The Emergence of Physical Chemosensors and Biosensors

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ABSTRACT

In this paper a review is given of the position and significance of integrated physical chemosensors and biosensors. After a discussion on the definition of chemical sensors in general, the concept of physical chemosensing is set against the concept of so-called direct chemical sensing. With the help of examples, an overview is given of physical chemosensors, arranged to the energy domain of which the device makes use. Not only scientific devices, but also successfully commercialised physical chemosensors will pass in revue.

Keywords: physical chemosensors, biosensors, microfluidics.

INTRODUCTION

Several definitions of chemical sensors and biosensors can be found in literature. The definition given by Schultz and Taylor [1] reads: *"measurement devices which utilize chemical or biological reactions to detect and quantify a specific analyte or event"*. Goepel and Schierbaum [2] say *"chemical sensors are (miniaturized) devices which convert a chemical state into an electrical signal"*. In a study of the National Materials Advisory Board [3] chemical sensors are defined as "*devices or instruments that determine the detectable presence, concentration, or quantity of a given analyte*". Others add the term "*real-time measurement*".

Although the tone of the definitions is similar, some distinct differences can be observed. The first one mentions the use of a chemical reaction, while the second definition speaks about "a chemical state". The third definition includes "instruments", while the other two refer to "devices". In any case, a (bio)chemical sensor contains different parts. The scheme of such a sensor is given in Fig. 1. Molecules in a fluid (target analyte) adhere on a recognition site (the chemical or biochemical interface), which is located on a transducer. The interface consists of a selective, chemically sensitive layer. The adherence causes a change that is converted into an electrical signal by the transducer. Interface electronics modify the transducer output to a proper electrical signal.

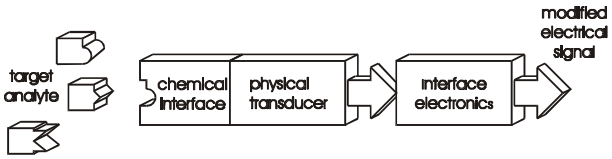

Fig. 1: *Schematic representation of a chemical sensor including a chemical interface.*

Thin-Film Chemical Interfaces

A vast amount of transducers for chemical sensing have been developed and are commercially available (e.g. transducers using surface plasmon resonance, surface acoustic waves, sheet resistance, capacitance, calorimetry, the ISFET, and other). However, they are offered mostly without the chemical interface. If an interface is offered along with the transducer device, it is meant only for research purposes. Even after more then two decades of intensive research efforts, the development of the chemical interface appears to be the bottleneck in the development of direct (bio)chemical sensors and sensor systems. Despite the prove we find in flora and fauna, where millions of (bio)chemical systems can operate in a reliable and controlled way, the transformation of such (bio)chemical systems into artificial senses appears virtually impossible, up till date. Professional books on chemical and biochemical sensors and systems published in the last 15 years confirm this [4,5,6,7,8,9,10]. The chemical interfaces lack stability, durability, selectivity or sensitivity and are hard to manufacture in a reproducible manner. In addition, they are very sensitive to contamination.

Another disadvantage of direct chemical sensing is the fact that for every application, a new chemical interface needs to be developed; it is seldom a generic technique. This makes a breakthrough to commercial products difficult to accomplish because of economical reasons; the production volumes are too low to allow for high research investments.

Total Analysis Systems

In the early 90's, a Swiss group initiated a new concept in the field of (bio)chemical analysis: the concept of *micro total analysis systems* or µTAS [11,12]. They stated that the requirements posed on direct chemical sensors are so high, "that realization in the near future is hardly possible" and suggested the use of knowledge

from the field of analytical chemistry in combination with miniaturization using microtechnology in order to gain analysis speed and decrease the amount of sample needed for the analysis. Fluid sampling, pumping, mixing, heating, selection, separation, reacting, detection, and data handling should all be done on one single chip, the so-called lab-on-a-chip. Since 1994, µTAS has its own Symposium and it is acknowledged as a field on its own [13].
Meanwhile, it has become clear that when the term *total analysis system* is taken too literally, the development of a commercial product is also a long way. Integration of so many functions into one chip is again hardly possible. Minor parts that affect the performance of major parts produced in the same chip, determine the overall quality of the system. Separate µTAS components have been developed into products by several companies*. It are mainly micro devices for fluid handling in microchannels. Sometimes, an optical detector is included.
The integration of thin film chemical interfaces for direct chemical sensing elements within the total analysis system is a high risk for the functioning of the whole system, even higher than in the case of the earlier discussed direct chemical sensors.
Another approach towards fast chemical or biochemical sensing is the use of *physical chemosensors*. This will be explicated in the next section.

PHYSICAL CHEMOSENSING

Physical chemosensors can be defined as devices that determine chemical properties of a fluid by measuring physical properties of, or phenomena in that fluid. They do not need a chemical interface where adsorption or desorption of molecules takes place. The schematic representation of a physical chemosensor is shown in Fig. 2. This concept attracts increasing attention because it guarantees less complexity and allows a dramatic faster development of commercial devices, contrary to direct chemical sensors [14,15,16].
It is interesting to see that following the definition of Schultz and Taylor these physical chemosensors would not be called chemical sensors. However, the definitions of Goepel and Schierbaum, and of the NMA Board, comprise what we call physical chemosensors.
Some physical chemosensors are selective, other are not. In the latter case, use is made of (physical) separation techniques to attain the required selectivity. These separators have been evolved greatly because of the developments in the field of µTAS. Examples of separation methods are electrophoresis, chromatography (affinity, or ion-exchange), mass spectrometry, centrifuge, or microfilters.
Many sensors that meet the definition of physical chemosensor or biosensor are being used and have been used for years, which proves their commercial feasibility. Examples will be discussed in a later section.

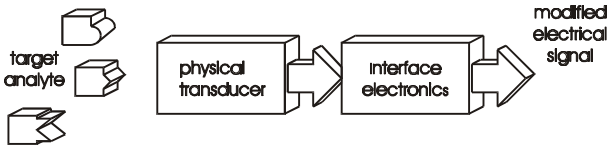

Fig. 2: *Schematic of a physical chemosensor, lacking a chemical interface.*

TECHNOLOGY

Silicon technologies available for sensor fabrication have become mature. Whether or not to use a silicon micro (or nano)system, and whether or not to combine electronic circuitry and sensor devices either in a single chip or in a single package is an interesting topic of discussion [17]. Fact is, that miniaturization of chemosensors and biosensors yields not only the known benefits of microsystems in general, but also some field-specific ones such as high-speed handling, simultaneous testing, and (quasi) real-time monitoring.
Wafer-to-wafer bonding technologies have become highly significant because of the need for microchannels in which the analytes and carriers can be transported and manipulated. The channels etched in one wafer are capped by a second wafer using anodic bonding or direct bonding. The anodic bonding is a less complex process yielding higher bond strengths and a higher reliability. Especially a newly developed glass-glass anodic bonding process [18,19] is expected to find its way in many fluidic devices because of its simplicity, low bonding temperature (as low as 120 deg. C), high bond strength (20 MPa), and the possibility to integrate metal microelectrodes.
Other interesting new developments for fluidic devices are the use of plastics and compact disc based structures [13]. Information on other parts of microsystems, such as pumps, channels, valves, reaction chambers, mixers, splitters, and electrophoresis channels can also be found in other proceedings [20].

ENERGY DOMAINS

Physical chemosensors mainly make use of four different energy domains: optical, thermal, mechanical, and electrical. Also the use of the magnetic domain is possible, but not many applications are found in this domain, up till date. There are some publications concerning the use of magnetic beads in microchannels as a means for flow rate control or even valves [e.g. 21].
A (non-exhaustive) list of physical properties and effects useful for physical chemosensing in the different domains is given in Table 1.

* *e.g. Aclara (www.aclara.com), Affymetrix (www.affymetrix.com), Agilent (www.agilent.com), Caliper (www.calipertech.com), Cepheid (www.cepheid.com), Kymata (www.microproducts.nl), Micralyne (www.micralyne.com), Nanogen (www.nanogen.com), Xensor Integration (www.xensor.nl)*

Optical principles are often used thanks to the field of analytical chemistry, where optical devices have been applied successfully for years. The majority of optical sensors in (bio)chemical analysis can be found in absorption and fluorescence measurement, for example in chromatography or capillary electrophoresis separation setups. Many optical sensors have been realized in silicon technology, the photo diode being the best known and oldest. Other examples are the spectrometer [22], colour sensor [23], and UV detector [24]. Spectral selectivity can also be obtained by adding optical filters to a detector. A limiting factor for the integration of optical sensing systems is often not the sensor, but the light source, lenses and filters. Wave guiding structures and evanescent wave excitation of chemicals are subjects of research in several groups [e.g. 25]. Examples that will be described in a later section are commercial pulse oximetry medical devices, a cell shape sensor using a diode array and optical thin film filters in high speed screening (HSS) devices.

Thermal effects existing for physical chemosensing are the thermo-mechanical principle (e.g. the thermal expansion coefficient of liquid mixtures), and heat capacity (amount of energy required to increase the temperature of a gas mixture at a fixed volume or a fixed pressure). But the best-known and most widely used device is the thermal conductivity detector (TCD). In a portable gas chromatograph heavy and large stainless steel parts are replaced by lightweight and small components. The thermal conductivity sensor consists of a heated microbeam provided with a temperature sensor (e.g. thermistors or thermopiles). If the concentrated gas peaks that leave the separation column have a thermal conductance that differs from the carrier gas, the thermal resistivity between the microbeam and the ambient changes, resulting in a temperature change of the microbeam [26]. The first example of an integrated system making use of such a device was the all-silicon gas chromatograph [27]. Many portable gas chromatographs contain such a TCD nowadays. Another application of the TCD is the measurement of CO_2 concentration in air, possible because the thermal conductivity of CO_2 deviates significantly from air.

By monitoring some of the **mechanical** parameters of a liquid mixture, such as the density, viscosity, and sound velocity, information about the composition is obtained. Surface acoustic wave devices have shown to be very useful for measuring these parameters in liquids. By applying different wave types having different wave-polarizations, sensitivity to various liquid properties can be "designed". Love wave devices have been used for viscosity sensing [28] and Lamb wave devices for viscosity, density and sound velocity, giving information about the composition of the liquid [29]. The presence of water in alcohol can be determined with a resolution of 10^{-4} volume percent [30].
The measurement of physical absorption of gases at a SAW resonator surface without the use of chemical films is the basis of a new commercial instrument that will be described in the next section.
Another acoustic application is imaging of intravascular plaques. Atherosclerotic plaques that rupture are a main cause for unstable angina pectoris and acute myocardial infarction. Early diagnosis can be achieved by

Table 1: *Examples of physical chemosensors in different energy domains*

Energy domain	***Physical property/effect***	***Device***	***Application***
Optical	Fluorescence	Photodiode, colour sensor	Biochemical analysis
	Light absorption	Photodiode	Oximetry, biochemical analysis
	Optical projection	Photodiode array	Cell selection, particle detection
	Spectrometry	Fabry-Perot or IR spectrometer	Biochemical analysis, gas analysis
Thermal	Thermal conductivity	Thermal conductivity detector	Gas-type sensor, gas chromatograph
	Thermo-mechanical	Pressure/displacement sensor	Gas composition
	Heat capacity	Temperature/pressure sensor	Gas composition
Mechanical	Viscosity	Love wave device	Food industry
	Density	Specific weight sensor	Food industry
	Sound velocity	Ultrasonic transducer	Food industry, body fluids
	Sound reflection	Ultrasonic transducer	Vein inspection
	Condensation	SAW resonator	Gas analysis, humidity
	Mass	Mass spectrometer	Molecular analysis
Electrical	Conductivity	Conductivity sensor	Biochemical analysis in CE
	Capacitance	Capacitor	Fluid condition, humidity
	Potential	Voltage probe	DNA analysis
	Electron capture	Electron capture detector	Gas analysis

intravascular acoustic imaging. An acoustic transducer (30 MHz) is placed at the tip of a catheter and, via the groin, brought to the heart to make an acoustic image of the plaques at the vascular wall [31].
The development of micro mass spectrometers seems very promising. It is a generic technique that will be applicable for a wide range of purposes. The drawback is the complexity of the system because it contains so many different parts [32].

Electrical methods include the measurement of conductivity, capacitance, and potential. Renewed interest in conductivity detection in micro capillary electrophoresis devices has lead to different detector configurations [33,34]. An example of a contactless 4-electrode conductivity detector for CE devices is given in the next section. In the field of molecular biophysics, information of DNA is obtained by applying nanoelectrodes measuring potential changes when a DNA molecule passes by in a nanochannel.
Capacitance measurements are applied to detect changes in dielectric properties, for example in food production.

EXAMPLES AND APPLICATIONS

Pulse oximeter

Probably the most successful physical chemosensors in the medical field is the pulse-oximeter. The absorption spectra of hemoglobin (Hb) and oxyhemoglobin (HbO_2) differ (Fig. 3), which makes it possible to measure the ratio of both concentrations in blood by measuring the absorption of light of two different wavelengths, e.g. 660 nm and 805 nm. Such a setup can be made of two separate systems, but also a colour sensor consisting of a single silicon chip can be used [23,35]. In pulse oximetry, the hart beat is monitored simultaneously. Several companies offer pulse oximeters that are clamped on a finger or the ear lobe and they are applied widely in hospital for the monitoring of patients [⌘].

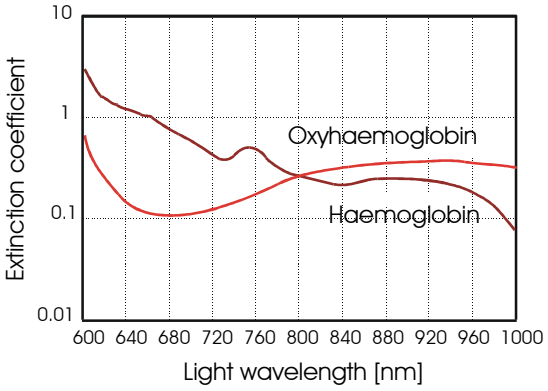

Fig. 3: *Absorption spectra of hemoglobin (Hb) and oxyhemoglobin (HbO_2).*

Particle-shape detector

An example of an optical measurement method where the use of optical equipment such as lenses or filters is omitted is the particle-shape detector based on optical projection on a diode array. The device consists of an optically transparent flow channel, with a light-source positioned above it. On the bottom of the flow channel a one-dimensional array of photodiodes is placed perpendicular to the direction of the flow. When a particle passes the array of photodiodes it will partially block the light. A cross-section of the shadow is registered by the array of photodiodes (Fig. 4) [36]. The channel diameter is typically 100 µm, the pixel pitch is about 2.5 µm. It is possible to recognize the shape of particles as small as 5 µm in diameter. An application is the detection of sickle cell development.

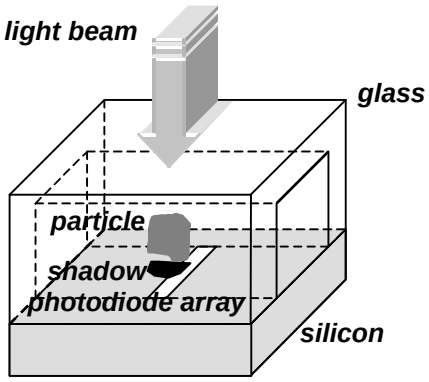

Fig. 4: *Schematic of the particle shape sensor.*

Contactless conductivity detection in CE

In capillary electrophoresis systems a sample is brought in a channel and by applying a high electric voltage over the liquid in the channel an electroendoosmotic flow is initiated. At the same time, separation of ions takes place. As a result, each ion has its typical retention time, depending on its mobility. For detection, often laser-induced fluorescence (LIF) is used. Measurement of the liquid electrical conductivity seems obvious because the separation method applied is based on electrical behaviour of the sample components. For a long time, conductivity detection appeared problematic and inaccurate compared to fluorescent detection.
Renewed interest in conductivity detection (labelling can be omitted and the conductivity detector can be made much smaller than the current optical measurement systems) has led to the design of a new integrated contactless 4-electrode detector with interesting features [37]. The detector has a linear response for a large frequency range and a detection limit of about 20 µM. In Fig. 5, a photo of a glass implemented CE device containing an integrated conductivity detector is shown. An application is the quasi real-time analysis of drain water in green houses.

[⌘] *e.g. www.oximetersonline.com, www.novametrix.com, www.nonin.com*

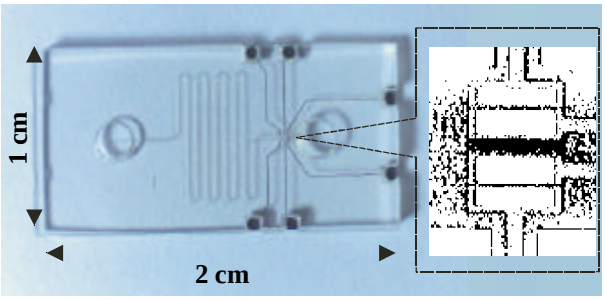

Fig. 5: *Contactless conductivity detector (insert) in a glass CE device.*

Electronic nose

The topic of the electronic nose and tongue has attracted a lot of attention. The mimicking of the human senses still appeals to the imagination. Several systems using an array of chemical interfaces have shown to be able to distinct between wines or French cheese. The reproducibility of these systems has not been proven yet, they need regular recalibration. Another system using a surface acoustic wave resonator was presented recently [16]. A sample is fed to a fast gas chromatograph (GC). As the separated gases leave the GC column, they adsorb (and desorb) at the SAW resonator surface, which results in a resonator frequency shift. Because the device lacks chemical interfaces, it is very fast. The whole process, including separation, takes less than 10 seconds. Fig. 6 shows how at the end of the GC column the gas hits the SAW resonator.

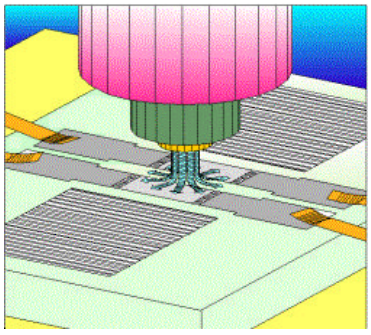

Fig 6: *A 500 MHz SAW resonator located at the outlet of a GC column (Courtesy Est, CA, USA).*

High-speed screening arrays

A fascinating development is the application of combinatorial chemistry using small reactor arrays made in a chip called high-speed screening (HSS) arrays. They allow for a large number of tests in a very short time. The sample volumes can be as much as 10^6 times smaller compared to the widely used 8x12 titer plates and the chip permits functional integration in every reactor. In addition to drug screening and DNA research, those HSS devices can be applied for enzymatic analysis and clinical chemistry. A silicon device containing a 5x5 array is shown in Fig. 7. The typical size of a silicon-implemented well is 200x200x25 μm^3, representing a volume of only 1 nl.

For read-out of the optical activity in the wells (fluorescence), a CCD camera is usually placed above the array chip [38]. Investigations have started to use integrated optical sensors in each well, instead of a camera. A photodiode provided with a thin film optical filter of crystalline silicon, shows a very high visible-over-UV selectivity [39], allowing analysis of enzymatic activity by means of NADH detection.

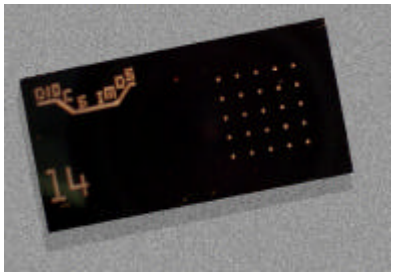

Fig. 7: *Silicon high-speed screening device 1x2 cm^2 .*

CONCLUSIONS

The development of physical chemosensors is less complex than the development of direct chemical sensors because the manufacturing of a chemical interface can be omitted and because a chemical reaction at the transducer is not required. The question is, if solutions for the typical problems of (bio)chemical interfaces will ever be found. An enormous effort has to be put in solving just one application. The search for more generic systems, like physical chemosensors in combination with physical separation mechanisms might seem more complex at first hand, but is in fact more promising from a commercial point of view. Nonetheless, not for all applications physical chemosensing will be possible.

The further development of physical chemosensors and the finding of new sensors and sensor systems based on this concept, and their appliance in new fields is an exciting challenge for the years to come. Highly interesting topics are cell research (e.g. migration behaviour of mRNA inside cells), creation of artificial viruses, or nano electrophoresis techniques for single molecule detection.

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