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Recent Advances in Optical Biosensors for Sensing Applications: a Review

Arun Uniyal[1,2] · Gaurav Srivastava[3] · Amrindra Pal[1] · Sofyan Taya[4] · Arjuna Muduli[5]

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Abstract
Merging engineering with medical science and adopting artificial intelligence to get further exact results specifically for preventive health care has made it challenging to detect the concentration or presence of biological analytes. The basic building blocks of such a system require recognition of an analyte, producing a signal that must be passed through a signal conditioning unit, and, finally, a detector that recognizes the specific analyte. The detection extends to the sensing of bacteria, tumor cells, tumor biomarkers, toxins, drugs, and other biomarkers with admirable accuracy with sensitivity. In optical biosensors, most commonly, it is the fluorescence technique. It measures the intensity, decay time, quenching efficiency, anisotropy, and quenching. Use plain sensor stripes, optical waveguide systems, arrays, and capillary-based technical sensors. This paper deals with the study of available optical biosensors, mentioning their working principle, merits, demerits, and application. The prime focus of this current study is the most widely used surface plasmon resonance (SPR) relied optical biosensors, including SPR imaging, and magneto-optical surface plasmon resonance. With this, some other optical biosensors are discussed, like evanescent wave fiber optic biosensor, evanescent wave fluorescence, and colorimetric polymerase chain reaction–based biosensor, as well as interferometric, ellipsometric, surface-enhanced Raman scattering biosensors, and Photonic crystal fiber sensor.

Keywords Biosensor · Surface plasmon resonance · SPR imaging · Evanescent · Fluorescence · Bioluminescent · Ellipsometric · Sensitivity

Introduction

An optical biosensor enables the real-time detection of various biomarkers. With their qualities like higher sensitivity and selectivity, cost-effectiveness, and their compact size [1], the optical biosensor becomes popular. The optical biosensors acquired with the potent analytical and detecting methodologies have made them a versatile biomedical research tool for healthcare, pharmaceutical industries, environmental monitoring, homeland security, and the sphere of battle. Optical biosensors are implemented by numerous innovative concepts and highly incorporative methods like micro electrochemical organizations, microelectronics, micro/nanotechnologies, biotechnology, molecular ecology, and chemistry. The rate of progression of this field is rapid in research and technological development that mainly focuses on environmental applications, healthcare, and the biotechnology industry [2–4]. Biosensors consist of sensing elements such as ligands and signal processing units (transducers). The main purpose of a biosensor is to generate a signal equivalent to the analyte absorption. The biorecognition element is a biological material that specifically recognizes and binds to the target molecule. The optical biosensor uses different biological materials as biorecognition essentials like antibodies, enzymes, antigens, receptors, whole cells, tissues, and nucleic acids [5–8]. The transducer is an element that converts the binding of the

✉ Amrindra Pal
amrindra.ieee@gmail.com

1 Department of EECE, DIT University, Dehradun, Uttarakhand, India

2 Department of ECE, Institute of Technology Gopeshwar, Chamoli, Uttarakhand 246424, India

3 Department of Electronics and Communication, University of Allahabad, Allahabad, India

4 Physics Department, Islamic University of Gaza, P.O. Box 108, Gaza, Palestine

5 Department of Electronics & Comm. Eng, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Andhra Pradesh 522502, India

target molecule to the bioreceptor into a measurable signal. It can be an optical, electrochemical, or thermal device. The detector is a device that measures the signal generated by the transducer. It can be an optical instrument, such as a spectrophotometer, or an electrical instrument, such as a voltmeter. The output may be in any form, like pictures, plots, tables, or numeric values [9]. Figure 1 shows the biosensing process to analyze the properties of the analyte.

The key strengths of biosensors are practically instantaneous interactive information of the tested sample, which is provided through rapid or real-time analysis. By this, corrective actions can be taken to contain the contamination before it can spread; biosensors, when used at the point-to-point care or for on-site testing, facilitate providing state-of-the-art molecular analysis, thus reducing the time as well as dependence upon a state-of-the-art laboratory; continuous analysis can be obtained by the configuration of many biosensor's technologies [11].

Direct and indirect recognition sensors are two categories of biosensors. Direct recognition sensors are those that measure biological interaction directly. These detectors assess physical changes like optical, mechanical, or electrical changes and do not require labeling for detection [12]. At the same time, the sensors dependent on secondary elements or indirect measurements for detection are referred to as indirect detection sensors. Unlike direct detectors, indirect detectors require the target to be bound to a labeled molecule [13, 14]. The main difference between direct and indirect assays is how the antigen is detected. In direct assays, antigens are immobilized on the sensor surface and subjected to binding interaction with the analyte of interest. The resonance angle is altered by the binding interaction between the analyte and the antibody, and this alteration is directly proportional to the concentration of the analyte.

While in an indirect assay, the antigen is first reacted with a primary antibody before being reacted with the secondary antibody, i.e., the binding process in this assay type involves two binding steps.

Figure 2 shows the direct analysis and the indirect analysis of an analyte. The miniaturization of biosensors may further minimize the cost of use. To obtain multiple parameters in real-time at multiple production steps or multiple times in the process, miniature biosensors integrated to form a lab-on-a-chip type module are a very powerful tool [15–19]. Biosensors may be integrated with online process monitoring schemes that allow finer automation and control of many critical and industrial monitoring facilities.

Evanescent Wave Fiber Optic Biosensor (EWFOB)

The working of EWFOB is based on two well-known phenomena: one known as the attenuated total reflection (ATR), as per Snell's law for ATR to happen $n_1 > n_2$ when the incidence angle $> \theta_{cr}$ (the critical angle), the value of the critical angle is given by [21]:

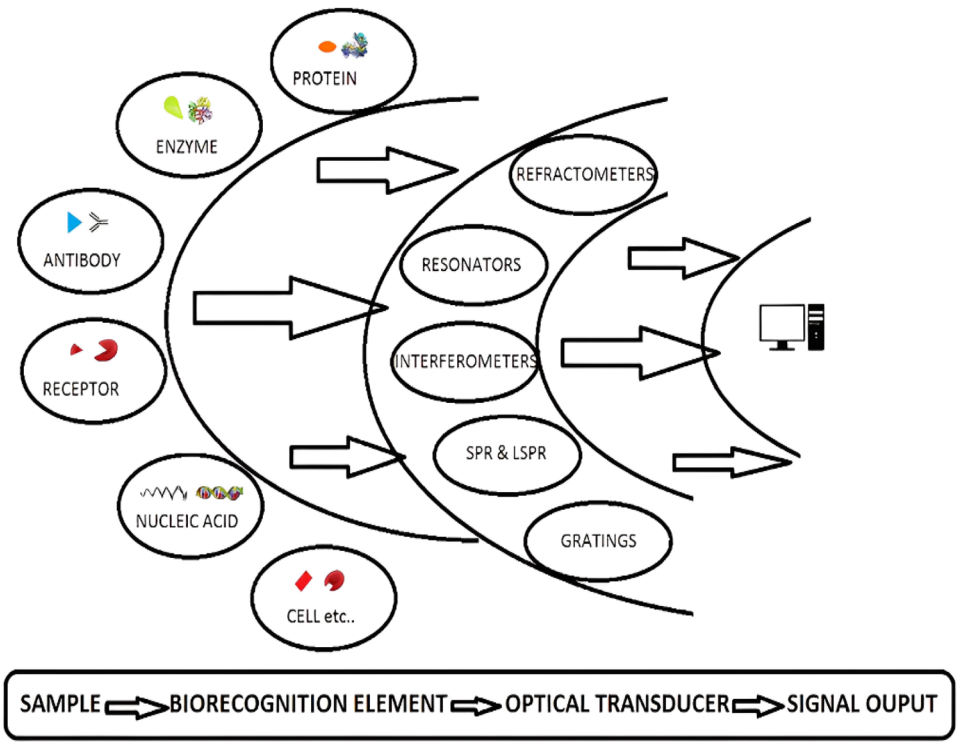

Fig. 1 The process of biosensing optical biosensors [10]

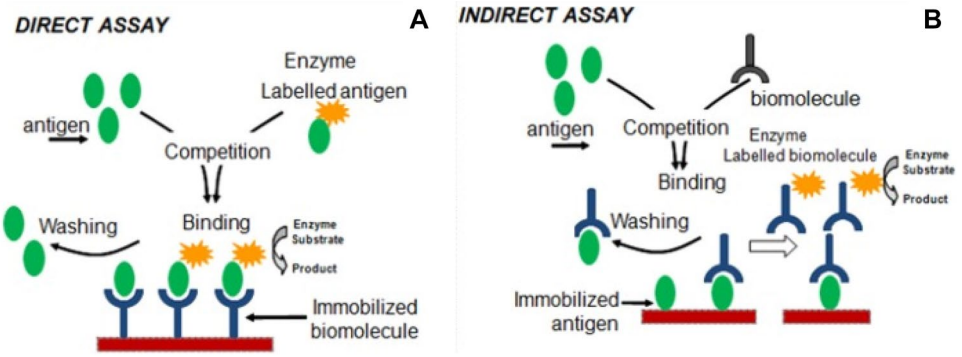

Fig. 2 Labeled diagram of the **A** direct assay and **B** indirect assay [20]

$$\theta_{cr} = \sin^{-1}(n_2/n_1) \tag{1}$$

where n_1, n_2 are RI of the core and cladding, respectively. Snell's law explains the optical properties of a given waveguide; however, it fails to provide a satisfactory explanation related to the components of the reflected light, especially the electromagnetic component, commonly referred to as evanescent wave (EW); this is another phenomenon used in EWFOB apart from ATR. These waves have a limited penetration depth. These are extended into the core surrounding (lower index medium) from the core (fiber) surface, typically 100 nm to several hundreds of nanometers as shown in Fig. 3. These waves decay exponentially with distance from the surface. This property is utilized to excite fluorophores that are close by or bound to the waveguide's surface. EWFOBs have been developed to detect a wide range of analytes. The advantage offered by these sensors is that they measure optical events, with almost no interference from the bulk solution, at the surface of the fiber [22].

The phenomenon is also observed in multimode waveguides. In the case of multimode fibers, the distance where the strength of EW reaches 1/e of its value at the surface is defined as penetration depth, d_p [24]:

$$d_p = \lambda / \left(4\pi \left[n_1^2 \sin^2\theta - n_2^2 \right]^{\frac{1}{2}} \right) \tag{2}$$

where, n_1 and n_2 are refractive indices defined as in expression (1), and θ is the angle of incidence [25]. To detect *S. typhimurium*, Kramer and Lim presented a fiber-optic–based biosensor and observed a limit of detection of 50 cfu/g in used irrigation water used for seed sprouting [26]. Valadez et al. demonstrated an EWFOS for detecting *Salmonella* in the breast of chicken and shell eggs. The computed data was compared with a time-resolved fluorescence assay. Their work gave out the detection limit of 10^3 cfu/mL (pure) and was specific for *Salmonella*, and the samples of chicken breast and egg come out to be 10^4 cfu/mL [27]. Figure 4 gives the findings of the *Salmonella* concentration detection in the phosphate buffered saline (PBS).

Applications

- It is able to excite fluorophores, bound to or found in close vicinity of the core (fiber) surface.
- EW-based systems provide relative immunity to the effects of matrix components or interferents beyond the reaction surface. This happens largely due to limited range of excitation.

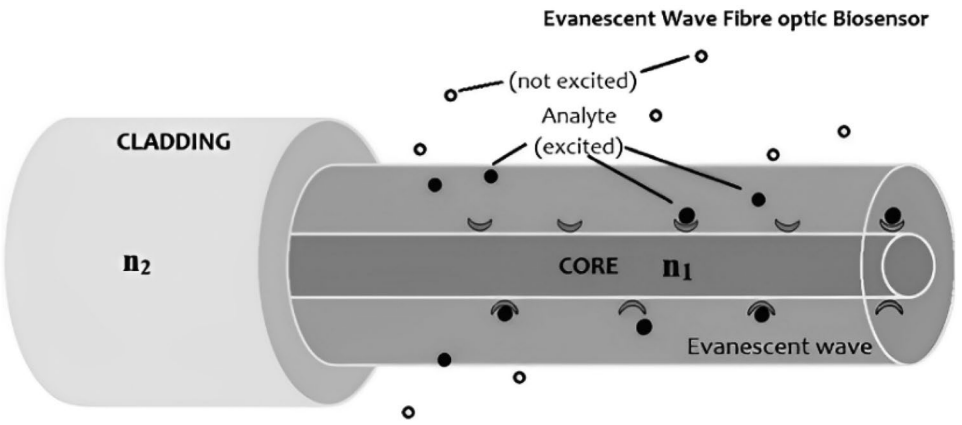

Fig. 3 EWFOB using partially clad fiber [23]

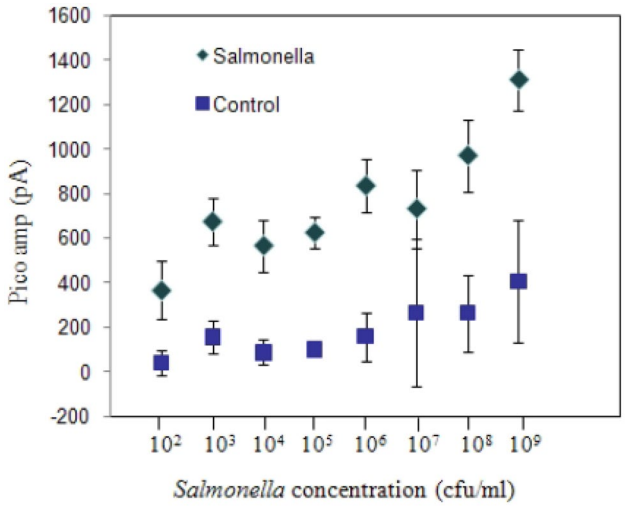

Fig. 4 Sensitivity of EWFOS employing serial dilutions of *S. enteritidis* cells suspended in phosphate buffered saline

Limitations

- Background absorbance of the fiber
- Limited stability
- Shortage in the availability of optimized parts required
- Delay in response times

Surface Plasmon Resonance (SPR) Biosensors

Surface plasmons are produced when polarized light interacts with two media with different refractive indices at their interface; here, the presence of metal film is necessary as one of the media. The SPR biosensors have a working principle based on EW propagation [28]. The photon of p-polarized light collides with the Au-metal film of the biosensor, through prism, as depicted in Fig. 5. These collisions

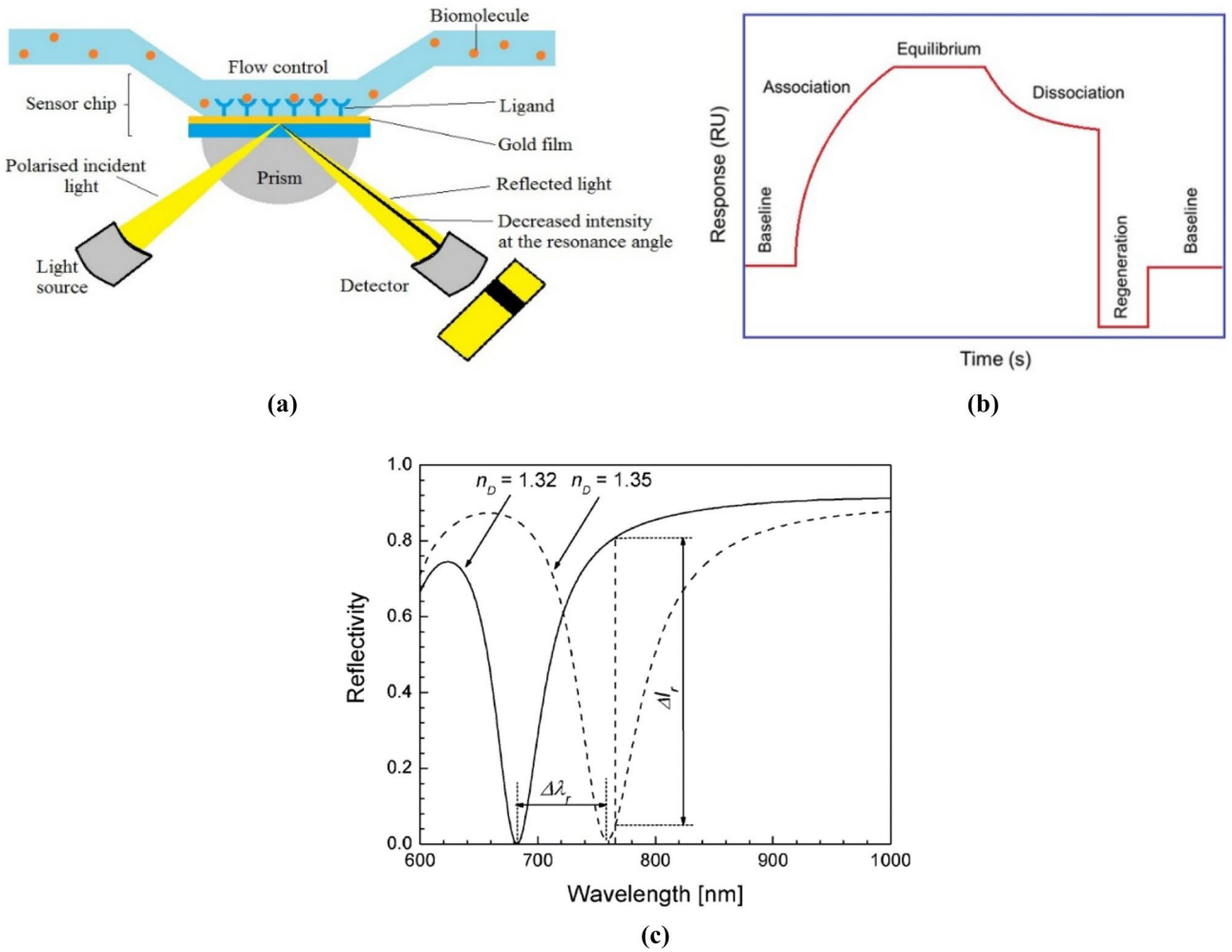

Fig. 5 **a** Schematic showing SPR chip's principle, **b** Sensorgram's analytical cycle steps [10], and **c** reflectance spectra using wavelength interrogation for RI of 1.32 and 1.35 inside sensing medium [31]

produce resonance oscillating electrons or surface plasmons, and these are quite sensible to the metal surface's environment [29]. Resonance angle is a particular angle, where the metal's electrons absorb the light and produces a minimum intensity at the output (detector). These electrons are also known as surface plasmons. These biosensors are highly sensitive, possessing extreme intensity at the surface, with their value decaying exponentially perpendicular to the metal and dielectric interface. Figure 5a represents a typical SPR experimental system. Here, the analyte and ligand interact while the ligand is fixed on the gold film's surface [10].

The response is documented in Fig. 5b which is called as sensorgram; these are then subjected to or compared with (fitted), which provides SPR analysis. The reflection intensity curve in the cell area closer to the material substrate experiences a drop due to SPR. This dark band in the reflected beam, which is an intensity loss, reveals information about the sensor surface. The association and dissociation phase in the sensorgram indicates the time when the binding between analyte and immobilized ligands is present and absent, respectively [30]. The equilibrium phase is attained when analytes almost fully occupy all the ligands. For detaching this binding, a regeneration buffer solution is passed through the inlet of a flow cell, which allows the reuse of the sensor surface. Using wavelength interrogation in SPR sensors, the component of the evanescent wave vector and surface plasmon wave (SPW) is computed by the coupling strength at a constant incident angle and different wavelengths giving the strongest coupling. Figure 5c gives the reflectance plots for two RIs of 1.32 and 1.35 using wavelength interrogation.

Some previous literature that demonstrated prism-based SPR sensors, like Sun et al., examined an SPR biosensor with multiple layers (BK7-Ag-$BaTiO_3$-graphene-analyte). They attained the highest angular sensitivity of 257°/RIU [32]. Shushama et al. analyzed an SPR biosensor having a hybrid structure containing layers of Si/MoS_2/graphene/analyte above the BK7 prism. It shows maximum sensitivity of 210°/RIU [33]. Wu et al. designed an SPR biosensor with a BK7 prism, black phosphorus, and dual layers of WSe_2, and the sensitivity enhances to 279°/RIU [34].

Applications

SPR is a highly popular optical detection technique for label-free, real-time biomolecular interactions in applications such as chemical vapor detection, environmental and food safety, life science, and electrochemistry. Due to their simplicity, SPR instruments are widely used. Some examples of applications are listed below [24, 35]:

- To investigate interactions between unbound analyte molecules and solution in terms of molecular bonding
- To examine molecules immobilized on or attached to the sensor surface
- Research—Biological Sciences and Pharmaceutical drug development
- Concentration analysis of any analyte—subject to the condition of availability of a specific ligand that can be immobilized on the sensor
- Food monitoring for rapid screening

Limitations

- Unable to distinguish between particular and non-specific binding interactions at the sensor's surface. For instance, even thorough washing cannot eliminate the non-specifically bonded substance. That is why some control samples are required to overcome this problem.
- The SPR biosensor can detect high molecular weight molecules as being mass sensitive; however, it cannot detect low molecular weight chemicals.

The widths and RI of different materials used in SPR biosensors are shown in Table 1.

SPR Imaging (SPRi)

SPRi is an advanced system that takes the process of SPR ahead. It combines the sensitivity of SPR with an image-capturing system in a microarray configuration which is

Table 1 Width and refractive index (RI) of the materials (at 632.8 nm) [36]

Layer sequence	Materials	Width	RI
1st (prism layer)	BK_7		1.5151
	CaF_2	–	1.4329
	SF_6		1.799
	SiO_2		1.4607
2nd (adhesion layer)	Chromium	2 nm	3.135 + 3.310i
	Cytop	3 nm	1.34
3rd (metal layer)	Au	45 nm	0.1378 + 3.6196i
	Ag	45 nm	0.0803 + 4.2347i
4th and 5th (2D-TMDC material layer)	Graphene	L × 0.34	3.0 + 1.1491i
	BP	L × 0.53	3.5 + 0.01i
	MXene	L × 0.993	2.38 + 1.33i
	$PtSe_2$	L × 0.375 (all for monolayer) Here, L is number of layers	2.9029 + 0.8905i
6th (sensing layer)	Analyte	–	1.33 + Δ*n*; Δ*n* is the RI alteration

beneficial for the simultaneous study of numerous interactions [37]. SPRi devices typically use the Kretschman configuration, which involves a plane-polarized light at a fixed angle and a charge-coupled device (CCD) camera for detecting the reflected light. This setup allows for the real-time observation of the entire biochip. Suppose the sensor surface is divided into various sensing spots. In that case, a multi-array format can monitor hundreds of bioreceptor/target bindings in parallel, with a digital image representing the intensity of the binding in a color scale. For various affinity systems, many SPRi has been reported, like DNA–DNA by Hayashi et al. [38] and Lecaruyer et al. [39], RNA–DNA by Yu et al. [40], and antibody–antigen by Rebe Raz et al. [41] and Yuk et al. [42].

The three main components of SPRi biosensors are the following: optics that illuminates a gold metal film, a camera detector usually a charge-coupled device (CCD) used to capture images and record changes in reflectance, and a high RI glass prism. Figure 6 shows the set up for SPR imaging.

Case 1: in the absence of biomolecules the maximum resonance of surface plasmons is achieved by exposing the sensor chip to the laser beam at a certain angle.
Case 2: in the presence of biomolecules, a shift is observed in the resonance angle (a higher degree shift), causing an increase in the intensity of reflected light at a certain angle. According to the change in the mass of the biomolecules, a further shift in the resonance angle takes place [43].

Applications

- SPRi can achieve a great future in chemical and medical fields for restorative targets and biomarkers screening as they are sensitive, high-performing devices that provide spaciously clear and resolved images of bio interactions.

Magneto-Optical–Surface Plasmon Resonance (MO–SPR)

The SPR sensing techniques are the currently popular methods for detecting interactions at interfaces as they are sensitive to the refractive index changes in the sensing medium. There is an unmet requirement for enhancement in the sensitivity of the existing SPR assays. This sensitivity increase is needed by introducing the magneto-optical–SPR (MO–SPR) technique. This method uses the transverse magneto-optic Kerr effect (TMOKE). This effect arises as a product of employing a magnetic field perpendicular to the propagation plane of the incident p-polarized light and in the plane of a layer with magnetic and optical features defining fluctuations in the intensity of the reflected light. When TMOKE gets united with plasmonic effects, novel detection configurations based on SPR are founded, giving rise to the MO–SPR technique. With refractive index alterations, the sensitivity improves in the order of one or even two [44].

Figure 7 gives an example of the MO–SPR concept; the measurement setup consists of an SPR module, applying electromagnet (externally) to generate the variable magnetic field.

Applications

- To assess bio-affinity interactions at interfaces, like the minimum resolvable RI changes for the SPREETA sensor.
- The modulation of the reflectivity (i.e., SPR) curve is obtained.

Limitations

MO–SPR chip fabrication technique contains some important drawbacks involving the following:

- Metallic multilayers or nanostructures (e.g., nano discs, nanocrystals) [44, 45]
- The intrinsic magneto strictive effect [46]. This effect changes the shape or dimensions of ferromagnetic materials during magnetization.
- Stability is also a concern when these chips come in contact with liquid saline samples [47, 48].

Magneto-plasmonic properties are improved by optimizing the structure using a thin layer of amorphous Au–Co alloy, covered by an Au layer forming a multilayered chip. A recent study [44] has established that this structure is also efficient in (saline) liquid media. This modified structure in

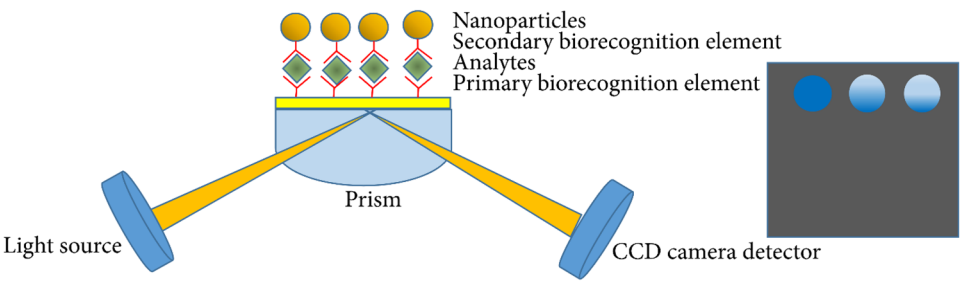

Fig. 6 Experimental setup for SPR imaging [43]

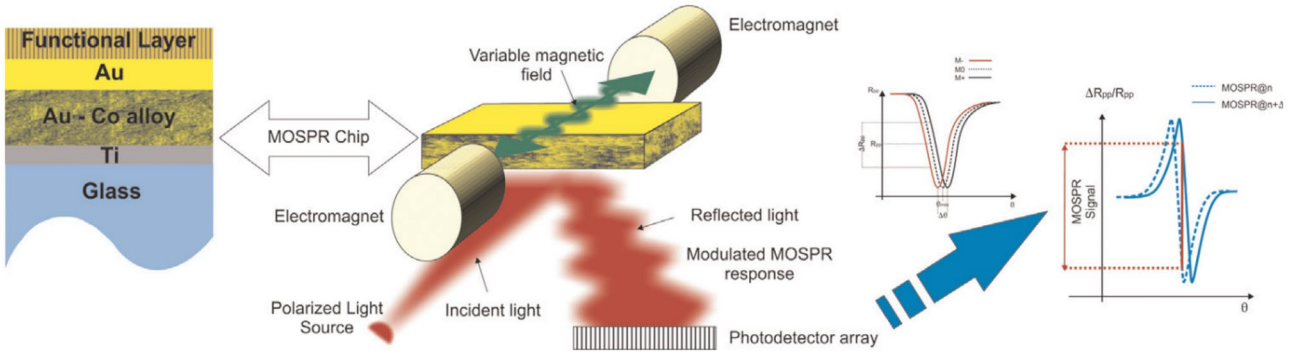

Fig. 7 Principle of MOSPR in the Kretschmann configuration [44]

an angle resolved MOSPR bioassay (ARMOSPR). Unlike most available SPR/ MOSPR setups where the reflectivity at a fixed incidence angle is used, ARMOSPR permits the assessment of the reflectivity curve in a broader angular range. This structure offers increased sensitivity and higher stability (comparable to the ones accomplished with other alternatives) for saline samples. The impact of MO-SPR on the biosensor's performance enhancement has been reported in some literatures [49–51].

Colorimetric Polymerase Chain Reaction (c-PCR)–Based Biosensor

Detection of specific DNA sequence is gaining popularity from researchers interested in clinical diagnosis, food analysis, pathology, etc. PCR is one such commonly used technique. In this, nearly from all DNA-based assays, a specific sequence could be amplified.

Colorimetric PCR–based biosensor is based on c-PCR technique with DNAzyme-containing probe. This technique is used to detect viral load quantitation of hepatitis B virus (HBV) DNA in nucleic acid assays. G-rich sequences built with tetrads of hydrogen-bonded guanine bases, formulate higher-order DNA and RNA structures known as G-quadruplexes. The DNAzyme used by Yang et al. [52] has been reported to show peroxidase-like behavior, G-quadruplex and bind with hemin that catalyzes the oxidation of different substrates by H_2O_2 to generate either fluorometric or colorimetric signals.

This method offers high sensitivity and has a broad range of linearity in addition to retaining key benefits of the TaqMan method. The TaqMan is one of the most common techniques used for this purpose [53]. The TaqMan method is limited due to high-cost, modified flurogenic oligonucleotide probes, and sophisticated equipment, which restrict this accepted technique not only to well-equipped laboratories but the accessibility of the mases [54, 55]. Cheng et.al. designed a novel HRPzyme–relied catalytic colorimetric method for the quick and simple detection of *V. parahaemolyticus* [56].

Applications

- To detect viral load quantitation of hepatitis B virus (HBV) DNA
- Using this DNAzyme, a variety of chemiluminescent assays have been designed.

Limitations

- High cost
- Complex equipment

Evanescent Wave Fluorescence (EWF) Biosensors

In EWF biosensors, the biological recognition, as well as the manifestation of consequent binding event(s), happens within the boundaries as defined by that of an evanescent wave (EW). The EW is a near-surface phenomenon, and detection based on EW excitation to generate the fluorescent signal is sensitive to surface, that is, only fluorescent molecules close to the surface are excited (as shown in Fig. 8), which helps to reduce background signals arising from bulk samples [57]. Many works based on the fluorescence biosensors exist in the literature, such as for the detection of biomolecules, a cheaper, label-free color indicating liquid has been proposed [58]. For fast analysis of *Salmonella* infections, immunosensors with photoluminescence properties have been proposed [59]. Another fluorescent biosensor for detecting copper ions uses pyoverdine as a basic recognition element [60].

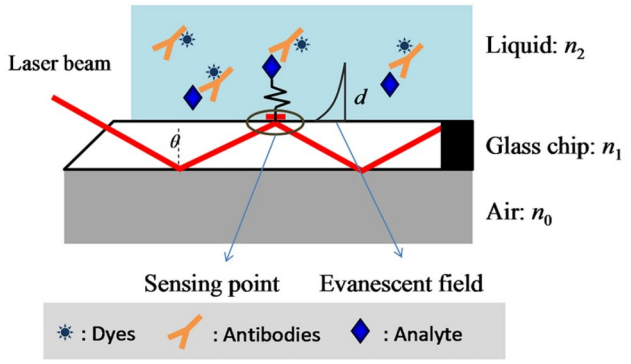

Fig. 8 Schematic diagram of an EW planar optical waveguide chip [43]

Applications

- There is a huge variety of biosensors for clinical diagnostics, biodefence, food testing, etc. which are based on this principle [57].
- It is anticipated that these sensors are set to have a major impact on the healthcare-related sector as well.
- The EW aptamer relied on a fluorescence biosensor for quick, sensitive, and highly selective detection of 17 β estradiol, an endocrine-disrupting chemical frequently found in environmental water samples. This portable biosensor system offers a detection limit of 2.1 nM [61].
- An excellent specificity was demonstrated by assessing the performance of this platform using up to 200 clinical samples. The subjects comprised healthy as well as individuals who tested positive for HIV, syphilis, and hepatitis C [62].
- To minimize background noise signal while only the signal from fluorophores captured is enhanced on the surface.

Limitations

- The complex background of this biosensor gives rise to interference.
- It is not applicable for the detection of small biomolecules or low-weighted biomolecules.

Ellipsometric Biosensors

These biosensor computes change in the polarization of light reflected off a surface. It provides a label-free, accurate, and real-time operation. It is a sensitive and cost-effective biosensor.

The setup of this biosensor mainly focused on two benchmarks: (1) the incident angle of the light beam should be 69° to enter the biolayer. (2) Sensitivity of the system should be able to quantify parameters like Δ (near 180°) and φ (near 0°) [63].

Figure 9a shows the construction of an ellipsometric biosensor that consists of an apparatus that quantify the parameters of the ellipsometric and a sensor cell. A coupled prism, which is semi-cylindrical in nature, is introduced into the system so that the incident angle of the light beam should not exceed the critical angle of the interface. The probe solution is inserted from the inlet, as shown in Fig. 9a, after which the biorecognition element in the Si wafer substrate interacts with the target analysts. At last, the unwanted substances are disposed as waste from the outlet. Figure 9b shows the LOD of Human IgG. The bio interaction process takes place when human IgG (15 to 1000 ng/mL) in PBS flows over the sensor cell. Various types of researches claim that these biosensors are best known for surface studying and finding the biolayer, and different strategies, like spectroscopic and imaging ellipsometry, are employed for sensing-based applications [64–66]. Rafique et al. proposed an ellipsometric relied biosensor for the real-time analysis of the Bordetella parapertussis [67].

Applications

- This biosensor is applicable for the detection of inf luenzaAvirus strains [68].

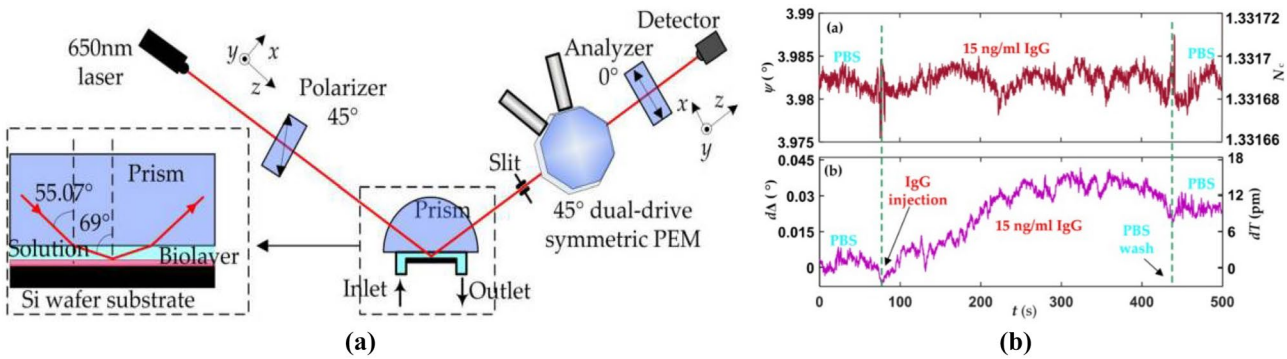

Fig. 9 **a** Schematic diagram of Ellipsometric and biosensor. **b** Limit of detection (LOD) of human IgG, (a)Ψ and (b)Δ signals [63]

- Microarray biosensor is based on ATR and has an approximate detection limit of CA19 − 9 of 18.2units · ml^{-1}, lower than the normal level's cut-off value.
- Detection of the serum tumor biomarker using this biosensor is done.
- The apparent equilibrium dissociation constants (avidity constant, 10 to 100 pM) are used as characterized parameters of viral receptor profiles.

Optical Waveguide Interferometric (OWI) Biosensors

The evanescent field sensing and optical phase difference measurement combination pave way for an integrated planar OWI biosensor which is also known as resonant waveguide grating (RWG).

In a grating sensor area probing the near-surface region with the evanescent field, the probed volume from any change in the RI generates a guided mode phase shift compared with a reference field (normally the propagating mode through the reference arm). An interference signal, produced by the interfering fields, is detected at the output of the sensor; this variation is proportional to the variation observed in RI, and the signal is related to the concentration of the analyte [69]. This biosensor requires a little number of samples to measure binding interactions in free solution. It always sustains a straightforward format and is less expensive as compared to other optical biosensors.

Earlier works used singlemode-no core-singlemode fiber coupler (SNSFC) structure relied biosensors for the detection of the *Staphylococcus aureus* with a limit of detection of 3.1 CFU/mL [70]. The instrumentation for detecting *S. aureus* using the developed fiber sensor is schematically shown in Fig. 10a. One of the input SMFs is connected to a broadband source of light (BBS), and an optical spectrum analyzer (OSA) is employed to determine the spectral response of the tapered SNSFC sensor. Whereas in Fig. 10b, dipping the optical fiber sensor within *S. aureus* solution (concentration = 70 CFU/mL), the spectral responses are being plotted down for different durations from 0 to 30 min.

Applications

- This biosensor is applicable for analyzing cellular processes and responses [71].
- Redistribution of cellular contents can be detected using this technique.
- This RWG method is very helpful in detecting the avian inf luenza virus [72].

Limitations

- Easily get affected by environmental issues like variation in atmospheric temperature, ambient vibration, climatic changes, etc.

Surface-Enhanced Raman Scattering (SERS) Biosensors

Surface-enhanced Raman spectroscopy (SERS) is a sensing technique that uses an intense optical field to enhance the Raman scattering of molecules adsorbed on the surface of a nanostructured metal like Au or Ag. The high optical field intensity allows detecting even trace amounts of analyte molecules, making SERS a powerful tool for biosensing. Previously Liu et al. proposed a long-range SPR (LRSPR) configuration with MgF_2 as the dielectric buffer layer for SERS detection (Fig. 11a). The SERS enhancement factor with the symmetric LRSPR configuration was as high as 8.6×10^7 [73]. Figure 11b gives the LRSPR curves at various RIs of the sensing media ($RI = 1.33$ to 1.40).

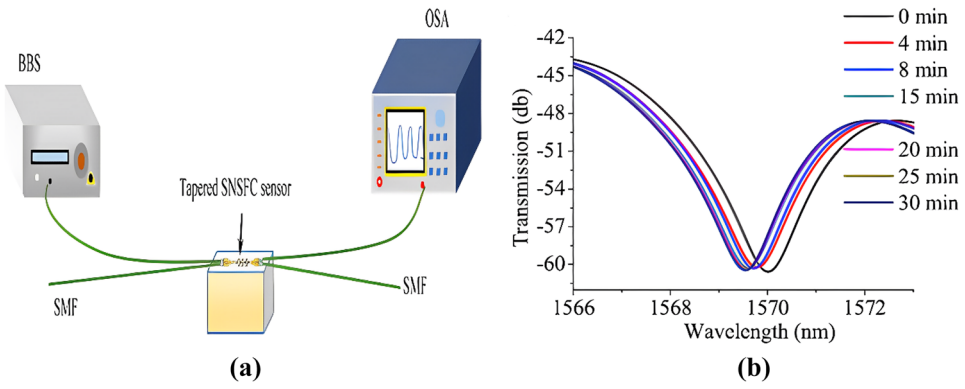

Fig. 10 **a** Experimental setup of the tapered SNSFC (optical fiber) and **b** transmission (dB) as a function of wavelength (nm) for the detection of *S. aureus* at various durations [70]

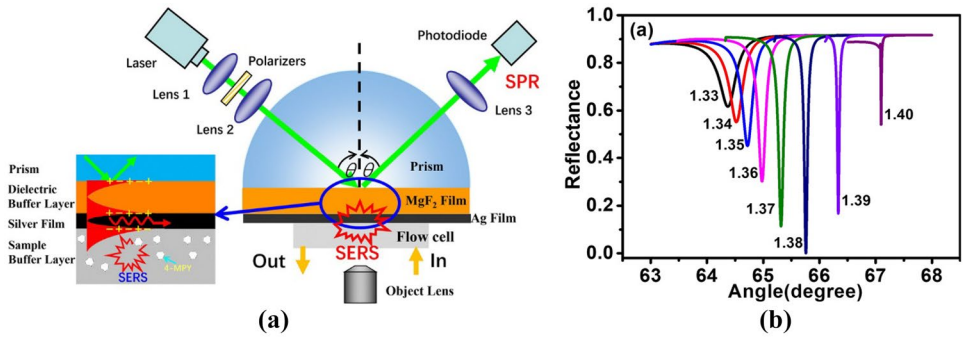

Fig. 11 SERS detection using LRSPR sensor **a** schematic and **b** different RI effects over LRSPR curves [73]

When polarization is induced in a molecule using an incident light (electro-magnetic), this effect is said to be the Raman effect. This polarization is linked to the magnitude of the incident electric field. In SERS, nano-roughened metallic substrate surface or nanoparticles made of Au or Ag in close proximity substrate surface are used because of the nanoscale optical properties offered by the substrate amplification of the order of 10–1000 takes place in this field (E) [74]. Some other works demonstrated SERS relied biosensors for the detection of hepatitis B [75], respiratory syncytial [76], rift valley fever virus [77], etc.

Applications

- To detect cancer proteins (∼ 100 pg), active surface SERS are fabricated on the tip of optical fibers. This is applied to the sensitive detection of a low sample volume (∼ 10 nl) [78].
- To improve the accuracy of detection as well as detection speed of a protein biomarker of endocrine-disrupting compounds in aquatic surroundings, SERS biosensor is commonly used with a detection limit of 5 $pgml^{-1}$ [79].

Photonic Crystal Fiber Sensor

In the optoelectronics field, many researchers have come up with potential applications of photonic crystals in biosensors [80]. In a photonic crystal fiber (PCF) sensor, minuscule air holes are positioned appropriately across the fiber's cross-section and length. The optical characteristics in a PCF can be modified by designing a suitable air hole pattern to achieve the desired value by altering the number, hole pitch, diameter, and ring air hole.

Figure 12 shows a cross-sectional view of the PCF RI sensor. The cladding part of the fiber has four air hole rings which help to polarize the light to the core part of the fiber. The air hole ring sensing is done by the solid core. They do the interaction between the evanescent field and analytes. It further increases the effective area, which results in greater sensitivity. Using single-mode fiber (SMF) and

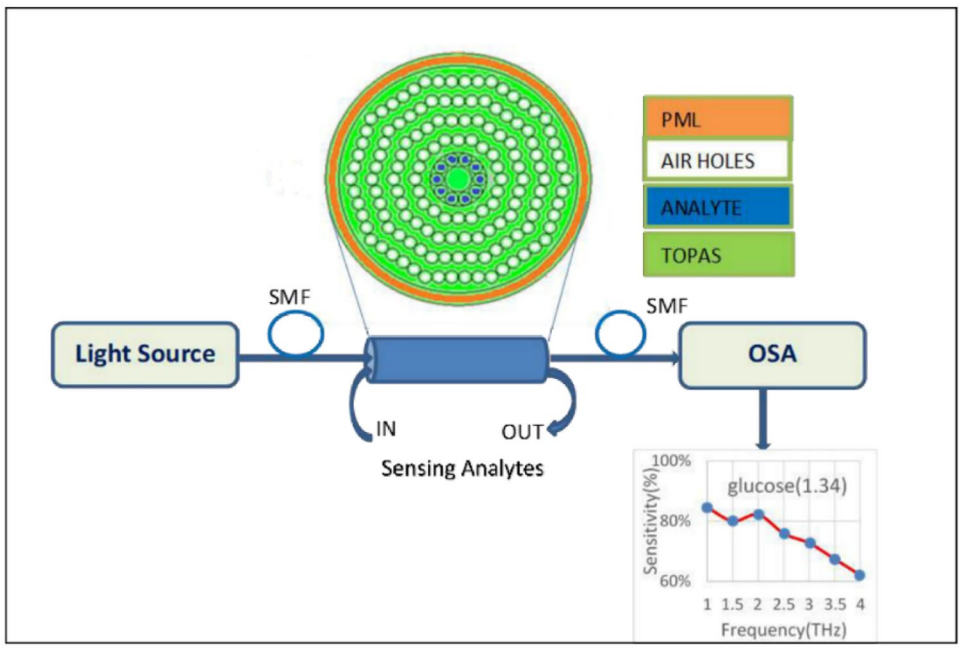

Fig. 12 Schematic of a PCF-based refractive index sensor [81]

Table 2 Label and label-free optical biosensor list with applications

Biosensor	Label free	Applications in different areas	Ref
SPR	Yes	Kinetic investigation of bio interactions Antigens detection in clinical samples Detection of proteins in biological samples Xenobiotics and pollutants in food	[14, 83, 84]
Magneto-optical–SPR	Yes	Allow bio affinity assays in saline solution Detection of minute analyte concentrations	[49]
Novel colorimetric PCR		Detect and monitor HBV infection Assess therapeutic response	[52]
EWFO	No	Corona discharge Radiofrequency interference Shock/vibrations and Harmonic induction	[23]
Integrating waveguide	–	Detection of pathogen Detection of bacterial cells Rapid and sensitive detection of spores and toxins	[85]

couplers, the input wave is launched into the PCF. The RI change in the sensing medium modulates the light intensity. The optical spectrum analyzer (OSA) analyzes this modulated light. This output of OSA is connected to a system where performance parameters are computed. Kumar et al. proposed a photonic crystal fiber sensor giving the highest sensitivity of 87.68% with low confinement loss of 1.4×10^{-9} dB/m with an effective area of 1.86×10^{5} μm^2 for blood cell detection [81]. Shuvo Sen et al. (2020) designed a TOPAS background material base PCF biosensor and

Table 3 Application based use of optical biosensors

Application	Aim/challenges	Biosensors used	Most preferred biosensor	Reason why?
Food analysis	Contaminants in food (biological toxins, allergens, pesticide and antibiotic residues, pathogenic microbes) Nutritional value of food products Timeliness and costs Losses take place during sample preparation	SPR SPRi LSPR Magneto optical SPR Integrated waveguide Planer waveguide for fluorescence EW fluorescence RIFS	EW fluorescence	With the detection limit of 2.1nM, EW fluorescence biosensor is a preferred choice over other options
Agriculture	Analyze the pollutants in crops and soils. Find and classify infectious diseases in crops	SPR SPRi LSPR Magneto optical SPR Integrating waveguide EW fluorescence RIFS	Magneto Optical SPR	With improved magneto-plasmonic properties, this biosensor proves itself as a powerful substitute as compared to SPR biosensors
Cancer detection	Diagnosis of generic symptoms Rapid detection of viruses Timeliness Highly sensitive biosensor is required	SPRi LSPR Magneto optical SPR Integrating waveguide EW fluorescence Bioluminescent optical fiber SERS	LSPR	The LSPR biosensor is an effective alternative as compared to other immunoassay techniques
Tumor detection	Rapid detection of viruses Diagnosis of generic symptoms Timeliness Sensitivity of biosensor	SPRi EW fluorescence Ellipsometric RIFS	RIFS	RIFS can detect circulating tumor cells within a range of $1000-100000$cells.ml^{-1} with a detection limit of 1000cells.ml^{-1}
Pathogen Detection	Sample preparation Matrix effects System integration Accuracy Timeliness and cost	Novel colorimetric PCR Integrated waveguide Planar waveguide EW fluorescence Bioluminescent optical fiber Optical waveguide interferometric	Planar waveguide	Planar waveguide Biosensors offer better sensitivity over other options due to the high field intensity at the surface

Table 4 Detection limit and range for optical biosensor for various applications

Applications	Biosensors	Detection limit	Range	Ref
Mycotoxin patulin	Immuno-chemical SPR	0.1 nM	0–80 nM	[86]
As (III)	SPR	1.0 nM	1 nM–1μnM	[5]
Soluble vascular endothelial growth factor receptor	SPR	25 $\mu g.L^{-1}$	25–500 ng/mL	[87]
Bisphenol A	SPR immunosensor	0.03 $\mu g.L^{-1}$	0.124–9.60 mg L^{-1}	[88]
HER-2	SPR	15 $ng.mL^{-1}$	-	[35]
CA 12–5	SPR	0.01 $U.mL^{-1}$	0.1 – 35 $U.mL^{-1}$	[89]
CA 15–3	SPR	0.025 $U.mL^{-1}$	1 – 40 $U.mL^{-1}$	[90]
CA 27.29	SPR	38 $U.mL^{-1}$	-	[91]
Human IgG	SPR	< 0.5 ng.cm2	0.5 – 5 μM	[92]
FK506-binding protein 12 (FKBP12)	SPRi	0.5 nM	0 – 22 nM(concentration)	[37]
C-reactive protein	LSPR	100 $pg.mL^{-1}$	Up to 1 $\mu g.mL^{-1}$	[93]
HE4	LSPR	4 pM	10 – 10000 pM	[94]
HIV-1	LSPR	200 $fg.mL^{-1}$	200 – 125 $pg.mL^{-1}$	[95]
Mouse IgG	Integrated waveguide	40 $pg.mL^{-1}$	40 – 300 $pg.mL^{-1}$	[85]
Staphylococcal enterotoxin B (SEB)	Integrated waveguide	30 $pg.mL^{-1}$	30 – 400 $pg.mL^{-1}$	[85]
Salmonella	Integrated waveguide	10 captured *Salmonella* cells (23.4 mV)	-	[96]
17**β-** oestradiol	Evanescent wave fluorescence	2.1 nM(0.6 $ng.mL^{-1}$)	0.2 – 3 $mg.L^{-1}$	[61]
Horse IgG	Fluorescence	0.71 $mg.mL^{-1}$	1 – 80 $ug.mL^{-1}$	[8]
Genotoxin	Bioluminescent optical fiber	10 $pg.L^{-1}$	0.7 – 0.8	[97]
Influenza A virus	Ellipsometric		10 – 100 pM	[68]
CA19-9	Ellipsometric	18.2 $units.mL^{-1}$	6.64 - 1020.51 U/mL	[98]
AFP^7	Ellipsometric	5 $ng.mL^{-1}$	20 - 200 ng/mL	[99]
Endocrine-disrupting compounds	Surface-enhanced Raman scattering (SERS)	5 $pg.mL^{-1}$	~3 nM	[79]
Diclofenac in bovine milk	Reflectometric interference spectroscopy	0.112 $\mu g.L^{-1}$	0.438-6.218 $\mu g.\ L^{-1}$	[100]
Tumor cells	Reflectometric interference spectroscopy	< 1000 $cells.mL^{-1}$	1000 – 100000 $cells.mL^{-1}$	[101]

achieved confinement loss of 5.84×10^{-8} dB/m and a maximum sensitivity of 82.26% [82].

Applications

In physical sensors, these sensors can detect temperature, pressure, displacement, curvature, RI vibration, torsion, and electric field. These parameters' measurement, monitoring, and control are of great interest for many applications.

Table 2 provides a list of various optical biosensors in use today depicting their applications as well as indicating label and label-free status of the biosensor.

Table 3 lists application-based classification for various optical biosensors used. It also provides the most favored biosensor with the reason for the same.

Table 4 provides a comprehensive list of detection limits and ranges for optical biosensors for various applications.

Conclusions

Medical, environmental, public security, and food safety are the major domains where biosensors are applied. Utilizing optical biosensors can largely enhance the probability of early detection, and attendant improved prognosis and may also pave the way for the facilitation of disease screening. Biosensors are most importantly required to grow in the field of biomedical, healthcare, and biopharmaceutical sectors. Newer and better miniaturized analytical tools can be obtained through these biosensors. Many sensitivity enhancement techniques are developed for biosensors that can improve the signal-to-noise ratio. There are many properties of biosensors, like robustness, reproductively, simplicity, and shelf life, which should be kept in mind while developing new biosensors for practical applications. Out of the available biodetection methods, optical biosensors have numerous advantages, especially in

terms of increased flexibility as well as assay speed. The high speed of detection becomes an advantage in any application. Optical biosensors have the ability to provide instantaneous interactive information by performing real-time analysis for their users. Optical biosensors are not only limited to medical and environmental domains but also find vast applications in civil, military, automation, public safety, reduced costs of testing, non-invasive testing, and food safety. The factors that determine which SPR model is promising can be considered as two factors: ease of fabrication and high sensitivity.

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Declarations

Competing Interests The authors declare no competing interests.

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