

Recent developments in optical transducers for chemical or biochemical applications¹

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Abstract

A variety of optical transducers is presented in the literature based on just a few given optical principles. Based on principles like micro-refractometry and -reflectivity, a classification is approached, especially for sensors used in bioanalytics. Two methods are discussed in detail, which are favoured in the group known as integrated optical Mach–Zehnder interferometers and reflectometric interference spectroscopy (RIFS). Recent applications as chemical sensors and biochemical probes in the fields of hydrocarbon monitoring and immunoreactions are demonstrated. Perspectives in routine interaction analysis, microstructuring of devices, direct detection of low-molecular-weight ligands, and parallel high-throughput screening are discussed.

Keywords: Microrefractometry; Reflectometry; Interference; Waveguides; Chemical and biochemical sensing

1. Introduction

20 years ago, optical devices were introduced in addition to electrodes as sensing elements. These so-called optodes [1] or optrodes [2,3] were originally used to monitor pH or CO₂ concentrations. Compared with this narrow field of application and the principle of either fluorescence or reflectance measurements, nowadays the number of different optical transducers mentioned in the literature has increased, as has the area of possible applications. At the beginning, only effects on the amplitude of electromagnetic radiation were measured. In the meantime, other properties such as phase, frequency, and state of polarization are used in optical devices. Multi-wavelength detection and multicomponent analysis provide additional ways to quantify components in complex samples.

All possible interactions between radiation and matter, such as dispersion (refractive index), reflection (diffuse, specular), scattering (Raman), changing transmission, or quenching of fluorescence, are used to monitor analyte/sensor interactions. On the other hand, a growing market in sensing and telecommunications has reduced the price/performance ratio of optical compounds, and provides miniaturized devices. Application of advanced optical principles and devices based on total internal reflection and evanescent-field

effects allow improvements of optical sensing devices that add to the common advantages of optical sensors [4].

In the following, first the optical principles are discussed and classified. Next an attempt is made to classify optical transducers according to the effects detected:

1. either intrinsic to the analyte or
2. caused by a marker or
3. caused by interaction between a matrix and the analyte.

Sensitive layers, which consist either of chemical or biological ('receptor') material, are an essential part of sensor systems. They are combined with optical transducers that are either extrinsic or intrinsic fibers, waveguides based on the evanescent field operating as microrefractometers, or transducers that use simple principles of refractometry and interferometry.

In particular, the wide field of waveguides used in sensing requires careful classification.

Within the last few years thousands of publications dealing with new or modified optical principles and transducer setups as well as a large variety of applications have been published. Out of these only a few which best represent the recent developments and therefore allow a prognosis of trends that can be expected in the coming years will be mentioned here. For a more detailed survey longer reviews have to be considered [5,6,10]. Some of these predicted trends have a very good chance of finding applications; others will only be of interest for research and only the future will prove their success.

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2. Optical transducers

In Table 1 many of the present optical transducer principles are listed. They are based on fundamental optical principles such as reflectance, fluorescence, interference, and polarization. Recently evanescent-field technologies have aroused great interest. In Fig. 1 the fundamental optical principles are demonstrated. They form the basis for many optical transducers using waveguides. Radiation passing the interface between two media is refracted (to the optical axis for increasing refractive index, off the optical axis for decreasing refractive index). In the latter case a critical angle exists beyond which radiation is totally reflected at the interface to a medium of lower refractive index. Radiation is guided in the waveguide (fiber, slab or stripe waveguide) according to Fig. 1(a,b). Coupled to this guided wave an evanescent field

exists close to the interface, which in the medium of lower refractive index decays exponentially as shown in Fig. 1(b). Any effect on this evanescent field results in a change of the effective refractive index inside the waveguide, which influences the wavelength and velocity of the guided wave. This change can be interrogated by the large variety of transducers listed in Table 1. A typical interrogation principle is surface plasmon resonance (see Fig. 1(d)), where the guided radiation transfers an impact to electrons in a thin metal film, which results in resonant coupling for certain optical conditions. Furthermore, the evanescent field can selectively excite fluorophores close to the interface (see Fig. 1(c)).

Most of the transducer principles mentioned in Table 1 have found applications in the area of chemistry and biochemistry. In the following only the results obtained by two methods favoured in our group are discussed in more detail.

Table 1
Optical transducers

Classification	Transducer	Principle	Literature
Extrinsic fiber optics	Optodes	Reflectance, fluorescence	[7-9,12]
Intrinsic fiber sensors	Fiber	Fluorescence	[11,12]
		Total internal reflection fluorescence	[13-19]
		Attenuated total reflection	[20-24]
		Fiber surface plasmon resonance	[25]
		Interferometer	[32,33]
Waveguides	D-shaped		
	Stripe (waveguide)	Intrinsic effect	[26]
		Young interferometer	[27]
		Mach-Zehnder interferometer	[28]
	Slab (film) waveguide	TE/TM differential mode interferometer	[29-31]
		Mode coupling 3×3	[34,35]
		Prism coupler	[36]
		Grating coupler	[37,38]
		Bidiffractive grating	[39]
		Chirped waveguides	[40]
		Input/output coupler on Mach-Zehnder chip	[41]
	Surface plasmon resonance	Monochromatic, resolving the angle	[42]
		Spectral	[43]
		Waveguide-based SPR	[44]
Reflectometry	Reflectometric interference spectroscopy		[49,51]
	Ellipsometry		[45]

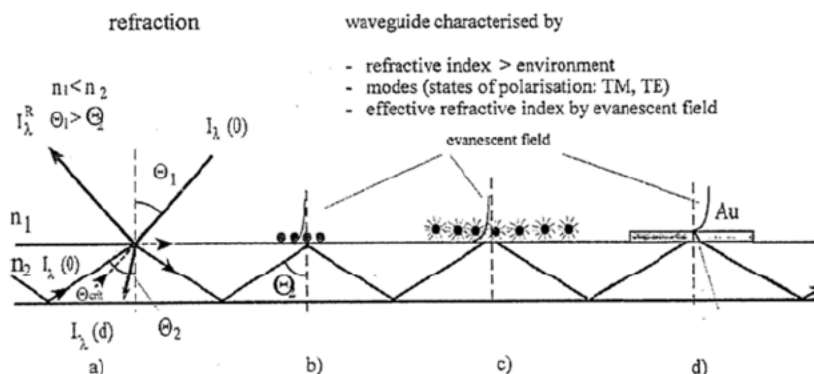


Fig. 1. Refraction, reflection, total reflection, and evanescent field as basic optical principles for various transducers: (a) refraction; (b) attenuated total reflection; (c) TIRF (total internal fluorescence reflection); (d) surface plasmon resonance.

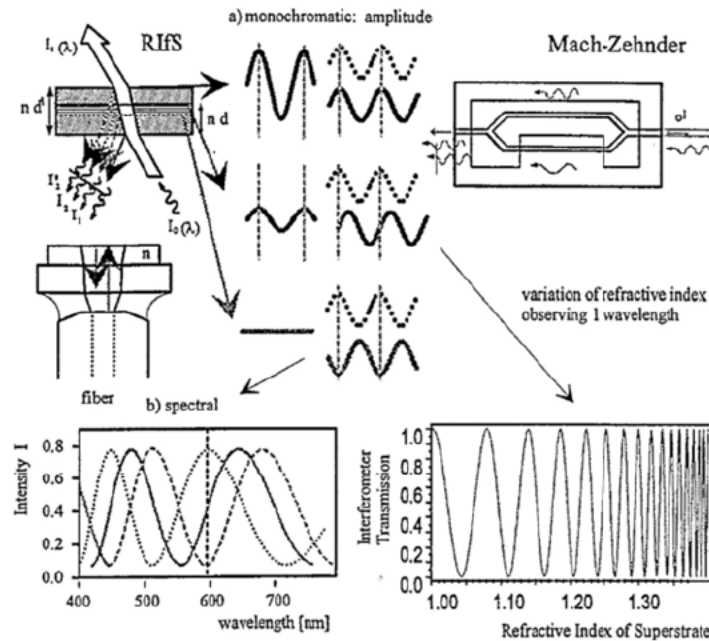


Fig. 2. Schematic principle of Mach-Zehnder interferometry (a) and white-light reflectometric interference spectrometry (RIFS) (b). For a better visualization of RIFS the pathway of incident line is drawn out of the perpendicular optical access. In practice perpendicular incidence is used.

Both methods are based on the principle of interferometry. One of these using integrated optical Mach-Zehnder chips operates as a microrefractometer, employing the evanescent field in combination with the measurement of interference effects. The other method, reflectometric interference spectrometry (RIFS), takes advantage of the sensitivity of white-light interferometry.

In the case of integrated optical Mach-Zehnder arrangements, the monomode waveguide is split into two parallel arms; one of these is used as a reference and the other can probe the analyte. Interaction between analyte and the evanescent field of the sample waveguide arm causes a change in the velocity of the propagation of light in this arm. Thus after the two arms are merged, the two guided waves superimpose and form (depending on the phase difference) constructive or destructive interference or an intensity somewhere in between (see Fig. 2 right). This phase difference depends on the interaction length, the wavelength of the radiation, the optical properties of the waveguide, the substrate and the material within the range of the evanescent field. The material on top of the waveguide, the superstrate, consists of a thin polymer film in the case of gas detection, or of a biomaterial in the case of bioanalytics. The refractive index of this superstrate influences the effective refractive index within the waveguide. By using evanescent-field theory and Maxwell equations it is possible to model these effects. A comparison between experiment and simulation demonstrates that the understanding of the dependencies is well known.

Reflectometric interference spectrometry uses the partial reflection of incident radiation at interfaces of layers and the

superposition of the reflected partial beams according to the principle of interference (see Fig. 2 left). A simple glass substrate is illuminated perpendicularly by a bifurcated fiber. A thin layer ($\approx 1 \mu\text{m}$ thick) is coated onto this substrate. At its interfaces partial beams are reflected into the second arm of the bifurcated fiber. Depending on the optical thickness of this layer phase differences appear, causing destructive, constructive or another type of interference. Monochromatic irradiation of this layer results in an amplitude specific for the thickness of the layer and the wavelength chosen. If white light is irradiated an interference pattern is obtained as given at the bottom left of Fig. 2 [49]. The optical thickness is a product of the refractive index of this layer and its physical thickness. Thus any change in either physical thickness or refractive index will cause a shift of the interference spectrum. This can be measured very sensitively, and accordingly changes in (nd) down to a few pm [50].

3. Selected applications of Mach-Zehnder and RIFS transducers

Applications of Mach-Zehnder chips have been published in the field of volatile organic compound detection by way of interaction between thin polymer films forming the superstrate and the gaseous analyte [46], monitoring of ammonia in the gaseous phase using bromocresol purple as an indicator molecule [47], and measuring either the formation of subsequent layers composed of biotinylated protein and streptavidin molecules [28], or detection of pesticides in a competitive test scheme using selective antibodies [48].

Reflectometric interference spectroscopy has been applied both to chemical and biochemical sensing [51]. In the first field of application a polymer layer is coated onto the substrate. Gaseous or liquid organic analyte molecules diffuse into this layer and are enriched, thus causing a swelling of this film. This in turn results in a change of the physical thickness (the change in refractive index is negligible) of this layer that can be measured quite accurately [52]. In practice, applications in the area of detection of volatile organic compounds, halogenated alkanes, halogenated hydrocarbons, ammonia [53], and organic compounds dissolved in water [54] have been published. In all these cases the interaction between analyte and polymer is reversible, but has a different response time depending on the properties of the analyte molecules and the matrix. This can be seen as an advantage which allows us to distinguish between the signals coming from two different analyte molecules by way of their response times [55].

Chemical modification of the polymer films allows the introduction of some selectivity of different types of polymers to different analyte molecules. The simplicity of the optical arrangement allows a sensor array consisting of 6 to 13 polymer elements to be set up. By using an optical multiplexer, a simple diode-array detector is able to monitor all transducer elements sequentially [56]. The optical setup and some results are demonstrated in Fig. 3. Using various methods of multivariate data analysis and chemometrics, multianalyte solutions can be calibrated and the constitution of unknown samples can be predicted [57].

RIFS can also be employed to analyse interactions between receptor layers of biomolecules and ligands by making use

of affinity reactions. Under such conditions a so-called interference layer has to be coated on the substrate material. This interference layer has a refractive index similar to that of the biomolecules. At this interference layer receptor molecules that will undergo affinity reactions with ligands (analyte molecules) are immobilized. This affinity reaction changes the physical thickness of the interference layer (+receptor layer) as well as its refractive index. The latter effect again is negligible and the changes in the physical thickness can be monitored by RIFS. This means that large analyte molecules (antibodies, proteins) can be monitored directly while they are interacting, whereas low-molecular-weight molecules are usually measured in a competitive test scheme [58]. A pre-incubation step is used during which the low-molecular-weight antigens (analyte: haptens) interact with an antibody, thereby blocking its receptor sides. If the analyte concentration is high, only few free antibodies will be left that are able to interact with the immobilized receptor molecules at this interference layer in a second step, and a low signal is generated. If, on the other hand, low analyte concentration is used, then a relatively high signal can be detected. With this approach pesticide concentrations have been successfully measured down to sub-ppb concentrations [59,60].

Apart from this application in analytics, this type of affinity reaction monitoring can be used to determine binding constants. Since the affinity reaction is monitored by way of time-resolved measurement, the adsorption constant can be directly determined by curve-fitting techniques. The same also applies to the desorption processes. The correlation of the theoretical and the experimental consideration allows the

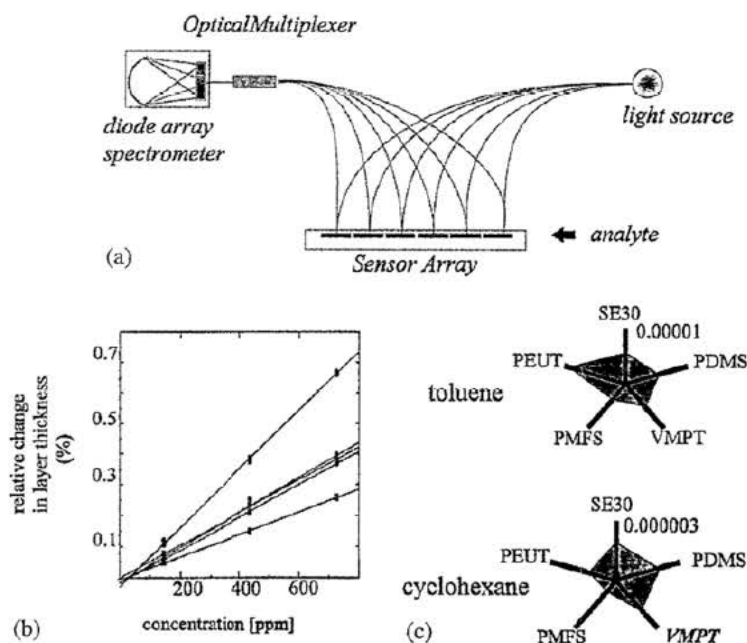


Fig. 3. The use of an optical multiplexer allows the measurement of mixtures with a polymer sensor array: (a) multiplexer; (b) calibration of one component; (c) polar diagrams demonstrating the different selectivity of polymer coatings.

determination of thermodynamic and kinetic parameters of such reactions [61].

Sophisticated surface modification increases the surface coverage of the receptor molecules and the preparation of very stable receptor layers [62]. The affinity reaction becomes diffusion controlled. Thus low limits of detection can be reached. Furthermore, these layers can be regenerated, i.e., they can be reused several hundred times in the case of pesticide detection [59].

4. Recent developments and perspectives

In the mean time, improved surface chemistry and increased sensitivity of surface plasmon resonance allow the

direct detection of low-molecular-weight analytes [63]. The same can be achieved by RIfS as demonstrated in the case of monitoring of the affinity reaction of biotin molecules with a layer of immobilized streptavidin receptor. Injection of 400 nM biotin changes the layer thickness by 20 pm. Since at present the resolution of the layer thickness measured could be reduced to 0.44 pm root-mean-square noise, the direct monitoring of interaction with low-molecular haptens becomes possible even with reflectometric interference spectroscopy [50]. In Table 2 the limits of detection for some optical transducers are compared according to results published recently.

Another approach is the direct detection of multianalytes. This can be achieved with BIAcore 2000 using four sensitive

Table 2
Limits of detection obtained by different direct optical bioanalytical methods

Method	Commercialization	Limit of detection	Lit. cit.
Surface plasmon resonance (angle dependent)	BIAcore Pharmacia	0.3 pg mm ⁻² (0.5‰ ML)	[63]
Waveguide surface plasmon resonance		2 pg mm ⁻² (1‰ ML)	[64]
Frustrated total reflection (angle dependent)	Resonant mirror fisons (Affinity sensors)	5 pg mm ⁻² (1‰ ML)	[65]
Grating coupler (angle dependent)	ASI	5–10 pg mm ⁻² (0.5‰ ML)	[66]
Dual-beam waveguide interferometer (intensity modulation in the waveguide)		few pg mm ⁻² (1‰ ML)	[67]
TE–TM differential mode interferometer (int. mod. in the waveguide, ratiometrical)		< 2 pg mm ⁻² (1‰ ML)	[31]
Reflectometric interference spectroscopy RIfS (thickness change, spectral)		1–5 pg mm ⁻² (1‰ ML)	[50]

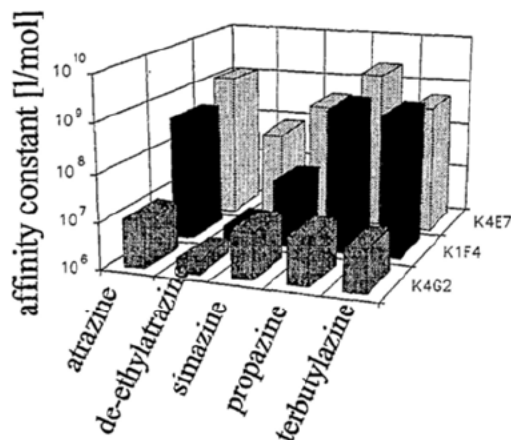
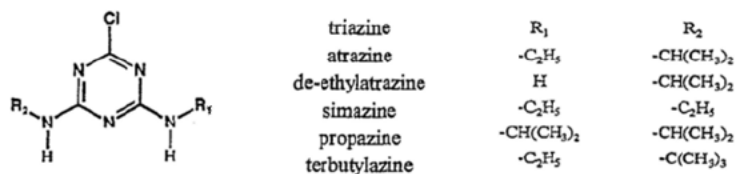


Fig. 4. Cross-reactivity of some triazine derivatives to antibodies: affinity constant for three antibodies graphed for five triazine derivatives.

surface plasmon resonance (SPR) elements or by way of optical multiplexing. The results of an examination of the cross-reactivity and the chances to detect some pesticides with different antibodies are shown in Fig. 4.

An increase in elements that can be detected in parallel is required in drug or pharmaceutical screening. Combinatorial chemistry and a search for new lead structures require the analytical examination of 100 000 to 1 000 000 samples per year. Apart from conventional ELISA approaches, direct optical detection of affinity reactions is a possibility to meet the requirements. However, in this case a parallel detection at as many sites as possible is necessary. One approach is the use of the micro-titer-plate format and to attempt to achieve high throughput screening by parallel detection of at least 96 sites at one time using imaging techniques [68].

Another target is miniaturization. Ellipsometry, mentioned as another possibility to characterize surfaces or even for use as a sensor, can be miniaturized by way of microsystem approaches [45].

Another approach is to integrate evanescent-field absorbance sensors (EFAS) into integrated optical glass substrate chips [69].

The performance of a Mach-Zehnder integrated optical chip can be increased by combining it with optical signal preprocessing on the chip (3 × 3 coupler) [35]. Such optical devices are currently quite expensive. However, the telecommunications market and the possibility of integrating the light source, sensor element, and detector in one chip demonstrate the future potential of this approach.

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