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Disposable Sensors in Diagnostics, Food, and Environmental Monitoring

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Disposable sensors are low-cost and easy-to-use sensing devices intended for short-term or rapid single-point measurements. The growing demand for fast, accessible, and reliable information in a vastly connected world makes disposable sensors increasingly important. The areas of application for such devices are numerous, ranging from pharmaceutical, agricultural, environmental, forensic, and food sciences to wearables and clinical diagnostics, especially in resource-limited settings. The capabilities of disposable sensors can extend beyond measuring traditional physical quantities (for example, temperature or pressure); they can provide critical chemical and biological information (chemo- and biosensors) that can be digitized and made available to users and centralized/decentralized facilities for data storage, remotely. These features could pave the way for new classes of low-cost systems for health, food, and environmental monitoring that can democratize sensing across the globe. Here, a brief insight into the materials and basics of sensors (methods of transduction, molecular recognition, and amplification) is provided followed by a comprehensive and critical overview of the disposable sensors currently used for medical diagnostics, food, and environmental analysis. Finally, views on how the field of disposable sensing devices will continue its evolution are discussed, including the future trends, challenges, and opportunities.

1. Introduction

Disposable sensors are affordable and easy-to-use devices for short-term or single-shot measurements. They transduce physical, chemical, or biological changes in their environment to an analytical signal. This class of low-cost sensors enables mining of critical analytical information by anyone, anywhere and at any time, without worrying about contamination and recalibration. Because of the increasing demand for testing at the point-of-need, out of central laboratories (for example, in resource-limited settings, where portability, usability and price matter the most), the global market of disposable sensors has recently experienced tremendous growth. This is especially the case in medical diagnostics, food, and environmental monitoring. A wide range of disposable sensing devices, such as home pregnancy tests or wearable blood glucose meters, have already been integrated into our daily lives.

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Discovery and development of different (bio)materials and sensing technologies play a fundamental role in the implementation of new sensors. A historical timeline of key events in sensors is presented in **Figure 1**. But do the material advances really matter for the evolution of sensors? The answer to this question is both "yes and no" since the development of novel functional materials often need to be combined with advances in other fields to create entirely new classes of sensors. For instance, immunoassays, based on the simple idea of employing labeled biomolecules (like antibodies[1]) for the detection of antigens,[2] have revolutionized diagnostics for more than a half century and paved the way for numerous disposable sensors. Immunoassays have, however, witnessed a major breakthrough only after the introduction of enzyme-linked immunosorbent assays (ELISA).[3] The secret behind the success of ELISA was its simplicity which was enabled by combining technical advances in different fields of research into a single platform. These include the application of i) enzymes as labels[4,5] (biotechnology), ii) optical signal readout by spectrometry[6] (sensor technologies), and iii) disposable microtiter plates[7] with engineered surfaces[8] (materials) as solid substrates to perform large numbers of measurements simultaneously.

As illustrated in this example, innovation in materials alone is not often enough to overcome the current limitations of disposable sensors; however, materials play a pivotal role in the development of advanced disposable sensing devices, both for reducing costs, environmental impact and improving performance/usability. Disposable sensors should, therefore, satisfy the following requirements: they must i) utilize inexpensive, sustainable, or biodegradable materials; ii) be compact with high modularity and fewer components; iii) allow for reliable and low-cost mass production; iv) have a short duration of analysis and fast response times; v) be simple to use or offer automated handling of samples with minimal user intervention; vi) operate without or with an affordable, portable instrument; and vii) deliver precise results in accordance with international quality standards. Furthermore, there are other technological (such as multianalyte detection) and nontechnological (for example, acceptance in daily practice) challenges for the successful translation of disposable sensors into commercial products.

Historically, the most important factor defining disposability has been the economic efficiency, i.e., high-throughput fabrication at extremely low costs and minimum quantities of materials for a single sensor.[9] The common way to achieve this has been to combine a dedicated readout device—generally portable, inexpensive and easy-to-use—with a disposable sensing unit (usually in the format of a cartridge, strip, etc.). In the commercial world, marketing single-use devices along with a nondisposable unit is called the razor/razorblade business model, in which a supplier would continuously provide a disposable sensor (for example, glucose test strip ≡ razorblade) that can be probed by a reusable reader (digital glucometer ≡ razor). There are, however, also devices where signal transduction is achieved either by the naked eye, limited to a qualitative or semiquantitative result, or with an integrated disposable unit for signal processing.[10]

The growing awareness for environmental sustainability, such as decentralized monitoring of water and air pollution, and the desire for worldwide better standards of food safety and healthcare (especially, in resource-limited settings, where millions of people do not have access to standard laboratories) are just some of the driving forces that motivate the development of next-generation low-cost disposable sensors with superior sensing characteristics.[11]

Herein, we will walk you through a journey of how disposable sensors are made and their applications. We start off with simple materials and hybrids, that are built into physical, chemical and biosensing structures containing natural, artificial, organic and inorganic functional elements for the recognition of analytes, and transduction and amplification of signals.

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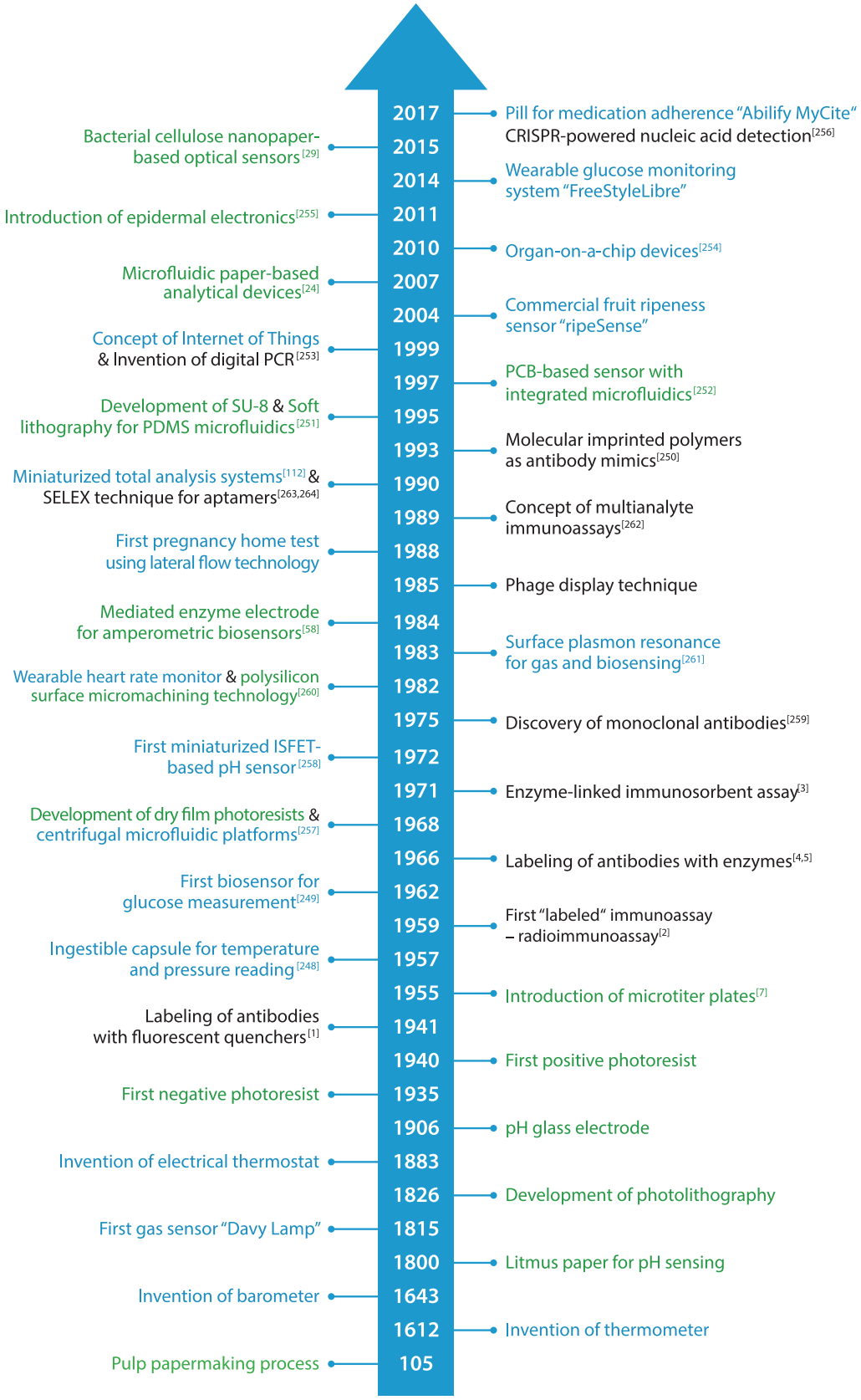


Figure 1. Historical timeline of the discovery of various sensors and their development with respect to materials (green), sensor technologies (blue), and biotechnology (black).[248–264]

Sensing structures with their functional elements can be integrated into higher order, more complex systems such as lab-on-a-chip (LOC) devices and applied to solve problems in healthcare, food and environmental monitoring. We comprehensively review disposable sensing devices reported recently by academia and industry, and provide a critical summary addressing the unmet needs and challenges. Finally, we share our vision and predictions for future trends and insights in disposable sensors, such as fully integrated "use-and-throw" devices, novel assay technologies and "green" materials.

2. Materials for Disposable Sensors

Despite the recent advances in material science, it is still not possible to produce a single one-size-fits-all material that meet all of the requirements of disposable sensors because of their wide range of applications. Hence, the ultimate material for disposable sensing devices does not exist beside a specific application or a certain type of sensor. For example, cellulose-based nonwoven materials, such as paper, offer a simple and low-cost solution for on-site testing applications. They are, however, not suitable for conformal wearable sensors due to their limited stretchability.

This section gives a short overview of the most common four classes of materials used for the construction of disposable sensors: i) standard materials for micro- and nanoelectromechanical systems (MEMS—also known as microsystems technology and NEMS), ii) synthetic polymers, iii) cellulose-based, and iv) hybrid materials. We focus on sustainability (recyclable, biodegradable, or even compostable),[12,13] fields of application, flexibility, cost, and other material properties (stretchability, transparency, etc.). A summary of advantages and limitations of some of the most important materials for disposable sensors is presented in **Table 1**.

2.1. Standard Materials for MEMS/NEMS

Thanks to high-precision semiconductor manufacturing technologies (originally developed for microelectronics), MEMS sensors, such as gyroscopes, accelerometers, pressure sensors, chemo- and biosensors, can now be produced on a large scale and at low cost. The current trend in miniaturization is leading the way for even smaller systems, compared to MEMS, hence the emergence of nanoelectromechanical systems.

Standard materials used in MEMS are silicon, glass (for example, quartz, soda lime, borosilicate), ceramics, and metals, whereas carbon-based materials (such as diamond, carbon nanotubes (CNTs), or graphene) take center stage in fabricating NEMS.[14] They generally have excellent electrical, mechanical, and thermal characteristics. Only glass, however, exhibits outstanding optical transparency.

In comparison with other materials for disposable sensors, standard MEMS/NEMS materials are costlier and more complex to process; manufacturing typically requires cleanroom facilities, expensive process equipment, and hazardous chemicals. These materials are also limited regarding their flexibility and stretchability. Cost barriers, however, can be overcome through increased volumes by producing smaller devices on larger substrates. For instance, 300 mm Si wafers have become an industry standard and 450 mm may be introduced in the

Table 1. A brief overview of advantages and limitations of different materials for disposable sensors.

	Cost	Recyclable	Biodegradable	Transparency	Flexibility	Stretchability
Standard MEMS/NEMS materials						
Silicon	○○○	●●	○	○○○	○	○○○
Glass	○	●●	○○○	●●●	○○○	○○○
Ceramics	○○○	●●	●	○○○	○○○	○○○
Synthetic polymers						
Elastomers						
PDMS	●●	●●●	●●●	●●●	●●●	●●●
Thermosets						
SU-8	○○○	○○○	○○○	●●	●	○○
PET	●●	●●	○○○	●●●	●●●	●●
PI	●	●●	●	●	●●●	○○○
Plastics						
PMMA	●●	●●	●●	●●●	●	○○○
PS	●	●●	○○○	●●●	●	○
PTFE	○○○	○○○	○○○	○○○	○○○	●●
Cellulose-based materials						
Paper	●●●	●●●	●●●	○	●●●	○○○
Nanocellulose	●●	●●●	●●●	●●	●●●	○○○
Cellophane	●●●	●●●	●●●	●●●	●●	●
Nitrocellulose	●	●●●	●	○	●	○○○

coming years. Standard MEMS materials can also be rendered flexible by backside thinning which reduces the thickness of the material. Stretchability can only be achieved by modifying the geometry, such as creating serpentine patterns. Although, historically, application of standard MEMS/NEMS materials to the construction of disposable sensors have been limited, the recent drops in price and improvements in material properties have substantially increased their use in disposable sensing devices.[15]

2.2. Synthetic Polymers

In contrast to standard materials for MEMS/NEMS, synthetic polymers are generally inexpensive and allow both, rapid prototyping and mass production, at low cost. There is also a large selection of polymeric materials available with different properties, such as stretchability, transparency, flexibility, etc. Because of this, they are commonly used in disposable sensors. Synthetic polymers can be classified into three different categories: elastomers, thermosets, and thermoplastics.[16,17]

Elastomers are weakly crosslinked polymers with a rubber-like elasticity that can easily be bent, stretched, or deformed. After the removal of external forces, they revert fully back to their original shape. The most common elastomer employed for disposable sensors—particularly for microfluidics[18] or wearables[19,20]—is poly(dimethylsiloxane) (PDMS) as it is optically transparent, gas permeable, biocompatible, chemically inert, and low cost. The disadvantages of PDMS are nonspecific adsorption of biomolecules and significant swelling in various organic solvents. PDMS-based manufacturing mostly requires a mold which may need to be micromachined (hence expensive). Due to the slow curing process, PDMS is generally considered to be incompatible with mass production. It is used, however, in many academic laboratories for prototyping.

Unlike elastomers, thermosets are stiff polymers, crosslinked irreversibly by heat or light. Once polymerized, they cannot be melted or reshaped. Polyimide (mainly as a flexible substrate) and epoxy-based SU-8 (as insulation or for creating microfluidic structures) are the most common thermosets used in disposable sensors. The benefits of thermosetting materials are their chemical stability, optical transparency and the ability to fabricate free-standing structures with high-aspect ratios. They are, however, expensive (especially SU-8), compared to other polymer-based materials, limiting their application in disposable sensors.

Thermoplastics, on the other hand, are thermosoftening polymers which can be molded and reformed above a specific temperature (i.e., glass transition temperature). They are widely used in the industry for mass production through different replication processes, such as hot embossing or injection molding. Typical thermoplastics employed for disposable sensors include polypropylene (PP), polystyrene (PS), poly(methyl methacrylate) (PMMA), cyclic olefin copolymers (COC), poly(ethylene terephthalate) (PET), and poly(tetrafluoroethylene) (PTFE). In contrast to other polymers, thermoplastics offer a wide range of stiffness and chemical resistance to organic solvents, lower gas impermeability, and reduced biofouling. These favor thermoplastics as a substrate material for disposable sensing devices, except for wearables.

2.3. Cellulose-Based Materials

Cellulose is a sustainable biopolymer that is used in umpteen industrial applications. Cellulose fibers have been produced and used in papermaking for over two millennia to create cellulose paper (or simply paper). Paper is an attractive material for disposable sensors owing to its following properties: i) paper is inexpensive, available in a wide variety of compositions, and ii) lightweight, flexible and biodegradable. iii) It is compatible with low-cost methods of fabrication like printing. iv) Paper supports fabrication of microfluidic structures, v) can be folded into 3D shapes (origami), stacked, and vi) allows integration of different functions (such as electronics) into a single device.[21,22]

Lateral flow assays (LFAs) for home pregnancy or fertility testing, that use nitrocellulose membranes as functional material, are by far the best examples of commercially available disposable sensors for point-of-care testing (POCT).[23] Traditional paper-based systems have, however, functional limitations for handling liquids: mixing, splitting, and separation are not easily achievable. The last 10 years have witnessed tremendous growth in the development of more-integrated paper-based disposable sensors as a result of invention of paper microfluidics.[24] Unlike other paper-based approaches, microfluidic paper-based analytical devices (μPADs) allow easy implementation of integrated fluidic operations, enabling multianalyte detection with improved performance. μPADs also cannot fully meet the needs of all disposable sensing applications, especially in terms of sensitivity.[10] To improve their analytical performance, nanomaterials, including various nanoparticles[25–28] or graphene nanomaterials,[29,30] or biodegradable coatings (for example, using biopolymers such as chitosan[31]) can be introduced to μPADs; however, this is a topic of on-going research.

In addition to cellulose and nitrocellulose papers (both varieties are opaque, and nitrocellulose is brittle), there is a large selection of other low-cost cellulose-based materials. The most notable examples are cellophane, nanocellulose-based materials, and cellulose-based woven textiles: i) cellophane is a thin, biodegradable, and transparent film made out of regenerated cellulose from wood, cotton, or other sources. It is primarily used as an environmentally friendly packaging material in food industry. Cellophane can be employed as substrate for the low-cost and scalable fabrication of disposable sensing devices (even with integrated microfluidics produced by hot embossing[32]). ii) Nanocellulose can be made of cellulose nanofibers, nanocrystalline cellulose, or bacterial nanocellulose. These materials may easily be formed into films, hydrogels, or aerogels with tunable porosity, hydrophilicity, flexibility and transparency, and can serve as a biodegradable substrate or sensing element in disposable sensors.[33,34] The flexibility of wood-based nanocellulose materials can also be increased by the partial removal of lignin/hemicellulose using a simple one-step chemical treatment. This process produces a 3D porous material with aligned cellulose nanofibers resulting in superflexible wood membranes which may be used in disposable sensing devices (especially, in wearables) requiring breathable and highly flexible materials.[35] iii) Cellulose-based fibers can be woven into textiles which can be used as a disposable substrate for emerging wearable sensors.[36–38] In contrast to paper, textiles can be more durable and yet flexible. High-speed

embroidery and other industrial methods facilitate mass-production of disposable devices using textiles that can be seamlessly worn over the body.

2.4. Hybrid Material Systems

To overcome the shortcomings of using a single material, in most cases, "hybrid" materials (i.e., multicomponent materials) are used to construct disposable sensors at lower costs with better performance compared to single material approaches.[17,39,40] The most common hybrids contain multiple materials[41] that combine a specific polymer with standard MEMS/NEMS materials,[18] paper,[42–44] or other polymers.[39,45,46]

In summary, the golden rules for choosing materials for disposable sensors can be outlined as follows: i) identify the real measurand (either a physical quantity or the concentration of an analyte); ii) choose a technique for signal detection; iii) summarize all requirements of the sensing application (for example, flexibility—important for wearables, transparency for optical readout, integrated electronics or microfluidics); iv) outline the features of all possible materials and fabrication technologies; and finally v) choose the best material for the final use, or, in the case of hybrid material systems, combine different materials to meet the specifications by eliminating the disadvantages of individual materials.

3. Signal Detection Techniques for Disposable Sensors

Disposable sensors commonly employ one or more of the following six methods for signal transduction: i) optical, ii) electrochemical, iii) mechanical, iv) magnetic, v) thermometric, and vi) microgravimetric. The electrochemical and optical techniques are the most frequently used and most sensitive ones for chemo- and biosensors, whereas the mechanical and thermometric methods play an important role in physical sensing. In this section, we briefly discuss the underlying principles of signal detection for disposable sensors. The most important sensor characteristics (accuracy, precision, selectivity, sensitivity, drift, and response time) are summarized in **Table 2**.[47,48]

3.1. Optical Methods

In optical sensors, the measurand either produces, directly or through a recognition process (for example, the formation of an antibody-antigen complex), an optical signal (color, fluorescence, or chemiluminescence), or causes a change in the optical properties of the environment (**Figure 2**). The optical signal produced may be observed by the naked eye or measured by a photodetector. Photodetectors (devices that convert optical signals into measurable electrical signals) are categorized into thermal (thermopiles) and photon detectors (photodiodes or photomultipliers).[49,50]

Optical methods have two main drawbacks: i) susceptibility to environmental interference (except electromagnetic), including the degradation of photoactive molecules due to photobleaching, etc., and ii) use of fragile (and at times expensive) optics that require careful handling. Advantages of optical techniques, however, outweigh the disadvantages; they are fast, sensitive, reliable, (mostly) nondestructive, and allow multiplexing. Optical methods are, therefore, increasingly used for disposable sensors, especially in combination with smartphones. Moreover, principles for optical detection like surface plasmon resonance (SPR)[51] or localized SPR[52,53] and surface-enhanced Raman spectroscopy (SERS)[54,55] also provide a method of label-free chemical and biological sensing.[56] The most important functional materials for optical sensing include dyes, gold and silver nanoparticles, quantum dots, photonic crystals and graphene nanomaterials.[57]

3.2. Electrochemical Methods

Similar to optical techniques, in electrochemical sensing, the analyte generates directly (electroactive species) or indirectly (via a biorecognition event or mediated enzyme electrodes[58]) an electrical signal proportional to its concentration (**Figure 3**). The most important electrochemical techniques are potentiometry, amperometry, voltammetry, impedance spectroscopy and conductometry.[59,60] While electrochemical chemo- and biosensors mainly require high-conductivity liquid electrolytes containing ions, solid electrolytes, such as yttria-stabilized zirconia, can be used in (potentiometric) gas sensors.

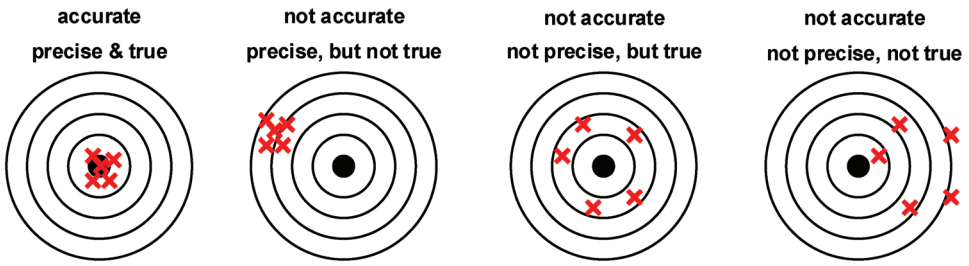
Potentiometry measures the changes in the open-circuit potential between two electrodes (working and reference) at equilibrium (no current flow), caused by the analyte in a concentration dependent manner. Amperometry and voltammetry, however, are dynamic techniques, which usually employ a third (auxiliary) electrode in a potentiostatic system to set the desired voltage at the sensing (working) electrode independent of the voltage drop across the solution. In amperometry, the current, arising from the oxidation or reduction of electroactive molecules, is measured at a constant (single-potential amperometry) or stepped potential over time (chronoamperometry). Voltammetry involves gauging the current during a potential sweep that can be linear, cyclic, or combined with pulses (for example, differential pulse or square wave voltammetry). In impedance spectroscopy, a sinusoidal potential over a frequency range is applied to the electrochemical cell. By measuring the current response, the resistance and capacitance of the system can be estimated, allowing the study of the surface and material properties. In conductometry, the resistance of an electrolyte is gauged by use of an alternating potential.

3.2.1. Electrode Materials

The choice of material for the working electrode is one of the most important factors when designing an electrochemical sensor. The electrodes must be suitable for the application (for instance, chemically resistant to the sample) and perform within specifications, such as sensitivity, selectivity, or long-term stability. Commonly used electrode materials for the fabrication of disposable sensors include i) inert metals[59]

Table 2. Important characteristics of sensors.

Accuracy		
The closeness (*precision and trueness*) of the sensor's output compared to the real value of a measurand. To determine the accuracy, the sensing system should be either tested with a standard measurand (with a known value), or its reading must be checked against a benchmark system with very high accuracy.		
Precision		Trueness
A measure of statistical variability (*random error*) which can be assessed by the standard deviation. Within precision, two terms can be differentiated:		The closeness of the average results of a sensor to the real value of a measurand (*systematic error*).
Repeatability	Reproducibility	
The degree of agreement between independent measurements taken under the identical conditions (same operator, instrumentation, material/analyte, and in a short-time interval).	The level of agreement when the measurements are conducted under various conditions (different operators, instrumentation, materials/analytes and in long-time interval).	



Sensitivity		Selectivity
The ratio of the change in the output signal of a sensor (Δy) to the variation of the measured quantity (Δx). This rate is either constant (linear) or vary (nonlinear) over the whole range of measurement.		The capability of a sensor to gauge a measurand in the presence of other interferences.
Limit of detection (LOD)	Limit of quantification (LOQ)	
The lowest concentration of an analyte which can be measured against a blank sample with reasonable reliability.	The smallest concentration of an analyte that can be determined with acceptable accuracy.	

Drift (*operational stability*)	Stability (*storage*)	Response time
The long-term stability of the sensor's output signal without changing the input. It can be induced by the changes in temperature, humidity, or by the degradation of sensor's transducers or electronics, between others.	The capability of a sensor to generate the same output signal when measuring a standard measurand (with a known value) over a period of time.	The required period of time for the output signal of a sensor to reach a stable value within a certain tolerance if it exposed to a measurand.

(gold, silver, palladium, or platinum); ii) semiconducting metal oxides[61,62] (such as zinc oxide, tin dioxide, and tungsten trioxide for gas sensors, indium tin oxide for transparent electrodes and iridium oxide for pH sensing); and iii) carbon-based materials[63,64] (including glassy carbon, diamond, or ink-based electrodes). In recent years, there has been a drive to create biodegradable and compostable electrodes (for example, using activated charcoal,[65] magnesium,[13,66] or melanin[67]) for different electrochemical applications. When commercially available, this new class of electrodes may reduce the environmental impact and cost of disposable sensing devices.

3.2.2. Modified Electrodes

Electrodes used for electrochemical transduction in disposable sensors can be modified with a range of other materials (for example, nanomaterials or conducting polymers) to enhance their sensing characteristics without increasing their cost substantially. Electrodes modified with metal nanoparticles (e.g., gold and platinum), carbon-based nanomaterials (such as CNTs or graphene), and their hybrid nanocomposites exhibit improved electrical conductivity, specificity or electrocatalytic properties in comparison to bare electrodes.[68,69] Especially in gas sensors, the modification of the surface of the electrodes by metals or metal oxides enhances the sensitivity, response, and recovery times.[62] Moreover, conducting polymers, such as polypyrrole, and polyaniline, can be employed as low-cost coatings to improve stability and electrocatalytic properties of electrodes for disposable sensors.[70]

3.3. Other Methods and Multimodal Analysis

Mechanical sensors (**Figure 4**) detect physical changes due to stress, deflection, or shift of mass caused by the measurand. They are primarily used for measuring physical quantities, such as force,[71,72] acceleration,[73] pressure,[74,75] and flow rate.[76] There are, however, also biosensors that employ mechanical methods for transduction. For instance, microgravimetry, which

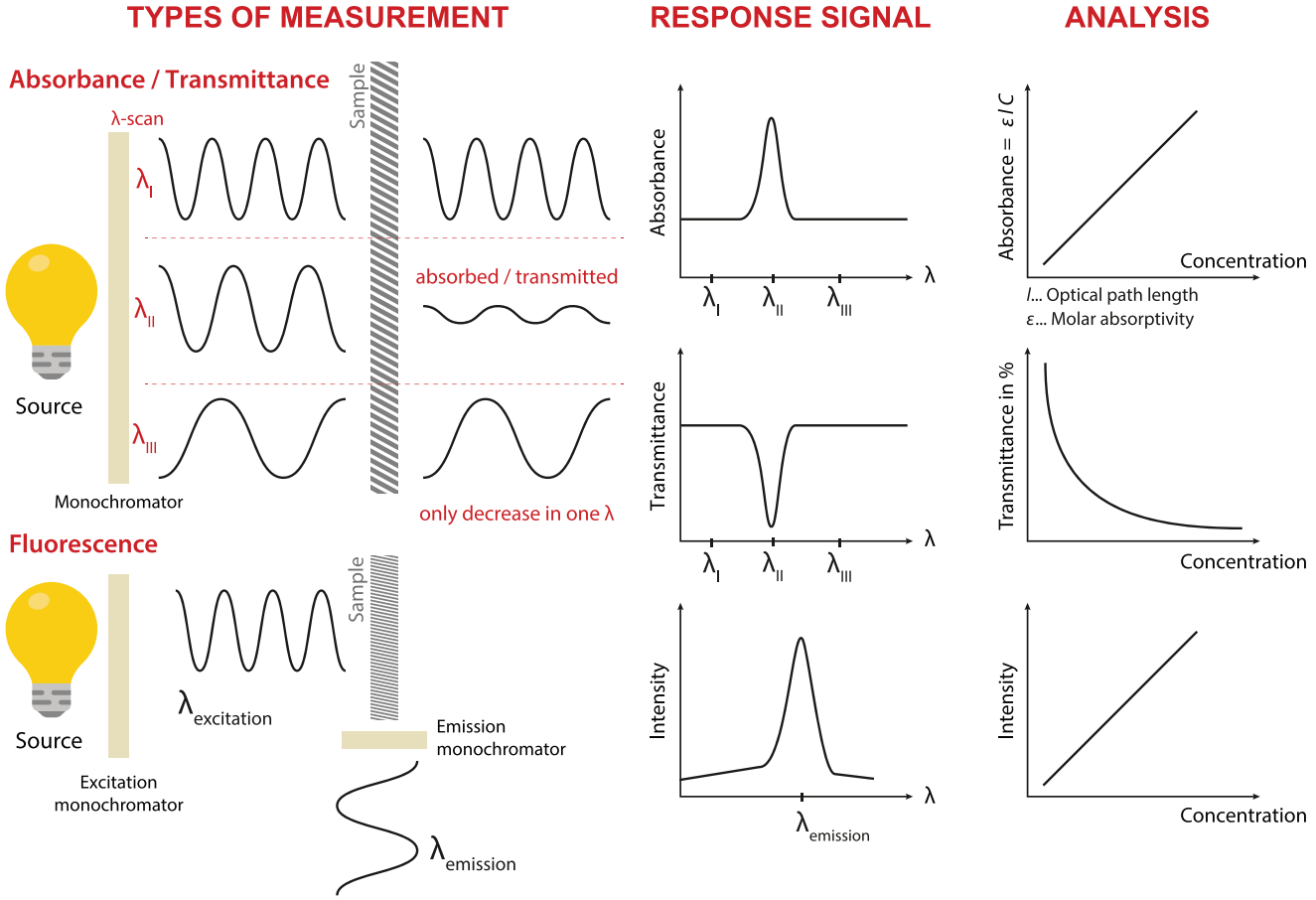


Figure 2. Optical signal transduction. Absorbance/transmission involves passing a beam of light (single or spectrum of wavelengths containing, for example λ_I, λ_{II}, and λ_{III}) through the sample and measuring the amount of light absorbed or transmitted (here, λ_{II}) on the opposite side using an optical detector. Note that in the illustration shown above, λ_I and λ_{III} do not interact with the sample; hence, the intensities of signals do not change. A monochromator can be used to scan (λ-scan) by selecting a specific wavelength from the source. The amount of light absorbed or transmitted varies (λ_{II}) with the concentration of the analyte in the sample. Fluorescence involves excitation of a fluorescent compound with a beam of light. The excited molecule itself then emits light with an energy smaller than the energy of the source ($\lambda_{emission} < \lambda_{excitation}$). The intensity of the emitted light depends on the concentration of the fluorescent compound in the sample.

is used for measuring changes in mass, offers an approach for label-free detection of biomolecules (**Figure 5**). Some notable microgravimetric sensors are quartz crystal microbalance (QCM)[77] and surface acoustic wave (SAW) devices.[78]

Thermometric sensing devices (**Figure 6**) transduce a change in temperature, induced by a measurand (either directly or by an endo/exothermic (bio)chemical reaction) to an electrical signal which may be employed in disposable sensors.[13,79–81] Thermometric sensors include but not limited to thermocouples, resistance thermometers, thermistors and diodes. In contrast, magnetic methods (such as Hall effect or magnetoresistance) are rarely used in the construction of disposable sensing devices (**Figure 7**); however, there is some promising ongoing research in this field.[82–84] For instance, in giant magnetoresistance sensors, binding of magnetic nanoparticles (as reporters of a biological event) onto the surface of a sensor leads to a change in its electrical resistance, enabling rapid and real-time quantification of biomolecules.[85]

As mentioned, there are a set of tradeoffs for each method of detection, therefore, multimodal analysis, comprising at least two modes of detection, is becoming more common.[10] The most frequently used multimodal methods in disposable sensors are based on optical–electrochemical detection.[86,87] By exploiting the strengths of different technologies for sensing, the shortcomings of each method can be overcome. Multimodal analysis offers more information along with enhanced sensitivity, selectivity and reproducibility, at the expense of increased complexity and cost. This may be a limiting factor for their application in disposable sensors (as they are generally low-cost).

4. Recognition Elements, Amplification Methods, and Sensor Integration

The conversion of (bio)chemical information into measurable signals generally involves biomolecular recognition and amplification of the gauged signal to increase selectivity and/or sensitivity. In this section, we describe various recognition elements and sensor modification strategies for signal enhancement. The integration of sensors into disposable fluidic systems, so called lab-on-a-chip devices, is also briefly discussed.

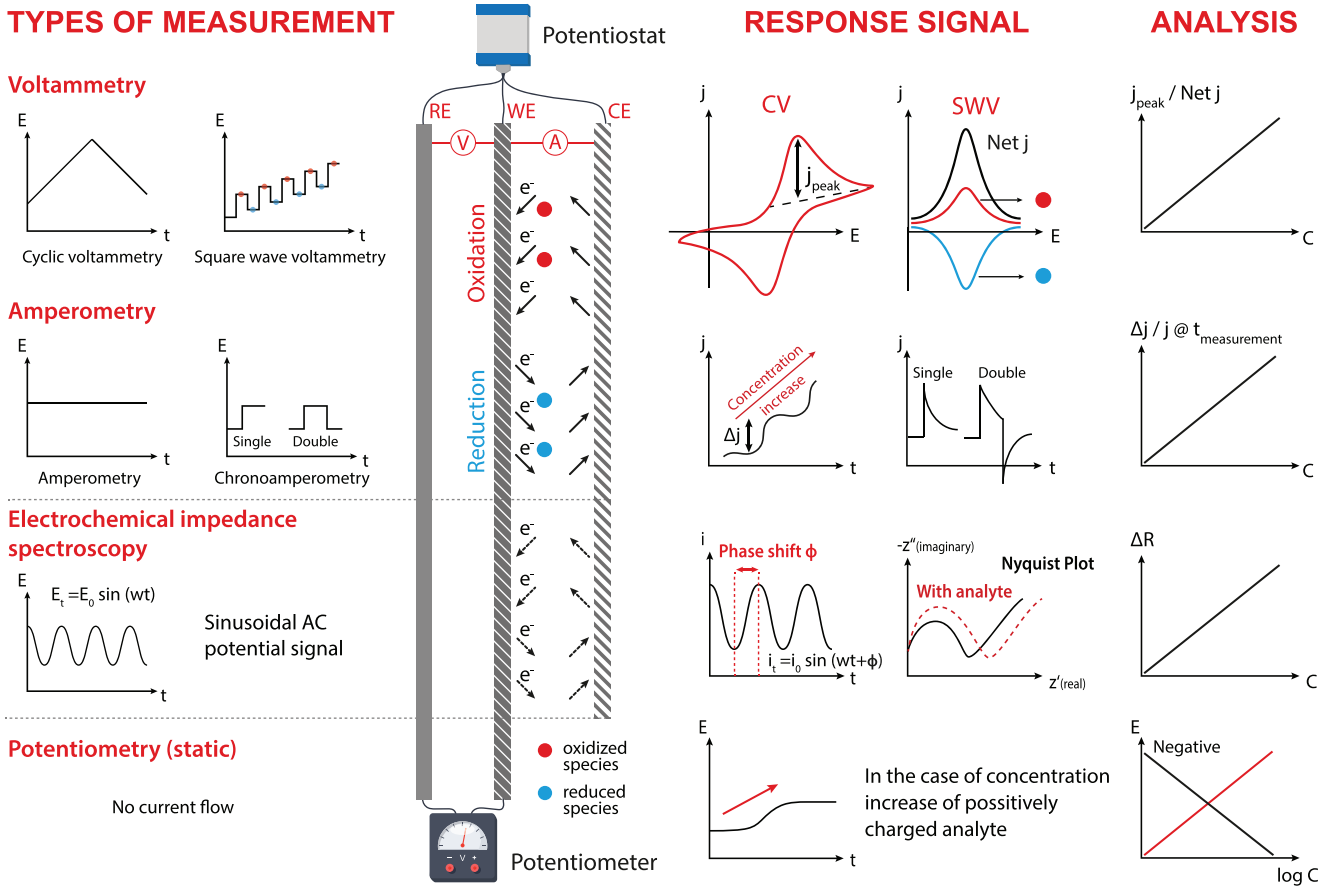


Figure 3. Electrochemical signal transduction. There are four main types of electrochemical methods of analysis: voltammetry, amperometry, electrochemical impedance spectroscopy (EIS), and potentiometry. In voltammetry, a potential sweep (linear, cyclic, i.e., cyclic voltammetry (CV), or pulsed, e.g., square-wave voltammetry (SWV)) with respect to the reference electrode (RE) is applied by a potentiostat (an electronic instrument) between the working (WE) and counter (CE) electrodes and the current generated is measured as the analytical signal. In amperometry, a constant or stepped (chronoamperometry) potential is employed instead. In potentiometry, the open-circuit voltage between the WE and RE is measured as the analytical signal which can increase or decrease depending on concentration of the analyte. In EIS, a sinusoidal potential over a frequency range is applied to an electrochemical cell. By measuring the current response, the impedance (resistance, capacitance etc.) of the system can be estimated, allowing the study of the surface and material properties.

4.1. Recognition Elements

Bioreceptors are recognition elements that have a high binding affinity toward a particular analyte, hence, can be used in disposable sensors. Recognition elements (**Figure 8**) can be either natural, artificial or bioinspired molecules derived synthetically from biology.[88–91] Biomolecular recognition is primarily achieved by noncovalent interactions, including hydrogen bonding, electrostatic, van der Waals forces and hydrophobic interactions. In the presence of a target molecule, recognition elements either undergo a (bio)chemical reaction, producing a measurable signal directly, or they are labeled with signaling molecules, such as enzymes, for signal transduction.

4.1.1. Natural Bioreceptors

Natural recognition elements are molecules that are naturally present in living organisms. They may be isolated directly from living organisms or synthesized in a laboratory. The most frequently used natural bioreceptors in disposable sensors include nucleic acids, enzymes, antibodies, membranes, bacteriophages, organelles, cells, and tissues (for example, living plant tissue for environmental monitoring[88]). In general, natural bioreceptors are highly specific, and inexpensive to produce at small scales, however, for some, large-scale (bulk quantities) manufacturing for industrial use tend to be difficult and costly. The selection of natural bioreceptors against specific analytes (for instance, small molecules, particularly toxic and nonimmunogenic ones) is limited. They generally exhibit high biological variability (from batch-to-batch), low stability (with the exception of few enzymes and nucleic acids), and poor performance under nonphysiological conditions (high/low pH, temperature, and/or in organic solvents).

4.1.2. Artificial Bioreceptors

The translation and application of engineering principles into biology has enabled the design, synthesis and use of artificial

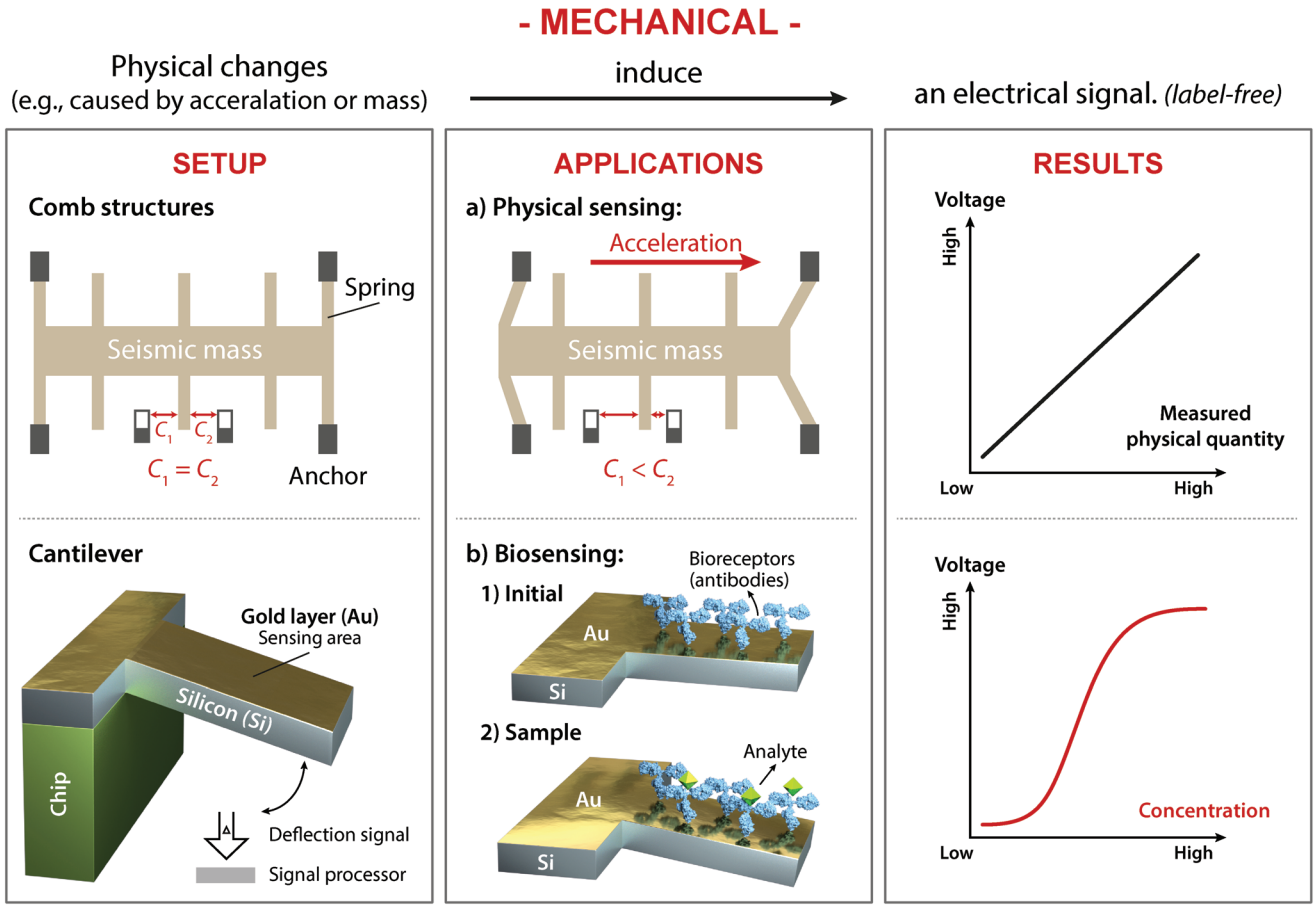


Figure 4. Mechanical signal transduction. Physical changes caused by acceleration or force can be converted to an analytical signal related to the magnitude of the physical quantity measured.

bioreceptors for sensing.[89,91] They can be either full or semi-synthetic and rationally engineered to improve or substitute the natural variants. The most prominent artificial bioreceptors are aptamers, molecularly imprinted polymers (MIPs), supramolecular receptors, synthetic peptides with receptor properties, macrocycles and recombinant (for example, antibody fragments or protein domains), or genetically engineered (for instance, multifunctional molecules such as abzymes—catalytic antibodies) natural biomolecules.[89] In contrast to their natural counterparts, artificial bioreceptors usually offer improved stability and high affinity at a lower cost that render them ideal for disposable sensors. The initial development and capital investment, however, are resource intensive and require specialized personnel.

The basic rules for selecting recognition elements for sensing can be outlined as follows: i) define the target molecule (large entities such as cells and macromolecules or small substances such as drugs and metabolites), ii) outline the requirements of the particular sensing application (like nonphysiological conditions or type of measurement such as single-point or continuous monitoring), iii) summarize the features of all possible recognition elements (for example, enzymes exhibit low sensitivity compared to antibodies, but allow for long-term measurements), and finally, iv) select suitable candidates (for instance, enzymes, antibodies or aptamers for antibiotics) and compare their performance to find the best fit. The following issues, however, must be considered in case of affinity (nonenzymatic) sensors: i) binding strength (affinity) of analyte/bioreceptor complex, ii) selectivity (specificity) by determining "cross-reactivity" with structurally similar compounds, iii) influence of nontarget substances "matrix effect" in complex matrices (such as whole blood or plasma), and iv) stability and storage conditions.[92] For disposable sensors, another obvious criterion is the cost which must be taken into account when choosing bioreceptors.

4.2. Signal Amplification Strategies

4.2.1. Modification with Micro- and Nanomaterials

In the past few decades, micro- and nanomaterials have been increasingly used to enhance signal transduction in (bio) chemical sensing as part of simple or complicated hybrid architectures. Depending on the need and type of sensor, these materials can be biological, synthetic or hybrids, and may have varying compositions (such as organic and inorganic; carbon, metal, alloys, or composites), dimensions

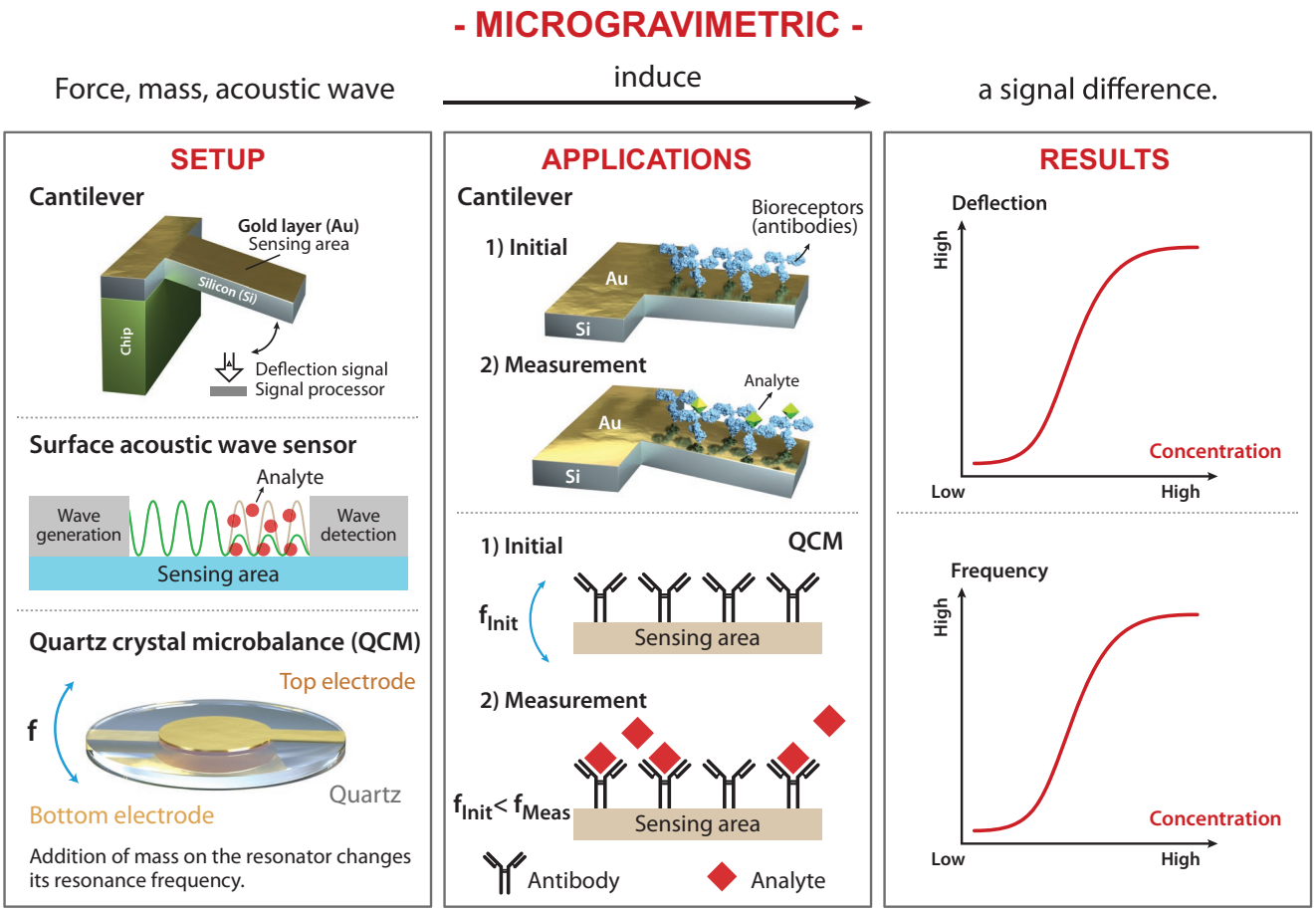


Figure 5. Micrograviметric signal transduction is a subclass of mechanical methods of transduction, however, due to its high sensitivity, micrograviметric methods are particularly suited for applications in label-free (bio)chemical sensing in disposable sensors. For example, increased mass due to captured analytes can bend a cantilever or shift the resonant frequency of a quartz crystal microbalance (QCM), producing an analytical signal. Surface acoustic wave type micrograviметric sensors can also detect analytes captured on a surface of a disposable sensor.

(nano or micro), and shapes (such as prisms, spheres, onions, flowers, etc.).[34,93–95]

"Traditional" metal nanoparticles (such as gold nanoparticles or quantum dots), carbon structures (such as CNTs or graphene) and other state-of-the-art micro/nanostructures are used for signal amplification as i) carriers of bioreagents (by decreasing the diffusion path of the target molecules and increasing the binding sites in bead-based systems[10]), ii) bulk and surface modifiers (for instance, by increasing the selectivity of sensors or favoring electron transfer in electrochemical sensors[96]), iii) labels in bioassays (such as magnetic nanoparticles[97] or fluorescent quantum dots[98,99]), and iv) tools for enhancing the signal generating events, simply by a chemical reaction (for example, reduction of silver ions on gold nanoparticles), or for increasing the number of signaling components (such as beads, micro/nanoparticles or nanovesicles with labels). The underlying mechanisms of different applications using micro- and nanostructures are depicted in **Figure 9**.

Micro/nanovesicles are excellent carriers not only of bioreagents but also detectable molecules (even nanomaterials) that enable signal amplification.[100,101] The implementation of multiple functions into single micro/nanostructure (for example multifunctional nanoparticles[95] or hybrid structures[93,102,103]) is, however, a big challenge.

The main drawbacks of micro- and nanomaterials are their complex synthesis and tendency to agglomerate in solution. They are, however, mostly inexpensive, easy to modify, and simple to integrate into various systems. Although these advantages strongly promote their use in the construction of disposable sensors, most of these devices have not yet transitioned from academia to commercial applications.

4.2.2. Addition of Membranes

Membranes constitute an important component of (bio) chemical sensors and can be classified into synthetic (polymeric or ceramic) or biological/natural (for example, eggshell and cell membranes) variants. In addition to being a protective layer, they can enhance the measured signals. Membranes can block interfering species by either ionic exchange (for example, Nafion[104]), electrical charge (by conducting polymers like PEDOT[105]) or size exclusion (using nanoporous alumina[106] or electropolymers[107]), and/or improve sensor functionalization with recognition elements

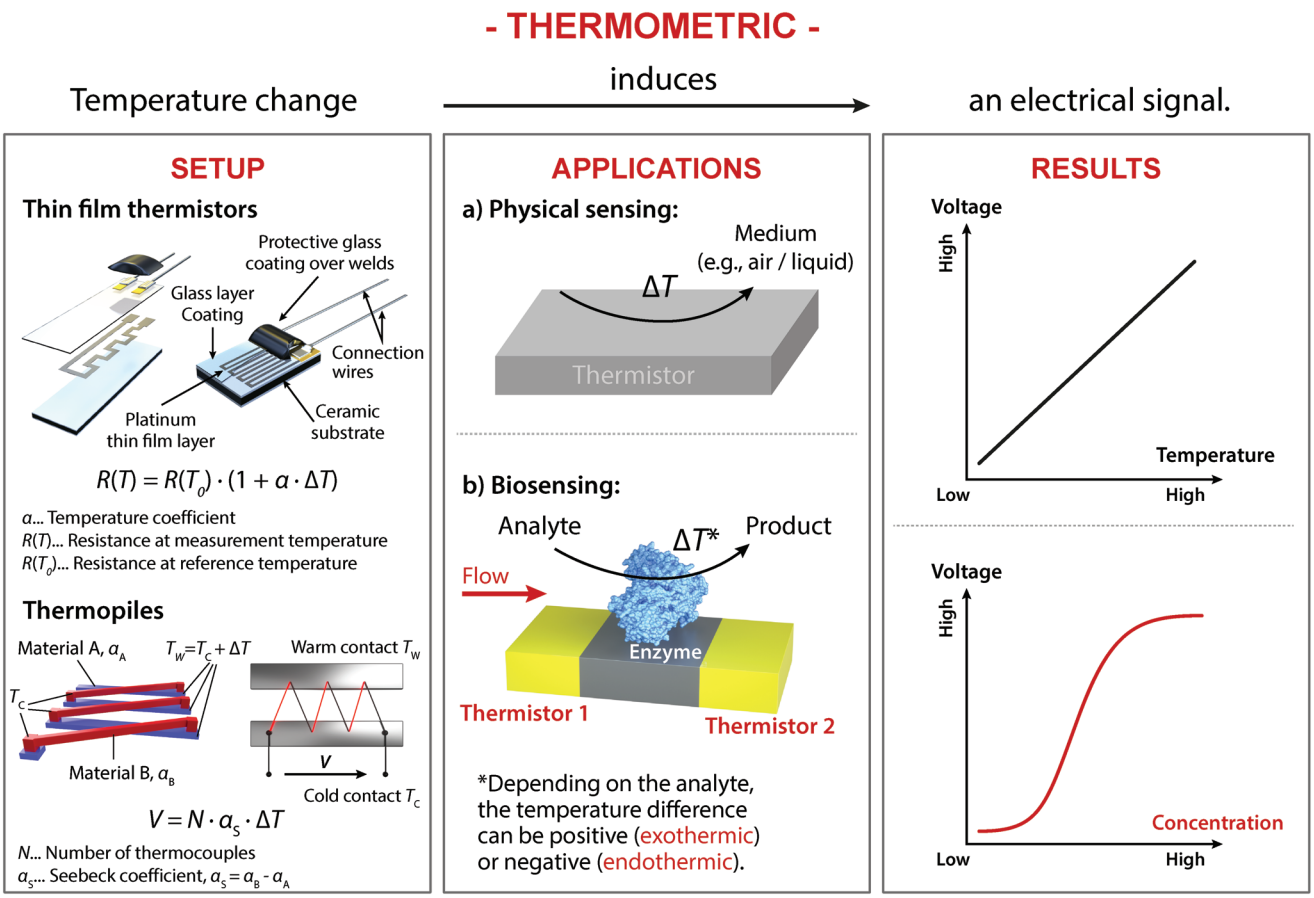


Figure 6. Thermometric signal transduction in disposable sensors. A temperature change caused by (a) the medium (such as gas or liquid) or (b) a target (bio)chemical substance (for example, a chemical reaction catalyzed by an enzyme for a certain substrate) produces an analytical (electrical) signal. Two notable examples are thin film thermistors (temperature-dependent resistors), and thermopiles. Thermopiles consist of a number of thermocouples, which generate a temperature-dependent voltage due to the thermoelectric effect (for example, Seebeck effect).

or nanomaterials[108] (such as molecularly imprinted membranes,[106] or layer-by-layer assemblies of membranes/films[109]). Natural membranes can be used as templates for the synthesis of nanostructures,[110] or as biorecognition elements. For instance, a cell membrane containing glucose transporter-1 has recently been reported for highly selective detection of glucose.[111] As membranes are easy to produce and offer various functions at low cost, they are used frequently in disposable sensors.

4.3. Integration into Fluidic Systems: Lab-on-a-Chip

For many analytical applications, sensing alone is not enough; this is especially the case for samples involving liquids. Most methods of analysis require sample preparation, comprising: sampling, pretreatment, dilution or enrichment in addition to signal detection and evaluation. In 1990, the idea of a microchemical total analysis system (μTAS) was presented which aimed at integrating one or several laboratory functions on a single miniaturized microfluidic chip.[112] Later, the term "lab-on-a-chip" was introduced to generalize all research involving miniaturization of (bio)chemical testing using disposable devices. The application of microfluidics in LOC devices has many advantages, some of which are i) cost-effective fabrication, ii) low sample/reagent consumption, iii) short analysis times, and iv) ability of integration, automatization and parallelization of different functions, and multiplexing (measurement of several analytes) at the same time.[10,113,114]

5. Fields of Application

5.1. Diagnostics

Until recently, diagnostic testing, consisting of preanalytics, analytics, and postanalytics, has been largely performed in dedicated central laboratories. This is capital-intensive as it requires numerous steps for sample preparation, large analyzers and specialized personnel. The samples from the patients are taken in the clinic or at the doctor's office and sent to a central facility for examination; it may take several days before the results are available, delaying any form of potentially life-saving intervention. Often a second appointment is also necessary to discuss the results, which is inconvenient, particularly for individuals

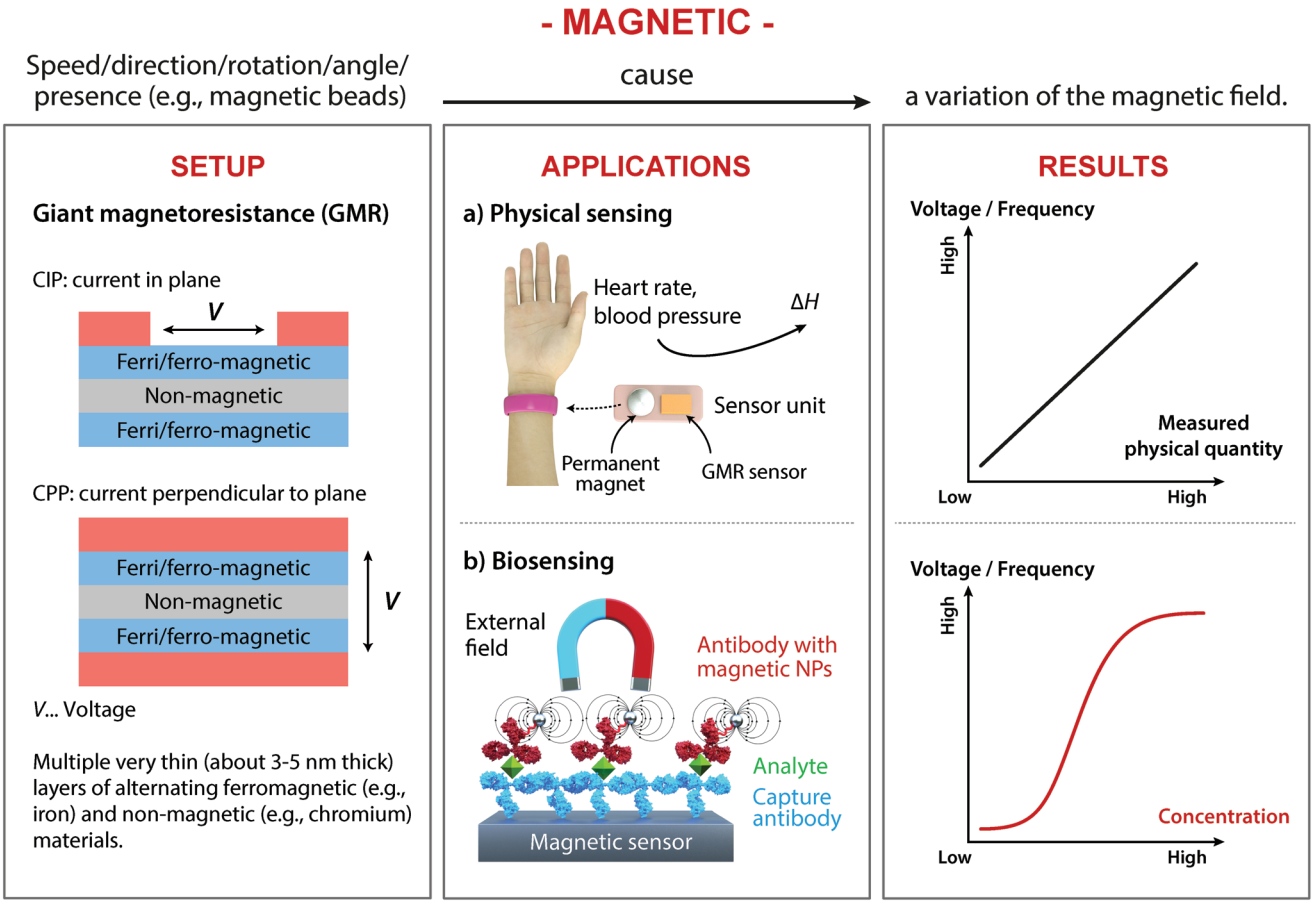


Figure 7. Magnetic signal transduction. A variation in the magnetic field caused by speed, direction, rotation, angle, or the presence of magnetic particles (like beads) results in an electrical signal, providing information concerning the magnitude or concentration of the analyte. One of the most promising examples using magnetic signal transduction is the giant magnetoresistance (GMR) sensor. GMR sensors can be built using multiple thin films of ferro- and non-magnetic materials, and in two different designs where the current can flow either in plane or perpendicular. GMR sensors can be applied to: a) physical (heart rate, blood pressure), or b) biological (detection of biomarkers) sensing.

living in rural communities. An emerging trend in the field of diagnostics is to shift the analysis from central laboratories to the point of need or the point of care (POC). In this scenario, healthcare professionals, or patients themselves, use (generally) disposable devices, based on paper, plastic, glass, etc. (in the future, these may be extended to wearable tattoos, patches, or contact lenses) to analyze samples of various human body fluids. The testing is often completed within minutes, resulting in faster follow-up treatments. Especially for acute diseases, such as myocardial infarction, fast diagnosis with a prompt treatment is vital.

5.1.1. Point-of-Care Testing

To achieve wide adoption, POCT devices have to meet the following four criteria. They must: i) be highly sensitive, in accordance with international quality standards (EU Directive 98/79/EC or FDA regulations); ii) have short sample-to-result times to accelerate intervention; iii) be inexpensive, accessible; and iv) easy to use, i.e., trivial sample-to-answer operation, allowing healthcare professionals or minimally trained users to perform the test. The last point is probably the most important one that determines the success of their adoption. For instance, the two most successful and widely employed POCT devices are the colorimetric (instrument-free) home pregnancy tests and electrochemical glucose test strips.[115] Both of these tests are extremely simple to use and practically need no sample preparation. The user does not need to mix reagents or perform washing steps. The ultimate disposable POCT system should, therefore, either automate sample preparation or require none. It is, however, not always possible to avoid sample preparation. For this purpose, microfluidic lab-on-a-chip technologies provide an attractive solution as they aim to automate and miniaturize different laboratory methods into portable, compact, standalone and disposable systems. Hence, most POCT systems (**Figure 10**) have a disposable microfluidic sample unit (such as cartridges, test strips, or centrifugal disks) and a high-precision reader (such as a handheld or benchtop analyzer) for on-site analysis. Once again, the razor/razorblade business strategy is usually used by the suppliers of these tests.

Next to home pregnancy and glucose test strips, hematology and cardiovascular diagnostics are probably some of the most

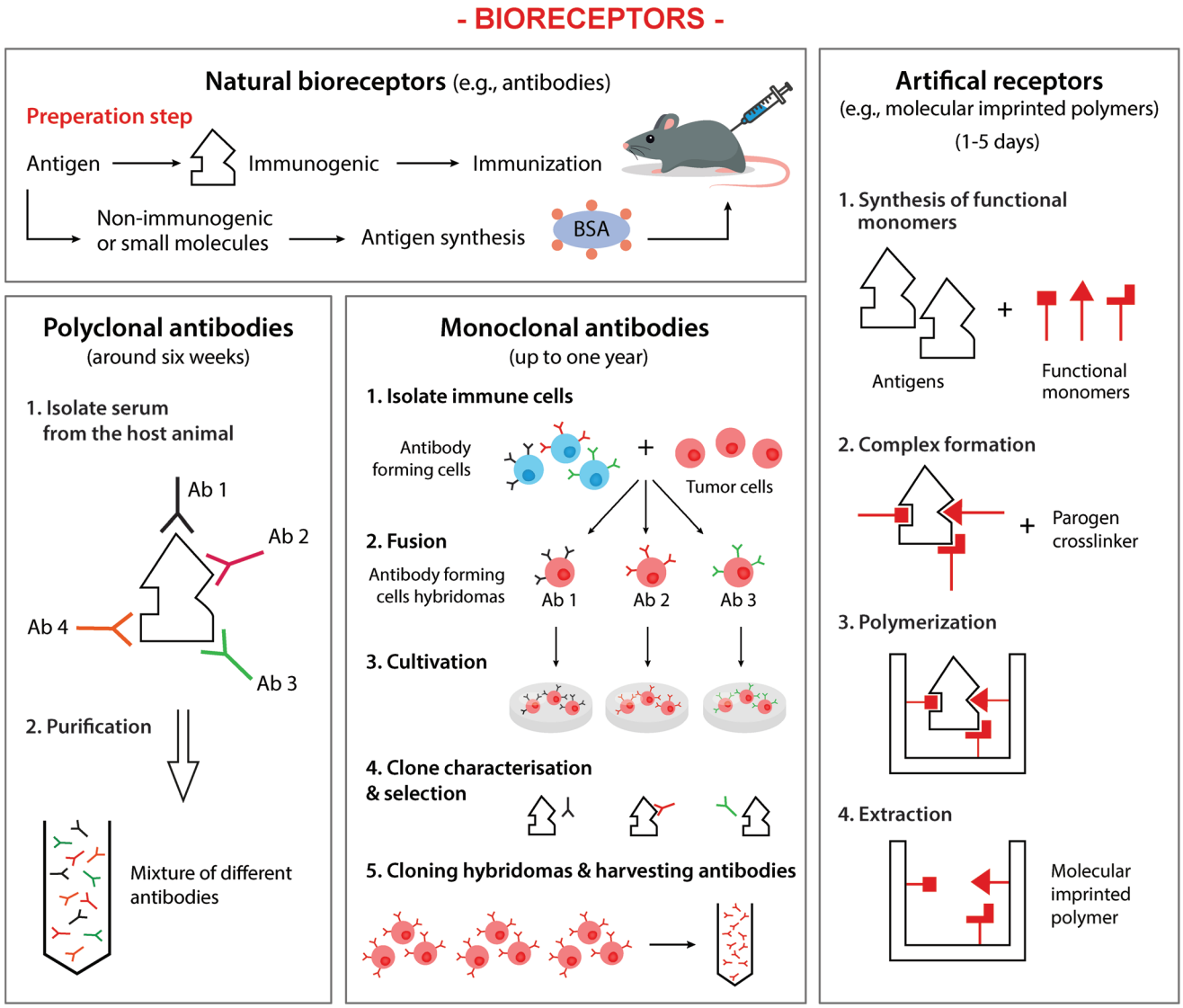


Figure 8. Schematics of the production of natural and artificial recognition elements illustrated on the example of antibodies and molecular imprinted polymers.

common POCT devices available on the market today. These tests rely heavily on disposable sensing elements and have recently received substantial commercial attention due to their importance in critical care, where fast (compared to centralized testing), and accurate diagnosis are required. The iStat (Abbott Laboratories), cobas h 232 (Roche), AQT90 FLEX (Radiometer), and LABGEO IB10 (Samsung) are capable of detecting various markers of cardiac injury on-site, notably myoglobin and creatine kinase muscle and brain (CK-MB), using cartridges, test strips or centrifugal discs as disposable sampling elements. The Afinion (Alere) and the spinit (biosurfit) can sense, among others, CRP (C-reactive protein), HbA1c (glycated hemoglobin) and cholesterol, by using a benchtop analyzer, based on single-use cartridges or centrifugal disks, respectively. Another system from Alere (DDS2) employs a small test panel and a handheld analyzer to detect drugs of abuse in oral samples such as cocaine, tetrahydrocannabinol, and amphetamine. Disposable sample units are generally made from low-cost materials such as polymers (for example, COC, PMMA, and PP) for centrifugal disks, paper for test strips or a combination of these materials for cartridges. The main features of current commercial POCT systems are summarized in **Table 3**.

POCT devices available on the market can detect, however, only a fraction of major clinical markers and are mainly limited by their multiplexing capability. Furthermore, most of them are too expensive and difficult to use to allow personal health monitoring on a daily basis. An emerging trend to overcome this challenge is the smartphone-assisted diagnostics.[116–118] Smartphones are becoming ubiquitous across the planet including the poorest regions in Africa. Almost all smartphones are equipped with cameras, powerful microprocessors and short/long range highspeed wireless communications capabilities (3G/4G, Wi-Fi, Bluetooth). In combination with disposable sensors, smartphones have provided internet-enabled affordable

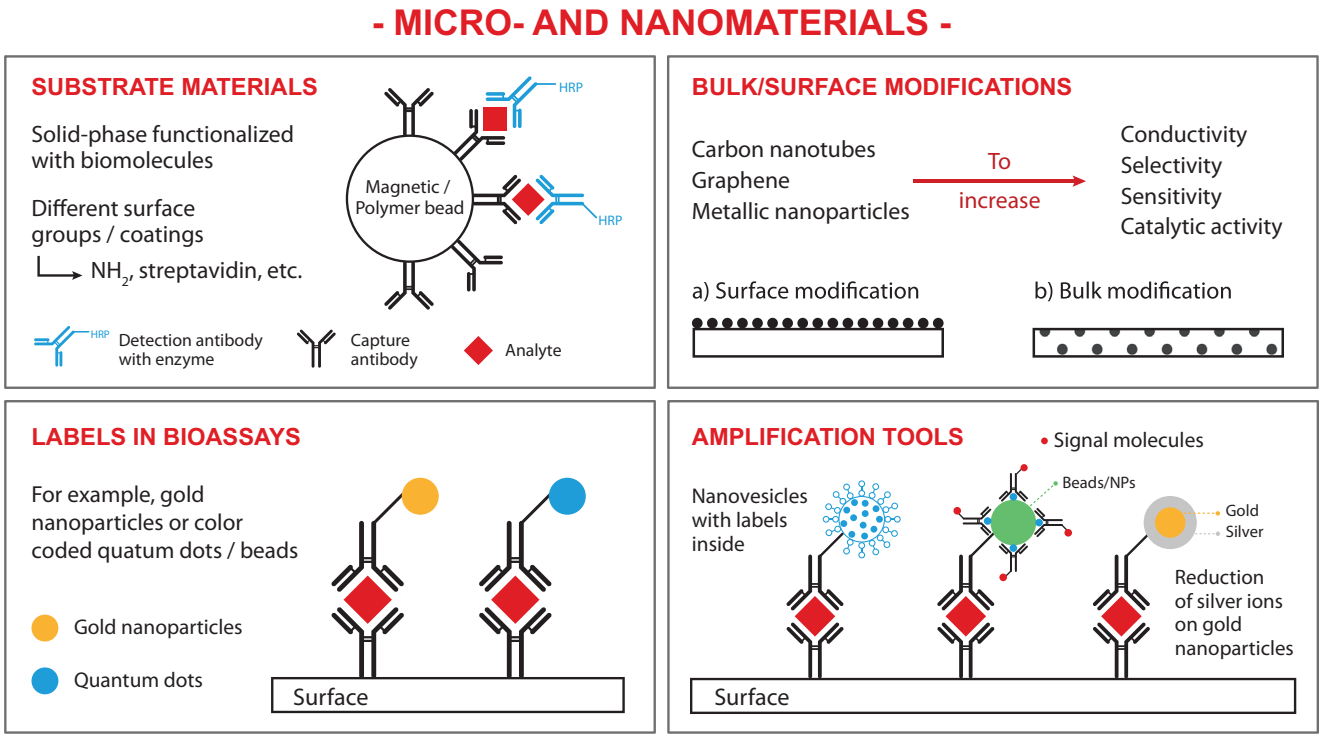


Figure 9. Overview of micro- and nanomaterials with respect to their use for signal amplification as substrate materials, labels in bioassays, and bulk/surface modifiers and tools for enhancing the signal generating events and signaling components.

testing capabilities to remote regions that had little or no access to diagnostics 10 years ago. Interestingly, free Internet services like Internet.org (a Facebook-led initiative) can even be accessed in many African and other countries (in Asia and Latin America) without a data plan which may further drive Internet-enabled diagnostics. For example, among others,[51,119–126] the imaging capabilities of smartphones have been exploited for the analysis of semen,[127] iron concentration in blood[128] or even amplification and fluorescent detection of genetic materials from viruses[129] using disposable sampling and sensing elements. The detection capabilities of smartphones can also be extended beyond just imaging. Inexpensive plug-and-play electrochemical analyzers for smartphones have already been implemented for use with disposable sensors, which can be battery-powered[130] or harvest their energy[131,132] from the smartphone without the need for additional sources of power. They can also communicate the results of electrochemical measurements over a wireless[130,133] or wired link[131,132] to both the immediate or remote user. In the coming years, it is almost certain that smartphones combined with disposable sensors will take center-stage in point-of-care testing.

To improve accessibility, reduce costs and complexity, paper (both cellulose paper and nitrocellulose membranes) has been extensively used for implementing disposable POCT devices. Paper-based systems are low-cost, relatively easy to fabricate, simple to operate and support multiplexed point-of-care testing (xPOCT).[10,134] Paper can also be incinerated at the point-of-use eliminating the potential spread of biological and chemical contaminants. Especially, since the introduction of µPADs in 2007,[24] a large number of µPADs for on-site diagnostics have been reported.[22] Paper-based detection can be colorimetric and may require no instrumentation for operation (signal readout by the naked eye[31,135–139]), which in turns reduces overall cost and complexity at the expense of sensitivity. The sensitivity, however, can be improved by the use of additional instruments, such as cameras (including smartphones), flatbed scanners (in the case of colorimetric detection)[140–142] or potentiostats (for electrochemical µPADs).[69,143] An interesting characteristic of paper is that it can be folded into 3D geometries using origami techniques. By folding into various shapes and forms, reagent handling[144] can be simplified; even self-powered, fuel-cell-type[145] disposable sensors may be created inexpensively.

It is unfortunately not simple to implement every bioassay using paper alone; the use of paper is generally limited to applications compatible with open-channel microfluidics. Materials, such as glass,[146] PDMS,[147] PS,[148] and others,[44,45,149] have also been used extensively in constructing disposable sensors. These materials can generally be transformed into functional, single-use microfluidic POCT sensors through microfabrication or molding/replication methods and are used for on-site detection of various analytes including antibiotics[150,151] or other substances.[152–154] Furthermore, similar to µPADs, it is possible to multiplex different assays into a miniaturized single LOC device using fluidic pumps (such as syringe, peristaltic or piezoelectric) for POC diagnostics.[10,155]

Undoubtedly, in the near future, a wider variety of disposable POC sensors (with more functions at a lower price-tag) will be available on the market.[156] To develop fully integrated, standalone disposable diagnostics, however, significant challenges must be overcome. The elimination of additional

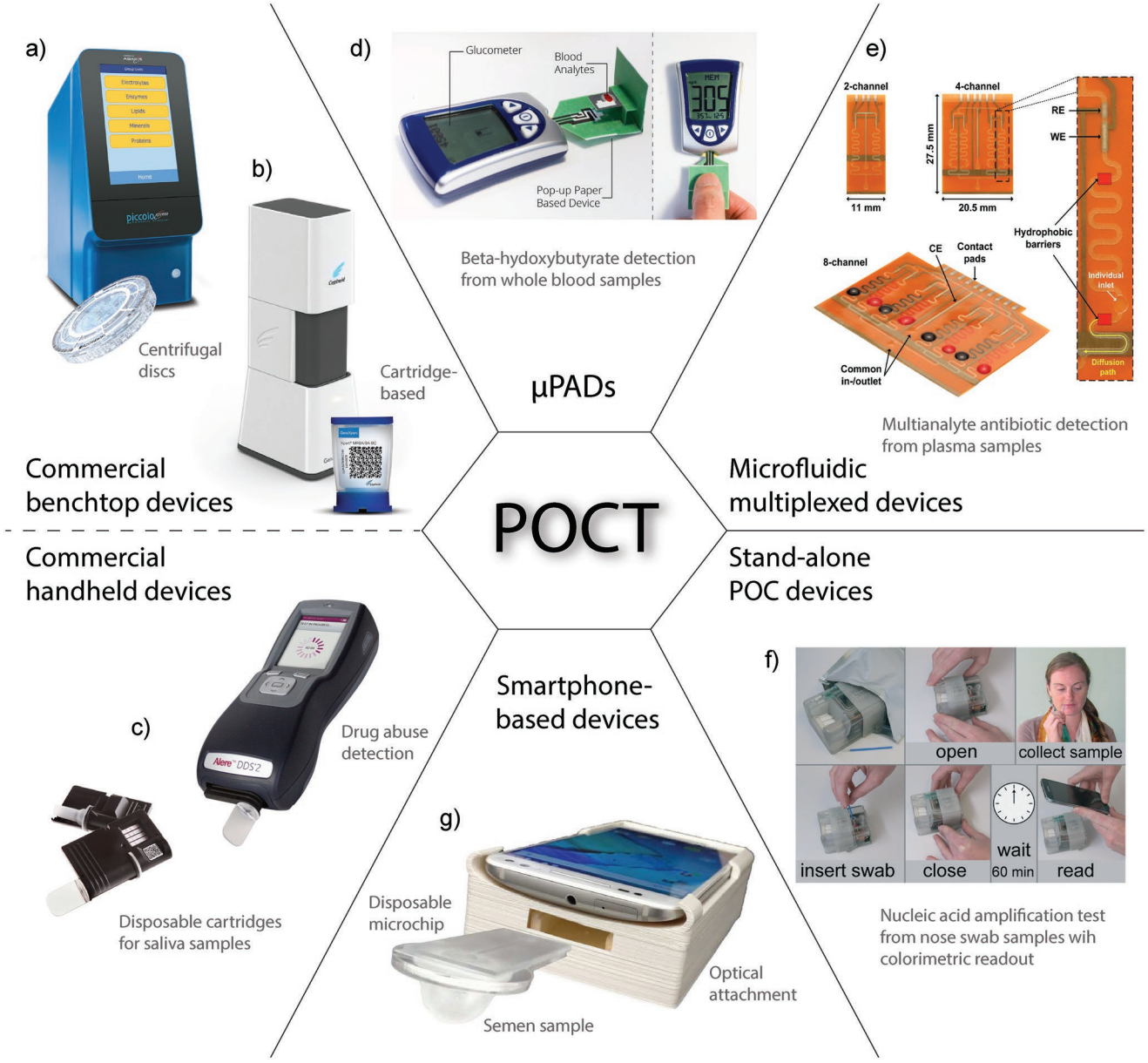


Figure 10. Overview of POCT devices. Commercial benchtop devices: a) Piccolo Xpress. Reproduced with permission. Copyright 2018, Abaxis. b) GeneXpert Omni. Reproduced with permission. Copyright 2018, Cepheid. Commercial handheld devices: c) Alere DDS2. Reproduced with permission. Copyright 2018, Abbott. POCT devices in research stage: d) paper-based "pop-up" device. Reproduced with permission.[144] Copyright 2016, American Chemical Society. e) Electrochemical microfluidic multiplexed biosensor for multianalyte antibiotic detection. Reproduced with permission.[151] Copyright 2016, American Chemical Society. f) A rapid, instrument-free, sample-to-result nucleic acid amplification test. Reproduced with permission.[138] Copyright 2016, Royal Society of Chemistry. g) Smartphone-based semen analysis. Reproduced with permission.[127] Copyright 2017, The American Association for the Advancement of Science.

hardware (handheld or benchtop analyzers), reduction in complexity and improved capabilities in multiplexing are the greatest challenges ahead of the scientists and engineers working on the next generation POCT devices. Strict regulations in the field of medical devices (by EU directives or FDA requirements), also hamper the growth of the global market for disposable POCT systems. Small companies and startups developing on-site diagnostic tools cannot easily afford navigating through the regulatory requirements without large sums of private investment, which leaves only the big players operating in this market, reducing the speed of innovation and competition.

5.1.2. Wearables

Wearable diagnostics (**Figure 11**) is an emerging phenomenon that brings diagnostics even closer to the individual than POCT devices, as these small instruments are directly attached to the user. The most common format employed for wearables

Table 3. Overview of some commercially available POCT systems.

Brand	System	Sample	Sample unit	Analyzing unit	Diagnostic fields[a)]	Sample-to-result time
Abbott	iSTAT Alinity	Blood	Cartridges	Handheld	1–6	2–10 min
Abaxis	Piccolo Xpress	Blood	Disks	Benchtop	1, 8	12 min
Alere	Afinion	Blood	Cartridges	Benchtop	1, 2	3–7 min
Alere	DDS2	Oral	Cartridges	Handheld	7	5 min
Atonomics	Trace	Blood	Cartridges	Benchtop	1, 2, 4, 6	3–10 min
Biosurfit	spinit	Blood	Disks	Benchtop	2	[b)]
Cepheid	GeneXpert (Omni)	Various	Cartridges	Benchtop	9	18–150 min
Micronics	AB0Rh Card	Blood	Cartridge		2	2 min
OPKO	Claros	Blood	Cartridges	Benchtop	4, 6	10 min
Radiometer	AQT90 FLEX	Blood	Cartridges	Benchtop	2, 6, 10	11–21 min
Roche	cobas h 232	Blood	Test strips	Handheld	4, 6	8–12 min
Samsung	LABGEO IB10	Blood	Disks	Benchtop	4–6	20 min

[a)]1) Electrolytes; 2) hematology, cardiovascular diagnostics; 3) blood gases; 4) coagulation; 5) endocrinology; 6) myocardial infarction; 7) drug screening; 8) liver diseases; 9) nucleic acid amplification and detection; 10) sepsis and infection screening; [b)]Not specified.

are printed or tattoo-like patches that are applied directly onto the skin. For example, by applying smart bandages onto wounds,[157] the temperature,[158] moisture,[159] pH value,[160] or the concentration of uric acid[161] can be measured to monitor the condition of the wound during its recovery. By connecting a printed circuit board (PCB) to the dressing, the healing process can also be kept under surveillance wirelessly by a mobile device.[161] Such disposable bandages would be especially useful for monitoring chronic wounds, such as diabetic ulcers, which usually require a long time to recuperate. The next generation of smart bandages is capable of real-time monitoring and treatment of wounds by on-demand drug delivery in a closed-loop manner.[162]

Noninvasive, (multi)parameter chemical analysis of ions or conductivity,[20,37,163] trace metals,[164] pH,[38,163] alcohol,[165–167] lactate,[39] or glucose[39,74,168,169] in sweat is another area of application for wearable sensors. Among them, glucose is by far the most important analyte since for diabetics and athletics the close monitoring of glucose levels is crucial and therefore, this has been a major focal point in wearables research. Conventional disposable glucose test strips do not offer automated, noninvasive, continuous measurements and require manual handling several times a day. To address this, wearable sensors capable of monitoring glucose levels in sweat have recently been reported; these sensors can be electrochemical[39,170] or colorimetric[171] and may also be capable of measuring multiple chemical analytes, in addition to glucose, at the same time. Electrochemical sensors have the advantage that the data from the sensors can be transmitted to a mobile device continuously using wireless electronics which may warn the user if a certain analyte is dangerously high or low. The colorimetric sensors, however, have the advantage that they can be read by the naked eye continuously without the need for additional instrumentation, but the sensitivity achieved is lower than electrochemical sensors.

Sweat-based monitoring of biochemistry of humans has two disadvantages: i) the production of sweat requires an increase in body temperature (for example, by physical activity) which limits their application. A recent study has investigated the use of a miniaturized iontophoresis interface[172] using stimulating compounds (pilocarpine) for autonomous extraction of sweat which may provide a solution to this problem. ii) The level of certain analytes (such as glucose) in sweat may not closely correlate with levels in blood.[173] Measurements made using the interstitial fluid, however, offer an alternative, more accurate route to measuring blood glucose indirectly. The interstitial fluid can be accessed either noninvasively[174] using a tattoo-like device or minimally invasively using an array of functionalized microneedles in the form of a patch (that penetrate the dermis).[175] Another interesting approach is the simultaneous monitoring of sweat and interstitial fluid using a disposable wearable biosensor.[176] Once translated into the market, these devices might offer an easy, accurate and pain-free method for the detection of various (bio)chemical analytes.

There is also a wide range of wearables that aim at monitoring physical signals—including acceleration, strain, radiation, and pulse rate—using disposable devices.[177] These devices may come in the form of a wristband (for instance, similar to the famous nondisposable activity tracker "fitbit") or tattoo-like devices. For example, to combat the high incidence of skin cancer, tattoo-like colorimetric UV-A and B radiation dosimeters have been built to track exposure of individuals to radiation from the sun.[178] These sensors can be seamlessly applied onto the skin and change color in a dose-dependent manner to inform users of their exposure to radiation. Optoelectronic sensors can also be integrated into ultrathin wearable devices which can provide more quantitative and precise measurements unlike colorimetric sensors. They can be equipped with near-field communication (NFC) capabilities to transmit digital information concerning sensors to a smartphone, wirelessly, without the need for an additional source of power.[179] Because of its simplicity, and the increasing number of NFC-enabled phones in the world,[180] we expect to see a larger number of NFC-enabled wearable sensors in the future.

Although the majority of wearable devices reported focus on a single mode of analysis, the combination of chemical (such as lactate, glucose, and pH) and physical (like temperature, strain,

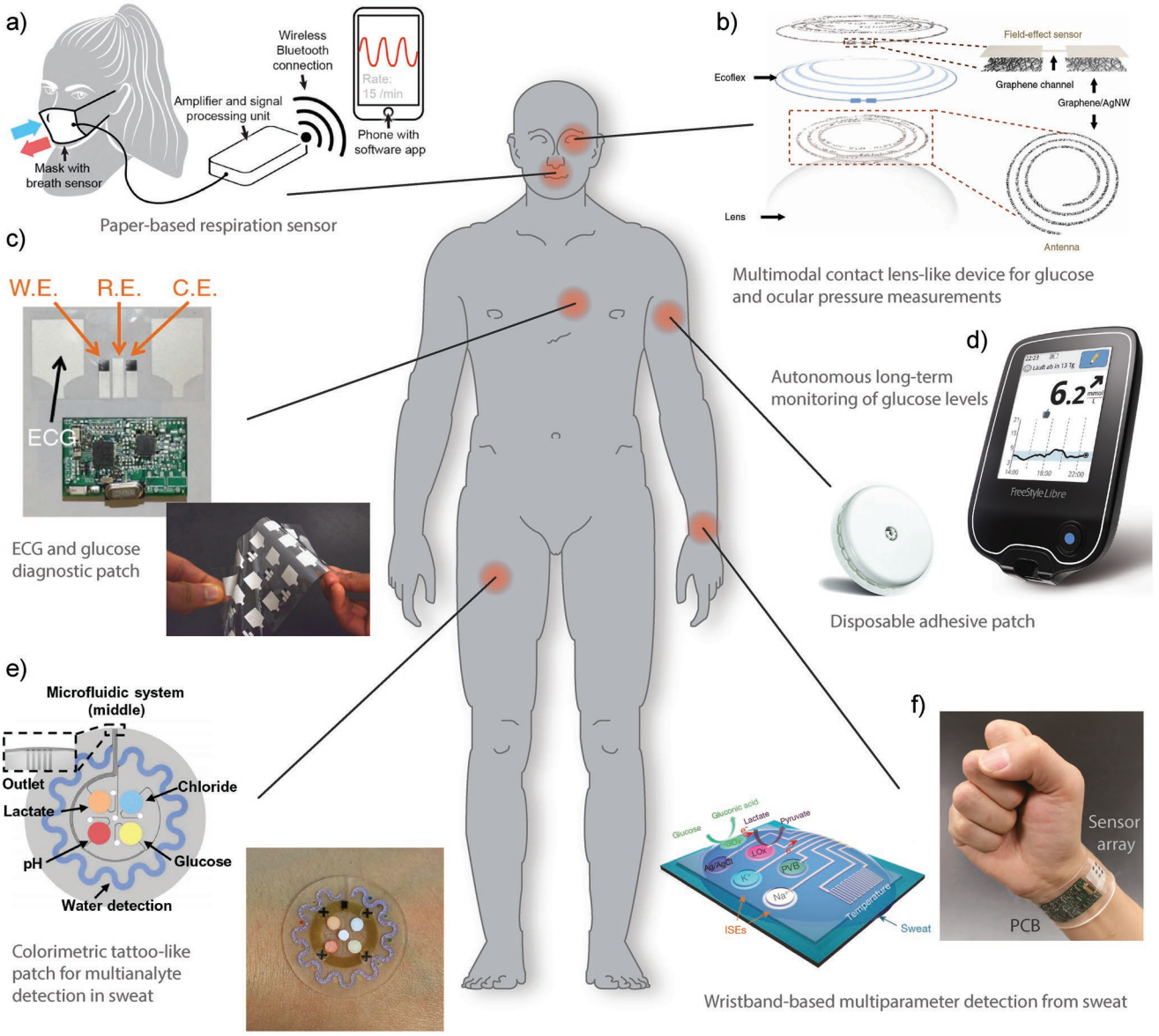


Figure 11. Overview wearable diagnostic devices: a) paper-based respiration sensor. Reproduced with permission.[183] Copyright 2016, Wiley-VCH. b) Multimodal contact lens-like wearable. Reproduced with permission.[182] Copyright 2017, Nature Publishing Group. c) ECG and glucose patch. Reproduced with permission.[46] Copyright 2016, Nature Publishing Group. d) Disposable patch "FreeStyleLibre" for autonomous long-term surveillance of blood glucose levels. Reproduced with permission. Copyright 2018, Abbott. e) PDMS patch. Reproduced with permission.[171] Copyright 2016, The American Association for the Advancement of Science. f) Smart wristband. Reproduced with permission.[39] Copyright 2016, Nature Publishing Group.

and ECG) modes of sensing in a hybrid device would provide a more complete picture of the state of health of the user. For example, by simultaneously monitoring the levels of lactate in perspiration and heart rate using electrocardiography under physical strain,[46] the user's fitness can be determined more accurately in comparison to using lactate levels (or electrocardiography) alone. Multisensor devices do not have to be larger than single mode sensors and can be packed into a disposable contact lens, allowing noninvasive analysis of biochemical markers in human tears,[181] while simultaneously measuring ocular pressure.[182] Clearly, bi- or multisensor devices would be more complex to fabricate and generally more expensive, but there may be scenarios where an increase in price is insignificant compared to the information that the sensor(s) would provide.

There is also a great demand for wearable diagnostics in patient care. For instance, single-use respiration sensors for monitoring breathing patterns[183] of patients in emergency settings or at home for the diagnosis of respiratory illnesses, like sleep apnea, are of great value. By exploiting the hygroscopic character of paper, combined with simple electronics, the breathing of a patient can be surveilled in an easy and low-cost manner.

Ingestible disposable sensors are an emerging extension of wearable devices that allow collection of information concerning

the state of health of the gut. Ingestibles may be capable of imaging and/or monitoring physical (pressure and temperature) or chemical (pH, electrolytes, enzymes, or metabolites) signals and can diagnose disorders and even monitor adherence to medications.[184–186] For the design of ingestible sensors, the critical factors are i) the physical dimension of the capsule for easy ingestion, ii) the use of low-power electronics, iii) the application of biocompatible but resistant materials (both for the capsule and biomolecules) due to highly acidic conditions, and iv) safe data transmission to an external receiver. Some ingestible disposable electrochemical sensors can be produced using digestible food-based materials, including carbon composites as conductors, corn and olive oil as binders, vegetables as biocatalysts and hollow food sleeves (such as green bean or penne) as packing, for measurements in saliva, gastric or intestinal fluids.[65] Since both ingestible and digestible sensors are edible, they do not require sample preparation, and are either metabolized or excreted from the body naturally.

In contrast to POCT, there are only a few commercial wearable diagnostic devices on the market. A notable example is the FreeStyleLibre from Abbott, which enables autonomous monitoring of blood glucose of up to 14 days. By placing the adhesive patch onto the skin, the skin is punctured; the measurement is carried out every 15 min and can be checked wirelessly with a handheld device. This is an outstanding example of a wearable system, giving the user the ability of living a normal life, while monitoring their condition regularly on a semiautomated basis. The next generation of disposable wearable blood glucose monitors will most likely be capable of delivering insulin in addition to detection, in a closed-loop format (similar to existing artificial pancreas systems).

With the recent advances in Internet of Things (IoT) and big-data analytics, disposable sensors integrated with electronics will become an essential part of our lives, woven into our clothes and attached to our bodies.[187] With the emergence of personalized medicine and care, (semi)continuous monitoring of various biomarkers will soon be common practice in our daily routine.[188] But, there are still many technical challenges to be resolved: i) power management appears to be a major obstacle for disposable wearable devices; conventional batteries are heavy, bulky, or have low energy density.[189] ii) Reduction in size, iii) implementation of a more intuitive user interface, and iv) a more affordable price tag will be important factors in determining the future adoption of wearables.

5.2. Food Analysis

Ensuring the safety and quality of food is an issue of paramount importance. Since the emergence of genetically modified organisms, organic foods and nutraceuticals in stores, consumers are ever more interested in knowing what goes in their food. Considering that many products contain a multitude of ingredients, determining exactly what is inside is challenging. Food is also often shipped from different parts of the world as a direct outcome of globalization, which can generate unexpected episodes of contamination. In addition, fraudulent food manufacture can produce health problems demanding stricter controls by the regulatory agencies (EU regulation 2002/178/EC or FDA Food Safety Modernization Act). Consequently, analysis of foodstuffs has never been more necessary and yet complicated; hence, analytical tools are required to ensure both safety and quality of food.

Although testing of most foodstuffs can be carried out in large laboratories, there are at least four disadvantages for using centralized quality control: i) because of the wide range of analytes, even centralized laboratories may be specialized in a single or a lower number of contaminants. This means that each sample must be sent to multiple laboratories at the same time. ii) The samples have to be shipped in highly controlled conditions to prevent possible alterations and may require a cold chain. This in turn increases the cost of shipping. iii) Transport times may delay distribution to consumers/retailers, reducing further the quality of food. iv) Centralized testing and the costs incurred as a result are reflected to the consumer, which increase the cost of food. Because of these reasons, it may be more effective to test foods at the point of need (home, packaging centers, manufacturing facilities, etc.) using disposable sensors (**Figure 12**).

There are at least four categories of analytes in food testing: i) contaminants (both biological and nonbiological); ii) nutritional ingredients such as aromas, macro- or micronutrients; iii) food additives (which may be harmful if the dose is exceeded); and iv) allergens. Due to their simplicity, accuracy, and reliability, the quantification of these analytes in food is generally performed on-site by single-use electrochemical, colorimetric, and chemiresistive transducers. While disposable electrochemical sensors require a liquid sample or liquids extracted from solid foods, colorimetric ones may work with liquids extracted or gases released from the sample of food. Chemiresistive sensors can only detect gases released from the sample which may be linked to one or more contaminants in a sample of food. Methods of transduction that require a liquid sample for measurement (i.e., electrochemical, colorimetric) may require multiple procedures for sample extraction, purification and dilution/enrichment which may be potentially destructive (meaning the sample cannot be consumed). This is especially the case if the food is solid. Methods that rely on sensing of gases (such as some colorimetric and chemiresistive transducers), however, are noncontact methods and do not generally necessitate extensive sample preparation and thus, are nondestructive.

Contaminants of biological (such as pathogens and toxins produced by pathogens and animals/plants) or nonbiological origin (like heavy metals, pesticides, and veterinary pharmaceuticals) in food are probably the biggest concern to producers, retailers, and consumers. Biological contamination by pathogens and parasites can be detected by destructive analysis of liquid samples for DNA or by measuring the concentration of toxins produced using colorimetric disposable lateral flow or flow-through assays.[190–192] Microbial contamination and degradation of fresh meats can also be monitored nondestructively by measuring the presence of volatile biogenic amines using disposable metalloporphyrin–CNT chemiresistive gas sensors.[193] In contrast to traditional microbial culture methods performed in central laboratories, the approaches for detecting biological contaminants using disposable sensors are substantially faster, easy to use, and less expensive. Nonbiological contaminants,

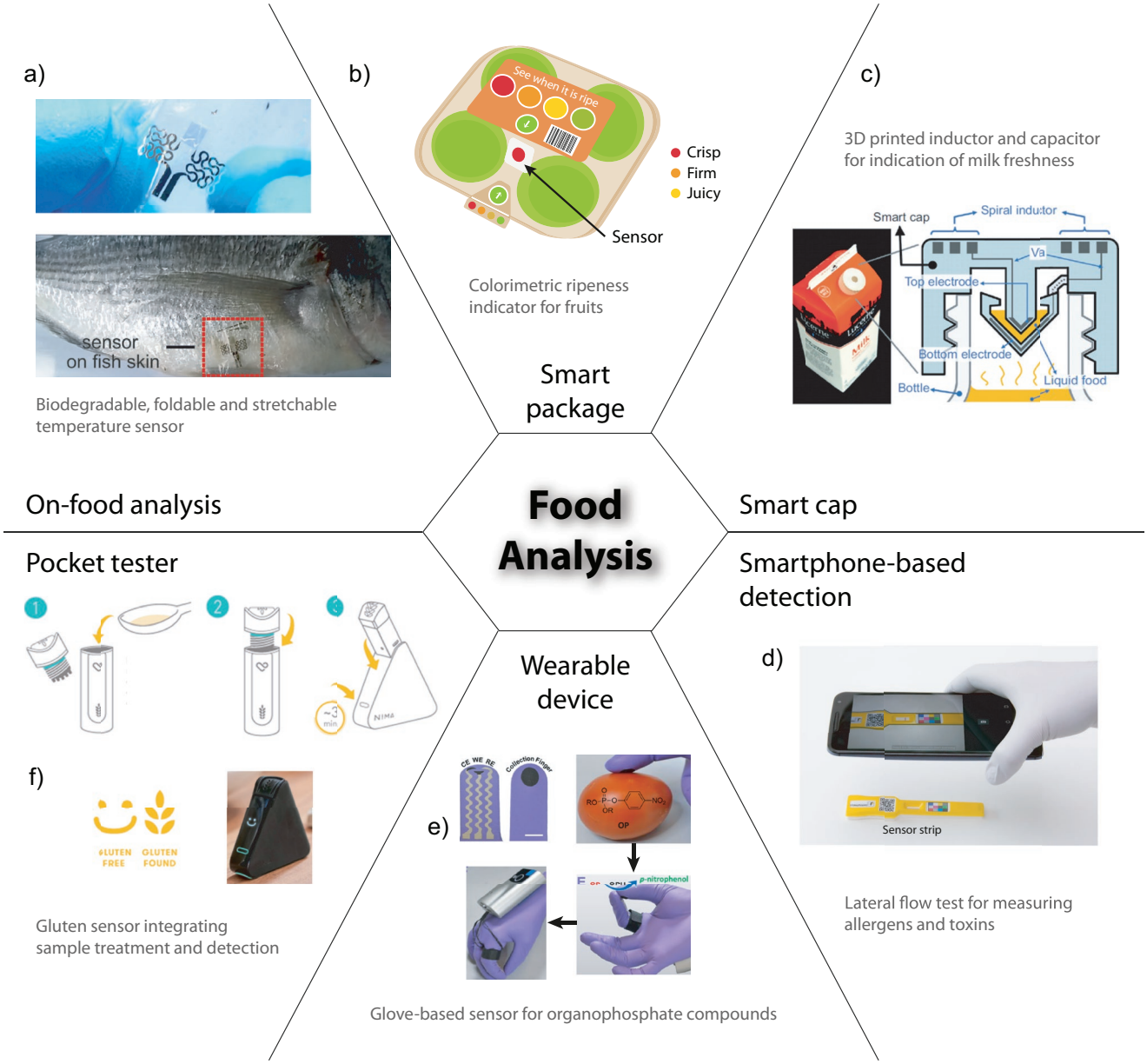


Figure 12. Disposable sensors in food analysis: a) foldable, stretchable, biodegradable, and wireless temperature sensor. Reproduced with permission.[13] Copyright 2017, Wiley-VCH. b) Naked-eye detection of fruit ripeness with commercial indicator, RipeSense. Adapted with permission.[206] Copyright 2016, Hindawi Publishing Corporation. c) Wireless "smart cap" for detection of milk freshness. Reproduced with permission.[209] Copyright 2016, Nature Publishing Group. d) Lateral flow test using RIDA SMART APP for measuring toxins. Reproduced with permission.[200] Copyright 2018, R-Biopharm AG. e) Glove-based sensor combined with a portable electrochemical detector for organophosphate compound detection. Reproduced with permission.[194] Copyright 2016, American Chemical Society. f) Commercial integrated device for detecting gluten with grinding and extraction capabilities. Reproduced with permission.[204] Copyright 2018, Nima Labs, Inc.

such as heavy metals and pesticides in food or drinking water, may not necessarily require antibodies or nucleic acids for detection and can be measured directly or enzymatically using disposable electrochemical transducers.[27,194,195] Compared to laboratory-based methods including liquid chromatography, they provide accurate enough results within minutes at a fraction of the cost. Although probably less important from the perspective of public health in comparison to contaminants, there is also a wide range of disposable electrochemical and colorimetric sensors for measuring concentrations of nutritional ingredients,[196,197] food additives,[198] and allergens[199,200] in foods, which consumers, manufacturers, and retailers may need to monitor to improve quality and safety.

For the fabrication of disposable electrochemical and colorimetric sensors for food analysis, cellulose and its derivatives, such as nitrocellulose, are among the materials most commonly used.[27,190,196,200,201] Cellulose-based materials have the obvious advantage that they can be ultralow cost, and various biomolecules can be immobilized or freeze-dried on the hydrophilic surface without much effort. Furthermore,

microfluidic and sensing structures can be created via printing which is cost-effective both at small and large volumes of production. Of course, cellulose-based materials may not always be the best material depending on the application: for instance, for the immobilization of antibodies for detecting mycotoxins in a flow-through type device, synthetic membranes such as nylon membranes, have been reported to work well.[192] When a higher analytical performance is needed, miniaturized disposable sensors produced by thin- and thick-film technologies (including photolithography[202]/stencil or screen-printing[203]) may also be used for testing food samples. In comparison to cellulose-based materials or synthetic membranes, miniaturized thin- and thick-film disposable sensors are generally fabricated on glass, or ceramic substrates which are more expensive and harder to dispose.

Unfortunately, there is only a small number of commercially available disposable sensors in the market for the analysis of food products. Since the extraction and preparation of samples are a major challenge for inexperienced users and consumers (especially from solid foods), the existing technologies aim to either reduce or eliminate manual handling (the same idea as in POCT devices). This in turn can improve user experience, decrease analytical errors, and may even increase the rate of adoption. For instance, Nima is a fully integrated sample-to-answer portable gluten/peanut tester[204] that can grind, extract and test (immunoassay) solid food samples using single-use test capsules. This system may be useful for individuals with insensitivities or allergies to gluten and peanuts. Another approach for analyzing foods is to use noncontact, nondestructive colorimetric labels that can be attached to food packaging which may indicate freshness using direct (chemical) or indirect (physical—temperature of storage) means. For example, ripeSense[205,206] can sense ripeness of fruits by reacting with the volatile compounds present inside the packaging which changes colors as the fruits ripen. Similarly, active colorimetric labels developed by Insignia Technologies allow monitoring freshness of food products and also change color as the freshness of the item decreases over time.[207] Other active colorimetric labels, such as the ones by Tempix, change color when a food product is exposed to elevated temperatures (i.e., when cold chain is broken) which increases the speed of degradation and waste. Temperature-sensitive labels do not directly provide information about the biochemical state of the food applied; however, they are inexpensive and still provide valuable details concerning transit conditions, which may be accounted for when estimating the shelf life. In addition to commercially available packaging sensors, there is a large number of academic prototypes[208] such as the "smart cap" that allows rapid detection of degradation of milk, wirelessly.[209] Driven by the edible electronics, another approach is to apply nondestructive disposable sensors directly on the food which would enable more extensive and detailed monitoring of physical and biochemical changes.[13,210–212] These sensors, however, must not contain any toxic compounds that may contaminate the food; this limits the number of materials available for use in constructing these devices. Because food waste has reached unmanageable levels both economically and environmentally, we are sure to see continued development of low-cost disposable sensors for monitoring freshness of food all along the supply chain.

5.3. Environmental Monitoring

Today, it is generally agreed by everyone (scientists, policy makers, and public) that environmental pollution has reached catastrophic proportions, threatening every single ecosystem across the globe. Pollutants can be air-, soil-, or waterborne, may move from one medium to other (for example, soil to water), and directly and indirectly impact human health.[213] Air pollution is the most alarming environmental problem in industrial countries (many European cities routinely fail to meet air quality standards[214]); water and soil pollution, however, predominantly affect developing nations (although to limited extent, developed countries are also affected). While disposable sensors are not generally used for monitoring air quality (some notable exceptions,[136] for instance, are the disposable diffusion tubes for measuring gaseous pollutants[215] or air sampling bags attached to flying robots[216]), inexpensive disposable sensors are used extensively for monitoring water- and soilborne contaminants (**Figure 13**).

Water- and soilborne environmental contaminants can be classified into three groups: i) inorganic (metallic, nonmetallic elements and compounds such as lead, cadmium, phosphates, or nitrites) and ii) organic chemicals (such as small molecules, pesticides, or pharmaceuticals); and iii) biological contaminants (viruses, bacteria, fungi, etc.). While detecting contaminants in soil requires more involved procedures of extraction, water samples usually need minimal pretreatment.

Detection of inorganic contaminants, especially heavy metals in samples of water and soil are perhaps one of the most important applications of disposable sensors in environmental analysis. Inorganics can be detected optically (mainly colorimetrically) or electrochemically using devices based on paper, polymer, silicon or glass substrates and carbon/metallic electrodes.[136,213,217–222] Similar to the sensors used in POCT, or food analysis, electrochemical sensors for environmental sensing generally offer better analytical performance in comparison to colorimetric sensors at the expense of increased complexity and cost (they require external readers, etc.). Inorganic analytes in environmental samples usually exist in low concentrations and to enhance analytical performance of a sensor, it may often be necessary to preconcentrate the analyte.[223,224] Cathodic/anodic or adsorptive processes are widely used in accumulating the target analyte on a solid surface which spatially increases its concentration to improve the limit of detection. For example, for detecting heavy metals, species deposited on the surface of the electrode can be stripped electrochemically, which produces a stronger analytical signal in comparison to the initial concentration and thus, improve sensitivity.[221,224,225] Signal-to-noise ratio (hence sensitivity) of environmental sensors can also be enhanced either by reducing the concentration of interfering compounds[226] or by integrating nanomaterials or functional biomolecules for recognition and signal amplification.[93,227] In the case of colorimetric sensors, use of imaging sensors such as smartphone cameras have also been shown to enhance overall sensing performance as demonstrated by the use of silver nanoprisms for label-free detection of Cl^- in environmental samples.[228] Because of the importance of inorganic contaminants, companies including Macherey Nagel[229] and Merck Millipore[230] market commercial paper-based test strips to detect a large number of inorganic species important

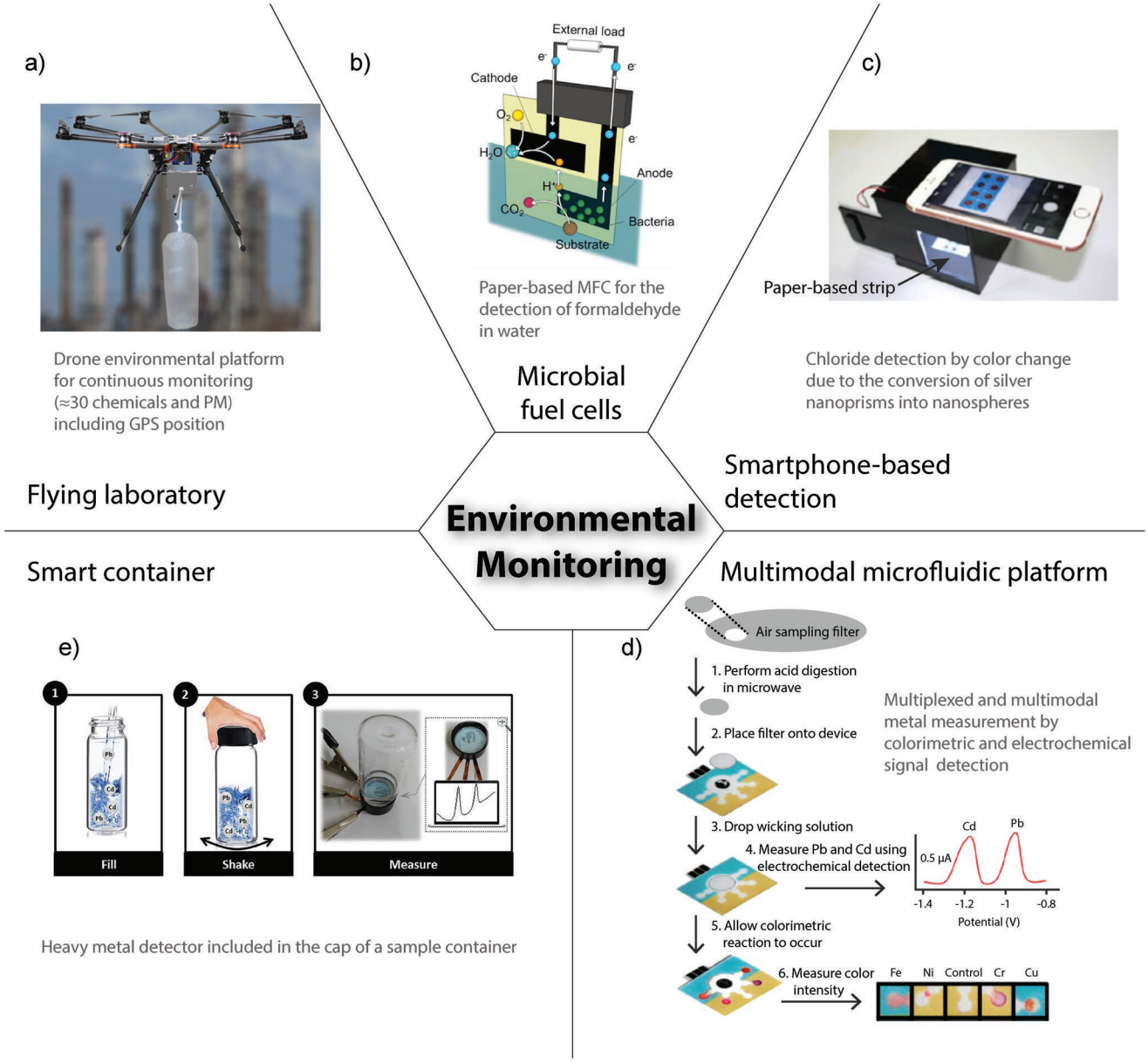


Figure 13. Disposable sensors for environmental monitoring: a) Commercial drone environmental platform "DR1000 Flying laboratory" for monitoring about 30 chemicals (CO_2, SO_2, H_2S, VOCs, ...) and PM1, 2.5 and 10. Reproduced with permission.[216] Copyright 2018, Scentroid. b) Screen-printed paper-based microbial fuel cell for detection of toxic compounds (like formaldehyde) in water. Reproduced with permission.[233] Copyright 2018, Elsevier. c) Paper-based test strip for chloride detection employing a smartphone. Reproduced with permission.[228] Copyright 2018, Elsevier. d) Paper-based colorimetric and electrochemical platform for multiplexed quantification of metals. Reproduced with permission.[87] Copyright 2014, American Chemical Society. e) Smart container using paper-based platform for multianalyte detection of lead and mercury. Reproduced with permission.[221] Copyright 2017, Elsevier.

in environmental analysis such as Al(III), Ar(V), Co(II), Fe(III), Pb(II), or Cl^-.

Because conventional water treatment is not designed to remove emerging contaminants, such as pharmaceuticals, pesticides, etc., from wastewater, these organic contaminants may be discharged into the environment. Such compounds are generally harmful to aquatic organisms and humans; therefore, it may be necessary to monitor their concentrations (inside and outside the treatment plants) using disposable sensors.[103] Molecularly imprinted polymers are one of the approaches available for recognizing and detecting these organic contaminants in environmental samples.[222,231] An emerging, exciting and unconventional method to detect and monitor pollutants in water and soil is to use microbes themselves as disposable sensors which can both recognize toxins and transduce their presence into measurable signals. Microbial fuel cells (MFCs) contain electroactive microbes that produce an electrical signal: a concentration dependent electrical current or voltage which are sensed using a solid electrode, when an environmental contaminant is detected.[232,233] MFCs can be made specific to a

certain contaminant or may provide collective information concerning the overall toxicity of a sample.

Although contamination of drinking water by biological contaminants (mainly through contact with animal or human feces) may appear in the western world to be a problem of the past, microbes in drinking water cause the death of over 5 million people worldwide according to the World Health Organization (WHO) with cholera being the number one killer (50% of all deaths[234]). Microbes in drinking water are generally detected through conventional microbial culturing, ELISA or PCR methods in central laboratories which are generally slow and/or labor intensive (once again similar to POCT and food analysis). Disposable sensors can be used to either sense the presence of whole microbes[235–238] or their genetic materials[239] in samples of water to quantify their concentrations at the point of need. Disposable microbial sensors may employ antibodies,[235] bacteriophages[236] or nucleic acids[239] for capture and recognition of specific microbes. Paper, metals and polymers[237] are commonly used for the construction of open- and closed-channel microfluidic devices which may use electrochemical, colorimetric or luminescent methods of transduction for quantification. Regardless of the method of sensing, the number of microbes in a sample of water may be too low. The samples may be concentrated by filtration,[236] or if the sample medium has a low ionic conductivity (for example, drinking water produced by reverse osmosis), dielectrophoresis[238] can be used to concentrate microbes in a certain region in order to increase their local concentration (and hence, enhance the limits of detection). With the translation of the technologies described from academic laboratories to the field through commercialization, inexpensive water quality monitoring using disposable sensors may save millions of lives across the planet.

There are also various attempts at creating systems that cannot only detect contaminants, but also eliminate them. For instance, polybrominated diphenyl ethers can be detected immuno-electrochemically and eliminated using a system based on PDMS/reduced graphene oxide.[240] Similarly, pesticide atrazine can be detected and degraded by using a microfluidic LOC platform.[241] Once detected immunochemically, hydroxyl radicals produced on the anode destroy the pollutant. Realistically speaking, we are still far from scaling these concepts and integrating them into treatment plants for detecting and eliminating contaminants for thousands of people. Miniature devices that could produce enough safe drinking for a single person, however, are most certainly not science fiction and can be done with today's technology.

Detection, control and elimination of (both existing and emerging) contaminants to reduce their impact on ecosystems and human health is a nonstop process.[242] In this ambitious, but essential task, disposable sensors will continue to play a central role. Next milestones for disposable sensing devices in environmental analysis include: i) the development of easy-to-use sensors that can be quickly repurposed for the detection of "new" emerging contaminants. ii) Although a number of multianalyte[86,87,136,217,221,226,243] and multimodal[86,87] disposable sensors already exist, to generate detailed models of the effects of environmental contaminants (which require large datasets), highly multiplexed platforms that provide extensive, "more complete" analysis of contaminants need to be implemented. iii) Internet-connected, transient disposable sensors that collect data, share and biodegrade without an environmental footprint. These systems may be able to create pollution maps autonomously with minimal user interaction. iv) Development of new classes of disposable sensors that can measure analytes currently limited to centralized laboratories.

Improved access to inexpensive, disposable sensing devices is enabling citizens to measure and participate in the protection of the environment and impact policy makers. This, in turn, forces governments to adopt new laws and regulations that would (hopefully) eventually help with the protection of the environment for the future generations.

6. Conclusion and Future Perspectives

Although there is a large range of disposable sensors that are either already available commercially or being developed in academic laboratories, with the emergence of smartphones, digital communication networks, and rapid prototyping methods (like 3D printing), the field of disposable sensing still has a lot room for growth. We have also not yet invented the ultimate material for disposable sensors that would be ultralow cost (also known as "zero cost") and offer superior material properties along with little or no environmental impact. We, therefore, expect that, in the not so distant future, disposable sensors will continue to be applied for decentralized mining of critical chemical, biological and clinically relevant information inexpensively with high precision (and potentially in real-time). Development of "zero-cost" disposable sensors that may be operated using open-source hardware and software (such as Arduino) will also improve accessibility and democratize sensing, i.e., individuals from even the poorest segments of the society or regions of the planet will be able to own or even make tools for sensing which they will be able to operate by themselves at anytime, anywhere and with minimal effort. As William Thomson (also known as Lord Kelvin) said: "If you can't measure it, you can't improve it," therefore, increased access to sensing may reveal details about our health, foods we consume or the environment that would previously be unknown. This information may allow us to transform our lives and the world for the better.

The future trends and challenges concerning disposable sensors will include i) development of new classes of disposable devices using "green" materials for sustainable, biodegradable and low-cost production (for example, in Europe, will be driven by recent EU rules for single-use plastics[244]); ii) miniaturization and use with portable devices like handheld analyzers or smartphones; iii) implementation of fully integrated, standalone "use-and-throw instruments" containing the elements for readout (such as disposable displays/LEDs, microcontrollers, opamps or even potentiostats[21,245]) and a source of electrical power (batteries, solar panels, etc.); iv) the application of functional nanomaterials for signal enhancement; v) integration of next-generation assay technologies (for example, CRISPR-powered diagnostics[246,247]) and recognition elements (such as aptamers and peptide nucleic

acids) for detecting new targets (such as miRNAs, exosomes, and circulating tumor cells); and vi) development of capabilities for integration with IoT and anywhere-care applications. vii) Disposable sensors may also be combined with systems capable of delivery of therapeutics. These systems (known as theranostics), for instance, could monitor healing of a wound and release drugs on demand, when an infection is detected. viii) Additionally, disposable sensors may be integrated with blockchain technologies for decentralized storage and quality control along a supply chain for food or pharmaceuticals. This would eliminate the need for testing using trusted, (generally expensive) independent third-party centralized laboratories or institutions.

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Note: The article numbers in refs. [46], [85], [206], [218] and [247] were corrected on July 23, 2019, after initial publication online. Figure 3 was also replaced to correct the *y*-axis unit for the potentiometry plot at the bottom middle.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

disposable sensors, environmental monitoring, food analysis, point-of-care testing, wearables

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