Chemical sensors as integrated analytical systems

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Articulo invitado

The term 'integrated analytical systems' illustrates the convergence of different strategies to connect the steps of the analytical process including simplification, automation, communication and miniaturisation. Although these strategies or trends are found in other scientific and technological fields, it is with chemical sensors and sensing systems that they take on defined role producing analytical instruments with additional advantages in terms of information, speed, robustness, portability and cost (see Table I).

Keywords: Integrated analytical system; chemical sensor; electronic nose; biochip; lab-on-a-chip.

El término 'sistemas analíticos integrados' ilustra la convergencia de diferentes estrategias para conectar las etapas de los procesos analíticos incluyendo simplificación, automatización, comunicación y miniaturización. Aunque estas estrategias o tendencias se encuentran en otros campos científicos y tecnológicos, es con los sensores químicos y sistemas sensores que ellas toman un papel muy definido, produciendo instrumentos analíticos con ventajas adicionales en términos de información, velocidad, robustez, portabilidad y costo (ver Tabla I).

Descriptores: Sistema analítico integrado; sensor químico; microsistema analítico; nariz electrónica; biochip; laboratorio en un chip.

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1. Integrated analytical systems

Integration is defined as the action or the effect of joining parts to form a whole resulting in new characteristics and functions from the constituent parts. Integration is a far reaching concept in technology, but is less used in science.

Within the confines of instrumentation, a 'system' may be defined [1] as a group of devices which forms a whole. The objective of a system is to form a network for a common purpose or for a common distribution method. *Analytical instruments* are systems or equipments which produce chemical information. The information sought in these systems is obtained from a well established sequence (analytical process). The main steps in this sequence involve sampling, sample transport and processing, separation, reaction, transduction, and signal acquisition and processing. Most analytical systems designed follow this sequence, either fully or partially. These steps can be carried out either in a 'discrete' mode –through a series of machines, devices or instruments, requiring human operation to maintain communication– or in an 'integrated' mode –use of different strategies without breaking the continuity between steps and with no human intervention once the process has begun.

Different attributes are associated with an 'integrated analytical system' (IAS): the number of units that make up the whole, how these units integrate (relationship, interconnexion, confination), the new functions carried out, and the objective or goal of the system. Thanks to integration, new analytical procedures, devices and instruments can be implemented, thus providing new perspectives, for instance, in simplification, miniaturization, automation, information, velocity, mobility, and cost of chemical analysis.

Another attribute of IAS's is their adaptability to change as a result of the environment, as in the case of optical or electrochemical measurements, which feature automatic temperature compensation. Furthermore 'smart' IAS's possess improved abilities to process analytical information –the ability to assess performance, to implement automatic calibration, compensation of baseline drift, or the ability to communicate with other systems, instruments, devices or machines.

To some people, the concept of integration refers only to (miniaturized) analytical devices fabricated by micromachining technologies, creating an analogy with the integrated circuits from the modern microelectronics industry. However, within analytical chemistry, integration can be conceived as a relationship between the different steps of an analytical process [2,3]

2. Chemical sensors

A chemical sensor is a simple IAS that integrates the reaction step and the measurement step, without a break in continuity. In effect, a chemical sensor is composed of two integrated parts: a receptor –highly selective recognition material– and a transducer –a material that 'translates' the recognition signal, be it optical, electrochemical, mass or thermal, into a signal that is usually electrical in nature.

This simple design of a chemical sensor –recognition + transduction– has led to the development of new analytical instrumentation. The design of these instruments is very practical and innovative with respect to the implementation of the analytical procedure in terms of simplification, miniaturisation, robustness, speed, mobility and cost.

Two aspects are fundamental in the development of chemical sensors. One of these is the availability of recognition materials, which permits must be as selective as possible. It is this selectivity which allows direct measurements (neglecting separation steps) or continuous measurements (in the case of making use of a reversible sensing mechanism). Highly selective recognition materials used are either synthetic –acyclic or macrocyclic ligands, cyclodextrines, molecularly imprinted polymers, etc.– or natural compounds –enzymes, microorganisms, animal or plant tissues, antibodies, DNA, etc. Chemical sensors that contain synthetic recognition materials are known as *chemosensors*, and those that contain biomaterials are known as *biosensors* [4,5].

TABLE I. Different attributes of integrated analytical systems

System	**Main integrated materials, components, devices or operations**	**Interconnection or relationship between integrated parts**	**Examples**
Supported reagents	Reagents and supports	Without break of continuity	Spot test papers and analytical strips Dip-and-read sticks Reactors Chromatographic packagings and columns Supported membranes
Chemical sensors	Receptors and transducers	Without break of continuity	Chemosensors and biosensors Electrochemical sensors Optochemical sensors
Flow analytical systems	Machines, devices and analytical operations	Flow conduits	Gas or liquid chromatographs Continuous flow analyzers Automated analyzers Multiparametric analyzers Total analysis systems (TAS)
Laboratory systems	Analytical modules, workstations and instruments	Communication interfaces	Laboratory information management systems Paperless laboratory Roboted analytical workstations
Distributed analytical systems	Distributed analytical instruments	Communication interfaces	Networked analytical instruments or laboratories Cybernetic systems
Array analytical systems	Selective sensor array Cross-selective sensor array	Sensor signal processing Munticomponent sensor signal processing	Multiparametric sensor system Sensor array Genosensor array Electronic noses Electronic tongues Taste sensors
Chemical microsensors	Receptors and transducers confined in a micrometric space	Without break of continuity	Ion-sensitive field effect transistors (ISFET) Amperometric mirosensors Integrated optical sensors Mass-sensitive acoustic-wave devices (BAW and SAW)
Analytical microsystems	Analytical operations and devices confined in a micrometric space	Monolithic flow microconduits	Sample-to-answer devices Micro total analysis system (uTAS) Laboratory-on-a-chip (LOC) MEMS Biochips
Nanosystem	Atomic and molecular devices confined in a nanometric space	Atomic and molecular forces or bonds	Nanoprobes Nanosensors

The another important aspect associated with sensor technology is the way in which the receptor and transducer materials are integrated, *i.e* the immobilisation of the receptor on the transducer. By immobilizing a species on the surface of a transducer, it is essential that they remain stable –the information content in the sample should be transfered from the receptor to the transducer with a minimum of distortion and over as long a period of time as possible [6,7].

3. Sensor array systems

In most incidences sensors are implemented in the detection of a single analyte. From a technological point of view, it is possible to integrate several sensing devices within the same platform, using similar or dissimilar (hybrid) technologies. These possibilities range from a group of ion-selective electrodes to an array of microfabricated sensors. These IAS's have opened a new class of instrumentation of great interest and potential in analytical chemistry, mainly due to the additional dimensionality of the data furnished by these array sensor systems

3.1. Redundant-sensor array systems.

There are systems formed by individually addressable, identical, chemical sensors. Using this type of system, the *chemical imaging* of 2D spatial distribution of an analyte is done by processing the individual electrode signals [8]. Each element of the array can also be fabricated as a needle with several sensing areas at regular intervals. With this configuration, 3D chemical information is possible. Arrays of redundant-multisensor micro-needles for pH, oxygen, potassium, etc. are required for monitoring local concentrations on organ surface tissues during organ transplant.

3.2. Selective-sensor array systems.

These systems are a group of sensors with different selectivity, *i.e.* a group of non-redundant sensors. In this case, each sensor responds to a single component in the multicomponent mixture.

There is considerable interest in the development of multianalyte sensor systems capable of the simultaneous detection of a range of chemical and biological substances. Included in this class of IAS's are multiparametric or multichannel analyzers, which, in comparison with the classical monoparametric analytical instrumentation, have additional advantages related to the economy of reagents, energy, room, weight, etc.

Within this section can also be included the known DNA microarrays or biochip produced by advanced microarraying technologies (see below).

3.3. Cross-selective sensor array systems.

These systems integrate a group of sensors with a cross-selective response pattern. They represent a new approach in measurement technology, creating opportunities to measure complex phenomena such as quality or process state, rather than measuring a number of single parameters separately.

There is a growing interest in using multivariate signal processing of sensor signals from complex media in order to extract information. Gas-sensor arrays have proven to be a practical way to measure concentrations in multicomponent gas samples. Gas sensors involving array systems can be based on almost any detection principles; however, metal oxide or conductive polymer based chemoresistors are the most common. In this respect, intelligent sensor array systems capable of integrating sensors with different cross-selectivity patterns, signal-collecting unit, and pattern-recognition computer engine, have been implemented. The output pattern of such a system represents a synthesis of all the components of a measured complex sample. Within this context it is possible to retrieve, with certain accuracy, the desired qualitative or quantitative multicomponent information. In fact, a complex sample –vapour, odour, headspace of complex liquids, etc.– presented to the sensor array produces a characteristic signature or pattern. By presenting many different samples, a database of signatures is built up. This database is used to train the pattern recognition system, in order to configure it to produce unique classification or quantification of the components and providing capabilities for the automation of qualitative or quantitative analysis.

These intelligent chemical array sensor systems are in a way similar to the human olfactory sense, and are known as 'electronic noses' [5,9]. In the human olfactory sense, a signal pattern is generated from the receptor cells in the olfactory bulb. A first treatment of data is carried out by the mitral cells, and the pattern is further processed by the olfactory cortex for recognition and learning. Although the selectivity of each receptor cell may be low, the combination of several selectivity patterns provides a very large information content. Similarly, the signal pattern from a sensor array is collected and handled by a computer, where a first pretreatment of data is carried out. This data is further processed by a pattern recognition routine.

Similar concepts, but for the analysis of liquids (wine, milk, water) have recently been described. These systems are related in similar ways to the sense of taste; thus, for these systems the terms 'electronic tongue' or 'taste sensor' have been coined [10,11].

This type of artificial sensorial array system is known also as a *biomimetic system* because it is based on an approach inspired by nature. The chemometric treatment of the data produced by these systems can alse be considered biomimetic, as artificial neural networks (ANN) can be applied. In addition if the array uses sensing materials such as molecularly imprinted polymers, which recognition mechanism resembles antibody-antigen interactions, the system is also considered a biomimetic one [12].

4. Analytical microsystems

Due to the lack of selectivity associated with sensors, it is not always possible to use them for analysis in a complex medium. It is this lack of selectivity that requires them to be incorporated into more complex systems. A more complex system would involve sample handling, separation, reaction, and detection stages integrated into a single instrument, with most stages automated and computer controlled. IAS's that group machines, devices and instruments to carry out an analytical process –partially or totally– are known as 'analytical systems' and when they perform the process totally are known as 'total analysis systems' (TAS). Examples of TAS are systems based on continuous flow analysis, electrophoresis, chromatography, or mass spectrometry [3].

Continuous advances in the microelectronics industry have resulted in its expansion into different fields such as chemistry and life sciences, the long term objective being to miniaturize common laboratory machines, devices and instruments to a credit card size. Examples are microsensors or 'microelectromechanical systems' (MEMS), *i.e.* integrated devices that combine both electrical and mechanical components, within a micrometer dimension and fabricated in glass, quartz or plastic [13].

The integration of fluidic microstructures with other types of analytical microstructures –*e.g.*, microreactors, microsensors and microactuators– has as its final goal the development of 'micro total analysis systems' (μTAS) [14,15], capable of performing the function of larger analytical instruments in smaller devices. Sampling, pre-treatment steps –enrichment, separation, and reaction– and detection can all be undertaken on these integrated devices. In the future, these analytical microsystems will be used as stand-alone units directly at the point of sampling –*in situ* or point-of-care testing–, to perform (automated) analysis without the need for a conventional laboratory. Due to their ease of use and operational simplicity, such systems should be capable of running for longer periods without servicing, or to be used by non-skilled personnel. The complete integration of these devices has not yet been achieved entirely in most cases, with one or several of the steps still being performed off-chip.

The term 'lab-on-a-chip' is being used for these types of systems, but in a broader sense than μTAS. Lab-on-a-chip includes any type of laboratory operation being analytical or not as those operations related to liquid handling, synthetic and combinatorial chemistry, reactor technology and biotechnology, drug screening, PCR amplification, etc .

The main advantage of these microlaboratories is their improved analytical performance, as the multifunctional design increases both speed and higher throughputs. In addition, these analytical microsystems have an increased mechanical stability due to their (monolithic) integration, lower resource consumption (sample, reagents, and mobile phase) and waste production, and suitability for inexpensive mass fabrication.

4.1. Array microsystems.

Instead of thinking about individual (bio)chemical reactions, as in common analytical systems, researchers are adopting a new paradigm in which many reactions are monitorized or several analytes determined simultaneously, thus making the study of complex processes or the analysis of complex samples possible. This is done through massively parallel processing, which allows for a high output of data per unit of time. Parallel processing is easily achievable using microsystems.

Array microsystems permit simultaneous detection, and can be considered the simplest type of parallel processing. Array microsystems allow a large number of reactions to occur within a very small area, without the need for huge amounts of material or robotics.

Advanced imaging technology has been exploited to interrogate a single substrate on which multiple sensing sites are deposited. For example, at the distal end of an imaging fiber bundle ($\varnothing < 1$ mm), which collects several thousand individual fibers, a small sensing regions have been created by site-selective photopolymerization of a monomer doped with fluorescent dyes through the distinct optical pathways. The Simultaneous monitoring of different chemical parameters (pH, CO_2 and O_2) using the CCD video acquisition of fluorescent temporal responses observed at one end of the bundle has been demonstrated with this technique [16].

Microarray technology represents the most recent, and exciting, advances in DNA analysis. The information obtained from the human genome project opens the door to tremendous analytical opportunities, especially for large scale DNA testing by faster, simpler and cheaper means than traditional hybridization assays. Hybridization-based DNA chips utilize the binding of labeled-target single strand DNA onto DNA probes that have been immobilized on surfaces[17].

DNA arrays, gene chips or biochips are often intermixed to describe this new type of device. The use of DNA microarrays is revolutionizing many aspects of genetic analysis, including the diagnosis of genetic diseases, the detection of infectious agents, drug screening, gene expression, forensic analysis, genotoxicity, food analysis, etc.

5. Conclusions

The term 'integrated analytical systems' illustrates the convergence of different strategies to connect the steps of the analytical process including simplification, automation, communication and miniaturization. Although these strategies or trends are found in other scientific and technological fields, it is with chemical sensors and sensing systems that they take on a definite role in producing analytical instruments with additional advantages in terms of information, speed, robustness, portability and cost.

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