

High-Q WGM microcavity-based optofluidic sensor technologies for biological analysis

Cite as: *Biomicrofluidics* 18, 041502 (2024); doi: [10.1063/5.0200166](https://doi.org/10.1063/5.0200166)

Submitted: 25 January 2024 · Accepted: 12 August 2024 ·

Published Online: 27 August 2024



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ABSTRACT

High-quality-factor (Q) optical microcavities have attracted extensive interest due to their unique ability to confine light for resonant circulation at the micrometer scale. Particular attention has been paid to optical whispering-gallery mode (WGM) microcavities to harness their strong light-matter interactions for biological applications. Remarkably, the combination of high- Q optical WGM microcavities with microfluidic technologies can achieve a synergistic effect in the development of high-sensitivity optofluidic sensors for many emerging biological analysis applications, such as the detection of proteins, nucleic acids, viruses, and exosomes. They can also be utilized to investigate the behavior of living cells in human organisms, which may provide new technical solutions for studies in cell biology and biophysics. In this paper, we briefly review recent progress in high- Q microcavity-based optofluidic sensor technologies and their applications in biological analysis.

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I. INTRODUCTION

Optical microcavities are a type of photonic device that can tightly confine light for resonant circulation in micrometer-scale volumes.¹ Recently, they have gradually become an innovative platform for studying many intriguing optical processes, such as cavity quantum electrodynamics (QED),² optical chaos,³ nonlinear optics,⁴ and optical frequency comb generation.⁵ Due to their ability to significantly enhance the interaction between light and matter, high-quality-factor (Q) optical microcavities have attracted significant attention for high-sensitivity sensing applications. Numerous designs of optical whispering-gallery mode (WGM) microcavities, known for their high- Q factors and small mode volumes, have been proposed for various biological applications. Optical WGM microcavities typically feature a well-engineered boundary where light is efficiently confined by total internal reflection, generating evanescent waves that exist beyond the boundary and decay exponentially in the radial direction. Consequently, optical WGM microcavities are highly sensitive to external perturbations and are exceptionally suited for ultrasensitive biosensing through evanescent waves.^{6–10} With their small size and high sensitivity, optical WGM microcavity biosensors are very promising for the development of miniaturized biological analytical tools, such as integrated portable devices for point-of-care diagnostics.

However, several challenges remain for optical WGM microcavity biosensors, including susceptibility to surface contamination and the need for surface functionalization. These shortcomings might be addressed by combining optical WGM microcavity sensors with another promising technology in biochemical analysis: microfluidic chip technology. This integration can pretreat liquid samples and deliver liquids for both functionalization and detection in a fully automated manner. Additionally, it offers the advantages of miniaturization, portability, reduced sample and reagent consumption, rapid analysis, high throughput, and the ability to integrate multiple functions. Therefore, the integration of optical microcavity sensors with microfluidic technology presents a significant opportunity for developing innovative optofluidic devices that benefit from the combined advantages of high- Q microcavities and microfluidic technologies for various biological applications, such as the detections of protein,^{11–15} virus,^{16,17} and heavy metal ions.¹⁸

Recently, various optical-microcavity-based optofluidic sensor technologies have been developed and demonstrated for a range of biological applications, including the detection of proteins, nucleic acids, exosomes, and viruses. These technologies can acquire detailed information about the type, concentration, and even the mass of biomarkers from very small amounts of serum, potentially enabling the development of many innovative devices for biological detection.

In this paper, we will review various integrated microfluidic chip technologies based on high-Q optical microcavities, demonstrating the exciting prospects of this technology for biological analysis.

II. MICROCAVITY-BASED OPTOFLUIDIC SENSOR TECHNOLOGIES

A. Principles of optical WGM microcavities

Optical WGM microcavities are analogous to acoustic whispering galleries, where sound waves travel along curved surfaces through multiple reflections. In optical WGM microcavities, light is confined for resonant circulation at the outer edge by total internal reflection. These microcavities are typically spherical or cylindrical structures composed of low-optical-loss materials such as silica, silicon nitride, and lithium niobate.¹⁹ They are designed to confine and accumulate light waves of specific wavelengths or frequencies that satisfy the condition for constructive interference, thereby forming very high-Q resonant modes. These modes result in a long photon lifetime and strong light-matter interactions, enhancing their effectiveness in various applications.

Generally, WGMs can be classified using three mode indices, i.e., azimuthal order m , radial order s , and polar order l , as well as their polarizations, i.e., transverse electric (TE) or transverse magnetic (TM) polarized modes, in optical microcavities. When a tapered optical microfiber or waveguide is coupled with an optical WGM microcavity, a transmission spectrum can be obtained featuring a series of absorption peaks that correspond to WGMs at their resonant wavelengths. Typically, these spectral peaks of WGMs exhibit a Lorentzian line shape, which can be expressed as⁹

$$T(\omega) = a_i \frac{(\gamma_i/2)^2}{(\omega - \omega_i)^2 + (\gamma_i/2)^2}, \quad (1)$$

where a_i is the amplitude, ω_i is the resonance frequency, and γ_i is the full width at half maximum (FWHM) of the WGM resonant peak.

The essential parameter of a WGM is its quality factor, i.e., the Q value. It describes the ability of a microcavity to store optical energy against optical power losses and reflects the average photon lifetime of a particular WGM in a microcavity. In general, the Q value of an optical microcavity can be calculated as

$$Q_i = \omega_i/\gamma_i \text{ or } \lambda_i/\lambda_{FWHM}, \quad (2)$$

where λ_i is the resonant wavelength and λ_{FWHM} is the FWHM of the resonant wavelength. If the effective refractive index of a WGM is n_{eff} , the free spectral range (FSR) between the transmission tips (i.e., between a WGM and its neighboring mode) of a circular WGM microcavity in terms of the frequency (or wavelength) is

$$\Delta f_{FSR} = \frac{c}{2\pi n_{eff} R} \left(\text{or } \Delta \lambda_{FSR} = \frac{\lambda^2}{2\pi n_{eff} R} \right), \quad (3)$$

where c is the speed of light in vacuum and R is the radius of the circular WGM microcavity. In sensing applications, the ratio of the FSR to the FWHM is another important figure of merit, that is, the finesse (F) of a WGM microcavity, defined as $F = \lambda_{FSR}/\lambda_{FWHM}$.

WGM microcavities are widely regarded as promising sensors for the ultrasensitive detection of biomolecules in microfluidic

environments and systems. When target molecules, such as proteins, approach the surface of a WGM microcavity, they induce an excess dipole moment via the evanescent field of the WGMs. Consequently, the resonant frequency of the WGMs shifts, which can be precisely evaluated by integrating over the surface differentials,⁷

$$\frac{\delta \omega_i}{\omega_i} \approx - \frac{\alpha_{ex} \sigma_m \int |\mathbf{E}_i(\mathbf{r})|^2 dA}{2\epsilon_c \int |\mathbf{E}_i(\mathbf{r})|^2 dV}, \quad (4)$$

where α_{ex} is the molecule-caused excess polarizability, σ_m is the molecular surface density, ϵ_c is the homogeneous permittivity of the WGM microcavity, and $\mathbf{E}_i$ is the electric field of a WGM.

Recently, active WGM microcavities made of active materials and functioning as micrometer-scale laser sources have drawn considerable attention for biosensing applications due to their unique far-field light coupling capabilities. Such WGM microlaser sensors allow for the use of both the resonant frequency and the intensity of the laser output for various biosensing schemes, including on-chip optofluidic enzyme-linked immunosorbent assays (ELISAs). Considering the bioreaction-induced optical loss around a WGM microlaser sensor, the relationship between the intensity of the laser output and the bioreaction-induced optical losses can be expressed as²⁰

$$I_{Laser} \propto I_{pump} \delta_c \left(\frac{g}{\delta_c + c_a \delta_{in} + c_b \delta_{ex}} - 1 \right), \quad (5)$$

where I_{pump} , g , δ_c , δ_{in} , and δ_{ex} are the intensity of pumping laser, gain coefficient of WGM microlaser, and coefficients of external coupling, intrinsic, and external optical losses, respectively. c_a and c_b are the coefficients that depend on the WGM distribution. Active and passive WGM microcavities have become powerful building blocks in the development of high-performance integrated photonic devices and microsystems for biological applications.

Notably, the sensing performance of WGM microcavity sensors can be further enhanced if they are properly combined with other light-matter enhancement mechanisms. For instance, Zhang *et al.* reported the synergy effect between WGM and surface plasmon, which can lead to an extra enhancement in Raman spectroscopy.²¹ Wang *et al.* presented an active-mode optical microcavity sensing platform in which Förster resonance energy transfer (FRET) is utilized to enhance the sensor's sensitivity for the real-time quantification of intracellular molecules at single-cell resolution.²² Together with a plasmonic enhancer and an optical tweezer, Houghton *et al.* presented a novel single-molecule dynamometer using WGM biosensors to quantify the enzyme activity during conformational changes.²³ Xiao *et al.* combined WGM microcavity with photoacoustic technique to stimulate the natural vibrations of mesoscopic particles and then couples them to a high-Q WGM microcavity for ultrasensitive readout.²⁴

B. Optofluidic biosensor technologies based on WGM microcavities

With the advancement of high-Q optical microcavities, particularly WGM microcavities, numerous new optofluidic sensor technologies, and microsystems have been developed for various biological

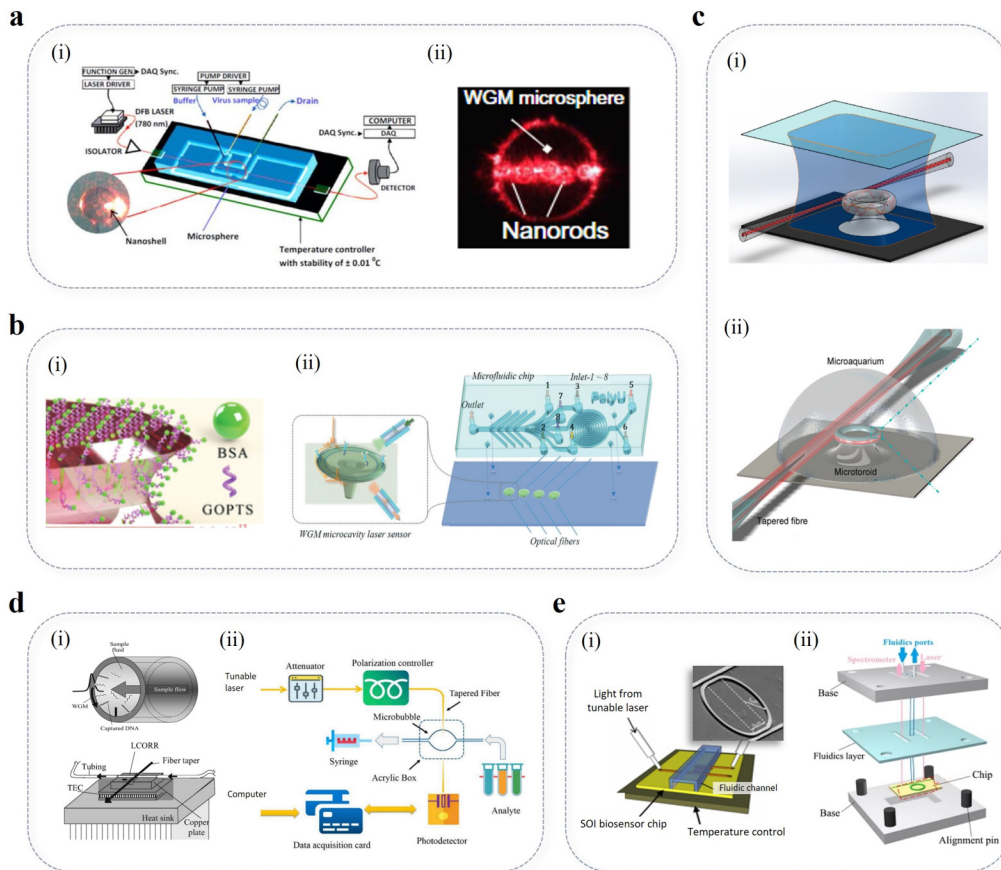


FIG. 1. Different types of high-Q optical microcavity sensors for optofluidic biological analysis applications. (a) Micro-sphere microcavity sensors for (i) label-free detection and sizing of the smallest individual RNA virus [adapted with permission from Dantham *et al.*, Appl. Phys. Lett. **101**(4), 043704 (2012). Copyright 2012 AIP Publishing LLC], (ii) monitoring polymerase/DNA interactions [adapted with permission from Kim *et al.*, Sci. Adv. **3**, e1603044 (2017), licensed under a Creative Commons Attribution (CC BY) License].²⁹ (b) Micro-disk microcavity sensors for (i) label-free detection of human IgG [adapted with permission from Guo *et al.* Small **16**(26), 2000239 (2020). Copyright 2020 Wiley Materials],²⁵ (ii) optofluidic ELISA of VEGF [adapted with permission from Ouyang *et al.*, Lab Chip **20**(14), 2438–2446 (2020). Copyright 2020 Royal Society of Chemistry].²⁰ (c) Micro-toroidal microcavity sensors for (i) detection of human chorionic gonadotropin [adapted with permission from Ozgur *et al.*, Anal. Chem. **91**, 11872 (2019). Copyright 2019 American Chemical Society],²⁶ (ii) selective biosensing without compromising sensitivity or reliability [adapted with permission from Ozgur *et al.* Sci. Rep. **5**, 13173 (2015), licensed under a Creative Commons Attribution (CC BY) License].³⁵ (d) Micro-capillary microcavity sensors for (i) the label-free detection of DNA sequences [adapted with permission from Suter *et al.*, Biosens. Bioelectron. **23**, 1003–1009 (2008). Copyright 2008 Elsevier],³⁸ (ii) ultra-sensitive detection of lead ion [adapted with permission from Fu *et al.*, Talanta **213**, 120815 (2020)]. Copyright 2020 Elsevier].⁴⁰ (e) Micro-ring microcavity sensors for (i) label-free real-time biosensing [adapted with permission from De Vos *et al.*, Opt. Express **15**(12), 7610–7615 (2007). Copyright 2007 Optical Society of America],²⁷ and (ii) sensors within poly-(dimethylsiloxane) microfluidic channels [adapted with permission from Wu *et al.*, Rev. Sci. Instrum. **90**(3), 035004 (2019). Copyright 2019 AIP Publishing LLC].²⁸

analysis applications, as illustrated in Fig. 1. Microsphere cavities, micro-toroidal cavities, etc., based on optofluidic biosensing have been mentioned.

1. Micro-sphere cavity-based optofluidic biosensors

Microsphere cavities are widely used for biosensing owing to their ease of fabrication and achievable high-Q values. Dantham *et al.* conducted an early study of microsphere cavity-based optofluidic biodetection [see Fig. 1(a-i)].¹⁶ Using a microsphere cavity, they reported the detection and sizing of the smallest

individual ribonucleic acid (RNA) virus, MS₂, in which a single dipole-stimulated plasmonic nanoshell was used as a microcavity wavelength-shift enhancer. Their experiments showed that such an enhancement mechanism allows the ultrasensitive detection of MS₂ viruses in a modest hybrid mode. An analytical theory for dipole plasmonic enhancement with plasmonic nanoshells was also presented along with the experimental results. This technology may enable the early detection of viruses at ultra-low concentrations for the identification and elimination of pathogens.

Another method for the label-free optical detection of single enzyme-reactant interactions and associated conformational

changes at a single-molecule level was demonstrated by Kim *et al.* [see Fig. 1(a-ii)].²⁹ They employed a device that combines plasmonic nanorods with a WGM microsphere cavity to monitor polymerase/deoxyribonucleic acid (DNA) interactions. Their experiments utilized two distinct recognition schemes to probe both the kinetics of polymerase/DNA interactions and the conformational changes in polymerase molecules. They successfully distinguished between low and high polymerase activities through characteristic differences in the signal amplitude and signal length distributions. This work established a promising label-free approach for investigating structural changes in single molecules, offering significant potential for advancing the understanding of biomolecular dynamics.

To address the limitations of current methods for monitoring cell death and protein release, which often require cell labeling or protein purification, Chen *et al.* introduced an optofluidic solution utilizing WGM microsphere microcavities for the label-free, specific detection of cytochrome c, a biomarker for cell apoptosis.³⁰ They demonstrated the immobilization of antibodies on the surface of WGM microcavity sensors using a biotin-streptavidin sandwich assay. Microfluidic components were also integrated to ensure precise, continuous flow control, and mixing. This integrated optofluidic platform provides label-free, real-time detection technology capable of monitoring proteins released from cells at nanomolar concentrations. Sun *et al.* demonstrated a WGM microcavity-based microfluidic chip for the simultaneous detection of two Alzheimer's disease (AD) biomarkers, i.e., A β 1-42 and p-Tau181, by surface-enhanced Raman spectroscopy (SERS).³¹ This approach provided a sensitive and reliable platform for the early diagnosis of AD, with potential applications for simultaneously detecting multiple analytes in assays.

2. Micro-disk cavity-based optofluidic biosensors

Another prevalent structure of WGM microcavities is the microdisk cavity, which can be conceptualized as an equatorial plane sliced from a microsphere cavity. Compared to microspheres, microdisk cavities offer the advantage of efficiently suppressing spurious WGMs due to their thinner design. Microdisk WGMs have been widely incorporated with microfluidic devices for bioassays. For instance, researchers in Canada have successfully employed microdisk WGM cavities as biosensors for the real-time detection of *Staphylococcus aureus*.³² The phage protein LysK, which is specific to staphylococci, was used to functionalize the WGM microcavities. The binding on the surface of the WGM cavities caused a shift in the resonant spectral peaks. The limit of detection (LOD) of this microdisk sensor was 5 pg ml⁻¹, which corresponded to 20 cells/ml. The specificity of the functionalization scheme was verified by a control testing of the detection of *Escherichia coli*. Despite the sensor's simple structure and high sensitivity, one of its limitations is that optical coupling with a microcavity using a tapered optical fiber can be sensitive to environmental disturbances.

Such issues caused by optical coupling can be alleviated by transforming passive WGM microcavities into WGM microlasers. Therefore, far-field coupling using optical fibers or objective lenses can be applied to collect the laser output for biosensing

applications. Guo *et al.* demonstrated a hyperboloid-drum (HD) microdisk WGM microlaser biosensor for the ultrasensitive detection of human IgG [see Fig. 1(b-i)].²⁵ Notably, this HD microdisk WGM microlaser biosensor showed an impressive LOD of 9 ag/ml for the detection of human IgG, showing approximately four orders of magnitude greater sensitivity than typical WGM biosensors. Their experimental results showed that WGM microlaser biosensors are promising for the detection of biomarkers in protein secretions and body fluids.

Kim *et al.* proposed an on-chip label-free biosensor based on an active WGM sensor, using silicon nanoclusters as stable active compounds.³³ The authors introduced a nanogap structure in WGM microresonators to enhance sensitivity. The fabricated sensors were integrated into a microfluidic channel to form a compact optofluidic device. The optical responses of the active WGM sensors were tested under both air and aqueous conditions and showed strong photoluminescence emission with WGM microcavity resonances. They also demonstrated a platform operating with a remote pump and readout, which reduced the complexity and cost of the measurement setup.

Goede *et al.* fabricated a microdisk WGM laser biosensor using Al₂O₃ doped with Yb³⁺ because it has low optical losses and can emit light in the range of 1020–1050 nm, which is outside the absorption band of water.³⁴ Their fabricated WGM microlaser achieved single-mode emission at a wavelength of 1024 nm with a linewidth of approximately 250 kHz. An LOD of 300 pM was achieved for the detection of rhS100A4 in urine. Their study revealed the advantages of WGM microlaser-based biosensors, particularly the WGM microlaser sensors fabricated by using Al₂O₃, over passive WGM sensors.

Ouyang *et al.* demonstrated an optofluidic ELISA using on-chip integrated polymer WGM microlaser sensors [see Fig. 1(b-ii)].²⁰ They used an optical 3D μ -printing technology to rapidly fabricate high-Q suspended-disk WGM microlaser sensors and then integrate them together with optical fibers on a microfluidic chip. The use of high-Q WGM microlasers in optofluidic ELISA offers advantages such as low-threshold laser oscillation and strong light-matter interactions. Such an on-chip WGM microlaser-based optofluidic ELISA technique can detect the vascular endothelial growth factor (VEGF) at a concentration level of 17.8 fg ml⁻¹, significantly surpassing the capability of conventional ELISA kits.

3. Micro-toroidal cavity-based optofluidic biosensors

The micro-toroidal structure is similar to that of a microdisk but has a smooth ring around the edge. Compared to micro-disks, micro-toroidal microcavities usually achieve a higher Q value and, thus, may achieve better biosensing performance in terms of sensing sensitivity and LOD.

Using a micro-toroidal microcavity, Ozgur *et al.* proposed a highly sensitive biosensor for rapidly detecting the performance-enhancing drug, human chorionic gonadotropin (hCG), in urine samples [see Fig. 1(c-i)].²⁶ They used frequency-locked microtoroid WGM resonators as biosensors to detect hCG at a concentration of 1 fM in simulated urine and 3 fM in the urine of pregnant donors. These results are three orders of magnitude better than the results

of mass spectrometry, which is the current gold standard for detection, in terms of LOD. Ozgur *et al.* proposed a surface modification strategy using a silane-based coating that is both protein-resistant and bioconjugable, enabling highly selective biosensing without compromising sensitivity or reliability [see Fig. 1(c-ii)].³⁵ This strategy was demonstrated using functionalized microtoroids that resist nonspecific interactions while being used as sensitive biological sensors.

Recently, Suebka *et al.* constructed a micro-toroidal optical-resonator-based biosensor. In this work, researchers investigated the best way to deliver the analyte to the surface of WGM microcavities integrated on an optical microfluidic chip biosensor from two perspectives: simulation and experiment.³⁶ They found that continuous injection was the fastest method for delivering analytes. Their results provide insights into mass transport mechanisms and optimizing the sensor's performance.

4. Micro-capillary/micro-bubble cavity-based optofluidic biosensors

Another commonly used structure is the capillary, which is a combination of microfluidic devices and WGMs. This scheme has a simple structure and directly uses a capillary wall to form the WGM pattern. A liquid is passed through the inner wall of the capillary to realize the interaction of biomolecules and WGMs. Wang *et al.* presented a capillary-based microfluidic WGM microresonator for the real-time monitoring of conformational changes in the G-quadruplex driven by K⁺ ions.³⁷ The resonance wavelength-shift mechanism was theoretically analyzed, and the resonance mode with the highest wavelength sensitivity was selected for monitoring. The experimental results confirmed the theoretical analysis and showed that G-quadruplex can be folded with a KCl concentration as low as 1 μ M. The proposed microresonator-based platform offers high sensitivity, integration, microfluidic capability, label-free detection, and real-time monitoring, rendering it suitable for DNA sensing and other applications. Their paper also provides details of the materials and methods used in the experiments.

Suter *et al.* and Zhu *et al.* proposed the using of WGMs in capillary tubes for biosensing. They discussed the use of a liquid-core optical ring-resonator (LCORR) sensor for label-free quantitative DNA and viral detection [see Fig. 1(d-i)].^{38,39} The LCORR is a sensing platform that integrates microfluidic and photonic sensing technology, allowing for low detection limits and sub-nanoliter detection volumes. Researchers have analyzed the LCORR response to different DNA and viral samples with varying strand lengths, numbers of base mismatches, and concentrations to evaluate its detection capability. They established a linear correlation between the LCORR sensing signal and molecular density, allowing for an accurate calculation of the molecular density on the surface. The researchers also demonstrated that LCORR was sensitive enough to differentiate between DNA and viral DNA with only a few base mismatches.

To strengthen the evanescent field inside the tube and enhance the interaction between WGMs and biomolecules, one option is to fabricate a microbubble based on a capillary tube using, for example, heating. Microbubbles have a thinner wall and, thus, leak more energy inside the bubble in the form of an evanescent field when the

WGM operates within the wall. Fu *et al.* proposed an ultrasensitive method for detecting lead ions using a microbubble-based WGM optofluidic resonator sensor [see Fig. 1(d-ii)].⁴⁰ Pb ions are harmful pollutants that can contaminate drinking water and pose health risks, particularly to children. The proposed method involves modifying the inner wall of a microbubble with the classic GR-5 DNAzyme and analyzing the mode field distribution of the microbubble. The optofluidic sensor exhibited a high bulk refractive index sensitivity and could detect lead ions at concentrations as low as 15 fM. The sensor exhibits good selectivity for the detection of Pb ions over other metal ions. The experimental setup and the fabrication process of the microbubble resonator are described in detail. The proposed sensor has potential applications in environmental monitoring and food safety analysis. Recently, a novel label-free DNA biosensor based on a high-quality optical WGM microcavity modified with 3D DNA nanostructure probes has been designed by Wan *et al.*⁴¹ The biosensor achieved an ultralow LOD by modifying the surface of the microcavity with DNA tetrahedral nanostructure (DTN) probes. DTN probes can efficiently improve probe density and depress entanglement between DNA probes, resulting in a 1000-time lower LOD than that achieved using 1D ssDNA probes. The WGM spectra of the high-Q microcavity were used to detect DNA inside the microfluidic channel. The proposed biosensor has broad applications in bioengineering and medical diagnostics.

Recently, Wang *et al.* have developed an ultra-sensitive label-free and quick-responsive DNAzyme biosensor based on a WGM resonator with a hybrid amplification from liquid crystals (LCs) and Au nanoparticles (AuNPs).⁴² When a DNAzyme is cleaved by the target analyte (L-histidine in this case), the DNA hybridization triggers an orientation transition of the LC molecules. With the amplification from the AuNPs, the resulted spectral wavelength shift can be employed to detect the target analyte with an ultra-low detection limit of around 0.5 fM. The proposed platform can be extended to detect various molecules by simply changing the DNAzyme sequence and, thus, is a promising solution for ultra-sensitive molecular detection.

5. Micro-ring cavity-based optofluidic biosensors

Microring cavities are increasingly important WGM resonators that are suitable for on-chip integrated optofluidic biosensing. In 2007, Vos *et al.* proposed a label-free biosensor based on microring cavities in a silicon-on-insulator (SOI) for sensitive real-time biosensing [see Fig. 1(e-i)].²⁷ The biosensor was designed to overcome the limitations of commercial microarrays that rely on the detection of labeled molecules. They utilized microring cavities that resonate at a specific wavelength, and any change in the refractive index of the cavity environment causes a shift in the resonance spectrum, which can be monitored for sensing. The device performed well in terms of absolute molecular mass sensing owing to its small dimensions. The biosensor was fabricated using deep UV lithography, allowing cheap mass production and integration with electronic functions for complete lab-on-chip devices.

Geidel *et al.* developed an optofluidic biochip by integrating optical ring-resonator biosensors into a self-contained microfluidic cartridge with active single-shot micropumps.⁴³ The microfluidic cartridge was designed to include multiple reservoirs for reagent

storage and single-use electrochemical pumps for the time-controlled delivery of liquids. Their optofluidic biochip could successfully perform an immunoassay but with relatively low sensitivity. Nevertheless, their work demonstrated the importance of automation and miniaturization in optofluidic biochemical analyses and revealed the advantages of photonic microsystems in biosensing. Wu *et al.* presented the design, fabrication, and characterization of an optofluidic chip by integrating highly sensitive label-free microring optical resonator sensors within poly(dimethylsiloxane) microfluidic channels [see Fig. 1(e-ii)].²⁸ Such a microring resonator-based optofluidic chip is capable of real-time quantitative detection of biomolecules and has great potential for applications in environmental monitoring and medical diagnostics.

Sun *et al.* demonstrated a gallium nitride (GaN) microring-based WGM microlaser biosensors, on which surface AuNPs were further assembled to enhance the optical field for sensing.⁴⁴ The synergistic coupling between the optical confinement of GaN WGM microcavity and the localized surface plasmon resonance of AuNPs results in a strong light-matter interaction, which enables significant enhancement of SERS signals for the real-time determination of biomolecules in human urine, such as creatinine.

A summary of the different microcavity-based optofluidic technologies used for biological analysis is presented in Table I.

III. BIOLOGICAL ANALYSIS APPLICATIONS

Optical-microcavity-based optofluidics has become one of the most promising technologies for ultrasensitive biological analyses. It has many distinct advantages, such as minimal sample requirements, ease of integration, high sensitivity, and rapid detection. It can be very sensitive to even single particles⁴⁶ and has been used for many different kinds of biological analyses, such as protein, nucleic acid, exosome, and virus detection, as well as for cell studies.

A. Protein studies

The optical WGM biosensors showed remarkable performance in the detection of proteins. Gohring *et al.* presented an optofluidic ring-resonator (OFRR) sensor for detecting human epidermal growth factor receptor 2 (HER2) breast cancer biomarkers in human serum samples, as shown in Fig. 2(a-i).⁴⁷ In their experiments, OFRR sensors were used to detect HER2 at concentrations of 13–100 ng ml⁻¹. Notably, using a hybrid microcavity of optical WGMs and plasmonic nanoshells, Dantham *et al.* presented an ultrasensitive biosensor that could detect a single thyroid cancer marker (thyroglobulin, Tg) with a mass of only 1 ag, as shown in

TABLE I. Comparison between different microcavity-based optofluidic sensing technologies.

Structure	Principal	Target biomarkers	LOD	References
Micro-sphere	Plasmonic enhanced mode shift	Smallest individual RNA virus MS2	Individual virus (6 ag)	16
	Binding-induced linewidth broadening and wavelength shifts	Polymerase/DNA interactions	Single-molecule level	29
Micro-disk	Mode shift	Cytochrome C	6.82×10^{-9} M	30
	Enzyme-linked immunosorbent assay (ELISA) using light intensity of active WGMs	Horseradish peroxidase (HRP)-streptavidin; vascular endothelial growth factor (VEGF)	0.3 ng/ml and 17.8 fg/ml	20
	Mode shift of active microcavity	Human IgG	9 ag/ml (0.06 aM)	25
	Mode shift of active microcavity	Streptavidin-biotin complex	6.7 nM	33
Micro-toroidal	Mode shift of WGM microlaser	Protein rhS100A4 in urine	300 pM (3.6 ng/ml)	34
	Mode shift of passive microcavity	Human chorionic gonadotropin (hCG)	120 aM	26
	Mode shift caused by adsorption events	Human IL-2 protein	0.3 fM	35
	Blue spectral shift of WGMs	(Potassium chloride) KCl	1 μ M	37
Micro-capillary	Mode shift of passive microcavity	Lead ions	15 fM	40
	Mode shift in real time	DNA	260 aM	41
	A hybrid amplification from liquid crystals (LCs) and Au nanoparticles (AuNPs)	DNAzyme	0.5 fM	42
	SERS	Biomolecules in human urine (urea, uric acid, and creatinine)	Urea: 19.86 mg l ⁻¹ ; uric acid: 23.5 mg l ⁻¹ ; creatinine: 4.89 mg l ⁻¹	44
Micro-ring	Mode shift	Avidin/biotin high affinity couple	10 ng/ml	27
	Mode shift	Bulk DNA	10 pM	38
	Mode shift	DNA	4 pg/mm ²	43
	Mode shift	Human IgG	0.5 μ g/ml	28
	Mode shift	Avidin	0.1 nM	45

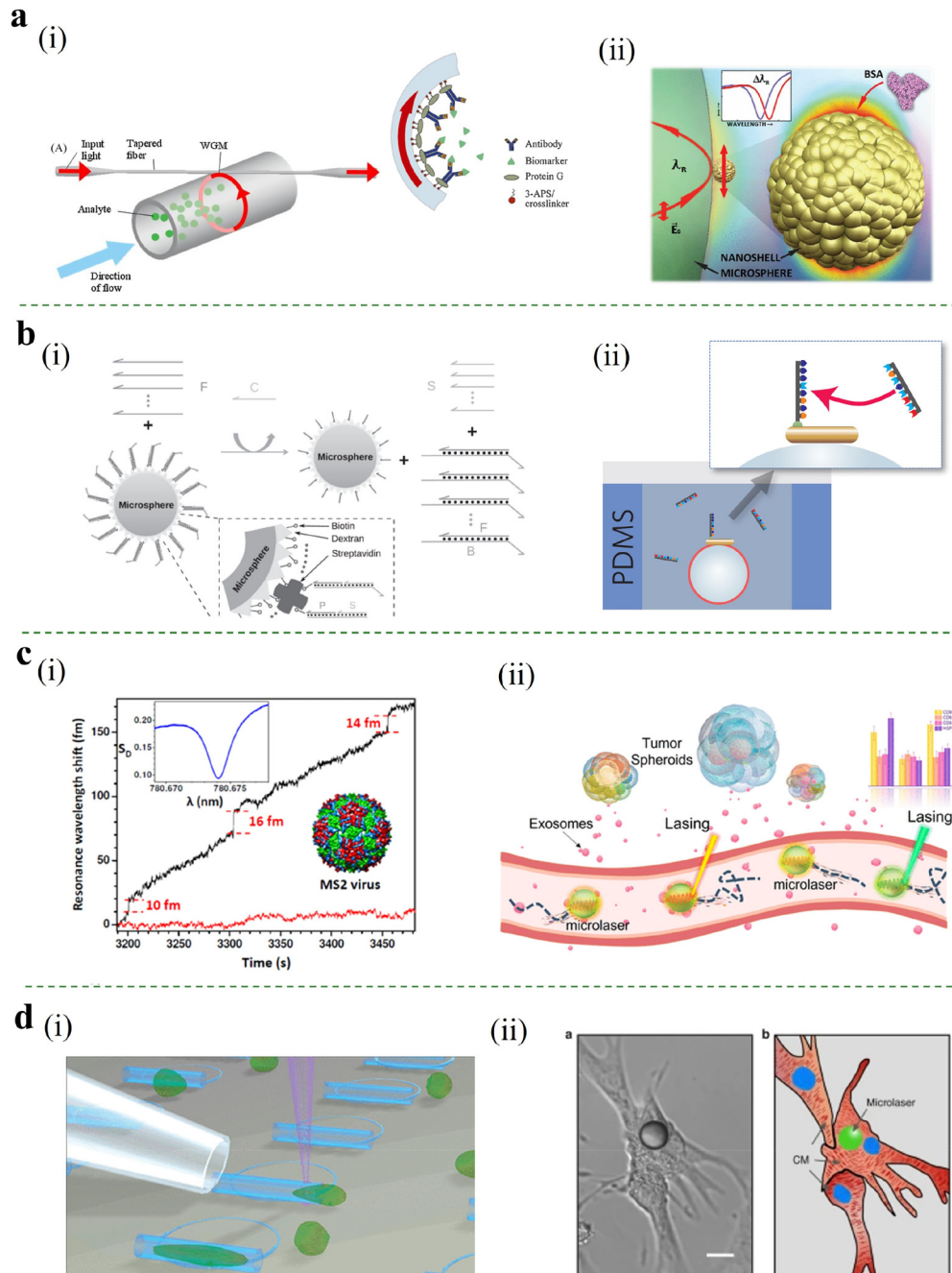


FIG. 2. Biological analysis applications of optical-microcavity-based optofluidic technologies. (a) Protein study: (i) detection of antibody and proteins [adapted with permission from Gohring *et al.* Sens. Actuators, B **146**, 226 (2010). Copyright 2010 Elsevier].⁴⁷ (ii) single protein detection [adapted with permission from Dantham *et al.* Nano Lett. **13**, 3347 (2013). Copyright 2013 American Chemical Society].⁴⁸ (b) DNA study: (i) analysis of DNA molecules [adapted with permission from Wu *et al.* Small **10**(10), 2067–2076 (2014). Copyright 2014 Wiley Materials].⁴⁹ (ii) on-chip DNA analysis [adapted with permission from Baaske *et al.* Nat. Nanotechnol. **9**(11), 933–939 (2014). Copyright 2014 Springer Nature].⁵⁰ (c) Exosome and virus detections: (i) Detection of MS2 viruses [adapted with permission from Dantham *et al.*, Appl. Phys. Lett. **101**(4), 043704 (2012). Copyright 2012 AIP Publishing LLC].¹⁶ (ii) detection of released extracellular vesicles [adapted with permission from Wang *et al.*, Nano Lett. **23**, 2502 (2023). Copyright 2023 American Chemical Society].⁵¹ (d) Cell study: (i) detection of individual mouse cells [adapted with permission from Smith *et al.*, Nano Lett. **11**, 4037 (2011). Copyright 2011 American Chemical Society].⁵¹ (ii) study of cardiomyocytes [adapted with permission from Schubert *et al.*, Nat. Photonics **14**(7), 452–458 (2020). Copyright 2020 Springer Nature].⁵³

Fig. 2(a-ii).⁴⁸ The LOD for detecting the mass of bovine serum albumin (BSA) protein reached 0.11 ag (66 kDa).

Protein detection using the WGM microcavity sensors can be performed quickly. Integration with microfluidics can enable high-throughput microcavity sensor systems to detect multiple proteins.⁴⁵ As the inherent complexity of biochemical pathways always alters disease states, multiplexed analytical technology with a more informative biomolecular understanding of disease onset and progression is urgently needed. Compared to conventional single-parameter assays, biomolecular insights obtained from multiparameter measurements may greatly improve disease diagnostics, prognosis, and theragnostics. Washburn *et al.* demonstrated that the concentrations of prostate-specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), tumor necrosis factor-alpha (TNF-alpha), and interleukin-8 (11,8) can be simultaneously determined in three unknown protein cocktail solutions.⁵⁴ Their work revealed that multiple immunoassays could be performed concurrently on a WGM biosensor-based optofluidic platform without the loss of sensitivity or measurement precision.

B. Nucleic acid studies

The detection of nucleic acids, including various types of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) molecules, using WGM microcavity sensors has also been widely reported.^{49,53,55,56} Most measurement strategies have investigated the hybridization of complementary nucleic acid strands, and their key measurement considerations include sensitivity, capability to detect subtle discrepancies such as single-base mismatches, and response time.

Nucleic acid detection using WGM microcavity biosensors can bypass the costly fluorophore functionalization steps required in conventional assays, ultimately achieving a low limit of detection. For instance, Wu *et al.* demonstrated a microsphere-type WGM biosensor that could detect a 22 nt oligomer at a concentration of 80 pM (i.e., 32 fmol),⁴⁹ as shown in Fig. 2(b-i). A DNA strand displacement circuit was integrated with a WGM microsensor for nucleic acid detection, in which the catalytic behavior of the circuit not only improved its sensitivity and specificity but also made the sensor reusable. Baaske *et al.* proposed a microsphere-type WGM microcavity biosensor platform to monitor single-molecule nucleic acid interactions, as shown in Fig. 2(b-ii).⁵⁰ With plasmonic enhancement using gold nanorods, these biosensors can specifically detect nucleic acid hybridization down to single 8-mer oligonucleotides.

C. Exosome and virus detections

The rapid and accurate detection of viruses has become increasingly important for the prevention of infection and pandemic outbreaks. Likewise, the detection of exosomes, which are small particles secreted by cancer cells, has drawn great attention in the study of molecular information about tumors. Conventionally, biological specimens must be profiled using molecular biological techniques, such as polymerase chain reaction (PCR). However, such techniques require extensive sample preparation and processing and may take several hours to complete. Recently, label-free

optical microcavity biosensors have become promising candidates for revolutionizing technologies for exosome and viral detection.

In 2008, Vollmer *et al.* reported a WGM biosensor for the detection of a single discrete binding event of the influenza A (InfA) virus.¹⁷ By monitoring the shift in the resonance frequency or wavelength, the size and mass (about 0.52 fg) of a bound virion are determined from the measured resonance shift. Lu *et al.* demonstrated an optical WGM microcavity biosensor platform combined with a thermally stabilized reference interferometer for detecting nanoparticles and viruses.⁵⁷ Their system can detect InfA virus binding at a concentration of 1 pM. The signal-to-noise ratio was enhanced from the previously reported 3:1 to 38:1. The detection of very small viruses was reported by Dantham *et al.*, as shown in Fig. 2(c-i).¹⁶ They demonstrated that the use of a WGM microcavity sensor can enable the label-free detection and sizing of the smallest individual RNA virus, i.e., the MS2 virus, whose mass is only ~1% of influenza A (6 vs 512 ag).

Remarkable progress has been made in the detection of exosomes.⁵⁸ For instance, Wang *et al.* proposed a liquid-crystal-microdroplet-based smart WGM microlaser sensor that can self-propel and analyze extracellular biomarkers,⁵¹ as shown in Fig. 2(c-ii). The lasing spectral responses of these WGM microlaser sensors were employed to monitor the cellular profiles of exosomes derived from multicellular cancer spheroids. The sensing capabilities of the WGM sensors in complex environments were tested using a microfluidic biosystem with different tumor-derived exosomes.

D. Cell study

WGM sensors have also been employed to investigate the behavior of individual cells, which are the fundamental structural and functional units of living organisms. These sensors have the potential to play an increasingly important role in the studies of cell biology, material-cell interactions, and biophysics. Smith *et al.* reported a method for the efficient capture and sensing of embryonic fibroblast mouse cells (NIH 3T3) using split-wall microtube WGM resonators, as shown in Fig. 2(d-i).⁵² Murib *et al.* introduced WGM microlaser sensors into cardiac cells to illuminate cardiomyocyte contractility under various experimental conditions, as shown in Fig. 2(d-ii).⁵⁶ Owing to their single-cell specificity, long-term tracking, and reduced sensitivity to scattering, WGM microlaser sensors can simplify experimental setups, reducing complexity and restrictions typically encountered in traditional research methods. These sensors offer new technological capabilities that extend far beyond current microscopy-based techniques.

IV. SUMMARY

In summary, high-Q optical-microcavity-based biosensing technologies have become increasingly important for various biological analysis applications. WGM microcavity sensors can be fabricated in many different shapes, such as microspheres, micro-disks, micro-toroidals, micro-capillary/bubbles, or micro-rings, and, thus, provide a group of highly flexible technological means to enhance light-matter interactions for ultrasensitive biological studies and biodetection applications.

By combining high-Q optical microcavities with microfluidic technology, many types of small-sized, high-performance optofluidic biosensors can be developed to address many of the current and pressing biological analysis challenges. They can be used to develop portable point-of-care testing and diagnostic tools for the rapid and accurate detection of proteins, nucleic acids, viruses, and exosomes. Such tools are in high demand for tackling public healthcare challenges, such as the COVID-19 pandemic. They can also be employed to study the behavior of living cells in humans, which may pave new pathways for the study of cell biology and biophysics.

ACKNOWLEDGMENTS

This work was financially supported by the Research Grants Council of Hong Kong SAR, China (Grant No. 15220721).

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Zhi-zheng Wang: Investigation (equal); Writing – original draft (equal). **Bin Zhou:** Investigation (equal); Writing – original draft (equal). **A. Ping Zhang:** Conceptualization (equal); Funding acquisition (equal); Supervision (equal); Writing – review & editing (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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