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## Recent Progress in Fiber Optic Biosensors: Applications

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### ABSTRACT

Fiber-optic biosensors will play a significant role in the development of biosensors because they can be easily miniaturized and integrated for the determination of different target compounds in a wide variety of application fields, such as industrial process and environmental monitoring, food processing, and clinical applications. Important developments can be seen in the field of optical fibre biosensors in the last years. More sensors for specific analytes have been reported, novel sensing chemistries or transduction principles have been introduced, and applications in various analytical fields have been realised. In general, biosensors are attractive because they can be easily used by non-specialist personnel and they allow accurate determination with either no or minimal sample treatment. Therefore, fiber optic biosensors may be especially useful in routine tests, patient home care, surgery and intensive care, as well as emergency situations. In this work, the analytical applications of fiber optic biosensors produced in the last years (since 2007) are reviewed.

**Keywords:** fiber optic biosensors; applications; review

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## INTRODUCTION

A biosensor is a self-contained, bionic, integrated device that includes a biorecognition element that can respond in a concentration-dependent manner to a biochemical species. Biosensors make use of biological components in order to sense a species of interest (which by itself need not be a "biospecies"). On the other side, chemical sensors not using a biological component but placed in a biological matrix are not biosensors by definition. The characteristic biosensor structure integrates: a bio recognition component, immobilized to an interface surface of a transduction element. The biological recognition elements of a biosensor interact selectively with the target analyte, assuring the selectivity of the sensors.

The signal transducer is the last essential component of a biosensor. It converts the recognition event into a measurable signal. The transducer will take many forms depending on the parameters being measured. The major transducer groups are electrochemical, acoustic, piezoelectric, optical, mass sensitive and thermal.

Optical techniques offer certain advantages in that they are simple and flexible and allow for multichannel and remote sensing. On the other hand, fiber optics serves analytical sciences in several ways. First, they enable optical spectroscopy to be performed on sites inaccessible to conventional spectroscopy, over large distances, or even on several spots along the fiber. Second, fiber optics, in being waveguides, enables less common methods of interrogation, in particular evanescent wave spectroscopy. Fibers are available now with transmissions over a wide spectral range.

Fiber-optic biosensors (FOBS) use optical fibers as the transduction element, and rely exclusively on optical transduction mechanisms for detecting target biomolecules. FOBS play a significant role in the development of biosensors because they can provide miniaturized and low cost systems. FOBS have been widely investigated because of their potential sensitivity, fast detection, biocompatibility and adaptability to a wide variety of assay conditions.

Over the last 30 years, there has been substantial development of fiber optic sensors and biosensors for many applications. Principles, advantages and applications of the fiber optic sensors and biosensors have been reviewed in diverse works published some years ago [1-5].

FOBS are diagnostic tools with specialized features that may be utilized in a variety of fields (medical, pharmaceutical, environmental, defence, bioprocessing or food). The fiber optic device serves as the transduction element and the transmitted signal is often proportional to the concentration of a chemical or biochemical to which the biological element. Therefore it may be used in a variety of spectroscopic techniques, such as chemiluminescence, absorption, fluorescence, phosphorescence or surface plasmon resonance (SPR) and the technology continues to evolve with new breakthroughs in optics, biochemistry, and chemical engineering.

In this review article, recent progresses in the field of fiber optic biosensors have been summarized.

## Absorbance Measurements

Pallotta et al. [6] developed a biosensor system based on the different absorbance of blue light exhibited by bile and pancreatic juice to predict the location of the sensor tip in relation to the bile and pancreatic ducts. This biosensor system incorporates fiber optic technology to measure blue light absorbance in the ducts.

Fiber based infrared sensing has been established as an efficient, non-destructive and highly selective technique for the detection of organic and biological species.

A fiber evanescent wave spectroscopy system using chalcogenide fibers was used by Lucas et al. to study the infrared absorption spectra of live cells as well as solutions of organic species [7]. It was demonstrated that chalcogenide glass fibers have a hydrophobic surface behaviour, which result in signal enhancement of up to 60% for non-polar species relative to water. The spectral enhancement shows a linear dependence on the polarity of the species in solution. This behaviour can be utilized to improve the detection signal of live cells used for optic biosensors since the cell membrane has a fairly low dielectric constant. The optic biosensor is designed to spectroscopically detect the cell response to various toxic agents. It is shown that the cells display distinct spectral responses when exposed to different type of toxicants such as genotoxic agents or cytotoxic agents. First the authors present how the hydrophobic behaviour of chalcogenide glass affects the spectroscopic properties of chalcogenide fibers and then present initial results on the variation of cell spectra in response to various toxic agents. This study emphasizes the potentials of chalcogenide fibers for the design of cell based optic biosensors.

Crespi et al. developed a near-infrared continuous wave spectroscopy instrument (based on the low extinction coefficient of tissue in the near-infrared region) that allows *in vivo*, real time non-invasive NIRS measurements in rat brain [8]. Optic fiber probes were used by the authors as the optical head of a novel, highly sensitive near-infrared continuous wave spectroscopy (CW-NIR) instrument. This prototype was designed for non-invasive analysis of the two main forms of haemoglobin: oxy-haemoglobin and deoxy-haemoglobin, chromophores present in biological tissues.

Sai et al. investigated the feasibility of developing an evanescent wave absorbance (EWA) based fiber optic biosensor by exploiting the absorbance properties of analytes in UV region [9]. Several analytes of interest such as bacteria, virus and some of the clinically important proteins and marker molecules absorb light in the UV region. In this study, the authors investigated the possibility to develop a label-free fiber optic biosensor based on EWA at 280 nm to detect the presence of such analytes. Advantages of the EWA based fiber optic biosensors include promising sensitivity, low interference of visible light in sensing in addition to simple immobilization chemistry. The fiber optic probes are cost-effective, easy to fabricate and use. Later, the same investigation group presents a novel label-free technique for the detection of pathogens based on EWA changes at 280 nm from a U-bent optical fiber sensor [10]. Owing to the cost-effectiveness and ease of fabrication, the proposed probe and sensor

design could be the best choice for the development of a portable device for pathogen detection in resource-poor conditions.

### **Reflectance Measurements**

A portable biochemical detection device based on optic fiber sensor is studied by Weiwei et al. [11] and multiple biochemical parameters can be tested in situ with this system. In this device, a light emission diode (LED) was used as light source and an optic fibre sensor was adopted. LED is small and good at monochromaticity, so it is suitable to be used in portable optic detection system as light source. The optic fibre sensor was designed in the shape of “YY” type to detect sample and monitor the status of the system at the same time in order to improve the stability of the system. As an example, the concentration of Hb in whole blood was detected with the system.

A double crossover thin film coated fiber optic reflectance biosensor (DTF FORS) was developed by Amin et al. using the Drop and Dry technique to form a thin film on the optical fiber end face to detect or sense streptavidin aerosols [12]. Standard aerosol measurement techniques of the differential mobility analyzer and the condensation particle counter were also implemented to measure the streptavidin aerosols generated using an atomizer. The reflectance intensity from the DTF changes upon its interaction with streptavidin aerosols because of their different refractive indices. The DTF FORS gave a rational and good response against any changes in the streptavidin aerosol concentration with excellent repeatability.

### **Fluorescence Measurements**

Thompson et al. [13] summarize the construction principles, operation, and calibration of fluorescence-based fiber optic biosensors. These sensors detect a chemical analyte by a transducer such as a protein molecule as a change in fluorescence wavelength or lifetime that can be measured remotely through of fiber optic.

Fluorophores have been used as effective signal mediators for detecting biomarkers in biosamples. The effects of thenanogold particle (NGP) size, the distance between an NGP and a fluorophore, the quantum yield (QY) of a fluorophore, and the solvent on fluorescence intensity are reported by Hong and Kang [14]. The fluorescence intensity affected by the mixture of the NGP and the solvent (nanogold particle reagent; NGPR) is also presented by the authors. The effect of these NGPRs on the sensitivity of cardiac marker biosensors is also demonstrated. They verified that the fluorescence can be enhanced by well-designed NGP–SAMs (self-assembled monolayer), possibly by reducing self-quenching of fluorescence via the strong surface plasmon polariton field on the surface of a nanogold particle. This enhancement appears to be dependent on the NGP size, the distance between a fluorophore and an NGP, and the QY of a fluorophore. Some organic solvents also enhance the fluorescence significantly. Ethanol was proven to be an optimal, biocompatible fluorescence enhancer without affecting the reusability of biosensors.

The influences of the near fields and scattering properties of the metallic nanoparticle on the fluorescence enhancement of the localized surface plasmon of gold nanoparticles coupled fluorescence (LSPCF) biosensor are discussed Ng and Liu [15]. The strong local field around metallic nanoparticles enhances the field intensity of the fluorophore, meanwhile the far-field detected signals of fluorophores is also enhanced by large scattering cross section of the nanoparticles. The fluorescence enhancement of the LSPCF biosensor is closely related to radius of gold nanoparticles, fluorophore-particle separation, and fiber-particle separation. This theoretical study provides a practical way to estimate the performance of the LSPCF biosensor system and the understanding of the mechanism of the fluorescence enhancement can help to develop high performance biosensing system.

Su et al. [16] proposed a method to meet the requirement of ultralow concentrations under conditions of reaction-limited kinetics. The authors performed an experimental demonstration on protein-protein binding kinetics at the pg/mL level with a sandwich immunoassay, using a LSPCF-FOB. The analytic model is based on a two-compartment model, with proper concentrations of the LSPCF probe and the target antigen in a stagnant system, to satisfy the condition of reaction limited kinetics.

Fluorescence sensing has become one of the dominant sensing technologies in medical diagnostics and biotechnology. The detection of a fluorophore is usually limited by its quantum yield, auto-fluorescence of the samples and the photo-stability of the fluorophores. Recently, there have been explosive developments in the Metal-Enhanced Fluorescence (MEF) technology. The presence of nearby metallic nanostructures can alter the free-space condition. Metal surfaces can increase or decrease the radioactive decay rates of fluorophores and can increase the extent of resonance energy transfer. In this sense, Su et al. [17] develop evanescent wave fluorescence biosensor with core/shell nanoparticles and they conclude that core/shell nanoparticles have capability to enhance the fiber optic sensing through amplifying fluorescence intensity and expect that their potential applications are used in a variety of biological applications.

Huang et al. [18] describe the synthesis of a long-wavelength latent fluorogenic probe BQC and fully characterize its fluorescence signal-revealing mechanism. The fluorescence response of BQC against biological thiol reductants was also evaluated on the developed work. Finally, various dehydrogenases oxidize their substrates with  $\text{NAD}^+$  as the electron acceptors to yield NADH which can be utilized by DTD to catalyze the release of the fluorogenic coumarin. The fluorescence signal revealed could be competitively inhibited by menadione, demonstrating its potential usefulness as a high-throughput screening indicator for DTD-targeted anticancer agents.

The research group of Grant et al. initially developed a calpastatin biosensor using a dual binding technique coupled with fluorescence resonance energy transfer (FRET) [19]. This dual binding technique was built upon in solution testing and tested in pure calpastatin samples from beef muscle. Later, the next generation of FRET based system immobilized calpastatin antibodies to optical fibers in the form of a sandwich immunoassay was constructed to detect

the level of calpastatin present in homogenized meat samples [20]. The results indicate that while the optical fiber biosensor would be useful in laboratory determination of differences in calpastatin activities, variable results showed that a new biosensor platform may increase accuracy and precision; therefore the aim of the posterior research of the same group was to use the same sensing mechanism, i.e., the sandwich immunoassay, coupled to a less variable waveguide system, i.e., capillary tubes [21]. The results reported in this research indicated that the capillary tube biosensors had less variability than the optical fiber biosensors.

Other fiber optic biosensors based on fluorescence measurements are summarised in Table 1.

**Table 1.FOBS based on fluorescence measurements.**

Applications	Remarks	Ref.
<i>Salmonella typhimurium</i>	Labeled antibody–protein G complexes formed via incubation of anti- <i>Salmonella</i> antibodies labeled with fluorescence resonance energy transfer (FRET) donor fluorophores and protein G labeled with FRET acceptor fluorophores; using silanization, labeled antibodies–PG complexes were then immobilized on decladded, tapered silica fiber cores to form the evanescent wave-sensing region	22
Organophosphate pesticides and chemical warfare agents	Biorecognition element is organophosphate hydrolase (OPH), which was conjugated with both biotin, to anchor it and a fluorescence reporter carboxynaphthofluorescein (CNF); avidin was attached to the polystyrene waveguide surface of a fluorescent detector, and the OPH–CNF–biotin biosensor conjugate was bound to the avidin	23
Serum protein	Fluorescent dye-immobilized porous glass coating on a multi-mode optical fibre; evanescent wave’s intensity at the fibre-optic core-cladding interface used to monitor the protein-induced changes in the sensor element	24
Thiols	New long-wavelength latent fluorimetric probe BCC (6); fluorogenic chemical transformation of BCC triggered by thiols is through a tandem reaction, thiol-induced benzoquinone reduction and quinone–methidetype rearrangement reaction; fluorescence signal revealed by this process is specific and exhibited in the near-red spectrum region with emission maxima at 595 nm	25
DNA	Using <i>p</i> -Hydroxyphenylimidazo[f]1,10-phenanthroline Ferrum(III) as indicator	26
Alpha-fetoprotein	Based on localized surface plasmon (LSP); integrates a sandwich immunoassay with LSPs on the surface of gold nanoparticle to improve specificity and sensitivity	27
Herbicides	Using microalgae immobilized in a sodium silicate sol–gel matrix to preserve the biological activity; three different species of freshwater green algae evaluated: <i>Dictyosphaerium chlorelloides</i> , <i>Scenedesmus</i> sp. and <i>Scenedesmus intermedius</i>	28
Interleukin-6 protein	Using combination tapered fiber-optic biosensor dip-probe; sandwich immunoassay used to generate specific fluorescence signal	29
Ethanol	An ultraviolet light emitting diode used as a fluorescence excitation source for nicotinamide adenine dinucleotide	30
Severe acute respiratory syndrome coronavirus nucleocapsid (SARS-CoV N) protein	Combination of sandwich immunoassay with the LSP technique; detection sensitivity of 1 pg/mL for recombinant SARS-CoV N protein in human serum; in comparison with conventional antigen capture ELISA, detection limit of LSPCF fiber-optic biosensor increased by 10 <sup>4</sup> -fold using the same monoclonal antibodies	31

Antibody–antigen interaction	Kinetic study with a sandwich assay;the system can be used to measure binding kinetics of biomolecules localized near the uncladded fiber surface where evanescent wave excitation of fluorescence is elicited by total internal reflection	32
Multiple small analytes	Immunoarray biosensor;through immobilization of two kinds of hapten conjugates onto the same fiber optic probe	33
Salicylate hydroxylase (SHL)	Synthesis of a new long-wavelength latent fluorogenic substrate SHLF for SHL; in presence of NADH and under aerobic conditions, SHL catalyzes the decarboxylative hydroxylation of SHLF followed by a quinonemethide-type rearrangement reaction concomitant with the ejection of a fluorescence coumarin	34
Swine-origin influenza A (H1N1) virus (S-OIV)	LSPCF-FOB which combines a sandwich immunoassay with the LSP technique using antibodies against the hemagglutinin (HA) proteins of S-OIVs	35
Interleukin-6	Using a combination tapered fiber-optic biosensor dip probe;this device relies on diode laser excitation and a charged-coupled device spectrometer and functions on a technique of sandwich immunoassay; in serum samples	36
Ultra-sensitive detection of molecular analytes	Highly swollen carboxylated poly(N-isopropylacryamide) hydrogel with up to micrometer thickness was grafted to a sensor surface, functionalized with antibody recognition elements and employed for immunoassay-based detection of target molecules contained in a liquid sample; molecular binding events detected by long range surface plasmon and hydrogel optical waveguide field-enhanced fluorescence spectroscopy	37
Proteins	Using hollow-core photonic crystal fiber;estrogen receptor (ER) from a MCF-7 breast carcinoma cell lysates immobilized inside a hollow-core photonic crystal fiber was detected using anti-ER primary antibody with either Alexa™ Fluor 488 or 555 labeled Goat anti-rabbit IgG as the secondary antibody	38
Glucose	Using glucose/galactose binding protein (GBP) labelled with the environmentally sensitive fluorophore, Badan; GBP–Badan attached via an oligohistidine-tag to surface of Ni–nitrilotriacetic acid-functionalized agarose or polystyrene beads	39
Fluorescent proteins	Time-resolved fiber-optic “Optrode” system for accurate real-time in situ detection	40

### Chemiluminescence and Bioluminescence Measurements

Magrisso et al. [41] create an instrument able to quantify all the extra- and intra-cellular parts of the chemiluminescence (CL) response simultaneously. This fiber based chemiluminescent sensor will provide timely and clinically relevant diagnostic and management information for patients undergoing an infection. The authors constructed a new proprietary fiber-based luminometer dedicated to phagocyte activity assessment, and have evaluated it as a putative tool for rapid, sensitive, reproducible and inexpensive measurement of the in vivo inflammation state of circulating phagocytes and the evaluation of the patient status during infection. The results obtained by the authors demonstrate improvements upon the applications of current CL measurement technology by the fiber-based luminometer prototype device in the analysis of circulating phagocyte activities. A distinctive feature of the instrument design is that neither samples, nor detector change their position during the measurement cycle, which helps decrease the size of the instrument. All the data shown were recorded using samples containing less than 0.5  $\mu\text{L}$  of whole blood. The optical fibers were used as both light guides and sample holders.

Bioluminescent assays gained increased attention thanks to advancements in genetic manipulation techniques, which offered the possibility to modify non emitting organisms, isolated from different habitats, into both luminescent and specifically responsive reporters. In this way, Fine et al. [42], in the construction of bioluminescent yeast cell based fibre-optic biosensors, demonstrate a novel approach for estrogenic endocrine disrupting chemical (EDC) biodetection by entrapping genetically modified *Saccharomyces cerevisiae* cells, containing the estrogen receptor alpha-mediated expression of the *luc* reporter gene, in hydrogel matrices based on calcium alginate or PVA. The authors emphasize the advantages of the method, such as the bioassay was characterized by a total duration time of 2.5 h; in addition it allows for the long term storage of the yeast cells which makes it possible to do the measurements without continuous or repeated cultivation of the cells that offers two more advantages: It decreases the work needed for routine use and it reduces variation between the measurements since a single batch of cells can be used for numerous measurements. On the other hand, hydrogels form a protective environment for the entrapped yeast cells protecting them from contamination, and thus allows the user to work under non-sterile conditions. Also, the bioassay is simple to perform and the hydrogels are both stable and easy to handle. It can also be used in highthroughput screening applications. Finally, the method is relatively inexpensive in comparison to the LC-MS-MS chemical analysis which requires an expensive instrument and well-trained personnel.

Later, the same investigation group evaluates the applicability of a bioluminescent yeast test for screening of aryl hydrocarbon receptor (AhR) ligands in environmental sediments [43]. Yeast is a eukaryotic microbe that is easy to store and cultivate without special facilities and it is generally more applicable to complex samples than are mammalian cells. The results obtained by the authors from the assay were consistent with those from both chemical analysis and H4IIE-luc bioassay. Moreover, the robustness of the yeast allows the application of the test to crude extracts or even sediment suspensions. This yeast assay can be useful in screening and prioritization of samples prior to chemical analysis and the strain can be used in the construction of fibre-optic biosensors

In other study, Eltzov et al. develop a real-time air toxicity monitoring system for indoor environments [44]. First were shown the capabilities of the bioluminescence bacteria to sense the presence of the toxic compounds in air and also shown was the influence of the immobilization method on the response of these microorganisms, tested with two different bacterial strains separately and several gaseous chemical compounds. After, this method was applied to the fiber optic mode. The observed simplicity of usage and maintenance makes this application an attractive system for close to real-time monitoring in the indoor air quality monitoring field.

Roda et al. report the development of a portable biosensing device relying on lens less contact imaging [45]. The device comprises a disposable cartridge containing immobilized bioluminescent whole-cell biosensors coupled with a CCD detector via a fiber-optic-based taper. The authors used an aqueous mixture of agarose, PVP and collagen to immobilize cells, thus obtaining ready-to-use reagents, which kept their vitality for at least 1 month at 4 °C. They



demonstrated the suitability of the cellular biosensor for a multiplex detection that measures two resolved bioluminescent emission wavelengths using the same substrate using a new yeast strain for androgens (green-emitting luciferase) with an internal vitality control (red-emitting luciferase). They also used a mixed population of green-emitting androgen and red-emitting estrogen responsive yeast strains obtaining light signal separation of luciferases emitting at different wavelengths.

### **Refractive Index Measurements**

Recently, Latifi et al. present a review on biconical tapered fiber sensors for biosensing applications [46]. A variety of configurations and formats of this sensor have been devised for label free biosensing based on measuring small refractive index changes.

The investigation group of Leung et al. investigates initially the detection of a model protein Bovine Serum Albumin (BSA) using antibody-immobilized tapered fiber optic biosensors (TFOBS) at 1550 nm under stagnant condition [47].

Later, they demonstrate the continuous detection of various concentrations of BSA starting from 1 pg/mL, and the detection of the target BSA in the presence of a contaminating protein, Ovalbumin (OVA). All the experiments were performed using both 1310 nm and 1550 nm distributed feedback (DFB) lasers simultaneously, and in a flow configuration [48]. In this study, the response of TFOBS to liquid refractive index was determined using glucose solutions and TFOBS were found to be sensitive to small changes in refractive index. The same group presents other study where TFOBS are coated with gold and housed in a flow cell [49]. Thiolated 15-mer single stranded (ssDNA) probes were immobilized on the TFOBS gold surface. Complementary 10-mer ssDNA target strands were then detected while they hybridized with the immobilized probes at concentrations as low as 750 fM. The sensor also showed selectivity against a single nucleotide mismatch.

Tazawa et al. describe a fiber optic coupler biosensor [50]. The change of refractive index due to biomolecular interaction on the surface of the coupler was detected as the change of the transmission power.

Maguis et al. report the relevance of a biosensor based on a tilted fiber Bragg gratings (TFBG) refractometer directly biofunctionalized onto the silica cladding surface [51]. In this work, they present an experimental comparison of three methods for immobilizing biomolecular probes on an optical fiber silica cladding surface. The biosensor based on a TFBG refractometer enables to directly detect, in real-time, target molecules. So, bovine serum albumin (BSA) (antigen) and anti-BSA (antibody) are used to study the reaction kinetics of the antigenantibody recognition by changing the antibody concentration in the three configurations employed for the antigen immobilisation.

Bahşi et al. developed a novel sol-gel derived  $\text{SiO}_2\text{-TiO}_2$  thin film based optical DNA biosensor using a prism coupler [52]. The DNA probe targeting the 20-mers (5'-

TAATATCGGTTGCGGAGGTG -3') has been designed to detect the *E. coli* O157:H7 EDL933 species. Homogeneous SiO<sub>2</sub>-TiO<sub>2</sub> hybrid films were produced by a sol-gel dip-coating method to provide a thin layer with a refractive index higher than the glass substrate for prism coupler measurements. Probe oligonucleotides were immobilized on the thin films. Target DNA strands were effectively hybridized with probe DNA strands. The immobilization and hybridization processes were confirmed by the increasing refractive index values.

In other recent investigation, through fabrication of long-period gratings (LPG) in photonic crystal fiber (PCF) with continuous water flow and via controlled surface modification of the cladding air channels using polyelectrolyte monolayer for subsequent biomolecular binding interactions, He et al. shown that LPG-PCF is a powerful optofluidic refractive index transduction platform that exhibits monolayer sensitivity at each and every surface adsorption or binding event [53]. This finding is of great significance in that it represents an important viable alternative to many existing affinity-based biological sensing and measurement approaches while offering many potential advantages such as easy system integration for high throughput, low cost, and massive parallel analysis with low sampling volume.

Herath et al. report a new type of refractive index-based biosensor using a fiber loop ringdown evanescent field (FLRD-EF) sensing scheme, in which the sensing signal is a time constant and detection sensitivity is enhanced by the multipass nature of the ringdown technique [54]. The authors demonstrate bulk index-based deoxyribonucleic acid (DNA) and bacteria sensing and surface index-based label-free DNA sensing using the FLRD sensing scheme combined with the EF sensing mechanism. This work presents the first DNA and bacteria sensors using the FLRD technique.

Yin et al. propose using a thin-core fiber modal interferometer (TCFMI) as a refractive-index (RI) sensor [55]. It has the advantages of low fabrication cost, ease of preparation, low temperature cross-sensitivity and high RI sensitivity and is thus a good candidate to integrate with biomaterials to deploy as a fiber-optic DNA sensor. The disposable TCFMI DNA sensor was prepared by layer-by-layer (LbL) self-assembly of a polyelectrolyte multilayer film and probe ssDNA on the fiber surface.

### **Other Techniques**

Rindorf et al. show that microstructured optical fiber (MOF)-based sensor elements can be integrated into a lab-on-a-chip component [56]. The lab-on-a-chip presented is successfully used in a selective DNA capture experiment. The design of the lab-on-a-chip allows for continuous control of liquid flow through the MOF and simultaneous optical characterization. The sample volume is only 10 nL, and the total internal volume is 300 nL. This lab-on-a-chip design allows for the integration of MOFs along with other existing lab-on-a-chip components.

The optical waveguide light mode spectroscopy (OWLS) has been widely used to study thin films deposited on the waveguide. In a thin dielectric film of a thickness of several hundred nm and high refractive index light can propagate only in discrete modes. As this wave is

evanescent, the propagation is sensitive to the boundary conditions of the wave guiding film. This makes it possible to use the waveguide as a surface sensor element. In this sense, Lukács et al. [57] present a work where purple membrane fragments isolated from the cell membrane of the bacterium *Halobacterium salinarum* and light-harvesting complexes were deposited on the waveguide with varying thicknesses. Purple membrane contains bacteriorhodopsin which upon illumination undergoes a series of intermediate states, the photocycle and pumps protons through the membrane.

Corres et al. develop a biosensor to determine the presence of anti-gliadin antibodies by measuring the interaction with antigen Gliadin [58]. The antigen is deposited using the electrostatic self-assembled (ESA) multilayer technique. Due to the absence of many washing and blocking steps as needed in conventional methods, it is possible to obtain a shorter performance time. The use of the ESA method, which can be carried out under standard temperature and humidity room conditions in the fabrication process, as well as the low cost of the materials and instruments used while the tapering of the fiber, can help to develop low cost sensors.

Atias et al. demonstrated the development of an alternative fiber-optic configuration designated for the construction of biosensing platforms [59]. This approach was developed and based on the chemical polymerization of pyrrole applied onto the surface of polymethyl methacrylate fibers to create a conductive surface, which enabled the subsequent electrogeneration of photoactive polypyrrole-benzophenone upon the fiber surface. Irradiation of the benzophenone groups embedded on the polypyrrole films using UV radiation at 350 nm enabled the attachment of enzymes based sensing matrices.

Zhang et al. realised a study which is centered at constructing multi-targeting FOB using CdSe/ZnS core/shell quantum dots (QD) as labels for biodetection [60]. The authors concluded that the water-soluble CdSe/ZnS core/shell QD coated with amphiphilic polymers is an effective replacement of conventional fluorescein isothiocyanate. Also, it is discussed that, on one hand, the size and mass of the QDs cause the interference with the human IgG mobility, resulting in the dropdown of the affinity and thus limiting the further improvement of the sensitivity of the FOB. On the other hand, the sensitivity of FOB can be improved by controlling the amount of IgG on the conjugates of QD-IgG or prolonging the time of detection. The most attractive potential of QDs is to enhance multianalyte assay capabilities. They demonstrated the realization of multiplexed assays in a single fiber of FOB using QDs as labels.

The work presented by Arregui et al. will deal with some of the different optical fiber sensors fabricated by means of the deposition of Layer-by-Layer nanostructured films [61]. Due to the precise control on the nanometer scale that this technique provides it is possible to optimize the response of the optical fiber sensors and also the fabrication of sensors based on sensing phenomena which are possible to observe only with nanocoatings. Sensors based on nanoFabry-Perots, microgratings, tapered ends, biconically tapered fibers, long period gratings or photonic crystal fiber have made possible the monitoring of temperature, humidity, pH, gases, volatile organic compounds,  $H_2O_2$ , copper or glucose. Finally, the possibility of

incorporating proteins, enzymes or antibodies makes this technique especially useful for the fabrication of biosensors for biological recognition.

Sang and Witte report a novel surface stress-based polydimethylsiloxane micro membrane biosensor and its application on *E. coli* detection [62]. Two biosensor test systems were built with a white light interferometer and a fiber optic interferometer, respectively. For the biological and medical applications, other kinds of cells or molecules can also be detected based on the biosensor test systems by functionalizing the membranes with different functional materials. The analysis of some pathological changes of cells or molecules can be carried out based on the alteration of membrane deflection.

Wang et al. demonstrated a fully distributed fiber-optic biological sensing platform based on a transient and traveling long-period grating in an immunoglobulin G-coated single-mode fiber [63]. The experiment results for immunosensing showed that this sensing scheme can detect specific antigen-antibody binding with elimination of cross-sensitivity to undesired agents using a standard binding block. This new fully distributed sensing platform can also be expected to measure a wide range of biological and chemical parameters using different functional coatings on the fiber surface.

A protein-protein (protein A and porcine IgG) binding assay has been used by Zhang et al. to demonstrate the operation and label-free biomolecular detection capability of the nanostructured Fabry-Perot interferometer at room temperature [64]. The Au-coated nanostructure layer inside the Fabry-Perot interferometer cavity offers significantly enhanced optical interference signals due to the localized surface plasmon resonance effect and the increased sensing surface area. Immobilization of protein A on the nanostructure layer and its binding with IgG inside the Fabry-Perot interferometer cavity can be monitored in real time, resulting in interference fringes shift.

The main objective of the study carried out by Beres et al. is to determine the optimum dimensions of the plastic optical fiber taper that best suits a biosensor probe for cells detection [65]. This technology employed in the construction of the biosensor fulfils the requirements of ease handling and simple construction. It was observed that the geometry of the taper interferes in the behaviour of the sensor. The use of U-shaped plastic optical fiber tapers chemically treated with immobilized antibodies, together with a simple optoelectronic system, enables the detection of target cells indicating the plastic optical fiber biosensor as a potential device to detect cells in aqueous medium.

A multilayered thin-film based on the layer-by-layer deposition of polyelectrolytes is used by Socorro et al. to develop a lossy mode resonance based biosensor which will be used to detect an immunoreaction [66]. This nano-coating is adsorbed onto a cladding removed multimode optical fiber. In this case, the light propagated by the fiber is modulated by the effect of an immunoreaction. The results obtained in this work show that a simple monitoring of both the construction and detection processes can be prepared in order to study the behaviour of the lossy mode resonance in every step.

In the last two decades, surface plasmon resonance (SPR) has secured a unique place among the several sensing techniques due to its high sensitivity and reliable procedure. SPR is probably one of the most suitable methods for real time detection and monitoring of biological binding reactions. Since its first application several research groups have reported a large number of publications related to chemical and biochemical sensing [2]. In recent times, chemical and biochemical sensors based on SPR and other label-free techniques have been developed by many researchers and subsequently commercialized. Applications in different fields ranging from medical diagnostics to environmental monitoring have been explored. In the SPR technique, a p-polarized light causes the excitation of a charge density oscillation (i.e., surface plasmon wave) along the metal–dielectric interface by satisfying certain resonance condition. The condition depends on many parameters such as angle of incidence, wavelength, and the dielectric constants of the metal and dielectric. The resonance is observed in terms of a sharp dip in output optical signal at either resonance angle or resonance wavelength. Any change in refractive index near the interface causes a change in the value of the resonance parameter. In this way, the fabrication and characterization of a SPR based fiber-optic sensor to determine the amount of naringin, which causes bittering effect in citrus fruit juices, have been reported by Rajan et al. [67]. The sensor relies on spectral interrogation of SPR. The probe is fabricated by immobilizing the enzyme naringinase on the silver coated core of the optical fiber. Several methodologies are available for immobilization. These are adsorption, entrapment by occlusion with cross-linked gels, encapsulation, cross-linking and covalent binding to polymeric support. To immobilize naringinase, gel entrapment technique is used by the authors. For the characterization of the probe light from a broadband source is coupled into the fiber. The resonance wavelengths are determined by placing fluids containing different quantities of naringin around the probe.

The manufacture of fiber-optic SPR sensors working in the NIR spectral region has been achieved by Masson et al. [68]. These sensors are in good agreement with the theoretical simulations performed by the authors. To achieve excitation in the NIR spectral region, the geometry of the sensor was modified by polishing two tapers at the distal end of the sensor. With these SPR-NIR sensors, sensing areas 50 times smaller than the conventional straight sensor fiber-optic SPR are easily manufactured and combined with up to thirteen-times improvement of the sensitivity.

Two optical configurations have been employed by Chau et al. for the gold nanoparticle-modified optical fiber sensors, including a transmission-based fiber-optic (TFO) configuration and a reflection-based fiber-optic (RFO) configuration [69]. Both configurations are based on attenuated total reflection (ATR) on the sensing region, where the normal cladding has been removed and replaced by a thin layer of sensing material. Modulation of the incident light results from the interaction between the sensing material and the evanescent wave which penetrates into the surrounding medium outside the fiber cores. The only difference between these two types is that a silver film was coated at the distal end of the unclad portion of the RFO probe and the reflected light by the sensing material is collected at the proximal end of the fiber probe. As such, the RFO configuration will make it possible to construct a miniaturized sensor head which can be directly inserted into a sample. This study reports the performance of

such a reflection-based LSPR fiber-optic probe and its comparison with the transmission-based LSPR fiber-optic sensor.

ForteBio's Octet optical biosensor harnesses biolayer interferometry to detect and quantify molecular interactions using disposable fiber-optic biosensors that address samples from an open shaking microplate without any microfluidics was employed by Abdiche et al. [70]. They recruited a monoclonal antibody against a panel of peptides to compare the Octet directly with Biacore's well-established 3000 platform and Bio-Rad's recently launched ProteOn XPR36 array system, which uses SPR to detect the binding of one analyte over four surfaces and six analytes over six surfaces, respectively.

Sai et al. describe the development of novel LSPR biosensor using gold nanoparticles coated U-bent fiber optic probes [71]. A simple procedure was used by the authors to fabricate U-bend probes from uncladded straight fibers. A complete optical set-up involved a fiber sensor probe, a light emitting diode and a detector that operates in visible range along with signal conditioning and processing electronics. In these studies, a spectrometer was used for analyzing the output obtained from the fiber probes. Label-free biosensing was demonstrated using these probes with the help of IgG-antiIgG as bioreceptor-analyte pair.

The objective of study realized by Jen et al. was to simulate the biochemical assays in the FO-LPR micro-fluidic chip and to investigate the effects parameters, such as the inlet concentrations of analyte or the flow rate on the biochemical binding kinetics [72]. The sensing element of FO-LPR was integrated with micro-fluidic chips to reduce sample and reagent volume, to shorten both response and analysis time, as well as to increase sensitivity.

Pollet et al. report on fiber optic SPR using DNA aptamers as bioreceptors [73]. The objective is to utilize the high stability of the ssDNA to develop reusable and cost-effective biosensors for DNA and protein detection. A mixed PEG ground layer will be used to optimize the biosensor selectivity. Small fiber-based SPR probes were produced in the laboratory and integrated in a fully automated setup. Mainly by using a tungsten white light source and removing the need for micro-fluidics, the system is approximately 2 factors less expensive than most commercially available SPR platforms.

A phytochelatin (PC) functionalized fiber-based biosensor utilizing the LSPR effect was developed to evaluate the concentration of Cd(II) [74]. First, a layer of the gold nanoparticle was immobilized on the outside of the fiber to couple with the evanescent wave. By using a self-assembling technique, a bioactive layer consisting of genetically synthesized PCs was immobilized by covalent coupling onto the gold nanoparticle layer and the optimal conditions of immobilization were examined by Lin and Chung. When the PCs binding with Cd(II) takes place, the local refractive index was altered and hence the transmission. Based on the correlation between binding rate and light attenuation, the concentration of Cd(II) can be determined. Several factors, including reactive rate, stability, and binding constant, were investigated as well.

A finite-element approach based on a full-vectorial H-field formulation in conjunction with the perturbation technique has been used to study the SPR based fibre optic biosensors to detect *E. coli* [75]. The effect of coupling length, modal confinement and modal loss are studied with and without the presence of *E. coli* in the outer medium.

In other study, the numerical simulation of biochemical binding kinetics of the FO-LPR microfluidic chip with grooved optical fibers was successfully performed [76]. The sensing element of the FO-LPR sensing platform was integrated with the microfluidic chip to reduce sample and reagent volume, to shorten both response and analysis time, as well as to increase sensitivity. The optical fibers were designed and termed as U-type or D-type based on the shape of the grooves. The U-shape groove was so narrow that it was not easy for the analyte to get close to the effective area. For the optical fiber with circular removal of cladding, the large area with open sites was exposed to the analyte simultaneously. The experimental results obtained by the researchs indicate that the D-type fiber performs better than the U-type fiber in terms of the mechanical property. This study demonstrates the feasibility of fabricating the grooved optical fibers by the femtosecond laser, and making a transmission-based FO-LPR probe for chemical sensing.

Spackova et al. propose a FO-SPR sensor based on spectroscopy of back-propagating SP-cladding modes which are excited by a guided core fiber mode via a Bragg grating [77]. In this sensor, spectrum of the transmitted light is measured and changes in the refractive index of analyte are observed as a spectral shift of the transmission dips associated with the excitation of SP-coupled-cladding modes. The sensor offers multiple sensing channels which can be simultaneously accessed through the wavelength division multiplexing. The sensing properties of the structure have been optimized in terms of length and refractive index contrast of the grating and thickness of the gold film.

Díaz-Herrera et al. presented a sensing system based on a configuration that incorporates a SPR transducer (doubly deposited uniform waist tapered fibre) with a dual-fibre Bragg gratings interrogation element [78]. This system can be used as a refractometer for the range of refractive indices of aqueous solutions and it is therefore very well suited for the development of biosensors. The experimental results, obtained by the authors, show that the performance of the system is encouraging, since the resolution of the usual SPR transducers was improved by an order of magnitude and the response of the system was made independent of optical power fluctuations. Additionally, the use of fibre Bragg gratings as interrogating elements also introduces some interesting features and possibilities, since it can provide temperature referencing and multiparameter sensing. Finally, it shall be emphasized that this interrogation scheme can be applied to any SPR transducer.

SPR sensors provide a useful means to study the interactions of biological molecules and the reaction of living cells on a sensor chip. In this way, Yanase et al. [79] constructed a relatively small, simple and portable system, using an optical fiber to detect the activation of living cells attached to the fiber tip in a real-time manner.

François et al. demonstrated a powerful and practical new form of SPR-based device based on the collection and spectral characterisation of the evanescent field surrounding a section of an optical fibre coated with silver [80]. This technique enables the construction of compact yet powerful devices; strict control of the thickness of the deposited silver is not required, which simplifies the fabrication of the sensor, and these devices also possess higher signal to noise ratio, which in turn has the capacity to improve the detection limit. This collection mode is a powerful approach that can distinguish two (or more) different refractive indices surrounding the sensing region, and as each spectrum is acquired from a specific sensing region, distributive refractive index sensing is possible. Moreover, one of these sensing regions can be used as a real time reference, which can be used to correct for temperature variations occurring during measurement and therefore eliminates the need for bulky temperature control systems.

Hsu et al. demonstrates the feasibility of the integration of the fiber optic-particle plasmon resonance (FO-PPR) biosensor with micro-fluidic technology [81]. With either AuNPs or AgNPs used in the sensor fiber, the chip-to-chip measurement reproducibility is reasonably good. Since the principle of FO-PPR measurements is based on absorption spectroscopy, the need for precise optical alignments is alleviated. Together with the simple instrumental setup, the FO-PPR biosensing system is potentially a low-cost and portable biosensor candidate compared to the bulky and more expensive commercial instruments.

Chabot et al. [82] showed that living cells must be modelled as a dielectric with a complex refractive index to take full advantage of long range surface plasmon resonance (LRSPR) sensitivity to scattering losses within the penetration depth of the evanescent field. LRSPR is more sensitive than SPR for detecting events that induce cellular morphology changes. Therefore, LRSPR is particularly well suited for cell studies where the objective is to detect and quantify cell adhesion, the reorganization of the cell cytoskeleton, the redistribution of the cell organelles, or the variation in the density of adhesion sites the substrate.

Zhang et al. presented the transmission spectra of the fibers modified using 3-aminopropyltrimethoxy silane (APTMS) and 3-mercaptopropyltrimethoxy silane (MPTMS) [83]. Star-shaped gold nanoparticles 80 nm to 120 nm in size were modified on the surfaces of the tapered fibers using these reagents. Sensitivity of the resulting transmission spectra was tested and the results show that the transmission spectra of the tapered fiber modified using MPTMS decreased more than those modified using APTMS, which indicates that the surface modification of the gold nanoparticles using MPTMS is better than that using APTMS. This finding is consistent with that of gold nanoparticles modified by amino groups and mercapto groups in the Au-S bond. The reproducibility of this study and the refractive index sensitivity of MPTMS-modified fiber were also investigated by the authors. The proposed surface modification technology has great potential in the development and application of biosensors. The fibers become more sensitive to the different concentrations of molecules after surface modification because the predominant optical characteristics of the gold nanoparticles can enhance LSPR. The proposed surface modification technology can benefit the development of new optical biosensors with higher sensitivity.



LSPR occurs when nanoparticles are bound to the surface of a sensor which is sensitive to the refractive index of the surrounding medium. The sensitivity of the sensor is highly dependent on the type of nanoparticles and their size, density and shape. Using an optical fiber as a sensor has various advantages, such as guided signal delivery and low energy loss. In this sense, a FO-LSPR sensor was developed by Jeong et al. [84] and the sizes of the Au-NPs used therein were controlled by reduction with chloroauric acid. The extinction cross-section was calculated to examine the dependence of the resonance intensity and sensitivity of the fabricated FO-LSPR sensor on the size and density of the Au-NPs situated on its end-face. The fabricated FO-LSPR sensor was used to detect the biotin-streptavidin interaction.

While substantial attention has been directed towards the development and performance of biosensors with DNA functionalized sensing layers for application in simple systems, such as single-component buffers, less effort has been directed to the development of surfaces suitable for use in more practical applications involving direct assays of complex systems. Janssen et. [85] developed a FO based melting assay for the sequence specific detection of DNA and in this work they show that modification of the functional layer of DNA receptors on the FO-SPR sensor through the incorporation of polyethylene glycol molecules can successfully address the common problem of surface fouling that often plagues SPR based DNA sensor implementations.

Kim et al. attempt to use graphene in the SPR sensor as replacement material for gold/silver [86]. Graphene, comprised of a single atomic layer of carbon, is a purely two-dimensional material and it is an ideal candidate for use as a biosensor because of its high surface-to-volume ratio. Graphene in the SPR sensor is expected to enlarge the range of analyte to bio-aerosols based on the superior electromagnetic properties of graphene. In this study, a SPR-based FO sensor coated with multi-layered graphene is described. The multi-layered graphene film synthesized by chemical vapor deposition on Ni substrate was transferred on the sensing region of an optical fiber. The graphene coated SPR sensor is used to analyze the interaction between structured DNA biotin and Streptavidin. Transmitted light after passing through the sensing region is measured by a spectrometer. As the light source, blue light which of 450 to 460 nm in wavelength was used. The fabricated graphene based FO sensor shows excellent detection sensitivity of the interaction between structured DNA and Streptavidin.

Recently, one simple and label-free biosensing method has been developed by Chang et al.[87] for determining the binding kinetic constants of antiovalbumin antibody (anti-OVA) and anti-mouse IgG antibody using the FOPPR biosensor. The FOPPR sensor is based on gold-nanoparticle-modified optical fiber, where the gold nanoparticle surface has been modified by a mixed self-assembled monolayer for conjugation of a molecular probe reporter (ovalbumin or mouse IgG) to dock with the corresponding analyte species such as anti-OVA or anti-mouse IgG.

An FO-LSPR sensor is fabricated using spherical Au-NPs in order to reduce the cost, shorten the fabrication time and facilitate the fabrication process with FOs [88]. The optical fiber is prepared with a flat structure, because of its simple fabrication, easy detection method and the possibility for various applications, etc. The fabricated FO-LSPR sensor is used to detect

the antibody–antigen reaction of a prostate- specific antigen (PSA) and interferon-gamma (IFN- $\gamma$ ). The FO-LSPR sensor for the detection of antigen PSA and antigen IFN- $\gamma$  can be applied to in-vivo systems combined with an endoscope or laparoscope, because of its real-time label-free detection, miniaturized flatted tip and fast sensitive detection.

### Applications

In the last years, fiber optical biosensors capable of detecting biomolecular interactions have become valuable tools for use in medical diagnosis and life sciences as well as environmental monitoring and other applications. The principal applications of these biosensors are summarized in table 2.

**Table 2: Applications of fiber optic biosensors**

Analyte	Remarks	Ref.
DNA	Based on a dual-peak long-period fiber grating; detection of interactions between biomolecules in real time	89
DNA	Using enzymatic signal amplification in an array of femtoliter-sized reaction vessels; this assay can be useful in biomedical applications where accurate and highly sensitive target analysis is critical	90
DNA	Fabricated nanoarrays using etched optical fiber bundles with two different sizes and pitches: 700 and 300 nm diameter optical fibers with 1 $\mu$ m and 500 nm center-to-center pitch, respectively; a variety of target sequences including <i>Bacillus thuringiensis kurstaki</i> and vaccina virus, two potential biowarfare agents, and interleukin-2 sequences, an immune system modulator that has been used for the diagnosis of HIV	91
DNA	Using a new biosensing platform based on quantum dots and total internal reflection fluorescence; clinical diagnosis, pathology and genetics applications	92
DNA	Comprising Si <sub>3</sub> N <sub>4</sub> micrograting arrays coated with a spin-on-glass material; this structure was located on a silicon groove, which was etched by a deep reactive ion etching process; specific detector of DNA molecules and antibody-antigen interactions	93
DNA	Based on fluorescence quenching; by using lock-in amplifier for signal measurement; sensor head fixed on a sensing membrane prepared by mixture of ethyl silicate, formamide, HCl and fluorescence indicator [Ru(phen) <sub>3</sub> ] <sup>2+</sup> -	94
Glucose	With an integrated fiber-optic hybrid sensor; design and dimensions of the cell adapted for its coupling with commercially available microdialysis techniques; continuous glucose monitoring; glucose level detected via oxygen consumption which occurs as a consequence of enzymatic reaction between immobilized glucose oxidase and glucose	95
Glucose	Comprises a needle-type hollow container, immobilized enzyme membrane and optic fiber probe with ruthenium complex; in fish blood	96
Glucose	Based on electrostatic self-assembly; the end face of a multimode fiber is coated with poly(allylamine hydrochloride) in combination with Prussian blue and the enzyme glucose oxidase	97
Glucose	Optical coatings formed from inorganic-organic hybrid polymers combined with a fluorophore and an enzyme; for in situ continuous monitoring in biotechnological production processes	98

Glucose	Using a hybrid sensor that consists of two oxygen optodes wherein one optode contains immobilized glucose oxidase; for continuous measurement in subcutaneous tissue	99
Glucose	Based on electrostatic self-assembly adsorption technique; up to 35 bilayers biofilm achieved from alternate deposition of enzyme glucose dehydrogenase and polyelectrolytes polyethyleneimine and poly(sodium 4-styrenesulfonate); the sensors used 7 days after its construction to see the enzymatic stability, showing no appreciable loss of activity	100
Glucose	Monolithic silica gel matrix with entrapped glucose oxidase; changes in intrinsic fluorescence used to determine the glucose concentration; silica gel support displayed a larger linear calibration range and higher sensitivity than other immobilisation systems	101
Glucose	Using novel genetically engineered binding polypeptides; in vivo applications	102
Glucose	By fluorophore-labeled and genetically engineered glucose/galactose binding protein (GGBP); acrylodan-labeled GGBP immobilized in hydrogel matrix at the tip of a small diameter optical fiber contained in a stainless steel needle; continuous glucose monitoring in humans	103
Glucose	Based on evanescent field-fiber loop ringdown; using refractive index-difference evanescent field attenuation effect as a sensing mechanism	104
6- benzylaminopurine	Using an opto-fluidic ring resonator biosensor and a Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) method	105 106
Ara h 1 protein	Three approaches of an immunoassay compared: a label-free assay, a secondary antibody sandwich assay and a nanobead signal enhancement FO-SPR biosensor	107
Ara h 1 protein	Several Ara h1 DNA aptamers selected; after selected aptamer used for bioassay development on a home-built fiber optic surface plasmon resonance biosensor platform	108
Bovine serum albumin	Layer-By-Layer (LBL) (Chitosan/Polystyrene Sulfonate) membrane-based Fabry-Perot interferometric FOB; based on the measurement of the changes in the thickness of the LBL multilayer film, resulting from the adsorption of proteins	109
Bovine serum albumin	Using of a long wavelength (1550 nm) laser and a tapered FO biosensor to monitor the real-time attachment of model protein bovine serum albumin to the antibody-immobilized surface of the taper	110
Atrazine	By immobilizing cells containing atrazine chlorohydrolase to the surface of a pH-sensitive optode	111
pH	Based on OF modal interferometer; two biocompatible polyelectrolytes, sodium alginate and polyethylenimine, alternatively deposited on the side surface of the thin-core fiber modal interferometer via a layer-by-layer electrostatic self-assembly technique	112
Genetic screening	Based on a FO surface plasmon biosensor and gold-labeled gene probes	113
Noadrenaline	Based on CuPc catalysis and fluorescence quenching	114
Glucose, ethanol, pO <sub>2</sub> -value and cell density	Based on a conventional thin layer flow-through cell equipped with a gold dual electrode; each Au surface initially modified by self-assembled monolayer of cysteamine; alcohol oxidase and pyranose oxidase immobilized each onto a gold surface by means of polyamidoamine dendrimer via glutaraldehyde cross-linking	115
Prostate-Specific Antigen	Using a localized surface plasmon coupled fluorescence FO biosensor, which combines a sandwich immunoassay with the localized surface plasmon technique	116
Toluene	Based on toluene ortho-monooxygenase from Burkholderia cepacia G4,	117

	which initiates toluene catabolism by ortho-hydroxylation;optical fiber coated with an oxygen-sensitive ruthenium-based phosphorescent dye served as transducer	
Halogenated hydrocarbons	Using enzyme-based biosensor developed by co-immobilization of purified enzyme haloalkane dehalogenase and a fluorescence pH indicator on the tip of an optical fiber	118
Guanosine 3',5'-cyclic monophosphate (cGMP)	Using a gold nanoparticle-modified optical fiber conjugated with anti-cGMP antiserum based on localized surface plasmon resonance	119
Urea	Based on urease encapsulated calcium alginate microspheres coated with polyelectrolyte nanofilms predominantly composed of cresol red dye;for estimating hemodialysis parameters	120
Toxic pollutants	Using a flow-through FO based bacterial monitoring system;two bacterial strains containing fusions of recA (DNA damage) and grpE (heat-shock) promoters to the lux operon (CDABE) immobilized on FO; for online monitoring of toxic pollutants in water	121
Ricin toxin	Using a FO biosensor RAPTOR(commercial available fluorescence-based optic fibre immunosensor); in water	122
Trinitrotolueno	Using aptamers as recognition elements	123
Enterococci	Using a combined ultrafiltration-biosensor procedure;adsorbed onto polystyrene waveguides for immunoassay analysis with a microfluidic FO biosensor (RAPTOR); in recreational coastal waters	124
Methyl parathion	Whole cells of <i>Flavobacterium</i> sp. Immobilized by trapping in glass fiber filter and used as biocomponent along with optic fiber system	125
1,2-dichloroethane	Using as biocomponent haloalkane dehalogenase in whole cells of <i>Xanthobacter autotrophicus</i> GJ10; these cells immobilized in calcium alginate on the tip of a FO fluoresceinamine-based pH optode	126
<i>Yersinia pestis</i>	Sandwich immunoassayusing the purified antibody against antigen F1 immobilized on polystyrene probes as the capture antibody and the monoclonal antibody-Cy5 conjugate as the detector with the FOB-3, based on evanescent wave	127 128
Ebola virus	Usinga photo immobilization methodology based on a photoactivatable electrogenerated poly(pyrrole-benzophenone) film deposited upon an indium tin oxide modified conductive surface FO	129
Mercury ions	Usingan evanescent wave DNA-based biosensor;DNA probe covalently immobilized onto a fiber optic sensor contains a short common oligonucleotide sequences that can hybridize with a fluorescently labeled complementary DNA	130
Mercury and arsenic	By attaching alginate-immobilised recombinant luminescent Hg- and As-sensor bacteria onto optical fibres	131
Calcium	Using a glass-PDMS microchip based sensor by reflectance measurements from arsenazo III immobilized on the surface of polymer beads	132

## CONCLUSIONS

Fiber optic biosensors are studied intensively because they are very useful and important tools for monitoring biomolecular interactions. In this review article, recent progress in the field of optical chemical biosensors has been summarized. As can be seen, in general, biosensors are the exceptional analytical system characterized by their high specificity and sensitivity toward substance. Fiber optic biosensors provide a simple and fast way in detection of interested molecules in variety of sample matrices. The different investigation groups are

trying to improve the design and sensing schemes of optical chemical biosensors. Biosensors can be classified by their bio-recognition system or depending on the method of signal transduction. With respect to the optical transduction, an important aspect for the development of optical biosensors has been the availability of high-quality fibers and optoelectronic components at a reasonable cost. In practice, fiber optics can be coupled with all optical techniques. Small, sensitive and selective fiber optic biosensors are expected in the near future. The combination of nanotechnology, molecular biology and photonics opens the possibility of developing nano-devices which have the potential for a wide variety of diagnostic and therapeutic uses at the molecular and cellular level.

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