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Review

Recent Development in Optical Fiber Biosensors

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Abstract: Remarkable developments can be seen in the field of optical fibre biosensors in the last decade. 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. This review consists of papers mainly reported in the last decade and presents about applications of optical fiber biosensors. Discussions on the trends in optical fiber biosensor applications in real samples are enumerated.

Keywords: Optical fiber, biosensor, applications, review

1. Introduction

Biosensor development is driven by the continuous need for simple, rapid, and continuous in-situ monitoring techniques in a broad range of areas, e.g. medical, pharmaceutical, environmental, defense, bioprocessing, or food technology.

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. Biological systems (such as tissues,

micro-organisms, enzymes, antibodies, nucleic acids, etc.) when combined with a physico-chemical transducer (optical, electrochemical, thermometric, piezoelectric) form a biosensor.

On the other hand, the development of optical-fiber sensors during recent years is related to two of the most important scientific advances: the laser and modern low-cost optical fibers. Recently, optical fibers have become an important part of sensor technology. Their use as a probe or as a sensing element is increasing in clinical, pharmaceutical, industrial and military applications. Excellent light delivery, long interaction length, low cost and ability not only to excite the target molecules but also to capture the emitted light from the targets are the main points in favour of the use of optical fibers in biosensors.

Optical fibers transmit light on the basis of the principle of total internal reflection (TIR). Fiber optic biosensors are analytical devices in which a fiber optic device serves as a transduction element. The usual aim is to produce a signal that is proportional to the concentration of a chemical o biochemical to which the biological element reacts. Fiber optic biosensors are based on the transmission of light along silica glass fiber, or plastic optical fiber to the site of analysis. Optical fiber biosensors can be used in combination with different types of spectroscopic technique, e.g. absorption, fluorescence, phosphorescence, surface plasmon resonance (SPR), etc.

Optical biosensors based on the use of fiber optics can be classified into two different categories: intrinsic sensors, where interaction with the analyte occurs within an element of the optical fiber; and extrinsic sensors, in which the optical fiber is used to couple light, usually to and from the region where the light beam is influenced by the measurand.

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.

2. Absorbance measurements

The simplest optical biosensors use absorbance measurements to determine any changes in the concentration of analytes that absorb a given wavelength of light. The system works by transmitting light through an optical fiber to the sample; the amount of light absorbed by the analyte is detected through the same fiber or a second fiber. The biological material is immobilized at the distal end of the optical fibers and either produces or extracts the analyte that absorbs the light.

A fiber optic pH sensor [1] and a fiber optic oxygen sensor [2] have been developed by Wolthuis et al., for use in medical applications. In the first case, the sensor uses an absorptive indicator compound with a long wavelength absorption peak near 625 nm; change in absorption over the pH range 6.8 to 7.8 is reasonably linear. The sensor is interrogated by a pulsed, red LED. Return light signal is split into short and long wavelength components with a dichroic mirror; the respective signals are detected by photodiodes, and their photocurrents are used to form a ratiometric output signal. In laboratory tests, the sensor system provided resolution of 0.01 pH and response time of 30-40 s. Following gamma sterilization, laboratory sensor testing with heparinised human blood yielded excellent agreement with a clinical blood gas analyzer. Excellent sensor performance and low cost, solid-state instrumentation are hallmarks of this sensor-system design. In the second, the sensor's

viologen indicator becomes strongly absorbant after brief UV stimulation, and then returns to the transparent state. The rate of indicator return to transparency is proportional to the local oxygen concentration. Indicator absorbance is monitored with a red LED. The solid state sensor system has performance comparable to existing oxygen measurement techniques, and may be applicable for both in vitro and in vivo oxygen measurements.

Molecular recognition processes are very important in the investigation of biological phenomena as well as development of fiber optic biosensor. As promising materials, biofunctionalized polydiacetylene lipids have many special properties. p-10,12-pentacosadiyne-1-N-(3,6,9-trioxaundecylanide) -α-D-mannopyranoside (MPDA) was synthesized from 10,12-pentacasadiynoic acid (PDA). The mixed monolayer MPDA/PDA was prepared by using Langmuir-Blodgett technique on glass and optical fiber, respectively. Molecular recognition of Escherichia coli (E. coli) resulted in a change of the film colour and can be quantified by UV-VIS absorption spectroscopy. The properties might be used for screening drugs and diagnosis [3].

On the other hand, thin films of polyaniline (PANI) and polypyrrole (PPy) have been shown to respond to pH and to the redox state of a solution, thereby undergoing spectral changes in the visible and near infrared. They also may serve as a matrix for enzyme immobilization. PANI films are easily prepared, and spectral changes depending on analyte concentration occur at wavelengths at which low cost lasers and LEDs are available. PANI and PPy are conductive organic polymers that can be driven between different oxidation states by chemical or electrochemical methods. PANI has two redox equilibriums associated with the polymer chain, and the optical properties of the polymer are functions of the state of protonation and the oxidation state. Since protons and electrons are directly involved in the polymer redox reaction, changes in optical spectra (e.g. absorbance) can be attributed to the concentration of protons or the number of electrons produced in an enzymatic reaction. PANI films of good optical quality can be produced by chemical means on almost any desired support including polystyrene, polycarbonate or glass. However, both optical and electrochemical PANI sensors tend to drift (in terms of conductivity or absorbance) in the order of 1% of the background signal per day. This makes daily recalibration necessary prior to measurements. Microtiterplates (micro-well) assays offer an alternative to conventional sensing because calibrators can be placed in one or more wells while actual assays are performed in the residual wells. This is one of the reasons why micro-well assays are commonly employed in routine analysis. In this way, a technique for coating the wells of microtiterplates with polyaniline layers and with polyaniline/enzyme layers is presented by Piletsky et al. [4]. The resulting wells are shown to be useful for assaying enzyme substrates (as exemplified for glucose via pH) and hydrogen peroxide (via the redox properties of the film). Analyte detection is based on monitoring the absorption spectra of the polyaniline, which turn purple as a result of redox processes, or green on formation of acids, by enzymatic reactions. Hydrogen peroxide (a species produced by all oxidases) and glucose (which yields protons on enzymatic oxidation) have been determined in the millimolar to micromolar concentration range.

Recently, Llobera et al. [5] present the characterization and optimization of flexible transducers with demultiplexing properties, suitable for on-chip detection. The micro-system consists of a hollow prism that can be filled with the fluid to be investigated. Two 2D (cylindrical) biconvex lenses modify the optical path before and after propagating through the prism, having parallel beams inside the prism and

focusing on the output optical fiber. Light is coupled into the system through a multimode optical fiber inserted into a channel. This channel enables the exact positioning of the fiber with respect to the biconvex lens, conferring the device with a simple, yet effective, self-alignment system. The same applies for the output fiber which enables the collected light to reach the photo-detector. The optimization of the hollow prisms has been done by measuring the absorbance as a function of the concentration for fluorescein and methylorange. Methylorange absorbs blue–green (λ = 490–510 nm) or blue (λ = 435–480 nm) light depending if its molecules are in its acidic or basic form, respectively. When a fixed concentration of methylorange is mixed with buffer with different pH, the fraction of each form of methylorange varies, causing a variation of the absorption spectrum of the solution. The working wavelength used in this work is only absorbed by the basic form (λ = 460 nm), hence, its absorbance will be minimum for low pH values. As the fraction of methylorange in its basic form increases (that is, as the pH increases), the absorbance of the working wavelength will increase. Hence, pH can be measured as a function of the absorbance of the methylorange in its basic form. Results show how the limit of detection (LOD) for fluorescein and methylorange diluted in phosphate buffer can be significantly lowered, by increasing the size of the prism or increasing the total deviation angle (the measurements showed a LOD in the μM range for both species).

Surface plasmon resonance (SPR) is an optical phenomenon caused by charge density oscillation at the interface of two media with dielectric constants of opposite sign, for example a metal and a dielectric. In this way, by tuning the plasmon resonance to a wavelength for which the outer medium is absorptive, a significant variation of the spectral transmittance of the device is produced as a function of the concentration of the analyte. With this mechanism, selectivity can be achieved without the need of any functionalization of the surfaces or the use of recognizing elements, which is a very interesting feature for any kind of chemical sensor or biosensor. Doubly deposited uniform-waist tapered fibers are well suited for the development of these new sensors. Multiple surface plasmon resonance, obtainable in those structures, can be used for the development of microspectrometers based on this principle [6].

Since the coming of the FTIR spectrometers, infrared spectroscopy has become an indispensable and efficient tool of analytical studies. Nevertheless, classical attenuated total reflection (ATR) or transmission registration need also to collect samples. An alternative method to acquire the infrared spectra consists of using some optical fiber, avoiding then the samplings. For this, the fiber is employed, on the one hand, to transmit the IR beams from the spectrometer to the sample, and on the other hand, as a probe by inserting a part of the fiber, called the sensing zone, into the studied environment. This technique is called fiber evanescent wave spectroscopy (FEWS) for fiber evanescent wave spectroscopy because it is generally considered that the principle of the measurement is based on the presence of evanescent wave around the fiber during the propagation of light into the fiber. A new generation of optical fibers has been developed based on the large transparency domain of an original family of IR chalcogenide glasses transmitting from 2 to about 12 μm.

Fiber-based infrared sensing has been established as an efficient, non-destructive and selective technique for the detection of organic and biological species. This technique combines the benefits of ATR spectroscopy with the flexibility of using a fiber as the transmission line of the optical signal, which allows for remote analysis during field measurements or in clinical environments. The sensing mechanism is based on the absorption of the evanescent electric field, which propagates outside the

surface of the fiber and interacts with any absorbing species at the fiber interface. This mechanism is analogous to that observed with an ATR crystal; however the fiber geometry creates a large number of internal reflections which enhances detection sensitivity. The availability of fibers with high infrared transmission in the spectral region between 400 and 4000 cm^{-1} allows one to collect the highly specific vibrational spectrum of organic chemicals and biomolecules. This technique, known as fiber evanescent wave spectroscopy (FEWS), has been applied to the detection of a wide range of chemicals and pollutants.

Since this spectral range comprises the "fingerprint" region of biomolecules, the FEWS technique has also shown promise for biomedical and clinical applications. It can be used as an efficient tool for chemical analysis of bio-fluids [7]. More recently, IR fiber sensors have been applied to monitor the metabolism of live whole cells. This ability to monitor metabolic processes in live cells has interesting potential for the design of bio-optic sensors. Disruption of the cell metabolism can be observed in response to minute amounts of toxicants, which would otherwise be far below the detection limit of IR spectroscopy. In effect, the cells act as a sensitizer for the IR sensor. Additionally, the process of monitoring a cell response permits detection of a wide range of compounds, which may have similar toxicological activities but different molecular structure. Hence biochemicals are detected based on their activity rather than identity, an important distinction critical in the design of sensors which may be challenged with a wide range of analytes to be detected.

Chalcogenide glasses are an ideal choice for the design of IR fiber bio-sensors based on materials properties. Mid-infrared fibers have been used previously for the characterization of live biological samples. An IR fiber optic neurotoxin biosensor was constructed by applying a biologically active cladding to the core of an infrared transmitting chalcogenide fiber [8]. Binding of the surface bound receptor protein was monitored by performing infrared difference spectroscopy on the fiber optic probe before and after its exposure to various concentrations of neurotoxin in solution. Signals measuring conformational changes as a result of these interactions are observed to saturate in agreement with established biochemical kinetics for the receptor. Fiber-optic components are shown to be much more sensitive than bulk optical components in performing these measurements. These fibers have also been functionalized with biological surface coatings such as enzyme films for selective bio-sensing [9]. In order to immobilize glucose oxidase on the surface of such an IR-transparent wave guide, crystalline bacterial cell surface layers (S-layers) were used as a carrier, instead of using silanes as an enzyme coupler as frequently described in the literature. S-layer proteins, which have the capability for self-assembling on suitable surfaces, were cross-linked and further activated with glutaraldehyde before the immobilization procedure. The reactive enzyme layer coating the core of the fiber serves to catalyze chemical reactions specifically when the fiber is used as chemical sensor. The chalcogenide fiber was coupled to a Fourier transform infrared (FT-IR) spectrometer which yielded spectra at various stages of the chemical processes as well as developments of signal bands as a function of time. The fiber was used as ATR element and could provide evanescent-field IR spectra in the range of 4000-800 cm^{-1} of the covering surface film thickness estimated at ~ 40 nm. All experimental surface modifications were carried out in situ in a 12-cm-long flow cell into which the fiber was positioned initially.

Lucas et al. [10] functionalize the surface of chalcogenide Te–As–Se fibers with live human lung cells that can act as sensitizer for the detection on micromolar quantities of toxic agents. First it

presents how the hydrophobic behavior of chalcogenide glass affects the spectroscopic properties of chalcogenide fibers. Then it presents 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 bio-optic sensors.

Near-infrared spectroscopy (NIRS) use depends on the relatively good transparency of biological tissue in the near-infrared range, which allows for transmission of photons through the tissue, so that they can be detected at the exit from the tissue. In particular, oxygenated haemoglobin (HbO2) and deoxy-haemoglobin (Hb) are the dominant absorbing elements between 700 and 1000 nm, and the transmission of light is relatively unaffected by water in the same region. Thus, the near-infrared region of the spectrum is the most favourable to the optical measurement of these parameters, so that NIRS provides a non-invasive, non-ionizing means to monitor total haemoglobin concentration (HbO2 + Hb) that is considered as total blood volume (HbT or V) as well as oxygen saturation in the living tissue. Optic fiber probes were used 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 [11].

3. Reflectance measurements

Interest has been shown in the detection of free radicals in view of the evidence implicating a primary or secondary role for them in the initiation or progression of many diseases, the majority of which are characterized by an inflammatory reaction. Naughton et al. [12] describe the development of a fibre optic sensor, based on immobilized nitrophenol that is of potential use for the continuous monitoring of OH radical production. This reflectance based sensor incorporates an OH radical sensitive chromophore, affording a decrease in its reflectance spectrum upon attack by this extremely reactive oxygen-derived radical attributable to the formation of nitrocatechol. Nitrophenol was immobilized onto XAD-7 methacrylate beads. Subsequently the beads were attached to the distal end of a polymethylmethacrylate fiber optic. Nitrocatechol, generated from the attack of OH radical on nitrophenol, exhibits a strong absorption band in the visible region of the electromagnetic spectrum (λ (max) = 510 nm).

Dyr et al. [13,14] evaluated the feasibility to follow the enzymatic conversion of surface-bound fibrinogen by thrombin to fibrin monomer and possible complex formation between surface-bound fibrin monomer and fibrinogen in solution using a SPR sensor. For the investigations of optical properties of immobilised molecular layers, the Kretschmann geometry of the attenuated total reflection (ATR) method was utilised. Density of fibrinogen bound to the surface depended on the concentration of fibrinogen in solution during the adsorption process. A fibrinogen monolayer was always formed. Fibrinogen in solution did not bind to surface-bound fibrinogen. Bound fibrinogen converted by thrombin to fibrin monomer interacted (rather slowly) with fibrinogen in solution. The rate of adsorption depended upon immobilised fibrin monomer density, fibrinogen concentration in solution, and on the presence of calcium ions. At low fibrin monomer density, the second layer was formed that contained about the same amount of protein as the first layer, at higher fibrin monomer concentration less than one molecule of fibrinogen per molecule of fibrin monomer was captured.

A novel approach for the detection of molecular interactions in which a colorimetric resonant diffractive grating surface is used as a surface binding platform is proposed by Cunningham et al. [15]. The grating, when illuminated with white light, is designed to reflect only a single wavelength. When molecules are attached to the surface, the reflected wavelength is shifted due to the change of the optical path of light that is coupled into the grating. By linking receptor molecules to the grating surface, complementary binding molecules can be detected without the use of any kind of fluorescent probe or particle label. The detection technique is capable of resolving changes of ~ 0.1 nm thickness of protein binding, and can be performed with the grating surface either immersed in fluid or dried. The readout system consists of a white light lamp that illuminates a small spot of the grating at nominally normal incidence through a fiber optic probe, and a spectrometer that collects the reflected light through a second fiber, also at normal incidence. Because no physical contact occurs between the excitation/readout system and the grating surface, no special coupling prisms are required and the grating can be easily adapted to any commonly used assay platform, such as microtiter plates and microarray slides. A single spectrometer reading may be performed in several milliseconds, thus it is possible to quickly measure a large number of molecular interactions taking place in parallel upon a grating surface, and to monitor reaction kinetics in real time.

Based on the principle of multiple-reflection in white-light interferometry, an optical fiber immobilized with protein molecule (antigen or antibody) is adopted as a high sensitivity biosensor to accomplish the real time monitor of the immunoassay [16-18]. The experimental results of rabbit-IgG with anti-rabbit-IgG immunoreaction show that by the aid of this biosensor, a biolayer change of approximately 0.70 nm in optical thickness can be detected by measuring the reflected spectrum phase shifting between the two interfaces of biolayer. Compared with others, this method has advantages, such as simple structure, lower cost, high sensitivity and reliability, label-free in immunoassay and direct monitor the immunoassay. This biosensor is easy to be integrated as a BIAcore (biomolecular interaction analysis core) for parallel direct detection of antigen-antibody interactions.

SPR biosensor has been widely used in the last 10 years to analyze the affinity between ligand and analyte [19]. The SPR condition is usually achieved in the attenuated total reflection (ATR) geometry by using prism-coupling optics. This optical setup is usually bulky and is incompatible with micrometer-sized probes. In place of the conventional SPR, interest in localized plasmon resonance (LPR) has grown in recent years, since LPR is quite compatible with such microsensors. The LPR of gold appears as an absorption band at about 550 nm in the presence of thin molecular layers on gold. In this condition, the LPR produces a large enhancement of the electric field around small gold particles or roughness of a gold surface, so that it is applicable in a highly sensitive affinity sensor of size less than microns. Kajikawa et al. propose a simple and sensitive optical sensing method for biological applications [20,21]. Since gold behaves as a dielectric with a large extinction index under blue or violet light, presence of a transparent surface layer on gold produces a large decrease in the reflectivity of the gold surface due to multiple reflections in the surface layer. Their call this phenomenon anomalous reflection (AR) of the gold surface. AR is applicable to affinity biosensors based on fiber optics, so that inexpensive and disposable micrometer-sized biosensor probes are possible based on this technique. Here, the authors demonstrate the application of AR to real-time measurements of the

adsorption process of octadecanethiol on gold and the affinity of streptavidin to a biotin-labeled monomolecular layer on gold.

Misiakos et al. [22] describe an optical affinity sensor based on a monolithic optoelectronic transducer, which integrates on a silicon die thin optical fibers (silicon nitride) along with self-aligned light-emitting diodes (LED) and photodetectors (silicon p/n junction). The LEDs are optically coupled to the corresponding photodetectors through silicon nitride fibers. Specially designed spacers provide for the smooth bending of the fiber at its end points and toward the light source and the detector ensuring high coupling efficiency. The transducer surface is hydrophilized by oxygen plasma treatment, silanized with (3-aminopropyl)triethoxysilane and bioactivated through adsorption of the biomolecular probes. The use of a microfluidic module allows real-time monitoring of the binding reaction of the gold nanoparticle-labeled analytes with the immobilized probes. Their binding within the evanescent field at the surface of the optical fiber causes attenuated total reflection of the waveguided modes and reduction of the detector photocurrent. The biotin-streptavidin model assay was used for the evaluation of the analytical potentials of the device developed. Detection limits of 3.8 and 13 pM in terms of gold nanoparticle-labeled streptavidin were achieved for continuous and stopped-flow assay modes, respectively. The detection sensitivity was improved by silver plating of the immobilized gold nanoparticles, and a detection limit of 20 fM was obtained after 20-min of silver plating. In addition, two different analytes, streptavidin and antimouse IgG, were simultaneously assayed on the same chip demonstrating the multianalyte potential of the sensor developed.

Recently, an optical fiber biosensor is introduced herein, which could directly detect biological interaction such as immunoreactions of antigens and antibodies without destroy the biolayer [23]. The test is based on the theory of multilayer-reflection principle in white-light interferometry. When immunoreactions occur, the reflected spectrum phase shifts. Immunoreactions could be detected by means of reflected spectrum phase shifting, or by biolayer thickness changing. Continuously detecting of thickness changing on a fractional nanometer scale with subsecond repetition times is allowed in this system. The detecting system has high sensitivity, high precision, and high speed, cost effective and working on a high reliability. The bioprobe is easy integrated as a BIAcore. The system and the experimental results on the reaction of rabbit-IgG with anti-rabbit-IgG are described in this work.

4. Fluorescence measurements

Fluorescence techniques provide sensitive detection of biomolecules. Furthermore, since fluorescence intensity is proportional to the excitation intensity, even weak signals can be observed. In last decade reagentless fiber-based biosensors have been developed. These biosensors are capable of detecting changes in cell behaviour, metabolism and cell death when exposed to toxic agents.

Fluorescence measurements are not used as often as absorbance and reflectance with enzyme optical fiber-based biosensors, as it is not common for enzyme reactions to produce fluorescent products or intermediates. Most fluorescence techniques employ a fluorescent dye to indirectly monitor formation or consumption of a transducer.

Several enzyme-catalysed reactions involve the production or consumption of fluorescent species. NAD^+ (nicotinamide adenine dinucleotide)-dependent reactions, catalysed by a group of

dehydrogenase enzymes, are some of the notable examples of this chemical phenomenon. In the general dehydrogenase reaction:

$$\text{Substrate} + \text{NAD(P)}^{+} \xrightarrow{\text{dehydrogenase}} \text{product} + \text{NAD(P)H}$$

NADH or NADPH is produced, which can be detected using fibre optics through its fluorescence at λ_{ex} = 350 nm, λ_{em} = 450 nm. Several optical sensors have thus been produced by integrating different dehydrogenase or oxidoreductase enzymes with optical fibres. These sensors are listed in Table 1.

A fiber optic-based biosensor which integrates a novel array of optical and electrical components, together with long fused silica fibers and proteins for detection of analyte in solution has been proposed by Anderson et al. [98]. The optical fiber core near the distal end is tapered and coated with either antibodies or DNA binding proteins. Assays are performed by flow of a solution containing the fluorescently tagged ligand molecules over the coated fiber. Within seconds, analyte recognition occurs and a fluorescence signal is transmitted back up the fiber. Applications for the biosensor include clinical diagnostics, pollution control, and environmental monitoring.

The use of DNA as a selective recognition element in biosensor design is a new and exciting area in analytical chemistry. Experiments have been completed wherein ssDNA was covalently immobilized onto quartz optical fibers to successfully demonstrate the basis for development of an optical biosensor for DNA. The non-optimized configuration described was able to detect femtomolar concentrations of cDNA with an analysis time of less than 1 h. These experiments indicate that biosensors which can selectively detect genetic material from biological may now be created, with advantages of low detection limits, reasonable analysis times, highly stable biorecognition elements, and regenerability. An alternative approach which may be used to create biosensors with long term chemical stability takes advantage of the stability of DNA. With the recent advent of DNA probe technology, a number of selective oligomers which interact with the DNA of important biological species, for instance salmonella, have been identified. These have been used to provide a new type of selective biorecognition element which is highly selective, stable, and can be easily synthesized in the laboratory as compared to other chemically synthesized biorecognition elements. As a result, species specific DNA probes may be exploited for biosensor development.

Piunno et al. [99,100] reports one of the first biosensors for direct analysis of DNA hybridization by use of an optical fiber. ssDNA was covalently immobilized onto optical fibers by first activating the surface of the quartz optical fiber with a long chain aliphatic spacer arm terminated in a 5'-0-dimethoxytrityl-2'-deoxyribonucleoside, followed by automated solid-phase DNA synthesis. Detection of dsDNA at the fiber surface after hybridization between immobilized ssDNA and cDNA was achieved by exposing the complex to an ethidium bromide solution followed by washings with hybridization buffer solution. The ethidium cation (3,8-diamino-6-phenyl-5-ethyl-phenanthridium) is a fluorescent compound which strongly associates with dsDNA by intercalation into the base stacking region and, in some cases, the major groove of the double helical structure. It is shown that the fluorescence response of the ethidium cation can be monitored in a total internal reflection configuration along an optical fiber to quantify the presence of dsDNA at the surface of the fiber, with the fluorescence intensity being directly proportional to the amount of cDNA initially present in

solution. This approach may be refined and used for rapid identification and quantitation of the presence of microorganisms such as pathogenic bacteria and viruses in bodily fluids, food and feed commodities, and may also find application in screening for genetic disorders.

Other fiber optic DNA biosensors and also other fiber optic biosensors based on fluorescence measurements are summarised in Table 1.

Optical biosensors based on fluorescence detection often use the combination of a fluorescent bioreceptor associated with an optical transducer. Fluorescent biosensors may also be obtained by immobilizing whole cells on the surface of a sensor layer. This bioactive layer is usually placed in front of the tip of an optical fibers bundle to generate a fluorescence signal. The optical fibers are required to send the excitation radiation to the fluorescent bioelement and convey the fluorescence radiation up to a fluorimeter. When algal cells are deposited on the surface of an opaque support, they are placed at some distance to the optical fibers bundle to allow the fluorescence radiation emitted by the illuminated area to be collected properly. In order to improve the simplicity and reliability of fluorescence based biosensors, optically translucent supports are used because their optical properties enable detection of fluorescence emitted by the algal cells even if they are entrapped in the bulk of the translucent support. Silica matrixes have interesting properties including optical translucence, biocompatibility and chemical inertness. The design flexibility of sol–gel technique and ease of fabrication can fulfil to create the support with structural and chemical features that could be compatible with biomaterials. While immobilization of enzymes and whole cells in sol–gel is a well-known technique in biosensor application, it is not yet used for the construction of vegetal-cell optical biosensors. On the other hand, when an enzyme is immobilized, a substrate is required and a fluorescent indicator may be added to enable optical detection of the analyte. In the case of detection based on chlorophyll fluorescence, those reagents are not necessary, and a reagentless biosensor can be constructed for toxic chemicals determination. Recently, Nguyen-Ngoc and Tran-Minh investigated translucent matrixes obtained from a sol–gel process for entrapment of fluorescent biomaterials in order to improve the fluorescent biosensor fabrication. Vegetal cells as bioreceptors have been tested for herbicides determination [101].

Also, a single, compact probe containing a manifold of chemical and biological recognition principles that could all be simultaneously and independently interrogated forms an excellent foundation for the development of clinical and environmental total analysis systems. Imaging fibers consisting of a fused fiber bundle that can each be optically addressed independently are very useful for optical imaging applications. In this sense, optical imaging fibers with micrometer-sized wells were used as a sensing platform for the development of microarray optical ion sensors based on selective bulk extraction principles established earlier for optodes. Uniform 10 μm sized microspheres based on plasticized poly(vinyl chloride) containing various combinations of ionophores, fluoroionophores and lipophilic ion-exchangers were prepared for the detection of sodium, potassium, calcium and chloride, and deposited onto the wells of etched fiber bundles. The fluorescence emission characteristics of individual microspheres were observed from the backside of the fibers and were found to selectively and rapidly change as a function of the sample composition [102].

Table 1. Fiber optic biosensors based on fluorescence measurements.

Applications	Remarks	Ref.
Lactate, pyruvate, ethanol	Using confined macromolecular nicotinamide adenine dinucleotide derivatives; flow-injection analysis (FIA)	24
Lactate, phenylpyruvate, pyruvate, formate, ethanol and mannitol concentrations in the range of 50-1500 μmol l^{-1}	Miniaturized fluorimeter with a low-volume membrane reactor and utilizes FIA; two types of membrane reactor: a) enzymes and a macromolecular nicotinamide adenine dinucleotide coenzyme derivative of polyethyleneglycol are retained in the direct vicinity of the sensor tip; b) solid-supported liquid membrane used to retain native coenzyme, while substrates and products transported via selective carriers through an organic membrane barrier	25
Lactate	Based on bacterial cytoplasmic membranes (CPM) as the biological recognition element and an oxygen sensitive dye layer as the transducer; CPMs from bacteria with an induced lactate oxidase system are adsorbed onto a cellulose disk that is fixed mechanically over an oxygen sensitive siloxane layer on the distal end of an optical fiber	26
Ethanol, mannitol	FIA; alcohol dehydrogenase + lactate dehydrogenase for ethanol ; mannitol dehydrogenase + lactate dehydrogenase for mannitol	27
Ethanol, urea	For ethanol increase of NADH fluorescence during the enzymatic conversion of ethanol using an enzyme system of ADH and AlDH; for urea based on a pH sensor measuring the change in fluorescence of the pH indicator fluorescein; both sensors are suitable for controlling fermentation processes when ethanol and urea are produced or consumed; software package FIACRE developed to run three different FIA processes simultaneously; it is applied to a model fermentation with Enterobacteriaceae Proteus vulgaris controlled by an urea optode	28
Glutamate	Enzyme layer composed of glutamate dehydrogenase (GDH) and glutamatepyruvate transaminase (GPT) for produce NADH at the tip of a fiber-optic probe; GDH catalyzes the formation of NADH, and GPT drives the GDH reaction by removing a reaction product and regenerating glutamate; optimal response obtained a pH 7.4 Tris-HCI buffer at 25 °C in 4 mM NAD^+ and 10 mM L-alanine	29
Glutamate	GDH directly immobilized onto optical fiber probe surface through covalent binding mechanisms; optical fiber surface initially activated by silanization, which adds amine groups to the surface; then affix functional groups CHO to the optical fiber surface by employing a bifunctional cross-linking agent, glutaraldehyde	30
Glutamate	Comprised of an L-glutamate-sensitive fluorescent gel, spin-coated onto the tip of an optical imaging fiber; gel composed of L-glutamate oxidase (GLOD); a pH-sensitive fluorescent dye, SNAFL; and poly(acrylamide-co-N-acryloxysuccinimide) (PAN); NH_3 is liberated from the interaction	31

	of L-glutamate with GLOD, which reversibly reduces the emitted fluorescence signal from SNAFL	
Fructose, gluconolactone, glucose	Glucose-fructose oxidoreductase; permeabilized cells confined in front of the fiber tip and changes in the NAD(P)H pool of membrane-bound enzyme complexes inside the cells monitored during enzymatic reactions	32
Fructose, glucose	FIA; using glucose-fructose-oxidoreductase isolated from Zymomonas mobilis confined in a measurement cell behind an urtrafiltration membrane	33
Acetylcholinesterases (AChEs)	By immobilizing fluorescein isothiocyanate (FITC)-tagged eel electric organ AChE on quartz fibers and monitoring enzyme activity; pH-dependent fluorescent signal generated by FITC-AChE, present in the evanescent zone on the fiber surface, was quenched by the protons produced during acetylcholine (ACh) hydrolysis	34
Nicotinic acetylcholine receptor	Using three fluorescein isothiocyanate (FITC)-tagged neurotoxic peptides that vary in the reversibility of their receptor inhibition: α-bungarotoxin, α-Naja toxin, and α-conotoxin	35 36
Ethanol vapor	By immobilizing alcohol oxidase (AOD) onto a tip of a fiber optic oxygen sensor with a tube-ring, using an oxygen sensitive ruthenium organic complex (λ_{exc}=470 nm; λ_{em}=600 nm); reaction unit for circulating buffer solution applied to the tip of the device; after experiment in liquid phase, the sniffer-device was applied for gas analysis using a gas flow measurement system with a gas generator; optical device applied to detect the oxygen consumption induced by AOD enzymatic reaction with alcohol application	37
Glucose	Biochemical assay based on homogeneous singlet/singlet energy transfer affinity assay; sensor probe indirectly measures glucose concentrations from the level of fluorescence quenching caused by the homogeneous competition assay between TRITC labeled concanavalin A (receptor) and FITC labeled Dextran (ligand)	38
Glucose	Based on coupling the swelling of a polymer gel to a change in fluorescence intensity; fluorophore, an amine functional group and enzyme glucose oxidase were each incorporated into a crosslinked polymer gel, which was formed on the end of a fibre optic rod; while the amount of fluorophore remains constant, the gel volume changes in response to a change in the ionization state of the amine moiety; change related to glucose concentration	39
Anticonvulsant drug phenytoin (5,5-diphenylhydantoin) in human blood and plasma	Using a self-contained fiber-optic immunosensor; signal depended on the degree of energy transfer from B-phycoerythrin labeled with phenytoin to Texas Red labeled anti-phenytoin antibody; Dextran 70K added to system to equalize oncotic pressure across the encapsulation membrane	40
Simultaneous analysis of multiple DNA sequences	A bundle of optical fibers assembled with each fiber carrying a different oligonucleotide probe immobilized on its distal end; hybridization of	41

	fluorescently labeled complementary oligonucleotides to the array monitored by observing increase in fluorescence that accompanied binding; approach enables fast (<10 min) and sensitive (10 nM) detection of multiple DNA sequences simultaneously	
DNA sensor	Using Lagmuir-Blodgett technique cinnamoylbutylether-cellulose monolayers transferred onto optical fibers or planar waveguides; films served as matrices for immobilization of biotinylated oligonucleotides via streptavidin; specificity of streptavidin layer or following bounded nucleic acid molecules controlled by enzyme- linked immunosorbent assay	42
16-mer oligonucleotides in DNA hybridization assays	Based on fluorescence excitation and detection in the evanescent field of a quartz fiber; biotinylated capture probe immobilized on the fiber surface via avidin or streptavidin	43
DNA sensor	Two methods for covalent immobilization of single-stranded DNA onto optical fibers: a) fused silica optical fibers derivatized with γ-amino-propyltriethoxysilane followed by extension with 12-nitrododecanoic acid via amide formation; terminal nitro moiety then reduced to amine to provide a hydrophobic spacer molecule suitable for covalent attachment of an oligonucleotide; b) fibers activated with 3-glycidoxypropyltrimethoxysilane and a hydrophilic spacer arm composed of 1-17-diamino-3,6,9,12,15-pentaoxaheptadecane covalently attached; oligonucleotides (dT20) then bound to either type of spacer arm through a phosphoramidate bond between amine terminus of the spacer molecule and 5'-phosphate of the DNA via a carbodiimide mediated condensation reaction	44
Specific determination of femtomolar DNA oligomers	13mer oligonucleotides attached to core of a multimode fibre; complementary sequence detected by use of a fluorescent double strand specific DNA ligand (YOYO and PicoGreen); evanescent field employed to distinguish between bound and not bound species; template DNA-oligomer immobilized either by direct coupling to activated sensor surface or using avidin-biotin bridge	45
Detection of genomic target sequences from Escherichia coli	A small portion of the LacZ DNA sequence is the basis for selection of DNA probe molecules that are produced by automated nucleic acid synthesis on the surface of optical fibres; fluorescent intercalating agents are used to report the presence of hybridization events with target strands	46
To fabricate a mercury biosensor	Using genetically modified Escherichia coli strain, containing lacZ reporter gene fused to heavy metal-responsive gene promoter zntA; plasmid carrying gene coding for enhanced cyan fluorescent protein also introduced into sensing strain to identify cell locations in array; single cell lacZ expression measured when array was exposed to mercury and a response to 100nM Hg^{2+} could be detected after 1-h incubation time; optical imaging fiber-based single bacterial cell array is flexible and	47

	sensitive biosensor platform that can be used to monitor the expression of different reporter genes and accommodate a variety of sensing strains	
Detection of hybridization of nucleic acids	Probe DNA was dT20, and target was Fluorescein-labeled non-complementary (dT20) or complementary (dA20) oligonucleotide; chronofluorimetric monitoring of adsorption and hybridization processes used to investigate oligonucleotide films of different density, in different salt concentrations, at temperatures of 25 and 40 °C, with concentration of the target DNA being 0.005-0.1 μM.	48
Thrombin and also a similar strategy could be used to study other analytes such as protein and small molecules	By aptamer connected with molecular beacon that consist of an oligonucleotide sequence containing complementary sequence sections at either end; these two sequence containing segments base pair with each other to form a hairpin shaped loop structure, the fluorophore and quencher were attached at 5'- and 3'-end of molecular beacon, respectively	49
Hybridization assays	Experiments were done to examine the effects of immobilization density and solution conditions on sensitivity, selectivity and dynamic range of hybridization assays done using a fiber optic nucleic acid biosensor based on TIRF	50
Hybridization assays	On the evanescent field excitation of fluorescence from surface-bound fluorophores; evanescent field made accessible through use of long, adiabatically tapered single-mode fiber probe; laser diode with a 785-nm wavelength used in a pulsed mode of operation to excite fluorescence in the tapered region of a fiber probe using the near-infrared fluorophore IRD 41	51 52
Determination of nucleic acid hybridization	1-hydroxyethyl-4-[(3-methyl-6-methoxybenzothiazole-2-ylidine) methine] quinolium bromide, a derivative of thiazole orange, use as a fluorescent indicator of DNA hybrid formation on a fiber optic genosensor platform	53
By using dinitrophenyl (DNP) hapten-loaded liposomes, concentrations as low as 500-fold diluted anti-DNP antibody and 0.76 CH_{50} ml^{-1} of complement were detected	Agar gel-immobilized liposomes containing carboxyfluorescein attached to the tip of optical fiber; complement-mediated immunolysis of liposome was fluorometrically detected through the fibre	54
Competitive binding immunofluorescence assay	Protein A covalently immobilized on activated sensing tip surface of quartz fiber or on activated surface of glass cover slips; surface then incubated with rabbit IgG to reach a reasonable binding density and homogeneous distribution for adequate detectability; sensor exposed to FITC labeled and unlabeled goat anti-rabbit IgG; fluorescence of sensor bound analyte, excited by Argon ion laser 476 nm line and emitted from sensing tip or sensing spot on the sample slips, is coupled back into the fiber	55
Quantifying serum antiplague antibody	Fiber probes with immobilized antiplague IgG coated with F1 antigen and then incubated with serum samples, quantity of antiplague serum	56

	antibodies which bound to the probe surface was then determined with fluorescent rabbit anti-human IgG	
Protein C in a plasma sample; immunosensor was also tested with human serum albumin and human plasma and with and without convective flow	Optimal primary antibody concentration is 65 μg ml^{-1}; its leaching as minor, stabilized within 3 days, and the sensor sensitivity change after 30 days of storage was minor; sample and secondary antibody incubation times reduced from 10 to 5 and from 5 to 3 min, respectively, while maintaining a reasonable signal-to-noise level	57
Antibody immobilization	Several heterobifunctional crosslinkers compared to N-succinimidyl 4-maleimidobutyrate for their ability to immobilize active antibodies onto glass cover slips at a high density	58
Proteins	Matrix uses a gold colloid monolayer attached to an end of a fiber as a substrate for protein attachment	59
Zinc	Sensor transduces the specific recognition of the ion by an enzyme (carbonic anhydrase) as a change in the fluorescence of an inhibitor which binds to the zinc in the active site	60 61
Zinc	Synthesis of difluorofluorescein monocarboxaldehyde platform and use for preparing ZP8, a new member of the Zinpyr family of neuronal Zn^{2+} sensors	62
Rapid and sensitive fluoroimmunoassays for biologic analytes	Using a laboratory breadboard device that employed a large 514 nm argon ion laser; also portable, multichannel biosensor was developed which uses 635 nm laser diodes, the assays were converted to use the cyanine dye, Cy5; detection antibodies were labeled with Cy5 and assays performed to detect F1 antigen of Yersinia pestis and the protective antigen of Bacillus anthracis	63
Applications of sol-gel encapsulated phycobiliproteins	Light transducing phycobiliproteins encapsulated in optically transparent sol-gel matrices	64
Proteins	A model biorecognition element-reporter group couple consisting of human serum albumin that was site-selectively labelled at Cys 34 with iodoacetoxy-nitrobenzoxadiazole; labelled protein encapsulated into sol-gel derived materials	65
Acetylcholine	Sensor consists of a pH-sensitive fluorescent indicator encapsulated with enzyme in a sol-gel network on a glass cap that can be fixed on an optical fiber and then integrated with a flow-through reactor for continuous monitoring	66
Protein A	Effectiveness of protein A, an immunoglobulin binding protein, for antibody immobilization on the surface of fiber probes	67
Organophosphorus pesticide	Sol-gel crystals derived from tetramethyl orthosilicate doped with cholinesterase using microencapsulation	68
Fiber optic cocaine biosensor	Replacement of quartz halogen lamp of fluorometer with high brightness blue-light-emitting diode enhanced evanescent excitation of	69

	benzoylecgonine-fluorescein bound to mAbs immobilized on quartz fibers and gave stronger optical signals	
Penicillin or glucose in the presence of a concurrent pH or 0_2 change, respectively	Biosensors are fabricated by site-selective photodeposition of analyte-sensitive polymer matrices on optical imaging fibres	70
Oxygen sensing in non-aqueous media	Using porous glass with covalently bound luminescent Ru(II) complexes in methanol, chloroform, toluene, cyclohexane, and n-hexane	71
Cellular detection of nitric oxide	Sensors incorporate cytochrome c', a hemoprotein known to bind nitric oxide selectively; cytochrome c' is labeled with a fluorescent reporter dye	72
New detection instrument for chemical/biological fluorescence lifetime-based sensors	Dual closed-loop optoelectronic auto-oscillatory detection circuit: primary loop consists of a fluorescence excitation light source, a fiber-optic delay line (with a gap for placement of a fluorescent sensor), an electronic phase shifter, a photo-detector, and a resonance-type RF amplifier; secondary loop consists of a long-wavelength-pass optical filter, multimode fiber, a PMT, and an electronic phase detector (which is connected to the phase shifter of the primary loop)	73
Picric acid	By replacing the hydrogen of the 4-amino group of a 4-amino-1,8-naphthalimide derivative with an N-acryloxyethyl group, the fluorophore has been covalently immobilized on an optical sensor surface by UV photopolymerization	74
Development of a multi-pathogen, immunoassay-based, fiber optic detector	For attaching quantum dots (QDs) to antibodies for use in biodetection applications; synthesized CdSe/ZnS core-shell QDs of differing size, functionalized their surfaces with several types of organic groups for water solubility, and covalently attached these functionalized QDs to rabbit anti-ovalbumin antibody protein	75 76
Application of evanescent wave sensing to a high-sensitivity fluoroimmunoassay of the clinically important human enzyme creatine kinase (CK) isoenzyme MB form (CK-MB)	Using a green helium-neon laser based fluorimeter and the antibody conjugated fluorophor B-phycoerthrin	77
Fluorescein	Comparison between evanescent wave generation and distal-face generation of fluorescent light	78
Evanescent wave fiber optic biosensor	Combination tapered fibers designed for improved signal acquisition	79
Antibody/antigen binding	Ray-tracing determination of evanescent wave penetration depth in tapered fiber optic probes	80
Evanescent wave biosensor	Fluorescent signal acquisition from step-etched fiber optic probes or from tapered fiber optic probes	81 82 83
Evanescent wave immunoprobe with high bivalent antibody activity	Using both kinetic methods and optical determinations of bound antigen, there are 2.4×10^{11} active antibodies per cm^2 probe area; 75% of the active	84

	antibodies are in bivalent form, with both binding sites capable of binding antigen	
A pH sensor array and an acetylcholine biosensor array	Combined imaging and chemical sensing using a single optical imaging fiber	85
Novel single mode tapered optical fibre loop biochemical sensor	Analyte labelled secondarily with a fluorescent dye, fluorescein isothiocyanate or tetramethyl rhodamine; when excited by input argon ion laser light from the near end of the taper, generated fluorescence is coupled into the guided mode of the fibre and collected at the far end of the taper	86
Portable multichannel fiber optic biosensor for field detection	Using a novel optical fiber bundle jumper for exciting and collecting fluorescence emission from the evanescent wave fiber optic probes; single fiber in the center of bundle couples laser excitation into the sensor probe, while the surrounding fibers collect the returning fluorescent emission light	87
Tapered single-mode optical fiber evanescent coupling	Investigation of two different geometries of nonadiabatic, tapered single-mode optical fiber	88
Design and application of fiber-optic evanescent wave biosensor	Using a red laser diode at 636.85 nm for exciting Cy5 fluorescent dye	89
Fluorescent coagulation assay for thrombin	Using a fibre optic evanescent wave sensor; coagulation of solution phase fluorescently labelled fibrinogen to unlabelled fibrinogen bound to surface of fibre optic observed in real time by evanescent wave sensor	90
Multi-probe fiber optic evanescent wave biosensor and its characterization	Using laser diode at 635 nm wavelength as light source; biosensor can interrogate five individual fibers at one time; assays for five separate analyses can be conducted on the same sample	91
Sencil™ project: Development of a percutaneous optical biosensor	Designed to be minimally invasive, disposable and easily readable to make frequent measurements of various analytes in vivo over a period of 1-3 months; uses photonic sensing of a chemical reaction that occurs in a polymer matrix bound to the internal end of a chronically implanted percutaneous optical fiber	92
Effect of taper geometries and launch angle on evanescent wave penetration depth in optical fibers	Evanescent wave penetration depths of the order of the size of living cells have been achieved by optimizing the parameters relating geometry of tapered fibers; theoretical results for variation of penetration depths of evanescent waves as a function of taper ratios of tapered fiber in various taper geometries, taper length and launch angles	93
Structure study of fiber optical evanescent wave biosensor	In order to improve its detection limit and field applicability, the evanescent wave strength of fiber probe and the compactness of the system are studied	94
Evanescent wave optic fiber biosensor	FITC-labeled goat anti-human IgG were covalently immobilized on 3-aminopropyltriethoxysilane and glutaraldehyde to modify the distal end of a fiber-optic probe	95
For detecting biomarkers in biosamples	A nanogold particle (NGP), when placed at an appropriate distance from a	96

	fluorophore, can effectively enhance the fluorescence by transferring the free electrons of the fluorophore, normally used for self-quenching, to the strong surface plasmon polarization field of the NGP	
A novel type of fiber optic biosensor	First microstructured polymer optical fiber (mPOF) fabricated from Topas cyclic olefin copolymer	97

5. Chemiluminescence measurements

A molecular assembly in which a conjugated polymer is interfaced with a photodynamic protein is described by Ayyagari et al. [103]. The conjugated polymer, functionalized with biotin, is designed such that it can be physisorbed on or chemically grown off a glass surface. The streptavidin-derivatized protein is immobilized on the biotinylated polymer matrix through the strong biotin-streptavidin interactions. The assembly, built on the surface of an optical fiber or on the inside walls of a glass capillary form an integral part of a biosensor for the detection of environmental pollutants such as organophosphorus-based insecticides. The protein in the system can be replaced by any biological macromolecule of interest. These authors study one specific case, the inhibition of the enzyme alkaline phosphatase. The enzyme catalyzes a reaction producing an intermediate compound that chemiluminesces, and the chemiluminescence signal is monitored to detect and quantify insecticides such as paraoxon and methyl parathion. Preliminary results indicate ppb level detection with response time less than 1 minute.

Chen et al. [104-106] report a technique to immobilize a multilayer enzyme assembly on an optical fiber surface. A multilayer of an enzyme, alkaline phosphatase, was immobilized by chemical cross-linking on an optical fiber surface. Chemiluminescence, ellipsometry, and surface plasmon resonance were used to characterize the structure and activity of the assembly. A chemiluminescence-based fiber optic biosensor utilizing this immobilization technique has been developed for the detection of organophosphorus-based pesticides.

A fiber optic biosensor based on the electrochemiluminescence of luminol has been developed for glucose and lactate flow injection analysis by Marquette and Blum [107,108]. The electrochemiluminescence of luminol was generated using a glassy carbon electrode polarised at +425 mV vs. a platinum pseudo-reference electrode. After optimisation of the reaction conditions and physicochemical parameters influencing the sensor response, the measurement of hydrogen peroxide could be performed in the range 1.5 pmol-30 nmol. Glucose oxidase or lactate oxidase, were immobilised on polyamide and collagen membranes. With collagen as the enzymatic support, the detection limits for glucose and lactate were 60 pmol and 30 pmol, respectively, whereas with the enzymatic polyamide membranes, the corresponding values were 150 pmol and 60 pmol.

A chemiluminescence biosensing system for antioxidants was developed by Palaoran et al. [109] based on luminol and hematin co-immobilized on a cellulose membrane disc. The concentration of the antioxidant was quantified through the measurement of the inhibition of the chemiluminescence emitted when hydrogen peroxide was introduced into the reagent phase. The instrumentation employed in the measurement was a fabricated luminometer employing optical fibers and a UV- enhanced photodiode transducer. The minimum detectable concentration was 100 μM, and the response time was less than 60 seconds.

The enhanced chemiluminescence (CL) reaction of the luminol-H_2O_2-horseradish peroxidase (HRP) system with immobilized HRP using microencapsulation in a sol-gel matrix has been used to develop a biosensor for p-iodophenol, p-coumaric acid, 2-naphthol and hydrogen peroxide [110]. The detection limits obtained for p-iodophenol, p-coumaric acid and 2-naphthol were 0.83 μM, 15 and 48 nM, respectively. Direct enzyme immobilization onto the end of the optical fibre permits the construction of a remote enhanced CL biosensor. This remote biosensor has been applied to hydrogen peroxide assay (detection limit 52.2 μM).

In other study, an optical fiber bienzyme sensor based on the luminol chemiluminescent reaction was developed and demonstrated to be sensitive to glucose [111]. Glucose oxidase and horseradish peroxidase were co-immobilized by microencapsulation in a sol-gel film derived from tetraethyl orthosilicate. The calibration plots for glucose were established by the optical fiber glucose sensor fabricated by attaching the bienzyme silica gel onto the glass window of the fiber bundle. The linear range was 0.2-2 mM and the detection limit was approximately 0.12 mM.

Recently, Magrisso et al. [112] describe the construction of a novel computerized multi-sample temperature-controlled luminometer for a fiber array-based biosensor to monitor circulating phagocyte activity. It can perform simultaneously integral measurements of chemiluminescence emitted from up to six samples containing less that 0.5 μl whole blood while the samples and detector do not change their position during the measurement cycle. The optical fibers in this luminometer are used as both light guides and solid phase sample holders. The latter feature of the instrument design simplifies the assessment process of both the extra-cellular and the intra-cellular parts of the phagocyte-emitted chemiluminescence using the same system. This new technology may find use in a wide range of analytical luminescence applications in biology, biophysics, biochemistry, toxicology and clinical medicine.

6. Bioluminescence measurements

A biosensor associates a bioactive sensing layer with a suitable transducer giving a usable output signal. Although the selective molecular recognition of the target analyte can theoretically be achieved with various kinds of affinity systems, in most biosensors, enzymes are concerned. The biocatalysts are generally immobilized on an artificial support placed in close contact with the transducer. Covalent immobilization is preferable because it prevents the leakage of enzymes from the support. This can now be easily achieved with the availability of commercially preactivated membranes. Sensing layers prepared with such membranes were used for the development of amperometric as well as luminescence-based fiber-optic biosensors. In addition to the target analyte, enzymatic reactions generally involve one or two other substrates, which must be added to the reaction medium when an enzyme based biosensor is operated. The sensing scheme, and therefore the transducer associated with the sensing layer, determines the sensitivity of an enzyme-based sensor. Due to the peculiar nature of one of the reaction products, i.e., light, which can be detected at a very low level, bioluminescence and chemiluminescence reactions associated with an optical transduction can be used to design highly sensitive biosensors.

In 1990, Gautier et al. [113] investigated highly selective and ultra-sensitive biosensors based on luminescent enzyme systems linked to optical transducers. In this way, a fiber optic sensor with

immobilized enzymes was designed; the solid-phase bio-reagent was maintained in close contact with the tip of a glass fibre bundle connected to the photomultiplier tube of a luminometer. A bacterial luminescence fiber optic sensor was used for the determination of NADH. Various NAD(P)-dependent enzymes, sorbitol dehydrogenase, alcohol dehydrogenase and malate dehydrogenase, were co-immobilized on preactivated polyamide membranes with the bacterial system and used for the determination of sorbitol, ethanol and oxaloacetate at the nanomolar level with a good precision. The same authors, also in 1990, described a multi-function biosensor for the determination of either ATP or NADH using a single bioluminescence-based fiber optic probe [114]. This was made possible by co-immobilizing the firefly luciferase from Photinus pyralis for ATP analysis with the bacterial luciferase/oxidoreductase system from Vibrio harveyi for NADH analysis, on the same pre-activated polyamide membrane. In 1992, Gautier describes the role of membranes in the design of the main types of biosensors proposed in this time [115].

The reproducible and easy immobilization of receptors on sensor surfaces is a prerequisite for the development of receptor-based fiber optic biosensors. Using a fused silica fiber as the transducer, binding processes of luminescently labeled ligands can be monitored by evanescent wave sensor technology. The vesicle fusion technique was chosen for the immobilization of membrane-bound receptors in order to preserve their binding specificity and activity, by embedding them in an environment similar to a lipid bilayer. The results of initial studies of repetitive cycles of lipid layer deposition and removal, indicating good reproducibility of lipid layer formation on the fiber, are presented by Klee et al. [116]. Using the binding of fluorescently labeled streptavidin to a biotinylated lipid layer as a model system for receptor-ligand interaction, good sensitivity, combined with low non-specific binding were observed.

The characteristics and performance of biosensors mainly depend on the properties of the bioactive layer associated with the transducer. Two approaches are addressed by Blum et al. [117]: the designs of a) a reagentless fiber-optic biosensor with cosubstrates embedded in the vicinity of the immobilized enzyme; b) a compartmentalized layer with sequential enzymatic reactions for improved signal detection. Concerning the reagentless biosensor, Blum et al. focus on the bacterial bioluminescent system involving two enzymes, oxidoreductase and luciferase, for NADH detection. When associating such a self-contained sensing layer with the transducer, the biosensor can be operated for 1.5 h without reloading. For the studies of compartmentalized enzyme layers, the sequential bienzymatic system lactate oxidase-peroxidase is chosen as a model. The hydrogen peroxide produced by the lactate oxidase reaction serves as a cosubstrate for the chemiluminescence reaction of luminol catalyzed by peroxidase. Compartmentalization of the bioactive layer is obtained by immobilizing the two enzymes separately on different membranes stacked at the sensing tip of the fiber-optic sensor. When using such a design, a 20-fold increase of the sensor response for lactate is obtained compared with a sensor including lactate oxidase and peroxidase randomly coimmobilized on the same membrane. Latter, the same research group developed a fiber optic biosensor for the specific and alternate determination of ATP, ADP and AMP [118]. The sensing layer is arranged by compartmentalizing the tri-enzyme sequence adenylate kinase - creatine kinase - firefly luciferase. The two kinases are covalently co-immobilized on a collagen membrane, whereas firefly luciferase is bound alone on a separate one. For the specific determination of each adenylic nucleotide, three particular reaction media are needed with

which flow-injection analysis can be performed in the 2.5-2500 pmol for ATP, 10-2500 pmol for ADP and 25-5000 pmol for AMP linear ranges. When the three nucleotides are present simultaneously in the same sample, the transient inhibition of adenylate-kinase activity by adenosine 5'- monosulphate enables their specific and alternate measurement.

Also, a portable biosensor has been developed to meet the demands of field toxicity analysis [119]. This biosensor consists of three parts, a freeze-dried biosensing strain within a vial, a small light-proof test chamber, and an optic-fiber connected between the sample chamber and a luminometer. Various genetically engineered bioluminescent bacteria were freeze-dried to measure different types of toxicity based upon their modes of action. GC2 (lac::luxCDABE), a constitutively bioluminescent strain, was used to monitor the general toxicity of samples through a decrease in its bioluminescence, while specific toxicity was detected through the use of strains such as DPD2540 (fabA::luxCDABE), TV1061 (grpE::luxCDABE), DPD2794 (recA::luxCDABE), and DPD2511 (katG::luxCDABE). These inducible strains show an increase in bioluminescence under specific stressful conditions, i.e. membrane-, protein-, DNA-, and oxidative-stress, respectively. The toxicity of a sample could be detected by measuring the bioluminescence 30 min after addition to the freeze-dried strains. Using these strains, many different chemicals were tested and characterized. This portable biosensor, with a very simple protocol, can be used for field sample analysis and the monitoring of various water systems on-site.

Recently, biotin was covalently coupled with alginate in an aqueous-phase reaction by means of carbodiimide-mediated activation chemistry to provide a biotin-alginate conjugate for subsequent use in biosensor applications [120]. The synthetic procedure was optimized with respect to pH of the reaction medium (pH 6.0), the degree of uronic acid activation (20%), and the order of addition of the reagents. The new biotin-alginate conjugate was used for the encapsulation of bioluminescent reporter cells into microspheres. A biosensor was prepared by conjugating these biotinylated alginate microspheres to the surface of a streptavidin-coated optical fiber, and the performance of the biosensor was demonstrated in the determination of the antibiotic, mitomycin C as a model toxin.

Also, ionic and colloid gold influence on luminous bacteria Photobacterium phosphorum B7071 bioluminescence have been studied by Gruzina et al. [121]. It was shown that both forms of gold inhibited bioluminescence of the studied bacteria depending on their concentrations and incubation time with cells. The approaches to creation of biosensor systems based on luminous bacteria and semiconductor structures or optical fibers are proposed.

Eltoukhy et al. [122] describes a bioluminescence detection lab-on-chip consisting of a fiber-optic faceplate with immobilized luminescent reporters/probes that is directly coupled to an optical detection and processing system-on-chip fabricated in a 0.18 μm process. The lab-on-chip is customized for such applications as determining gene expression using reporter gene assays, determining intracellular ATP, and sequencing DNA.

On the other hand, hydrophobic phosphorescent Pt-porphyrins have been used for the development of luminescent polymer films designed for fibre-optic oxygen sensors [123]. Luminescent and quenching characteristics of several Pt-porphyrins incorporated into polymer matrices have been studied to optimize the preparation of sensitive coatings for fibre-optical sensors. The films thus obtained have been used for fibre-optical oxygen monitoring in solutions. More recent, a simple system

for enzymatic flow-injection analysis of metabolites is described by Ovchinnikov et al. [124], which is based on the phosphorescence lifetime based detection of molecular oxygen using phase-modulation techniques and a simple instrument phosphorescence phase detector equipped with a fibre-optic probe. The phase detector is connected to the oxygen sensor membrane and allows real-time continuous monitoring of the phosphorescence phase shift. This parameter is related to the phosphorescence lifetime of the oxygen probe, therefore giving a measure of the dissolved oxygen concentration, and its changes as a result of the enzymatic oxidative reaction with the substrate. The sensor membrane is positioned in a compact integrated flow-through cell and exposed to the flow stream. Using glucose as a test analyte and glucose oxidase enzyme, two different sensor setups were tested: 1) the membrane type biosensor in which the enzyme is immobilized directly on the oxygen sensor membrane; 2) the microcolumn type biosensor in which the enzyme is immobilized separately, on a microparticle sorbent (controlled pore glass) and put into a microcolumn with the oxygen sensor membrane placed at the column outlet. In either case a new type of oxygen sensitive material was used, which provides a number of advantages over the existing materials. In this material the oxygen-sensitive coating was applied on a microporous scattering support, the latter comprised of a layer of cellulose particles on polyester support.

7. Refractive index

Akkin et al. [125] describe a fiber-based optical biosensor, which is capable of detecting ultra-small refractive index changes in highly scattering media with high lateral and longitudinal spatial resolution. The system is a dual channel phase-sensitive optical low coherence tomography system that measures relative optical path length differences between the orthogonal modes of the polarization-maintaining fiber.

Tubb et al. [126] describe a new design of optical fibre surface plasma wave chemical sensor. The basic sensor consists of a tapered single-mode optical fibre with a thin layer of silver evaporated onto the tapered section. The gradually changing diameter of the fibre along the taper and the variation in silver depth around the taper result in a distributed coupling between the guided mode of the fibre and the surface plasma wave. As a result, the coupling to the surface plasma wave occurs over an enlarged spectral range. The device shows good sensitivity to refractive index with refractive index changes of $5x10^{-4}$ being detectable.

Also, a biosensor based on long period grating (LPG) technology has been used to demonstrate the detection of large molecules (proteins) and small molecules (pesticides) [127]. The LPG sensor is a spectral loss optical fiber based system that provides direct detection of large molecules, by using an antigen or antibody modified hydrogel, without the need for secondary amplification. The binding of the specific target results in a mass increase that produces a localized refractive index change around the LPG region and thus a spectral shift in the observed wavelength loss band. The magnitude of the observed shift can be correlated to target concentration. The HIV protein p24 was directly detected at 1 ng/mL with a specific signal that was 5-7 times that of the system noise. A direct and indirect competitive assay was demonstrated with the target atrazine. The sensitivity of the two competitive assay formats was in the range of 10-50 ng/mL.

The investigation group of Cheng presents a novel class of label-free fiber-optic localized surface plasmon resonance sensor which retains many of the desirable features of the propagating surface plasmon resonance sensors, namely, the sensitivity to the refractive indices of bulk liquids and the ability to interrogate biomolecular interactions without a label [128,129]. The sensor was constructed on the basis of modification of the unclad portion of an optical fiber with self-assembled Au colloids. The sensor is easy to fabricate and can be constructed by simple optical designs. Moreover, the sensor has the potential capability for on-site, in vivo, and remote sensing, can be easily multiplexed to enable high-throughout screening of biomolecular interactions, and has the potential use for disposable sensors.

Optical sensors based on the excitation of surface plasmons (SP) have proven to hold great potential for biomolecular interaction analysis and detection of biological analytes. In order to reach out from centralized laboratories, the surface plasmon resonance (SPR) sensors have to be developed into robust portable sensing devices capable of operating in the field. In this way, an optical fiber SPR sensor based on polarization-maintaining fibers and wavelength modulation is presented by Piliarik et al. [130]. It is demonstrated that this design provides superior immunity to deformation of optical fibers of the sensor and, thus allows for more accurate SPR measurements under realistic operation conditions. Experimental results indicate that this fiber-optic SPR sensor is able to resolve refractive index changes as low as $4x10^{-6}$ under moderate fiber deformations.

The micro- and nano-scale miniaturization of chemical and biochemical sensors is of great scientific and technological interest and in the last decade, much effort was focused on miniaturizing fiber-optic SPR sensors. In this way, a highly sensitive micrometer-sized optical fiber affinity biosensor is reported based on the localized SPR in gold nanoparticles adsorbed at an end-face of an optical fiber; this sensor probes the affinity between biological molecules in real time without any labeling of the analyte; the highest resolution of 10^{-5} in refractive index units is demonstrated with a red-light-emitting diode used as a light source [131]; a novel class of fiber-optic biosensor that exploits the localized SPR of self-assembled gold colloids on the grating portion of a long-period fiber grating is proposed [132]; Chang et al. [133,134] present a sensitive nano-optical fiber biosensor made by shaping a fiber to form a taper with a tip size under 100 nm; a 3-D coded finite-difference time-domain approach verifies the excitation of the surface plasmon wave and the differences among its intensities in media of various refractive indices; Lin et al. [135] developed a side-polished multimode fiber sensor based on SPR as the transducing element with a halogen light source; the SPR fiber sensor is side polished until half the core is closed and coated with a 37 nm gold thin film by dc sputtering; the SPR curve on the optical spectrum is described by an optical spectrum analyzer and can sense a range of widths in wavelengths of SPR effects; the measurement system using the halogen light source is constructed for several real-time detections that are carried out for the measurement of the index liquid detections for the sensitivity analysis; the sensing fiber is demonstrated with a series of refractive index liquids and a new type of the fiber-optic microsensor for SPR was created on the basis of the fabrication technology of optical fiber probes in near-field scanning optical microscopy (NSOM) [136]. The newly developed SPR microsensors were prepared by coating a gold-metallic film on the chemically etched single-mode fiber containing a conical core. They were applied to the real-time monitoring of the refractive index (RI) of transparent liquids flowing in the microfluidic device.

In the last years, high sensitivity chemical and biological sensors based on etched core fiber Bragg gratings that detect change in the index of refraction of surrounding solutions, were developed to measure the index of refraction of different solutions [137-140] and compact three segmented multimode fiber modal interferometer for high sensitivity refractive-index measurement also have been described [141].

On the other hand, fiber-optic waveguides based Micro-Opto-Electro-Mechanical Systems (MOEMS) form a significant class of biosensors which have notable advantages like light weight, low cost and more importantly, the ability to be integrated with bio-systems. Iintegrated microfluidic fiber-optic waveguide biosensor is presented by Chandrasekaran and Packirisamy [142]. The phenomenon of evanescence is employed for sensing mechanism of the device. Herein, the fiber-optic waveguide is integrated with bulk micromachined fluidic channel across which different chemical and biological samples are passed through. The significant refractive index change due to the presence of biological samples that causes the evanescent field condition in the waveguides leads to optical intensity attenuation of the transmitted light. The study of the modulation in optical intensity is used to detect the properties of the species used in the evanescent region. The intensity modulation of light depends upon the geometry of the waveguide, the length of evanescent field, the optical properties of specimen used for producing evanescence and the changes in the properties by their reaction with other specimen. Therefore, this device is proposed for biosensing applications.

8. Other techniques

Pepper [143] discuss the potential use of nonlinear optical phase conjugation to enhance the performance of various classes of optical interferometric sensors and optical fiber biosensor devices, with potential application to trace-compounds detection of explosives and other species. Examples include Michelson interferometers, laser homodyne sensors, ellipsometers, and modulation spectrometers. Compensated interferometric devices using nonlinear optical phase conjugation may lead to a new class of fieldable remote sensor which is robust, compact, inexpensive, and portable, with the capability of functioning in real-world environments.

An interferometric optical fiber microcantilever beam biosensor has successfully demonstrated real time detection of target molecules [144]. The microcantilever biosensor effectively combines advanced technology from silicon micromachining, optical fiber sensors, and biochemistry to create a novel detection device. This approach utilizes affinity coatings on micromachined cantilever beams to attract target molecules. The presence of the target molecule causes bending in the cantilever beam, which is monitored using an optical displacement system. Dose-response trials have shown measured responses at nanogram ml^{-1} concentrations of target molecules.

A D-type fiber biosensor based on SPR technology and heterodyne interferometry is presented by Chiu et al. [145]. The sensing device is a single-mode optical fiber in which half the core is polished away and a thin-film layer of gold is deposited.

A fiber-optic sensor is designed based on multicavity Fabry-Perot interferometry for the study of optical thickness in self-assembled thin-film layers [146]. This miniature sensor is applicable not only to the measurement of self-assembled polyelectrolyte layers but also to the immobilization of proteins such as immunoglobulin G.

Recently, a new method of optical switch design is proposed, which is used in optical fiber biological protein chips [147].

Also, in the last year, Rindorf et al. [148] present the first incorporation of a microstructured optical fiber (MOF) into biochip applications. A 16-mm-long piece of MOF is incorporated into an optic-fluidic coupler chip, which is fabricated in PMMA polymer using a CO_2 laser. The developed chip configuration allows the continuous control of liquid flow through the MOF and simultaneous optical characterization. While integrated in the chip, the MOF is functionalized towards the capture of a specific single-stranded DNA string by immobilizing a sensing layer on the microstructured internal surfaces of the fiber. The sensing layer contains the DNA string complementary to the target DNA sequence and thus operates through the highly selective DNA hybridization process. Optical detection of the captured DNA was carried out using the evanescent-wave-sensing principle. Owing to the small size of the chip, the presented technique allows for analysis of sample volumes down to 300 nL and the fabrication of miniaturized portable devices.

Such as we described above, there is an increasing demand for sensitive detection systems which are required to detect analytes in often very dilute and diverse circumstances. Fiber-optic biosensors have recently gained a lot of interest, and different schemes have been proposed and applied to detect a wide variety of analytes. The antibody-antigen or enzyme-analyte recognition or reaction provides the basis for the sensitivity and/or selectivity of the reaction. The transduction of the biochemical signal to an electrical signal is often a critical step wherein a large fraction of the "signal loss", for example, fluorescence (by quenching) may occur. This leads to deleterious effects on the sensitivity and selectivity of the biosensor, besides decreasing the quality of the reproducibility of the biosensor. A fractal analysis is presented for the binding of pyrene in solution to β-cyclodextrin attached to a fiber-optic chemical sensor [149]. The fractal analysis provides novel physical insights into the reactions occurring on the fiber-optic chemical surface and should assist in the design of fiber-optic chemical sensors [150,151].

Noto et al. [152] report on molecular weight dependence measurements for an optical resonance biosensor. A dielectric micro-particle is evanescently coupled with an optical fiber for the resonance stimulation, and a shift of the resonance wavelength is measured to monitor protein monolayer formation on the micro-particle surface. Wavelength shifts for proteins over two orders of magnitude in molecular weight are measured.

Walt use optical imaging fibers to fabricate a chemical and biochemical sensor that utilizes the ability of living cells to respond to biologically significant compounds. The sensor is created by randomly dispersing single NIH 3T3 mouse fibroblast cells into an optically addressable fiber-optic microwell array such that each microwell accommodates a single cell. The cells are encoded to identify their location within the array and to correlate changes or manipulations in the local environment to responses of specific cell types [153,154].

The fabrication and testing of a novel waveguide based biosensor for sensing in microchannels is presented by Deverkadra and McShane [155]. Unlike evanescent wave sensing, which has large intrinsic losses, an absorption based sensing scheme was introduced. The fabricated waveguide sensor has excellent transparency in the UV-Vis region of the spectra and is able to perform simultaneous detection of multiple analytes in microchannels. The optical interconnection to the device was achieved

using self-aligned V-grooves etched on the silicon wafer using KOH etching. The fabricated device has applications in micro total analysis systems for measuring various analytes in the microchannels, tissue engineering for continuous measurement of the oxygen in the artificial scaffolds, and fluorescence-based measurement by attaching fluorescent dyes to the waveguide end face in the microchannel.

Finally, Konry et al. [156,157] demonstrate that it is possible to create surface-conductive fiber optics, upon which may be electropolymerized a biotinylated polypyrrole thin film, which may then be used to affinity coat the fiber with molecular recognition probes. This fiber-optic electroconductive surface modification is done by the deposition of a thin layer of indium tin oxide. Thereafter, biotin - pyrrole monomers are electropolymerized onto the conductive metal oxide surface and then exposed to avidin. Avidin biotin interactions were used to modify the fiber optics with biotin-conjugated cholera toxin B subunit molecules, for the construction of an immunosensor to detect cholera antitoxin antibodies.

9. Applications

Optical fibers have been used for a variety of sensing applications. The small physical dimensions and the ease with which they can be used for multiplexed analyte detection make them ideal platforms for sensing. Bioanalytical microsystems based on miniaturized biosensing elements could find wide applications in DNA analysis, drug discovery, medical diagnostics, and environmental monitoring as well as in protection against bioterrorism. Miniaturization, portability, multianalyte potential, and interfacing with electronic functions are critical elements for biosensing devices to meet the demands in these fields.

Optical fibers have been used to develop sensors based on nucleic acids and cells. Sensors employing DNA probes have been developed for various genomics applications and microbial pathogen detection. Live cell-based sensors have enabled the monitoring of environmental toxins, and have been used for fundamental studies on populations of individual cells [158].

Advances in nanotechnology have recently led to the development of fiber optics-based nanosensor systems having nanoscale dimensions suitable for intracellular measurements. The possibilities to monitor in vivo processes within living cells could dramatically improve our understanding of cellular function, thereby revolutionizing cell biology. Fiber optic sensors provide significant advantages for in situ monitoring applications due to the optical nature of the excitation and detection modalities. Fiber optics sensors are not affected by electromagnetic interferences from static electricity, strong magnetic fields, or surface potentials. Another advantage of fiber optic sensors is the small size of optical fibers, which allow sensing intracellular/intercellular physiological and biological parameters in microenvironments. Biosensors, which use biological probes coupled to a transducer, have been developed during the last two decades for environmental, industrial, and biomedical diagnostics. Nanotechnology has been revolutionizing important areas in molecular biology, especially diagnostics and therapy at the molecular and cellular level. The combination of nanotechnology, biology, and photonics opens the possibility of detecting and manipulating atoms and molecules using nanodevices, which have the potential for a wide variety of medical uses at the cellular level. The nanoprobes were fabricated with optical fibers pulled down to tips with distal ends having sizes of approximately 30–50 nm. The nanoscale size of this new class of sensors, allows for measurements in the smallest of

environments. One such environment that has evoked a great deal of interest is that of individual cells. Using these nanobiosensors, it has become possible to probe individual chemical species in specific locations throughout a cell [159,160].

Biosensors utilizing immobilized antibodies have become increasingly useful due to the specificity of antigen–antibody interactions and the fact that the biosensors can be used where typical cuvette-based spectroscopic measurements are not practical. Of particular usefulness are fiber optic-based biosensors, as the fiber upon which the antibody is immobilized serves as a conduit for measuring optical changes occurring during the antigen–antibody binding event.

Fluorescence-based biosensors provide advantages over other forms of biosensors in that the high signal- to-background discrimination associated with fluorescence is coupled to the antigen binding event. Biosensors utilizing fluorescence may also take advantage of evanescent wave excitation, where excitation light propagating through the fiber excites fluorophores within close proximity (.100 nm) to the fiber surface. Excitation via this technique results in fluorescencefrom labeled antigens only when the antigensbound by antibodies are within the evanescent wave. Thus, background signals from bulk solution contribute little or nothing to the total measured fluorescence, in contrast to cuvette-based measurements where signal from unbound antigen may dominate. Evanescentwave biosensors are also extremely useful for conducting analyses in opaque media, heterogeneous solutions, or colloidal suspensions.

One continuing problem of using fluorescence-based fiber optic biosensors is that of variations in signal response among individual fibers. Wadkins et al. [161] addressed this problem by labeling a portion of the immobilized capture antibody with the fluorescent cyanine dye Cy5.5 (emission λ_{max} = 696 nm). The antigen was then labeled with fluorescent Cy5 (emission λ_{max} = 668 nm). Both fluorophores were excited by 635 nm light, and their emission was collected using both a fiber optic spectrometer and a biosensor optimized to collect fluorescence at two wavelengths. The fluorescence from the Cy5.5-labeled capture antibody served as a calibration signal for each fiber and corrected for differences in optics, fiber defects, and varying amounts of capture antibody present on the fiber.

Also, Alexa Fluor 647 (AF647) is a relatively new fluorescent dye, which has peak excitation at 650 nm and peak emission at 665 nm. It has a molecular weight of aproximately 1300. These properties are similar to the more commonly employed dye Cy5. On the other hand, the RAPTOR is a portable, automated biosensor that, like its predecessor the Analyte 2000, is useful for on-site analysis of food, water, or clinical samples for biological contaminants. The performance of the AF647 was explored as an alternative to Cy5 for immunoassays on the RAPTOR. The RAPTOR performs sandwich fluoroimmunoassays on the surface of small polystyrene optical waveguides for analyte detection. Primarily, due to the self-quenching characteristics of Cy5, AF647 is substantially more effective in fluoroimmunoassays, yielding over twice the signal for any given analyte concentration. The limitations of Cy5 were elucidated with an immunoassay for ricin, while the advantages of AF647 were demonstrated in both direct binding assays as well as in a sandwich immunoassay for staphylococcal enterotoxin B [162]. The principal applications of these biosensors are summarized in table 2.

Table 2. Applications of fiber optic biosensors.

Analyte	Remarks	Applications	Ref.
Sensitivity of 0.01 nmol l^{-1} obtained from detection of Cy5 serial solutions with various concentrations	Based on principle of evanescent wave while light	Legionella pneumophila	163
Biological agent	Analyte 2000 fiber optic biosensor, which performs four simultaneous fluorescent sandwich immunoassays on the surface of tapered optical probes	Aerosolized bacterial sample	164
Bacillus globigii spores, ovalbumin, Erwinia herbicola, and MS2 coliphage	Employing evanescent wave illumination on polystyrene fiber optic waveguides, RAPTOR performed fluorescent immunoassays	During a 4-day laboratory trial assaying 144 blind samples	165
Giardia cysts (parasitic protozoan)	Using a fluorescent sandwich immunoassay on surface of short polystyrene optical probes with capture antibody adsorbed to probe surface; target analytes bound to fiber by capture antibodies are detected with fluorescently labeled tracer antibodies, which are held in a separate reservoir	Water quality monitoring	166
Escherichia coli O157:H7 and Shiga-like toxins	Polyclonal antibody immobilized on polystyrene fiber waveguides through a biotin-streptavidin reaction that served as the bacteria and toxin capture entity; AF647 dye-labeled antibodies against E. coli O157:H7 or SLTS incubated with the waveguides used to detect cells or toxin and generate a specific fluorescent signal, which was acquired by launching a 635 nm laser-light from an Analyte 2000; fluorescent molecules within several hundred nanometers of the fiber excited by evanescent wave, and a portion of the emission light from fluorescent dye transmitted by the fiber and collected by a photodetector at wavelengths of 670 to 710 nm quantitatively	Ground beef samples	167
Escherichia coli O157:H7	Using antibody-immobilized biconical tapered fiber sensors	First order kinetic model proposed to quantify rate of attachment to pathogen to sensor surface	168
Detection of Escherichia coli O157:h7	With a portable evanescent-wave biosensor with silica and polystyrene waveguides; by launching light from a 635-nm laser diode	In 10 and 25 gram ground beef samples	169
Pathogens	Based upon antigen-antibody interactions; sensor	Food-borne	170

	comprises a nanoporous GeSe channel waveguide fabricated on a substrate, with an intermediate cladding buffer layer ($GeSe_2$), which is required when the substrate does not transmit at the desired λ; light from a laser source is then coupled through a fiber and prism into the waveguide and collected with the help of a lens into a detector	pathogens	
Detection of live Pseudomonas aeruginosa	Using a sensing film containing a fourth-generation hydroxy-terminated polyamidoamine (PAMAM) dendrimer (i.e., G4-OH) and SYTOX Green fluorescent nucleic acid stain	In water and air	171 172 173
Detection of Protein A produced by Staphylococcus aureus	In immunosensor, using a 40 mV argon-ion laser that generated laser light at 488 nm together with plastic optical fiber and antibodies to protein A physically adsorbed onto the fiber; principle of detection involved a sandwich immunoassay with fluorescein isothiocyanate conjugated with anti-(protein A) immunoglobulin G to produce signals of the antigen-antibody reaction	In clinical specimens and foods	174
Staphylococcus aureus and Streptococcus pneumoniae colonies	By evanescent wave fibre optic sensor; biosensor monitors interactions between analytic (bacteria) and the evanescent field of an optical fiber passing through the culture media where the bacteria grows	Detecting and monitoring aerobiological pathogen contamination in hospital environment	175 176
Detection of listeria monocytogenes and salmonella enteritidis	Two optical evanescent wave immunosensors evaluated: Antibody-coupled fiber-optic biosensor and SPR immunosensor; in fiber optic sensor, polyclonal antibodies for test organisms immobilized on polystyrene fiber wave-guide with streptavidin-biotin chemistry	In food	177
Detection of listeria and Salmonella typhimurium	Using principle of fluorescence resonance energy transfer (FRET);labeled antibody-protein G (PG) complexes formed via incubation of anti-Salmonella antibodies labeled with FRET donor fluorophores (AF546) and PG labeled with FRET acceptor fluorophores (AF594); using silanization, labeled antibodies-PG complexes were then immobilized on decladded, tapered silica fiber cores to form evanescent wave-sensing region	In ground pork samples	178 179
Salmonella	Compact fiber-optic immunosensor using tapered fibers and acoustic enhancement	Biomedical applications	180

Monitoring of the genetic responses of all the cells in the array	Cell array biosensor composed of thousands of individual bacteria cells; single cell array produced by immobilizing cells on optical imaging fiber; high-density array of microwells fabricated on optical imaging fiber's distal face by selectively etching individual fibers cores; each microwell used to accommodate a single living bacterium	A reporter gene that responds to the presence of environmental pollutants	181
Detection of Yersinia pestis fraction 1 antigen	Using argon ion laser (514 nm) to launch light into a long-clad fiber and measures fluorescence produced by an immunofluorescent complex formed in the evanescent wave region	In phosphate-buffered saline, serum, plasma, and whole blood	182
Nucleic acids	Fiber optic evanescent wave biosensor by using a 1 mm crystal fiber and a 635 nm laser diode; optical fiber chemically modified to produce a silylated surface; covalent binding occurs applying an amino-terminal nucleic acid to surface of fiber; to test sensitivity and specificity of biosensor, three consecutive trials were performed: direct detection of Cy5-dCTP serial dilution, model hybridization of two oligonucleotide probes and oligonucleotide probe hybridization with the target nucleic acid labeled with Cy5 by PCR amplification	Detection of bacterial DNA	183
Nucleic acids	Based on chemiluminescence; DNA probes covalently immobilized onto distal end of optical fiber bundle; hybridization of HRP (horseradish peroxidase)-labeled complementary nucleotides to the immobilized probes was detected by enhanced chemiluminescence	Detection of DNA hybridization; diagnostic applications	184
Nucleic acids	Short single-stranded DNA (ssDNA) oligonucleotides can be grown on the surface of fused silica by automated nucleic acid synthesis; immobilized ssDNA deposited at a desired average density	Control of selectivity coefficients and relative surface affinities	185
Nucleic acids	Thiazole orange dyes derivatized with ethylene glycol linkers of various lengths, and covalently linked to the 5′ end of the oligonucleotides after solid-phase synthesis; labeled oligonucleotides exhibited enhanced fluorescence upon hybridization to complementary DNA sequences at the surfaces of optical fibers, providing for a self-contained labeling strategy	Development of a self-contained DNA biosensor on a fiber optic surface	186 187
Nucleic acids	Surfaces of two sets of fused silica optical fibers	Fluorimetric	188

	were functionalized with hexaethylene oxide linkers from which decaadenylic acid oligonucleotides	detection of T/AT triple-helical DNA formation	
Nucleic acids	Based on hybridization and temperature-induced dissociation of synthetic oligonucleotides.; hybridization pair consists of biotin labeled 38 mer oligonucleotide immobilized to streptavidin-coated optical fiber and fluorescently-labeled near-complementary oligonucleotide reporter sequence	Detection of radiation-induced or chemically-induced oxidative DNA damage	189
Nucleic acids	Based on the combination of photon counting and laser induced fluorescence in the evanescent field on the optical fiber surface	Characterization of nucleic acid hybridization	190
Nucleic acids	Evanescent wave DNA biosensor based on novel molecular beacons (MB) which are oligonucleotide probes that become fluorescent upon hybridization with target DNA/RNA molecules; biotinylated MBs designed and immobilized on an optical fiber core surface via biotin-avidin or biotin- streptavidin interactions	Analysis of specific γ-actin mRNA sequences amplified by polymerase chain reaction	191 192 193
Simultaneous detection of multiple genes	Optical fibers were first treated with poly-l-lysine, and then were made into fiber-optic DNA biosensors by adsorbing and immobilizing the oligonucleotide probe on its end; assembling fiber-optic DNA biosensors in a bundle in which each fiber carried a different DNA probe	Hybridization of fluorescent labeled cDNA of p53 gene, N-ras gene and Rb1 gene to DNA array was monitored by CCD camera	194
Benzo[a]pyrene DNA adduct	Antibody-based submicron fiber biosensor	Monitoring human exposure and health effects associated with polycyclic aromatic compounds	195 196
Adenosine diphosphate (ADP)	Hexokinase, pyruvate kinase, and glucose-6-phosphate dehydrogenase are coimmobilized in a polyurethane membrane and fixed to a commercial fiber-optic probe; ADP is continuously phosphorylated/dephosphorylated in a cycle catalyzed by the kinases; glucose-6-phosphate formed in hexokinase reaction is oxidized by dehydrogenase, leading to the formation of NADH	Biological applications	197
Adenylic nucleotides (ATP, ADP and AMP)	Luciferin incorporation in the structure of acrylic microspheres with subsequent confinement in a	Measurement of ATP, ADP and AMP	198

	polymeric film	with the same probe	
Hemoglobin protein	By fine tailoring mode dispersion and sensitivity of dual-peak LPGs using light-cladding-etching method	In sugar solution	199
Thrombin	Based on DNA aptamers used as receptors; anti-thrombin DNA aptamers immobilized on silica microspheres, placed inside microwells on distal tip on imaging optical fiber, coupled to a modified epifluorescence microscope	Competitive binding assay using a fluorescein-labeled competitor	200
Detection of activity of telomerase	Based on total internal reflection fluorescence measuring activity of telomerase on sensor surface	In tumor cells	201
Monitoring protein binding kinetics	For measuring the association and dissociation rate constants of the reaction between biomolecules; study qualitative and quantitative aspects	Biomolecular recognition in real time	202 203
Protein detection	Use of a fiber optic coupler as a platform for bioassays/biosensing	Medical diagnostics, environmental monitoring, and food safety	204
Proteins	Lipoproteins interact with unmodified optical-fiber surface; immunoglobulin G does not bind to glass surface; upon glass surface modification with silane, immunoglobulin G binds significantly to optical fiber; high-density lipoproteins and low-density lipoproteins show a differential interaction with glass surface, and their interaction was altered upon modification of glass surface with cholesterol	Study the interaction of blood proteins with solid surfaces	205
Protein C (PC)	Immuno-optical fiber biosensor that utilizes PC-specific biomolecules (PC probes) tagged with fluorophores; method involves immobilizing monoclonal antibody against PC (anti-PC) on the surface of an optical fiber; when PC in a sample is adsorbed to the anti-PC on the fiber, it can be reacted with the fluorophore tagged PC-probe	To diagnose PC deficiency, to monitor PC level in blood of PC deficient patients, and to measure PC in other PC-containing samples, such as PC producing animal cell culture broth or transgenic animal milk	206
Protein C	A tapered quartz fiber is enclosed in a glass tube (capacity 300 μl) and monoclonal antibody against PC (anti-PC) is immobilized on the surface of this fiber	Medical and biological applications	207 208
Total protein	Based on the principles of fiber optic evanescent wave spectroscopy; applies a dye-immobilized porous glass coating on a multi-mode optical fiber	Liquid sample	209

Protein substances	Optical immune sensors based on photoluminescence of porous silicon and fiber optics in combination with enhanced chemical luminescence	In air	210
Binding and studying 6×His-tagged proteins	Novel graft copolymer, poly-(L-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG) with part of the PEG chains carrying a terminal nitrilotriacetic acid group was synthesized for polymeric interface	Biological applications	211
Glutamate	Encapsulated GDH in silica sol-gel film on tip of optical fiber; GDH catalyzes oxidative deamination of glutamate to α-ketoglutarate and simultaneous reduction of NAD+ to NADH; To quantify glutamate, observing rate of change of NADH fluorescence as a function of time; important consideration for continuous in vivo monitoring is incorporation of a self-sustaining NAD+ source	Photochemical enzyme co-factor regeneration for continuous glutamate monitoring with a sol-gel optical biosensor	212
L-glutamate	Comprised of an L-glutamate-sensitive fluorescent gel, spin-coated onto the tip of an optical imaging fiber	From the foregut plexus of the Lepidopteran, Manduca sexta	31
Two fluorophores termed the donor and the acceptor	Using the distance-dependent chemical transduction method of FRET	Detection of myocardial infarction	213 214
Detect porcine reproductive and respiratory syndrome virus	Using gold nanoparticles and FRET	Medical diagnostics	215
Detection of antibodies directed against antigens of Ebola virus strains Zaire and Sudan	Using photo immobilization methodology based on a photoactivatable electrogenerated poly(pyrrole-benzophenone) film deposited upon an indium tin oxide modified conductive surface fiber optic	In animal and human sera	216
Detection of antibodies to viral antigen	Based on a poly(pyrrole-benzophenone) film	For the diagnosis of hepatitis C virus	217
Ammonia, urea, urease and IgG	Using Brilliant Yellow in thin cellulose acetate membrane as pH sensor; by use of gas permeable membrane, urease-immobilized membrane and IgG immobilized membrane	Physiological and clinical applications	218
Bilirubin	By an enzyme-based fiber-optic fluorescence biosensor; bilirubin is oxidized to biliverdin by bilirubin oxidase, and determined by measuring fluorescence intensity change caused by oxygen consumption in enzymatic reaction; bilirubin oxidase is immobilized onto an affinity membrane which is	Biological applications	219

	layered onto an optical indicating membrane		
Bilirubin	Detected indirectly, based on fluorescence quenching of tris(4,7-diphenyl-1,10-phenanthroline) ruthenium chloride by dissolved molecular oxygen	In serum	220
Bilirubin	Following the variation of its yellow absorption band in presence of biocatalytic system haemoglobin/glucose oxidase/glucose	Biological applications	221
Bilirubin and other pigments in bile	Measuring blue light absorbance in the ducts; optical sensing system could be incorporated into a manometry catheter to aid sphincter of Oddi manometry shortening procedure time and reduce radiography exposure	Discriminating between biliary and pancreatic ductal systems	222
A wide variety of both high and low molecular mass analytes	Fiber optic evanescent wave immunosensors	Medical diagnostics	223
Colchicine	Using fluorescent dye N-vinylcarbazole, which contains a vinyl unit making it photo-copolymerizable in the presence of a monomer, 1,2-cyclohexanediol diacrylate, on a quartz surface of an optode slide. Prior to the photopolymerization process the quartz surface was modified with γ-(methacryloxy)propyl trimethoxysilane to introduce vinyl units	In pharmaceutical tablets	224
Cholesterol	Silicone-entrapped tris(4,7-diphenyl-1,10-phenanthroline) ruthenium(II) complex, the luminescence of which is sensitive to oxygen changes, is used as an optical transducer of the oxidation of cholesterol by cholesterol oxidase	Serum samples	225
Cholesterol	Based on fluorescence quenching; $Ru(phen)_3^{2+}$ used as fluorescent reagent to prepare fluorescent membrane, and cellulose acetate used as carrier of immobilized cholesterol oxidase; dissolved oxygen and cholesterol content in cholesterol solution were detected by means of phase-shifting and phase lock means	Biological applications	226
Choline-containing phospholipids	Phospholipids are hydrolyzed by the enzyme phospholipase-D to choline which is analyzed with a fiber-optic biosensor based on choline oxidase and oxygen transduction; optimum biosensing layer consists of enzyme immobilized on a nylon membrane and placed onto an oxygen sensitive layer formed by a luminescent Ru(II) complex, tris(4,7-diphenyl-1,10-	In serum	227

	phenanthroline)ruthenium(II), dispersed in a silicone membrane		
Choline	Based on luminol electrochemiluminescence integrated in a flow injection analysis; choline oxidase immobilised either covalently on polyamide (ABC type) or on UltraBind preactivated membranes, or by physical entrapment in a photo-cross-linkable poly(vinyl alcohol) polymer alone or after absorption on a weak anion exchanger, diethylaminoethyl Sepharose	Biological applications	228
Glucose	Using cellulose acetate membrane containing glucose oxidase, 2,7-diaminofluorene dihydrochloride, and sodium N-(3-sulfopropyl)-3,3',5,5'-tetramethylbenzidine; reflectance changes at 580 nm	Biochemical analysis	229
Glucose	Based on oxygen optrode, which measures the consumption of oxygen via dynamic quenching of fluorescence of indicator by molecular oxygen; Glucose oxidase (GOD) is immobilised onto surface of this oxygen optrode by adsorption to carbon black and by crosslinking with glutardialdehyde	Continuous determination of glucose	230
Glucose	Optical fiber oxygen sensor, based on the dynamic quenching of the luminescence of tris(1,10-phenanthroline)-ruthenium(II) cation by molecular oxygen, complex is adsorbed onto silica gel, incorporated in a silicone matrix possessing a high oxygen permeability, and placed at the tip of the optical fiber; enzyme immobilized on surface of oxygen optrode	Measurements have been performed in a flow-through cell in air-equilibrated glucose standard solutions of pH 7.0	231
Glucose	Use conconavalin A as a specific receptor	For sugars and carbohydrates	232
Glucose	Based on electrostatic self-assembly; end face of multimode fiber coated with poly (allylamine hydrochloride) in combination with Prussian blue and enzyme glucose oxidase	Biological applications	233
Glucose	With needle-type hollow container (18-gauge needle), immobilized enzyme membrane and optic fiber probe with ruthenium complex; enzyme membrane prepared from glucose oxidase, azide-unit pendant water-soluble photopolymer and ultra-thin dialysis membrane; optic fiber probe inserted into rolled enzyme membrane placed in needle-type hollow	In fish blood	234

	container		
Glucose	Glucose oxidase is immobilized on cellulose acetate membranes through covalent - cross linking process with glutaraldehyde and Bovine serum albumin	Biological applications	235
Glucose	Using adsorption LB films	In blood	236
Glucose	By means of fluorescence emission spectra of soluble and insoluble glucose oxidase	Biological applications	237
Glucose	Hybrid sensor: two oxygen optodes wherein one optode contains immobilized glucose oxidase	In subcutaneous tissue	238
Glucose	Based on enzymatic reaction of glucose oxidase that catalyzes oxidation of glucose to gluconic acid and hydrogen peroxide while consuming oxygen; Tris(1,10-phenanthroline)ruthenium chloride, an oxygen indicator, used as transducer; ruthenium complex and glucose oxidase incorporated into acrylamide polymer that is attached covalently to a silanized optical fiber tip surface by photocontrolled polymerization	Biological applications	239 240
Glucose	Three different combinations of oxygen transducer and sol-gel immobilized GOx: a) GOx sandwiched between sol-gel layer doped with Ru(dpp) and second sol-gel layer composed of pure sol-gel, b) sol-gel layer doped with Ru(dpp) covered with sol-gel entrapped GOx, c) both GOx and sol-gel powder containing GOx incorporated into single sol-gel phase	Biological applications	241
Glucose	Sol-gel derived ceramic-carbon composite electrode for fabrication of biosensor; based on luminol electrochemiluminescence; electrode consists of graphite powder impregnated with glucose oxidase in a silicate network. In this configuration, the immobilized enzyme oxidizes glucose to liberate hydrogen peroxide and graphite powder provides percolation conductivity for triggering the ECL between luminol and the liberated hydrogen peroxide	Biological applications	242
Glucose and oxygen	Oxygen: Dichlorotris(1,10-phenantroline)-ruthenium(II) hydrate incorporated into an adhesive inorganic-organic hybrid polymer coating (ORMOCER®); Ruthenium/ ORMOCER® layer used with optical fibres to form extrinsic or intrinsic sensor. Glucose: fluorescence is quenched by oxygen	Biological applications	243

	depletion within the layer, which can be linked to glucose by incorporation of suitable enzymes		
Hydrogen peroxide and L-lactate	Optode uses the H_2O_2 dependent oxidation of homovanillic acid by horseradish peroxidase (HRP) as the sensing reaction; HRP was immobilized on a membrane and combined with a bifurcated fiber optic probe; for lactate, use a lactate oxidase-HRP membrane	Biological applications	244
Lactate	Based on bacterial cytoplasmic membranes as the biological recognition element and an oxygen sensitive dye layer as the transducer; CPMs from bacteria with induced lactate oxidase system adsorbed onto a cellulose disk	Detection of lactate with no interference from glucose, fructose or glutamic acid	26
Detection of the lactate dehydrogenase	Fiber optic evanescent wave immunosensor; polyclonal antibody preparation was used in both one-step and two-step assays	Clinical diagnosis	245
Detection of fibrinolytic products	Sol-gel-based biosensor; constructed to be selective toward D dimer antigens, which form from dissolution of cross-linked fibrin clots	In stroke treatment	246
Penicillin	Based on co-immobilization of a pH indicator, fluorescein isothiocyanate and penicillinase on a preactivated biodyne B membrane attached to the end of a bifurcated optical fiber; in conjunction with a flow injection analysis	In some pharmaceutical samples	247
Penicillin	Based on the enzyme penicillinase; fabricated by selective photodeposition of analyte-sensitive polymer matrices on optical imaging fibers	To quantify penicillin produced during a Penicillium chrysogenum fermentation	248 249
Pyruvate	Dual-enzyme fiber-optic biosensor: enzyme layer composed of lactate oxidase and lactate dehydrogenase fabricated at tip of sensing optrode; biosensor based on luminescence detection of consumed reduced nicotinamide adenine dinucleotide and measured fluorescence intensity is related to the bulk concentration of pyruvate	Biological applications	250
Analysis of different amino acids	Biosensor works according to the measurement principle of flow injection analysis; consists of a fluorosensor and a measurement cell operating under pressure; In measurement cell, enzymes and molecular weight enlarged coenzyme PEG (MW 20000)-N6-(2-	Biological applications	251

	aminoethyl)-NAD(H) are confined behind a solid ultra-filtration membrane		
Continuous monitoring of adriamycin in vivo	First, an accurate optical design was used to enhance the intensity of light from a 100 μm optic fiber so the fluorescence signal can be detected. Second, new sol-gel method was used to fix the fluorescence substance 4-(N,N-dioctyl)amino-7-nitrobenz-2-oxa-1,3-diazole (D-70) on the tip of the fiber	Monitoring blood concentrations of drugs and metabilities in the biomedical field	252
Anesthetics and other lipid-soluble compounds	Monitors anesthetic-induced changes in fluorescence emission by labeled liposomes entrapped in a hydrogel at the end of two optical fibers	In gas, liquid or solid phases (e.g., blood and tissue)	253
Cocaine metabolites	Analyte 2000, a four-channel fiber optic biosensor using a competitive fluorescence immunoassay	In urine	254
Cocaine	Monoclonal antibody made against benzoylecgonine, a major metabolite of cocaine, was immobilized covalently on quartz fibers and used as the biological sensing element in the portable fluorometer. Benzoylecgonine-fluorescein (BE-FL) was used as the optical signal generator when it bound to the fiber	In coca leaf extracts	255
Ionic surfactants	Consists of a silanized silica optical fiber, onto which acrylodan-labeled bovine serum albumin is immobilized	Biological applications	256
Detection of toxins and other large molecules	Capture antibodies immobilized on the exposed core, which has been tapered for improved sensitivity	Clinical and environmental analyses	257
Detection of staphylococcal enterotoxin B	Fiber optic surface plasmon resonance (SPR) biosensor: based on spectral interrogation of surface plasmons in a miniature sensing element based on a side-polished single-mode optical fiber with a thin metal overlayer. For specific detection of SEB, the SPR sensor is functionalized with a covalently crosslinked double-layer of antibodies against SEB	Biological applications	258 259
Mycotoxin fumonisin B1 (FB1)	Monoclonal antibodies produced against FB1 covalently bound through a heterobifunctional silane to an etched 800 μm core optical fiber. An evanescent wave effect was utilized to excite fluorescein isothiocyanate labeled FB1 (FB1-FITC) molecules near the surface of the fiber	Biological applications	260
Mycotoxins: fumonisins and aflatoxins	Two formats, competitive and non-competitive: a) Fumonisin monoclonal antibodies were covalently	In maize	261

	coupled to an optical fiber and the competition between FB_1 and FB_1 labeled with fluorescein for the limited number of binding sites on the fiber was assessed; b) mycotoxin aflatoxin B_1 was a non-competitive assay using the native fluorescence of this mycotoxin		
Clostridium botulinum toxin A	Evanescent wave of tapered optical fiber for signal discrimination; 50 mW argon-ion laser, which generates laser light at 514 nm, used in conjunction with optical fiber probe that is tapered at distal end; antibodies specific for C. botulinum covalently attached to surface of tapered fiber; sandwich immunoassay using rhodamine-labeled polyclonal anti-toxin A immunoglobin G antibodies for generation of specific fluorescent signal	Biological applications	262
Genotoxicants	Whole-cell bacterial sensors genetically engineered to react to target toxicants by the induction of a selected promoter and the subsequent production of bioluminescent light through a recombinant lux reporter	Environmental monitoring	263
Ricin	Evanescent wave fiber-optic biosensor; sandwich immunoassay scheme; anti-ricin IgG immobilized onto surface of optical fiber in two different ways: a) antibody directly coated to silanized fiber using a crosslinker, b) avidin-coated fibers incubated with biotinylated anti-ricin IgG to immobilize antibody using an avidin- biotin bridge	In buffer solution and river water	264
Direct determination of organophosphate nerve agents	Using recombinant Escherichia coli with surface-expressed organophosphorus hydrolase	On-line monitoring of the detoxification process for organophosphate pesticides-contaminated wastewaters	265 266
Polychlorinated biphenyls	Quartz fiber coated with partially purified polyclonal anti-PCB antibodies; optical signal generated by binding and subsequent fluorescence of the fluorescein conjugate of 2,4,5-trichlorophenoxybutyrate to Ab-coated fiber	Environmental monitoring	267
Detection of imazethapyr herbicide	Purified sheep antibody immobilized on quartz fibers; mixture of fluorescein-labelled imazethapyr analog and free imazethapyr was presented to the fiber	Environmental monitoring	268

	for direct competition of the antibody binding sites or displacement of a previously fluorescein labelled fiber		
Toxic compounds: some herbicides	Based on kinetic measurements of chlorophylla fluorescence in Chlorella vulgaris cells; microalgae immobilized on removable membranes placed in front of tip of an optical fiber bundle inside a homemade microcell	Measure concentration of a toxic chemical in the form of a single drop or dissolved in a continuous flow	269
Detection of photosynthetic herbicides	Based on use of reaction centre isolated from Rhodobacter sphaeroides, a purple bacteria; by time-resolved absorption	In water	270
Herbicides	Optical whole-cell biosensor using Chlorella vulgaris	Environmental monitoring	271
Detection of methsulfuron methyl	Based on competitive immunoreactions between coating-haptens and free haptens in solutions with corresponding antibodies; ovalbumin-methsulfuron-methyl conjugate immobilized on a microscope slide. Horseradish peroxidase labeled goat anti-rabbit IgG used to generate an optical signal	Environmental monitoring	272
Pesticides propoxur (Baygon®) and carbaryl	The biorecognition element is covalently immobilized onto controlled pore glass beads (CPG) and packed in a thermostatized bioreactor connected to a flow-through cell that contains CPG- immobilized chlorophenol red placed at the common end of a bifurcated fiber optic bundle	In spiked vegetables (onion and lettuce) using ultrasound extraction	273
Detection of organophosphorous-based pesticides	Using chemiluminescence and molecular self-assembly	Environmental monitoring	274
Organophosphorous compounds	Biosensor consisting of acetylcholinesterase/viologen hetero Langmuir-Blodgett film	In contamined waters	275
Captan	Biosensor consisting of a glutathione-S-transferase-immobilized gel film	In contamined waters	276
Methyl parathion	Using Flavobacterium sp. whole cells adsorbed on glass fiber filters as disposable biocomponent	Environmental monitoring	277
Pesticides	Functionalized biosensing surfaces were developed for chemiluminescent immunoassay	In vitro pesticide residual analysis	278
Liquid pollutants	On the surface of a planar substrate composing single-mode channel waveguides	Environmental monitoring	279
Environmental pollutants	Based on immobilized living algae cells; measuring principle was determination of chlorophyll	Environmental monitoring in laboratory	280

	fluorescence depending on the load of water probes with toxic compounds using fiber-optic-based electronic equipment; micro-organisms used Scenesdesmus subspicatus immobilized on filter paper and covered with alginate	and field investigations	
Monitoring waste water pollutants	Two algal whole cells biosensors; both optical and conductometric biosensors based on inhibition of algal alkaline phosphatase and esterase activities. Chlorella vulgaris cells are immobilised on a membrane placed in front of an optical fiber bundle for optical sensing or deposited on the surface of an electrode for conductometric sensing	Environmental monitoring	281
Detection of environmental pollutants and monitoring of bacteria for bioremediation	Two different types: a) continuous flow immunosensor based on displacement of fluorescently-labeled antigen from antibodies immobilized on beads, antigen injected into flow stream that passes over a 100 μL bed volume of antibody-coated beads saturated with fluorescently-labeled antigen, displacement of labeled antigen causes increase in fluorescence, proportional to antigen concentration, to be observed downstream; b) fiber optic biosensor, utilizes long, partially clad optical fibers; antibodies immobilized onto fiber core in unclad region at distal end of fiber. Upon binding of antigen and a fluorescent molecule, a change in fluorescence signal is observed	Environmental monitoring	282
2,4,6-Trinitrotoluene	Using a portable fiber optic biosensor; larger "breadboard" system capable of monitoring a single probe was replaced by a lightweight, portable sensor that can monitor 4 optical probes simultaneously	Transition from laboratory to on-site environmental monitoring	283
Small molecule analytes	Fieldable environmental monitor based on antibodies, fiber optic probes, and compact optoelectronics; antibodies immobilized to surface of etched optical fiber tips; displacement reaction between target molecules and fluor-labeled target analogs monitored remotely	In groundwater	284
Determination of low biochemical oxygen demand (BOD)	Artificial wastewater solution employed as standards for calibration of the BOD sensor	In river waters	285
BOD	Sensing membrane at tip of fiber consists of layers of (a) an oxygen-sensitive fluorescent material, (b) Trichosporoa cutaneum immobilized in poly(vinyl	Environmental monitoring	286

	alcohol), and (c) a substrate-permeable polycarbonate membrane to retain the yeast cells. The layers are placed, in this order, on an optically transparent gas-impermeable polyester support. Tris(4,7-diphenyl-1,10-phenanthroline)ruthenium(II) perchlorate is used as the oxygen indicator		
BOD	Based on different microorganisms immobilized in ormosil matrixes	Environmental monitoring	287 288
Heavy metals	From inhibition of alkaline phosphatase present on the external membrane of Chlorella vulgaris microalgae; microalgal cells immobilized on removable membranes placed in front of the tip of an optical fiber bundle inside a homemade microcell	Environmental monitoring	289
Heavy metals	Using whole-cell luminescent bacterial sensors in suspension or immobilized onto fibre-optic tips	In EILATox-Oregon samples	290
Heavy metals	Based on the inhibition of urease activity, where the urease is immobilised on ultrabind membrane	Environmental monitoring	291
Heavy metals	Based on immobilized engineered microorganisms and bioluminescence measurements; A strain of microorganisms from Alcaligenes eutrophus (AE1239) was genetically engineered by inserting a luxCDABE operon from Vibrio fischeri under control of a copper-induced promoter	Environmental monitoring	292
Heavy metals	Highly sensitive and selective catalytic DNA biosensors	Environmental monitoring	293
Copper	Protein molecule, site-specifically labeled with a fluorophore that is attached to the distal end of an optical fiber	In sea water	294
Nitric oxide	Based on a dye-labeled heme domain of soluble guanylate cyclase	Cellular applications	295
Nitric oxide	Gas sensor with nanoporous structure prepared by uniformly immobilizing NO_2 sensing reagents at the pores during the sol-gel process	In air samples	296
Trichloroethene and tetrachloroethene	Based on monooxygenases and sol-gel entrapped fluoresceinamine	water samples, without sample preparation step	297
Trinitrotoluene (TNT)	Trinitrobenzenesulfonic acid labeled with a fluorophore and used as the analyte competitor; evanescent wave fiber-optic biosensor	In water	298 299 300 301
pH	Optical fibre pH sensor with an MPC (2-	Physiological	302

	Methacryloyloxyethyl Phosphorylcholine) membrane has been produced and the in vitro properties of this sensor were assessed in the buffer solutions, both with and without protein	applications	

10. Conclusions

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. These biosensor types have been the objective of a large number of investigations in the last years and they provide numerous ways of performing the rapid, remote, in-line and on-line determination of a lot types of analytes in a wide range of application fields. They are under continuous development and research in this area places increasing emphasis on the works concerning the sensors' performance, such as micro-structural stability, leaching, reversibility, response time, repeatability, sensitivity and selectivity, instead of simply demonstrating the sensing potential. Also, rapid advances have been made in improving immobilization protocols.

Likewise, one of the major advantages of using optical biosensors in conjunction with optical fibers is that it permits sample analysis to be done over long distances and this has important implications for field monitoring. However, the main drawback apart from being relatively expensive is that optical fibers may suffer from miniaturization problems. Notwithstanding, the application of optical fiber-based nanosensors has become an area of significant interest and various methods have been developed to alleviate the problems arising from miniaturization. In this sense, optical fiber SPR probes present the highest level of miniaturization of SPR devices, allowing for chemical and biological sensing in inaccessible locations where the mechanical flexibility and the ability to transmit optical signals over a long distance make the use of optical fibers very attractive.

In summary, 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.

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