Essays in Biochemistry (2016) **60** 91–100
DOI: 10.1042/EBC20150010

Optical biosensors

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Optical biosensors represent the most common type of biosensor. Here we provide a brief classification, a description of underlying principles of operation and their bioanalytical applications. The main focus is placed on the most widely used optical biosensors which are surface plasmon resonance (SPR)-based biosensors including SPR imaging and localized SPR. In addition, other optical biosensor systems are described, such as evanescent wave fluorescence and bioluminescent optical fibre biosensors, as well as interferometric, ellipsometric and reflectometric interference spectroscopy and surface-enhanced Raman scattering biosensors. The optical biosensors discussed here allow the sensitive and selective detection of a wide range of analytes including viruses, toxins, drugs, antibodies, tumour biomarkers and tumour cells.

Introduction

Optical biosensors offer great advantages over conventional analytical techniques because they enable the direct, real-time and label-free detection of many biological and chemical substances. Their advantages include high specificity, sensitivity, small size and cost-effectiveness. Multiple advanced concepts and highly multidisciplinary approaches including microelectronics, microelectromechanical systems (MEMSs), micro/nano-technologies, molecular biology, biotechnology and chemistry are applied in the implementation of new optical biosensors. The research and technological development of optical biosensors has experienced an exponential growth over the last decade. Optical biosensor research and development has been directed mainly towards healthcare, environmental applications and the biotechnology industry. The potential applications of biosensors in the fields of medicine, the environment and biotechnology are numerous, and each has its own requirements in terms of the concentration of analyte to be measured, the required precision of output, the sample concentration required, the time taken to complete the probe, the time necessary to enable reuse of the biosensor and the cleaning requirements of the system [1].

Biosensors can be classified into different groups depending on the method of signal transduction: optical, electrochemical, thermometric, piezoelectric or magnetic. Optical biosensors are the most commonly reported class of biosensors. Optical detection is performed by exploiting the interaction of the optical field with a biorecognition element. Optical biosensing can be broadly divided into two general modes: label-free and label-based. Briefly, in a label-free mode, the detected signal is generated directly by the interaction of the analysed material with the transducer. In contrast, label-based sensing involves the use of a label and the optical signal is then generated by a colorimetric, fluorescent or luminescent method. Simple molecules such as glucose can be detected by enzymatic oxidation using label-assisted sensing. The glucose analysis of blood is the most commercially successful (so far) application of a biosensor, i.e. the handheld glucose meter used by diabetics. However, in some situations, e.g. antibody–antigen interaction where a label is conjugated with one of the bioreactants, labelling can alter the binding properties and therefore introduce systematic error to the biosensor analysis.

An optical biosensor is a compact analytical device containing a biorecognition sensing element integrated with an optical transducer system (Figure 1). The basic objective of an optical biosensor is to produce a signal which is proportionate to the concentration of a measured substance (analyte). The optical

Version of Record published
30 June 2016

PORTLAND PRESS

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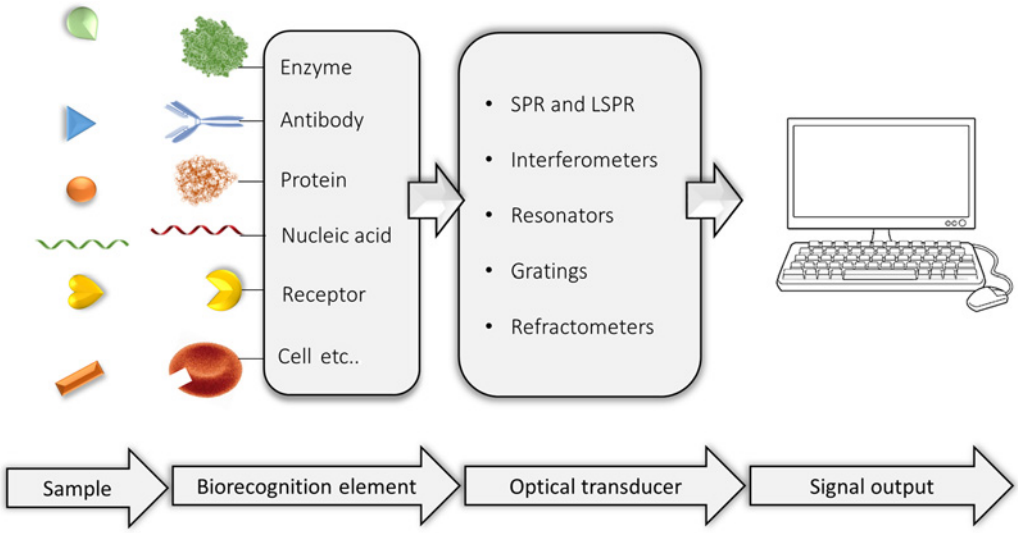

Figure 1. Optical biosensors

biosensor can use various biological materials, including enzymes, antibodies, antigens, receptors, nucleic acids, whole cells and tissues as biorecognition elements. Surface plasmon resonance (SPR), evanescent wave fluorescence and optical waveguide interferometry utilize the evanescent field in close proximity to the biosensor surface to detect the interaction of the biorecognition element with the analyte. There are a huge number of variations in the construction of optical biosensors and this review will focus on a few that have been selected on the basis of their widespread application and tending towards the detection of the most biologically relevant substances.

Surface plasmon resonance biosensors

The physical phenomenon of SPR was first observed in 1902. This observation of an esoteric optical phenomenon evolved through decades into a full understanding of surface plasmon physics and in 1983 SPR was first successfully used to construct an SPR-based sensor to detect biomolecular interactions [2]. The first commercial SPR-based biosensor instrument was launched by Pharmacia Biosensor AB, which was later renamed Biacore. SPR instruments are currently produced by multiple manufacturers and the SPR-based biosensor is currently the predominant optical biosensing method.

The SPR phenomenon occurs on the surface of metal (or other conducting materials) at the interface of two media (usually glass and liquid) when it is illuminated by polarized light at a specific angle. This generates surface plasmons and consequently a reduction of the intensity of reflected light at a specific angle known as the resonance angle. This effect is proportionate to the mass on the surface. A sensorgram can be obtained by measuring the shift of reflectivity, angle or wavelengths against time. In all configurations, the SPR phenomenon enables direct, label-free and real-time changes of refractive index at the sensor surface, which is proportionate to the biomolecule concentration. To measure a ligand–analyte interaction, one interacting molecule must be immobilized on the sensor surface. A practical SPR instrument combines an optical detector part, usually measuring intensity shift, a sensor chip with a gold surface and a layer enabling ligand immobilization, which is integrated with a fluidics system enabling a flow-through operation. The operating principle of a typical SPR instrument is presented in Figure 2.

The SPR chip contains a functional layer which enables the immobilization of interacting molecules. Current instrumentation is dominated by immobilization based on a self-assembled monolayer covered with a carboxymethylated dextran. This configuration enables the effective immobilization of protein using N-hydroxysuccinimide (NHS) chemistry.

In a practical experiment one interaction component, e.g. the ligand, is permanently attached to the chip surface and another interacting component, e.g. the analyte, flows over the surface and binds to the ligand. A typical SPR

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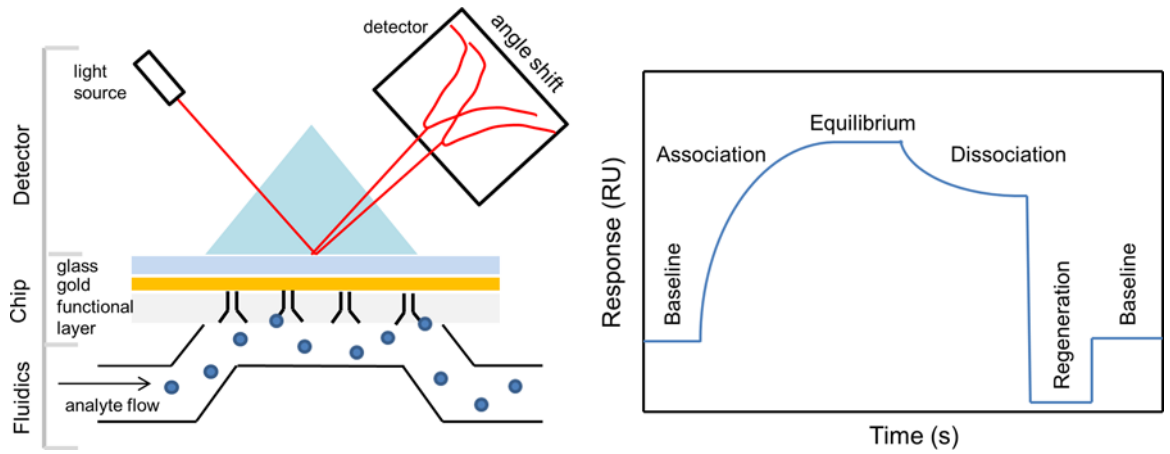

Figure 2. The principle of SPR instrument (left) and typical SPR sensorgram showing the steps of an analytical cycle (right)

experiment is documented in Figure 2. The ligand (A) is immobilized on the surface and interacts with the analyte (B). If this binding happens at a 1:1 ratio (Langmuir binding) then binding kinetics can be described by eqn (1). Experimental traces of response against time, as documented in Figure 2, are then fitted and a practical result of SPR analysis are then kinetic constants k_{on}, k_{off} and equilibrium constants $K_a = k_{on}/k_{off}$ and $K_d = 1/K_a$. The equilibrium dissociation constant K_d (mol $\cdot$ l^{-1}) is generally used as a descriptive parameter of ligand–analyte binding or any biomolecular interaction in general.

$$A + B \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} AB \tag{1}$$

The detection of surface binding by SPR is a widely used concept. However, in practical life there are multiple other effects that can occur and complicate SPR analysis, which include non-1:1 binding stoichiometry, avidity, non-specific absorption of ligand and mass transfer limitation Dealing with those is well described in specialized monographs [3].

For practical applications there are three types of SPR analyses: *kinetic analysis*, *equilibrium analysis* and *concentration analysis*. *Kinetic* and *equilibrium* analyses are commonly used to characterize any molecular interaction: ligand–analyte binding, antibody–antigen interaction, receptor characterization etc. No comparable technology is available to characterize biomolecular interaction in real time without labelling and therefore SPR is currently a prime tool for discovery research in biological sciences and pharmaceutical drug development. The SPR technique also has multiple applications in the *concentration* analysis of any analyte if a ligand specific to it is available and can be immobilized on the SPR chip. The concentration is then obtained by measuring direct binding or alternatively from the rate of binding in a mass transport limited mode. Concentration analysis has wide application in multiple fields: clinical diagnostics, environmental analysis, food etc. An SPR biosensor assay was used for the diagnosis of different stages of Epstein–Barr virus infection in clinical serum samples by the simultaneous detection of the antibodies against three different antigens present in the virus [4]. A soluble vascular endothelial growth factor receptor was determined using an SPR chip with an immobilized ligand and a detection limit of 25 μg $\cdot$ l^{-1} was achieved [5]. Rapid screening methods employing SPR portable biosensors have great potential in food monitoring. The sensitive on-site analysis of antibiotics in milk samples was realized by a portable six-channel SPR biosensor [6] and the mycotoxin patulin was detected by an immuno-chemical SPR biosensor with a detection limit of 0.1 nM [7]. An SPR biosensor was also used for the sensitive and anion-selective detection of As(III) with a limit of detection of 1.0 nM [8].

SPR imaging

SPR imaging (SPRi) takes the SPR analysis a step further by merging the sensitivity of SPR and spatial imaging in a microarray format allowing the simultaneous study of multiple different interactions. SPRi allows simultaneously studying multiple different interactions on an array of precisely patterned molecules (Figure 3). High throughput,

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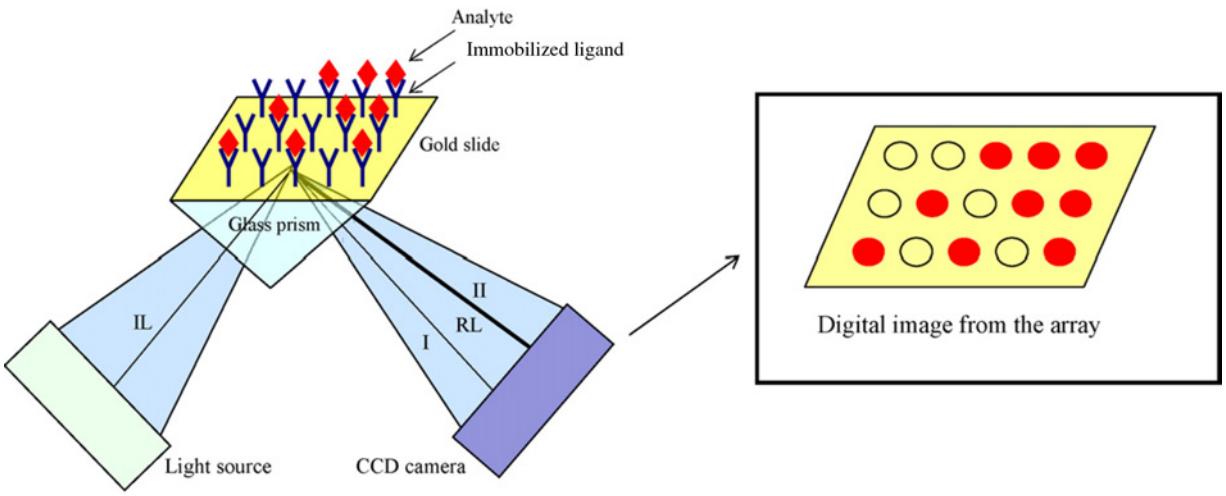

Figure 3. A schematic illustration of the set-up for the SPR imaging (reprinted with permission from Elsevier [9])

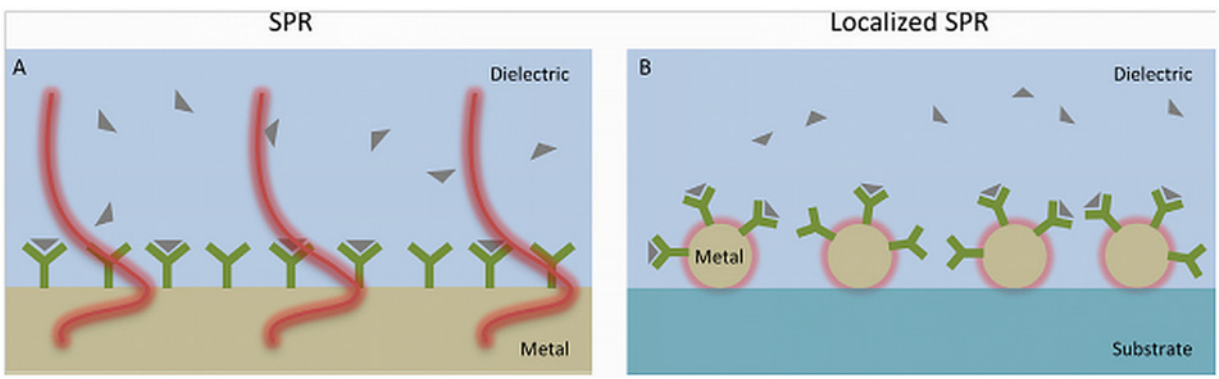

Figure 4. Schematic diagrams showing the detection principle of plasmonic biosensors based on (A) SPR and (B) LSPR imaging (reprinted with permission from Elsevier [13])

sensitivity and obtaining the spatially resolved images of biointeractions open up a great future for SPRi to be applied in clinical chemistry and medicine for the screening of biomarkers and therapeutic targets [9]. For example, a succesful application of this method was the kinetic study of the binding between an immunosuppressive drug (FK506) and its target protein (FK506-binding protein 12 (FKBP12)) in a high-throughput SPRi format with a detection limit of 0.5 nM [10].

Localized surface plasmon resonance

Localized SPR (LSPR) is based on metallic nanostructures (MNPs) (Au, Ag, etc.) having unique optical properties which are not seen in larger metal structures. A particularly striking example of such phenomenon is the red colour of aqueous dispersions of colloidal gold particles, which is a manifestation of LSPR. The optical phenomenon of LSPR occurs when incident light interacts with MNPs, the electromagnetic field of the light induces collective electron charge oscillations confined in MNPs and the subsequent absorbance of light within the ultraviolet–visible (UV-VIS) band (Figure 4). Thus, the major difference between SPR and LSPR is that induced plasmons oscillate locally on the nanostructure rather than along the metal/dielectric interface [11,12] (Figure 4).

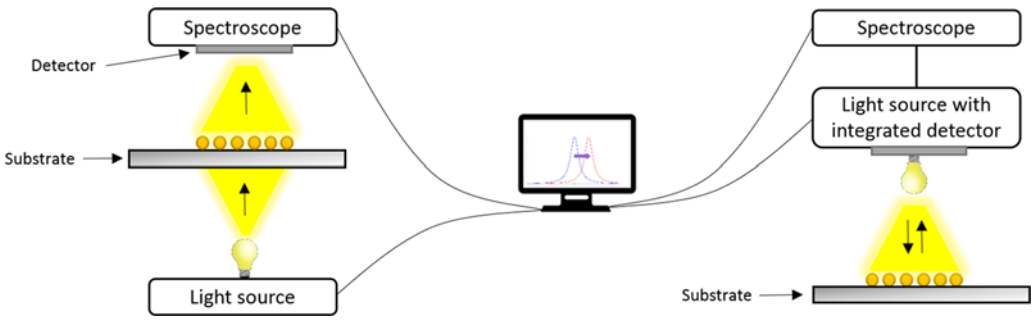

Figure 5. Schematic illustration of LSPR transmission (left) and reflection (right) modes (reprinted with permission from MDPI [14])

The biosensing event based on LSPR spectral shifts, often referred to as 'wavelength-shift sensing', is caused by the surrounding dielectric environmental change when a binding event occurs. However, properties of LSPR are greatly dependent on several factors, such as the material used, dimension, shape and inter-particle distance of the MNPs involved. All of these factors are reflected as a colour change and absorption peak shift. These parameters are a matter of sensor fabrication. Thus, by manipulating these parameters, it is possible to control/optimize LSPR sensor properties such as sensitivity. The LSPR sensors are more adaptable in terms of biosensor fabrication compared with commercial SPR biosensors. The LSPR sensors can either be fabricated by immobilizing MNPs on a substrate such as a glass slide, or an optical fibre, or by simply suspending MNPs in solution to form a solution-phase-based LSPR sensor. Various optical geometries are used in LSPR sensors; the two most common geometries and modes of operation are transmission and reflection modes (Figure 5) [14].

Nowadays, LSPR-based sensing platforms are considered to be the next-generation plasmonic label-free methods. Current commercialized SPR instruments, such as the well-known Biacore^{TM} series, are expensive and bulky, which limits the extent of their application. LSPR-based detection is more easily miniaturized to increase throughput of detection and reduce operational costs. Characteristics required for state-of-the-art analytical devices, such as LSPR-based portable screening tools, are robustness, sensitivity, specificity and low cost of production. They can serve as very effective alternatives to numerous applications, for instance, in clinical diagnosis and food monitoring [14]. It was shown that, compared with a reference conventional high-resolution SPR biosensor, an LSPR biosensor can deliver the same performance as the SPR system while involving significantly lower surface densities of interacting molecules [15]. For example, an LSPR multiarray biosensor was used for screening antigen–antibody interactions including immunoglobulins, C-reactive protein and fibrinogen with detection limits of 100 ng $\cdot$ l^{-1} [16]. In the study focused on the clinical diagnostics of ovarian cancer, based on the detection of HE4 by the anti-HE4 antibody as a probe assembled on to the LSPR nanochip surface, a broad linear range (10–10 000 pM) was achieved with a detection limit of 4 pM [17]. Mycotoxin ochratoxin A was quantitatively detected by LSPR involving gold nanorodes and an aptamer at concentrations lower than 1 nM [18].

Evanescent wave fluorescence biosensors

In these biosensors, the biological recognition and the consequent binding event occur within the confines of an evanescent wave. The evanescent wave arises from the manner in which light behaves when confined in an optical waveguide or fibres. Guided light is totally internally reflected when it meets the interface of the waveguide/fibre and a surrounding medium with a lower index of refraction, as a result an electromagnetic field called an evanescent wave extends out from the interface into the lower index medium. The evanescent wave decays exponentially with distance from the surface, generally over the distance of 100 nm to approximately a wavelength. Since the evanescent wave is such a near-surface phenomena, detection employing evanescent wave excitation to generate the fluorescent signal is surface-sensitive, meaning that only fluorescent molecules near the surface are excited (Figure 6). This geometric limitation can help to minimize unwanted background signal from a bulk sample while only enhancing the signal from fluorophores captured on the surface. A profuse variety of biosensors was developed based on this principle

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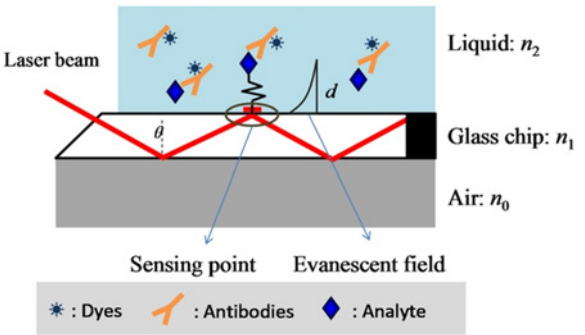

Figure 6. Schematic diagram of an evanescent wave planar optical waveguide chip (reprinted with permission from NPG [22])

with a wide array of applications ranging from clinical diagnostics to biodefence to food testing [19]. Moreover, with the recent commercialization of a number of waveguide-based sensors it is anticipated that these sensors will make a major impact on healthcare-related fields. The performance of this platform was assessed using >200 clinical samples from subjects comprising healthy individuals and those positive for HIV, syphilis and hepatitis C [20], and excellent specificity was demonstrated. The evanescent wave aptamer-based fluorescence biosensor was used for the rapid, sensitive and highly selective detection of 17β-oestradiol, an endocrine-disrupting compound frequently detected in environmental water samples. This biosensor was constructed as a portable system with the detection limit of 2.1 nM [21].

Bioluminescent optical fibre biosensors

This technique uses recombinant bioluminescent cells and the bioluminescent signal is transferred from the analyte by an optical fibre. An *Escherichia coli* strain, genetically modified to emit a luminescent signal in the presence of genotoxic agents, was immobilized on to a fibre optic and the optrode response to the genotoxin atrazine achieved a detection limit of 10 pg $\cdot$ l^{-1} [23]. A live cell array bioluminescent biosensor fabricated by immobilizing bacterial cells on the optical fibres arranged in a high-density array of microwells was developed. Each microwell accommodated a single genetically engineered bacterium responding to a specific analyte and the array biosensor enabled the multidetection of genotoxins [24].

Other optical biosensors

Optical waveguide interferometric biosensors

An integrated planar optical waveguide interferometric biosensor is a combination of evanescent field sensing and optical phase difference measurement methods. By probing the near-surface region of a grating sensor area with the evanescent field, any change of the refractive index of the probed volume induces a phase shift of the guided mode compared with a reference field, typically of a mode propagating through the reference arm of the same waveguide structure. The interfering fields of these modes produce an interference signal detected at the sensor's output, whose alteration is proportional to the refractive index change and the signal is related to the concentration of the analyte [25]. This technique, also called resonant waveguide grating (RWG), is suitable for detecting the redistribution of cellular contents, studying cellular responses and cellular processes [26], and was also applied to the detection of the avian influenza virus [27].

Ellipsometric biosensors

An ellipsometric biosensor measures changes in the polarization of light when it is reflected from a surface. This platform was applied in detecting the binding of influenza A virus strains with a panel of glycans of diverse structures. The

Table 1. Key points of reviewed optical biosensors including selected biological applications

Biosensor	Multiplexing	Commercialization	Label-free?	Selected biological applications	Reference(s)
SPR	+ +	+ + +	Yes	Kinetic analysis of biointeractions Antigens in clinical samples Proteins in biological samples Xenobiotics and toxins in food Carbohydrate-specific interactions	[2] [4] [5] [6–8] [9]
SPRi	+ + +	+ + +	Yes	Screening of biomarkers and therapeutic targets Screening of drug–target protein interactions	[9] [10]
LSPR	+ +	+	Yes	Detection of DNA hybridization Screening of antigen–antibody interactions Cancer biomarker detection Toxin detection	[15] [16] [17] [18]
Evanescent wave fluorescence	+ + +	+ + +	No	Clinical diagnostics, biodefence, food testing Clinical biomarkers Toxin screening	[19] [20] [21]
Bioluminescent optical fibre	+ +	+	No*	Response of cells to genotoxic agents Multidetection of genotoxins by live cell array	[23] [24]
Waveguide interferometric	+ +	+	Yes	Study of cellular responses and processes Virus detection	[26] [27]
Ellipsometric	+ +	+	Yes	Characterizing viral receptor profiles Detection of serum tumour biomarker	[28] [29]
RIfS	+ +	+ +	Yes	Xenobiotics in food Detection of circulating tumour cells	[30] [31]
SERS	+	+	Yes	Detection of cancer proteins Protein biomarker in environment	[32] [33]

*Use of genetically modified bioluminescent reporter cells.

apparent equilibrium dissociation constants (avidity constants, 10–100 pM) were used as characterizing parameters of viral receptor profiles [28]. Microarray biosensors based on total internal reflection imaging ellipsometry for the detection of the serum tumour biomarker CA19-9 had an estimated detection limit of CA19-9 of 18.2 units $\cdot$ ml^{-1}, which is lower than the cut-off value for a normal level [29].

Reflectometric interference spectroscopy biosensors

Reflectometric interference spectroscopy (RIfS) is a label-free and time-resolved method where the simple optical set-up is based on white light interference at thin layers. Changes in the phase and amplitude of polarized light provides information about the thickness and refractive index of the adsorbed protein layer. This method was used for the detection and quantification of diclofenac in bovine milk and the obtained limit of detection was 0.112 μg $\cdot$ l^{-1} in the complex milk matrix [30]. An RIfS biosensor for the detection of circulating tumour cells was capable of the selective detection of cancer cells within a concentration range of 1000–100 000 cells $\cdot$ ml^{-1} with a detection limit of $<$1000 cells $\cdot$ ml^{-1} [31].

Surface-enhanced Raman scattering biosensors

Surface-enhanced Raman scattering (SERS) is a biosensing technique which enhances the intensity of the vibration spectra of a molecule by several orders of magnitude when it is in close proximity to nano-roughened metallic surfaces or nanoparticles made of gold or silver. A SERS-active surface fabricated on the tip of the optical fibres was applied to

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the sensitive detection of cancer proteins (∼100 pg) in a low sample volume (∼10 nl) [32]. A SERS biosensor for the fast and sensitive detection of a protein biomarker of endocrine-disrupting compounds in an aquatic environment, with a limit of detection of 5 ng $\cdot$ l^{-1}, has been reported [33].

Conclusions

Optical biosensors are expected to grow most in importance in the healthcare, biomedical and biopharmaceutical sectors. They can provide new analytical tools with reduced size as well as facilitate large-scale high-throughput sensitive screening of a very wide range of samples for many different parameters [34]. Various sensitivity-enhancement techniques for optical biosensors have been developed which improve the signal-to-noise ratio and reduce the detection limit [35], and optical biosensors have been successfully tested in many fields such as medicine, pharmacy, food safety, environment, biotechnology, defence and security. On the other hand, the broad practical application of optical biosensors is still under development and is limited mostly to academic and pharmaceutical environments. The exceptions are lateral flow assay biosensors commercialized as test strips for home-testing, point-of-care testing or laboratory use, for example home pregnancy tests, which are reviewed in Chapter 12. A summary of key points of each optical biosensor reviewed here, with examples of use in studying biological problems, is given in Table 1.

When developing new optical biosensor devices for practical applications all the methodological and practical aspects such as robustness, reproducibility, simplicity and shelf life should be carefully taken into account. The main challenge for further research and innovation in the field of optical biosensors is that the optical detection principle allows construction of sensitive, simple and cheap analytical devices with a wide variety of possible applications in portable biosensor systems for *in situ* screening and monitoring, for example, in personalized medicine, remote areas or in developing countries where the availability of inexpensive diagnostic tools could save many lives.

Summary

- This article includes a brief classification, description and examples of the applications of optical biosensors in medicine, pharmacy, food safety, the environment, biotechnology, defence and security.
- Surface plasmon resonance biosensors, localized surface plasmon resonance biosensors, evanescent wave fluorescence and bioluminescent optical fibre biosensors, interferometric, ellipsometric, reflectometric interference spectroscopy and surface enhanced Raman scattering biosensors were discussed.
- Optical biosensors allow the sensitive and selective detection of a wide range of analytes including viruses, toxins, drugs, antibodies, tumour biomarkers, and tumour cells.
- Optical biosensors provide new analytical tools with reduced size as well as facilitate large-scale high-throughput sensitive screening of a wide range of samples for many different parameters.
- The optical detection principle allows construction of simple and cheap analytical devices with many potential applications in portable biosensor systems for *in situ* detection which can be used in personalized medicine, remote areas and developing countries.

Abbreviations

LSPR, localized SPR; MNP, metallic nanostructure; RIfS, reflectometric interference spectroscopy; SERS, surface-enhanced Raman scattering; SPR, surface plasmon resonance; SPRi, SPR imaging.

Funding

The financial support received from the Slovak Scientific Grant Agency [grant number VEGA 2/0162/14] and from the Slovak Research and Development Agency [grant number APVV-14-0753] is acknowledged. This work was funded by the European Commission Framework Programme 7 through the Marie Curie Initial Training Network PROSENSE [grant number 317420, 2012–2016]. This publication is the result of the project implementation: Centre for materials, layers and systems for applications and chemical processes under extreme conditions – Stage II, ITMS No.: 26240120021 supported by the Research & Development Operational Programme funded by the European Regional Development Fund (ERDF).

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Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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