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Pedro Martín Vázquez, Frédéric Brunel, Jean-Manuel Raimundo. Recent Electrochemical/Electrical Microfabricated Sensor Devices for Ionic and Polyionic Analytes. ACS Omega, 2020, 5 (10), pp.4733-4742. 10.1021/acsomega.9b04331 . hal-03702575

HAL Id: hal-03702575

<https://hal.science/hal-03702575>

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Recent Electrochemical/Electrical Microfabricated Sensor Devices for Ionic and Polyionic Analytes

Pedro E. Martín Vázquez,[‡] Frédéric Brunel,[‡] and Jean-Manuel Raimundo*Cite This: *ACS Omega* 2020, 5, 4733–4742

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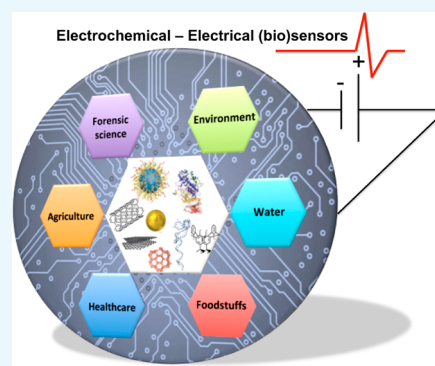


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ABSTRACT: The recent technological advances combined with the development of new concepts and strategies have revolutionized the field of sensor devices, allowing access to increasingly sophisticated device structures associated with high sensitivities and selectivities. Among them, electrochemical and electrical sensors have gained the most interest because they offer unique intrinsic characteristics and meet the requirements to be integrated in more sophisticated devices including microfluidics or lab-on-chips, opening access to multiplex and all-in-one detection devices. In the present article, we outline and provide a short and concise overview on the most recent achievements in the field of electrical detection of ionic species as they display versatile roles in many important biological events and are ubiquitous in environment.



1. INTRODUCTION

The introduction of microfabrication techniques¹ into the field of analytical sensors has recently led to tremendous development of microfabricated devices notably for monitoring hazardous and/or harmful analyte traces. These devices are not only designed and suitable for environmental purposes but also of great importance to directly assess biological samples in the field of *in vitro* or *in vivo* diagnostics and food processing.² Among the myriad of analytes, ionic species represent one of the largest foreseen targets. Indeed, ions and polyionic structures are ubiquitous in environment (water, soil, etc.) and display versatile roles in many important biological processes and cellular events (enzymatic reactions, antigen–antibody recognition, DNA hybridization, neuronal transmission, etc.).³ However, although they are beneficial in many life processes, their possible disruptions may cause adverse effects on human health and could generate environmental alterations.

Conventional analytical methods reported in the identification and quantification of ionic or polyionic species are mainly based on spectroscopic techniques such as inductively coupled plasma-mass spectroscopy (ICP-MS), atomic absorption spectroscopy (AAS), as well as ion chromatography coupled with conductivity detection (IC-CD), liquid chromatography coupled with mass spectroscopy (LC-MS and LC MS/MS), gas chromatography coupled with mass spectroscopy (GC and GC-MS), or capillary electrophoresis (CE) affording precise and accurate measurements.⁴ These techniques require expensive and sophisticated instrumentation, complicated sample preparation, and expert manpower and are

occasionally inappropriate. They are also somewhat tedious and time-consuming. To meet these drawbacks, scientists have strived to endeavor efficient methods and devices for the rapid and sensitive analysis of ionic pollutants based on microfabricated sensors. To this end, nanotechnologies combining chemistry, physics, electronics, and biology have appeared to be of great interest in the development of sensing electrochemical devices as they offer unique characteristics such as miniaturization, low cost, ease-of-use, specificity, selectivity, and real-time monitoring capabilities at the point-of-need compared to other technologies based on optical (surface plasmon resonance, fluorescence, and absorption), mass (piezo- or magnetoelectric), and thermometrics as output signal transducers.

The objective of the present article is to provide a short and concise overview on recent achievements in the field of electrical detection of ionic species. We believe that those technologies will have a breadth and deep impact in the forthcoming years due to the perpetual demand of point-of-care and wearable sensing devices as well as their implementation and integration in more sophisticated devices including microfluidics and lab-on-chips for theranostic applications.

Received: December 17, 2019

Accepted: February 12, 2020

Published: March 5, 2020



2. GENERAL CONSIDERATIONS

2.1. Sensor Specifications. The recognition process constitutes the key step in sensing devices and depends strongly on both the analyte morphology (shape, geometry, size, etc.) and the bonds established within the receptor (hydrogen bonds, electrostatic, π - π interactions, etc.). However, other specifications, which can affect the recognition process, have to be taken into account and not be neglected such as the nature and type of the analyte (neutral, zwitterionic, ionic, or polyionic species), the complexity of the medium (solution, gas, biofluids, etc.), the temperature, the pH, the presence of putative interferences, and more. Besides, major challenges need to be solved upon device operation in order to (i) prevent the molecular damage; (ii) enhance the signal-to-noise ratio, the sensitivity, and the selectivity; (iii) improve the repeatability, reliability, and accuracy; (iv) optimize the reversibility, the linearity, and response time; and (v) preserve the storage and operational stability (drift) to increase the device lifetime.

2.2. Sensor Performance Characteristics. Regardless of the configuration of the sensor devices, the realization of efficient and robust sensors is combined with the fabrication of flawless surfaces, embedding the appealed receptors, analogously to cellular membranes, to ensure high performance. Therefore, the assemblage and operation of an electrochemical sensor require the formation either of a self-assembled monolayer (SAM) or even more complex structures, encompassed with conducting polymers, carbon and non-carbon nanomaterials, polymers, covalent or metal-organic frameworks, composites, etc., at the surface of a metallic electrode or organic substrate as well as organic-inorganic hybrid that could be, but not exclusively, a semiconductor or a metallic oxide. Thus, suitable ultrathin organic films tethering or embedding the desired synthetic or natural receptors that solely bind to the analyte of interest are critical. These thin films not only serve to graft the (bio)receptors to the device surface but also play a crucial role in enhancing signal-to-noise ratio and sensitivity.⁵ Furthermore, the modified surfaces act as specific barriers and help to abate the ion diffusion, reduce the nonspecific adsorption and fouling, and ensure the biocompatibility for medical purposes. The sensor performances are based not only on the unique combination of the (bio)-receptor, the surface chemistry, and methods used to achieve such functionalization but also on the structure, geometry, and configuration of the sensor device. Moreover, regarding specifically the bioreceptors (antibodies, DNA, enzymes, etc.) that are delicate molecules associated with a horrible environmental profile in the nonphysiological conditions pH/temperature/organic solvents, their conformation and structural integrity need to be preserved during all the fabrication steps and device operation in order to improve the sensor lifetime. Therefore, the whole key parameters need to be carefully checked and characterized at each step (physically, chemically, spectroscopically, and electrically) in order to ensure the successful integration of the receptor, the optimal surface modification achieving the best device implementation and fabrication. A nonexhaustive list includes the effect of the surface orientation and morphology, the interface properties, the (bio)receptor itself (nature, structure), the surface energy (contact angle goniometry), the thickness, the deposition methods and deposition parameters (solution or vacuum deposition processes), the post- and pretreatments, and so on.

These are some of the controllable parameters of vital importance to achieve the best sensor devices.

The aforementioned receptor can be either a natural, synthetic, or bioinspired molecule, which can detect a wide variety of ionic and polyionic species on the basis of its structure. Those include heavy metals, anions, complex molecules or bioactive molecules,⁶ cells, tissues,⁷ and organisms (bacteria, viruses). The transduction of an input signal into an electrical output signal can be achieved by amperometry, voltammetry, conductometry (dynamic techniques), or potentiometry (at equilibrium without current flow) connected or not to amplifiers. Depending on the structure of the sensor devices, direct (generation of electroactive species, variation of the conductance) or indirect (biorecognition event or a mediated-process electrode) measurements can be achieved. In addition, nanotechnology contribution allowed the possibility to nanoscale-down the size of the sensor devices, giving rise to their implementation and integration in more sophisticated devices such as microfluidics and lab-on-chips.

3. MICROFABRICATED ELECTROCHEMICAL SENSORS

Electrochemical sensors comprise a wide variety of techniques applicable to the field in which two- or three-electrode devices

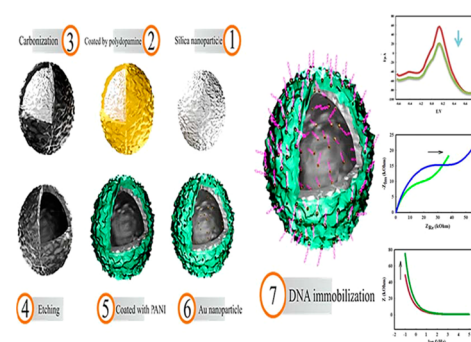


Figure 1. HCS-PANI nanocomposite electrodes used for the detection of HBV DNA biomarkers by a DPV technique. (Reprinted with permission from ref 11. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

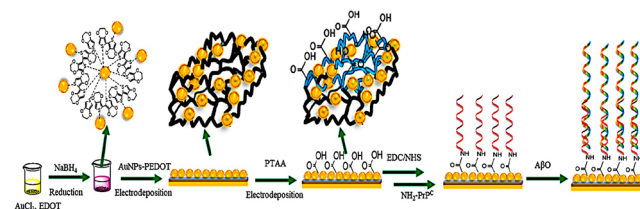


Figure 2. Stepwise preparation of the AuNPs-PEDOT-PTAA/PrP^C sensing surface and A β O detection. (Adapted with permission from ref 12. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

are usually employed. Among others, one can cite potentiometry, amperometry,¹⁶ cyclic voltammetry,^{16,18} chronocoulometry-amperometry, electrochemical impedance spectroscopy (EIS),¹² electrochemical quartz crystal microbalance, electrochemical surface plasmon resonance, scanning electrochemical microscopy, and combined electrochemistry with AFM or waveguide-based techniques.⁹ Besides, nano-

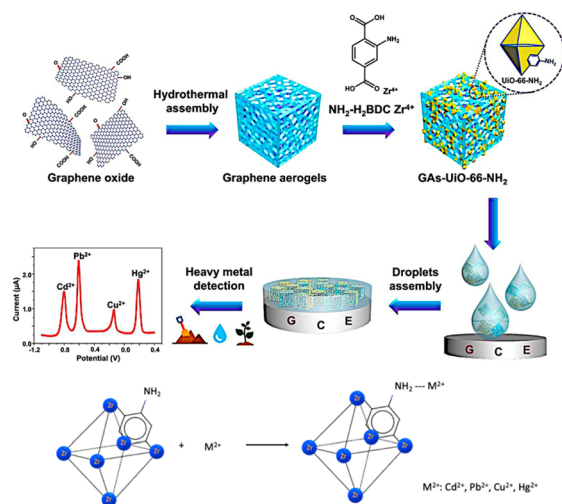


Figure 3. Schematic illustration of a composite GA-Uio-66-NH₂ modified glassy carbon electrode for the simultaneous detection of heavy ions by DPSV. (Adapted with permission from ref 14. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

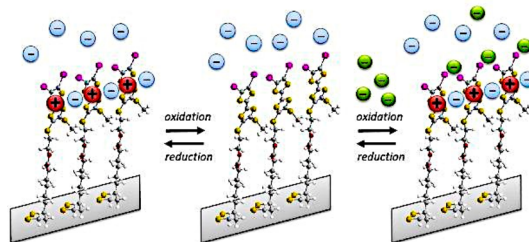


Figure 4. Schematic illustration of the electrochemically driven halogen bonding in the presence of PF₆⁻ and halide anions upon redox activation. Detection was performed by CV. (Reprinted with permission from ref 16. Copyright (2019) Royal Society of Chemistry. Further permissions related to the material excerpted should be directed to the Royal Society of Chemistry).

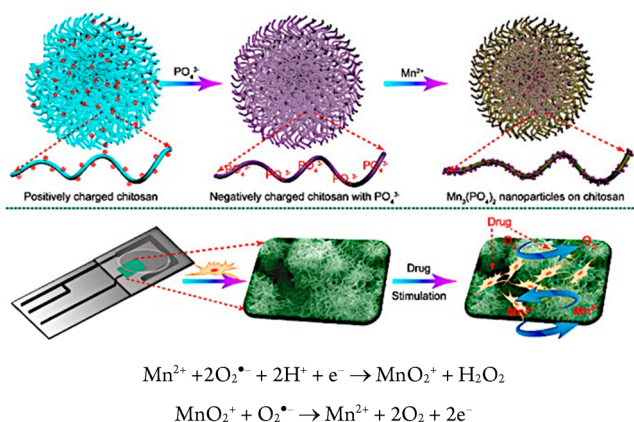


Figure 5. Schematic illustration of the preparation of the nano-composite CTS-Mn₃(PO₄)₂ and detection mechanism. (Adapted with permission from ref 18. Copyright (2019) Elsevier Science. Further permissions related to the material excerpted should be directed to Elsevier Science).

technologies have dramatically contributed to the miniaturization of these types of sensor devices, allowing the possibility

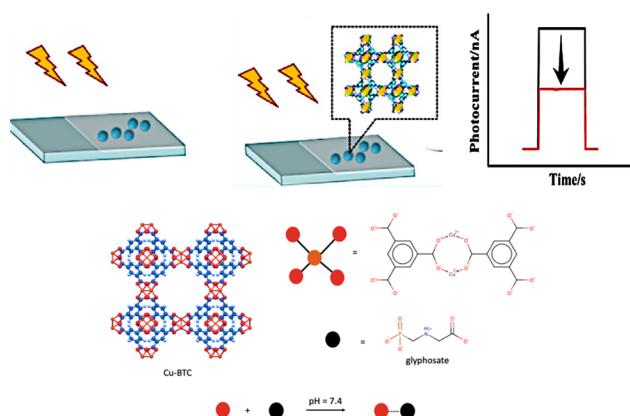


Figure 6. Schematic illustration of the analytical principle of Cu-BTC/CN-NS-based electrochemical sensor. (Adapted with permission from ref 19. Copyright (2019) Elsevier Science. Further permissions related to the material excerpted should be directed to Elsevier Science).

to generate highly sophisticated devices. They present the advantage to display higher sensitivity notably respective to biomolecule detection due to reduced analysis volumes and high electrode surface areas.

3.1. Sensing Biological Anionic Targets. In this context, carbon-based materials (CMs), graphene (2D), carbon nanotubes (1D), graphene oxide (GO) or its reduced form (rGO), fullerene (OD), graphite (3D),^{14,19} and related structures represent certainly one of the pre-eminent classes of applied materials.¹⁰ Indeed, besides their intrinsic optical or electrical properties, they present the benefits to boost the electrocatalytic effect and exhibit higher stability and resistance to passivation. They have been used in conjunction with a wide variety of biomolecules (nucleic acids, aptamers, enzymes, and peptides) for the realization of specific biosensors.⁸ The high demand of biological targets, typically for medical purposes, such as proteins, bacteria, cells, and more particularly DNA/RNA sequences, has largely driven the development of new microchip sensor fabrication and techniques. Indeed, the ability of sensing a specific DNA/RNA sequence in a biological sample allows the rapid diagnostic of numerous diseases, making these specific analytes the most promising targets in the area of research of lab-on-chip detectors. Generally speaking, DNA microarrays are used for sequence-specific detection; it consists of a DNA biosensor where specific DNA strands are immobilized on a solid support in a “DNA spot” used to detect hybridization with the complementary sequence. An indirect reading of the detection is readily obtained by using either fluorescent dye or labeled primers. In certain cases, the detection process is coupled at the upstream to a specific treatment of the sample such as preconcentration (isotachopheresis, ITP), extraction, or amplification (PCR) techniques affording an improvement of the limit of detection (LOD). In this regard, Saliman et al.¹¹ have recently developed an ultrasensitive electrochemical DNA sensor based on the subtle combination of hollow carbon spheres (HCSs) with a conducting organic polymer (polyaniline, PANI) to achieve the detection of Hepatitis B virus (HBV) (Figure 1).

The association of carbon-based structures with PANI permits us to improve the figures of merit, both stability and electron transfer rate, of such conducting polymers in biological samples. The postfunctionalization of the nano-

composite electrode with a specific probe improves the selectivity toward the analyte. To this aim, HCS-PANI nanostructures have been functionalized with a specific probe of the HBV DNA marker. In order to ensure the grafting of the probe onto the nanocomposite, an electrodeposition of gold nanoparticles was previously made. Evaluation of the selectivity was performed using noncomplementary or mutant strands revealing the highest affinity to the HBV DNA. Thereby, a limit of detection of 3.62 fM (i.e. $\approx 10^9$ DNA/mL) by the DPV technique is attained, and it has been proven that it can be used in real samples. Finally, repeatability and reproducibility were performed leading to a relative standard deviation of 1.37%.

Noncarbon materials (NCMs) owing their optical, electrical, or magnetic properties have also been largely developed for biosensor applications. They include indifferent nanoparticles (metallic or oxides), core–shells, quantum dots, wires, composites, and others, associated with a large variety of combinations, putting them in a bright growing in-sensor research perspective. Due to their structures and intrinsic properties, they can be viewed as signal amplifiers, biomimics, internal probes, or active interfaces (electron relay, immobilization surface for the receptors). To improve their electrochemical properties or sensitivity, these NCMs are often combined with graphene-based materials or conductive or insulating polymers, etc. A representative example developed recently by Qin et al.¹² is shown in Figure 2 for specific diagnosis and prognosis of Alzheimer's disease (AD).

In their work, a modified conductive electrode has been prepared from gold nanoparticles and poly(3,4-ethylene dioxythiophene) (PEDOT). This composite has been subsequently modified by the electropolymerization of poly(thiophene-3-acetic acid) (PTAA) in order to immobilize the PrP^C (cellular prion protein) bioreceptors of the A β O (amyloid β oligomer) biomarker. All fabrication steps as well as the PrP^C–A β O binding have been monitored by EIS analysis. Ultrahigh sensitivity of the device was demonstrated at the subfemtomolar level (from 10^{-8} to 10^4 nM). The authors have pointed out the dependence of the response based on the fabrication process of the electrode. However, optimized device fabrication electrodes display a good stability over 1 month and linearity of the readout signal during this period with a device storage at 4 °C.

3.2. Sensing Ions. The detection of “heavy metals” remains a major concern because they are responsible for several environmental and health problems when they are in concentrations as low as ppm or even ppb. Heavy metal ion contamination comes, in most cases, from anthropogenic activities. Among them, Cu²⁺, Pb²⁺, As⁵⁺, Cr⁶⁺, Cd²⁺, and Hg²⁺ are the most toxic representatives due to their nonbiodegradability and environmental/body accumulation concerns, although microelectrode array devices¹³ have been developed and have proven, in the past decade, to be ultrasensitive methods for individual heavy metal detection. Simultaneous multiple detection remains quite challenging but is of crucial interest for practical use. To this aim, Lu et al.¹⁴ have recently developed a modified glassy carbon electrode (GCE) with the GA–UiO-66-NH₂ composite (Figure 3), obtained from the incorporation of the metal–organic framework UiO-66-NH₂ into a graphene aerogel matrix (GA). The modified GA–UiO-66-NH₂-GC electrode was then used as an electrochemical sensor for the simultaneous detection of multiple heavy metals including Cu²⁺, Pb²⁺, Cd²⁺, and Hg²⁺ in soil, water, and

vegetables by a differential pulse stripping voltammetry (DPSV) technique. Interestingly, in a concerted way, an excellent limit of detection was attained for each ion using this modified electrode for Cu²⁺ (8 nM), Pb²⁺ (1 nM), Cd²⁺ (9 nM), and Hg²⁺ (0.9 nM), respectively, with high accuracy and reliability. Ion detection came from the interaction of ions with the amino group of MOF as shown in Figure 3. Accuracy and reliability were verified by performing measurements with interfering ions (at a concentration of 5-fold-order greater) and in real samples including river water, soil, and vegetable. The largest relative standard deviation (RSD) among all measurements was 3.2%, and the recovery for Cd²⁺, Pb²⁺, Cu²⁺, and Hg²⁺ was found to be between 86.7 and 104.7%.

For the last two decades, anions that are ubiquitous in many physiological life processes and agricultural and environmental areas have attracted peculiar attention. Synthesis of artificial hosts for anion recognition received significant interest and became an important area of research in supramolecular chemistry in order to develop efficient and specific systems of recognition that could be further implemented in sensor devices. Among them, halide anions (F[−], Cl[−], Br[−], I[−]) represent an important class and have been extensively studied¹⁵ but are still of great importance due to their practical use in medicine and industrial processes for instance. Recently, Hijazi et al. have demonstrated the possible use of halogen–halogen interactions as a supramolecular recognition path in an electrochemical device modulated by a redox process. Hence, a SAM-coated gold electrode surface, which is end-capped with a tetrathiafulvalene (TTF) unit bearing iodine atoms at the terminal position, has been used as a sensitive layer (namely, 4-ethylthio-(5-(1,2-dithiolan-3-yl)-pentanoate)-4',5'-di(iodo)-5-methylthio-tetrathiafulvalene).¹⁶ By coupling this system with cyclic voltammetry (CV) they have successfully evidenced a halogen–halogen interaction controlled upon redox activation of the TTF unit in the presence of the halides of interest (Figure 4).

During their study, this electrochemically driven system has been proven to be particularly suitable for bromide and chloride detection with a LOD of 6 μ M for Cl[−], paving the way to new opportunities in the electrochemical sensor field.

Halides are currently not the only anions of interest, and a myriad of inorganic or organic anions can be found in the literature, driving the specific design of sensors for the foreseen applications.¹⁷ Those can be either electroactive or not, depending on their structure. Electrochemical direct access of their level can be easily determined even in complex matrixes. To this aim, different material combinations can be found to fit with the specific sensor specifications and applications. Wang et al.¹⁸ have implemented a microchip for the *in situ* detection of O₂^{•−} radical species using fabricated screen-printed electrodes from ultrasmall Mn₃(PO₄)₂ particles (55% w/w) embedded in chitosan (CTS–Mn₃(PO₄)₂) (Figure 5).

Herein, the chitosan presents both the advantages to ensure the biocompatibility of the nanocomposite and facilitate the diffusion of the electrolyte due to the formation of a nanowire-woven microspherical structure incorporating the Mn₃(PO₄)₂ nanoparticles. This peculiar nanostructuration also possesses the benefit to avoid the oxidative-stress-related cytotoxicity that might be induced by nanoparticles. Interestingly, under physiological conditions, the sensor exhibits good specificity and selectivity even in the presence of putative interfering analytes such as ascorbic acid, uric acid, or H₂O₂. The amperometric response recorded at an applied potential of 0.7

V transduces the electrocatalytic activity of the CTS– $\text{Mn}_3(\text{PO}_4)_2$ composite in which $\text{O}_2^{\bullet-}$ oxidizes Mn^{2+} into MnO_2^+ and H_2O_2 and then $\text{O}_2^{\bullet-}$ reduces MnO_2^+ to Mn^{2+} and O_2 . The excellent biocompatibility associated with a LOD of 9.4 nM with a linear range from 57.9 nM to 5 μM makes the CTS– $\text{Mn}_3(\text{PO}_4)_2$ composite highly attractive in sensing devices.

3.3. Sensing Molecules/Molecular Anionic Targets.

One of the most challenging groups of pesticides is the polar pesticide group (glyphosate, glufosinate, fosetyl, difenzoquat, chloromequat, trimethylsulfonium, etc.), which is attracting, nowadays, more and more attention as they often occur as residues in food and are not always included in pesticide monitoring programs. Recently, Cao et al. developed, to this aim, a photoelectrochemical device sensor to monitor glyphosate (Figure 6).¹⁹

The active layer combines two main components: (i) a graphite phase nitrogenized carbon nanosheet (CN-NS), possessing both semiconducting and good photocatalytic features, and (ii) a composite material Cu-BTC (copper-benzene-1,3,5-tricarboxylic acid) as a metal–organic framework (MOF) exhibiting catalytic properties. In the bare photocatalyst composite, the MOFs play a dual role: they improve the photocurrent conversion of the CN-NS upon irradiation with visible light, and their porous structure allows efficient capture of the analytes. Thus, in the presence of glyphosate, the photocatalyst composite exhibits a linear concentration-dependent reduction of the generated photocurrent due to the formation of a sterically hindered Cu–glyphosate complex. The photoelectrochemical sensor demonstrates a LOD of about 1.3×10^{-13} M with good linear range from 10^{-12} to 10^{-3} M associated with low standard deviation after 10 successive measures (3.9%) and good stability after 2 weeks. The sensitivity is not affected even in the presence of some common interferents such as glufosinate, trichlorfon, carbendazim, acetochlor, and malathion or some ions such as Cl^- , NO_3^- , SO_4^{2-} , Fe^{3+} , Zn^{2+} , Ca^{2+} , K^+ , and Na^+ . All these characteristics demonstrate the great potential of such hybrid composites for the sensing of a variety of analytes in the future by combining the right components.

Electrochemical devices have been extensively studied and continue to fascinate the sensor research field due to their ease of fabrication and implementation. Nevertheless, in certain circumstances these devices face some threats and problems that are important to solve as the research field is moving quickly toward flexible and wearable devices.

4. MICROFABRICATED ELECTRICAL SENSORS

Among the miniaturizable devices, field-effect transistors fulfill the needed requirements in the field of electrical sensor technologies.²⁰ Since the very seminal work of Bergveld in the 70s,²¹ the development of ion-sensitive field-effect transistor (ISFET) devices has dramatically increased and evolved during the last five decades. Several device structures in combination with a large variety of materials have been widely used as, for instance, semiconducting carbon nanotubes,³² nanowires,²⁶ and organic semiconductors,^{25,31} particularly for biosensing and environmental applications.²² In addition, different structures and architectures can be achieved depending on both the nature of the semiconductor, inorganic (MOSFET),^{30–33} or organic (OFET)^{25,28,31} and device geometry. OFETs can offer several advantages compared to MOSFET for the foreseen applications and appear more promising for

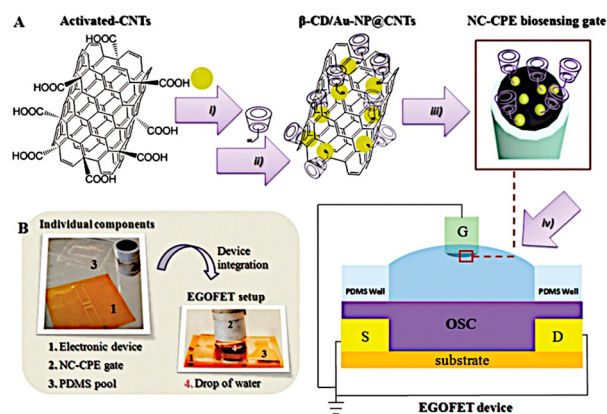


Figure 7. NC-CP electrode as an alternative to conventional metal-gated electrode in sensing devices. (Reprinted with permission from ref 24. Copyright (2019) Royal Society of Chemistry. Further permissions related to the material excerpted should be directed to the Royal Society of Chemistry).

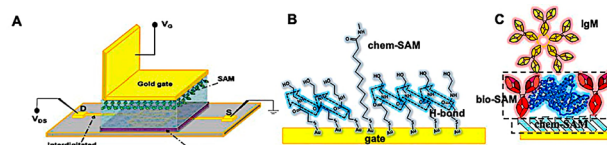


Figure 8. Label-free detection of the IgM/IgG single molecule. (Adapted with permission from ref 25. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

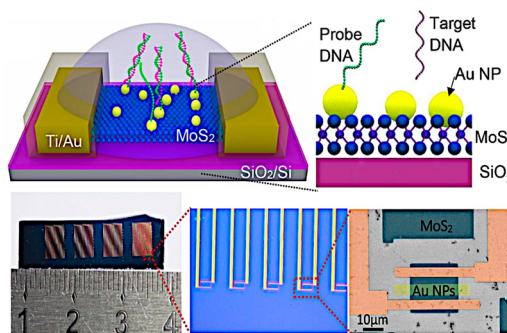


Figure 9. FET-based DNA biosensors. (Adapted with permission from ref 26. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

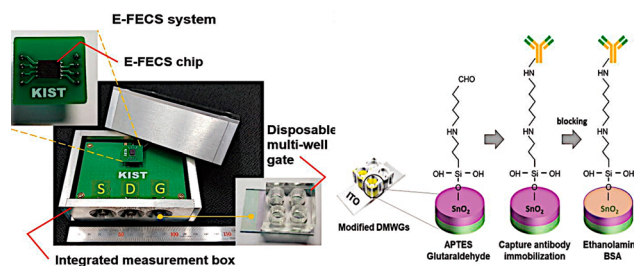


Figure 10. Disposable multiwell gate (DMWG) modified with a cancer biomarker. (From ref 27. Copyright (2019) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Further permissions related to the material excerpted should be directed to Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

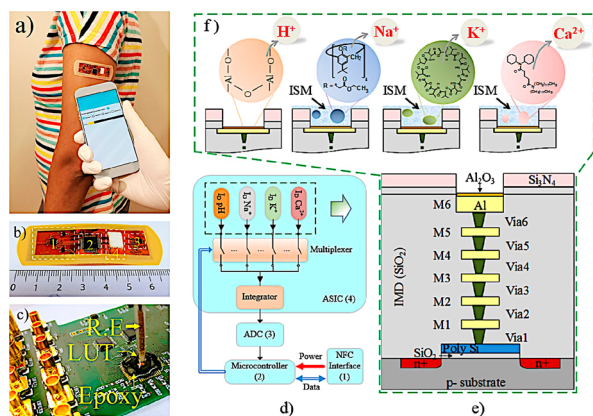


Figure 11. Multiplexed analysis of cations. (Reprinted with permission from ref 29). Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

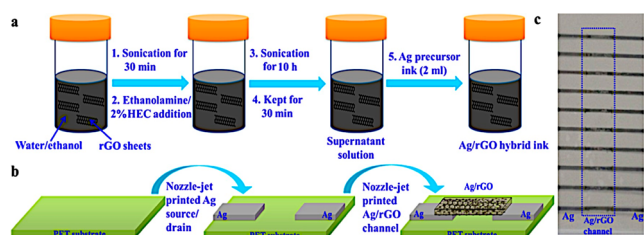


Figure 12. Inkjet printing of a Ag,rGO-based nanostructure as an active component in an FET sensor for PO_4^- sensing. (Reprinted with permission from ref 31. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

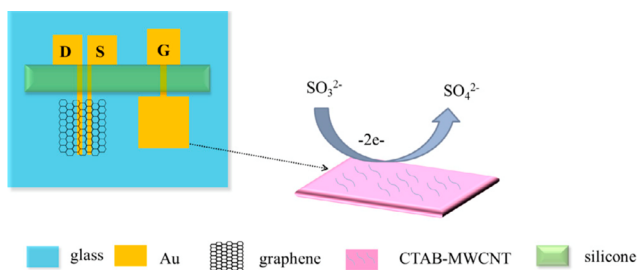


Figure 13. Novel SGGT sensor for the specific detection of sulfite in beverages. (Adapted with permission from ref 32. Copyright (2019) Elsevier Science. Further permissions related to the material excerpted should be directed to Elsevier Science).

detecting low concentrations of analyte and relevant for studying biochemical interactions.²³ Among the typical devices, one can cite electrochemical organic transistors (EC-OTs), charge-modulated field-effect transistors (CM-OEFs), and electrolyte-gated organic field-effect transistors (EG-OFETs). Each of them could be designed with specific configurations, typically the bottom-gate top-contact structure (BG-TC), the bottom-gate bottom-contact structure (BG-BC), the top-gate top-contact structure (TG-TC), and the top-gate bottom-contact structure (TG-BC) that will influence the sensitivity properties of the designed sensors. Moreover, the proper functionalization of the two main electronic active interfaces of the OFET (i.e., the gate electrode or the organic semiconductor) is crucial to achieve novel and efficient sensing devices.

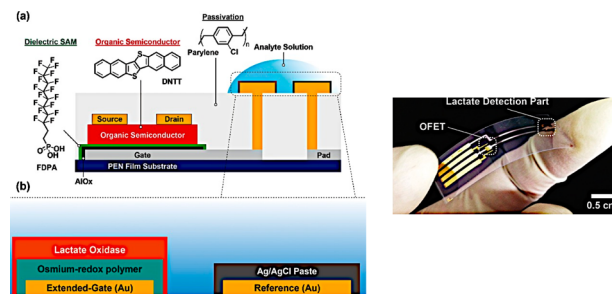


Figure 14. OFETs for aqueous lactate solution detection. (Adapted with permission from ref 33. Copyright (2019) Japan Society for Analytical Chemistry. Further permissions related to the material excerpted should be directed to the Japan Society for Analytical Chemistry).

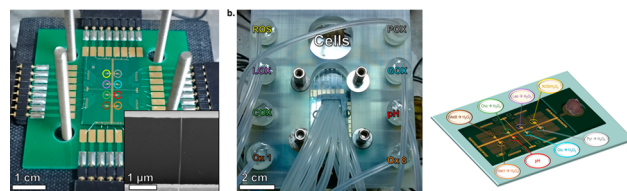


Figure 15. Nanowire-based FET sensors for the detection of metabolites. (Adapted with permission from ref 34. Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the American Chemical Society).

4.1. Sensing Biological Anionic Targets. In a recent work, Munoz et al. have used in an elegant manner carbon nanotubes (CNT) as a conductive component for the fabrication of a nanocomposite carbon paste electrode (NC-CPE) in an EG-OFET to replace and widen the conventional metal-gated electrode system.²⁴ NC-CPE is still underexploited in sensing devices and opens new opportunities and benefits due to their intrinsic properties (ability to tailor the conductivity of the composite, ease of fabrication, robustness, compatibility with several functionalization approaches, possibility to renew their surface). By integrating gold nanoparticles functionalized with thiolated β -cyclodextrin (β -CD), they succeeded to sense tryptophan in PBS solutions at pH 7.4 (Figure 7).

The aim of the gold nanoparticles is to ensure an appropriate orientation of the β -CD's cavity on the CNT surface and electrical contact. The electrical properties of the transistor can be tailored by adjusting the composition ratio of the modified CNT and the matrix polymer. This unique EG-OFET biosensor shows excellent analytical response with a detection limit at the picomolar range (1.0 ± 0.1 pM) and a good linear response from 10^{-12} to 10^{-9} M associated with good stability and repeatability. More interestingly, by polishing the NC-CPE's surface, it is possible to recover the sensing layer without loss of the sensitivity properties.

In a similar way, Macchia et al. recently claimed the possibility to detect proteins at the physical limit. To do so, they achieved the label-free single-molecule detection (IgG, IgM) by covalently modifying a gate electrode of an EG-OFET with a SAM made from anti-IgM or anti-IgG.²⁵ The antibodies were grafted on a chemical layer (chem-SAM) comprised of mixed alkanethiols (3-mercaptopropionic acid (MPA)/11-mercaptoundecanoic acid (MUA) at a ratio 10:1). Hence, IgM or anti-IgG was grafted on the MUA, while unreacted

carboxylic groups were blocked with ethanolamine. The uncovered area was then filled with bovine serum albumin (BSA) protein (Figure 8).

During the device fabrication, they evidenced a high degree of antibodies grafted on the surface and proved that both BSA and the presence of a H-bonding network in the chem-SAM are essential to achieve good performance in the sensing of single molecules that can be useful for early detection of diseases.

Noninvasive diagnostics of diseases at the early stage is of great importance to anticipate the treatments and improve the quality of life of patients. To reach these goals, there is an urgent need to develop research and care strategies associated with low-cost and high sensibilities. Any pathology produces unique biomarkers that are characteristics of the physiological disorder and can be exploited as an internal probe or using specific DNA strands as probes. In this context, Liu et al.²⁶ have fabricated a high-performance FET-based DNA biosensor through CVD of a MoS₂ monolayer dedicated to trisomy 21 syndrome screening in blood samples of pregnant women. Herein, the deposition of AuNPs within the MoS₂ channel is followed with immobilization of the specific DNA probe (Figure 9).

With this system, they have been able to achieve detection of the target DNA fragment (chromosomes 21 or 13) with a LOD below 100 aM. This sensitivity associated with a high specificity (3-nucleotide polymorphism discrimination) satisfies the requirements of the Down syndrome diagnosis.

Detecting specific blood biomarkers is a promising strategy to access early diseases diagnosis. For instance, colon cancer secreted protein-2 (CCSP-2) has been identified as a colorectal cancer (CRC) biomarker and has been used by Jeun et al. to develop a CRC-sensor based on a FET.²⁷ For real-life clinical applications a disposable multiwell gate has been fabricated on which the modified FET chips were sealed with an epoxy resin to ensure complete stability and compatibility with the blood environment (Figure 10).

In this device, they have used an ISFET device under dual-gate operation in which the DMWG gate (SnO₂) has been chemically modified with a CCSP-2 antibody, while the unreacted sites were treated with ethanolamine followed by incubation with BSA to prevent nonspecific adsorption of blood proteins. The novel electrical sensor exhibits high sensitivity with a LOD of 10 ag·mL⁻¹ and a linear response in the 1 fg·mL⁻¹ to 10 ng·mL⁻¹ range. Interestingly, the sensor is able to detect the biomarker in a wide range of samples from early stage tumors to metastatic disease and has been clinically validated. Nonetheless, the device still suffers from a lack of stability and needs to be improved prior to market development.

4.2. Sensing Ions. Cation analysis and detection by FETs have been extensively studied since the early development of the ISFET. Numerous devices have been fabricated and tested for the detection of heavy metals, first for environmental and food concerns, but have been then progressively extended to medical purposes. Although efforts are still being made to improve the cation detection in FET devices and for fabrication to fully organic devices,²⁸ the general tendency of the ongoing research is the realization of multiplexed analysis of complex matrixes using wearable devices. Therefore, more sophisticated devices are needed to allow the possibility to determine the concentration of different analytes or bio-analytes within one run analysis. Zhang et al.²⁹ have recently

reported the fabrication of a wearable sweat sensor (10 × 20 μm²) based on the CMOS technology (Figure 11).

Three different cations (K⁺, Na⁺, and Ca²⁺) and pH (H⁺) have been recorded simultaneously in the course of the analysis, and they exhibit high sensitivities that are close to the Nernstian limit. The high specificity for each analyte was brought by the surface functionalization with ion-specific membranes in conjunction with, respectively, Al₂O₃ (pH), valinomycin ionophore (K⁺), calix[4]arene (Na⁺), and ETH 5234 ionophore (Ca²⁺). Interestingly, a demonstrator was fabricated with ultralow electrical consumption (2 pW per sensor) including a readout interface and NFC communication (for pH and Na⁺) with *in vitro* measurements suited for wearable sweat sensing.

Besides, anions have been the subject of peculiar attention because of their importance in many biological or biochemical processes. Also, compared to their cationic counterpart, they present various shapes, structures, and sizes, rendering them somewhat more delicate to detect.³⁰ Hence, they have stretched a lot of efforts in the synthesis and design of artificial receptors prior to their integration in real detection devices. Moreover, easy manufacturing processes for implementing sensors are sought to reduce the fabrication steps and costs. In this context, Bath et al.³¹ have used the inkjet printing technology, as a patterning tool, to fabricate on PET substrates an Ag/rGO-based nanostructure sensor for the detection of phosphate. The fabrication process is depicted in Figure 12.

The sensor displays excellent performances with a LOD of 1.20 μM even in the presence of interfering ions such as TTP, Ca²⁺, Mg²⁺, K⁺, HCO₃⁻, and SO₄²⁻ associated with long-term stability and reproducibility.

In food safety and quality control, the titration and detection of preservative and food additive amounts are of great significance due to their potential toxicity and must follow the food regulations. Among them, sulfite is of major interest since it is present in several beverages (juices, alcohols) and has suspicious effects on human health. To this context, Wang et al. have designed a novel solution-gated graphene-based transistor (SGGT).³² In this device, the gold gate electrode was modified by a nanocomposite prepared from multiwall carbon nanotubes (length 0.5–2 μm, diameter >0.8 nm) and cetyltrimethylammonium (CTAB), while graphene is used as a semiconductor (Figure 13).

Continuous sulfite detection with this SGGT leads to a wide linear response range (from 1 to 10 μM, 95 mV per decade) associated with a low LOD (30 nM which is 30 times greater compared to SGGT with unmodified gate) and high selectivity when putative competitive analytes were tested such as K⁺, NO₂⁻, CO₃²⁻, HCO₃⁻, SO₄²⁻, NO₃⁻, and ethanol. The performances of the device led the authors to further detect sulfite in real alcoholic beverage samples (vodka and the Chinese Laobaigan liquor) and compared them consecutively to the AOAC Official Monier-William standard method. Similar results were attained in both cases, testifying to the relevance of this innovative device and opening new directions for practical sample sensing.

4.3. Sensing Molecules/Molecular Anionic Targets. Continuous accurate detection in aqueous media of anions is of great importance in the field of healthcare and requires well-designed OFETs. In this context, Minamiki et al. have recently designed and fabricated a biosensor based on OFETs for the detection of the lactate as a biomarker.³³ Extended gate-type OFETs, with a small sensing area of 1.65 mm², have been

Table 1. Electrode Materials Used for the Sensing of Analytes in the Described Electrochemical or FET Devices^a

electrode materials	analytes	methods/technique	LOD	ref
GCE/HCS-PANI/Au-Probe	HBV DNA biomarker	DSPV	3.62 fM	11
PrP ^C /AuNPs-PEDOT-PTAA/Au	amyloid β oligomer	EIS	10 ⁻⁸ nM	12
GCE (ϕ : 3 mm)	Cd ²⁺ , Pb ²⁺ , Cu ²⁺	MEAs: CV, DPSV	1 μ M	13
GCE/GA@UiO-66-NH ₂	Cd ²⁺ , Pb ²⁺ , Cu ²⁺ , Hg ²⁺	DPSV	Cd ²⁺ : 0.02 μ M Pb ²⁺ : 1.5 nM Cu ²⁺ : 7 nM Hg ²⁺ : 2 nM	14
Au/SAM of di(iodo)-TTF	Cl ⁻	CV	6 μ M	16
screen printed/CTS@Mn ₃ (PO ₄) ₂	O ₂ ^{•-}	biochip: CV, amperometry	9.4 nM	18
ITO/Nafion/Cu-BTC MOF/g-C ₃ N ₄	glyphosate	EIS, PEC	0.13 pM	19
β -CD/AuNPs@CNTs (20%)	tryptophan	EGOFET	1 pM	24
Au/SAM of MAP-MUA (10:1)@anti-IgM (or anti-IgG)-BSA	IgM/IgG	SiMoT-EGOFET	11 zM	25
MoS ₂ /AuNPs@DNA probe	DNA fragment (chromosomes 21, 13)	FET biosensor	100 aM	26
ITO/SnO ₂ @CCSP-2 antibody	CCSP-2	FET biosensor	10 ag·mL ⁻¹	27
Al/Al ₂ O ₃	H ⁺	3D-EMG-ISFET	58 mV/pH Na ⁺ (-57 mV/dec)	29
Al/Al ₂ O ₃ /ISM(X)	Na ⁺ , K ⁺ , Ca ²⁺		K ⁺ (-48 mV/dec) Ca ²⁺ (-26 mV/dec)	
printed Ag-rGO/Ag on PET	PO ₄ ³⁻	FET	0.2 μ M	31
Au/CTAB-MWCNTs	SO ₃ ²⁻	SGGT	30 nM	32
Au/HRP-Os@LOX	lactate	extended-gate OFET	0.1 mM	33
SiNW/DHA + oxidase enzymes	metabolites via H ₂ O ₂	FET	100 nM	34

^aAQ: 9,10-anthraquinone; AuNPs: gold nanoparticles; β -CD: β -cyclodextrin; BSA: bovine serum albumin; CCSP-2: colon cancer secreted protein-2; CNTs: carbon nanotubes; CTAB: cetyltrimethylammonium; CTS: chitosan; Cu-BTC MOF: copper-benzene-1,3,5-tricarboxylic acid MOF; CV: cyclic voltammetry; DHA: 9,10-dihydroxyanthracene; di(iodo)-TTF: 4-ethylthio-(5-(1,2-dithiolan-3-yl)-pentanoate)-4',5'-di(iodo)-5-methylthio-tetrathiafulvalene; DPSV: differential pulse stripping voltammetry; EGOFET: electrolyte-gated organic field-effect transistors; 3D-EMG: three-dimensional-extended metal gate; EIS: electrochemical impedance spectroscopy; FET: field effect transistor; GA: graphene aerogel; g-C₃N₄: graphite phase nitrogenized carbon; GCE: glassy carbon electrode; HCS: hollow carbon sphere; HRP-Os: horseradish peroxidase/osmium redox polymer complex; HBV: hepatitis B virus; IgM/IgG: immunoglobulin M/G; ISM (X): ion-selective membrane; ISM (Na⁺): Na ionophore X (1% w/w); Na-TFPB: sodium tetrakis[3,5-bis(trifluoromethyl)-phenyl] borate (0.55% w/w); PVC, polyvinyl chloride (33% w/w); and DOS, bis(2-ethylhexyl) sebacate (65.45% w/w); ISM (K⁺): valinomycin (2% w/w), sodium tetraphenylborate (NaTPB) (0.5% w/w), PVC (32.7% w/w), DOS (64.7% w/w); ISM (Ca²⁺): calcium ionophore (1.2% w/w), 2-nitrophenyl octyl ether (66% w/w), PVC (32.5% w/w), and Na-TFPB (0.3% w/w); ISFET: ion-sensitive field effect transistor; LOX: lactate oxidase; MEAs: microelectrodes arrays; MPA: 3-mercaptopropionic acid; MOF: metal-organic framework; MUA: 11- mercaptoundecanoic acid; MWCNTs: multiwalled carbon nanotubes; PANI: polyaniline; PEC: photoelectrochemical; PEDOT: poly(3,4-ethylene dioxithiophene); PET: poly(ethylene terephthalate); PTAA: poly(thiophene-3-acetic acid); rGO: reduced graphene oxide; SAM: self-assembled monolayer; SGGT: solution-gated graphene-based transistor; SiMoT: single-molecule transistor detection; SiNW: silicon nanowire; UiO-66-NH₂: MOF.

developed and successfully modified by a horseradish peroxidase/osmium redox polymer complex and lactate oxidase as a sensing layer (Figure 14).

The device made from DNTT (dinaphtho[2,3-*b*:2',3'-*f*]thieno[3,2-*b*]thiophene) as an organic semiconductor operates under low voltage and exhibits excellent electrical characteristics and stability in aqueous media. Moreover, the sensor has shown excellent responses and sufficient sensitivity, in PBS solution, to lactate (0–10 mM), and no responses were obtained with common interferent analytes found in sweat such as urea, glucose, *p*-cresol, MgCl₂, CaCl₂, and NaCl, making this device a system of choice for foreseen application.

As already mentioned, simultaneous and real-time detection of multiple analytes is of great significance notably for biomedical applications. To reach such an objective lab-on-chip based on field effect transistors has stimulated a lot of interest, as they meet the foreseen requirements. Nanowire-based FET sensors have been envisioned for the detection of biological/chemical species but are still underexplored. For this purpose, Krivitsky et al. have developed a sensor based on a

nanowire FET exhibiting tailored redox properties, allowing the simultaneous real-time sensing of several metabolites (Figure 15).³⁴

In their work, they have covalently grafted molecular redox-active species, based on a 9,10-anthraquinone derivative (AQ) that is sensitive to reactive oxygen species (ROS) on a *p*-type silicon NW-FET array surface. ROS, such as H₂O₂, are able to oxidize DHA (dihydroquinone) into AQ, which is reversibly reduced in the presence of a mild reductant (i.e., diethylhydroxylamine (DEHA)) or by applying an electric potential. The SiNW-FET conductivity is alternatively switched from an “off” state to an “on” state when DHA is oxidized to AQ in the presence of H₂O₂ followed by the addition of DEHA. In order to convert the analyzed metabolites into H₂O₂, the redox-active center is combined with oxidase enzymes that are specific to the desired metabolites. The use of microfluidics allows the possibility to introduce all components in the appropriate compartments at the microliter scale. Six different metabolites have been tested (H₂O₂, glucose, pyruvate, lactate, choline, and pH), and the

device has been calibrated prior to real metabolite screening for a minimal number of 10^4 – 10^6 cells/mL with a LOD for H_2O_2 in the range of 100 nM. Finally, the performances have been evaluated on a section of solid tumor, highlighting the effectiveness of the developed sensor in real conditions. Interestingly, their sensor has shown reversibility and reusability capabilities and has demonstrated real-time metabolite monitoring by simulating a hypothetical cancer treatment by adding 2-deoxy-D-glucose, a known glycolysis inhibitor which modifies the concentration of glucose, pyruvate, and lactate. Although their sensor device is not optimized yet, they have nicely evidenced the possibility to achieve multiplex detection and monitoring.

OFET sensors have stretched the greatest keen interest in the last decades as they offer unique characteristics and a wide variety of architectures, and they can be fabricated, allowing them to meet the desired requirements. They are compatible with the societal demand encompassing real-time sensing and monitoring with wearable devices. Even if the ultimate Holy Grail sensor is not obtained yet, the general trends demonstrate great advances in that direction.

5. CONCLUSIONS AND OUTLOOK

The last decades have witnessed an intense development of the sensor field for applications in a variety of areas (health, environment, foodstuffs) in order to improve, for example, their selectivity, specificity, and reliability due to a high societal demand. To this aim, integration of nano-organic-based materials (NOMs) in electrochemical and electrical sensors is responsible for these technological achievements because they can be interfaced with electronic mobile devices. NOMs can further be hybridized with other materials to optimize their properties or obtain synergistic effects. They are directly used to modify the electrode surfaces, as support for grafting the sensing elements, or act as artificial receptors, signal modulators, and so on (Table 1).

Although huge gaps have been filled since the very seminal works, some fabrication procedures to achieve the modified electrodes are somewhat prohibitive, tedious, and complicated, restricting their technological transfer and their possible commercialization for practical use. The existing issues must be solved in order to ensure their full integration and be used at the point-of-need. In addition, the robustness of the sensors has to be proved and must be validated following the regulations. Device improvements will contribute to the access of reliable measurements, accurate responses, and reusable devices associated with high stabilities under long-term storage and operation and ruggedness. Moreover, intrusive and nonintrusive wearable self-powered devices and/or ingestible sensors to monitor patients' health will be of great interest in the future, but there are still numerous technological hurdles to surmount. Furthermore, development of multiplex sensors is needed to have all-in-one detection devices not only for different substances but also for a family of contaminants in more and more complex matrixes. Some examples have been recently developed, but a lot of challenges remain to be overcome. The nanotechnologies will help to fulfill the needed requirements, taking into account also the close collaboration of different research areas to develop new concepts and strategies to provide commercially viable devices.

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Notes

The authors declare no competing financial interest.

Biographies

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Frédéric Brunel received his M.Sc in 2012 from the University of Science of Montpellier, France. He then completed his Ph.D. under the supervision of Dr. Michel Camplo on the design and synthesis of innovative systems derived from antibacterial phosphonium-based ionic liquids at Aix Marseille University in 2016. After several postdocs covering different research fields including supramolecular chemistry, sensor elaboration, and synthesis of biocidal material, he currently works as a Research Engineer for the CNRS at CINaM (Centre Interdisciplinaire des Nanoscience de Marseille).

Pedro E. Martín Vázquez achieved his M.Sc degree in Material Engineering (2015) at the Autonomous University of Nuevo Leon. In 2015, he joined the Ph.D. program under the guidance of Dr. Alejandro Torres on the synthesis of inorganic semiconductors. During his doctoral studies, he has been laureate of the CONACYT program and spent 12 months in the group of Prof. Jean-Manuel Raimundo at CINaM (Marseille, France) working on the synthesis of push–pull derivatives for optoelectronic devices including sensors. His present research interest is focused on the fabrication of organic–inorganic hybrid photovoltaic devices.

ACKNOWLEDGMENTS

This work was supported by the Centre National de la Recherche Scientifique (CNRS) and the Ministère de l'Enseignement Supérieur et de la Recherche (MESR). P.E.M.V. thanks also the CONACYT agency for his doctoral financial support n°553260/295449. For the sake of clarity,

only some recent articles have been cited herein. This does not detract from the quality of other articles published in the domain that would not be cited in the present article.

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