QUÍMICA ANALÍTICA (2000) 19 [Suppl 1]: 54-60

QUÍMICA ANALÍTICA
Elsevier Información Profesional, S.A

Optical sensors based on evanescent field sensing Part I. Surface plasmon resonance sensors

Abstract

In the last years, a great interest has focused on the development of selective and sensitive sensors for the detection of very low levels of chemicals and biological substances and for the measurement of molecular interactions in-situ and in real time. These requirements can be achieved with optical sensors, mainly those based on evanescent wave principles, because they allow direct monitoring of small changes in optical properties. A review of the fundamental aspects and applications of optical evanescent wave sensors is presented here. This review is divided in two parts. The first one will be focus on Surface Plasmon Resonance Sensors and the second one on Integrated Optical Evanescent Wave Sensors. Applications in environmental monitoring, biomedical analysis and industrial processes control will be discussed. The commercial devices on the market and an outlook of future prospects of this technology will be reviewed.

Keywords: optical waveguides, surface plasmon resonance, integrated optics, biospecific molecular interaction.

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Received November. 17th, 1999 / Accepted January, 21st, 2000

Introduction

The development of optical sensors for detection of biological and chemical species has been a very active research field both in academic and in industrial laboratories during the last decades [1,2]. It becomes clear that this technology can become a serious alternative to conventional assay techniques because they can avoid expensive, complex and time-consuming procedures. A large number of applications for these sensors ranges from biomedical, industrial control processes, veterinary field to food industry or environmental monitoring. Ideally, for all these applications, it will be desirable to have a compact sensor with response time as low as possible, allowing real-time measurement and with a high sensitivity. This hold specially for optical transducers in comparison with others sensing schemes [1,2].

A large variety of optical methods have been employed but those which can give a direct signal after a molecular interaction (without the use of labels) have attracted quite attention: Direct optical techniques include Ellipsometry, Total Internal Reflection, Monomode Dielectric Waveguides and Surface Plasmon Resonance [3]. Since the first approach to a SPR sensor, suggested by Nylander et al. [4] for the detection of a gas using a silver-coated prism, this method has been improved greatly with commercial prototypes and many applications. Since this technique was applied to biosensing of an antibody-antigen interaction [5], the SPR measurement showed a great potential for affinity biosensors, allowing real-time analysis of biomolecular interactions without the need of labels. Since then, SPR sensors have received a enormous attention, with more than 380 publications in the year 1997 [6]. Some commercial devices have reached the market for some years ago and new prototypes are appearing continuously. Extended reviews about Surface Plasmon Resonance Sensors can be found in the literature [3,6-9].

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Surface Plasmon Resonance: Physical Principle

The SPR is an optical phenomenon due to a charge density oscillation at the interface of two media with dielectric constants of opposite signs (as for example a metal and a dielectric) (for a more detailed explanation see reference [10]). Optical excitation of a surface plasmon is caused by evanescent wave and can be achieved when a light beam (p or TM polarised) incidents at the interface between a thin metal layer and a dielectric media at a defined angle, called angle of resonance (see Figure 1).

When resonance occurs, a sharp minimum in the intensity of the reflected light at that angle of resonance is observed: a plot of incident angle vs. reflectivity shows the dip at that angle, as can be observed in Figure 2.

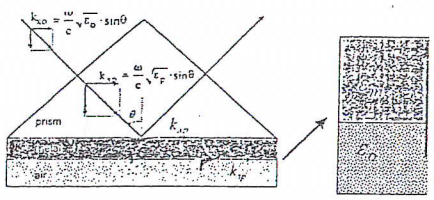

Figure 2. (Illustration of the sharp minimum produces in the reflected intensity as a function of the incident angle, due to the SPR excitation at the resonance angle.

To excite a surface plasmon wave with an electromagnetic wave incident to the surface, the resonant condition has to be fulfilled, that is, the propagating vectors of both the surface plasmon (κ_{sp}) and the electromagnetic waves ($\kappa_{x,d}$) must be equal (see Figure 1 a). It should be noted that the surface plasmons are TM waves and, therefore, can only be excited by p-polarized light.

The notation used in the following will be: sp = surface plasmon, d= dielectric medium, o = air, m= metal. The wave vector of the incident light in air (κ_o) is :

$$\kappa_o = \frac{\omega}{c}\sqrt{\varepsilon_o}$$

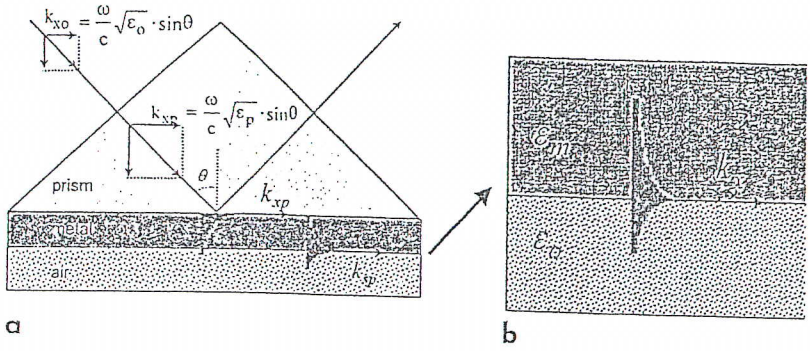

Figure 1. (a) Schematic representation of the Kretschmann configuration showing the excitation of the SPR via the evanescent field (k=wave vector of the incident light, θ=incident angle, ε=dielectric constant). (b) detail of the propagation of the plasmon field at the interface between the metal and the dielectric media (e0,M= dielectric constant of air and metal, respectively, kx=component of the wave vector parallel to the surface) (Notation: sp=surface plasmon, d= dielectric medium (prism), o=air, m=metal).

where ω is the frequency and ε_o the dielectric constant in air. Once in the dielectric medium, its component parallel to the surface ($\kappa_{x,d}$) (observed at Figure 1b) that has to verify the resonant condition is:

$$\kappa_{xd} = \frac{\omega}{c}\sqrt{\varepsilon_d}.\sin\theta = \frac{2\pi}{\lambda}\sqrt{\frac{\varepsilon_m.\varepsilon_d}{\varepsilon_m+\varepsilon_d}}$$

where θ is the incident angle, ε_m is the dielectric constant of the metal and ε_d is the dielectric constant of the prism. It can be concluded from this equation that the SPR propagation can supported only if $\varepsilon_{mr} < -\varepsilon_d$. This means that the surface plasmon can only exist if the dielectric permeability of the metal and dielectric medium are of opposite sign. This condition is only achieved at frequencies in the infrared to visible part of the spectrum by several metals of which gold and silver are the most employed. The use of silver give more sensitive devices but with less stability than for gold. In general, surface plasmons are generated at frequencies in the range of visible light with loss increasing rapidly as wavelengths go to the IR [11]. The thickness of the metal film is critical for the minimum reflectance value and the optimal thickness depends on the optical constants of the boundary media and on the wavelength of light [12]. For gold, the optimal thickness is 45 nm at λ=790 nm .

Usually, there are two ways of optical excitation to achieve the resonant condition: total reflection in prism-coupler structures [6] and diffraction at diffraction gratings [6]. The most common used is the first one due to its simplicity, and it is called the Kretschmann configuration, already showed in Figure 1 (a).

The resonant angle is very sensitive to variations of the refractive index of the medium adjacent to the metal surface, which is within sensing distance of the plasmon field and then any change of the refractive index as, for example, a homogeneous change of material (e.g. gas) or a chemical interaction can be detected through the shift in the angular position of the plasmon resonance angle. In both cases the surface plasmon resonance curve shifts towards higher angles. This fact can be used for sensing applications.

SPR optical sensors

The resonance angle is dependent on the wavelength of the incident light and on the refractive index of the prism, metal and sample layers to be detected. If only the last one changes, the SPR can be used as a sensor which detects refractive index changes of the adsorbed layers at the surface, Changes in refractive index are related to mass changes and then allow the sensing of an interaction of analyte molecules with

their specific receptors, previously deposited at the metal surface.

When monochromatic light is used to excite the SPR response, there are two ways of measurement: to follow the variation of coupling resonance angle or to follow the intensity of the reflected light at a fixed angle, as is schematically shown in Figure 3 a) and b).

In the first one (Figure 3 a)), the sample and the detector are fixed upon a rotating table in such a way that the detector moves at twice the angular speed of the sample. The resonant condition is observed as a very sharp minimum of the light reflectance when the angle of incidence is varied. When a (bio)chemical reaction takes place a shift in the resonance curve is observed. This shift can be related quantitatively to the analyte of interest.

In the second one (Figure 3 b)), by choosing an angle of incidence at the half width of the resonant dip and measuring the intensity of the reflected light at that constant angle, close to the plasmon resonance, real time changes in the refractive index due to process adsorption of molecules onto the metal surface can be measured with high sensitivity. This way of measurement can be applied only when small changes in the refractive index are produced as happens e.g. in a biomolecular interaction. Continuos monitoring at the same angle provides a real-time analysis of the binding events involved in the reaction . A great deal of information (e.g. specificity, concentration, kinetics) can be obtained from this plot.

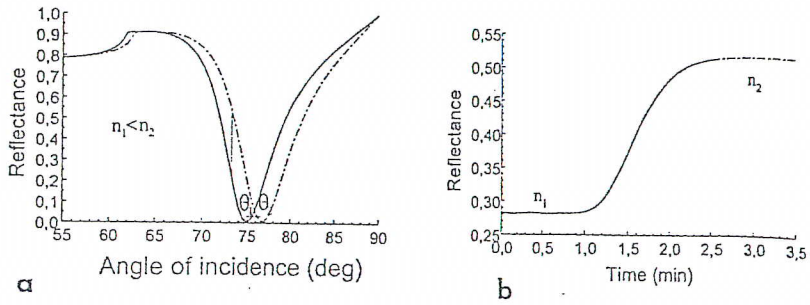

Figure 3 Refractive index change at the outer media of a SPR sensor can be detected by measuring the change in intensity of the reflected beam (a) as a function of the angle of incidence (b) as a function of time at a fixed angle of incidence.

If we use polychromatic light, one more parameter is added (the wavelength of the intensity dip) making possible wavelength modulated detection [13-15], increasing, in this way, the operating range of the sensor.

An example of an experimental set-up used for the SPR measurements is shown in Figure 4. Usually, Lasers or LEDs are used as light sources and photodiodes are used for detection. Some modern SPR devices use linear arrays of charge-couple devices (CCDs) to detect reflected light from the surface. In this way it is possible to detect at a wide range of angles and avoids the need for mechanically controlling the angular position of the detector.

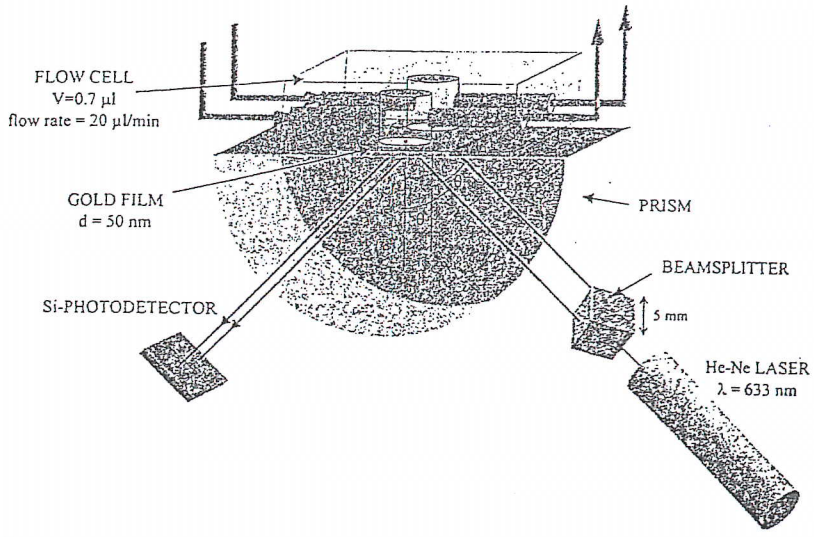

Figure 4 A SPR experimental set-up in the Kretschmann configuration (developed at author's laboratory). A glass hemicylinder is covered with a glass slide coated with gold (50 nm), using a matching oil and then exposed to the sample solutions using a flow cell with two channels. The reflected intensity of both channels are measured in a photodiode. (More details in the figure itself).

Types of SPR sensors

Numerous types of SPR sensors have been developed. The most common one (and the base of most of the commercial devices) is based on bulk optics using a prism coupler (the already mentioned Kretschamann configuration) because is more suitable for sensing. Other SPR sensors are based on grating coupler [16] or on optical waveguides (optical fibers or integrated optical waveguides) [17-24].

In the grating coupler configuration, if a metal-dielectric interface is periodically distorted, the incident light is diffracted forming a series of beams directed away from the surface at a variety of angles that can be coupled to a plasmon wave [17]. This sensor has been demonstrated and used for monitoring biomolecular interactions in aqueous environment [17,18]. The optical interrogation system is almost the same as that used for prism-coupler SPR but in the grating-based SPR sensor is not necessary to accurately control the thickness of the metal as it is necessary in the prism-coupler, but then an accurate control of the grating depth is required. Another drawback of this sensor is that the

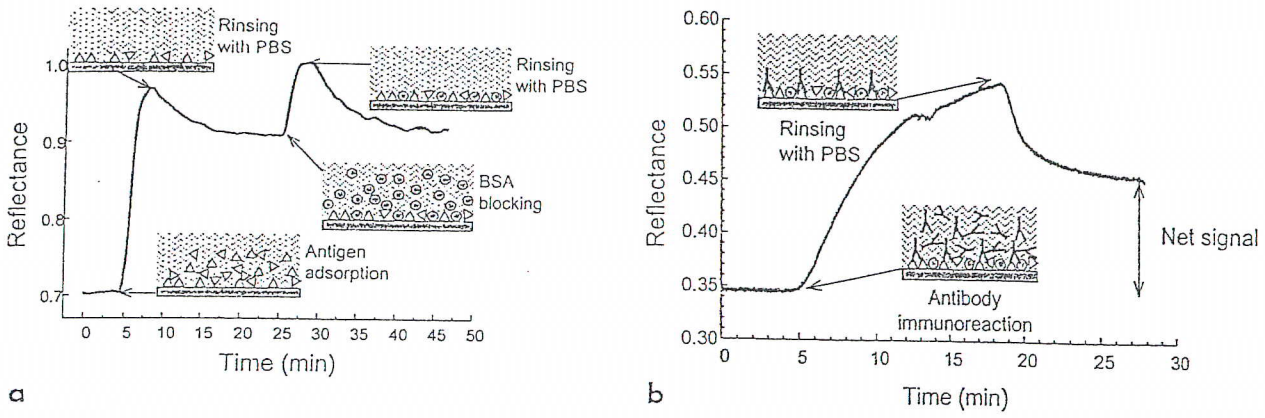

Figure 5 A schematic diagram of the SPR response in real-time during a biomolecular interaction measured at fixed angle (a) The receptor adsorption, rinsing with buffer and blocking of unnocuppied sited for prevention of non-specific adsorption is shown (b) Once the receptor layer is prepared, a solution of the complementary analyte is introduced. After the biospecific interactions take place the surface is rinsing with buffer to remove unbound analytes and a net signal for quantification is obtained.

light must be incident through the sample, and thus the flow cell and samples must be transparent at the wavelength used.

Optical fiber SPR are the smaller devices of this technology, allowing the use of this technique in far away localisation. Sensors based on monomode and multimode optical fiber have been reported [19,20,21]. The use of optical multimode fibers for SPR sensors was first proposed by Jorgensen and Yee [19]. The cladding of the fiber is partially removed and a gold layer is deposited symmetrically around the exposed fiber core. This type of fabrication limits the interaction area to a few millimetres. Another drawback of using multimode fiber SPR sensors is the difficulty of obtaining homogeneous coatings deposition and a good chemical functionalization of the sensor surface because the modal light distibution is affected by mechanical and surface changes.

SPR sensors based on integrated optical waveguides have been also developed [22,23]. These sensors combine the resonant coupling of guided light modes inside the waveguide with SPR at a gold-coated surface. Homola et al [24] used a prism to couple monochromatic light into and out of a waveguide with a narrow strip of gold along the optical path. Similar to monomode optical-fiber SPR devices, these sensors have quite limited operating range [6].

A linear correlation between resonance angle shift and surface protein concentration has been demonstrated [9], allowing real-time detection of mass change without the use of labels. The sensor sensitivity, stability and resolution depend on the properties of the optical system used and the (bio)chemical medium. The sensitivity and resolution reached by the SPR sensors have been extensively discussed theoretically and experimentally [6,11,25,26.27]. The sensitivity of SPR using prism coupler is higher than the devices using grating couplers [28]. Refractive-index resolution of the SPR sensors based on prism coupler ranges, generally, from $2x10^{-5}$ to $5x10^{-5}$ RIU (Refractive Index Units). [24,29,30,31] although a refractive index resolution better than $3x10^{-7}$ has been reached [32]. In general SPR allows the detection of adsorbed thin films of subnanometer thickness. The detection limit of modern SPR devices is about 1 pg mm^{-2} of analysed biomaterial [6], which is still not enough for direct detection of low concentration of low weight molecules.

The main limitation of this technique is that the sensitivity depends on the molecular weight of the analyte implying that low concentrations of small molecules cannot be detected in a direct way. In these cases a sandwich [33] or competitive [34] assay can be employed. Some improvements of surface chemistry and sensitivity of SPR are now allowing the direct detection of low molecular weight analytes in some cases [35].

Receptor layer

For sensing purposes, a layer of receptor molecules that is capable of binding the analyte molecules in a selective way has first to be immobilised at the upper surface of the metal (the sensor surface). When the complementary analytes are flowing over the surface they can be directly recognised by the receptor and a binding occurs. As a result the SPR resonance angle changes. In this way, the interacting components do not need to be labelled and complex samples can be analysed without purification.

As the SPR is a generic sensor system for mass detection cannot discriminate between non-specific adsorbed molecules and specifically bound analyte. For that reason the use of non-specific site blockers (e.g. bovine serum albumin), high ionic strength buffers, surfactants and spiking of samples with adsorbing molecules are required.

In Figure 5 a) and b) an example of a SPR measurement it is shown in

real-time (more details in the Figure caption). Since the measurement is in real time rather than relying on reaching equilibrium the experimental times in commercial prototypes are relatively short: a complete curve can be analysed in 10-15 min. In Figure 6 can be observed the shift of the resonance curve reflecting the biospecific interaction described in Figure 5 a) and b).

Several biomolecular interactions have been exploited in SPR sensors as for example antibody-antigen, receptor-ligand or hormone-receptor because a wide variety of affinity ligands can be used: antibodies, antibodies fragments, genetically engineered antibodies derivatives, lectins, membrane receptors, nucleic acids, gene fusion protein, hormones, viruses, bacteria,....

The immobilisation of the receptor molecule on the metal surface is a key point for the performance of the sensor. The chosen immobilisation method must retain the stability and activity of the bound biological receptor. Generally, direct adsorption (passive adsorption) to the metal surface is not adequate, giving significant losses in biological activity and random orientation of the receptors. Despite these difficulties the direct adsorption is widely employed since it is simple, fast and does not require special reagents.

Various surface chemistries for stable and defined binding of the molecular receptors have been developed based on affinity immobilisation and/or covalent bonding. A detailed description of the chemistry involved will be omitted, readers can be found more information in references cited in the following.

In the affinity bonding, a high affinity-capture ligand is non-reversibly immobilised on the sensor surface. One approach is to use a streptavidin monolayer immobilised on the gold surface and biotinylated biomolecules for recognition [36]. Another approach is to form a Self-Assembled Monolayer (SAM) of compounds with thiols groups (e.g. alkanethiols) on the gold surface, the receptor can be coupled to the tail of the SAM via a functional group (-NH2, -COOH,...) [36].

The use of an extended hydrogel matrix maximises the interaction volume probed by the plasmon field, in this way the surface capacity increases dramatically and therefore the sensitivity of the device as well. The carboximethyldextran hydrogel approach has been widely used [37]: the receptor molecules are attached to flexible dextran chains and are freely accessible in a three-dimensional space thus minimising steric hindrance and increasing the sensitivity. A review of methods for controlled coupling to carboximethyldextran surfaces can be found in reference [37]. A variety of surface activation chemistries can be used to couple the receptor to the hydrogel via amine, thiol, disulphide or aldehyde groups. Typically, surface concentrations of 1-5 ng.mm^{-2} of receptor are coupled, depending on the application.

The use of a flow injection cell allows kinetic measurement over a wide dynamic range and also reduces the incubation time needed for the biomolecular interaction in comparison with systems without flow. It is also preferred because it minimises the consumption of reagents and the irreproducibility in the mixing preparations, avoids the diffusion limited rate of the chemical reaction and reduces changes in concentrations due to adsorption onto the walls [10].

The regeneration of the surface is one of the problems of the SPR sensors. It is desirable to use regenerable sensors for performing continuous measurements, and, in this way, reducing costs and handling and enhancing the reproducibility. For regeneration of the SPR sensor surface one can apply denaturing conditions to break the antigen-antibody bond. Usually it can be achieved using 10-100 mM HCl or 10 mM glycine pH 1.7-2.2 [37]. With this treatment more than 50 analysis can be performed using the same receptor.

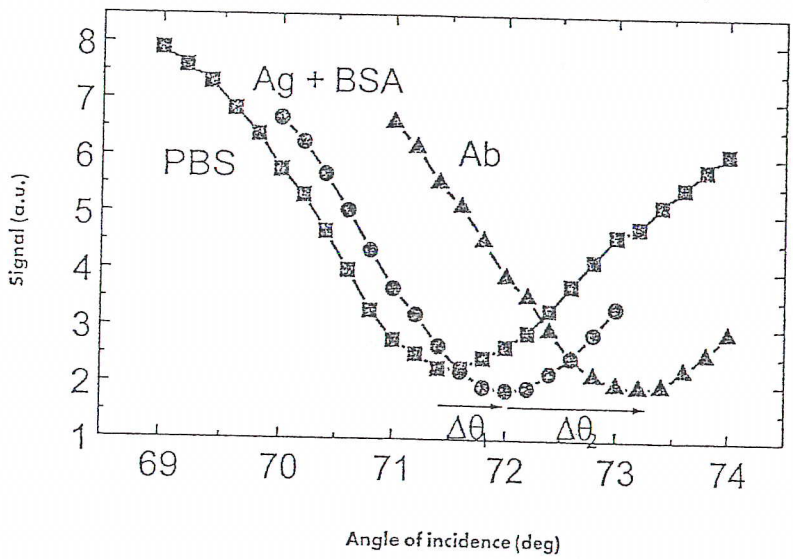

Figure 6 Displacement in the resonance curves corresponding to the biospecific interaction described in Figure 5. The receptor immobilisation gives a shift of the resonance angle of 0.5° (corresponding to a layer of 3 nm) and the biomolecular interaction gives a shift of 1.2° (corresponding to a layer of 7nm).

Applications

SPR sensors have been applied for gas determination and quantification. For example, they were em-

ployed for the determination of hydrocarbons, aldehydes and alcoholes by adsorption in a polyethylene glyco films [38]. Other gases determined have been: chlorinated hydrocarbons, tetrachloethene, toluene, NO_2, H_2S, NH_3, etc. [39,40].

However most of the research and commercial interest have been in the area of biosensors: as it has been mentioned several times before, an attractive features of this technique is the ability to determine concentration and binding kinetics of molecular pairs without the need of labels. The first application as biosensor was demonstrated in 1983 [5]. In 1994, the first application on real-time biospecific interaction monitoring appeared, demonstrating the feasibility of making kinetics analysis of that interaction. For that reason, SPR Biosensors have been applied extensively in the life sciences, for biotechnology quality control and in clinical analysis. For example, they have been used to analyse biomolecular systems as antibody-antigen, hormone-receptor or drug-receptor.

In life sciences this technique has been applied in biomolecular engineering, drug design, monoclonal antibody characterisation, epitope mapping, phage display libraries, virus-protein interaction among others interesting problems [41-47].

The application of optical immunosensors for environmental monitoring started some years ago [48,49]. The SPR technology has been applied to many environmental problems, mainly for the detection of pollutants in the aquatic environment, such as the detection of phenols [48,50], pesticides (atrazine, herbicides...) in the range 0.05-5.0 µg/ml [48,51]. Recently an integrated SPR sensor has been presented [52] with a lower limit of detection, using an indirect assay, of the herbicide simazine of 0.16 $\mu g/L^{-1}$ using anti-simazine antibodies and 0.11 $\mu g/L^{-1}$ using anti-simazine Fab fragments, with a complete test cycle in 20 min.

In the last years the interest has raised in the development of genosensor technology for gene sequence analysis and for nucleic acid-ligand binding studies. In this technology, a single-stranded DNA (probe DNA) is immobilised on the SPR sensor surface (usually using the high affinity streptavidin-biotin interaction) and is used to measure specific binding processes such as the formation of DNA-DNA and DNA-RNA hybrids. Detection of DNA hybridization has many potential applications including DNA sequencing, diagnosis of genetic diseases and DNA tests [53-56].

SPR sensors and their applications can been found in the literature in databases as Current Contents, Medline or Chemical Abstract. Some recommended web sites are, www.biacore.com, www.biosensor.com, www.ti.com/spr/.

Commercial devices

The first commercial SPR was launched by Pharmacia Biosensor AB (today Swedish BIAcore AB) in 1990. Since then, the device has been refined and now BIAcore offers several models (BIACORE® 1000, BIACORE® 2000, BIACORE® 3000, BIACORE® x, BiacoreQuant™, Biacore Probe™). The biosensors of BIACORE 1000 to 3000 are fully automated instruments, with a disposable sensor chip, an optical detection unit, an integrated microfluidic cartridge, an autosampler, method programming and control software. Less expensive manually controlled alternatives are the BIACORE® x and BiacoreQuant™. The latest one (Biacore Probe™) is a fibre optic SPR that enables dipstick-type sampling. Others companies which offer SPR devices are: Texas Instruments (USA) with the TI-SPR-1 Experimenters kit and Spreeta™ Evaluation kit: Quantech (USA); BioTuL Bio Instruments (Germany); Xantec Analysensysteme GbR (Germany) and EBI Sensors (USA). The device of Texas Instruments is a novel miniature SPR (the total volume is about 7 cm^3) in a compact chip. with multiwavelength source and angle deflection measured by a photodetector array [57]. The sensor performance is restricted by the S/N ratio due to the electronics components, limiting the system sensitivity. Recently a new SPR device has been marketed by Xantec Analysensysteme (Germany) with the name of IBIS.

Future trends

Today the SPR sensors compete with other types of evanescent wave biosensors (see Part II) but they have the advantage of the easy implementation and fabrication [58]. Actually the majority of references of biosensors comes from SPR mainly due to the fact that the BIAcore commercial system has been on the market the longest.

The real and major competitors for SPR sensors are the standard immunoassays in clinical and biotechnological fields. The SPR biosensors are commonly employed only for research and in some analytical laboratories. There is still a long way to replace completely the conventional immunoassays in clinical laboratories. It is needed to improve basic aspects of the sensor as sensitivity, stability, cost and handiness. It will be desirable to work on the improvement of the detection limits (but this depends on the application), multichannel performance for the simultaneous measurement of different analytes, possibility of internal referencing and the improvement of biotechnological techniques for producing receptors molecules against any analyte with enough stability and selectivity even in complex media.

There is still a gap for cheap, disposable and portable commercial device with high throughput screening and multisample detection. Direct detection of multianalytes can be achieved at this moment only with BIACore2000 and 3000 using four sensitive elements that are interrogated by optical multiplexing.

SPR can also be used as an imaging technique (Surface Plasmon

Microscopy, SPM). This technique has been studies and applied for sensing [12]. For the development of multianalyte sensor systems will be quite helpful, with a direct application in the development of high throughput screening sensors.

Conclusions

During the last decade the SPR sensors have been widely developed giving helping technology for real-time and in-situ detection of biomolecular interactions. The function and different types of SPR sensors have been described. The applications of this sensor technology in many important fields as environmental control, clinical analysis, pharmaceutical products etc have been mentioned in this review. Future progress of this sensor technology will improve the detection limits, the surface chemistry, the multianalyte screening and will allow the development of a sensitive, small, fast and reliable sensor system for in-situ measurements.

Acknowledgements

The authors would like to thank the support through CICYT projects TIC97-0594-C04 and AMB981048-C04.

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