guidance and performance analysis [29–34]

Ring resonator configurations

Optical ring resonator sensors have been implemented in a number of configurations, as illustrated in Fig. 2.

1. *Microspheres made of liquid* [21, 35], *fused silica* [2], *and polymers* [36, 37]. They are inexpensive and easy to fabricate. Despite being a good platform for the purpose of rapid proof-of-concept and basic research, it is challenging to mass produce and integrate microspheres into an array format for most practical applications. Additionally, the polymer based ring resonator also suffers from relatively low Q-factor, which may limit its sensing performance.
2. *Ring, disk, or toroid-shaped resonators fabricated with dielectric materials (for example silicon-on-insulator and polymers) on a silicon wafer* [3, 6, 14, 15, 18, 38–46]. They can be mass-produced using micro/nanofabrication technology and scaled up to an array format for multiplexed detection.
3. *Capillary-based ring resonators* [9, 19, 31, 47–49]. These are naturally integrated with capillary based microfluidics for convenient sample delivery. In particular, recent demonstration of capillary electrophoresis and micro-gas chromatography using capillary based ring resonators attests to the powerful combination of analyte separation capability of the capillary and the sensing capability of the ring resonator [4, 19]. This type of ring resonator can be fabricated using a fiber-drawing method [47, 48] or by a self-assembly method [49]. When pressurized and heated, hollow bubbles can also form along the capillary [50].
4. *Micro/nano fiber coil based ring resonators* [51]. These take advantage of convenience in optical fiber coupling. However, they are delicate and difficult to handle. Mass production and integration of micro/nanofiber ring resonators into a device have yet to be demonstrated.

Current state of the ring resonator sensors

RI-based sensing

Most ring resonator sensors use RI change as the sensing signal. RI detection can be applied in both bulk detection

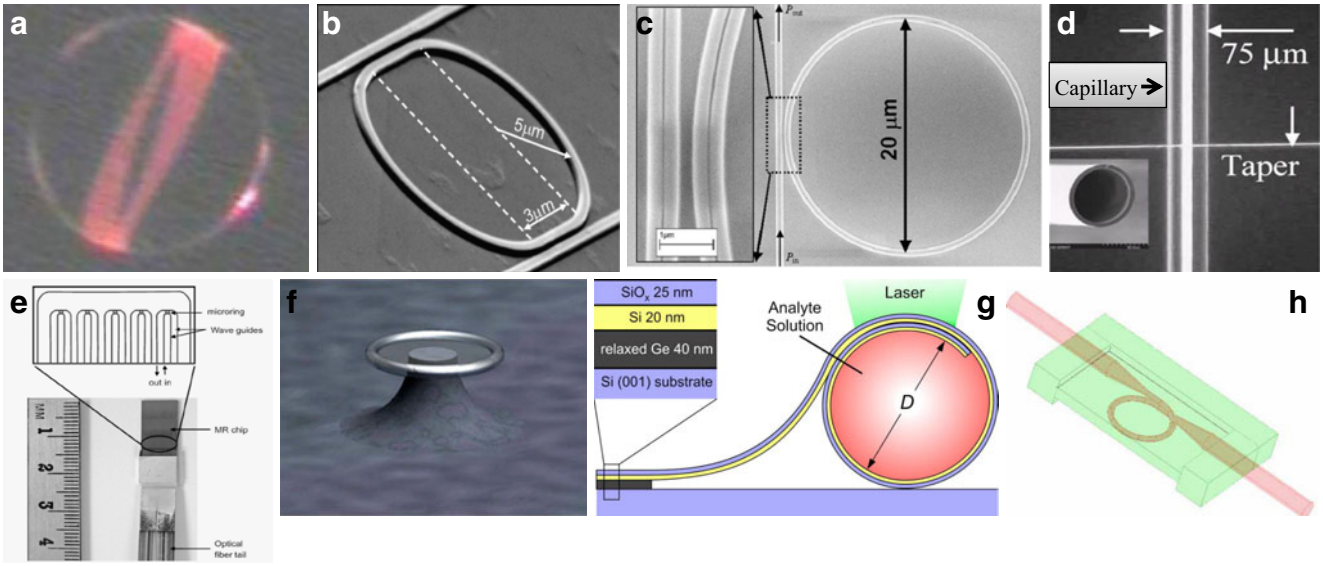

Fig. 2 Various ring resonator sensor configurations. (**a**) Microsphere. (**b**) Silicon-on-insulator planar ring resonator. (**c**) Slot waveguide ring resonator. (**d**) Capillary-based ring resonator fabricated by the drawing method. (**e**) Planar ring resonator array. (**f**) Microtoroid. (**g**) Capillary-based ring resonator fabricated by the rolled-up method. (**h**) Microfiber coil-based ring resonator. Reprinted with permissions from Refs. [38, 41, 42, 44, 49, 51]

and surface detection when analytes are in the liquid or gaseous phase. The sensing principle is described by Eq. 1. When analytes are present in the evanescent field of the resonant mode, the RI experienced by the resonant mode changes, as analytes usually have RI different from that of the surrounding medium. This RI change leads to a spectral shift in the resonant mode, which can be detected directly or indirectly (through intensity or phase detection) (Fig. 3).

Bulk RI detection for analytes in liquid

Bulk RI change is induced by the presence of analyte (chemicals, DNA, protein, etc.) in the bulk liquid. It is proportional to the analyte concentration. Detection of chemicals, for example ethanol, sodium chloride, and ethylene glycol, has been demonstrated. Bulk RI detection usually lacks detection specificity. Therefore, in most cases it is used merely to characterize the sensing performance of the ring resonator. However, one bulk RI detection application worth mentioning is measurement or monitoring of chemical movement/separation by capillary electrophoresis (CE) [4], which adds specificity to the detection. Nevertheless, such detection after separation of biological analytes (for example protein or DNA) remains largely unexplored. To date, 2.8×10^{-7} RIU (refractive index units) in bulk RI change has been achieved experimentally, with a noise-equivalent detection limit (NEDL) of 3.8×10^{-8} RIU [52], corresponding to a protein concentration of the order of 0.1–1 $\mu g mL^{-1}$.

Surface RI detection for analytes in liquid

Surface RI detection is also referred to as label-free immunoassay detection. To implement such detection, capture molecules (or recognition molecules), for example antibodies, DNA oligomers, and peptides, are immobilized on the ring resonator surface to provide detection specificity. The sensing signal (e.g., the spectral shift) is generated on specific binding of analytes to capture molecules, which changes the RI near the surface. A few theoretical models have been established to correlate the sensing signal to the molecular surface density [8, 10, 29, 31]. Recently, detection of 1.6 $pg mm^{-2}$ in surface mass density was achieved, with the NEDL approximately 0.14 $pg mm^{-2}$ [52]. Small molecule detection using biotin (molecular weight 244 Dalton) down to 10 $nmol L^{-1}$ was also demonstrated [52].

Detection of DNA in buffer solution was first reported by Vollmer et al., and shows the discrimination of single-base-mismatched DNA [5]. Later, detailed analysis of DNA on the ring resonator surface was achieved, and experiments were carried out to detect 25-mer DNA strands below 10 $pmol L^{-1}$ [53]. Gradually, DNA detection is shifted towards more clinically related applications. For example, the ring resonator has been used in DNA methylation analysis to detect methylated DNA down to the $nmol L^{-1}$ range and to differentiate DNA strands with different numbers of methylcytosines [20]. Using single-stranded DNA capture probes, 150 fmol miRNA was detected in 10 min with the capability of discriminating between single nucleotide polymorphisms [16].

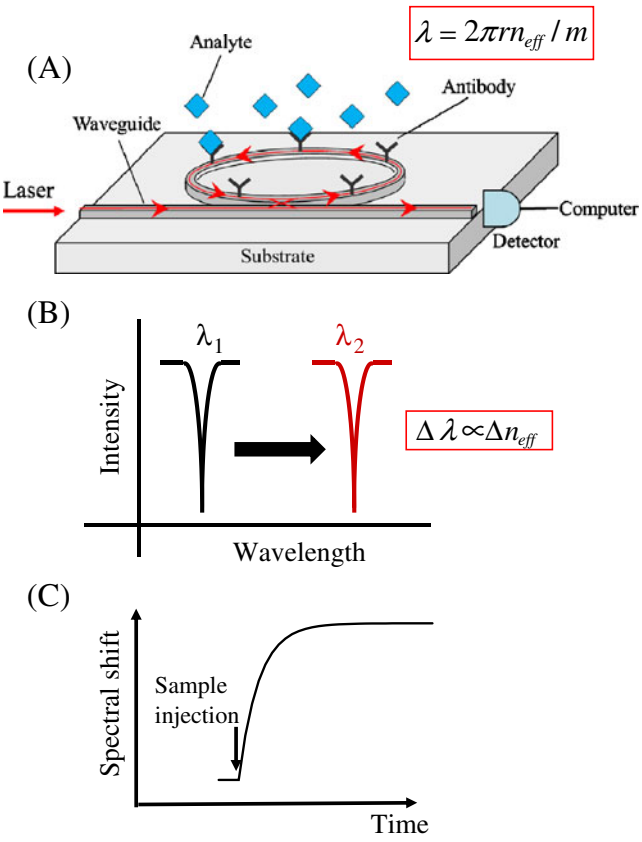

Fig. 3 (**a**) Illustration of a ring resonator biosensor that detects the binding of analyte to the surface. A tunable laser is coupled to the ring resonator. When the laser is in resonance with the resonant mode in the resonator, a spectral dip is shown at the detector to indicate the spectral position. (**b**) The resonant mode shifts in response to the local RI change induced by the molecular binding. (**c**) A sensorgram can be obtained by monitoring the spectral shift in real time

Detection of protein was initially conducted in buffer solution also [2]. A detection limit of 60 fmolL^{-1} was demonstrated [14]. Currently, protein detection is focused on clinically relevant analytes in more realistic media (for example serum and cell culture media) [12, 13, 15, 17, 54]. For example, the cancer biomarkers CA15-3, HER2/ECD, and CEA, within their respective clinically significant range (approximately 1–200 ngmL^{-1}) have been successfully detected in serum [12, 13, 54]. Multi-analyte detection has also been carried out using a ring resonator array [17]. It should be emphasized that for label-free detection of analytes in complex media, non-specific binding significantly reduces sensor performance. To minimize non-specific binding, the ring resonator surface is usually blocked with blocking reagents after immobilization of the capture molecules. After the sample is introduced, a rinse step is also necessary to wash away the non-target molecules weakly attached to the sensor surface, thus further reducing non-specific binding. Currently, a well-blocked non-fouling ring resonator surface has non-specific binding of approximately 1 pgmm^{-2} [12], which sets the practical limit for detectable analyte concentrations without pre-concentration or amplification procedures.

Detection of viral particles and cells is different from DNA or protein detection, as their size is comparable with, or even much larger than, the decay length of the evanescent field [10]. Using a capillary-based ring resonator, detection of viral particles (M13) down to approximately 1000 pfu mL^{-1} with a dynamic range spanning seven orders of magnitude has been achieved [9]. The detection time was within 10 min, owing to the excellent fluidics that facilitate analyte capture. Single-particle detection of much smaller influenza A (~1 fg in mass) was also demonstrated [10]. Recently, the ring resonator was shown to be able to attract nano-sized particles to its surface and to trap them [55]; this may provide a means to enhance virus particle capture efficiency and detection sensitivity.

Cell detection seems more challenging, because only part of a cell lies in the detection range defined by the evanescent field and the sensing signal has larger fluctuations because of random arrival of cells [8, 56]. The detection limit is usually on the order of 10^4–10^5 cfumL^{-1} [42, 56]. Although this result is comparable with that obtained with other types of label-free optical sensors, it may still be a few orders of magnitude less sensitive for some applications (for example in the food industry for bacterium detection and in healthcare for circulating tumor cell detection). One alternative may be to detect the cell lysate rather than the whole cell, as demonstrated in recent work [56].

The results presented above show the great sensing capability of ring resonator technology and make it highly competitive in comparison with other label-free optical sensing techniques. Certainly the ultimate test for the ring resonator would be the detection of a single molecule attached to the ring resonator surface. Such detection was first reported in 2007 using the thermo-optic effect [57]. However, more recent work shows that the thermo-optic effect contributes far less to the sensing signal [58]. Therefore, follow-up work needs to be carried out to elucidate the actual sensing mechanism and applications of such single molecule detection need to be further explored.

Surface RI detection for analytes in gas

An important application in this category is chemical vapor sensing, a relatively new area for ring resonators. RI-based vapor sensing relies on a thin polymer or inorganic coating on the resonator surface as the transduction layer to capture and concentrate molecules [6, 33, 44, 59, 60] (Fig. 4a and b). The interaction between the transduction layer and the analyte leads to a change in the thickness and the RI of the transduction layer, and hence a change in the spectral

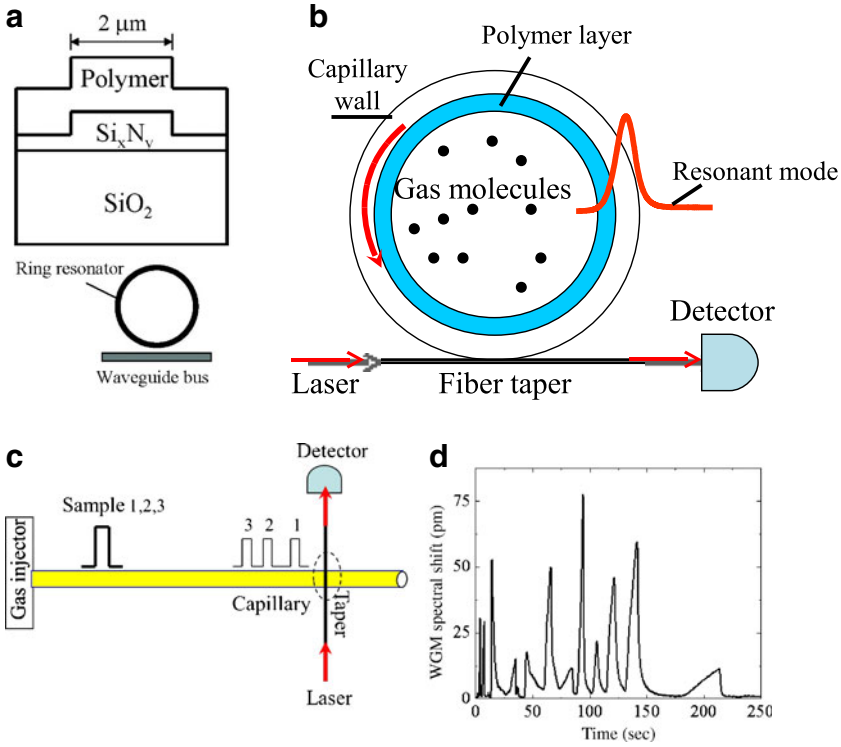

Fig. 4 (**a**) Planar ring resonator for vapor sensing. Its surface is coated with a layer of vapor-sensitive material, for example polymer. *Upper figure*: cross-sectional view. *Lower figure*: top view. (**b**) Capillary-based ring resonator for vapor sensing. Its inner surface is coated with a layer of polymer for vapor separation and detection. (**c**) Schematic diagram of capillary ring resonator-based vapor separation and detection. (**d**) Sensing signal is generated when each analyte arrives at the detection position defined in (**c**)

position of the resonant mode. Various VOCs ranging from alkanes and alcohols to explosives and chemical-weapon precursor simulants have been detected, with ppm or ppb detection limits [6, 44, 60–62]. Theoretical models have also been established to correlate the sensing signal with analyte concentration and to guide sensor design [33]. However, in contrast with biodetection in which biorecognition molecules are used to capture analytes, the vapor capture layers are highly non-specific for vapor molecules. Combination of the ring resonator vapor sensor with gas chromatography (GC), which separates different vapor molecules, significantly enhances the detection specificity, as demonstrated recently [19, 59, 60] (Fig. 4c). For example, over 10 analytes were separated and detected within 4 min with a detection limit on the order of 100 pg [19] (Fig. 4d). Another important application is the detection and sizing of particles in air or aerosols. Using microtoroids with ultrahigh Q-factors (~10^8), Zhu et al. recently successfully detected a single nanoparticle deposited on the ring resonator surface [18]. Nanoparticles can also be detected using the backward scattering resulting from the interaction between the particle and the ring resonator [63].

Non-RI based detection

Non-RI-based detection means the sensing signal comes from another optical property, for example fluorescence, Raman, or optical absorption, which takes advantages of enhanced light–matter interaction distance and enhanced electric field near the resonator surface for increased sensitivity. In fluorescence measurement, the analyte can be a natural chromophore (i.e., auto-fluorescent) or must be labeled with fluorophores such as dyes. The fluorescence signal enhancement is proportional to the resonator Q-factor [64, 65]. Because of the high Q-factor, two-photon excitation is also possible to excite biochemical samples whose absorption band is usually in the UV region. Recently, the optofluidic ring resonator laser has also been demonstrated; this enables sensitive intra-cavity fluorescence detection of biomolecules [66].

Absorption measurement has been carried out for detection of analytes in either liquid or gas phase [41, 67, 68]. This can be done by tuning the resonant wavelength across the absorption band of the analyte for enhanced absorption path length. Alternatively, when the ring resonator has extremely high Q-factors, the degradation of the resonant mode Q-factor can be measured, which is caused by the extra loss induced by optical absorption [41].

The ring resonator can also be combined with surface enhanced Raman spectroscopy (SERS) for tremendously increased SERS signal. Experimentally, a gain over two orders of magnitude has been demonstrated, which enables detection of 400 pmolL^{-1} R6G in a micro-sized liquid channel [69]. Recent theoretical analysis shows that 10^4-fold enhancement can be achieved [70]. Additionally, by use of a high-Q droplet based ring resonator, stimulated Raman emission can be obtained for identification of species in liquid [21].

Outlook

As discussed previously, the ring resonator is very promising and highly competitive sensing technology. On the device development front, it has now moved from the early stage of proof-of-concept demonstrations and theoretical model establishment to further device and system development, and actual applications. Research efforts are increasingly focused on detecting samples from more realistic and complex media. One such area is the development of portable and rapid diagnostic devices for point-of-care applications. The objective is to rely on sensitive label-free ring resonator sensing technology to replace currently adopted fluorescence based detection, for example enzyme-linked immunosorbent assay (ELISA), which involves fluorophore labeling, relatively large sample quantity, and expensive and time-consuming procedures, and can only be carried out at centralized laboratories with dedicated personnel. Towards this end, there are a few requirements that the ring resonator sensor should meet (certainly these requirements are also applicable to applications other than healthcare):

1. *Implementation of array-format detection.* Mass-produced ring resonator arrays will enable multiplexed detection, which is used in ELISA detection. Although many ring resonator configurations discussed earlier have excellent sensing capability, presently only planar ring resonators fabricated on a substrate by microfabrication technology can be mass-produced and have potential capability of performing multiplexed detection.
2. *Further reduction in cost.* Most ring resonator systems currently employ an external tunable diode laser, which is relatively expensive. Miniaturized on-chip and inexpensive laser sources, in conjunction with new detection schemes other than direct monitoring of the spectral position shift, may greatly reduce the price and weight of the final product.
3. *Further improvement in the detection limit, in particular, in the presence of complex media.* Currently, the detection limit for biomarkers in blood samples is on the order of 1 $ngmL^{-1}$. Improvement of this detection limit will enable detection of many important biomarkers in the $pgmL^{-1}$ range. This may involve integration with upstream sample pre-treatment components (for example preconcentrator and filter, etc.) and downstream detection components, and the development of non-fouling (or ultralow fouling) sensing surfaces to minimize non-specific binding. Furthermore, amplification schemes such as using sandwich-type detection can also be employed.
4. *Further reduction in sample volume (which enables use of finger-pricked blood samples and lowers reagent consumption).* This may require efficient integration with microfluidics and sample-delivery components.

Another important and promising area is vapor detection. One direction is to combine ring resonators with vapor separation technology, for example GC and molecular sieves. However, the ring resonator–GC system may require a number of other components that make the system more complex. An inexpensive and simple alternative is to employ pattern recognition technology that uses an array of ring resonators coated with a variety of polymers, in particular, molecularly imprinted polymers.

A few other research areas are also under investigation.

1. Detection of single molecules and single viral particles will not only demonstrate the ultimate sensing capability of the ring resonator, but also enable the studies that reveal the details of biological processes by eliminating ensemble averaging effects. During the press of this article, detection of a single particle of 36 nm in radius was demonstrated with the noise equivalent detection limit of 17 nm in radius [71]. Using a specially designed capillary based ring resonator, detection of a particle of about 10 nm in radius is possible [72]. This represents the convergence of single molecule (< 10 nm in radius) sensing and single particle sensing.
2. Manipulation of molecules or nano-sized particles via strong optical force generated by the optical mode in a ring resonator may create a new means to capture, transport, separate, arrange, or even assemble molecules/particles [55, 73].
3. Optofluidic ring resonator lasers will have tremendous potential to be developed into a miniaturized, spectrally tunable, coherent light source for high-resolution laser spectroscopy and metrology in bio/chemical detection. They will also enable highly sensitive intra-cavity molecular detection [66].
4. Combining the ring resonator with other detection technology, for example Raman spectroscopy and SERS, may enable sample analysis that would otherwise be difficult to accomplish [21, 69, 70].

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