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SPR Biosensors for Detection of Biological and Chemical Analytes

Jakub Dostálek[1] · Jon Ladd[2] · Shaoyi Jiang[2] · Jiří Homola[1] (✉)

[1]Institute of Radio Engineering and Electronics, Prague, Czech Republic
homola@ure.cas.cz

[2]Department of Chemical Engineering, University of Washington, Box 351750, Seattle, WA 98195-1750, USA

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1 Introduction

Surface plasmon resonance (SPR) biosensors present a mainstay technology for research of macromolecules and their interactions in life sciences and pharmaceutical research. In addition, SPR biosensors hold potential for many other applications of paramount importance, including detection of contaminants related to environmental monitoring, human health indicators for medical diagnostics, and foodborne pathogens and toxins implicated in food safety and security. Existing commercial SPR biosensors are not designed for in-field detection or continuous monitoring of chemical and biological analytes. In order to address analytical needs in theses areas, development of SPR

biosensors suitable for out-of-laboratory applications and analysis of complex real-world samples is pursued in research laboratories worldwide.

2 Concept of SPR Biosensor System for Field Use

The SPR biosensor systems for analysis of complex samples in the field have to integrate several key elements. These include, in particular, a *sample preparation unit*, a *fluidic system*, a *biorecognition element*, and an *SPR optical platform* (Fig. 1).

In this biosensor system, a sample is pretreated in the sample preparation unit and delivered by the fluidic system into contact with the biorecognition element immobilized on the sensor surface. The SPR optical platform converts its specific interaction with the analyte into the sensor output.

This chapter is devoted to a description of the state of the art in the development of these key elements and their integration for SPR biosensor instruments for field use.

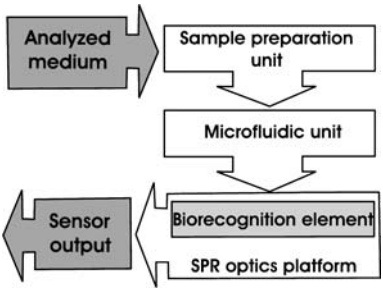

Fig. 1 Scheme of key modules supporting an SPR biosensor instrument

3 Sample Preparation Unit

SPR biosensors are devices that are suitable for analysis of aqueous samples. Therefore, in order to detect target analytes in different real-world matrices (e.g., tissue, meat, soil, and air) the analyte has to be transferred to a liquid by a sample preparation unit. Numerous sample pretreatment methods for gas, solid, and crude liquid samples compatible with SPR biosensors are available. For detection in gas environments such as air, real-time trapping of analyte into an aqueous solution is possible by using collectors such as a wetted-wall cyclone particle collector [1]. Several optical biosensors have been integrated with these collectors and installed on aerial vehicles for real-time detection

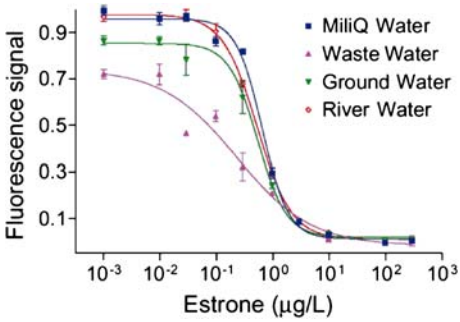

Fig. 2 Changes in the calibration of a fluorescence-based biosensor for detection of estrone due to the non-specific interaction of biorecognition elements with residual matrix components [9]

of airborne substances [2, 3]. Solid matrices such as tissue or soil are usually homogenized and suspended in a buffer or solvents. Then, the matrix separation is performed by filtration [4], centrifugation [5], or immunomagnetic separation [6]. Liquid samples, either collected directly or obtained as supernatants from solid or gaseous matrices, can be analyzed with an SPR biosensor directly.

Additional sample treatment is necessary prior to sample injection into an SPR biosensor when crude samples are analyzed (e.g., blood, waste water, or supernatants from solid matrices). In these samples, residual matrix components can non-specifically interact with the biomolecular recognition elements (e.g., dissolved organic carbon [7]) and variations in sample properties such as pH and ionic strength can alter the specific interaction between an analyte and a biomolecular recognition element. The matrix effects can lead to variations in sensor calibration [8–10] resulting in false sensor responses. In order to reduce these effects, analyzed aqueous samples can be buffered to stabilize their pH and ionic strength and filtered to remove residual matrix components. Figure 2 illustrates the effect of matrix composition. Calibration curves are shown for an estrone fluorescence-based biosensor performing detection in water samples from different sources (samples were buffered prior to their analysis).

4 Fluidic Unit

In SPR biosensors, a fluidic unit is necessary to provide precise control of sample delivery to the sensor surface as the amount of analyte captured by the biorecognition elements (and thus the sensor response) depends on the flow conditions at the sensor surface [11, 12].

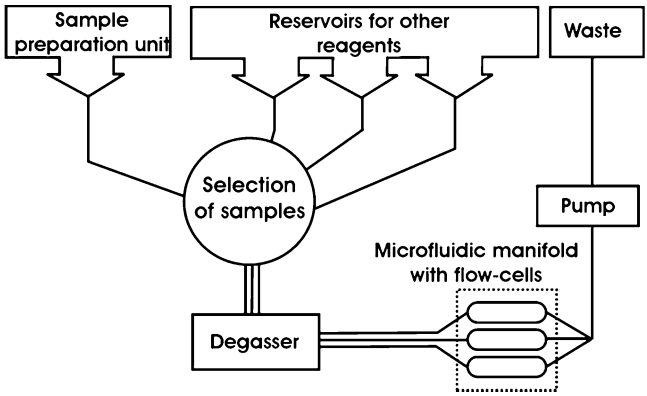

Fig. 3 Scheme of a typical fluidic unit supporting an SPR biosensor

In general, the fluidic unit needs to encompass reservoirs to contain analyzed liquids and other reagents (e.g., solutions for sensor regeneration and sensor surface washout), a pump to flow these liquids through the sensor, valves to control their injection, and flow-cells for their distribution on the sensor chip (Fig. 3). Peristaltic pumps are frequently used to flow liquid samples through the sensor flow-cell [2, 13]. Selection of samples and reagents is typically achieved with selection valves [2] which can be substituted with air vents placed within reservoirs [13]. The fluidic channels and flow-cells can be produced by combining conventional machining (e.g., drilling of input and output ports) with microfabrication of the fluidic manifold using technologies such as molding of plastics [14], casting in poly(dimethylsiloxane) [15, 16], and laser cutting of thin polymer layers [17, 18]. The fluidic system can be combined with degassers for the removal of air dissolved in a sample as it can produce air bubbles at the sensor surface interfering with the SPR biosensing [2].

To date, several SPR biosensor systems with integrated automated fluidic system have been reported [2, 19, 20]. However, these devices rely on bulky components (e.g., external pumps and valves), which limits their further miniaturization. In future, we expect that development of more compact fluidic units will benefit from current advances in the micropumps and microvalves [21] and microfluidic technologies pursued for Micro Total Analysis Systems (μTAS) and Lab-on-a-Chip devices [22–24].

5 SPR Optical Platform

In order to create a portable/mobile SPR biosensor for applications in the field, easy-to-use SPR biosensor instruments that can deliver high accuracy

detection in real-world environmental conditions need to be developed. To meet these requirements, these biosensor instruments have to encompass a robust and compact SPR optical platform providing reference channels for the compensation of fluctuations in SPR sensor response due to changes in optical properties of the analyzed sample and variations of environmental conditions. Moreover, to enable simultaneous detection of multiple analytes, SPR optical platforms have to support multiple independent sensing channels.

A large variety of SPR optical platforms have been developed (see Chap. 4 in this volume [63]). The SPR sensors allowing the highest degree of miniaturization of the SPR optics are based on optical fibers [25–28]. These sensors have potential for localized detection including in vivo diagnostic applications. However, the fiber optic SPR sensors exhibit a limited accuracy, which up to now has hindered their applications for detection of chemical and biological analytes. In order to provide more accurate SPR sensor instruments, several miniaturized SPR optical platforms relying on bulk optics and the attenuated total reflection (ATR) method have been developed. These include the SPR platform based on angular modulation of SPR proposed by Elkind et al. [29], Kawazumi et al. [30] and Thirstrup et al. [31]. Another compact SPR sensor platform based on the wavelength modulation of SPR and wavelength division multiplexing of sensing channels [17] has been recently developed (Fig. 4).

SPR sensor platforms supporting easy-to-interchange sensor chips are desired to allow fast and simple replacement of chips or introduction of a sensor chip with a desired biomolecular recognition element. In a majority of the

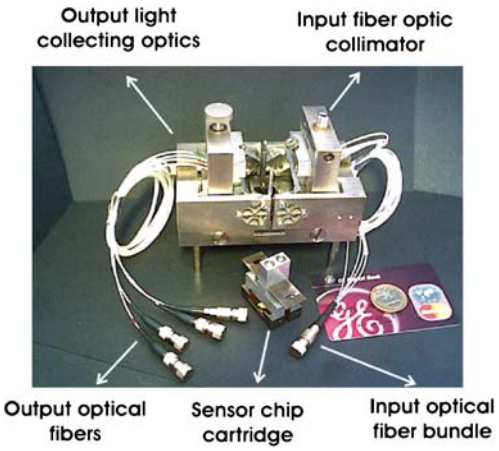

Fig. 4 Compact optical bench supporting an eight-channel SPR sensor relying on wavelength modulation of SPR and WDM multiplexing of sensing channels; developed at the Institute of Radio Engineering and Electronics, Prague

current SPR biosensor platforms an optical contact of the sensor chip with a coupling prism needs to be established. The optical contact is typically achieved by means of a refractive index matching oil or a soft polymer which, for in-field applications, makes the loading of a sensor chip rather inconvenient. Therefore, SPR optical platforms based on light-pipes [31, 32] and diffraction gratings [33] have been proposed to avoid the necessity of establishing an optical contact.

SPR biosensors for analyzing complex matrices in realistic environmental conditions need to discriminate between the refractive index changes due to specific interaction with an analyte and those due to background refractive index variations. Fluctuations in the background refractive index are typically caused by changes in composition of the sample (e.g., residual matrix components) and by temperature variations. The discrimination between these changes can be achieved by using reference channels [32] or by means of decomposition of SPR variations using multiwavelength spectroscopy of surface plasmons [17, 34–36]. The effect of temperature changes, which can affect the interaction of the biorecognition element with analyte as well as the performance of optical components (e.g., lightsource spectrum and detector efficiency are a function of temperature), can be reduced by stabilizing the temperature of the SPR optical platform [20].

6 Molecular Recognition Element

Numerous biorecognition elements and methods for their attachment to surfaces can be used with SPR biosensors (see Chap. 5 in this volume [64]). In applications of SPR biosensors for detection of chemical and biological analytes, biorecognition elements and their immobilization have to be selected with respect to desired specificity (detection of individual molecules or biological activity of overall sample), mode of operation (continuous monitoring or rapid detection), stability and storability (long term storage and operation in realistic environmental conditions).

SPR biosensors relying on a variety of biorecognition elements (including antibodies [37–40], hormone receptors [41, 42], and whole cells [43]) have been used for detection of analytes. Among these, antibody biorecognition elements are the most popular due to their high affinity, versatility, and commercial availability [44]. As an alternative to biorecognition elements, other receptors such as molecular imprinted polymers (MIPS) [45] and organic synthetic receptors [46] were investigated due to their potential higher stability in environmental conditions. However, to date the accuracy and specificity these SPR sensors are still significantly lower then their biorecognition element-based counterparts. In continuous monitoring SPR biosensors, biorecognition elements with lower affinity are preferred for achieving

reversible interaction with target analyte [47]. SPR biosensors for rapid detection employ high affinity biorecognition elements to achieve the lowest detection limits.

Immobilization of biorecognition elements presents an important challenge to sensor development. Sensor sensitivity and specificity are two concerns that influence biorecognition element immobilization techniques. Sensitivity is related to the amount of biorecognition element that is available on the surface for analyte binding. When antibodies are used as the biorecognition element, the orientation and conformation of the antibodies can vary the amount of available analyte-binding sites on the surface. Recent studies showed that orientating the analyte-binding pockets away from the surface can increase the sensitivity of SPR biosensors [48]. Specificity is another important concern for surfaces of SPR biosensors. Integration of non-fouling materials as a background for sensor surfaces has become an important focus of SPR biosensor development. Oligo (ethylene glycol) (OEG) is one material used to resist non-specific adsorptions of biomolecules. Mixed self-assembled monolayers (SAMs) consisting of a non-fouling background and a binding element have come to the forefront as a simple, yet effective means for addressing the issue of non-fouling sensor surfaces [49–52]. While these surfaces make great strides in limiting the amount of non-specific adsorption of proteins [53, 54], other surfaces resistant to bacteria and other extremely complex matrices are still needed. Recently zwitterionic SAMs were reported to show good non-fouling characteristics for both proteins and live bacteria [55].

The stability of the biorecognition elements immobilized on the sensor surface is an important factor for use of SPR biosensors in field applications. In general, long-term storage and exposure to environmental conditions could decrease the functionality of the immobilized biorecognition element. In SPR biosensors, protein biorecognition elements are mostly used. Storage characteristics of protein arrays were studied by, e.g., Angenendt et al. [56]. He showed that his protein arrays, consisting of five different antibodies, could be stored for a period of 8 weeks. Proteins are known to be more stable in a solution than anchored to a surface. Therefore, a novel method has been introduced to reduce the amount of time that protein biorecognition elements must stay immobilized on the sensor surface. This method implements site-directed immobilization of a protein–DNA conjugate to a surface that is modified with a single strand DNA (ssDNA) [49, 51, 57]. In this work, the protein conjugate consists of an antibody chemically linked to an ssDNA target that has a sequence complimentary to the one bound at the surface. The antibody–DNA conjugate is immobilized on the surface via sequence-specific hybridization. Using this methodology, DNA arrays that are more stable than protein arrays can be prepared and stored. Antibodies can be immobilized on such a sensor chip prior to detection from a solution. In addition to maintaining the stability of immobilized proteins, this approach offers other advantages. Sensors relying on DNA-directed immobilization of biorecogni-

tion elements have shown as much as a 50-fold increase in sensitivity over conventional protein sensors [49, 51]. Furthermore, dehybridization has been shown to be an easy and effective means to recycle the DNA sensor surface.

7 Detection Format

In SPR biosensors for detection of chemical and biological analytes, detection formats need to be chosen depending on the size of target analyte and whether detection or continuous monitoring is needed.

Detection of analytes can be performed using either direct detection methods or indirect detection methods. In the case of direct detection methods, an analyte or parts of an analyte are bound to the sensing surface producing the sensor response. Direct detection methods include direct detection of the analyte, sandwich assays, and competitive assays. In indirect detection methods, the analyte induces a change in the state of a secondary system component, which subsequently induces a sensor response. The most commonly used indirect detection method is the inhibition assay.

In a sandwich assay, as seen in Fig. 5a, one antibody is immobilized on the sensor surface. Analyte is then flowed over the sensor surface and captured by the immobilized antibody. Following analyte capture, binding of a second antibody (normally a polyclonal antibody) to the analyte at the sensor surface is measured. This amplification has a twofold effect: improvement of lower detection limits and verification of the bound analyte.

Competitive assays, as seen in Fig. 5b, are based on two analytes competing for the same recognition site at the sensor surface. One of the analytes is free and the other is typically conjugated to a larger protein, usually bovine serum albumin or casein. The concentration of the conjugated analyte is fixed from solution to solution. The two analytes are mixed in a solution and passed across the sensing surface. The sensor response will be inversely proportional to the concentration of analyte in the target solution.

In an inhibition assay, as seen in Fig. 5c, the analyzed sample is preincubated with an antibody for the targeted analyte. Subsequently, the mixture is injected in the SPR sensor with an analyte derivative immobilized on the sensor surface and the binding of the unreacted antibody to the analyte derivative is measured. As with the competitive assay, the sensor response is inversely proportional to the concentration of target analyte in the incubation solution.

Detection of medium-sized and large analytes ($> 10\,000$ Da) is usually performed directly [37, 58]. As direct binding of low molecular weight analytes at the sensor surface does not usually produce sufficient refractive index change, they are typically detected using a competition assay [39], sandwich assay [40], or inhibition assay [38].

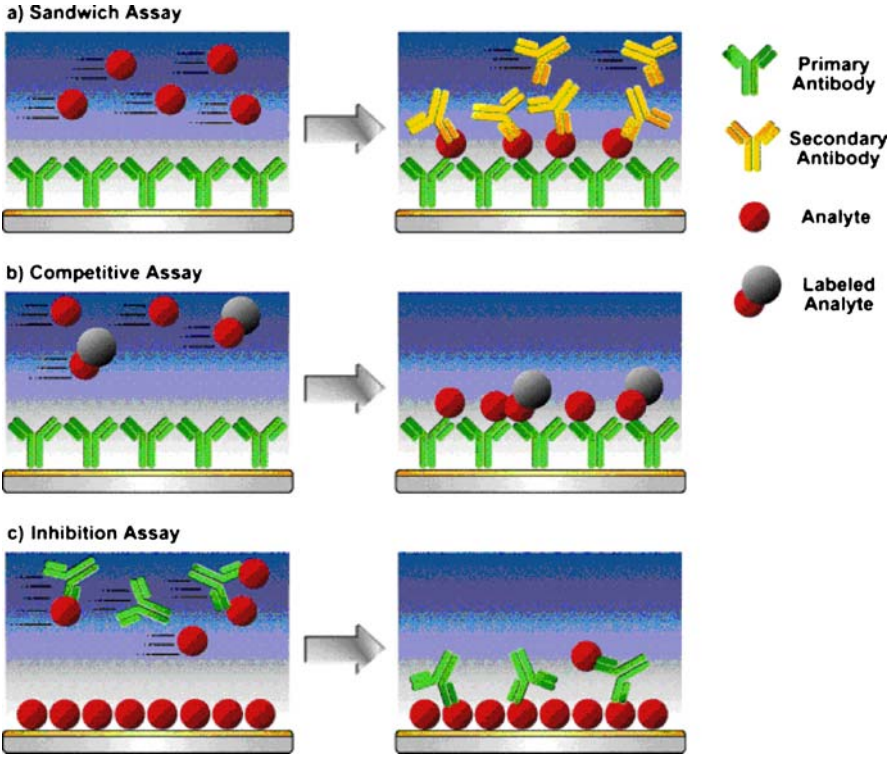

Fig. 5 Cartoon representations of three different assays typically used in detecting analytes with an SPR biosensor. **a** Sandwich assay involves the capturing of analyte by a sensing element immobilized on the sensor surface. This is followed by the binding of a secondary antibody for amplification. **b** In a competitive assay, native analyte and analyte conjugated to a larger protein compete to bind to an immobilized sensing element on the surface. **c** In an inhibition assay, analyte is incubated with a fixed concentration of antibody. This incubation solution is then passed across a surface of immobilized analyte. Free antibody binds to the sensor surface, creating an inverse relationship between concentration of analyte in the sample and sensor response

SPR biosensors for rapid detection of chemical and biological analytes usually use direct or indirect assays in conjunction with high-affinity biorecognition elements. For these elements, their interaction with an analyte is, under normal conditions, irreversible. Regeneration of the sensor surface for its repeated use can be performed by changing pH [59], using detergents [45], or with enzymes [38, 60] by which analyte bound to the biorecognition element is released leaving the sensor available for subsequent measurements (Fig. 6). In SPR immunosensors, typically tens of regeneration–detection cycles are possible without significant reduction of activity of the biorecognition elements [59, 61, 62].

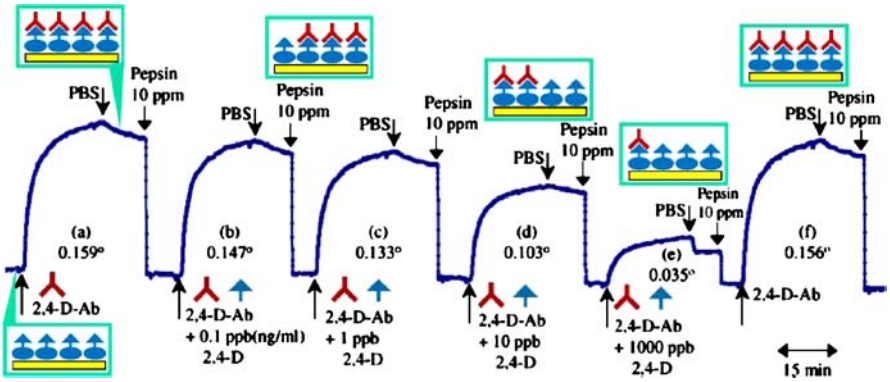

Fig. 6 SPR biosensor for detection of 2-4 dichlorophenoxyacetic acid (2,4-D) relying on inhibition assay and antibodies irreversibly interacting with the analyte; sensorgram obtained for several detection and regeneration cycles [62]

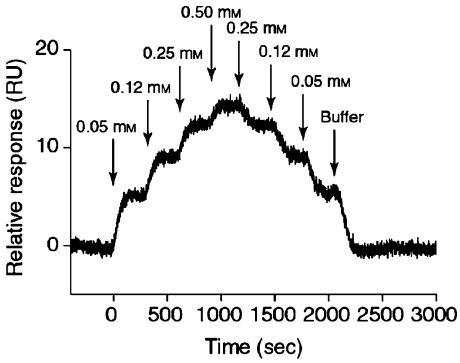

Fig. 7 SPR biosensor for continuous monitoring of maltose using direct detection of analyte and weak-affinity antibodies [47]

Additionally, SPR biosensor technology can be used for continuous monitoring of analytes. This performance can be achieved by using biorecognition elements interacting reversibly with target analyte. This type of sensor was investigated by Ohlson [47], who demonstrated continuous monitoring of maltose using weak-affinity antibodies and direct detection of analyte (Fig. 7).

8 Integration of SPR Biosensor System

Over the last few years, we have witnessed development of several portable SPR sensor instruments aimed for field applications. Based on SPREETA SPR

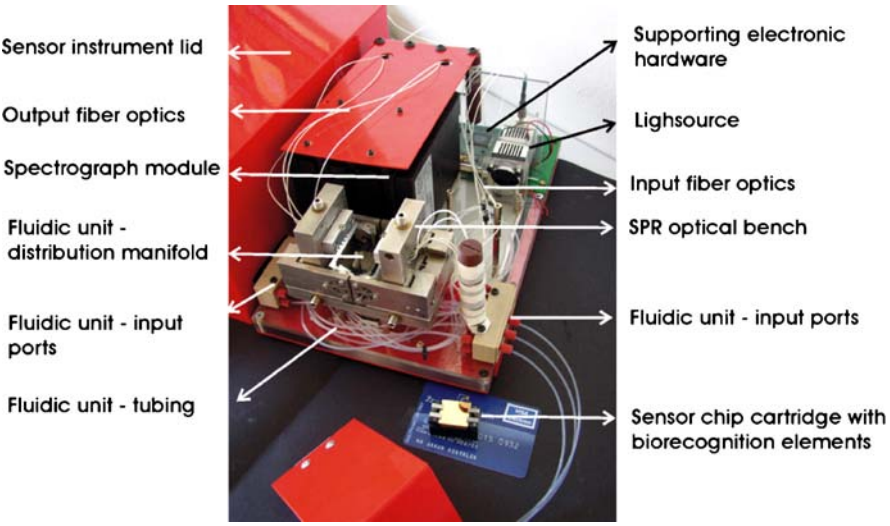

Fig. 8 Portable SPR sensor system developed at the Institute of Radio Engineering and Electronics, Prague with SPR optical platform, fluidic unit, temperature stabilization, and supporting electronic hardware

sensor (commercialized by Texas Instruments) two prototype portable sensors with one and two channels were reported by Sessay et al. [19] and Naimushin et al. [20], respectively. These portable devices encompassed SPR optics, electronic hardware, and basic fluidic systems. Currently, based on this platform Naimushin et al. developed a sensor system for detection of airborne analytes [2, 20]. This device was equipped with a sample preparation unit for collecting of analyte from aerosols. Using an aerial vehicle it was applied for measuring the spatial distribution of a model analyte (ovalbumin and horseradish peroxidase) dispersed in the atmosphere using a sandwich assay. An eight-channel portable SPR biosensor system has been recently developed at the Institute of Radio Engineering and Electronics, Prague based on a compact SPR optics bench, depicted in Fig. 4. This system (Fig. 8) incorporates a temperature-stabilized SPR optical platform, a fluidic unit, and supporting electronics. The SPR optical platform takes advantage of a special sensor chip cartridge that does not require optical matching and can be easily plugged into the sensor.

9 Summary and Outlook

In the last decade, we have witnessed a concerted research and development effort to bring SPR biosensor technology to the field and meet the need for

the rapid detection and identification of chemical and biological substances in important areas such as medical diagnostics, environmental monitoring, food safety, and security. These applications present SPR sensor technology with unique challenges in terms of complexity and diversity of sample matrices (gaseous, liquid, and solid samples), type of deployment (mobile or portable versus permanently installed sensor system), detection environment (field, mobile laboratory, industrial plant, etc.), and mode of operation (rapid detection versus continuous monitoring). To address these challenges, the SPR sensor systems have to integrate multiple key functions such as sample collection and preparation, sample delivery, capture of analyte from the sample by biomolecular recognition elements, and measurement of the amount of captured analyte using the SPR method.

In recent years, first prototypes of SPR biosensor systems integrating these elements have been reported and their application for detection of biological analytes in the field have been demonstrated. Undoubtedly, advances in the development of the key elements – sample preparation technology, microfluidics, biomolecular recognition elements, SPR optical platform – will further stimulate this effort and eventually lead to in-field SPR sensor systems becoming a commercial reality.

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