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Sensors as green tools in analytical chemistry

Manel del Valle

This article comments on green aspects of (bio)chemical sensors for qualitative and quantitative analysis applications. First, the aspects that connect chemical sensors and biosensors with the main trends of green analytical chemistry are discussed. To continue, a set of paradigmatic examples of sustainable assays pertaining to the (bio)sensing field have been selected and explored in some of their variants. These are the use of a smartphone camera together with a microfluidic paper platform to perform colorimetric or fluorometric assays, the use of the portable glucose meter as transducer for a variety of (bio)assays different of glucose, or the coupling of sensor arrays with advanced chemometric processing for smart sensing (electronic noses and electronic tongues).

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Introduction

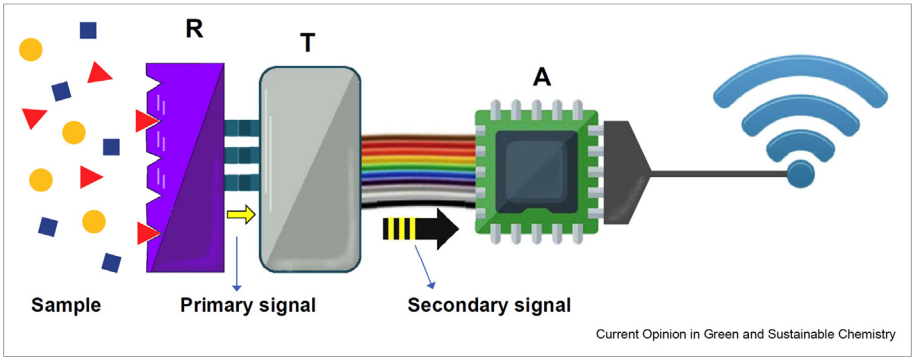
This article will reflect on chemical analysis carried out with chemical sensors or with biosensors, with respect to sustainability or ecological aspects, what has been referred as green chemistry. If analytical chemistry is in charge of searching for chemical information, the greening in the obtaining of this information comprises reducing requirements for sample and reagents, performing analysis in less time, with less effort, with less trained people, even condensing the own information complexity to the required level, and achieving this in a minimally equipped laboratory; or even more, involving doing the analysis on-site, outside the laboratory [1].

Kaljurand and Koel [2] established the pyramid of requirements of instrumental methods according to applications needed and current research trends. Ordering them with the criteria of green chemistry, there originates a landscape of different techniques with varying complexities, ranging from stand-alone miniature sensors to incredibly complex facilities, just think on requirements to perform a neutron activation analysis or a synchrotron radiation spectrum. In this list, (bio) sensors are commonplace utilities that perhaps do not provide maximum specificity and accuracy, but they generate little or no waste and consume minimal amounts of reagents, solvent, or energy. Sensors may be used for many of the analysis demanded, where a quick estimation, or just a yes/no check may suffice. And this type of devices may provide relevant benefits especially considering the time savings in the decision taking or diagnosis stage, when used for on-site process analysis or for the point-of-care (POC).

When we think on a chemical sensor, the IUPAC definition must be recalled: a chemical sensor is a device that transforms chemical information, ranging from concentration of a specific sample component to total composition analysis, into an analytically useful signal [3]. Nonetheless, this definition, being too generic, deserves a more clear, pragmatic description: *chemical sensors are small-sized devices comprising a recognition element, a transduction element, and a signal processor capable of continuously and reversibly reporting a chemical concentration* [4]. This definition brings in the generic scheme of a sensor, as seen in Figure 1, where it must be also considered that it may become a biosensor whether the recognition element (R) involves a biochemical/biological component. Examples of the latter may be enzymes, antibodies, protein receptors, DNA or RNA fragments, even live microorganisms, cells or tissues.

This definition suggests a close interaction between the recognition element and the analyte, introduces the ideas of reduced dimensions and the possibility of real-time measurement. (Bio)sensors are thus based on the combination of a recognition layer and a physical transducer, and their use is perfectly suited for in situ remote monitoring, for example, of pollutants. The sensor concept involves intrinsically a cheap, small, and easy-to-use device, so highlighting the importance of portability; all these features are accompanied by minimal use of sample, reagents, and solvents, implying also minimal waste production. To accomplish all this, operation of the (bio)sensor must be of high efficiency, a fact achieved by its enhanced selectivity. This efficiency is further stressed if aspects such as speed of operation, disposable use, in situ operation, and instant provision of

Figure 1



Sketch of the operation of a chemical sensor. Only one sample component, the analyte, is recognized by the recognition element (R). The primary signal generated in the recognition process is converted into an electrical signal by the transducer (T). This signal is next amplified, conditioned, processed and presented as measured data (A). When the recognition element is of biological nature, the device is termed biosensor.

results are pondered. And in these days, being in the time of networks, sensor devices may be deployed in a region, and through communication links, provide instant or spatial mapping of analytes.

With illustrative aim, this article has intention to highlight on sensor concepts inspired by the principles of green analytical chemistry [5]. Three paradigmatic examples are presented and discussed. These are the use of a smartphone camera as measuring device, the biosensing schemes alternative to the glucose estimation that can be developed with use of the ubiquitous personal glucose monitor, and the use of arrays of sensors plus computer data treatment, in smart applications aimed to qualitative applications or resolution of multiple analytes.

Analysis with the smartphone camera

A clear fact that has become evident in the sensor field is the production of application-specific, portable and compact analytical instruments, the POC analyzer, which has made possible testing of certain analytes at any moment, and by anyone. With these devices, the diagnostic and quick assessment of status of an illness has been decoupled from a central laboratory and has made possible a closer and friendly relation with the health practitioner. In a trend to make these POC analyzers less analyte dependent, and with a more generic applicability, they started to exploit and extend existing technologies (i.e. mobile phones, specially their integrated camera) to the field of analysis [6]. This trend simplifies the requirements of analytical instrumentation for a planned assay, what justifies its connection to the sustainability and green analytical chemistry issues [7].

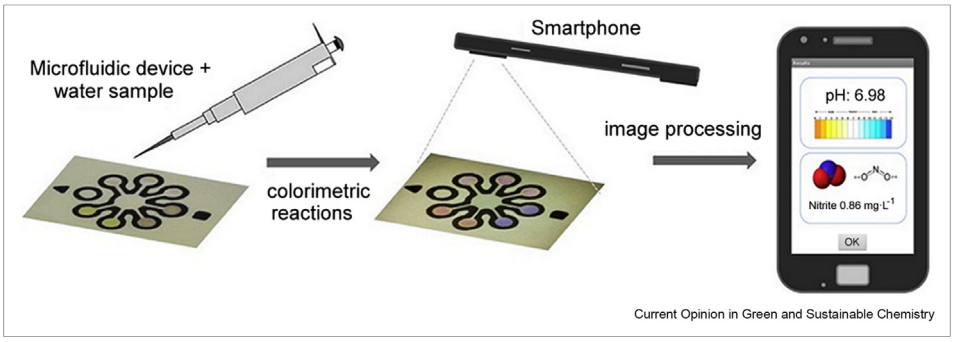
Many diagnostic chemistries are based on formation of color or luminescence and need to be performed in certain support to visualize the optical changes and give way to the image acquisition. When thinking on how to do this, together with which would be the proper way to dose any necessary reagent, very soon the paper platform came into play, and possibilities developed within the spot test approach were retaken. Among these, the possibility of performing microfluidic operation using channels defined in sorbent paper, with storage of reagents in certain receptacles later used when the liquid sample is placed in contact with the strip become a way to perform many different tests, from single step reaction, to multiple step, in sequence procedures [8].

A model example to describe in detail this smartphone-paper support colorimetric sensing device is the one for the simultaneous analysis of nitrite and pH [9]. The system combines colorimetric reaction, with pH indicator change and a low-cost paper-based microfluidic device. The application was devised with seven sensing areas, which contained the corresponding immobilized reagents; these were solubilized and produced selective color changes after a sample solution was placed in the sampling area. The reported device is schematized on Figure 2.

The chambers contained two pH indicators (phenol red and chlorophenol red) in duplicate spots, three replicate chambers with nitrite reagents (sulphanilamide and *N*-1-naphthylethylenediamine), plus a control chamber for white correction. After reaction, the image captured with the built-in camera was processed, and the observed color and its intensity was related to pH and nitrite concentration, respectively.

This potential of sensing and integrated communication joined together is probably going to benefit this coupling and its chemical applications for long time. The exceptional capabilities that the combination gives to

Figure 2



Paper-based microfluidic device with eight reagent sensing spots, and the measurement using an Android camera smartphone after reaction with the liquid sample. The RGB measure of the color intensity on each spot permitted the estimation of pH and nitrite content in the sample. Reprinted with permission from a study by Lopez-Ruiz et.al. [9]. Copyright 2014, American Chemical Society.

(bio)sensing were already forecasted in the first works in the field by the Whitesides' group. In these [10], they made a strong bet on paper-based microfluidic platforms, with easy-to-use camera phone detection and existing communications infrastructure, able in its conjunction to transfer results from the assay site (placed anywhere), to the trained medical professional, who could send final diagnostic back to the field.

By noting the type of biological receptor used, there are different variants to consider [11]. For example, when enzymes are used, there is the interesting application from Whitesides' laboratory, developed using a paper microfluidic platform and smartphone detection [10], where they detected glucose and protein content in urine. In a related example case, reaction microspots were designed on paper by wax printing technique [12] for estimating bacterial presence. The use of specific substrate culture with color indicator permitted identifying three food borne pathogens, again, by assessing specific color intensity with the use of a scanner device. To finish with the examples connected to enzymes, it should be commented the example using inhibition of acetylcholinesterase, in this case to identify the presence of neurotoxic (or pesticide) compounds [13].

The highly selective biosensing assays achievable with use of antibodies have been also translated into the technology that employs paper microfluidic supports and optical measurement through the smartphone camera. A first example to mention is the one developed to measure the stress hormone cortisol in saliva [14]. This system was used with success in the International Space Station during the VITA mission for the monitoring of astronaut's health condition [15]. Similarly, immunoassay was also the variant to detect food borne pathogens (*Salmonella* spp. and *Escherichia coli*) [16], detecting the fluorescence signal with a smartphone camera and a properly devised dark chamber. Viruses have been also detected with such principles helping to diagnose specific forms of infective outbreaks [17]. For instance, a system to detect avian influenza viruses and to establish their geographical transmission was culminated using a smartphone-based fluorescent diagnostic device [17]. Response to virus subtypes H5N3, H7N1, and H9N2 was found positive, and validation was completed against human specimens containing the H5N1 highly infective virus form. By dissemination of this kind of cheap and available platform, using the functionalities of a smartphone for detection and communication, it would be possible to obtain immediate diagnostic results on-site and at the same time build an international real-time surveillance network for emerging public health threats with geographically distributed diagnostic tools.

The last biomolecule to consider as recognition element is DNA, both as gene probe to detect gene analyte, or as aptamer to detect third substances. Although there are not many works to comment, there are clearly the two variants: a first detecting genes, e.g. the Kaposi's sarcoma herpes virus [18], an infectious cancer that became known during the first years of AIDS epidemic, or the gene BRCA1, a genetic marker of inherited breast cancer [19]; considering the second variant using DNA aptamers, the recent work for detecting residues of Streptomycin antibiotic may be mentioned [20].

Biosensing with the personal glucose monitor

A second episode of biosensing using the simplest instrumentation is the use of the personal glucose monitor, designed in principle to perform analysis of glucose by diabetic patients. In the short time elapsed since the extension of use of the portable glucometer to assays other than glucose, it has been described the analysis of ions, organic molecules (drugs, vitamins or

toxins), proteins (disease or tumor markers) plus disease causing agents, such as viruses or pathogenic bacteria.

Once researchers noticed that the personal glucose meter is a pocket-sized amperimeter/potentiostat, widely useable thanks to its ubiquity and low price, they started reporting sensing schemes, in which a final glucose product was detected, normally generated in a chain of events connected with the recognition of the sought analyte. A recent review describes thoroughly most of the variants gathered in the literature [21]; in this section, we will comment some examples covering different biomolecule recognition variants.

To adapt the personal glucose monitor for a generic case, the assay must be reformulated into a scheme producing glucose as measured species. An easy way to do this is to use invertase as enzyme label, and let it hydrolyze the sucrose disaccharide (table sugar) into glucose and fructose. This idea is illustrated in Figure 3 that depicts a DNA biosensing assay in a sandwich scheme. Beads are used with a DNA probe to recognize a DNA analyte in a sample, that it is also designed to attach a signaling DNA fragment modified with the invertase enzyme. When the non-reacted species are washed away, the addition of sucrose as the developer substrate will produce hydrolysis and appearance of abundant glucose next detected with the personal glucose monitor. In this example, a positive reading of glucose will correspond to the presence of the target DNA gene, being this related to an illness, a pathogenic microorganism or the adulteration of food.

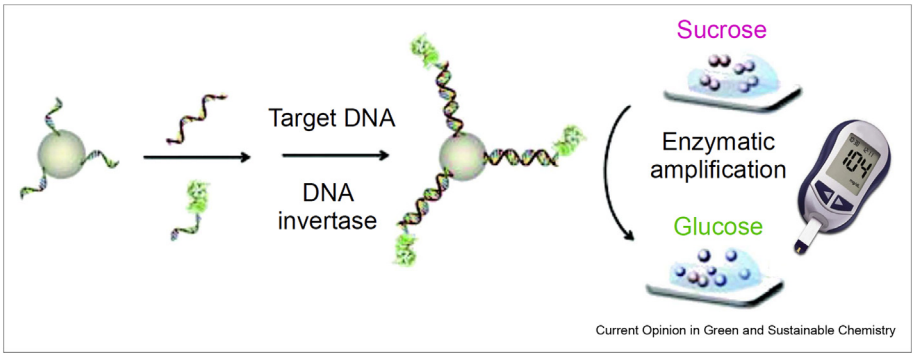
The first proposal of extending the use of personal glucose meters to analytes different from glucose was the pioneering paper of Xiang and Lu in 2011 [22]. In this exemplary work, they adapted different aptamer recognition elements, conjugating them with the enzyme invertase and showing how it was possible to adapt it to determine small organic molecules, a protein, and an inorganic ion, in this case through the use of a DNAzyme biomolecule. The organic molecules detected were cocaine and adenosine, the protein interferon-γ, and as third example the metal ion uranyl. Shortly after this first communication, other works from the same laboratory reported similar assay for a DNA fragment [23], in this case specific for detection of hepatitis B virus (the scheme on Figure 3), or the use invertase-labeled antibodies for detection of the prostate-specific antigen or the food toxin ochratoxin A [24]. Other interesting examples are those detecting micro-RNAs in blood, species related to expression of tumors of different nature [25,26].

In the collection of the different variants, it is worth mentioning the procedure to detect pathogenic viruses, for instance, the *Zaire Ebola* virus [27] or *Salmonella* in milk [28]. In a recent variant of the concept, an immunoassay was devised to detect procalcitonin, a biomarker for sepsis; the assay used glucose-loaded liposomes, which were subsequently lysed and detected [29]. All of this demonstrates the plethora of bio-recognition variants, the different types of tests performed, and the ongoing search for mechanisms to sweeten the detection solution.

Smart sensor array systems

The last example to describe is the use of sensor arrays. This approach was suggested some years ago, using arrays formed by poorly selective (cross-selective) sensors and computer processing. The idea is that each sensor may respond to more than one sample component and the response of each sensor may be the summation of the effects exerted by a series of components. These combinatorial principles may allow then for

Figure 3



The mechanism of target DNA detection by a personal glucose monitor via the sandwich hybridization assay using the magnetic beads coated with the Capture DNA (MBs-DNA) with the DNA analyte and a signaling DNA conjugated with invertase enzyme. Reprinted with permission from a study by Xiang and Lu [23]. Copyright 2012, American Chemical Society.

differentiating an enormous number of cases, as it happens with the animal senses.

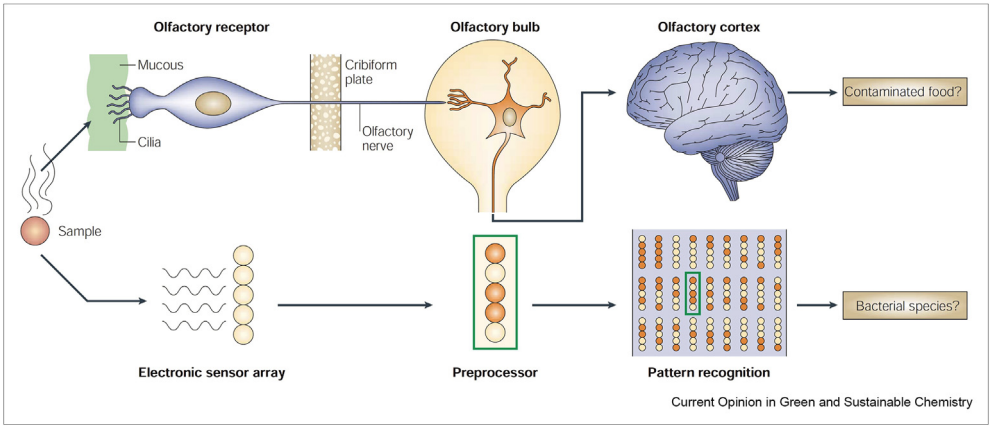
The idea was first assayed with arrays of gas sensors, in the seminal article by Persaud and Dodd [30]; this work coined the electronic nose concept. In this, different volatile compounds could be detected by simulating the different stages of the human olfactory system using semiconductor gas sensors. The obtained signal responses were processed with artificial intelligence tools, in the case, artificial neural networks. The principles used in the approach can be seen in Figure 4. The sensor array takes the simile of the olfactory receptors, whose signals are first preprocessed and then identified by comparison with patterns stored in the brain; the electrical signal from the sensors is first preprocessed to extract their informative component and then processed with artificial intelligence tools to perform the identification.

The direct application field of artificial olfaction is the food field, where it tries to complement or alternate the human sensory panel [31]. Sensory panels are vital tools for the food industry, also in the beverage or cosmetic areas, used in qualification of acceptability/suitability of a lot or a product variant. But it is also evident how difficult is to obtain and to use them, or the efforts necessary for their training; and their availability will be partial, as once in operation they may get tired or saturated; or even, they may not be used, because of toxicity or danger in the exposed situation. It is in these circumstances where the artificial olfaction (and artificial taste) can find applications of evident interest. Evaluation of food freshness, authentication studies, or multiple aspects in food quality control are some of the typical applications. In medicine, another of the hot application fields, the artificial nose can be useful for non-invasive diagnostic by the assay of volatile compound mixtures in breath, urine, sweat, or even, in wounds [32].

Arrays of cross-sensitive sensors can be operated also with liquid samples, receiving in this case the term electronic tongue [33]. The application can be more related to mimicking the human sense of taste, in an artificial taste application, or it can be a more general analysis application, receiving the electronic tongue qualifier. With the use of arrays of cross-sensitive sensors, accurate and reliable results can be obtained, per example think on the possibilities of counterbalancing the presence of interfering species; instead of performing classical wet chemistry approaches to get rid of the annoying species, with the electronic nose/tongue principles a new approach can be assayed: let's measure all components present and let's compensate in a response model for the interfering ones. This idea represents a maximum level of simplicity in the chemical part, where the maximum information possible is obtained from direct sensing, and a complex model is built to consider all possible effects. In this approach, maximum simplicity is put on the wet part, and all the hard work is shifted to the computing aspects. Who will discuss if such an approach is not an emblem of reduction of chemical effort and of sustainable operation of sensors.

Recognition and transduction methods in the electronic tongue are various, although the electrochemical methods are predominant [34]. From these, two main types of electronic tongues are developed, the potentiometric electronic tongue, that uses an array formed by potentiometric sensors or ion-selective electrodes (conventional [35] or prepared on paper [36]), and the voltammetric electronic tongue, that uses an array

Figure 4



Electronic nose devices are sensor systems bioinspired in the human olfactory system. The electronic modules simulate the different stages of the human olfactory system, resulting in volatile odor recognition, which can be used, for example, to recognize spoiled food or to discriminate type of bacterial infections. Reprinted by permission from Springer Nature: Nature Reviews Microbiology [32], Copyright 2004.

formed by different type of voltammetric sensors. For this purpose, different metal electrodes can be used, or alternatively, electrodes modified with different catalysts or materials providing specific electrochemical properties. Finally, it is also necessary to comment how biosensors may be used with these systems. Being the biosensors elements capable of higher selectivity, the applications are more centered on specific groups of substances, allowing us to produce results comparable with those furnished by heavy analytical instrumentation, e.g., HPLC. In a first example, a bioelectronic tongue (that is an electronic tongue comprised with biosensors) was designed to resolve and quantify the type of phenolic compounds present in wine [37]; in a second example, an inhibition bioelectronic tongue was used to discriminate pesticides dichlorvos and methylparaoxon [38].

Conclusions

As already declared for electrochemical sensors [39,40], (bio)sensors in general have proven to fulfill the requirements of green chemistry and sustainability. Conditions of minimum use of sample, reagents, materials, and resources together with the reduced effort to produce a result suit, or can adopt modern environmental needs. The conjugation with biotechnology and, more recently with nanomaterials, has made these features even more evident. Certain paradigmatic examples exist where even the technical requirements for instrumental measurement can be adapted or borrowed, bringing to an ultimate end the simplicity of the setups. And in case of global needs of massive testing, as it has happened with the COVID-19 epidemic, the three selected paradigms have demonstrated the possibilities and options they can offer for quick, cheap, and simple tests, as it is the case of the immunoassay for COVID antibodies combining a lateral flow strip and detection of chemiluminescence with the smartphone camera [41], the example that detect the antibodies using enzyme labeling to produce glucose detected by the personal glucose monitor [42], or the use of an artificial olfaction system for screening of patients for COVID-19 diagnose by analyzing volatiles in their exhaled breath [43]. The speed in which these devices were setup and evaluated only gives confirmation of the possibilities offered.

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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