Wearable Physical, Chemical and Biological Sensors

Fundamentals, Materials and Applications

Edited by
Eden Morales-Narváez
Can Dincer

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Dedication

In memory of my father, Jacobo Morales-Castillo, who was always proud of my achievements. I also dedicate this book to my beloved family and my wonderful mentor, Arben Merkoçi.
–Eden Morales-Narváez

To my adorable and supportive wife Bilge Nur Dincer, my devoted mom Idil Zaimoglu and my lovely father, Nazim Ersin Dincer (RIP), and for my amazing mentees, Wilfried Weber, and Arben Merkoçi.
–Can Dincer

Chapter 1

Introduction

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-We will always have time for rejections, but not for timely collaborative opportunities

(A conversation between the Editors)

Wearable physical, chemical, and biological sensors can play a key role in preventive healthcare and health monitoring approaches. The capability to continuously monitor organ-related biomarkers, environmental exposure, movement disorders as well as other health and fitness conditions using miniaturized and integrated devices that operate in real time leads to several benefits such as avoiding or delaying the onset of disease, saving resources allocated to public health and the ability to take well-chosen decisions related to medical diagnostics or treatment procedure. Research and development of wearable sensors involve multidisciplinary teams with expertise in mechanics, electronics, chemistry, photonics, biology, microfluidics, materials, medicine etc. Worn as glasses, facemasks, wristwatches, fitness-like bands, tattoo-like devices or bandage-like patches, wearable devices are also being boosted by the Internet of Things in combination with mobile devices (such as smart phones or smart watches). Beside health applications, wearable devices can also play a critical role in smart agriculture by providing resourceful information devoted to environmental protection.

This book offers insightful discussions on how to design, fabricate and operate wearable sensors in terms of materials, biorecognition elements, transduction methods, signal amplification strategies, and system design considerations, including the regulatory landscape. In addition, the current state-of-the-art on physical, chemical, biological sensing as well as hybrid approaches along with their advantageous functionalities and inherent challenges, and future perspectives are covered in depth. In particular:

Chapter 2 discusses the relevance of advanced materials in the development of wearable sensors, where the integration of outstanding optical and/or

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electrical properties into biocompatible, flexible, stretchable, lightweight substrates plays a critical role.

Chapter 3 highlights the relevance of biofunctionalization processes as well as biorecognition elements in wearables, which is crucial to achieve high specificity and selectivity in wearable biosensing. The main biorecognition elements employed in wearables are summarized and some prominent examples are described.

Chapter 4 overviews the signal detection techniques employed in wearable sensors. Offering outstanding examples, several optical and electrical interrogation techniques are critically illustrated and discussed.

Chapter 5 underscores the use of microfluidics for sampling in wearables, particularly the fabrication methods for microfluidic devices are discussed, along with various body fluids to be collected. Highlighting the capabilities of nanomaterials, signal amplification strategies for wearables are also covered.

Chapter 6 deals with healthcare data analytics for wearable sensors, emphasizing big data and artificial intelligence. Challenges ahead related to healthcare data analytics such as network scalability, power consumption, data accuracy, privacy and security, as well as regulatory landscape are also underscored.

Chapter 7 offers an overview on wearable physical sensors. Self-powered and non self-powered physical sensors are in-depth discussed. The rationale behind the integration of triboelectric nanogenerators or piezoelectric nanogenerators into self-powered wearables is elucidated along with insightful examples. Besides, different approaches of non self-powered wearable physical sensors are elaborated, including capacitive, electret, field-effect transistor and resistive ones. Their current applications to monitor bodily activities such as movement, blood pressure, pulse, and respiration rate are also extensively discussed.

Chapter 8 provides an informative summary on wearable chemosensors. Herein, various chemical biomarkers, analytical parameters of wearable chemosensors as well as different sample types like saliva, interstitial fluid or tears, are critically discussed.

Chapter 9 highlights the state-of-the-art on wearable biosensors, particularly involving biofluids analysis with special emphasis in interstitial fluid and sweat, since they are amenable to continuous monitoring for wearable devices.

Chapter 10 underscores the characteristics of wearable hybrid sensors, which according to their function can be multimodal (integrating different transduction techniques) or multiplexed (integrating different measurands/analytes) in order to monitor different human health-related signals (such as biochemical and physiological, etc.).

Chapter 11 overviews wearable devices for plant protection, particularly for plant monitoring and detection of agrochemicals. This cutting-edge concept represents a powerful approach aiding at enhancing environmental protection and facilitating a sustainable development of agriculture.

Chapter 12 discusses the impact of new digital technologies, such as the Internet of Things, big data analytics, machine learning, deep learning, artificial

intelligence, and smart devices, on the wearable sensing technologies. This chapter also highlights the relevance of wearable sensors in the development of future smart cities.

We are sure the reader will find valuable guidance to the basics of wearable sensors for beginners who are interested in starting to work with wearable devices. On the other hand, the advanced readers who are already developing wearable physical, chemical, and biological sensors will get the chance to see the current state-of-the-art in this exciting field as well as to extend their knowledge with compelling insights with respect to materials, bioreceptors, signal readout techniques, amplification strategies, and system design considerations.

Chapter 2

Materials for wearable sensors

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2.1 Introduction

The integration of advances in material science, biotechnology, and nanotechnology is now making the diagnosis of various biomarkers in body fluids possible at-home settings. This shift in the diagnosis arena from lab-based setups to a more personalized or point-of-care (POC) setup is important for continuous monitoring of various biomarkers at an individual level, and at the same time makes it possible to discover many metabolic patterns or diseases, which earlier went unnoticed.[1] The detection of sudden hypoglycemic levels in diabetic patients by continuous glucose monitoring (CGM) devices[2] or strokes[3] by sensor patch are few examples where the POC sensors play an unmatched role.

Among all the sensing devices, the wearable sensors are gaining attention of the scientific community due to its seamless sensing of the analytes in the body with new technologies being incorporated for efficient sample extraction, isolation, and analysis. For the continuous monitoring by wearable sensors, noninvasive measurement of analytes in different body fluids is preferred as it follows a painless accumulation of biomarkers from interstitial fluid (ISF), sweat, saliva, and other body fluids, without the need for puncturing the subcutaneous surface.[4,5] This way it eliminates the primary and secondary infection that can occur due to the contact between blood and the sample collecting instruments.[6]

The basic design of a biosensing device consists of a biorecognition element (BRE, see Chapter 3), a transducing element, and a processor.[7] The BREs are selected for their affinity or catalytic activity to selectively detect the analytes of interest, and the transducer converts this biorecognition event into a measurable signal.[8] The processor or electronic element analyzes the data and displays it in a more user-friendly form. The wearable sensors or biosensors are a more recent form, which has accumulated various advanced techniques from many different fields of science and technology.[9] customer.care@icicibank.com

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The wearable sensors can be generally classified into electrical, electrochemical, and optical sensors based on their mode of action (see Chapter 4). Optical wearable sensors are developed based on the change in property of the incident light upon interaction with skin or other body tissue. The light collected by a detector after scattering or absorption can be correlated with the presence/concentration of analytes. Skin offers a passive way to monitor other organs through optical interfaces, though skin behaves like three isolated layers with different optical characteristics. The outer stratum corneum, middle epidermis, and inner dermis can be studied using different wavelengths of incident light, as shown in Fig. 2.1.[10] The recent advances in stretchable photonic devices offer additional control over light propagation and light-matter interactions.[11] The use of light responsive materials like quantum dots (QDs), upconversion nanomaterials, and transition-metal dichalcogenides have paved the way for development of better optical devices.[12] Among all the wearable sensors, electrochemical sensors provide the highest sensitivity, selectivity, and portability for on-site diagnosis. Electrochemical sensors generate electrical response proportional to the concentration of analytes and express it in terms of the change in charge, potential, or current.[13–16] They measure the transfer of electrons to the electrode surface from the recognition or catalytic center. Here, the electrochemical sensors can be grouped into amperometry/voltammetry, potentiometry, and impedance spectroscopy/conductometry based on the type of electrochemical transducers used.

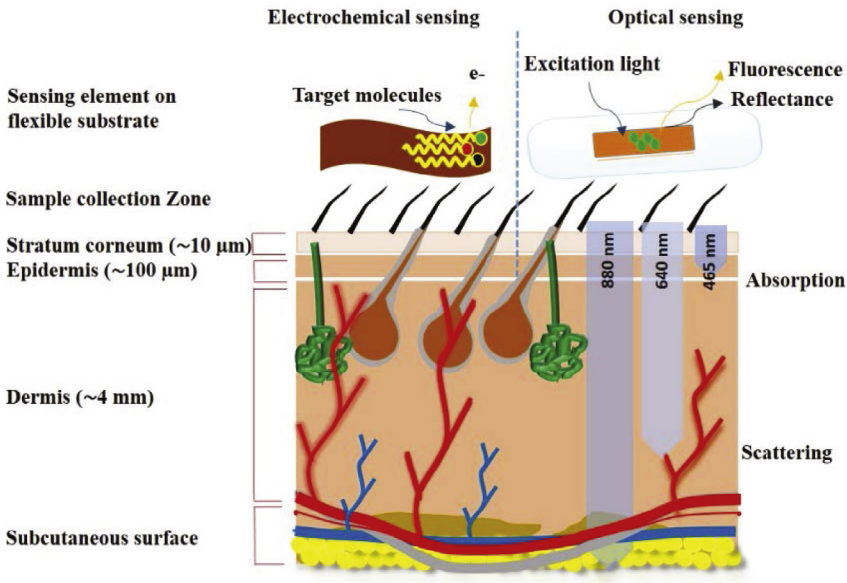

FIG. 2.1 The basic design and working of wearable biosensors on a soft substrate for health monitoring.

The mechanical, optical, and electrical properties of these wearable sensors are tailored to fit different body parts, and equally to monitor the reactions in different body fluids. Various nanomaterials of different size, property, and combinations are used for these purposes (see Chapter 5). The traditional sensors are based on rigid electrodes, which are hard to use for on-body sensing. The soft and stretchable materials used in wearable sensors are designed to attach to the body surface and work under stretched and twisted conditions, and can be integrated with textiles.[17] These materials are progressively used in integration with electronics and photonics for a wide range of biosensing and cross disciplinary functions like developing human machine interfaces. The basic design and working principles of a wearable biosensor is depicted schematically in Fig. 2.1. In this chapter, the types of materials used in designing wearable sensors are discussed focusing on soft polymer substrates, integration of nanomaterials, and the biofunctionalization strategy.

2.2 Materials for wearable (bio)sensors

2.2.1 Designing a wearable (bio)sensor

Wearable sensors are designed to obtain the analytical signals based on a single step reaction mechanism, using only a small skin attached patch/sensor, where all the required reagents and sensing materials are embedded. The electrodes or sensing area are developed on the soft substrate by printing or by micro/nanofabrication techniques.[18]

Optical transducers in the wearable biosensors monitor the changes in optical characteristic (transmission, absorption, reflectance, interferometric pattern, etc.) of the target biomarkers. Each biomarker has characteristic optical properties and changes in it is monitored by optical methods (different spectroscopic and interferometric techniques) or by using optically active materials such as plasmonic arrays and photonic crystals.[19] An optical biosensor is designed based on the type of biomarkers recognition strategies and the transducer used. Pulse oximetry is a commonly used wearable optical sensor, where different wavelengths of light are used to monitor the heart rate and level of oxygen in the blood. The heart rate is measured by using photoplethysmogram, and the difference in the absorption of red light by deoxyhemoglobin and oxyhemoglobin is used to monitor the level of oxygen in blood.[20]

Electrochemical biosensors are essentially designed as either a two-electrode or a three-electrode system, where the working electrode (WE), a reference electrode (RE), and a counter electrode (CE) are employed to monitor the biorecognition events.[21–24] In the case of wearable electrochemical sensors, all these electrodes are mainly developed on a soft surface, and the most important challenge is to maintain the stability of these electrodes under stressed, strained, and varied environmental conditions. The working electrodes are designed to be chemically inert against body fluids with a wide working potential range in acidic/basic/neutral electrolytes, high conductivity, facile surface modifications,

and excellent deformability.[17] The design of a WE cannot usually meet all these criteria, and thus various physical/chemical strategies and nanomaterials are used to increase contact area and reduce the contact resistance. The basic design of a wearable electrochemical sensor contains: (i) a flexible substrate, (ii) an electrode, (iii) insulation layer, (iv) data transmission layer, (v) biorecognition element layer, (vi) passivation layer, and (vii) analyte collection layer.[25] An insulating layer (using dielectric paste or epoxy) is designed above the electrode to define the reaction area and to separate the interconnects from the sample.[26] In the next layer, redox reaction mediators (such as Prussian blue) are deposited as an ink or in combination with polymers to monitor the electron transfer kinetics.[27] The next layer, biorecognition element layer, is designed for the specific sensing of analytes. The passivation layer, often developed by using Nafion, is important for specific sensing and preventing the fouling of the electrodes.[28] The final layer is the sample collection layer, which is highly important in case of samples like sweat or tear, where the collected sample volume is not adequate for a continuous monitoring.[29] Various strategies, such as sample (for example, sweat) uptake layers, microfluidics, and chemical agonist molecules are adopted in this layer to collect a sizable amount of sample for monitoring.

2.2.2 Substrate materials

The inorganic materials are the best suited for the manufacturing of wearable devices, but due to their brittleness, it could not be used in a sensor where it has to be attached to a curvilinear surface with different degree of stretching and bending. Thin films developed from these inorganic materials can be integrated onto a small region and curvature of the body surface, however, the bending characteristics of these thin films cannot match the complex motions of the human body parts.[18] The inorganic and silicone-based materials possess Young's modulus (the slope of stress strain curve, i.e. degree of elasticity) 10,000 times more than human skin making them inoperable on skin interface.[30] Thus, materials with the high stretchability and flexibility are used for designing the wearable sensor that can be fitted on the curvilinear human skin, and can function with optimum capacity after many cycles of deformation.[31] The materials used in the wearable sensors should be (i) flexible to allow bending, (ii) twisting, and (iii) stretchable to move along 3D curvatures, which is generally accomplished using and designing advanced materials.[16,25,32] A good substrate material for wearable biosensors should possess following characteristics: (i) mechanical properties (like high elastic modulus, low stiffness, and high deformability), (ii) electrical properties (such as high electrical insulation, dissipation factor, and electrical stability), (iii) thermal properties (including low coefficient of linear thermal expansion and moisture absorption, and high thermal stability), (iv) chemical inertness, (v) transparent, and (vi) ease of fabrication methodology for low-cost mass production.[33] Various polymers fitting these criteria are mostly employed as the substrate material, and also due to the possibilities of

functionalization. Several strategies are adopted to make these polymers even more wearable friendly, such as reducing the stiffness of the polymers by adding side chains to the axis or increasing the length of the side chains.[25,34]

Thin sheets of polymers, such as polyimide (PI), polyurethane (PU), polyethylene naphthalene (PEN), polyethylene terephthalate (PET), etc., are some of ideal materials for the development of wearable sensors.[35] Low cost, strain tolerance, easy modifications steps, possibilities of mass manufacturing, and control over the ionic and electronic transport at the body-electronic interfaces, make these conducting polymers (CPs) an integral part of wearable sensors.[36] The mechanical and electrical properties of some of the commonly used polymers[37] are summarized in Table 2.1. The polymers have been used for the sensing of ions, metabolites, nucleic acids, proteins, bacteria, etc., in nonwearable chemical and biological sensors.[38] Among them, poly(3,4-ethylenedioxythiophene) (PEDOT) and poly(3,4-ethylenedioxythiophene) polystyrenesulfonate (PEDOT:PSS) are commonly employed as a flexible substrate for creating wearable sensors. Though PEDOT:PSS is not naturally flexible to an appreciable extend, but by conjugating it with other molecules, such as additives (like Polytetrafluoroethylene resin) or ionic liquids, it acquires a higher mechanical stretchability and electrical conductivity.[39] Triton X-100 ($C_{14}H_{22}O(C_2H_4O)_n$, $n = 9–10$) has been used as a dough in PEDOT:PSS to increase its stretchability, conductivity, and self-healing property.[40] PEDOT:PSS has been employed for various roles in wearable sensors, such as Emaminejad et al. developed a sensor for sweat chloride and sodium sensing, where PEDOT:PSS was used as an ion–electron transducer (to minimize the potential drift of the ion-selective electrode).[29] This wearable sensor device was built on a PET substrate by photolithography, and an agonist molecule was used to extract sweat samples which can be used for cystic fibrosis and glucose level monitoring. The sensor and its working mechanism involving agonist molecules are displayed in Fig. 2.2A. PET, known as polyester, a widely used polymer in packaging industry,[41] is also employed in the development of wearable sensors due to its thermal and electrical stability, flexibility, transparency, moldability, and chemical resistivity.[33] With some modifications, PET can be used for biological applications, such as a PET-based nanofiber mat functionalized with methacrylic acid and gelatin was employed by Ma et al. to culture endothelial cells for applications in blood vessels development.[42] Gao et al. developed a fully automated sweat collection and multiplexed sensing module for glucose and lactate in human perspiration on a flexible PET substrate.[26] The PET substrate was fabricated with chitosan containing glucose oxidase (GOx) and lactate oxidase (LOx), and Prussian blue (PB)-mediated carbon ink for electrochemical sensing. Various microfabrication techniques such as photolithography, electron beam evaporation, lift-off and oxygen plasma etching were employed to design this sensor. The wearable electrochemical sensor was able to simultaneously detect glucose, lactate, other metabolites, and temperature on the skin surface. The first mouth guard-based electrochemical biosensor was also developed on PET substrate

TABLE 2.1 Various polymer substrates used in fabrication of soft electronics for health monitoring (Reused with permission from Sreenilayam et al. ©Elsevier, 2020).

Substrate material	Surface energy (mN m^{-1})	Transparency (%)	Water absorption (%)	Surface roughness	Solvent resistance	Glass transition temperature (°C)	Young's modulus (Mpa)
Polydimethylsiloxane (PDMS)	20.4	-	>0.1	-	Poor	125	1
Polyethylene Terephthalate (PET)	44.0	90	0.6	Poor	Good	70–110	2–4.1 × 10^3
Polycarbonate (PC)	34.2	92	0.16–0.35	Good	Poor	145	2.0–2.6 × 10^3
Polyurethane (PU)	38	-	0.2	-	Good	80	7
Polyimide (PI)	43.8	35–60	1.3–3.0	Good	Good	155–270	2.5 × 10^3
Polypropylene (PP)	30.2	84–90	0.01	Good	Good	0	0.008–8.25 × 10^3
Polyethylene naphthalate (PEN)	-	88	0.3–0.4	Good	Good	118	0.1–0.5 × 10^3
Polyethersulfone (PES)	-	89	1.4	Good	Poor	223	2.2 × 10^3

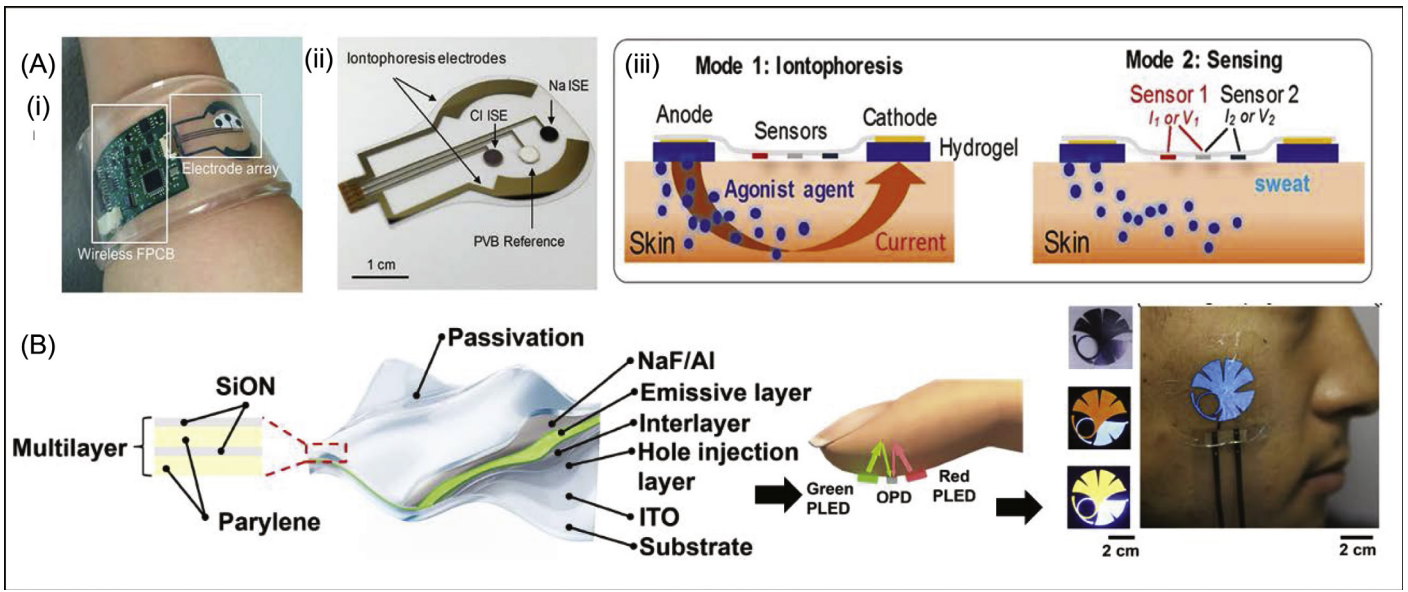

FIG. 2.2 (A) Electrochemical wearable sweat sensor built on a PET platform with PEDOT:PSS as an ion-electron transducer showing (i) electrode array, (ii) iontophoresis circuit, and (iii) mechanism of sweat extraction *(Reused with permission from Emaminejad et al. © National Academy of Sciences 2017)*; (B) ultraflexible wearable skin electronics showing polymer light-emitting diodes and organic photodetectors for sensing and displaying the results on human skin *(Reused with permission from Yokota et al. © American Association for the Advancement of Science 2016)*.

for saliva detection by Kim et al. PET is the most commonly used material in the contact lens-based tear sample analysis, where the electrodes as well as data transmission modules were fabricated on PET substrate.[43,44] Here, the working electrodes were deposited with enzymes for sensing applications, and wireless connection was used for electrochemical data transmission. The central part of the contact lenses does not contain any structures and thus, the user's vision is not blocked due to the transparent nature of PET. Polyvinyl chloride, another polymer was used to entrap color pigments by Kim et al. for a fingernail colorimetric sensor for rapid pH monitoring.[45] The polymer was used to entrap three different color agent to detect three different pH zone *i.e.* bromothymol blue (pH 6.0–7.6), bromocresol green (pH 3.8–5.4), and cresol red (pH 7.2–8.8).

Elastomers are another class of polymers used as substrate materials for wearables since it can undergo large deformation and regain its original configuration upon stress release due to its configuration entropy.[46] Elastomers possess silanol groups which can be used for further surface modifications, and can be conjugated with other inorganic molecules.[47] Polydimethylsiloxane (PDMS) is a commonly employed elastomer in the development of soft substrate and microfluidics for wearable biosensors due to their flexibility, chemical inertness, water resistivity, transparency, biocompatibility, and highly flexible surface chemistry.[33] PDMS shows low electrical conductivity, which can be tuned by adding different nanomaterials. In sweat-based analysis, the extraction and collection of sweat samples is an important issue due to the sparse amount of sample and high evaporation rate. Recently, soft and flexible microfluidic platforms using PDMS elastomers were reported for the collection of sweat and detection of various analytes. Bandodkar et al. developed a skin interfaced microfluidic assisted colorimetric and electronic sweat sensing system using PDMS.[48] PDMS was used for realizing the microfluidic channel and the sensing layer. Koh et al. developed a microfluidic-based colorimetric detection system on a PDMS layer using it's transparency and mechanical strength to withstand the skin interface.[49] The PDMS layer was designed to hold color reagent for the detection of chloride, glucose, lactate, pH, and sweat volume for the colorimetric signal readout. PDMS exhibits some permeability to water and small molecules, for which the operational time frame and sensing chemistry used should be carefully chosen. Zhang et al. developed a multiplexed wearable enzymatic colorimetric assay integrated into a PDMS-based microfluidic system for urea, pH, and creatinine detection in sweat.[50]

Liu et al. reported a living fluorescence sensor by using two layers of elastomers to 3D bioprint living cells responsive to various compounds.[51] Both layers, that is, upper flexible Sylgard 184 layer and the lower Silgel 613 skin adhesive elastomers were spin coated, and genetically programmed cells were placed onto the hydrogel. This tattoo-like fluorescence biosensor was skin attached without requiring any other adhesive, and can be further developed for other wearable biosensing applications. Ballard et al. reported an optical contact lens-based lysozyme sensor by modifying it with three silicone hydrogel polymers,

Senofilcon A, Balafilcon A, and Etafilcon A, with different protein absorbing capacity.[52] They used Balaficon A for further studies based on the dynamic range of protein required for the assay (though Etafilcon A showed maximum protein absorption), and employed the contact lens for lysozyme assay after wearing it for an optimized time of 15 min.

Polymer light emitting diodes (PLEDs), a flexible polymer-based material is commonly used for sensing and displaying health parameters on skin. The PLED can be a widely used as disposable optical sensor as it can be mass produced at low-cost using ink-jet printing. PLEDs can be used in place of solid-state LED lights in medical wearables as it can form higher-fidelity sensor-skin interface due to its flexibility, and for its reduced noise in optical sensing.[53] Multiple color PLEDs in the sensing system is preferred over single color PLED (primary color being red, green, and blue), as it can be used ratiometrically to monitor more than one parameter. Han et al. reported printing more than one color emitting material by a simple blade printing method.[53] Yokota et al. demonstrated an electronic skin (e-skin) sensor system by combining PLED and organic photodetectors for sensing and displaying on the skin.[54] By using red and green PLEDs, they developed a pulse oximeter to measure the oxygen concentration in blood, and to display the result on the skin. The passivation layer was realized by using multiple alternating parylene and SiON layer, as displayed in Fig. 2.4B. Fiber optics is another commonly used material in many implantable and wearable diagnostic devices due to its flexibility, biocompatibility, and biodegradability.[55]

The structural shape of the inorganic materials embedded in the polymer in sensor design is an equally important aspect of developing the flexible sensors.[56] The wavy or serpentine form reduces the effect of strain allowing stretchability in controlled buckling or in-plane bending of the active conducting materials of the sensor. Wavy form of active materials is developed by lithography from wafer-like materials, and it can support the uni or biaxial stretching by accommodating the wavelength and amplitude of the applied strain.

2.2.3 Nanomaterial integration for tailored substrate materials

The polymers and elastomers used in the substrate material need to be optimized for its optical, electrical and mechanical properties, whereas the nanomaterials are employed as dopants. The nanomaterials utilized for this purpose can be classified into carbon-based materials and metallic/inorganic nanomaterials. Often a combination of various (hybrid) nanomaterials is integrated with optimized size, shape and nature to achieve desired characteristics. The nanomaterials are applied as interconnections, and different structures are designed to withstand the uni/bidirectional stress when attached to the body surface.

The metallic nanoparticles can be grouped into novel/other metal nanoparticles, monometallic/bimetallic, and based on their size to one or two-dimensional dimensional (1D/2D) nanoparticles.[57–60] In the development of wearable sensors,

the use of various 1D and 2D nanomaterials are more noticeable due to their conducting and optical properties. According to percolation theory, 1D nanomaterials can achieve (i) better conductivity with very low amounts of materials, (ii) high persistence length ensuring direct transfer of charge, and (iii) the possibility of achieving high transparency and high conductivity, simultaneously.[61–63] Optical transparency usually requires a very thin conducting film, which has a very high risk of breaking under strain. Monolayer ultrathin silver nanowires (AgNW)[64] and gold nanowires (AuNW)[65] are reported to be highly transparent and can work as soft electronics at 50% strain. Wang et al. developed a lactate sensor based on an AuNW based sensor, where the AuNW was used for its conductivity as well as for enzyme immobilization.[66]

AgNW is one of the most commonly employed and preferred nanomaterial for wearable electronics due to its excellent conductivity, mechanical robustness, and it can be spin or bar coated onto both rough and soft substrates.[67] However, AgNW is readily oxidized in air or water and undergoes corrosion in the presence of electrolyte solutions. Thus, it is employed in combination with other materials[68] or a passivation layer of PEDOT:PSS,[69] rGO,[70] or MoS_2[71] on AgNW to maintain its conductivity and stability. Zhang et al. reported an AgNW sensor for lactate detection in sweat, where 3-aminophenulboronic acid-based molecularly imprinted polymer (MIPs) matrix were used for high selectivity.[72]

2D gold nanomaterials, Au nanosheets in conjugation with CNT and PANI were employed for glucose detection by Oh et al., where a network of nanosheets was used to increase the sensitivity of the skin interfaced sensor with a good detection ability at 30% stretching condition, as shown in Fig. 2.3A.[73] Similarly, Bae et al. reported a porous gold nanolayer-based glucose detection system, which showed excellent sensing even after 1000 cycles of 30% stretching the sensor.[74] MXene, a new class of 2D nanomaterials, is progressively used as a graphene analog for various biosensing applications.[75] Lei et al. employed $Ti_3C_2T_x$, a MXene in combination with PB as a sensing material for perspiration analysis in wearable devices.[76]

Zero-dimensional nanoparticles are also utilized in the wearable electrochemical biosensors due to their catalytic and conducting properties. Since the discovery of intrinsic enzymatic activity of nanoparticles,[77,78] many metal nanoparticles, such as AuNP, PtNP, AgNP, CuNP, PdNP have been explored for their catalytic activity to non-enzymatically detect various reducing species and reactive oxygen species.[79] Zero-dimensional metal nanoparticles are incorporated with graphite-based carbon nanomaterials for their synergistic electrochemical behavior. A platinum nanomaterial decorated graphitic ink was developed by Abellán-Llobregat et al. for the printing of a nonenzymatic glucose biosensor on a stretchable polyurethane (PU) substrate.[80] Pt was added to a graphite ink and reduced with $NaBH_4$, and then printed on a cured PU sheet with Ecoflex® PBAT (polybutyrate adipate terephthalate). The sensor design and mechanism for glucose detection are described in Fig. 2.3B. Lee et al. developed a AuNP conjugated sensing device with gold mesh and graphene for

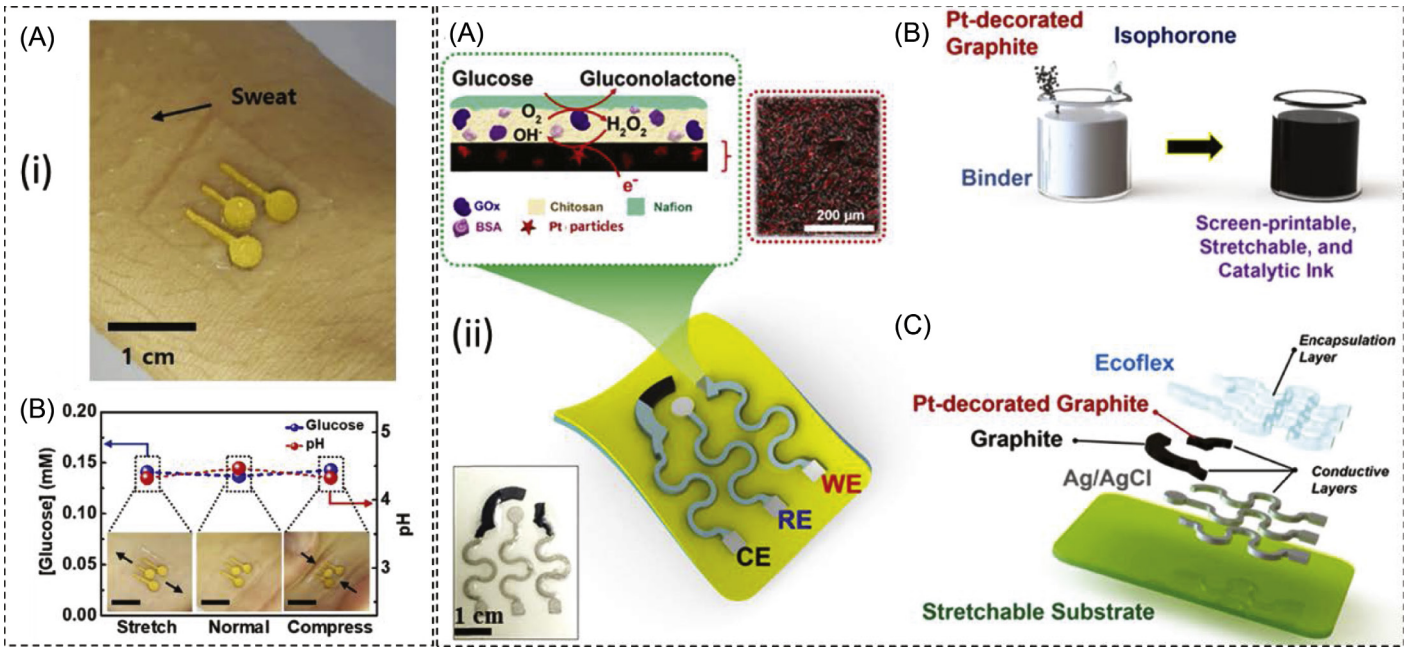

FIG. 2.3 **The use of various nanomaterials in wearable sensor fabrication.** (A) A skin interfaced sweat glucose sensor (i) developed by using stretchable Au nanosheets, and showing comparative performance for glucose and pH monitoring under mechanical deformation (ii). *(Reused with permission from Oh et al., © American Chemical Society 2018).* (B) Design of the wearable glucose sensor with three-electrode setup. (i) The WE was fabricated with Pt-decorated graphite. Schematics illustrating the preparation of the conductive ink (ii), and the layer-by-layer setup of the sensor (iii) *(Reused with permission from Abellán-Llobregat et al., ©Elsevier, 2017).*

stretchable sensor with a drug delivery module.[81] This sensor exhibited multiple sensing units with different combinations of materials, i.e. humidity sensor built on PEDOT, glucose sensor via PB-mediated electrode, pH sensor using PANI modification, and the tremor and temperature sensor with graphene. The graphene-AuNP hybrid system was found to be more electrochemically active than graphene electrode surface, and enabled the sensitive detection of glucose. Both above mentioned examples can detect glucose under the physically deformed states of the substrate. Pu et al. developed a AuNP-graphene sensor on a stretchable PCB, where the graphene layer was modified by inkjet printing followed by AuNP electrodeposition.[82] This follows a very simple method of graphene modification of PCB without using CVD or any other transfer method. GOx was then electropolymerized, and the implemented sensor can measure glucose in the range of 0–40 mg/dL.

Carbon-based nanomaterials have been widely studied in wearables due to their flexibility, transparency, conductivity, and mechanical strength.[83] One such material, that is, graphene, has been used in the development of different types of electronics as well as energy harvesting devices for biochemical analysis.[84] Xuan et al. developed a wearable electrochemical sensor using the catalytic activity of rGO in combination with AuPtNPs and GOx for glucose detection.[85] The rGO was modified by the Hummers method, transferred onto a lithographically developed Au layer, and functionalized with GOx through (N-ethyl-N′-(3-(dimethylamino) propyl) carbodiimide/N-hydroxysuccinimide) (EDC-NHS) crosslinking chemistry. Xuan et al. developed another wearable glucose biosensor using 3D porous nanomaterials using a one-step laser printing of graphene with AuPtNP and AgNW.[86] Carbon nanotubes are another carbon-based nanomaterial, widely used for its unidirectional conductivity and ease of fabrication. Luo et al. demonstrated a LOx modified CNT for wearable electrochemical lactate sensing on gloves.[87] Chang et al. developed a method to directly grow CNT on PI substrate, and used it to detect human serum albumin.[88]

The nanomaterial-based optical wearable detection exploits total internal reflection, surface plasmon resonance (SPR), localized surface plasmon resonance (LSPR), optical light mode spectroscopy, photonic crystal microcavities, surface enhanced Raman spectroscopy (SERS), nanoplasmonic resonator, and colorimetric platforms.[19,89] Metallic nanoparticles like plasmonic gold nanostructures, QDs, transition-metal dichalcogenides, organic semiconductors and its hybrid with various other polymers respond to light differently and exhibit fluorescence, phosphorescence, and/or plasmonic and photothermal effects, which are widely utilized in wearable photonic devices.[12] Nanoconjugation of these materials offers unique and improved optical properties, like the dramatic increase in light absorption of single-layer MoS_2 in presence of plasmonic nanoscale metal to 51% than its natural 10–20%.[90] Won et al. developed a wearable SERS-based contact lens glucose sensor by using a layer of silk and AgNW layer with 4-mercaptophenyl boronic acid (MPBA).[91] Silk was used as a filter for the larger tear proteins, whereas AgNW-MBPA enabled an enhanced SERS

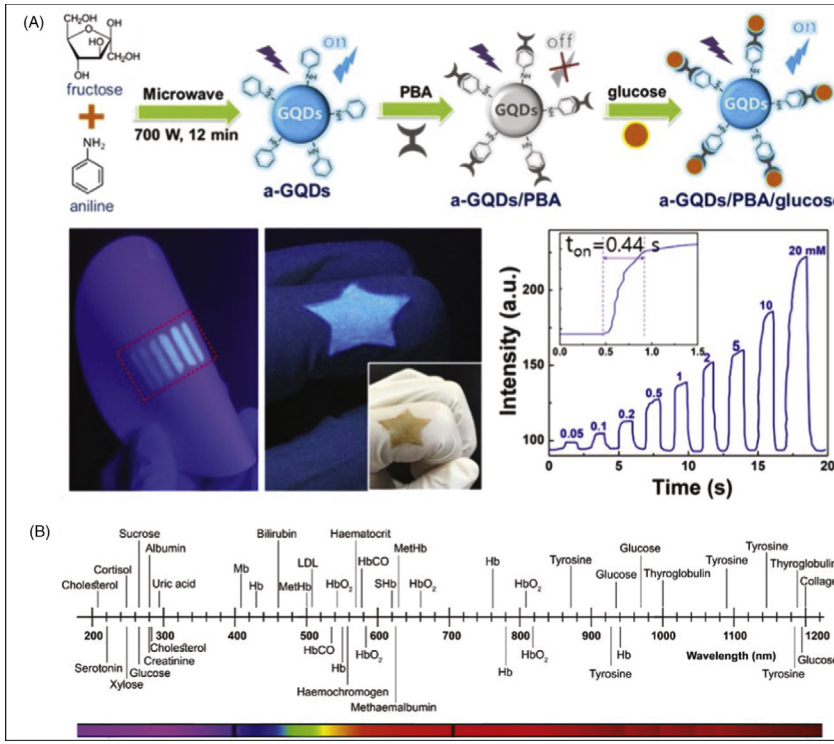

FIG. 2.4 (A) Synthesis procedure of a-GQDs, its application for glucose detection on a latex glove under daylight and UV-light, and fiber optic-based fluorescence spectra for different glucose concentrations *(Reproduced with permission from Tam et al. ©Elsevier, 2021)*; (B) the absorption peak for important biomarkers *(Reproduced with permission from Dhanabalan et al. ©Wiley-VCH GmbH, 2020)*.

activity. Tam et al. reported a paper-based fluorescent glucose sensor using aniline functionalized graphene quantum dots (a-GQDs), and phenyl boric acid (PBA) as fluorescence quencher.[92] The sensor was produced by an inkjet printer to detect glucose in blood and tear samples, and later integrated to a fiber optic module for a highly sensitive detection. The synthesis of nanomaterials used in the sensor and working principle are schematically depicted in Fig. 2.4A. Also, the characteristic detection zone of many important biomarkers are highlighted in Fig. 2.4B.[19]

2.2.4 Natural biopolymers

Biopolymers like chitin, chitosan, silk, (nano)cellulose, polydopamine, etc., can be used for development of soft electronics/photonics.[93] They are highly (i) biocompatible, (ii) biodegradable, (iii) can be stretched and bent, (iv) can be built

into many shapes and designs, and (v) less expensive with possibility of mass manufacturing.[94,95] The strong mechanical property due to hierarchical arrangement of fibers, and possibility of chemical modifications due to abundance of functional sites and reactive centers, these biopolymers are attractive materials for the development of wearable electronics.

Paper is a biopolymer with several properties like sustainability, biocompatibility, biodegradability, high mechanical strength, hydrophilicity, high porosity, broad chemical-modification capabilities and high surface area.[96,97] Due to ease of chemical modifications and microfluidics integration, paper has been utilized for the development of multiple colorimetric and electrochemical sensors.[98,99] Xiao et al. reported a skin interfaced colorimetric pH and lactate sensor by incorporating a paper modified with lactate hydrogenase and pH indicator as sensing matrix.[100] Cotton and hydrophilic silk threads were used as sweat reservoir, and can be further adopted for biosensing of other analytes in low resource settings.

Silk fibroin (SF) is another biopolymer with high tensile strength, excellent mechanical flexibility and optical functions, and insulating nature is applied as a support and packaging materials to flexible electronics.[101–103] SF has been used for the development of colorimetric immunosensors,[104] gas sensors,[105] and also as cathode material for battery development.[106] SF with a graphene oxide (GO) coating was reported to achieve excellent conductivity, and retained its property even after 1,000 cycles of stretching and, used as flexible substrate in a glucose sensor.[107] Ryan et al. introduced a machine washable conducting e-textile by depositing PEDOT:PSS with a SF textile.[108] Mannoor et al. developed a bacterial detection system on silk-graphene composite.[102] The wireless wearable sensor was modified with a sensing peptide, attached to tooth enamel, and can detect a single *E. Coli* using the electrical resistance. Pal et al. developed a SF-based wearable electrochemical sensor by molding it with PEDOT:PSS and a conductive ink SPP-PEDOT:PSS for the individual detection of ascorbic acid, dopamine and glucose.[109] This sensor can be attached to skin as shown in Fig. 2.5A. Xu et al. developed a wearable sensor for ascorbic acid detection based on a silk substrate, where the SF:PEDOT:PSS acts as a working electrode.[110] Matzeu et al. proposed a large scale printed sensing interface of SF across a T-shirt for sweat pH and lactate monitoring on upper torso.[111] The variation in pH and lactate can be quantified by monitoring change in RGB channels employing common charge-coupled device cameras.

Cotton based textile is another widely used biopolymer for development of both electrochemical and optical wearable sensors. Caldara et al. reported a textile-based optoelectronic device for pH monitoring by using a xerogel of 3-glycidoxypropyltrimethoxysilane (GPTMS) precursor and Methyl Red, where the change in colour was monitored by white LED and a photodiode.[112] The sensor was able to monitor pH 4.0 to pH 8.0 (comparable to sweat pH) with a resolution of 0.05 pH unit. The same group developed another pH sensor by incorporating litmus to GPTMS on textile and achieved a 0.5 pH unit variation in comparison to standard pH meter.[113] Piper et al. presented a wearable sensor

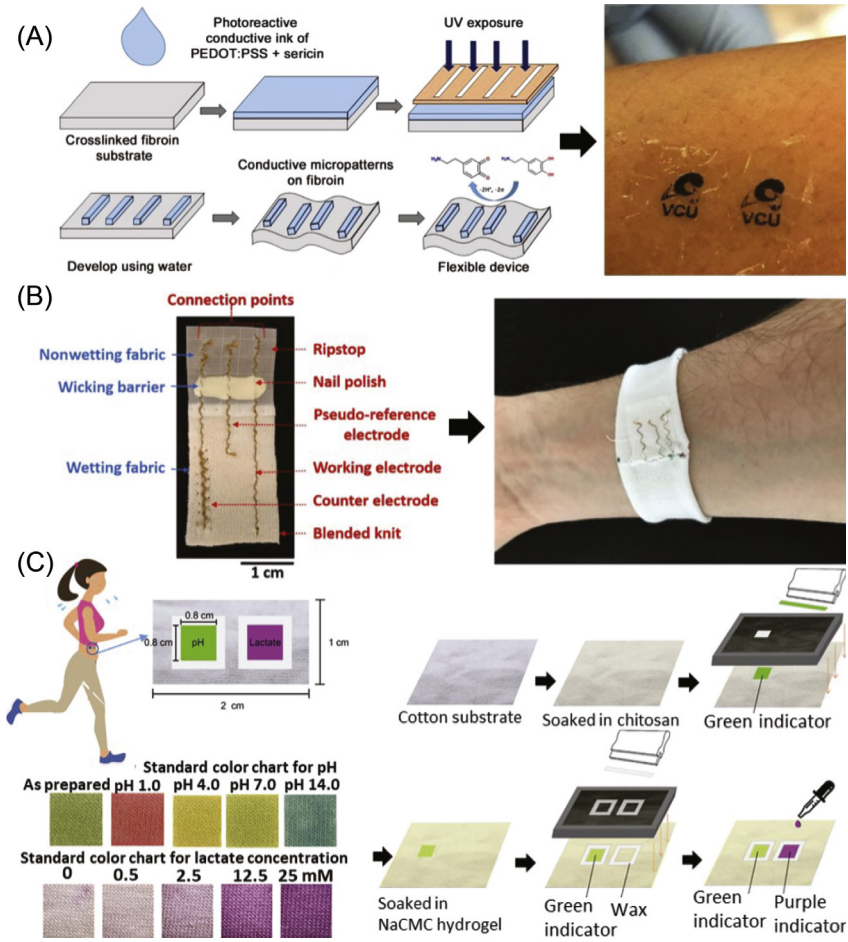

FIG. 2.5 (A) Graphical representation of the different fabrication steps of a SF-based wearable electrochemical biosensor with PEDOT:PSS polymer for non-enzymatic detection of ascorbic acid and dopamine, and GOx-based glucose detection *(Reproduced with permission from Pal et al. ©Elsevier 2016).* (B) Textile-based stitched sensing device for glucose monitoring from sweat *(Reused with permission from Pieper et al. ©Elsevier 2021)*; (C) Colorimetric sensor developed on textile and chitosan for pH and lactate monitoring *(Reused with permission from Promphet et al. ©Elsevier 2019).*

to monitor glucose level in sweat by stitching conductive gold coated threads, as depicted in Fig. 2.5B.[114] The gold-coated threads can be easily functionalized to detect various biomolecules, and also offer an easy and low-cost device fabrication method. Promphet et al. reported a cotton fibre-modified with cellulose nanofiber/chitosan-graphene oxide for colorimetric detection of glucose and urea.[115] GOx and urease as enzymes, and trehalose and phenol red as the chromogenic substrate are employed for detection of glucose and urea, respectively.

Chitosan is a polysaccharide polymer isolated from chitin used in biosensors for its biocompatible, ease of modifying the functional groups, and hydrogel forming capacity.[116,117] In many wearable glucose sensors, chitosan is used as an entrapment and stability layer for GOx,[26,29] where the presence of chitosan is necessary for the long lifetime of the sensor. In microneedle-based sensors, chitosan is used as a matrix for enzyme immobilization and to reduce the biofouling effect due to body fluids analyzed.[118] There are other reports where chitosan is used as a matrix for wearable sensing applications, such as, chitosan-PEDOT-carbon nanotube-based biodegradable green electronics reported by Miao et al.[119] Promphet et al. developed a chitosan modified textile-based sensor for sweat pH and lactate sensing.[120] Methyl orange and bromocresol green were used for pH, and LOx for lactate sensing, and chitosan was used as a dye fixator due to its interaction with charged groups of dyes. The fabrication steps of the sensor and images describing color change with respect to various pH and lactate concentration are illustrated in Fig. 2.5C.

2.3 Functionalization of substrate materials

Integration of nanomaterials on soft substrates is based on both, the nature and synthesis procedure of the nanomaterials, and the characteristics of the employed substrate. This integration can be classified generally into coating, transferring of nanomaterials film, and printing/drawing. The nanomaterials prepared in solution can be directly coated on the stretchable sensing matrix by drop, spray, and/or spin coating.[121] A combination of such methods are followed for effective electrode fabrication, such as the AgNW layer can be transferred onto the soft PDMS substrate followed by vacuum filtration to form a uniform layer.[122] Chemical vapor deposition is another method also commonly used for transferring carbon nanomaterials on the substrate layer.[123] Lithography can be also used to produce highly reproducible structures for biosensing.[124,125] A simpler process of making designs is printing, such as ink jet or screen printing, where the nanomaterials are added to carefully selected fillers, binders, and additives to increase the catalytic activity of the WE.[126] The ratio of the carbon-based[127–129] and inorganic materials such as Ag flakes,[130] AgNW,[131] Au, and Cu within a polymer or solvent blend need to be carefully optimized to achieve the desired conductivity and flexibility.[132,133] Morales-Narváez et al. reported wax printing of different sizes of plasmonic or photoluminescent structures on a bacterial cellulose membrane for optical detection of important biomarkers.[96] For optical sensor development, the required materials are either directly printed on the flexible substrate or first printed on a carrier before transferring to the flexible substrate (such as stamp printing).[11] Stamp printing is favored for crystalline materials, whereas amorphous materials are deposited directly on the soft substrate. Specific printing methods are chosen for specific objectives, such as nanostencil lithography is preferred for developing sub-100 nm structures on any substrate.[134]

The polymer and elastomer materials can be directly functionalized with BREs for sensing applications. The main goal of these functionalization strategies is to properly orient the biomolecules to either capture the analytes (i.e., for antibodies), and to maintain proper 3D structure of the BREs (i.e., for enzymes) for maximum catalysis and signal generation.[135,136] The addition of BREs on the polymers by chemical surface modification is preferred and the synthesis of specific functionalization sites would be more complex and unstable. With PEDOT, the main challenges for functionalization are (i) the need for organic solvents and high curing temperature for polymerization of PEDOT and (ii) lack of functionalization groups on pristine PEDOT.[137] Likewise though a very successful material for bioelectronics development, the challenge with PEDOT:PSS functionalization is the toxicity and high overall anionic surface that inhibit the interaction with most of the biomolecules at physiological pH.[138] These led to the development of many derivatives with hydroxymethyl, chloromethyl, azidomethyl, carboxylic acid, aldehyde functional groups.[139] Even though direct immobilization of enzyme GOx on PEDOT surface for direct electron transfer-based detection of glucose has been also reported, the covalent functionalization showed better performance for biosensing applications.[140] Hai et al. developed a poly(EDOT-co-EDOTOA) film by polymerization of PEDOT with oxylamine moiety, and modifying it with sialyllactose (Sia-α2,6′-Gal-Glu (2,6-sialyllactose) or Sia-α2,3′-Gal-Glu (2,3-sialyllactose)) for detecting human influenza A virus (H1N1) infection.[141] The interaction of 2,6-sialyllactose with the surface hemagglutinin was employed for the potentiometric detection of H1N1 virus. PEDOT can be modified with hydroxyl groups, which later can be used for the attachment of biorecognition elements via EDC-NHS chemistry to detect various molecules.[142] PEDOT has also been used as an electrochemically active material for wearable sensing, as shown by the work of Zhang et al. for the detection of myopia.[143] A corneal microelectrode was fabricated by photolithography, and the PEDOT with sulfur doped graphene was realized via vapor phase polymerization (VPP). The electrode was further modified with tyrosinase enzyme to detect dopamine, a biomarker for myopia diopter, in human tear samples. Parlak et al. developed a wearable organic electrochemical transistors using PEDOT:PSS layer interconnected with MIPs for the detection of cortisol in sweat samples.[144] PDMS is used in most of the microfluidic sensing devices, where its surface is required to immobilize different BREs. The hydrophobic nature of PDMS though hinders adsorption of the biomolecules, proteins, and cell matrix on PDMS surfaces by physical adsorption. This interaction is due to the hydrophobic methyl groups of PDMS and the hydrophobic core of the proteins.[145] The covalent modifications of PDMS for biomolecule adsorption involves salinization by (3-Aminopropyl) triethoxysilane and (3-Aminopropyl) trimethoxysilane, polymer grafting, hydrogels, sol-gels, dopamine coating, etc. PET can also be functionalized with EDC-NHS chemistry for biomolecule attachment by a two-step modification.[146]

2.4 Wearables sensors for noninvasive healthcare monitoring

Noninvasive sensing of analytes is one of the most important applications of wearable technologies, where numerous analytes can be detected without using the painful extraction of blood or serum.[9,147–149] Sweat, saliva, breath, ISF, tear, and excretory samples are the main noninvasive samples used for health monitoring. For every non invasive sample, the biomarker profile and extraction method are different, and modifications on the sensor surface should be accordingly followed.

Contact lens-based electrochemical sensing is another area of wearable sensors rapidly growing for ocular diagnosis, where a contact lens manufactured from poly(methyl methacrylate) (PMMA) or PDMS functionalized with various BREs or nanomaterials is used for detection of different biomarkers.[150] Also, the cost of one disposable contact lens is $1 or less, and is worn daily by more than 45 million people only in the USA.[151] Tear samples contains biomarker for allergic reactions, cancer, cystic fibrosis, autoimmune diseases, glucose, herpes simplex virus infection, pterygium, trachoma, and eye diseases like thyroid ophthalmopathy, ocular chlamydia trachomatis, diabetic retinopathy conjuctivochalsis, etc.[151] Though Google closed their smart contact lens-based glucose sensor program citing the lack of correlations between the blood glucose level and tear level, it is still approached by many other groups to develop improved versions. The first tear-based biosensor proposed by Babak A. Parviz led to the development of many other sensors for tear analysis using a plastic substrate.[44] Chu et al. presented a contact lens-based glucose sensor on a PDMS layer and 2-methacryloyloxyethyl phosphorylcholine.[152] The sensor design and working principle are shown in Fig. 2.6A. Kim et al. reported another contact lens sensor with wireless transmission using graphene and AgNW for glucose monitoring.[153] Elsherif et al. developed an optical tear glucose monitoring sensor on a contact lens by printing a layer of photonic crystal modified with phenylboronic acid-based hydrogel.[154] The hydrogel swells in presence of glucose changing its overall periodicity, which can be detected by smartphone cameras. The sensor was able to detect glucose continuously in the range of 0–50 mM. The design and working principle of this wearable sensor are illustrated in Fig. 2.6B.

For sweat sensors, the continuous monitoring by wearable devices requires a skin interface material capable of fitting to the curvilinear surface for a longer period of time. The electrode system for the detection of electrochemically active molecules like glucose, lactose, and various ions has to deal with very small sample volumes and fast evaporation. Jia et al. developed a printed tattoo-based device using a three-electrode setup for lactate sensing, employing LOx.[155] They used carbon fibers decorated with conductive carbon as working electrode for amperometric detection of lactate, with linearity up to 20 mM. Sekini et al. developed a fluorescence-based microfluidic sensor to continuously monitor chloride, sodium and zinc concentrations.[156] The paper-based

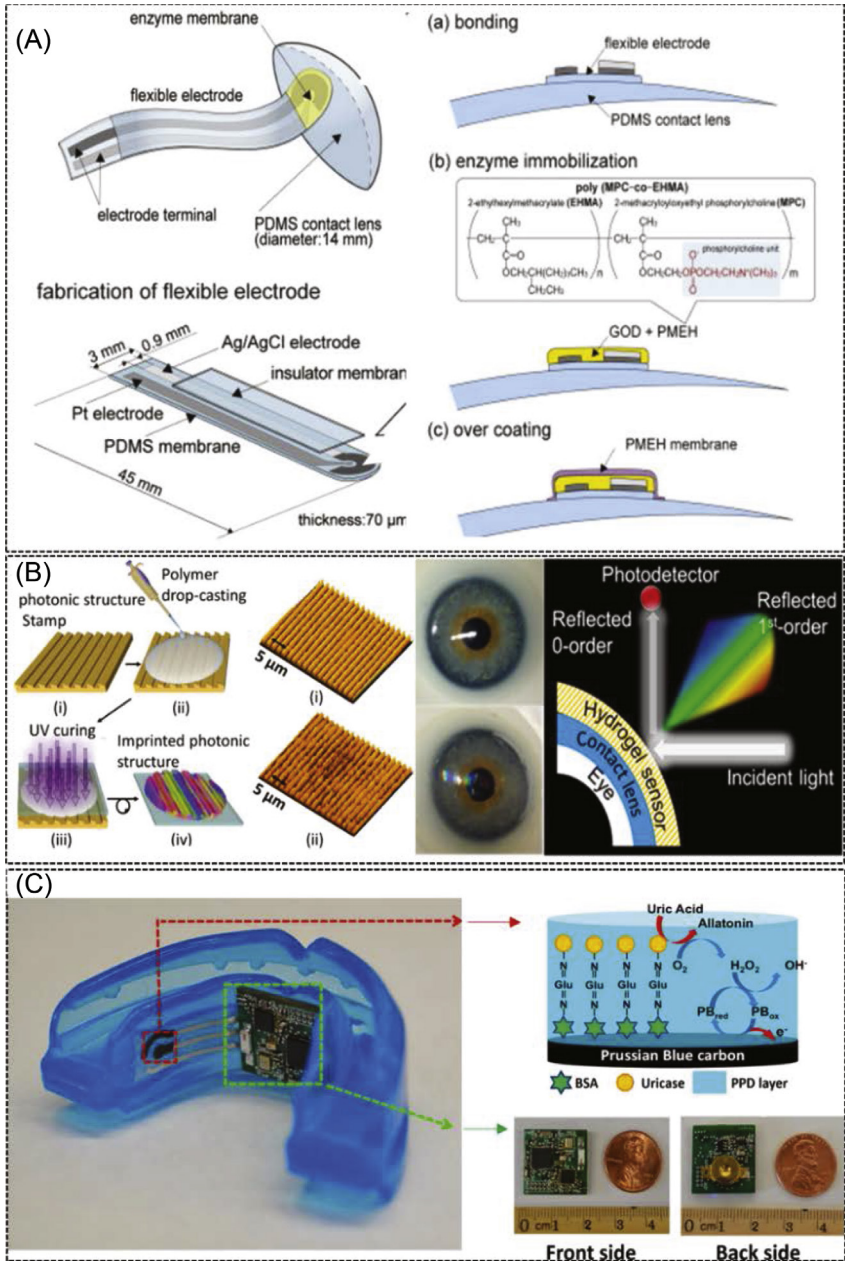

FIG. 2.6 **The noninvasive diagnostics by using wearable biosensors.** (A) Wearable electrochemical biosensor for tear glucose monitoring *(Reused with permission from Chu et al. © Elsevier 2011)*. (B) Photonic crystal and glucose responsive hydrogel-modified contact lens for optical glucose monitoring *(Reused with permission from Elsherif et al. © American Chemical Society 2018)*. (C) An electrochemical mouthguard sensor for urea monitoring in saliva (i), its sensing mechanism (ii), and the wireless sensing circuit board (iii) *(Reused with permission from Kim et al. © Elsevier 2017)*.

sensor incorporated a microfluidic channel layer to collect and analyze multiple analytes simultaneously in the sweat sample efficiently, whereas the lucigenin fluorescent probes are used for the signal readout using a smartphone.

Saliva is slowly becoming an alternative sample of blood for disease diagnosis with a plethora of biomarkers for physiological conditions to cancer and infectious diseases.[157–160] Special attention is towards biomaterials and nontoxic materials while designing salivary electronics to avoid health hazards. Kim et al. reported a mouth guard sensor on a PET substrate directly printed onto it.[161] The sensor was able to detect lactate in the LDR of 0-1 mM in saliva samples. The same group developed another simple sensor for salivary uric acid levels using uricase. Herein, PB-modified graphite ink as WE was employed which is fabricated by screen printing on a soft PET substrate.[27] The basic design and working mechanism of this sensor are illustrated in Fig. 2.6C. Recently, biofuel-based electrochemical sensors are being developed for ocular diagnosis, where the glucose or lactate in the tear itself is utilized to generate energy via small in-built circuits.[162,163] Self-healable and self-powered sensing systems are two other domains currently gaining rapid growth in health monitoring. Some representative work on noninvasive sensing of important molecules is summarized in Table 2.

2.5 Conclusion and future perspectives

The future developments of wearable devices will largely rely on the materials incorporated in the sensor design. The mechanical stability of the materials used in the wearable sensors is important for the flexibility, stretchability, and shelf life of the integrated sensor system. The currently applied strategies involves the use of composite materials (e.g., polymer–particle) or complex fabrication processes, which either reduces the sensing (electrochemical/optical) performance or the robustness of the sensing process.[171] Thus, synthesis of high-performance materials and scalable simple fabrication strategies should be prioritized. Also, the development of battery-free wireless devices for the continuous monitoring and data transmission, or low-power miniaturized devices, and energy harvesting rectenna (rectifier and antenna) are the major challenges to develop a more sustainable wearable devices.[20,172] Environment friendly materials, such as bio-based and biodegradable (or even compostable) flexible materials should be integrated to the wearable sensors.[173,174]

The emergence of lab-on-a-chip-based sensing concept led to the development of wearable sensors interfacing skin and other body surfaces for specific and robust methods of quantification of biological markers. Despite many successes in creating wearable sensors to detect multiple analytes, the current progresses are restricted to lab-based proof-of-concept models or prototypes. For their wider practical applications in health monitoring, wearable biosensors need to be based on low-cost platforms with higher sensitivity and selectivity. The wearable biosensors are to be improved for the detection of complex

TABLE 2.2 Examples of wearable biosensors for noninvasive monitoring of human health.

Noninvasive samples	Detection method	Materials used in sensor fabrication	Target biomarkers	BREs	Related health monitoring	References
Sweat	Amperometric	PET and PEDOT:PSS	Glucose, Na^+ and K^+	GOx	Cystic fibrosis and diabetes	29
	Amperometric	PDMS and AgNW	Lactate	MIPs	Glucose metabolism and sport performance	72
	Amperometric	Carbon fibers and conductive carbon ink	Lactate	LOx	Sport performance	155
	Impedimetric	3D patterned Au nanomaterial, PDMS and PVP	Cortisol	Antibody	Cushing's syndrome	164
	Colorimetric	Evolon® nonwoven fabric	Lactate	LOx	Fatigue	165
	Colorimetric	Cellulose nanofiber/chitosan-graphene oxide	Glucose Urea	GOx Urease	Diabetes Kidney failure	115
	Colorimetric	Chitosan/cotton with sodium carboxymethyl cellulose	pH Lactate	LOx	Dehydration Ischemia	120
	Colorimetric	PMMA on silicone	Creatinine Urea	Creatinase Urease	Kidney disorder	50
	Fluorescence	Cotton with lanthanide metal-organic frameworks	Chloride	Eu^{3+} emission	Cystic fibrosis	166

(continued)

TABLE 2.2 (Cont'd).

Noninvasive samples	Detection method	Materials used in sensor fabrication	Target biomarkers	BREs	Related health monitoring	References
Saliva	Amperometric	PET	Uric acid	LOx	Hyperuricemia	27
	Amperometric	PET	Lactate	LOx	Sport performance	161
	Amperometric	Carbon-Prussian blue ink on PET	Glucose	GOx	Diabetes	167
	Amperometric	SF15 and silicone elastomeric spacer Eco30	Na^+	-	Hypertension	168
	Amperometric	Polyethylene terephthalate glycol	Glucose	GOx	Diabetes	169
Tear	Amperometric	PET on contact lens	Glucose	GOx	Diabetes	43
	Amperometric	PET sheet	Glucose, vitamin B_2, C, and B_6	GOx	Diabetes	170

biomarkers such as proteins and nucleic acids for real-time monitoring of diseases. The innovation in novel materials synthesis, better sample extraction procedures, signal amplification strategies, signal processing, and transmission can lead to the effective sensing of different body fluids. The wearable sensors could be integrated to textiles or other accessories (like googles, face masks, diapers) for seamless sensing without affecting the daily life of user.

Declaration of conflict of interest

The authors declare that they have no conflict of interest.

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List of acronyms

AgNW	Silver nanowires
AuNW	Gold nanowires
a-GQDs	Aniline functionalized graphene quantum dots
BRE	Biorecognition element
CA	Chronoamperometry
CC	Chronocoulometry
CE	Counter electrode
CGM	Continuous glucose monitoring
CNT	Carbon nanotube
CP	Conducting polymer
CVD	Chemical vapor deposition
DPV	Differential pulse voltammetry
EDC	3-(dimethylamino) propyl) carbodiimide
GO	Graphene oxide
GOx	Glucose oxidase
GPTMS	3-glycidoxypropyltrimethoxysilane
ISF	Interstitial fluid
LDR	Linear dynamic range
LOD	Limit of detection
LOx	Lactate oxidase
LSPR	Localized surface plasmon resonance
LSV	Linear sweep voltammetry
MIP	Molecularly imprinted polymer
MoS_2	Molybdenum disulfide
MWCNT	Multiwalled carbon nanotube
$NaBH_4$	Sodium borohydride
NHS	N-hydroxy succinimide
PANI	Polyaniline
PB	Prussian blue

PBA	Phenyl boric acid
PBAT	Polybutyrate adipate terephthalate
PCB	Printed circuit board
PDMS	Polydimethylsiloxane
PEDOT	Poly(3,4-ethylenedioxythiophene)
PEN	Polyethylene naphthalene
PES	Polyethersulfone
PET	Polyethylene terephthalate
PETG	Polyethylene terephthalate glycol
PLEDs	Polymer light emitting diodes
PI	Polyimide
PPG	Photoplethysmography
POC	Point-of-care
PSS	Polystyrenesulfonate
PU	Polyurethane
RE	Reference electrode
rGO	Reduced graphene oxide
RGB	Red green blue
SERS	Surface enhanced raman spectroscopy
SF	Silk fibroin
SPR	Surface plasmon resonance
SWV	Square wave voltammetry
QDs	Quantum dots

References

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Chapter 3

Biorecognition elements

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3.1 Introduction

The biosensors are considered as powerful analytical tools thanks to their specific biorecognition element for the detection of analytes at a transducer giving a quantitative or qualitative physical signal. A biosensor can be simply defined as a device that listens to the chemical language of a biological system and then translates it into a digital quantitative or qualitative language that can be easily understood by scientists. A biosensor is composed of three main components, a biorecognition element (antibody, enzyme, etc.) that can recognize the targeted analyte selectively, a transducer that can convert the biorecognition event into a physical signal, and signal output device that can translate the data into a digital readable signal (Fig. 3.1A).[1–4] The biorecognition elements should be selective and sensitive at a low-concentration level to the desired analyte in presence of other interfering molecules. Otherwise, the interference could limit the selectivity and sensitivity of the developed biosensor. The understanding of the advantages and drawbacks of each biorecognition element and how it affects the biosensor analytical performance is very important to develop a successful biosensor and to enhance its features. Several strategies on the implementation of the biorecognition elements in the wearable biosensor have been reported.[5–11] Electrochemical biosensors have been widely explored for the detection of a plethora of analytes thanks to their outstanding characteristics, including low-cost, fast response, high sensitivity, and selectivity.[8,9] On the other hand, several optical biosensors have been also reported using different optical techniques, including colorimetric, surface plasmon resonance (SPR), fluorescence, chemiluminescence, etc.[12]

The advances in the biorecognition element (antibodies, enzymes, aptamers, nanozymes, CRISPR/Cas, etc.) used to develop the wearable biosensors have paved the way to build more sensitive, selective, and long-term stable biosensing devices. Many approaches have been used, and successful examples have

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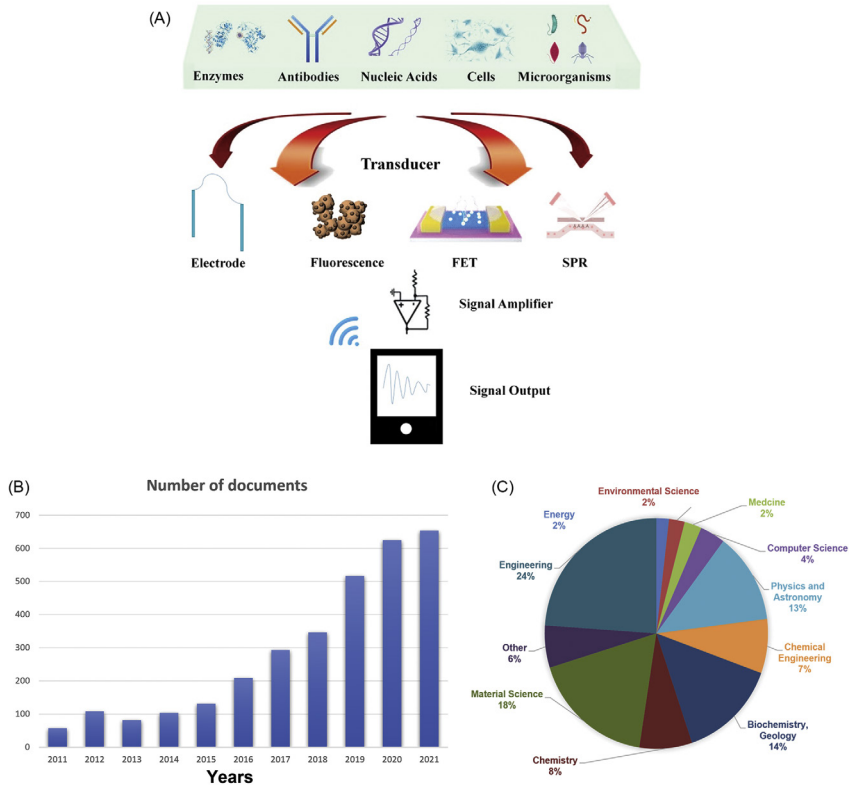

FIG. 3.1 (A) Typical biosensor is generally defined as an analytical system which schematically consists of a biorecognition element, a transducer element, a signal transmission and amplifier element.[16] Reprinted with permission from Elsevier. (B) The analysis of Scopus search results related to the wearable biosensors from 2011 to September 2021. (C) The subject areas of wearable biosensors during the same period.

already reached the market.[13,14] Due to the promise of the huge glucose sensing market, this commercial activity focuses largely on minimally invasive glucose monitoring biosensors. A successful example commercialized by Abbott is FreeStyle Libre system.[15] This wearable biosensor was based on electrochemical measurements for glucose in ISF.

A simple analysis of the search on wearable biosensors field at SCOPUS database in the last decade showed a significant increase in the number of published documents especially in the last three years (Fig. 3.1B). This confirmed clearly the importance given by the scientific community to this emergent research topic taking advantage of the outstanding advances in smart technologies. Both electrochemical and optical wearable biosensing devices are widely

explored recently. Fig. 3.1C indicates the subject areas of the application of wearable biosensors. Multidisciplinary areas are interconnected to provide cutting-edge wearable biosensing technologies.

The main objective of the present chapter is to focus on the use of different biorecognition elements in wearable biosensors as well as their important and successful applications. Possible solutions of the current challenges to increase the wearable biosensing devices' performance are also covered. Moreover, the prospects in this field are also presented and highlighted.

3.2 Biorecognition elements in wearable biosensors

This section points out the main biorecognition elements used in the development of highly sensitive, selective, and accurate wearable electrochemical and optical biosensors.

3.2.1 Antibodies

Immunosensors, also known as antibody-based biosensors, rely on the principle of natural antigen-antibody interaction.[17] The immunosensors exhibit high sensitivity with the ability to detect biomolecules in concentration levels from nM to fM. Two types of sensing methods are usually followed in immunosensors, labeled and label-free techniques.[18] Indeed, in label-free based immunosensors, the interaction between antigen and antibody can be quantified by measuring the changes in sensor surface properties that are translated by an appropriate transducer into electrochemical, piezoelectric, or optical immunosensors. While, the label-free biosensing methods are used for the quantification of bulky targeted analytes, including cells and proteins,[18,19] immunosensors based on labels are especially useful for the detection of smaller molecules. The label could be any material or chemical that can react with the antibody or antigen and evaluate the amount of the analyte.[20,21]

Many configurations of antibody, antigen, as well as labeled antigen, can be categorized as a direct sandwich, competitive, and indirect configurations as presented in Fig. 3.2. The direct sandwich configuration consists of the capture antibody layer immobilized onto the sensor surface and fixed on the desired antigen on the other side. The addition of this reporting antibody as a second step leads to the antigen detection. In this strategy, the antigen should be polyclonal to be able to bind both capture antibody and the reporting antibody. Regarding the indirect configuration, this approach is different from the direct sandwich in the binding site of the reporting antibody that binds to the capture antibody in the indirect method. The third approach consists of a competitive assay that can be implemented by both reporting antigen and reporting antibody.

It is noteworthy that direct sandwich methods are favorable for larger molecules with many antibody binding sites, however, a competitive method is efficient for smaller molecules with single binding sites.[22]

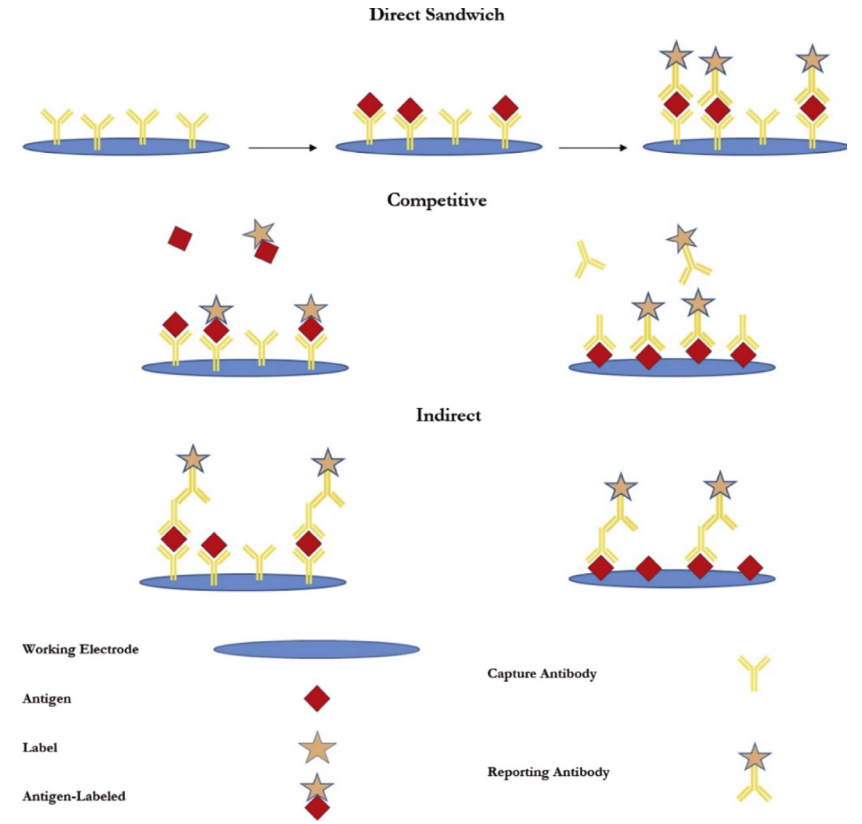

FIG. 3.2 Schematic illustration of different conventional (direct sandwich, competitive, and indirect) configurations in immunosensors.[23] Reprinted with permission from Elsevier.

Recently, many electrochemical wearable immunosensors have been designed and applied for the determination of different health biomarkers.[9,24–26] Electrochemical impedance spectroscopy (EIS), and voltammetry are the most used techniques for the development of wearable electrochemical immunosensor to monitor the antigen-antibody interaction in the presence of a redox probe. The optical wearable immunosensors are based on the change in fluorescence, absorbance, or luminescence while the targeted analyte is binding demonstrating prominent applications especially in low-cost resource settings. Usually, the optical immunosensor uses a customized smartphone as a reader to quantify the biochemical binding.[22] Various optical point of care (POC) immunosensors have been developed.[27–29]

3.2.2 Enzymes

Recently, the enzymatic biosensors (especially the electrochemical ones) have attracted much attention as a powerful tool for the introduction of novel wearable

biosensors.[30–33] The integration of enzymes as biorecognition elements with electrochemical transducers has been considered as one of the well-established bioelectronic systems thanks to their outstanding selectivity and catalytic properties due to the enzyme's natural behavior.[34,35] The use of enzymes as catalytic systems exhibits favorable sensing at mild physiological conditions of temperature and pH.[36] Moreover, enzymes are highly specific by catalyzing only a particular catalytic reaction. This outstanding enzyme feature enables wearable electrochemical biosensors to function selectively in biological fluids.[37–39] The transformation of traditional enzymatic approaches into much developed enzymatic wearable biosensing platform has been evolving.[40] Hence, the wearable enzymatic electrochemical biosensors paved the way for the extension of the applications of these sensors in personalized healthcare and fitness. In this context, Abbott have developed a commercialized continuous glucose monitoring device "FreeStyle Libre" that provides real-time glucose readings of glucose levels. This wearable small device offers an excellent alternative to replace the finger stick of traditional blood glucose testing.[15]

The immobilization process of enzymes onto the working electrode surface of the biosensor is considered as a crucial parameter in the development of enzymatic wearable biosensors. Indeed, the immobilization of the enzyme affects the lifetime of the biosensor, enhances its stability, and reduces the analysis response time. Several immobilization techniques, including covalent binding, physical adsorption, entrapment, and covalent crosslinking have been extensively used to immobilize the enzymes onto the surface of the electrochemical transducer.[3,41,42]

There are different mechanisms of enzyme-based wearable biosensors. Most applied approach is based on the conversion of the analyte as an enzymatic substrate into a product allowing its measurement using a transducer.[43] Another strategy is monitoring the targeted analyte that can act as an enzyme inhibitor.[44,45] Moreover, the enzyme can be also employed as a labeling transducer especially for biological affinity recognition systems. In the last decade, the enzymatic wearable biosensing approaches have been used to detect many analytes, including lactate, glucose, alcohol, neurotransmitters, and stress hormones in biological fluids. Hence, lactate oxidase, glucose oxidase, and alcohol oxidase are the most used enzyme as biorecognition element in wearable biosensors.[9,46–54]

A successful example of the use of enzymes as a biorecognition element for wearable electrochemical biosensors was developed by Bandodkar et al.[55] Indeed, they developed a noninvasive sensing strategy for monitoring glucose levels using a skin-worn temporary tattoo biosensor using amperometric measurements coupled to a reverse iontophoresis operation. This sensing strategy relies on the use of a lower current density to extract the glucose from the skin interstitial fluid (ISF) followed by the amperometric measurements at the glucose oxidase-modified, Prussian blue-mediated carbon working electrode. This flexible, cost-effective, non-invasive sensing strategy using a successful biorecognition element clearly showed the importance of these applications that

can be mated easily with the human skin. Enzyme-based optical wearable biosensors have been also reported.[56,57] Indeed, the colorimetric biosensors are becoming popular due to their simplicity that rely on a camera of a smartphone as readout device. In this context, Vaquer et al. have reported a wearable analytical device capable of lactate determination using an enzymatic sensor made of filter paper. The change of light color was captured using a smartphone. The lactate enzymatic sensor achieved a low limit of detection (LOD) of 60 μM within the concentration range of 10–30 mM. The developed wearable optical enzymatic biosensor was successfully applied to detect lactate in sweat samples.[58]

3.2.3 Nucleic acid-based recognition elements

The nucleic acids are macromolecules involved in transmitting the genetic information of every organism from one generation to another. Nucleic acids are composed of nucleotides that have a structure comprising, a sugar (ribose or deoxyribose), phosphate, and a base (purine or pyrimidine). Two main types of nucleic acids can be distinguished as single-chain ribonucleic acid (RNA) and double-chain deoxyribonucleic acid (DNA). The different base types that make up the DNA chain are cytosine, adenine, cytosine, thymine, and guanine. Similarly, RNAs have same bases with uracil in place of thymine. Moreover, each base is linked through hydrogen-bonded with another base of the complementary chain in certain favorable configurations. Hence, cytosine binds with guanine and adenine binds with thymine.[59] Likely, one strand of DNA can be complementary joined with another chain forming a double strand. This biorecognition event is characterized by its high specificity. In the case of a biosensor using nucleic acids as recognition element, when the transducer is exposed to the sample containing the target, the hybrid is formed on the transducer surface.[60]

The electrochemical genosensors also knowns as DNA biosensors are analytical tools that consist of a biorecognition unit (single strand DNA [ssDNA], also named a probe), which provides the biosensor selectivity, and an electrochemical transducer that translates the recognition event into a measurable electrical signal. Different approaches are reported to immobilize the DNA to prepare the electrochemical wearable genosensors. Usually, the DNA immobilization is based on multi-site attachment using simple adsorption methodologies. ssDNA immobilization on the electrochemical transducer surfaces using one-point attachment is considered. The attachment of ssDNA molecule by a 3′ or 5′ end results in a strong hybridization reaction. The nucleic acid as biorecognition elements have found many applications to the development of wearable biosensors.[26,61–64]

The drawbacks of the natural receptors have led the researchers to focus on employing the synthetic receptors, known as having their high stability, low-cost, scalability, and being animal-free development/production. In the next section, we are focusing especially on the use of affimers, CRISPR/Cas,

molecularly imprinted polymers (MIPs), and nanozymes as recognition elements in the development of wearable biosensors.

3.2.4 Other biorecognition elements

3.2.4.1 Aptamers

Aptamers are synthetic oligonucleotides or peptides adapted to bind to target molecules, which can be highly specific nucleic acids. They are generally generated through selection among numerous sequences at random or a gene bank by a method named Systematic Evolution of Ligands by EXponential Enrichment (SELEX).[65] The sequences obtained have a variable analyte-specific core and conserved side sequences. Normally, the specificity attained by the analyte is sufficient that it needs only about 20 oligonucleotides to be synthesized. Aptamers are considered advantageous over antibodies due to their considerable small size, chemical long-term stability, low-cost, and their easiness of modification without the need for cell cultures or animal hosts.[66–68] In addition, aptamers as biorecognition elements can be used against many target analytes including small organic molecules to proteins, cancer cells, viruses, and bacteria.[69] Recently, they are also being investigated as bioreceptors in the field of wearable biosensors.[70,71]

3.2.4.2 Affimers

Another interesting type of biorecognition elements are the affimers which are usually known as peptide aptamers.[72] Affimers are a new developed class of labeling probes (~10–12 kDa, ~2 nm) that are isolated from large phage display libraries (~10^{10}).[73,74]

This allows screening of large quantities of protein-binding molecules for specific selection of high affinity binders of the target protein. Importantly, cross-reactivity to proteins related to the target can be minimized via counter-selection by gene engineering. Affimer proteins are generated from bacterial expression systems[75] and can, therefore, easily be produced in large quantities with minimal batch-to-batch variation. Together, these characteristics make affimers suitable to readily replace antibodies in a variety of applications.[72] The ability to quickly isolate affimers with high specificity and affinity that can be used in different applications in biosensing. These characteristics of affimers as biorecognition elements could make them suitable to build future wearable biosensing devices.

3.2.4.3 CRISPR/Cas

Clustered regularly interspaced short palindromic repeats also known as CRISPR and CRISPR associated proteins (Cas), also referred as CRISPR/Cas systems, is defined as a nucleic acid-based adaptive immune system that plays a role of acts protecting microorganisms from viral infection.[76] Usually, the CRISPR/Cas systems rely on the bacterial ability to store a fragment of foreign

phage genome in the CRISPR loci, as a memory of past encounters; these loci, together with surrounding repeats, are then used by Cas endonuclease proteins as guides to selectively recognize sequences in the foreign genomes and fight the invader.

Along with the biological impact of these programmable enzyme systems, CRISPR/Cas systems have gained an increasing attention in several biotechnology research fields where selectivity is critical, including gene editing, transcription regulation, and development of innovative biosensing devices.[77–79]

Therefore, due to their selectivity and programmability, CRISPR/Cas systems have been rapidly adapted as a recognition element in the development of biosensors and biosensing systems for the detection of nucleic acids, which are important targets in molecular diagnosis. Indeed, Nguyen et al. have recently demonstrated the development of a face mask based on a lyophilized CRISPR-powered sensor for wearable, noninvasive optical detection of SARS-CoV-2 viruses at ambient temperature within 90 min.[64] This device contains an Origami-based sample preparation unit for lysis, isothermal amplification, and CRISPR-powered signal generation of nucleic acids that can be activated by the user after sampling. The optical signal readout was then performed using LFAs by the naked eye.

3.2.4.4 Molecularly imprinted polymers

MIPs have been extensively explored as potential alternative to natural receptors.[80,81] The principle of the synthesis and preparation of MIPs consists of the generation of imprinted cavities that are complementary in shape, size as well as functional interactions with the imprinted template.[82–85] Templates can be small molecules or ions to large proteins, virus, bacteria, and whole cells.[80,86,87] The operating principle of MIPs is the "lock and key" mechanism, where the template molecule is imprinted within a polymer so that the polymer can selectively interact with the template molecule alone. Potentially, MIPs offer a low-cost, sensitive and selective sensing approach that is also durable.[88]

Biomimetic sensors can detect biological events by mimicking their natural detection mechanism. MIPs are a promising biomimetic sensing strategy that forms artificial receptors to capture the desired molecule. MIPs have been used in several branches such as environmental, food, and drug delivery.[82,89,90] The aim of using MIPs as a biorecognition element is to mimic the performance of natural antigen-antibody systems.[91] The combination of the molecular recognition element with methods that monitor the state of the recognition elements, such as the aforementioned electrochemical or optical detection techniques, offers promising strategy for selective and sensitive sensing of various targets.[92] Currently, the imprinting of polymers is the most cost-effective, scalable, and generic strategy to design and fabricate synthetic receptors.[93] MIPs provide many advantages, such as high affinity and selectivity as biological receptors, high stability, long lifetime, as well as their easiness of preparation, which reflect the growing attention in this field.[85] The MIP-based electrochemical sensors enable a specific recognition site for targeted analytes in many applications especially in the implementation of MIPs in wearable electrochemical sensors.[80,94–98]

Recently, electrosynthesized MIP films as sensing platform have started to gain the attention of the researchers thanks to their advantages including easiness of sensor fabrication, reusability due to regeneration capacity of MIPs, low-cost and less time to process the electropolymerization.[87,99] Indeed, Zhang et al. have reported a flexible electrochemical biomimetic sensor based on sliver nanowires (AgNWs) and imprinted polymer for the detection of lactate in the perspiration samples. In this study, the AgNWs exhibited excellent electrical conductivity and flexibility. The developed sensor is based on a flexible screen-printing substrate for the monitoring of lactate in the skin biofluids. The imprinted polymer film was prepared by electropolymerization of 3-aminophenylboronic acid (3-APBA) monomer in the presence of lactate as the template molecule in phosphate buffer saline (PBS) on the AgNWs structure. Then, the lactate molecules were removed from the polymer network leaving behind specific cavities capable for the detection of lactate in sweat samples. As presented in Fig. 3.3, the skin lactate sensor is composed of silver/silver chloride (Ag/AgCl) reference electrode, carbon modified with MIPs and AgNWs as working electrode, and unmodified carbon as counter electrode. The implemented MIP-based wearable biosensor exhibited high selectivity, and sensitivity for detection of lactate in sweat samples collected from volunteers and measured using differential pulse voltammetry as an electroanalysis technique. This novel strategy based on noninvasive, flexible, lactate biosensing clearly showed a proof-of-concept of MIPs applied to a wearable device.

Despite the several successful applications of MIPs in the development of wearable sensors, there are still many drawbacks and challenges to be overcome: (1) In fact, the MIPs exhibited high sensitivity toward the detection of small molecules while they exhibit a low sensitivity towards the biorecognition of large molecules and biological compounds such as proteins, viruses, and bacteria. Moreover, the current MIPs synthesis techniques for these large compounds still facing a limit of imprinted binding sites. Thus, the sensitivity should be improved to detect trace concentration level of larger biomolecules. (2) There is a great demand for eliminating the issue of nonspecific binding, especially for the applications in physiological fluids rich in proteins.[100]

3.2.4.5 Nanozymes

As introduced by Wei and Wang, the term of nanozyme is defined as nanomaterial-based artificial enzyme that can mimic enzyme properties.[101] The concept of nanozymes has attracted enormous attention of scientists working in different fields thanks to the tremendous advantages of nanozymes including high stability, simple preparation, low-cost and easy surface modification. Currently, various nanomaterials have demonstrated their enzyme-like activity especially oxidoreductase and hydrolases.[102] Nanozyme-based oxidoreductase-like activity, including catalase and peroxidase have been extensively employed in biosensors.[103] It is noteworthy that the nanozymes cannot compete with functional natural enzyme in term of specificity, but they can exhibit better stability that makes them prominent alternatives in building next generation of wearable biosensors.[104,105]

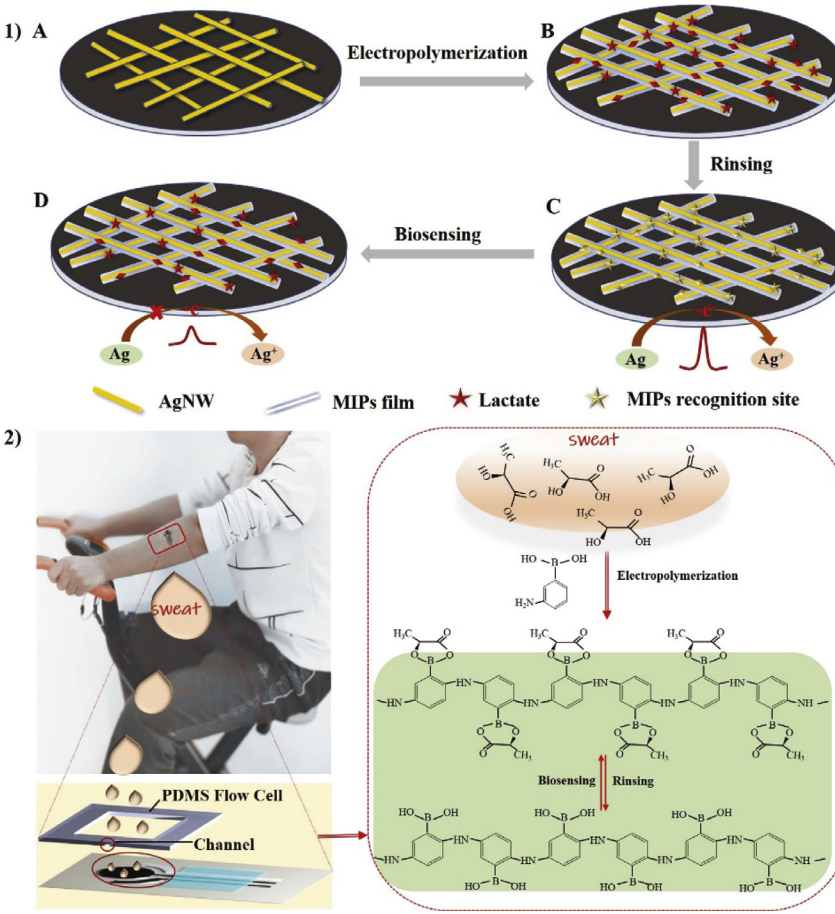

FIG. 3.3 The scheme shows the fabrication of the MIPs-AgNWs electrochemical biosensor for the epidermal monitoring of lactate. (1) (A) AgNWs spin-coated on the carbon working electrode (WE). (B) Lactate MIPs-AgNWs on WE. (C) Lactate imprinted recognition cavities of lactate MIPs-AgNWs electrochemical biosensor. (D) Lactate biosensing with imprinted recognition sites in buffer solution or human sweat. (2) Image of a screen-printed biosensor chip with three-electrode setup applied on a volunteer's arm, and the working principle of MIP formation and lactate biosensing using MIPs. Reprinted with permission from Elsevier.[98]

3.2.4.6 Lectin as biorecognition elements

Lectins are proteins of non-immune origin that can interact with carbohydrates with high specificity without a need for modification.[106] The Concavaline A (Con A) is the most frequently used lectin protein as the sugars are selective lectin. Con A is useful for immobilizing enzymes, including horseradish peroxidase and glucose oxidase on the surface of transducer to create biosensors for hydrogen peroxide or glucose.[107–109]

Due to their specificity to bind to bacterial surface sugar, Con A is also employed as a modification agent for electrodes that can be used as electrochemical sensors for sensitive detection of cancer cells and pathogens.[110] Another biorecognition element that can be also mentioned is boronic acid that is usually known by its high interaction at physiological pH values with 1,2 or 1,3 diols. This famous interaction has been already widely used for biosensing platforms in order to measure molecules that contains diol including sugars, dopamine as well as for bacteria.[111,112]

3.3 Immobilization strategies for biorecognition elements

The immobilization of the biorecognition elements onto the surface of the transducer helps in stabilization of the biomolecules and affects largely the analytical performance of the developed biosensor. The biorecognition elements can be directly immobilized onto transducer surface or through a support that can be attached to the transducer. It is noteworthy that keeping the active part of the biorecognition element accessible for target is very important, while maintaining its bioactivity and conformational stability. Therefore, a suitable immobilization technique should be fast, soft, and makes it easy to fix the biorecognition element at the transducer surface. There are many important parameters that can affect the immobilization including the size of biomolecule, the polarity, the shape, and the presence of functional groups. The widely used methods for the immobilization of biorecognition elements are covalent binding, crosslinking, adsorption, entrapment, and affinity binding.[113]

3.3.1 Covalent binding

This method consists of the formation of covalent interaction between the sensor surface and the biorecognition element and is considered as the most used immobilization technique. Indeed, the covalent binding is done through the functional groups of the biomolecule, including hydroxyl, amino, carboxylic, and thiol that are usually employed to bind antibodies and enzymes.[114] The formation of covalent bonds between the transducer and the biorecognition element usually requires the linker functional groups. Among them, succinimide and aldehyde-based reactive group are mainly used. The covalent binding as immobilization technique ensures a strong chemical binding of biomolecules and inhibits their desorption. However, the covalent binding usually requires long time to bind the biorecognition elements as well as the use of other (and mostly toxic) chemicals.

3.3.2 Crosslinking

The crosslinking method is based on crosslinkers that have free reactive ends and are used to form covalent bonds that are strong and can attach biomolecules

onto the transducer surface. Glutaraldehyde and glyoxal are well known crosslinkers that are usually employed for biosensors development.[113,114] When the crosslinker is used, the bioreceptors should be bound without affecting its conformation significantly, because small changes may influence the binding of a ligand to a protein. Enzymes as well as cells can be immobilized on transducers by addition of crosslinking agents.

3.3.3 Entrapment

This technique consists of a polymeric gel that is prepared in a solution that contains the biorecognition element. The polymeric structure is expected to hold the bioreceptor (mostly an enzyme) inside and allows the substrate and products to pass through it. Starch, polyacrylamide, chitosan, and sol-gel like polymers are used for the entrapment of bioreceptors since they can provide a proper environment.[113] The entrapment as an immobilization technique for biorecognition elements is one of the easiest techniques where the mediators and stabilizing agents can be deposited simultaneously on the sensing layer. Thus, it offers a great potential for developing wearable biosensors.[115]

Electropolymerization is a simple technique that is used for the entrapment of recognition biomolecules, mainly enzyme molecules, at the surface of the electrochemical transducer. Indeed, the enzymes present in the solution close to the electrode are trapped inside the polymeric growing network during the polymerization process initiated by oxidation of the monomer by performing cyclic voltammetry or chronoamperometry. Most of the used polymer films for the immobilization of the enzyme are conducting polymers, including polyaniline, polypyrrole, or polythiophene.[116,117]

3.3.4 Adsorption

The adsorption of bioreceptors is also a well-known and simple technique which based on attaching the biorecognition elements onto the transduce surface using Van-der Waal's forces, hydrogen bonds, multiple salt linkage and through the formation of electron transition complexes. Indeed, many macromolecules, such as cellulose, silica gel, hydroxyapatite, and collagen have a great ability to adsorb biomolecules.[113] It should be noted that the size of the biomolecule plays a role in the adsorption process. This method can be also used for cell immobilization because some cells naturally adsorb onto various surfaces.[118]

3.3.5 Affinity binding

3.3.5.1 Biotin-avidin interaction

The avidin-biotin (or biotin–streptavidin) interaction is considered as one the strongest noncovalent interactions. This interaction is characterized by dissociation constant between protein and ligand of the order of 10^{-15} M.[119] The

complex formation is fast, and once formed resists high temperatures, pH variations, and dissociation when exposed to detergents or denaturing agents. Neutravidin, is used in some specific cases to reduce nonspecific binding to maintain high affinity for biotin.[120]

Moreover, biotin is a biomolecule, endogenous biotin can cause specificity problems, especially when performing assays with some biotin-rich tissues and extracts including liver, milk, brain, eggs, and corn. In addition, the strong interaction between biotin and avidin may also affect the application where this binding is required, as there is a need for harsh conditions to break the avidin-biotin bonds which may denature the target proteins.[108]

3.3.5.2 Antibody-binding proteins

Another affinity-based immobilization method commonly used to capture antibodies in immunoassay systems involves a bacterial antibody-binding protein.[120] Protein A and protein G are the most used. These proteins can specifically bind to antibodies via their nonantigenic (Fc) regions. This allows the availability of the antigen binding sites of the immobilized antibody to bind the target analyte. Because these proteins can interact directly with the Fc region of the antibodies, the biotinylation of the antibody is not needed. Protein A has a molecular weight of around 42 kDa and was isolated from the cell of *Staphylococcus aureus*. Protein A contains five Fc binding domains located at its amine ($-NH_2$) terminal. The optimal binding exhibits a pH 8.2, while the binding is also effective at neutral to physiological conditions (pH 7.0 to 7.6). However, the interaction between protein A and IgG is not equivalent for all species. Even within a species, protein A interacts with some subclasses of IgG and not others and it is limited to three human IgG subclasses including IgG 1, 2 and 4. Protein G is the second bacterial antibody binding which is isolated from a cell surface protein of group C and G *streptococcus* containing three Fc binding domains towards near its C-terminal. Protein G has specificity for subclasses of antibodies from different species. The optimal binding is at pH 5.0, although the binding is also efficient at pH 7.0 to 7.2. Protein G has better affinity compared to protein A for most mammalian IgGs.[121–123]

3.4 Applications of wearable biosensors for monitoring body fluids

Wearable biosensors are considered as revolutionary analytical tools for diagnostics. The outstanding features and advantages of these analytical tools, including their cost-effectiveness, rapid analysis, continuous monitoring, user-friendliness, and connectivity make them favorable over the traditional instruments. A typical approach which is common for disease diagnosis usually involves the monitoring of numerous biomarkers present in invasive biological fluids like blood and urine that are not favorable for real-time monitoring.[124] For the wearable biosensors, alternative body fluids are desirable such as sweat,

saliva and tears. In this section, some successful applications of biorecognition elements in wearable biosensors applied to these body fluids will be presented.

Table 3.1 presents a comparison of the representative electrochemical and optical biosensors for the detection of different biomarkers from different target biofluids, including sweat, saliva, tear, and sweat. It can be clearly noticed that the enzymes are the most used biorecognition elements for the development of wearable biosensors. Moreover, amperometry has been also heavily explored a

TABLE 3.1 Overview of the biorecognition elements used in wearable electrochemical and optical biosensors.

Biorecognition element	Analyte	Body fluid	Measurement method	LOD	Reference
Lactate oxidase	Lactate	Sweat	EIS	NR	46
Uricase	Uric acid	Saliva	Chronoamperometry	100 μM	125
Pyruvate oxidase	Phosphate	Saliva	Chronoamperometry	38 μM	126
Lactate oxidase	Lactate	Sweat	Chronoamperometry	137 μM	53
Lactate oxidase	Lactate	Sweat	Amperometry	NR	127
Glucose oxidase	Glucose	Saliva	Amperometry	5 μM	128
Glucose oxidase	Glucose	Tear	Amperometry	50 μM	129
Glucose oxidase	Glucose	Sweat	Amperometry	10 μM	130
Cortisol antibody	Cortisol	Sweat	DPV	7.47 nM	61
Cortisol antibody	Cortisol	Sweat	EIS	88 pM	26
ssDNA probe	mRNA 21	Saliva	DPV	NR	62
MIP	Lactate	Sweat	DPV	220 nM	98
MIP	Cortisol	Sweat	Amperometry	1 pg ml^{-1}	97
CNTs/AuNPs	Glucose	Urine	LSV	NR	131
CuO	Glucose	Tear	Amperometry	2.99 μM	132
Boronic acid-containing fluorophores	Glucose	Tear	Optical/fluorescent/diffraction	NR	133
Glucose oxidase	Glucose	Tear	Optical camera	NR	134
Polystyrene CCA in 4-BBA-modified PVA hydrogel	Glucose	Tear	Optical/diffraction	50 μM	135
Boronic acid derivatives	Glucose	Tear	Optical/diffraction	1 μM	136

detection electroanalysis technique (see Chapter 4). Other biorecognition elements, including the antibodies, molecularly imprinted polymers, are also used. The developed wearable biosensors are heavily applied for different body fluids with more focus on sweat samples.

3.4.1 Sweat

Human sweat is considered a source of tremendous biomarkers that provide information about the patient's health status. Hence, the sweat sample is one of the real samples that found a plethora of applications of wearable electrochemical biosensors. Human sweat contains different metabolites, hormones, proteins, electrolytes, sodium, ammonium, calcium, etc.[11] It should be noted that sweat-based wearable biosensors can generate real-time information about the health status of a patient as well as fitness monitoring. The wearable biosensors can be categorized into two different groups: tattoo (also known as epidermal) and textile/plastic-based sensors. The flexible plastics have been extensively explored to fabricate wearable sensing devices since they are inexpensive, and their surface properties can be easily modulated for immobilizing reagents.[137] The tattoo-based biosensors provide better contact with the skin. They have been extensively employed for the sensing of glucose,[55,138–140] urea,[5] alcohol,[14,38] and lactate[53,105] concentration levels in human sweat. Wearable biosensors present a potential technique for real-time monitoring of biological changes in sweat samples, thanks to their enormous advantages of noninvasive sample collection and miniaturisation.[141,142] The wearable sweat biosensors belong to a practical sensing technology that certainly paves the way toward the integration of personalized and real-time clinical and physiological diagnosis.[143]

3.4.2 Saliva

Saliva is a complex oral fluid that is produced by salivary glands.[144] The saliva components include a variety of biological agents including substances produced from salivary glands (organic substances, electrolytes, proteins, and enzyme), permeating substances from blood (sugars, hormones, and growth factors), virus, microorganisms, and their products as well as external substances, such as drugs and foreign chemicals. It should be noted that many of these salivary agents are effective as clinical biomarkers.[145]

However, saliva testing has several complications compared to blood testing. Firstly, the concentrations of biomarkers are several orders lower in saliva compared with blood levels. The sensor should provide a high sensitivity along with low detection limits. Moreover, the background noise, interferences from coexisting biological species, and viscosity of saliva are all must be considered before its application in clinical diagnostics. This includes avoiding food with high sugars or acidity, avoiding consumption of alcohols, caffeine, and nicotine, documenting a strong physical activity or the presence of oral injury, avoid eating a major meal before one hour from sample collection, and rinsing the

mouth with water and wait for 10 min before collecting the saliva sample.[146] Besides, there are challenges due to the lack of standardized sampling methods and procedures. The salivary flow rate affects the concentration of the analytes. Factors such as age, medications, gender, individual hydration, diet, exercise, smoke, appetite etc., affect the composition of salivary analytes, which makes the saliva diagnostics not so much reliable as blood analysis.[144] On the positive side, several technical advancements in biosensors that include novel flexible electrode devices, microfluidics, smartphone sensing, as well as other optical techniques, paper-based electrodes, and wearable sensing have been introduced recently.[145,147] Moreover, the implementation of novel materials, advances in use of the bioreceptors, synthesis methods, and high-quality material characterization techniques are fueling the salivary analysis to solve the current major issues with sensitivity, selectivity, and reproducibility.

Kim et al. have reported a novel mouthguard-based electrochemical biosensor for uric acid monitoring in saliva samples.[125] The wearable biosensor was fabricated by employing screen-printing technology on flexible polyethylene terephthalate substrate for the measurement of uric acid in artificial and human saliva samples. Moreover, the applicability of the wearable biosensing strategy has been successfully demonstrated by applying this device to monitor hyperuricemia patient samples (Fig. 3.4). This mouthguard biosensor could be attractive for the continuous noninvasive monitoring of uric acid in saliva samples and can be extended for other analytes.

3.4.3 Tear

Human tears are composed of complicated physiological fluid with 98% of water and 2% of low and high molecular weight compounds, including

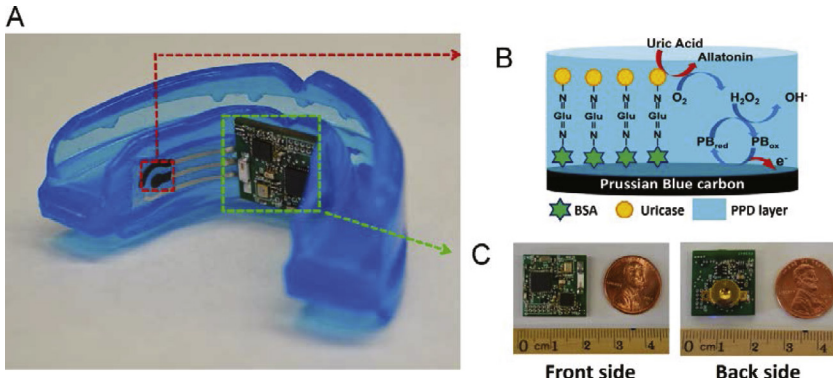

FIG. 3.4 (A) Photograph of the mouthguard biosensor integrated with wireless amperometric circuit board. (B) Reagent layer of the chemically modified printed Prussian-blue carbon working electrode containing uricase for UA biosensor. (C) Image of the wireless amperometric circuit board: front side (left) and back side (right).[125] Reprinted with permission from Elsevier.

small organic molecules, enzymes, proteins that are secreted by lachrymal glands.[148,149] Various compounds have been found in tear fluid, including glucose, lactate, urea, ascorbate, and neurotransmitters.[150] Recently, the tear-based wearable biosensors have attracted much attention as prominent strategy for real-time monitoring of ocular as well as different common diseases.[129,150–152]

In this context, scientists have developed a biosensor employing an actual ocular contact lens.[153] The contact lens-based biosensors provide an attractive platform thanks to the comfort of the wearer, excellent oxygen permeability, the consistent yield of the biofluid, which leads to accurate and real-time monitoring ability. Even though many successful studies have been developed, tear-based wearable biosensors are still at the infant stage and have not yet been commercialized due to several technical challenges. The main drawbacks of this biosensing strategy are the samples collection of analytes, time delay with respect to circulating blood levels, detrimental side products, size, as well as the transparency of the device. All these technical challenges should be overcome to bring tear-based biosensors to the market.

3.5 Current challenges and prospects

The early diagnostics of disease biomarkers becomes a global necessity, especially in third-world countries as most people have less access to medical care systems. Hence, there is a high demand for on-site, non- or minimally-invasive, and wearable diagnostic devices for measuring disease biomarkers at the point of care.[10,154–157] The classical diagnostic tools require long turnaround times, highly skilled personnel, laborious instruments, and are expensive.[158] An alternative approach to these methods is the use of low-cost POC devices to detect specific disease biomarkers saving time, money, and effort.[14] Hence, the development of more reliable, simple, end-user friendly, and convenient systems is of great demand to overcome the medical need. In this context, since wearable biosensors offer outstanding properties such as high accuracy, ease of use, and cost-effectiveness as POC tools, they can be very useful to fulfill the requirements in the field.[39,159–161] These platforms have gained increasing attention thanks to their high potential in various applications, especially for the real-time monitoring of health parameters at POC settings.[14,137,162]

Earlier, a plethora of wearable physical sensors has been widely investigated to address the high need in monitoring biophysical signals including respiration rate, vascular dynamics, brain activity and skin temperature.[163–167] In particular, wearable biophysical sensors require either complex algorithms or external measurements to precisely diagnose a disease by providing direct information about a specific disease biomarker in body fluids.[129,168] It should be noted that the market share of wearable biosensors is increasing, and its revenues are expected to reach 73 billion USD by 2022.[164,169] This significant increase in the demand for wearable devices is due to the preference for the rapid diagnosis, enabling a home healthcare. As a result, the need of developing

novel and improved POC tools has been increasing to meet the requirements of end-users. Currently, extensive efforts are devoted to create wearable biosensors incorporating a biorecognition element (i.e., antibody, enzyme, aptamer, affimers, etc.). The wearable biosensors demonstrated a promising potential to meet this increasing demand thanks to their high accuracy, specificity, friendly use, and possibility of integration into handled devices. Hence, the development of novel biosensing systems is highly desirable. The importance of this field is evident from the significant increase of novel reported proof-of-concept studies.

In recent years, the wearable biosensors have been extensively explored. Tear, sweat, ISF, and saliva are the most used biological fluids to apply the developed wearable biosensing devices. Even though this great advance in this field, there are still numerous technical limitations that should be addressed to get these biosensors successfully commercialized. The main challenges are the biofouling of the sensing surfaces, the acquisition of low sample volumes, as well as biocompatibility. Another important issue that these biosensing platforms face is the lack of correlation between the biomarker concentrations in blood and in other biological fluids such as sweat, tear, and saliva. For example, the salivary biosensors usually offer reliable measurements of amylase, lactate as well as other proteins, however, they still lack to provide a precise detection of glucose.

To meet the high demand for wearable biosensing devices, the ongoing and future research in this field should focus on the following points:

1. The development of new device architectures for wearable biosensors will be further investigated.
2. The synthetic receptors (MIPs and nanozymes) as recognition element are still in the infant stage for the development of wearable biosensors, therefore, more synthetic receptors should be extended for a plethora of applications.
3. The MIPs offer capability to regenerate/reuse the sensing surface using optical/electrochemical stimuli or solvent wash out. This feature makes MIPs recognition elements important to be implemented in the development of wearable biosensors targeting continuous/long-term monitoring.
4. The nanozymes as novel catalysts can be more exploited for the implementation of wearable biosensors. Their advantages such as low-cost preparation, long stability, and good selectivity make them the suitable alternatives for traditional biorecognition elements.
5. The use of lectin-based protein as biorecognition element could be further explored mainly for glycated targets.
6. Related to the detection techniques, the electrochemical biosensors are heavily used in wearable approaches thanks to their capability for continuous measurement, but there is still a need to develop more optical approaches that make the analysis possible by the naked eye, or more precisely using smartphone cameras.

7. The sample collection strategies in wearable biosensors should be further explored. Herein, we believe microfluids will play a crucial role and thus, their implementation in wearable biosensors would be of great interest.

By overcoming all the above-mentioned drawbacks with advanced or next generation biorecognition elements, the acceleration of the commercialization process of the wearable biosensors will lead to a major shift in the healthcare systems towards personalized medicine.

Declaration of conflict of interest

The authors declare that they have no conflict of interest.

List of acronyms

LSV	Linear sweep voltammetry
DPV	Differential pulse voltammetry
CV	Cyclic voltammetry
WE	Working electrode
3-APBA	3-aminophenylboronic acid
PBS	Phosphate buffer saline
Ag/AgCl	Silver/silver chloride
NR	Not reported
CNTs	Carbon nanotubes
AuNPs	Gold nanoparticles
AgNWs	Silver nanowires
EIS	Electrochemical impedance spectroscopy
MIPs	Molecularly imprinted polymers
CuO	Copper oxide
PVA	Poly (vinyl alcohol)
$-NH_2$	Amine
PCCA	Polymerized crystalline colloidal array
UA	Uric acid
DA	Dopamine
POC	Point-of-care
ISF	Interstitial fluid
Con A	Concavaline A
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
ssDNA	Single strand DNA
CRISPR	Clustered regularly interspaced short palindromic repeats
SELEX	Systematic evolution of ligands by exponential enrichment

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Chapter 4

Signal detection techniques

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4.1 Introduction

The enormous advances that have occurred currently in science and technology have impacted directly self-information related areas. The possibility of obtaining signals, records, and data individually has located wearable sensors in a privileged position. The huge growth they have experienced, over the last decade, has generated an almost mature but continuously growing subfield. Moreover, with the unceasing improvement in digital communication and computational power, data collected by individual wearable sensors can be easily processed and linked to the physiological status providing important information about diseases, allowing to find previously unknown correlations.[1]

In centralized analysis, the different steps can be performed with equipment that can be physically distributed along the lab for maximum efficiency. When using wearable devices most of the steps have to take place in a platform as if it were a shrunk lab. Therefore, these tiny devices perform a sample-to-result process, with detection as the main step, which usually is also the most easily miniaturizable.[2] However, it has been one of the main challenges for analytical microsystems, since very sensitive techniques are needed as a consequence of the ultra-small sample volume used in reduced-size environments.

Apart from obtaining self-information about (bio)chemical and (bio)physical parameters, these platforms are excellent to obtain data about the surrounding environment, what is considered the external exposome.[3] A recent and interesting review reports advances in nanomaterial enabled chemical sensors for wearable environmental monitoring applications, grouping the devices into three major transduction principles: electrical (changes in resistance, conductance, or impedance), photochemical (colorimetric or fluorimetric), and electrochemical (changes in electrical potential or current).[4] Some of these examples deal with the determination of contaminants in air,[5] toxic agents,[6] uncontrolled UV radiation exposure,[7] or pesticides in food[8,9] to inform about quality and also potential risks. When detection is very complicated, wearable platforms are only employed as passive samplers. This is the case of the analysis of air pollutants such as volatile organic compounds or polycyclic aromatic hydrocarbons,

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that are extracted and further determined by gas chromatography coupled to mass spectrometry[10] in well-equipped laboratories. The discontinuity between sampling and detection, which is performed offline, illustrates that, in many cases, integrating the detection is still a challenge. However, important advances are being made not only to decrease the size of the components, but also to use flexible and stretchable materials with high compactness.[11]

Then, wearable devices can be "oriented" towards the body or the environment, depending on the target to be determined. More stringent requirements (like biocompatibility) are found in those devices contacting the body. The detection, as one more step in the process, has to be carefully designed, evaluating also the environmental sustainability of the device. This is a key issue since massive use is intended. From a "circular economy" approach, it is important to choose materials that, once the service life of the devices has ended, they could be reused to minimize waste and save resources.[12]

On the other hand, these platforms are aimed to be actuated by end users, incorporating new agents into the process, different from those conventional. Even in many situations they can be user-free. In any case, detection has to be kept as simple as possible. Therefore, flexibility in the design of the device and the methodology, mainly directed by the detection principle chosen, is extremely important. An example is the "Quantified self" community (self-knowledge through numbers),[13] with many individuals collecting data to help themselves investigate a health problem or make progress towards a goal. Often, they involve just a single person who is both the subject and the investigator. In this context, wearable devices with easy-to-perform detection (i.e., signal measurement and conversion into understandable results) become extremely useful for increasing the societal knowledge through massive amount of individual data.

Concerning the principle of signal detection, possibilities are enormous, but in this chapter, an overview of the most commonly (optical and electrical/electrochemical) employed in wearable devices is presented. Their main features and characteristics are reviewed and, without being exhaustive, some illustrative examples are included.

4.2 Signal transduction in wearable sensors

Signal measurement and transduction is one of the steps of the process aimed to obtain information about (bio)physical or (bio)chemical parameters. In many cases quantitative information is required, but qualitative analysis (yes/no responses) are increasingly common.[14–16] Although with different meaning, sensitivity, and specificity remain as relevant properties, together with accuracy and precision (that becomes reliability[16]) (Table 4.1). In wearable devices the inter-device precision becomes very important, with mass-production as one of the variables that allow to achieve low relative standard deviations. On the other hand, other productivity-related properties such as analysis time, cost, disposability, or

TABLE 4.1 Important features in qualitative and quantitative analysis.

	Qualitative	Quantitative
Representativeness	This is the most relevant feature for both qualitative or quantitative analysis. It refers to the coherence of the results with the samples. It can be related to the samples received to be analysed, to the object or system under study (adequate sampling process), to the analytical problem or in the upper level, to the information required.	
Precision	Qualitative analysis is usually combined with accuracy in a new feature: reliability. Decentralized analysis implies the use of many different devices for analysis, under different conditions, and operated by different individuals. Therefore, the reproducibility becomes very important as well as the inter-device precision.	
Accuracy	Results in reliability, combined with precision: proportion of true positive and negative answers [100-false positive rate (%) – false negative rate (%)]. False positive (or negative) rates are the probability that a test sample is a known negative (or positive), given that it has been classified as positive (or negative) by the method.	It is characterized by the sytematic error (positive or negative, absolute or relative), defined as the difference between a result (mean value between several obtained following the same methodology) with the true value. To have an appropriate view, precision has to be also considered.
Sensitivity	The ability of a method to detect truly positive samples as positive. It can be calculated as the probability, for a given concentration, which the test will classify as a positive result, given that this is a "known" positive.	Variation of the analytical signal with the concentration. In a linear calibration curve, the sensitivity corresponds to the slope of the linear interval.
Selectivity	The ability of a method to detect truly negative samples as negative. It can be calculated as the probability, for a given concentration, which the test will classify as a negative result, given that this is a "known" negative.	Ratio between concentrations of interferent and analyte (C_{int}/C_{an}) above which, an error (either positive or negative) is produced in the result.
Unreliability region	It not expressed as a numerical value, but as a region of probabilities of committing error. It corresponds to the region in which false responses are obtained (either false positive or false negative).	It is the numerical value related to the interval in which the measured result may be found with a given probability. Usually named uncertainty.

(*continued*)

TABLE 4.1 (Cont'd).

	Qualitative	Quantitative
Limit of detection (LOD)	The lowest concentration of the analyte which the test can reliably detect as positive in the given matrix (valid when assessing a maximum permitted concentration level, where LOD coincides with the upper limit of the unreliability region). The opposite would operate for assessing a minimum permitted concentration level. Here the LOD coincides with the lower limit of the unreliability region.	The minimum concentration of the analyte that provides a signal that can be statistically distinguished from the signal of a blank sample (usually the mean value of the blank plus 3 times the standard deviation of the blank).
Other performance parameters	The cut-off value means the concentration level where the qualitative method differentiates samples (positive from negative) with a certain probability of error, usually 5%.	The limit of quantification is the minimum concentration of the analyte that provides a signal that can be reliably quantified (usually the mean value of the blank plus 10 times the standard deviation of the blank).
Productivity-related features	Rapidity, costs and risks are features of great importance in methods for decentralized analysis, imposing a serious limitation even when the rest of features achieve high levels. Miniaturization usually decreases analysis time (shorter diffusion distances). Mass production of devices usually reduces costs, as does the use of low volume of sample, reagents and the generation of low amount of waste. Simple procedures are developed for using by untrained personnel.	

safety, together with other related to fabrication (like type of materials, comfortability…) become crucial.

The development of sensors exploiting various transduction principles is characterized by a strong competition to reach high detectability, portability and robustness. Even an evaluation about which measurement, photons or electrons, yields better biosensor performance has been made by comparison of chemiluminescent and amperometric enzymatic assays,[17] indicating that slightly higher detectability and wider dynamic ranges are obtained by chemiluminescence. However, as they usually require longer acquisition time, the rapidity of electrochemical biosensors will allocate them to real-time monitoring and wearable approaches. It is clear that there are many different alternatives; applications will decide the best option. Since electrochemical techniques are interfacial in most of the cases, they result very appropriate in the design of wearable devices. Moreover, the required equipment (potentiostat) is amenable to miniaturization. In the case of optical techniques, reduced-in-size components are very convenient, although in many cases readout is still made employing external optical

systems. The possibility of visual detection by the naked eye is a simple alternative provided by optical signal transduction. In the following subsections, different approaches regarding optical and electrical/electrochemical detection are presented in more detail.

4.3 Optical detection

In broad terms, optical methods are those based on the measurement of the electromagnetic radiation that emanates from matter or interacts with it, either strong (as in absorption or emission) or weakly (as in refraction or scattering). Methods are commonly classified as spectroscopic and nonspectroscopic respectively, although there are some scattering phenomena (i.e., Raman spectroscopy) that are commonly included in the first group because quantized frequency changes occur. In those non-spectroscopic methods there is no need to consider a corpuscular treatment of the radiation.

Although all the spectrum of the electromagnetic radiation is considered from gamma rays to radiofrequencies, most of the devices here examined operate in the near ultraviolet/visible/near infrared regions (i.e., 150 to 350 nm (near UV) / 350 to 750 nm (VIS) / 0.75 to 2.50 μm (near IR, also known as NIR)). Taking into account the energy that corresponds to these wavelengths, changes in electronic, vibrational and rotational energy levels are involved in deep interactions. When the absorbent species is in the form of atoms, only changes between pure electronic states occur (there are no vibrational or rotational levels). When the visible region of the electromagnetic spectrum is concerned, a color develops and thus, colorimetric detection is feasible (either with transmission or reflectance readouts). Emission of radiation after photoexcitation (like fluorescence) is commonly used when high sensitivity is required. In this section, methods that are mainly based on the interaction with infrared radiation, especially focused on the measurement of blood oxygen or other related parameters (also with Vis/NIR combination), as well as colorimetric and fluorescent methodologies (usually developing colors) are presented. In Fig. 4.1, the excitation and response signals of the main optical methods are illustrated, together with the resulting concentration-dependent analytical signal.

In all the cases, and once the (bio)physical or chemical event has happened, data are collected on the local environment and platforms usually process and transmit wirelessly the information to a remote device, most usually by radiocommunications[19] (Fig. 4.2). Common radio technologies include Bluetooth, radiofrequency identification (RFID), ZigBee, near field communication (NFC) and 433- and 860-MHz short-range devices.[20] Optical (bio)chemical sensors are easily integrated thanks to their ease of miniaturization, the high sensitivity of certain modes and the diversity of optically responsive indicator chemistries. In a radio-based wireless optical chemical sensor, after interaction of the analyte and (bio)receptor, the optical signal is converted into an electrical signal by the detector and this is then transmitted to a remote wireless receiver or network,

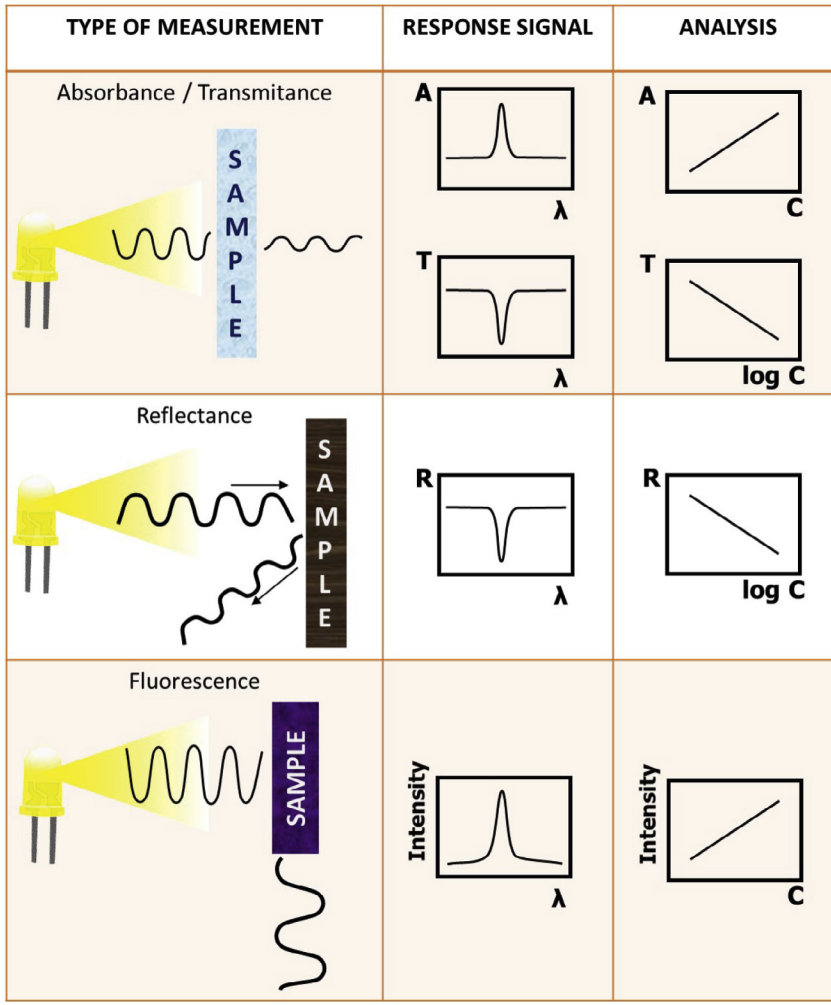

FIG. 4.1 **Scheme of the excitation signal, response signal and analysis response for the main optical detection techniques in wearable devices** *(adapted from 18).*

where the data can be analyzed in more detail (Fig. 4.2A). For wearable sensors, it is essential to ensure complete mobility. In this context, one of the advantages of an optical system, is that the output signal can also be read by the naked eye or a camera (Fig. 4.2B). Both approaches, radio and visual readout systems are receiving increasing interest.

One of the platforms increasingly used is the pervasive smartphone that can act as readout and data analysis unit. Apart from this ability (also useful for other principles of detection), in the case of optical sensors, the increasing quality of integrated cameras enables the smartphone to serve as a detector, as well.[20]

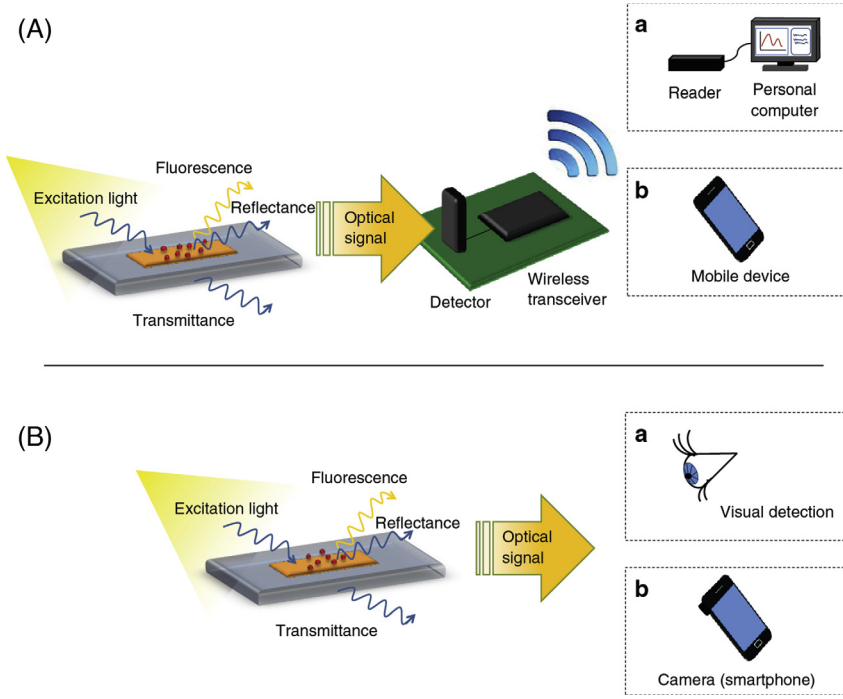

FIG. 4.2 (A) Schematics of a wireless optical (bio)chemical sensor, sending data to a personal computer (a) or a mobile device (b). (B) Optical sensor with wireless visual readout (a) or using remote camera (b), without radio communication. *Reprinted from 19, 2018 Walter de Gruyter GmbH.*

4.3.1 Photoplethysmography

In the case of the skin (which occupies a high body surface), direct optical readout is possible. Optical measurements performed through the skin offer noninvasive, contactless modes (previous chemical interaction is not required) for acquiring essential information of relevance to physiological health. In these cases, skin constitutes the optical pathlength with dimensions that depends on where the target is located[21] in each of the three different layers (Fig. 4.3A): (1) stratum corneum (highly keratinized), (2) epidermis (containing pigments such as melanin which absorbs mainly UV radiation), and (3) dermis (highly vascularized, absorbs in the visible range due to hemoglobin, carotene, and bilirubin). Light scattering occurs in keratinized cells (stratum corneum), large melanin aggregates (epidermis) and collagen fibrils and bundles (dermis).

Photoplethysmographic (PPG) sensors allow continuous and real-time monitoring of physiological conditions, enabling self-healthcare without being restricted by location. Therefore, it is a very active research field, especially in those human skin-compatible devices.[22] PPG sensors use low intensity infrared light that is strongly absorbed by blood being able to detect blood

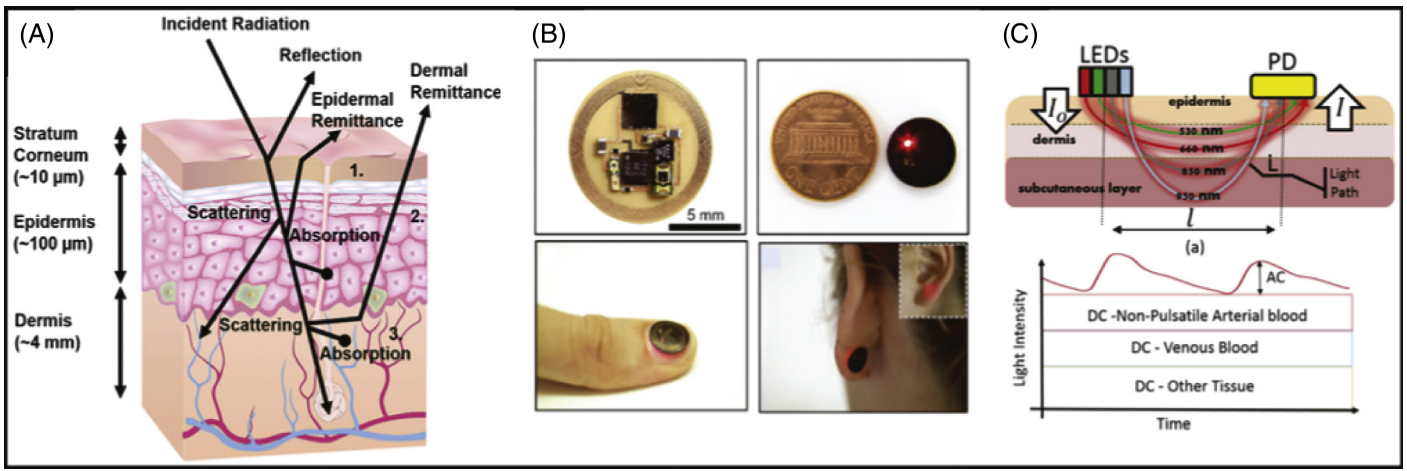

FIG. 4.3 (A) Schematic diagram of optical pathways in skin. *Reprinted from 31, 2018 RSC.* (B) Image of (top, from left to right) unencapsulated (a microcontroller drives infrared and red-light emitting diodes in time sequenced manner, with the photodetector in between) and encapsulated device for wearable pulse oximetry, and (bottom, from left to right) the device mounted on a thumbnail and on the back of the earlobe. The inset shows the front of the earlobe during operation. *Reprinted with permission from 27. Copyright© 2017 John Wiley and Sons.* (C) Diffuse-reflectance PPG signal in multiple optical wavelength measurement (top) and component of PPG signal (bottom). *Reprinted from 28 (2012) with permission from Elsevier.*

flow (volumetric variations).[23] The main application of dual-wavelength PPG is pulse oximetry, used to calculate the arterial oxygen saturation by means of its relationship with hemoglobin. In a theoretical estimation, the oxygen saturation of the arterial blood can be expressed as the percentage of oxygenated hemoglobin. Usually they employ two wavelengths, one red and other infrared (660 and 940 nm, respectively). Significantly lower absorption in red and slightly higher absorption in infrared are observed for oxyhemoglobin.[24] Oximeters exploit near field communication technology and integrate light-emitting diodes (LEDs) and photodetectors for direct readout, enabling, in extremely miniaturized embodiments, mounting devices conformally on the skin or on fingernails for optical assessment of the underlying tissue. Measurement of the transmitted or reflected incident radiation (transmission or reflectance modes) are possible. In transmission configurations, the light source is located opposite to the detector (only possible in fingernails and earlobes). Soft systems should be employed when combined with skin (skin-like), but a complementary strategy focused on device miniaturization can be employed for finger/toenails, with absence of nerve endings, and minimal interfacial water loss. For light source positioned adjacent to one another, backscattered reflection should be utilized (Fig. 4.3B and C). A comparison between transmission and reflectance pulse oximeters reveals faster response for the second mode, which is recommended to monitor clinical situations with rapid changes in oxygen saturation.[25]

Apart from oxygen, glucose has been also tried, but interferences in its absorption features with those of hemoglobin, proteins and fats makes it difficult.[26] Combination of Vis and near infrared radiation (NIR) LEDs is common;[27,28] an example is the application of Vis-NIR spectroscopy to detect blood glucose (BG) continuously and noninvasively (Fig. 4.3C).[28] NIR light may penetrate through several skin layers and reach the arteries in the subcutaneous tissue, while visible light is able only to reach the capillaries and arterioles region, located in the dermis. Then, collecting the reflected lights at different wavelengths and levels of BG, multivariate analysis can be made from multiple spectra. Bilirubin could also be measured, but the vast majority of chemical analytes are not easily measurable in contactless modes. Therefore, in these cases invasive sampling is required.

Considering physical parameters, heart rate variability is one of the parameters that can be evaluated by using a wearable earlobe sensor, with an IR LED and a phototransistor mounted on the opposite sides of a clip, wired to a microcontroller box.[29] Beat-to-beat time intervals evaluated generate a representative signal that can be an interesting alternative to electrocardiographic signals. They can be also of interest as a screening tool for coronary arterial disease and atherosclerosis,[30] using earlobe but also fingertip or toetip devices, powered by a smartphone.

A recent review[22] indicates an important activity in the field with silicon photodiodes as widely available, cost-effective and nontoxic electronic devices

with light-responsive properties from the UV to the IR range. Other inorganic photodiodes are possible, but organic materials are attracting also much attention due to their high flexibility, easy processing and low fabrication cost for large volume. Integration of organic LEDs (OLEDs) with organic photodetectors (OPDs) will allow implementation of all organic-based conformal PPG sensors.

4.3.2 Colorimetric detection

Among all the principles that fall under the umbrella of the optical (spectroscopic) methods, colorimetric and luminescent are the most common. The first ones respond to those that involve the measurement of color, that is, the wavelengths of the visible region of the spectrum that are not absorbed. Therefore, when white light falls over an object, the object absorbs part of this light, transmitting/reflecting the rest, depending on its transparency. These transmitted/reflected wavelengths will be seen as complementary to those absorbed. Color can be intrinsic to a species or can be generated by a reaction. On the other hand, in conventional instrumental analytical methodologies, an optical system (radiation source, lenses, filters, detector etc.) is employed to measure the absorbed or transmitted/reflected radiation. This can be more or less complicated and also variable in size, with components that decrease the size for easier integration. However, in the simplest detection format, the eye, a natural optical system, and white light as radiation source could be employed, although only semiquantitative analysis could be made. These methodologies are usually referred as visual or naked-eye detection.

Therefore, colorimetry is generally related to the absorption of radiation, with transmission/reflection as principal modes. In the case of decentralized analysis, exploring simpler detection modes for (bio)chemical parameters is of great interest, especially considering the importance and the amount of information required nowadays. Therefore, colorimetry fits perfectly with this purpose and is one of the main approaches employed. In most of the cases, colorimetry is combined with a reaction format, in which the substance of interest is detected via a color change after a specific reaction with a suitable reagent. Reactions can be simple and well-known as for example, in monitoring nitrite using the Griess reaction.[32] Increasing the complexity, also many biological interactions can give a final color after reaction with labeled species and then, color detection is possible. As stated in an interesting review,[33] one of the first reports of quantitative colorimetric determination was made by Lampadius in 1838,[34] and the first optical apparatus for quantitative analysis developed by Müller in 1853.[35] The number of studies and publications were increasing constantly up to 2007 when there was a massive rise after the introduction of microfluidic paper-based analytical devices (μPADs) by Whitesides,[36] employing colorimetric reactions initially and also cameras, scanners and smartphones. When the colorimetric reaction is performed on

a solid substrate, a reflectance detection mode is mainly used, based on the measurement of the light reflected from the surface of a testing zone. Digital images can be captured with identification purposes (using the tone) or quantification (based on the comparison of the intensity to a calibration curve). LEDs, solid-state semiconductors with a current flow that results in light emission with a wavelength that depends on the energy difference between valence and conduction bands can be employed for miniaturized instrumental colorimetric detection in combination with miniature detectors such as charge-coupled devices (CCDs) or complementary metal-oxide semiconductors (CMOS). However, the advances in digital image capturing[19] are relegating these elements to other applications.

Thus, in this context of capturing digital images and in many of the wearable devices, the use of smartphones has been one of the main advances.[37,38] Apart from the function of active/passive interface for wirelessly control of more complicate devices as well as storing/processing data, the use of the camera is enormously useful. Although characteristics of current cameras do not comply with the demands of precision spectrophotometry such as accurate energy calibration, low stray light, rapid response and ruggedness, they are very helpful for taking a digital image that can be further processed. Moreover, the multifunctionality of the smartphones allows combining tests with applications as, for example, MyHealthGut for celiac patients.[39] Going one step further, even for conditions that typically require blood tests for diagnosis, smartphone artificial intelligence technologies could enable non-invasive screening, as in the smartphone application of Emory University that analyses images of fingernail beds to estimate hemoglobin levels.[40] However, several important points should be considered. For example, the color depends not only on the colored object but also on the illumination and the detector. The color also depends on the agent that produces it (dyes, nanoparticles etc.), the substrate where color develops and the distance between the sample and the detector. Other factors when capturing images, such as homogeneity or exposure time, have to be also taken into account.[41]

Detection/quantification is possible by measuring a concentration-dependent characteristic. Once the image has been captured by the camera there are two main possibilities. One consists of dividing it in two-dimensional grids that are aligned in dots (pixels) in such a way that next to each pixel are transistors responsible for processing light and dark (grayscale). This is a colorless information, but some filters can assign a color to each pixel. In this way, different filters can be assigned to different color spaces. The most commonly used systems are CMYK (cyan, magenta, yellow and black) and RGB (red, green and blue, the three primary colors). The first one is more common in printing and the second one, that mimics the human vision, in image capture. The RGB system stores the intensity information of these components in a range that spans from zero to 255, useful to establish a relation with analyte concentration. Apart from these, there are many other possible.[37] The HSV space describes a color

by means of three different components: hue (H), saturation (S) and value (V). Hue is commonly defined as the dominant wavelength of the spectral radiance of a color. Saturation defines the purity of the color. And value, usually referred to as brightness, represents the intensity of light present in the described color. HSV can be easily obtained from the RGB color space using equations. HSV-derived color spaces also exist: HSB (B stands for brightness), HIS (I stands for intensity) or HSL (where L is luminance). All of them are part of powerful, fast and low-cost analysis methods to measure target analyte with color changes of digital images obtained by the built-in camera of a smartphone (digital image colorimetry, DIC,[42] on smartphone).

In this context, wearable devices produce an image that can be detected by the eye, or by the camera of a smartphone. An example of a wearable chemical sensor of the first type is based on a fingernail platform. Beauty products can be merged with chemical sensing, to enable monitoring the surrounding environment, for example, pH.[43] The colorimetric sensor relies on coating artificial nails with a recognition layer containing pH indicators (covering the range 3.8 to 8.8) entrapped in a polyvinyl chloride (PVC) matrix (Fig. 4.4A). Color changing fingernails offer fast and reversible response to pH, repeated use and intense color change easily detected by the naked eye. In a similar way, pH indicators (single or in a mixture, depending on the range that have to be covered) can be incorporated in different matrixes, such as hydrogel films (water insoluble cross-linked polymers able to absorb large amount of water).[44]

Regarding the analysis of human fluid samples, the time for using blood as the main and only sample for routine (bio)chemical analysis is getting close to be over. Other non-invasive samples are being increasingly used. When wearables are concerned, materials and device designs for adequate sample collecting, reaction and/or detection have to be carefully studied. In the case of sweat sensing on skin, soft, flexible and stretchable microfluidic systems should be employed. Sweat is naturally generated during exercise and thus, can provide very rich information about the physiological condition of the individual. Ionogels, as the one consisted of N-isopropylacrylamide and N,N′-methylene-bis(acrylamide) can incorporate pH indicators (methyl red, bromocresol green, bromocresol purple and bromothymol blue) for its determination.[45] Incorporation of the microfluidic system into an adhesive plaster or into a wristband allows monitoring during exercise (Fig. 4.4B). Since fresh sweat is continuously passing through the sensing area, continuous real analysis is possible.

Continuing in the context of sweat samples for monitoring analytes during exercise, microfluidic systems, including embodiments that integrate wireless communication electronics, which can intimately and robustly bind to the surface of skin without chemical and mechanical irritation have been proposed for water content as well as chloride, hydronium ions, glucose and lactate colorimetric determination during indoor and outdoor cycling activities.[46] This multianalyte determination is based on the fact that sweat glands produce perspiration that travels spontaneously through a microfluidic network and a

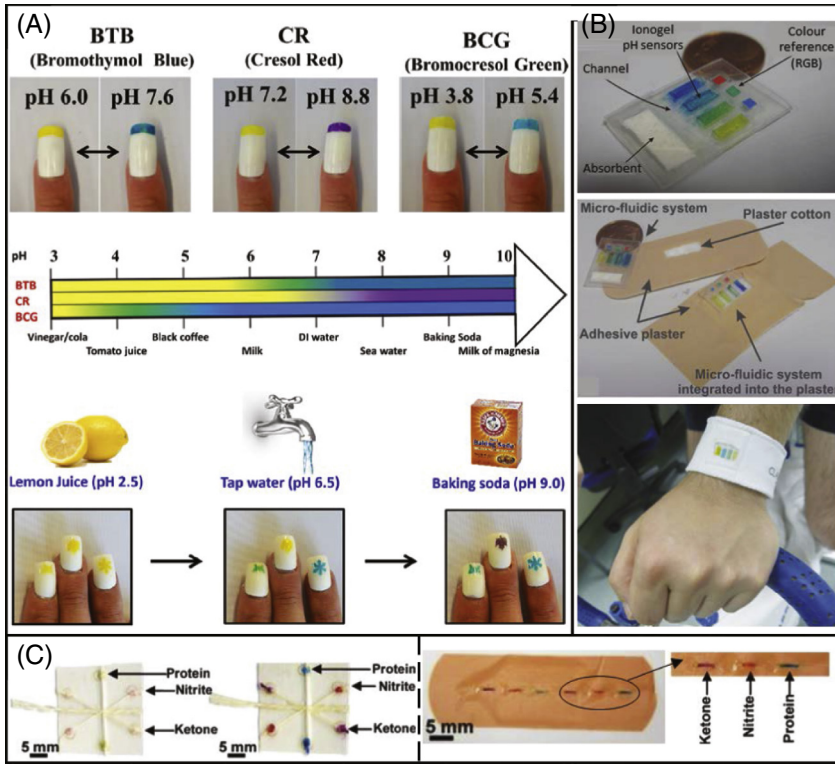

FIG. 4.4 (A) Colorimetric response and application pH ranges of BTB (bromothymol blue), CR (cresol red) and BCG (bromocresol green) dye-loaded nail sensors (top); colorimetric response chart at various pH values (medium) and application to real samples (bottom). *Reprinted from 43, with permission from Elsevier*. (B) Pictures of a microfluidic platform employed for pH sweat monitoring during exercise (top), integrated into a plaster (medium) and into a wrist-band (bottom). *Reprinted from 45, with permission from Elsevier*. (C) Colorimetric enzymatic assays performed using a branching of threads (left) and a band with thread inserted (right). *Reprinted with permission from 47. Copyright 2010 American Chemical Society*.

set of reservoirs. Quantitation can be made by digital image capture using a camera. Reaction and colorimetric detection are performed in central cellulose pads with immobilized reagents. Enzymatic reactions allow the detection of lactate and glucose, by producing a change in color. The pH is measured using a universal indicator that produce colorimetric responses over a medically relevant range. Chloride detection involves a competitive binding between Hg^{2+} and Fe^{2+} with a specific ligand so that the presence of Cl^- produces the precipitation of mercury(II) chloride ($HgCl_2$) and the complexation of iron ions to a blue color. In an serpentine channel, cobalt(II) chloride ($CoCl_2$) contained in a hydrogel matrix served as colorimetric indicator for water content since the generation of $CoCl_2 \bullet 6H_2O$ complex generates a color change.

A new field of research started also with the use of other type of porous microfluidic devices, of common use in daily life, that did not require delimiting

hydrophobic barriers to confine the flow in specific directions. Thread-based analytical microdevices or μTADs (in similarity to those μPADs), allow the use of unidimensional microfluidic elements in woven array, branching or sewn devices (Fig. 4.4C).[47] The work, pioneered by Whitesides' group was followed with many reports on interesting e.g., knitted, woven or twisted thread-based devices.[48]

Apart from sweat samples, and as was commented before, skin presents an attractive site to sample circulating biomarkers, due to its ease of access and presence of blood vessels and interstitial fluids. However, to access large molecular weight biomarkers (>10 kDa) such as proteins and nucleic acids, it is necessary to physically penetrate the skin surface and access underlying tissue fluid. Hollow mironeedle-optofluidic biosensors have been developed for therapeutic drug monitoring. The inner lumen can be functionalized to be used as a microreactor during sample collection to trap and bind target drug candidates during extraction, without requiring sample transfer. Integration with an optofluidic device allow rapid, although not wearable, detection.[49] Some integrated alternatives (silicon buried dual-junction photodiode-based devices) were proposed as first steps of integration of an optofluidic wearable biosensor for continuous monitoring of analytes within human interstitial fluid (ISF).[50]

Another application with enormous interest from the point of view of wearability and related somehow with skin is wound healing. An interesting review summarizes the wearable technology for chronic wound monitoring including current dressings, advancements and future prospects.[51] Chronic wounds affect around 2% of the world population with high costs to the healthcare system. Indicator biomarkers specific to chronic wounds include blood pressure, temperature, oxygen, pH, lactate, glucose, interleukin-6 and infection status. In one of the examples, a pH-sensitive optical fiber has been fabricated using polydimethylsiloxane precursor doped with rhodamine B dye. Embedding the fiber in gauze fabric and hydrocolloid wound dressing allows assessment of pH and also pressure on the wound region.[52] The fiber has to be connected to a light source and a photodetector for continuous monitoring of the transmitted optical power.

In a more general manner, there are different substrates that result very appropriate for devices aimed to perform low-cost analysis. This is the case of paper that, once reinvented, revolutionized analysis.[36] In this context, μPADs fabricated through craft cutter printing were employed for glucose salivary diagnostics integrated into a silicone mouthguard using a 3D-printed holder.[53] Glucose monitoring after chocolate ingestion with instrument-free naked-eye detection indicate that these platforms may emerge as powerful wearable tools fabricated in a simple and low-cost way. Regarding materials, hydrogels, which were presented here in some examples, are soft materials very useful in the field of wearable devices, allowing specific strategies of analysis. This is the case of glucose sensing employing phenylboronic acid functionalized hydrogel films that recognize cis-diol motifs[54] and can be integrated in complements

to generate wearable analytical platforms. A diffuser structure has been engineered on the hydrogel consisting of laser-inscribed arrays of microlenses that focus the incoming light at different focal lengths and directions resulting in a diffused profile of light in transmission and reflection readout modes. The sensor was integrated in a contact lens and placed over an artificial eye. A smartphone's photodiode was employed for quantitative measurements.

In most of the cases, physical or chemical entities are measured, in the last case elements or molecules, more or less complicate. Apart from proteins, the detection of nucleic acids is of paramount relevance since it paves the way to the detection of pathogenic agents, as in the case of the SARS-CoV-2. An innovative design of a wearable mask includes a water blister that after punction produces the flow through wicking material, moving viral particles from the sample collection zone to a zone for reactions (lysis, isothermal amplification and CRISPR/Cas12a detection of amplicons).[55] Final output is visualized by a lateral flow assay strip that is passed externally through the mask (Fig. 4.5A).

All the examples commented indicate that transmittance/reflectance measurements offer many possibilities that have to be explored to achieve complete wearability and autonomy in necessary applications.

4.3.3 Fluorescence detection

In colorimetric methods, transmittance or reflectance of the incident radiation (visible region of the spectrum) is measured. On the contrary, luminescence refers to the emission of radiation. Atoms or molecules can be excited, with changes from the basal energy state to upper levels by absorption of radiation (photoluminescence, such as fluorescence or phosphorescence) or other mechanisms (chemical reaction in chemiluminescence, electrochemical reaction in electrochemiluminescence, biological reaction in bioluminescence, or also by means of thermal or electrical energy using, for example, flames or sparks). When the energy for emission to the basal state corresponds to a wavelength of the visible region of the spectrum, a color is seen. Hence, different modes could be considered: reflectance/transmittance and fluorescence, depending on the species causing the phenomenon: chromophores or fluorophores. In the first case the color is seen under natural or artificial ambient white light but in the second case a specific radiation source (for example, a UV lamp) is commonly required.

Fluorescence-based detection is very useful for wound healing applications. In this context, the continuous monitoring of reactive oxygen species (ROS) is essential for the prevention of chronicity and pathogenic infection. Optical core-shell microfibrous textiles incorporating single-walled carbon nanotubes have been fabricated for real-time monitoring of hydrogen peroxide concentrations in in-vitro wounds (Fig. 4.5B).[56] The environmentally-sensitive and non-photobleachable fluorescence of the nanostructures enables continuous analyte monitoring without decay in signal over time and spatial peroxide concentration determination. This approach is very promising for integration into commercial wound bandages.

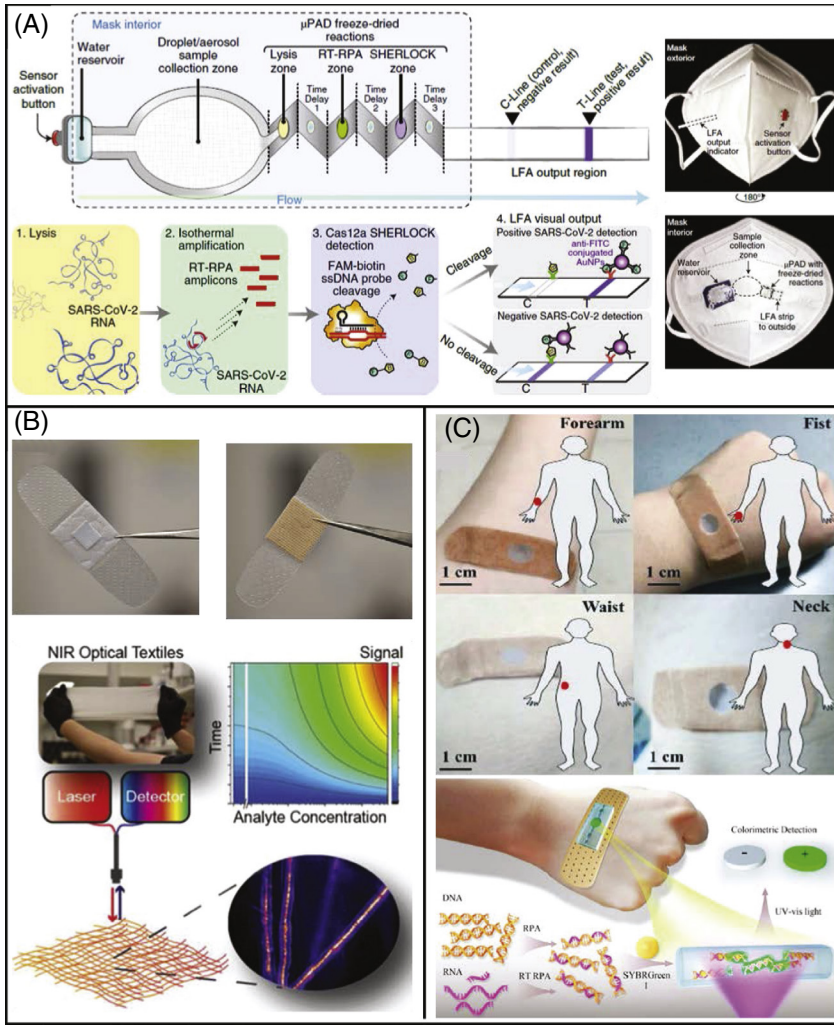

FIG. 4.5 (A) A facemask for SARS-CoV-2 diagnostic in aerosol based on a lateral-flow assay integrating the lysis of the virus. *Reprinted with permission from 55. Copyright © 2021 Springer Nature*. (B) Integration of optical fibrous samples, incorporating carbon nanotubes, into a commercial wound bandage (top) and schematics showing the ratiometric optical detection of hydrogen peroxide (bottom). A light source and detector are required. *Reprinted with permission from 56. Copyright © 2021 John Wiley and Son*. (C) Photographs of the wearable microfluidic bandage-like sensor on the forearm, fist, wrist and neck respectively (top); schematics of its working principle for nucleic acid detection: positive and negative colorimetric results after illumination with a UV lamp (bottom). *Reprinted from 58 (2019), with permission from Elsevier*.

Other interesting application is the detection of biomolecules such as nucleic acids. Using fluorescent indicators and miniUV-lamps, their emission is also visible with simple equipment. This is the case of a bandage-like wearable flexible microfluidic recombinase polymerase amplification (RPA) sensor constructed for the rapid and visual detection of nucleic acids (Fig. 4.5C).[58] This sensor is triggered by human body heat (30–37°C) and allows for visual nucleic acid (conserved nucleic acid fragment of Zika virus) detection within 10 minutes. This could prompt individuals who become infected with the virus to order prescriptions and allows treatment of patients anywhere and at anytime in a timely manner. The feasibility of this device is demonstrated with human serum, but it may be applied for online pathogen detection at wound sites, tumor biomarker diagnosis in vivo, or position-dependent detection of epidermal cell molecular lesions in the future. Regarding different biomolecules, proteolytic activity on fluorescently labeled peptides could be demonstrated by combination with quantum dots (QDs). If there is no proteolytic activity, the fluorescent dye remains close to the QD and yellow/orange emission is observed. After cleaving the peptide, the dye diffuses away and there is a change to green color.[59]

Fluorescence needs a light source to produce excitation. In this context, smartphones can also include one OLED (organic LED) emission from the screen, or also use the flashlight[21] to produce excitation and later detection (photoluminescence). On the other hand, increasing the sensitivity is a continuous challenge. In both qualitative and quantitative analysis, being able to detect the lowest concentration is a never-ending task. In this context, the use of photonic crystals (PCs) is an interesting strategy, especially for paper and flexible substrates, that are the basis of many wearable platforms.[60] PCs are artificial microstructures (although there are substances with PC properties in nature) that are regularly arranged using media with different refractive indices. They have a periodic dielectric structure on an optical scale that acts selecting wavelengths to pass through them.[61] Optimizing the structure, the energy and speed of the photons could be greatly reduced (slow light effect[62]), enhancing the optical signal and, in turn, the sensitivity. Some examples are shown in Fig. 4.6A, where a PC structure together with the electronic network has been integrated on fish-based paper, to measure lactic acid and urea in sweat as well as the movement status of the human body, monitored through the fluorescence-enhancing effect of PCs and resistance changes caused by body movements.[63]

Another application of smart wearables has been developed for tear analysis combining a capillary, a reservoir and a paper-based microfluidic device for sample collection, dilution and analysis of electrolytes (Fig. 4.6B).[64] In this case, also a hybrid monitoring system (for eye movement as well as glucose and lactoferrin concentrations) has been developed. In both examples, ordered structures are suitable for optical but also electrochemical detection. A disordered structure may limit the performance of electrochemical devices by reducing the effective available surface and creating complex diffusion pathways that cause pore blockage. Ordered materials are also attractive due to their periodic

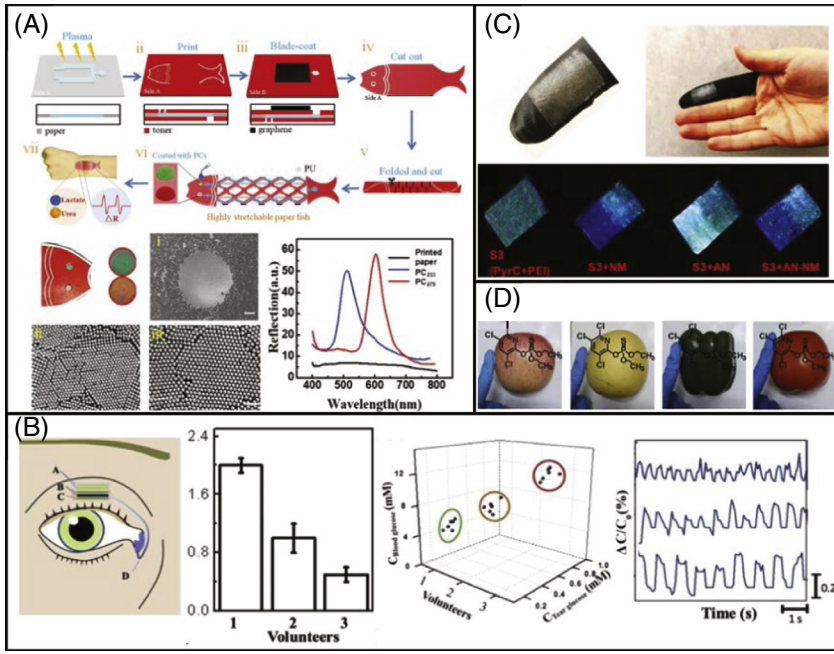

FIG. 4.6 (A) (Top) Schematic illustration of the paper fish sensor fabrication process: (i) office paper treatment with plasma to obtain hydrophilic channels, (ii) and (iii) printing with fish pattern (front) and with toner and graphene coating (back), (iv) and (v) cut out, folding and further cut out, (vi) eye coating with PCs and (vii) attachment to human body for real time motion monitoring and sweat lactate/urea detection. (Bottom) Optical microscopy images of PCs assembled on the fisheyes. Scanning electron microscopy images of the (i) PC_{233}, 400 μm scale, (ii) PC_{233}, 1 μm scale, and PC_{279} 1 μm scale (233 and 279 refer to the diameter, in nm, of SiO_2 nanoparticles). Reflectance spectra of the corresponding PCs and printed paper. *Reprinted with permission from 63. Copyright 2018 John Wiley and Sons*. (B) Schematic of wearable sensor for eye movement monitoring (A, twin electrode supercapacitor) and tear glucose (B, parallel electrodes for electrochemical biosensing) and lactoferrin detection (parallel electrodes). A cotton thread (D) connects the ends of the electrodes and the tear lacrimal gland. Graphs show responses for three volunteers related to lactoferrin (first) and glucose (second, compared to values obtained with a commercial device) determination as well as capacitance changes produced by eye movement (third). *Reprinted from 64 (2019), with permission from Elsevier*. (C) Wearable nanofiber sensor: (top) images of the nanofiber mat deposited on the finger of a nitrile glove; (bottom): changes in the fluorescence in the presence of nitromethane (NM) as well as increase in fluorescence in the presence of ammonium nitrate (AN) and AN-NM. S3: sensor using 1-pyrenecarboxaldehyde (PyrC) on polyethylene imine (PEI). *Republished with permission of the Royal Society of Chemistry, from 65; permission conveyed through Copyright Clearance Center, Inc*. (D) Wearable glove sensor for OP detecting on different agrofood surface: apple, pear, green pepper, and tomato. *Republished with permission of the Royal Society of Chemistry, from 9; permission conveyed through Copyright Clearance Center, Inc*.

structures, which present large surface areas, high porosity, low tortuosity and interconnected macropores.[64] Lactoferrin is determined by fluorescence (enhanced by PCs) and glucose electrochemically.

There are some wearable devices specifically useful for monitoring the surrounding environment, as is the case of glove sensors that allow non-invasive

detection of explosives[65] or pesticides.[9] In the first case, a carboxaldehyde is anchored on polyethylene imine. This is doped into polyurethane and the resulting material is electro-spun into nonwoven nanofiber mats, which can be deposited onto a nitrile glove (Fig. 4.6C). If a nitroalkane (component of explosives) is present, Henry's reaction takes place producing a nitroaldol that displays a yellow to orange color, quenching the fluorescence (blue emission). However, in the presence of a different explosive component, ammonium nitrate, an increase in the emission intensity is observed. In the second case, organophosphorus pesticide (OP) detection on the surfaces of agricultural products can be made using swipe collection, without needing chopping and extracting. The glove (Fig. 4.6C) integrates a flexible material (carboximethylcellulose aerogel) and two fluorescent labels: Eu metal organic frameworks (EuMOFs) for red and nanosized carbon dots (CDs) for blue emissions (after irradiation with UV light from a portable lamp). Then, detection by the naked eye (red to blue emission transition due to an increase in the OP concentration) is highly sensitive owing to the double signal sensing strategy in which EuMOFs are the working fluorescence center and CDs are the reference fluorescence center.

Advances in miniaturization of the optical components is of paramount relevance to increase the wearability of complete analytical platforms. In this context, organic semiconductors enable the fabrication of a range of lightweight and mechanically flexible optoelectronic devices. Most organic semiconductor lasers, however, have remained rigid until now, predominantly due to the need for a support substrate. Membrane-based substrate-less and extremely thin organic distributed laser that offer ultralow-weight and excellent mechanical flexibility have been developed and their integration on contact lenses has been demonstrated (Fig. 4.7A).[11]

Apart from these approaches based mainly on transmittance and fluorescence, measurement of scattered, as well as reflected light are possible. Coupling with light sources and detectors are also required but wearing a sensing component is advancing one more step toward complete wearability. A scattering-based approach that delivers a signal that can be considered a fingerprinting is Raman scattering. Surface-enhanced Raman scattering (SERS) is the basis of a wearable sensor for label-free molecular detection (Fig. 4.7B).[66] With the aim of detecting drugs in sweat, a patch has been fabricated comprising a sweat-absorbing layer, a SERS active layer, and a dermal protecting layer that allows laser penetration. A silk fibroin protein is a layer that absorbs aqueous solutions and filtrates molecules larger than its nanopores. In this layer, a plasmonic silver nanowire layer is formed to enhance the Raman signal of the molecules that penetrate through the SERS patch in a label-free manner. It has been demonstrated for 2-fluoro-methamphetamine (2-FMA) detection on human cadaver skin.

It can be seen through several examples that, unless miniaturized components are integrated (such as the case of LEDs), the use of an external readout system is still required for optical signal measurement. Maximum integration will provide maximum autonomy and thus, "everywhere" wearability. The advantages of radiofrequency electronics and near field communication have

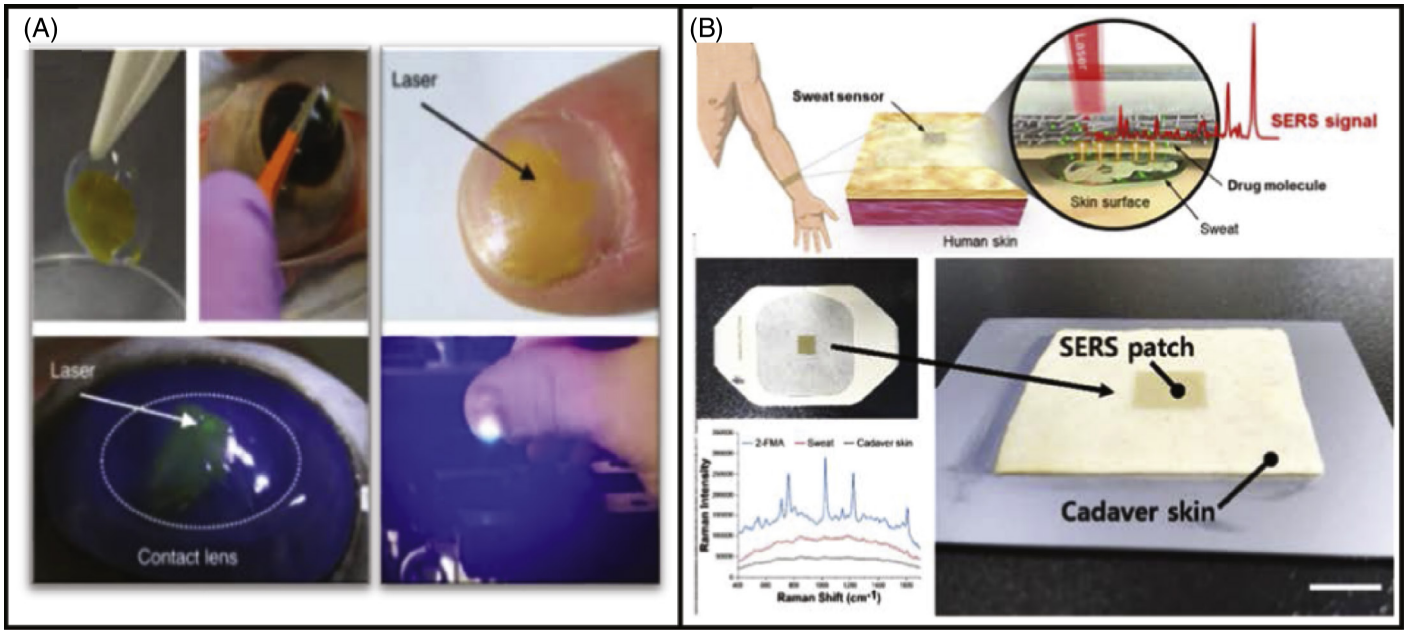

FIG. 4.7 (A) (Left top) Membrane laser transferred onto a contact lens and contact lens being placed on a bovine eye; (left bottom) reflection of a white light source from a second-order membrane laser on bovine eye. (Right top) Optical excitation of a membrane laser on a fingernail; (right bottom) emission spectrum recorded from the same laser. *Reprinted from 11*. (B) (Top) Schematic illustration of a wearable SERS patch sensor describing a label-free detection of drug molecules in sweat. Photograph of the SERS patch and attachment on the human cadaver skin (scale bar: 1 cm); (bottom left): 2-FMA detection on the human cadaver skin. *Reprinted with permission from 66. Copyright 2021 American Chemical Society*.

been already commented. They bypass the need for batteries and enable data transmission to off-skin (or alternatively clothes etc.) receivers, such as smartwatches and phones.[67] Now that consumers are getting used to some wearable sensors, especially those focused on the determination of physical parameters, then those that include biological recognition molecules or biochemically reactive species are expected to be quickly accepted.[67]

4.4 Electrical and electrochemical detection

The development of wearable devices requires small-size and lightweight platforms that must be robust enough to withstand the daily life of the subject. Advances in electronics and electrodes have allowed to integrate different electrical/electrochemical approaches in miniaturized but robust platforms for in-/on-body analysis. Moreover, electrochemical reactions are events that occur at the interface electrode/solution, i.e., at the surface of the electrodes (hence, tiny volumes/sizes are necessary) contacting solutions (very advantageous for detecting analytes in biofluids).[68] Electrochemical measurements usually need highly conductive media (containing electrolytes); however, examples of gas sensors using solid electrolytes, such as yttria-stabilized zirconia, are also reported.[69]

The area of the electrodes involved in electrical and electrochemical detection methodologies can be miniaturized without losing sensitivity (as in for example, ultramicroelectrodes) and electrodes can be also designed in non-planar surfaces. On the other hand, the required instrumentation is simple and compact since the signal obtained is electrical and therefore, it is not necessary further conversion as happens in optical detection (photon to electron).[70] Therefore, the electronic circuit necessary for performing the measurement and collecting the signals can be integrated into a wearable gadget or patch and the data can be wirelessly sent to a smartphone or other mobile platform for processing and displaying the results (Fig. 4.8).[70–74]

Integration of electronics occurs in different degrees. Incorporation of devices in accesories such as e.g., rings is possible with components located in different layers, embodied in the ring box.[86] The card with screen-printed electrodes is at the top, connected with the potentiostat located underneath (Fig. 4.8A). A portable potentiostat can be easily coupled to the wrist over a glove that has electrodes screen-printed on the finger. Due to the short distance, wired connection is used (Fig. 4.8B).[137] Electrodes are oriented towards the surrounding environment, aimed to detect chemical threats and drugs, respectively. Regarding saliva analysis, wearable devices can be fabricated on polymeric materials where the electronics are embedded. It is the case of a pacifier that, in a design similar to that of the ring,[86] includes electronics in the main central body connecting the electrodes for glucose determination. These, in turn, contact a microfluidic system designed for saliva sampling (Fig. 4.8G).[84] Mouthguards are appropriate platforms for embedding wearable

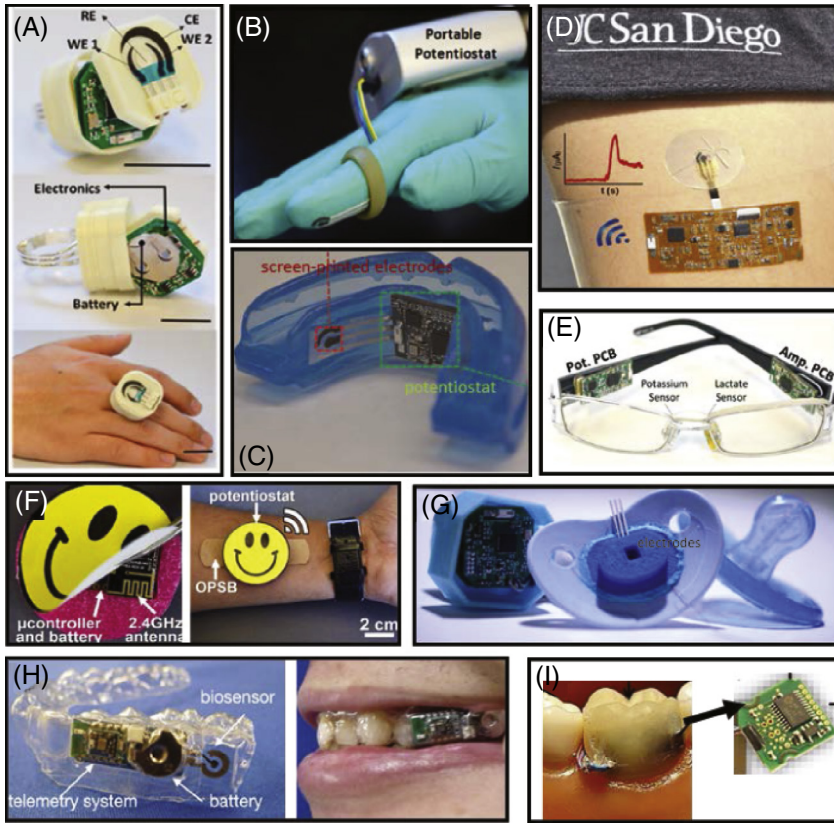

FIG. 4.8 **Overview of wearable devices with integrated electronics**. (A) Different pictures of the ring-based device for detecting explosives and chemical threats. *Reprinted with permission from 86. Copyright 2017 American Chemical Society*. (B) Glove-based device for fentanyl detection. *Reprinted from 137 (2019), with permission from Elsevier*. (C) Mouthguard sensor for enzymatic uric acid detection. *Reprinted from 75 (2015), with permission from Elsevier*. (D) Skin-worn device for glucose and lactate detection in sweat with flexible printed potentiostat. *Reprinted with permission from 128. Copyright 2017 American Chemical Society*. (E) Eyeglasses-based sensor for potassium and lactate detection in sweat. *Republished with permission of Royal Society of Chemistry, from 83; permission conveyed through Copyright Clearance Center, Inc*. (F) Packing of the electronics (left) integrated in a bandage (right) required for simultaneous detection of pH and uric acid. *Reprinted from 74 (2018), with permission from Elsevier*. (G) Pacifier-based sensor for glucose monitoring in saliva. *Reprinted with permission from 84. Copyright 2019 American Chemical Society*. (H) Mouthguard-based device for glucose monitoring in saliva (left), already placed in the mouth (right). *Reprinted with permission from 76. Copyright 2020 American Chemical Society*. (I) Electronics integrated in a tooth able to analyze the tooth surface and transmit this information. *Reprinted from 77 (2020), with permission from Elsevier.*

platforms, not only the electronics but also the electrodes, as in one employed for uric acid detection (Fig. 4.8C).[75] In a simpler platform, that is made of a transparent polymer and can be continuously worn as an orthodontic device, apart from the biosensor, telemeter and battery are included (Fig. 4.8H).[76]

Even more discrete is a "biotooth" sensor with tiny electronics to analyze tooth fracture and metabolites secreted (Fig. 4.8I).[77] The degree of integration is very high in these two last cases. On the other hand, eyeglass arms are excellent elements for integration of wearable sensors as in the multimodal device, potenciometric and amperometric, designed for the determination of potassium and lactate respectively (Fig. 4.8E).[83] Due to the enormous amount of contact surface, skin is one of the main targets of wearable devices. Hence, electronics can be also found included in patches (Fig. 4.8D)[128] and bandages (Fig. 4.8F).[74] In the first case, electrodes connect to a microfluidic system for sweat sampling, and in the second one, the potentiostat is located over the bandage. These are some of the many illustrative examples that can be found in the bibliography that indicate the potential of the electrochemical techniques, where not only the sensor but also the electronics (considering also, in some cases, microcontroller and battery) are easily included in the platform. Connection with mobile platforms is very frequent and also combination with microfluidics, for liquid sample analysis.

All the afore mentioned examples together with their low cost, rapid response and low-power requirements, make electrical and electrochemical approaches the most frequently used detection system in wearable (bio)sensing devices.[78–80]

4.4.1 Electrodes: Fabrication and materials

Besides the suitable design and selection of electrodes, the integration of those required is also key to achieve a successful electrochemical wearable sensor. Electrodes can be miniaturized without a significant loss in sensitivity or robustness, which is one of the main reasons why these type of sensors are so numerous. The screen-printed electrodes, which meant a landmark in the development of electrochemical sensors, are very commonly used for creating wearable devices. This type of electrodes is fabricated depositing a conductive ink through a screen or mesh that controls the thickness of the ink layer and the geometry of the electrode. Screen-printed electrodes were traditionally implemented on ceramic rigid planar substrates such as alumina. Due to their small size, they can be used in wearable sensing platforms as for example, a patch for continuous measuring of ethanol in sweat.[81] In this case, a commercial ceramic-based screen-printed electrode was utilized as transducer for the integrated enzymatic sensor. However, rigid supports are not the best option for wearable devices since, most of the times the integration of the electrodes should consider, not only the device itself, but also the wearer's body. Thus, electrodes for wearable sensors should be ideally foldable, stretchable and able to bear several bending cycles without losing their analytical characteristics. Thereby, screen-printing technology has been widely applied on flexible polymeric substrates for developing wearable gadgets such eyeglasses (for detecting glucose, lactate, alcohol, electrolytes or vitamins in sweat or tears[82,83]), pacifiers (for determining glucose in saliva[84]), or rings (for detecting drugs in saliva[85]). Although many

of these gadgets are aimed to analyze biological samples, the development of accessories to environmental analysis is also common; for example, rings for detecting explosives and nerve agents in liquid- or gas-phase samples,[86] or gloves for detecting nerve agents, illicit drugs or explosives on different surfaces.[87]

Printing the electrodes on textiles is also a very common approach to obtain wearable sensors.[4,70,88–91] The choice of the textile, according to characteristics such as stretchability, porosity or hydrophilicity, but also to the possibility of modification with dyes or other substances to improve its properties as textile, is key to obtain operating and mechanically stable electrodes. Another approach to fabricate sensors on these materials is the development of conductive textile fibers by modifying threads with conductive materials, mainly composites based on nanomaterials and conductive polymers. Both natural fibers, such as cotton and wool, and synthetic fibers have been used as substrates for e-textiles.[4,92] In this context, textile-based sensors are thought to be reusable and, therefore, the stability and resistance of electrodes after washing cycles is a challenge to consider and under active research.[93]

Paper is another material very commonly employed as substrate of stencil- or screen-printed electrodes. Although it seems not to be the most suitable material for wearable sensors due to its low mechanical resistance, paper-based electrodes have been used in different types of wearable devices and can also be embedded in robust platforms. A mask for the detection of hydrogen peroxide in exhaled breath,[94] or an origami microfluidic device for detecting glucose in sweat onto the skin[95] are some examples. With the aim of decreasing the hydrophobicity of the paper and therefore, improving its resistance and durability, cellulose-based papers pretreated with fluorinated alkyl silanes have been employed in patches or bandages.[74,96] The integration of electrodes on bandages to obtain wearable devices commonly aimed to monitor wounds,[74,97,98] but also to detect analytes related to skin-related illnesses,[99] is mainly performed printing the electrodes on hydrophobic/insulator layers[74,97] integrated in the band or directly onto the soft zone of the bandage.[97,99] Paper, and also fabrics, are porous materials that could easily integrate microfluidic strategies together with electronics.[100]

Tattoo-like sensors offer a useful alternative for direct and continuous analysis of sweat. Since they are directly adhered onto the skin, they must be stretchable, soft, and ultrathin. This skin-worn devices are usually fabricated printing the electrodes on adhesive resistant polymeric sheets and, alternatively, on tattoo paper.[4,101]

Although stencil-/screen-printed technologies are widely employed, many other technologies are also used for preparing the electrodes required for detection systems in wearable sensors, such as inkjet printing, 3D-printing, roll-to-roll gravure printing, lithographic or chemical vapor deposition,[4,91,102] to generate thick- and thin-film electrodes (with the thickness in the micro- or nanometer scale, respectively). Apart from electrodes prepared on flat substrates,

microneedle-based electrodes are being incresaingly used in wearable sensors, mainly with the aim of analysing ISF and monitoring important biological analytes. To perform electrochemical detection on the tip of a microneedle, the electrodes should be the same tip or be close to it. Solid and hollow microneedles have been employed.[103] The first act as electrodes and can be obtained by sputtering or by coating stainless-steel wires with conductive inks. When hollow microneedles are used, the electrode is located inside the needle and can be prepared inserting conductive wires or filling the needle with a conductive material, commonly in the form of paste or ink. Hollow microneedles offer also the possibility of internal biomodification for selective detection.

Regarding the materials of the electrodes, the most common are metals, highly conductive, in the form of films, and also carbon, very advantageous from the electrochemical point of view.[4,57] Because of the need to obtain flexible, stretchable and robust electrodes without losing conductivity, the use of nanomaterials has been widely exploited. Thus, gold nanomaterials are frequenty used due to its biocompatibility, but nanostructures of platinum, silver or aluminum among others have been also used. The high electrical conductivity of transition-metal nanomaterials has converted these materials in an interesting alternative for fabricating wearable devices.[105,106] Regarding carbon, its lower cost, mechanical and chemical robustness and good behaviour for electrochemical measurements make carbon-based (nano)materials very interesting for wearable applications. Carbon-black, carbon-nanotubes and graphene, (0D, 1D, and 2D, respectively, carbon materials) are among the most used.[91,104,106,107]

Polymers are common substrates of wearable devices, mainly because their outstanding chemical and mechanical properties. Conductive polymers, such as polyaniline (PANI) or poly(3,4-ethylenedioxythiophene) (PEDOT) are suitable alternatives for electrode fabrication.[90,109] The transparency of the last one, makes it a good option for multimodal (optical/electrochemical) detection.

Although single-material electrodes have been used in wearable sensors, the combination of different nanomaterials (metalic and/or carbon-based) and the fabrication of nanocomposites (polymers and nanomaterials) are alternative approaches aimed to overcome the limitations of single materials and to improve the performance of the electrodes.[4,57,79,80,106,108]

Apart from conventional devices of two-electrode potentiometric or three-electrode potentiostatic systems, the employ of field-effect transistors is increasing notoriously. Thus, they are commented below in a specific section (4.4.2.4).

4.4.2 Electrical/electrochemical detection techniques

In electrical/electrochemical techniques, an electrical parameter is monitored to obtain the analytical signal. When methods based on these techniques are used for analytical purposes, the presence of the analyte (species to be detected/determined), produces a change in the electrical magnitude measured. Then, the analytical signal, i.e., the electrical signal that is proportional

to the analyte concentration, or indicates its presence, can rely on two different approaches. The signal can be generated: (1) directly by the analyte, in case it is an electroactive species or (2) indirectly by specific interaction with selective (bio)reagents. The reactions with these (bio)reagents not only provide the detection signal, but also allow the selective recognition of the target.[18]

The main electrochemical techniques used in wearable sensors are amperometry (by far the most common because of its simplicity), voltammetry and potentiometry. The last one is usually chosen for measuring pH or determining ions, such as Na^+ or K^+.[109,110] While potentiometry is a static technique that only requires two electrodes (working and reference) to measure the potential difference between them under open circuit conditions (i.e., when no current flows between the electrodes), amperometry and voltammetry are dynamic techniques that usually employ a potentiostatic system of three electrodes (working, reference and auxiliary). In this way, the third electrode (also referred to as counter electrode) avoids the flow of current between working and reference electrodes ensuring the stability of the potential and minimizing the ohmic drop. Both amperometry and voltammetry, measure the flow of electrons over time (i.e., current), but in the case of amperometry the current is recorded at a fixed potential with time (i-t curve). Voltammetric curves are obtained by scanning the potential in a forward direction (linear sweep voltammetry, LSV), which can be reversed in a backward scan (cyclic voltammetry, CV). This is the most common electrochemical technique, usually employed as a "diagnostic" technique for knowing the electrochemical behavior of analytes. A linear ramp is commonly used but other modes can be used to increase the sensitivity of the methodologies, as in pulsed techniques (like differential pulse voltammetry, DPV or square wave voltammetry, SWV). Adding a previous preconcentration step is another way to enhance the sensitivity (for example, in stripping techniques).[126]

Although potentiometric techniques need simpler equipment (a potentiometer and two electrodes), voltammetric and amperometric techniques, which require a potentiostat, are more frequently used (not only for wearable devices, but also for all kind of (bio)electrochemical sensors) because of several reasons: (1) potentiometry commonly requires ion selective elements which are available for a not very wide assortment of species, (2) voltammetry and amperometry show a large versatility regarding the electroactive species that can be determined, either directly or using indicators/labels whose signal can be related with the analyte concentration, and (3) a potentiostat is one of the most easy-to-do analytical equipments,[111] and can be easily integrated in platforms for complete wearability (Fig. 4.8). In Fig. 4.9, the excitation and response signals of the main electrochemical methods together with the resulting concentration-dependent analytical signal are summarized.

Electrical/electrochemical techniques based on measurements of conductance, resistance or impedance are also used for detection in wearable devices although their use in bioanalysis is less extended.[4] Herein, an alternating potential is applied over a frequency range and the measurement of the current, the resistance or the capacitance of the system is performed. These techniques are

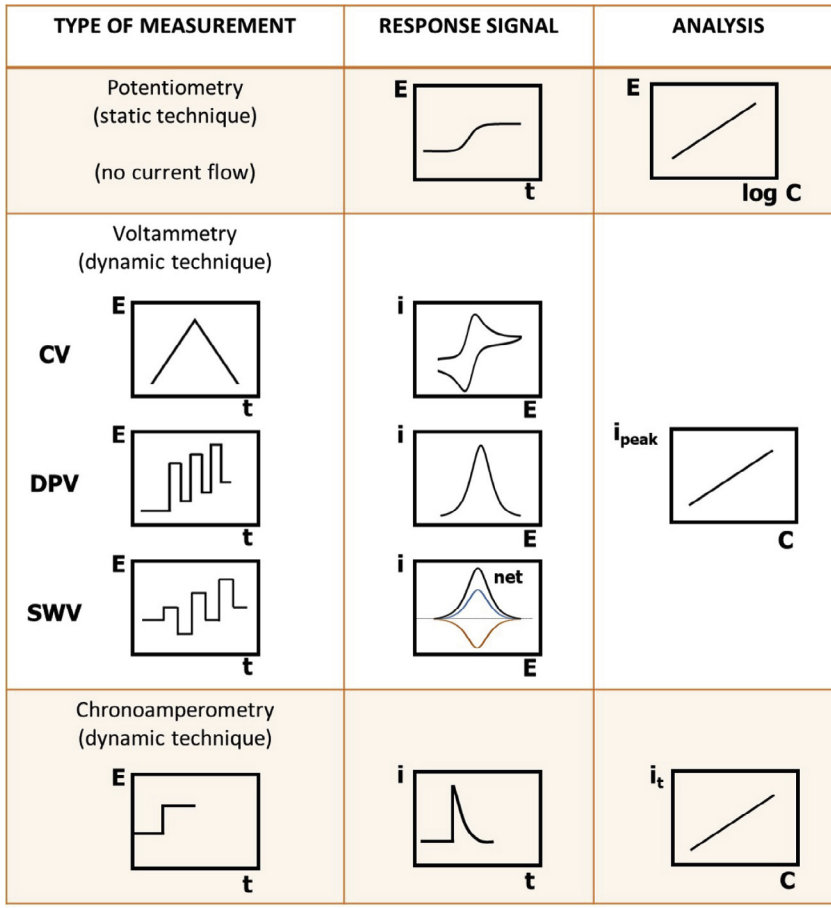

FIG. 4.9 Scheme of the excitation signal, response signal and analysis response for the main electrochemical techniques used in wearable devices. In potentiometry, the open-circuit potential between indicator and reference electrodes is measured and constitutes the analytical signal. In voltammetry, a potential sweep is applied and the generated current is measured as the analytical signal. In amperometry, a stepped (chronoamperometry) potential is used and the measured current at a fixed time is the analytical signal. E, potential; i, intensity of current; t, time; i_t, intensity of current measured at a fixed time; C, concentration.

frequently used for the characterization of electrodes through the study of their surface and their ability to transfer electrons, and have the advantage of not requiring redox-labeled reagents. The use of impedance detection for wearable sensors is limited, since measurements take more time and a more sophisticated equipment is required. However, miniaturized all-in-one electrochemical portable workstations integrating bipotentiostat/galvanostat with built-in impedance analyzer are also available.[112] There are examples of wearable devices using impedance detection for metabolites[113,114] or biomarkers[115] in sweat.

Conductometry is based on the measurement of the resistance (or conductivity, its reverse magnitude) of an electrolyte to the current flow while an alternating potential is applied. This technique has been employed for bioanalytical wearable devices to monitor sweat conductivity.[117,118] Chemiresistive sensors are based on changes in resistance produced by the presence of the analyte. These kind of sensors are very interesting for the development of wearable devices for gas detection.[4] Although their use for biochemical analysis is limited, approaches for sweat pH or salinity determination have been reported[117,119,120] and could be very interesting for monitoring other bio(physical) parameters. Regarding other less conventional detection techniques, it is remarkable that wearable devices based on field-effect transistors (FETs) and biofuel cells are becoming increasingly common.[120,121]

4.4.2.1 Potentiometric detection

Potentiometric detection is based on the measurement of changes in the open-circuit potential between the working (or indicator) and the reference electrodes, separated by a selective membrane, due to the different concentration of the analyte (an ion) at both sides of the membrane.[126] In wearable devices, this detection technique is mainly used for pH monitoring or other ion, different from H^+, determination (such as Na^+, Ca^{2+}, Mg^{2+}, K^+) in sweat.[109,110] Hence, a wide variety of potentiometric wearable platforms, from eyeglasses,[83] to textiles,[88] patches,[96,122,123] bandages[98,105] or tattoos[124] (with different degree of body integration) exist (Fig. 4.10).

Due to its simplicity, potentiometry is the second detection technique employed in electrochemical wearable sensors, after amperometry.[80] It requires just two electrodes and a potentiometer to measure changes in potential. Moreover, solid contact potentiometric sensors used in wearable devices can be easily coupled to low-power consumption electronics.[125] However, in some cases, potentiometry could show low sensitivity and can be affected by interfering ions able to interact with the selective membrane.

In Fig. 4.10A, a picture of the bandage employed for pH monitoring fabricated using flexible silicone-burrer-coated paper sputtered first with Cr, Au or Ag and, in the case of the working electrode, with tantalum oxide, is presented. Because of the simplicity of the required electrochemical cell, it is commonly employed for the development of multiplexed potentiometric wearable devices to monitor several ions simultaneously.[88,95,122] Hence, a textile-based wearable device based on ion-selective membranes for monitoring K^+ and Na^+ coupled to screen-printed electrodes was developed (Fig. 4.10B).[88] This device showed high resistance to mechanical deformations since it was able to withstand repeated bending, crumpling and washing process without significant effects on its response. In Fig. 4.10C, a scheme of the materials for the construction of the textile-based wearable device for K^+ and Na^+, along with an image of the stretchable electrodes on different textiles and typical signal response for both ions are presented. Another example is a wearable platform able to monitor pH

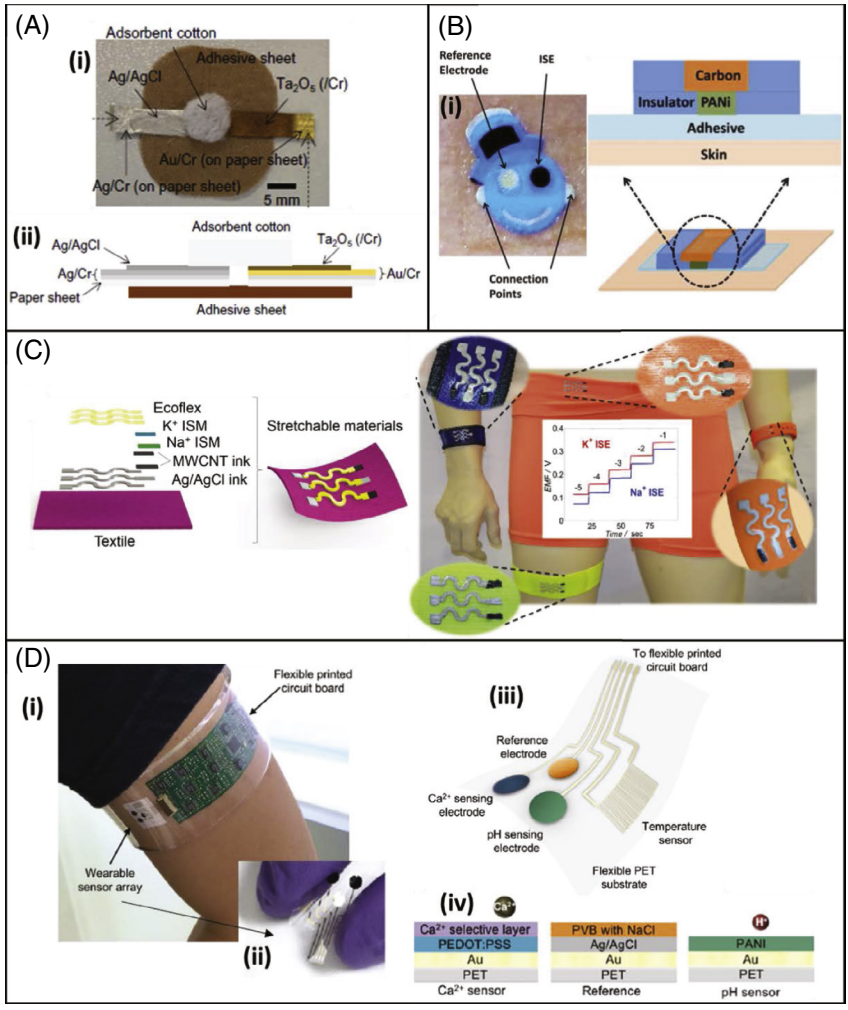

FIG. 4.10 **Overview of potentiometric wearable sensors:** (A) Photograph (i) and scheme (ii) of the bandage for pH monitoring fabricated using flexible silicone-burrer-coated paper sputtered first with Cr, then with Au or Ag, and finally, the working electrode, with tantalum oxide. *Reprinted with permission from 105*. (B) Photograph (i) and scheme (ii) of the construction of the tattoo-like solid-contact sensor for pH monitoring based on pH-sensitive conductivity of PANI. *Republished with permission of Royal Society of Chemistry, from 124 permission conveyed through Copyright Clearance Center, Inc*. (C) Scheme of the materials for the construction of the textile-based wearable device for K^+ and Na^+ detection (i) and image of the stretchable electrodes on different textiles and typical signal response (E *vs*. t) for both ions (ii). *Reprinted from 88 with permission from Wiley*. (D) Photograph (i) of the flexible array patterned on PET containing Ca^{2+}, pH and temperature sensors fully integrated on the wearer's arm, inset (ii) with, a more detailed photograph of the array. Scheme (iii) of the components of the array and schematics (iv) of the membrane composition of sensing electrodes. *Reprinted with permission from 122. Copyright 2016 American Chemical Society*.

and Ca^{2+} in sweat, urine and tears.[122] It consists of a flexible array patterned by photolithography on a polyethylene terephthalate (PET) substrate which includes pH, Ca^{2+} and temperature sensors (Fig. 4.10D). For measuring Ca^{2+} concentration and pH, ion-selective electrodes were coupled with a polyvinyl butyral (PVB)-coated Ag/AgCl reference electrode. The electrode selective to Ca^{2+} was prepared using calcium ionophore II and PEDOT:PSS (polystyrene sulfonate), and the pH sensor was based on PANI.

4.4.2.2 Amperometric detection

Amperometric detection relies on the measurement of the intensity of the current due to the reduction or the oxidation of an electroactive species, at a fixed and constant potential (when the current is measured at a fixed time on a quiescent solution it is called chronoamperometry). The response signal is a (chrono) amperogram that represents the current intensity *vs*. time (Fig. 4.9).[126] The analytical signal corresponds to the measured current at a fixed time. The amperometric approach, in which convection is employed for mass transport and a stationary response is obtained, has a difficult application in wearable devices. In any case, since the potential is stepped, the faradaic component of the current (due to the electron transfer, i_f), decays as a function of $t^{-1/2}$. However, the capacitive component of the current (the electrode also acts as a capacitor, i_c), decreases exponentially (*vs*. e^{-t}). Since the sensitivity is proportional to the i_f/i_c ratio, and the faradaic current decreases more rapidly than the capacitive current, sampling the current after a time where capacitive current is negligible, increases the sensitivity. Because of its simplicity (it just requires applying a potential and monitoring the current with time) and ability for providing fast and continuous responses, amperometry is considered very suitable for wearable sensors.

Amperometry is commonly used in biosensors as for example, enzymatic sensors in which the enzyme provides high selectivity for the target molecule in biological fluids (like saliva, sweat, interstitial fluid and tears). The combination of this selectivity with the sensitivity provided by amperometry make them excellent wearable sensor platforms. Oxidase enzymes are the most used and, due to the significant variety of this class of enzymes, wearable sensors have been developed for important analytes, such as glucose, alcohol, lactate or uric acid, which can be appropriate enzymatic substrates.[127] In these sensors, the concentration of the analyte can be determined through the oxidation of the enzymatically-produced hydrogen peroxide.[81] However, this oxidation requires a high potential which, in turn, increases the risk of interferences. Because of this, it is common the use of mediators, such as Prussian blue, ferricyanide or ferrocene, which act as electron acceptors decreasing the overpotential required.[73,81–85,95,128] Besides the frequently used oxidase enzymes, wearable sensors based on other enzymes have been reported: glucose dehydrogenase for glucose determination,[129,130] tyrosinase for levodopa monitoring,[131] ascorbate oxidase for ascorbic acid detection[132] (Fig. 4.11A) and β-hydroxybutyrate dehydrogenase for ketone bodies detection.[133]

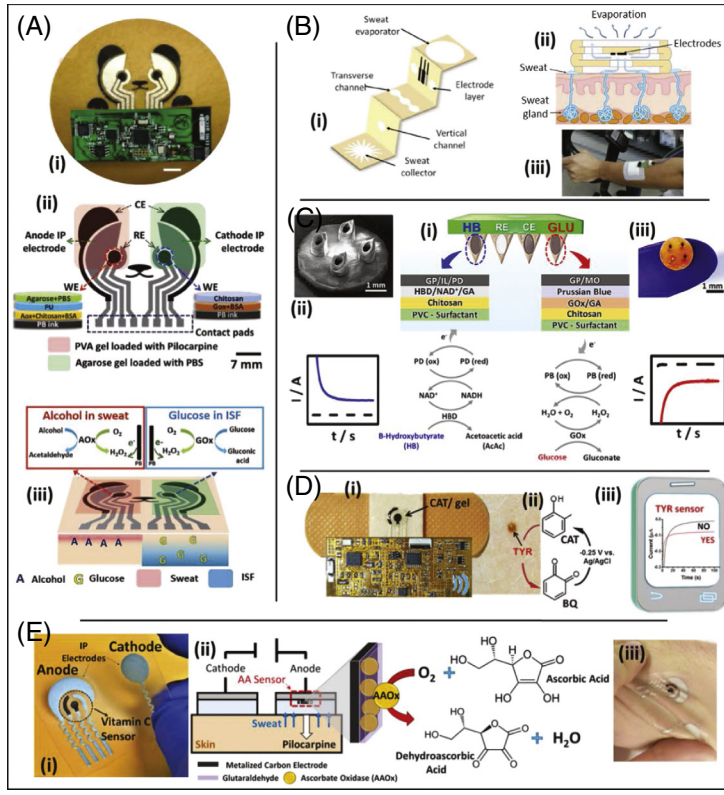

FIG. 4.11 Overview of amperometric wearable sensors based on enxymatic reactions: (A) Photograph of a tattoo-like sensor with integrated potentiostat, placed on the wearer's skin, for simultaneous detection of glucose in ISF and alcohol in sweat, based on two independent screen-printed electrochemical cells and oxidase enzymes (i). Schematic representation of the electrode layout with iontophoretic gels and composition of working electrodes (ii) and of the enzymatic recognition and transduction events (iii). *Reprinted from 134.* (B) Scheme of an origami paper-based microfluidic device which includes sweat collector, channel for sweat transport to the electrodes, screen-printed electrodes and sweat evaporator (i). Schematic representation (ii) and photograph (iii) of the 3D-device applied on the human skin. *Republished with permission of Royal Society of Chemistry, from 95; permission conveyed through Copyright Clearance Center, Inc.* (C) Schematic representation of the microneedle array for determining ketone bodies simultaneously with glucose or lactate using two working electrodes modified with the corresponding enzymes and the corresponding enzymatic recognition, transduction events and response signals (i). SEM (ii) and optical (iii) images of the 2 × 2 array of hollow microneedles. *Reprinted with permission from 133. Copyright 2020 American Chemical Society.* (D) Photograph of a bandage-based sensor for tyrosinase determination with a miniaturized potentiostat (i). Scheme of the enzymatic reaction and transduction events (ii). Schematic representation of the response signal in absence and presence of tyrosinase (iii). *Reprinted with permission from 99. Copyright 2018 John Wiley and Sons.* (E) Electrode design of the tattoo-like device for simultaneous sweat production stimulation and detection of ascorbic acid (i): cathode and anode electrodes are used for sweat stimulation by ionophoretic pilocarpine delivery and the three-electrode electrochemical cell for detection. Schematic of the sweat stimulation and of the enzymatic reaction for ascorbic acid detection (ii). Photograph of the tattoo-sensor under mechanical twisting (iii). *Reprinted with permission from 132. Copyright 2020 American Chemical Society.*

The combination of more than one enzyme for detecting different analytes in the same device allows the easy construction of multiplexed wearable devices. A wearable device based on screen-printed electrodes for detecting glucose in ISF and alcohol in sweat was developed (Fig. 4.11A).[134] In this case, two independent electrochemical cells were printed, and the enzymes glucose oxidase and alcohol oxidase were immobilized on the working electrodes of each cell respectively. The detection in both types of samples (sweat and ISF) was achieved through parallel reverse iontophoretic ISF extraction through the skin and iontophoretic delivery of pilocarpine (inductor of sweat production) into the skin. With this aim, two additional electrodes were screen-printed (anode and cathode, Fig. 4.11A).[134] Iontophoresis is a very advantageous way to stimulate the production of sweat for wearable devices since just two more electrodes are needed allowing to obtain simple, but mechanical resistant to stretch and bending designs (Fig. 4.11E).[132] A more invasive sampling is made with the use of a microneedle array developed for detecting ketone bodies simultaneously together with glucose or lactate (Fig. 4.11C).[133] In this case, two microneedles acted as working electrodes, in which the corresponding enzymes were immobilized (β-hydroxybutyrate dehydrogenase and glucose oxidase or lactate oxidase) sharing reference and counter electrodes. Less invasive way to sampling sweat is taking advantage of absorption ability of paper. Paper allow to construct microfluidic channel to transport the sweat from skin to the electrochemical cell (Fig. 4.11B).[95]

Enzymatic biosensors are usually developed for the detection of the enzyme substrates. However, when the enzyme is an analyte of interest, it can be determined recording the analytical signal (in the case of amperometric sensors, the current intensity) that the sample provides in presence of a fixed concentration of a substrate. One of these enzymes is tyrosinase, whose overexpression in skin cells can lead to melanoma formation.[99] Hence, with this strategy, bandage- and microneedle-based wearable sensors were developed for its detection on and under the skin surface. Catechol was used as substrate since tyrosinase is a polyphenol oxidase, that oxidizes catechol immobilized on the sensor to benzoquinone. Then, the generated benzoquinone is reduced amperometrically and the obtained current intensity can be related with the concentration of tyrosinase in the sample (Fig. 4.11D).

Voltammetric sensors can be considered within amperometric techniques since current is also measured. The same happens with devices based on the use of field-effect transistors (FETs). However, due to their significance and increasing use (especially, voltammetric techniques) and technical importance (as is the case of FETs) they are considered in independent sections.

4.4.2.3 Voltammetric detection

Voltammetric detection is based on the measurement of the current intensity produced as response to the application of a potential scan. In this case, the response signal consists of current *vs*. potential representation (voltammogram) in which one or more peaks usually appears and their peak current intensity is the analytical signal that can be used for quantitative purposes.[11,126] As commented before,

there are different voltammetric techniques depending on the way the potential scan is performed: with linear potential ramp (LSV or CV) or with overimposed pulses (DPV or SWV) (Fig. 4.9). In comparison with amperometric techniques, voltammetric detection requires more complex potentiostats (since it is necessary an excitation signal generation) but it provides more information regarding the redox behavior of the electroactive species. Indeed, since CV is simpler and faster than DPV and SWV, is usually used as a first evaluation step to study the electrochemical behavior of the species on a particular electrochemical cell. Nevertheless, pulse-based techniques offer higher sensitivity because they are able to better discriminate between the faradaic (due to the electrochemical process) and the capacitive (due to double-layer charging) component of the current.[126] Hence, for signal readout in wearable devices, DPV and SWV are the most used voltammetric techniques.

DPV has been used for monitoring drugs such as caffeine[135] and acetaminophen[136] in sweat or saliva. In this last example, the screen-printed electrochemical cell was combined with a smartwatch. In this device, an "undistorted potential window," in which the analyte signal is clearly discriminated from interference signals, was created by using a Nafion™-coated and hydrogen-terminated boron-doped diamond electrode (Fig. 4.12A).[136]

On the other hand, SWV offers fast response and high sensitivity, especially when the redox target has a reversible electrochemical behavior. Wearable SWV-based devices have been reported for the detection of vitamins in tears,[82] drugs (such as tetrahydrocannabinol in saliva[85] or fentanyl in liquid and powder samples[137]), and chemical threats (such as methyl paraoxon -an organophosphorus nerve agent- and 2,4-dinitrotoluene) in liquid or gas-phase samples.[86] Although enzymatic sensing devices usually are based on amperometric principles, enzymes can also be coupled to voltammetric techniques. An example is a microneedle array that uses two different working electrodes for simultaneous measurement of fentanyl and methyl paraoxon with the same device. Fentanyl was directly detected by anodic SWV and methyl paraoxon was enzymatically determined by hydrolyzing it to *p*-nitrophenol, detected also by SWV (Fig. 4.12B).[138]

In order to improve the sensitivity, a preconcentration step can be performed before the voltammetric detection as in anodic stripping voltammetry (ASV), very common for the determination of heavy metals. It consists of a previous electrochemical reduction of metal ions onto the working electrode and then, stripping of deposited metals by voltammetric oxidation. Based on this approach, a wearable microsensor array was developed for multiplexed determination of heavy metals in human body fluids such as sweat and urine (Fig. 4.12C).[139] The microarray consists of two working electrodes, one gold electrode for Pb, Cu, and Hg detection and the other of bismuth for Zn, Cd, and Pb detection, sharing reference and counter electrodes.

4.4.2.4 Field-effect transistors-based detection

In the last years, FETs have attracted increasing interest for the development of sensors. A typical FET is a multilayer device consisting of a dielectric insulating layer

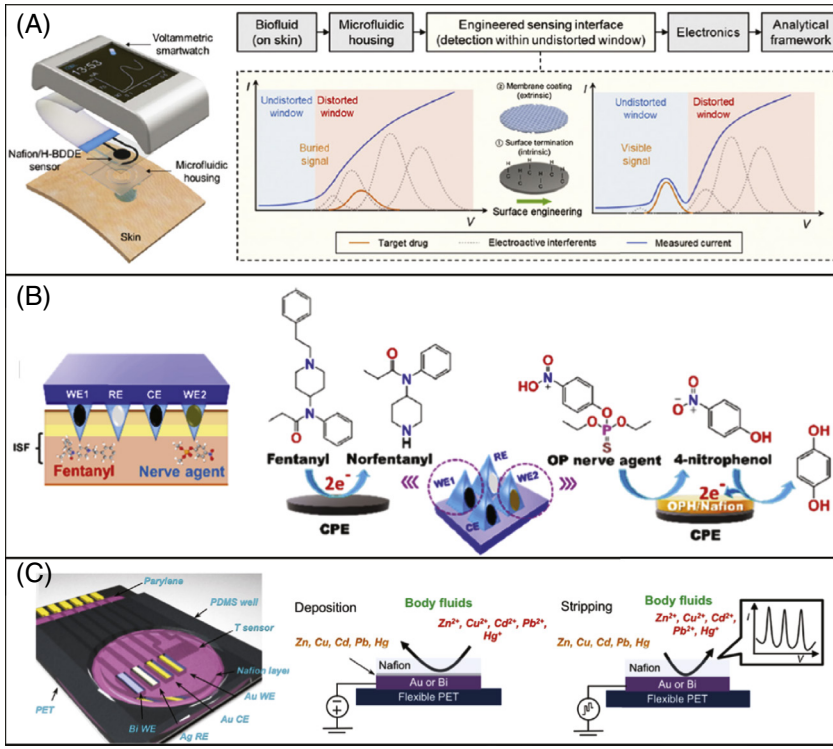

FIG. 4.12 Examples of voltammetric wearable devices: (A) Smartwatch-integrated voltammetric sensor using screen-printed electrodes for determining acetaminophen by DPV: illustrative scheme of the smartwatch component with the sensor (left) and operational workflow of the wearable device for acetaminophen monitoring (right) using the sensing interface to create the "undistorted potential window" to avoid interferences. *Repreinted from 136*. (B) Microneedle array with two working electrodes (scheme on the left) for fentanyl and methyl paraoxon detection; the fentanyl is directly oxidized by SWV and the methyl paraoxon is enzymatically determined detecting the product of its hydrolysis by SWV (on the right, schematic representation of the detection principle). *Reprinted with permission from 138*. (C) Microarray for multiplexed heavy metal ASV detection: scheme of its components with gold and bismuth working electrodes (left) and schematic representation of the ASV detection steps, deposition and stripping (right). *Reprinted from 139*.

interfaced with a semiconductor layer, and three terminals (drain, source and gate electrodes), which can be made of metal layers and/or other conductive materials such as polymers or metallic nanoparticles (Fig. 13A).[79,140,141] Succinctly, in a FET-sensor the current that flows between source and drain is monitored while a tunable voltage is applied at the gate terminal. The application of this voltage produces, an electric field redistribution in the dielectric layer generating a dual-electrical layer and then, charge carriers (electrons or holes depending on the energy-level relationship between the semiconductor and drain/source electrodes) flow in the channel region of the semiconductor layer, producing changes in the electrical measurements.[140] FETs are easy to integrate into small devices and there are a wide variety

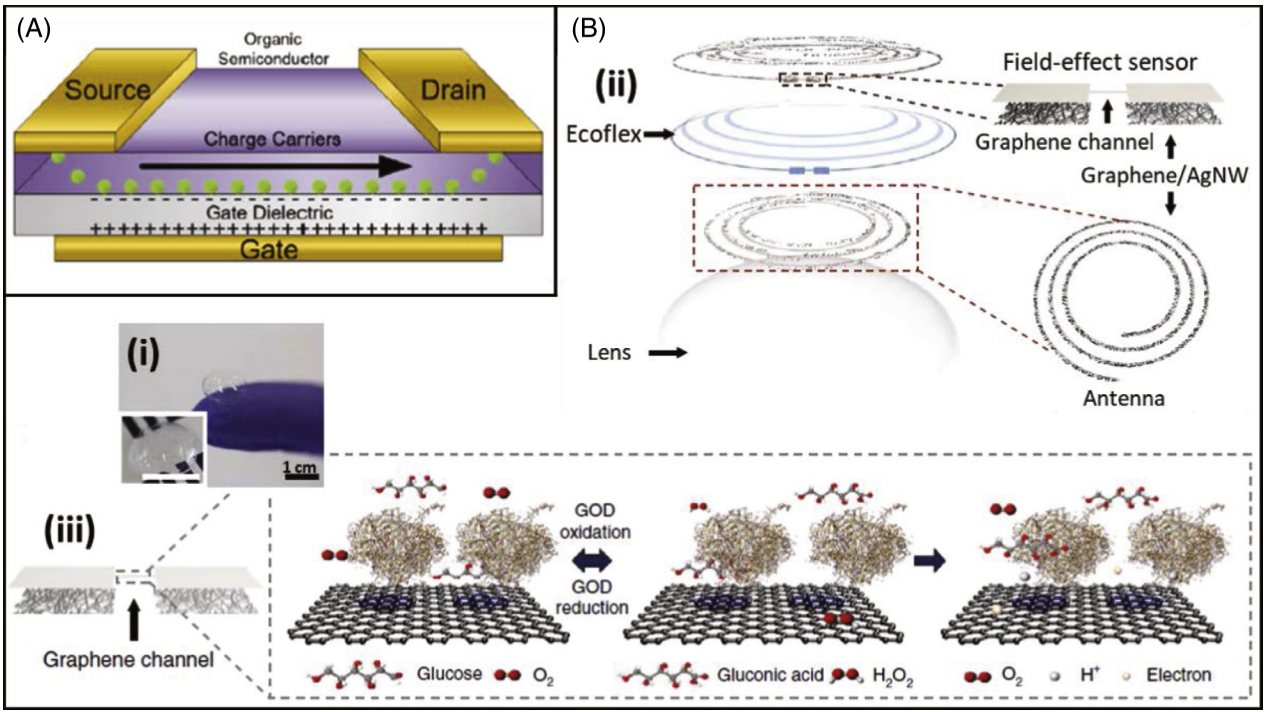

FIG. 4.13 (A) Components and mechanism of a typical FET. *Reprinted from 140.* (B) Enzymatic FET sensor for glucose monitoring integrated into a soft contact lens: photograph (i) of the contact lens-integrated sensor with a close-up in the inset; scheme (ii) of its single components; schematic representation (iii) of the glucose detection with the glucose oxidase-modified graphene channel. *Reprinted with permission from 150. Copyright 2017 American Chemical Society.*

of semiconductor materials, both inorganic and organic, which can be used to construct them. Therefore, FETs are very interesting for the development of biosensors. In these cases, the biorecognition element is usually immobilized on the semiconducting or dielectric layers, and when the analyte is captured by the bioreceptor, the distribution of the charge carrier density changes, and thus, a change in the measured current occurs, which can be related with the analyte.[140]

FET-based wearable sensors employed for monitoring physical parameters, such as pressure or temperature, were widely described.[140] The development of FET-(bio)chemical wearable sensors is clearly increasing.[142] FET-based wearable sensors for monitoring pH and ions (like Na^+ or K^+)[143,144] or electroactive species such as dopamine, adrenaline or ascorbic acid[145] in sweat have been developed. Enzymatic FET wearable devices were also reported for the detection of metabolites such as glucose, uric acid and lactate.[147,148] An enzymatic wearable sensor based on indium(III) oxide (In_2O_3) nanoribbon transistor with a gold gate electrode was applied to the determination of glucose in biological fluids and its performance was demonstrated on an artificial eyeball and a hand.[149] Source and drain electrodes were modified with glucose oxidase, chitosan and carbon nanotubes. When glucose interacted with the enzyme, hydrogen peroxide was produced which, under a bias voltage, was oxidized producing a decrease in pH. This lead to the protonation of hydroxyl groups on the In_2O_3 surface that, in turn, produced changes in the FET electric field, which could be related with glucose concentration. Based on a similar detection approach, an enzymatic glucose sensor, fabricated using a graphene-silver nanowire hybrid structure as source/drain electrodes and graphene as channel in a parylene substrate, was integrated on soft contact lens to demonstrate in vivo glucose sensing on a rabbit eye (Fig. 4.13B).[150] Wearable FET-based affinity sensors have been also reported for the detection of biomarkers such as cortisol or cytokines.[151,152]

4.4.3 Multimodal detection

When the determinaton of more than one analyte is aimed, to wear several different sensing devices is, obviously, not practical. With this in mind, it is very common the development of wearable sensors to determine more than one analyte at the same time by including different transducers in which different detection parameters and/or recognition elements are combined, as in previously commented examples for potentiometric, voltametric and amperometric detection.[88,96,105,122,133–135,139] Another approach for obtaining more information from the same sample is combining different detection principles in the same device to, either determining the same analyte by both methodologies, or determining different analytes. An example of the first case is the multimodal microneedle wearable device developed for the simultaneous detection of levodopa (a medication for Parkinson's disease) by two methods: i) amperometrically, after the enzymatic oxidation (using tyrosinase as enzyme) to dopaquinone and detection of this enzymatic product; ii) directly, by recording the square wave voltammogram of levodopa.[131] This

device consists of three microneedles: one acting as reference electrode and the other two as working electrodes. In one of them, SWV is performed and in the other, modified with tyrosinase, a chronoamperogram is recorded (Fig. 4.14A). The detection of the same analyte through two different methods in the same device provides additional information and therefore, more reliable results. The strategy of combining different techniques for the simultaneous determination of several analytes using the same wearable platform is more common. Indeed, there are several examples of combining an enzymatic amperometric system for metabolite determination with a potentiometric system for monitoring pH or ions,[83,153] but also with voltammetric systems for determining electroactive species.[82,85] An illustrative example of the first case is the development of eyeglasses able to perform potassium (by potentiometry) and lactate (amperometrically after lactate oxidation with lactate oxidase, using Prussian blue as mediator) determination in sweat (Fig. 4.14B).[83] One interesting example combining amperometric and voltammetric techniques is the wearable ring sensor developed for determining tetrahydrocannabinol (THC) and alcohol in saliva. This ring sensor performs the direct detection of THC by SWV while the alcohol is enzymatically measured (using alcohol oxidase and Prussian Blue as mediator) by chronoamperometry (Fig. 4.14C).[85]

Regarding optical detection, the use of different approaches to determine several analytes is common, especially when colorimetric detection is concerned. The use of multimodal strategies, but employing different principles (electrochemical and optical) is also possible, especially when visual readout results very useful for detection, and further electrochemical techniques can be employed for quantitative determination. Apart from this, it is very common the simultaneous measurement of biophysical and biochemical parameters as is the case of eye movement monitoring as well as glucose (electrochemical) and lactoferrine (fluorescence) determinations.[64]

4.5 Conclusions and outlook

Wearable sensors able to determine physical and chemical parameters are achieving a level, from both scientific and technological point of views, close to maturity. The degree in difficulty increases when moving towards certain chemical and specially biochemical parameters that require stringent properties. Acceptance by end users is considerably raising, mainly in clinical and sport-related fields, where they have impacted first. This is motivating enormously researchers and technicians in this appealing but challenging field. The first target was human body, essentially soft, unlike the first wearable sensors, that were rigid. Hence, no conformal contact between them could be established. Moreover, they could dislocate while people moved producing inaccurate results. However, material science has delivered various supplies with excellent properties (flexibility, stretchablility, biocompatibility etc.)

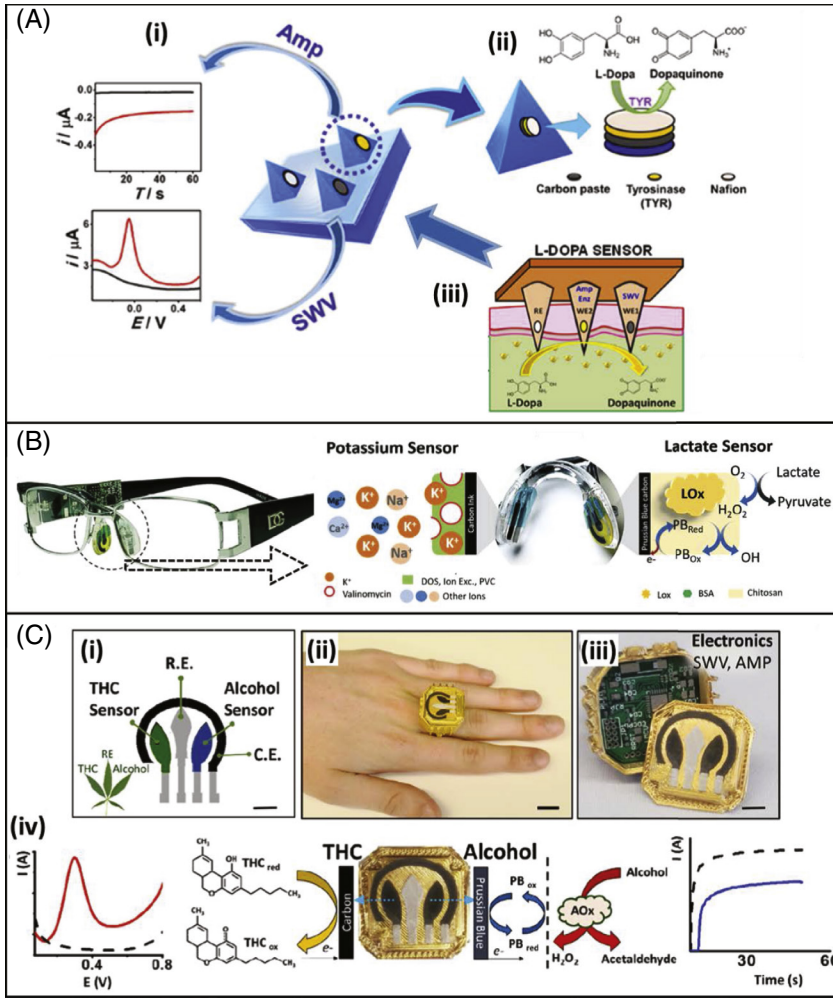

FIG. 4.14 **Multimodal wearable sensors.** (A) Microneedle device with two working electrodes for levodopa detection by two techniques: scheme (i) of the levodopa detection by SWV and amperometry using the same array; enzymatic reaction (ii) required for levodopa detection by amperometry; scheme (iii) of the microneedle sensor for levodopa monitoring. *Reprinted with permission from 131. Copyright 2019 American Chemical Society*. (B) Photograph (left) of the eyeglasses with the integrated sensor in the nose pads and scheme (right) of the detection approaches for potassium (potentiometry) and lactate (amperometry along with enzymatic detection) determination. *Republished with permission of Royal Society of Chemistry, from 83; permission conveyed through Copyright Clearance Center, Inc*. (C) Sensor for simultaneous detection of THC and alcohol: sensor design (i), photograph (ii) of the ring sensor, image (iii) of the integrated electronics and replaceable screen-printed electrochemical cell, schematic representation (iv) of THC detection by linear sweep voltammetry and enzymatic alcohol detection by amperometry. *Reprinted from 85 (2017), with permission from Elsevier*.

able to be worn or integrated with textiles and accesories. In this context, the revolutionary wearable device had to perform imaginatively the properly integratation of all the elements required to produce accurate results.

The analytical process, including signal detection as the main step, is performed in tiny platforms. All the principles of detection are evolving for fitting in these small platforms, but electrical/electrochemical and optical are the most common. Among them, electrochemical techniques fit seamlessly due to the interfacial nature of the measurements and the simplicity of the equipment. Measurement of resistance, capacitance, impedance (as main electrical) as well as potential or current (as the main electrochemical, although the previous can also be related to chemical events) are the basis of the analytical signals that correlate with the concentration of analytes. Electrodes became just conductive surfaces on different materials like hydrogels, paper, textiles and strategies such as the use of microneedles and microfluidics, were assessed to integrate sampling and sample transportation to the measurement area. Equipment became also wearable and potentiostats were included in patches, pacifiers, rings etc. Amperometric measurements are by far the most common, and when combined with biocatalysts (e.g., enzymes) and bioaffinity reagents (e.g., antibodies), selective as well as sensitive methodologies were obtained. Conventional systems with two (mainly potentiometric) or three electrodes are employed but applications with field effect transistors, easy to be miniaturized, are also increasing.

On the other hand, the other important principle of signal transduction is optical. Colorimetry and fluorescence modes are the most common. Naked-eye detection is instrument-free and fast but combination with smartphones for image capturing and processing is increasing exponentially. When sensitivity is required, fluorescence is preferred over transmittance/reflectance readout modes. The visible region of the electromagnetic spectrum is commonly used but also near infrared, in such a way that multiple light emitting diodes with optical wavelengths under Vis-NIR range can be combined. Infrared is also employed in photoplethysmographic records to study variations in oxygen saturation or heart rate.

The interest in multimodal detection is increasing, and probably optical and electrochemical principles will merge in devices that will provide useful information and allow developing interesting applications. The existence of materials that are both conductive and transparent together with the miniaturization of all the required components and equipment for the different principles approach this possibility.

(Bio)physical parameters are the most common targets of wearable sensors and were the first objective, maybe because they can be measured, in most of the cases, in contactless mode. However, information on (bio)chemical parameters is also required, and samples like saliva, sweat, tears, breath are analyzed. They are preferred to invasive samples that would require trained personnel for doing the analysis at a fixed time and place, i.e., in a centralized way. Sweat is

a particularly attractive sample due to its ease of collection and presence of biomarkers related to important health conditions. Apart from sweat, skin is very attractive for the great amount of analytes of interest that could be approached for obtaining information and therefore, patches and bandages are common. However, wearable devices for other body parts, such as teeth or add-ons like contact lenses, mouthguards or pacifiers have been developed. It is increasingly common to find examples of multiplexed and multimodal devices measuring both biophysical and biochemical parameters that provide more complete information.

Democratization of analysis requires wearability and, in turn, a good choice of the detection principle, the main step of the analytical process, has to be made since it will influence the rest of the steps and the properties of the methodology. In this context, in Table 4.2, advantages, disadvantages, challenges

TABLE 4.2 Comparison of some of the advantages, disadvantages, challenges and opportunities of the most common detection techniques in wearable devices.

Advantages	
Electrical/Electrochemical	*Optical*
Electrical • Low-cost • Easy to integrate • Useful for physical and (bio)chemical parameters • Continuous and real-time measurements **Electrochemical** *Potentiometry* • Simple and low-cost instrumentation • Easy to integrate • Continuous and real-time measurements • Not affected by color or turbidity of samples *Amperometry* • Simple instrumentation (no potential scan required) • Easy to implement • Interfacial measurements (electrodes can be easily miniaturized as e.g., films) • Conversion from photon to electrons is not required • Not affected by color or turbidity of samples	**Photoplethysmography** *Transmittance or Reflectance* • Continuous and real-time measurement • Monitoring of various cardiovascular aspects (oxygen saturation, heart rate, blood pressure…) • Very intuitive and easy to use **Colorimetry** *Absorbance/Transmittance or Reflectance* • Useful for liquid/solid samples • Large number of species develop a color after reaction • Easy detection by image capture • Low-cost analysis **Fluorescence** • Very sensitive • Combination of fluorophores that emit at different wavelengths (e.g., red/green) • Hydrogel and flexible materials can include agents for chemosensing

Advantages	
Electrical/electrochemical	*Optical*
Voltammetry • Diagnostic technique • Several modes are possible (e.g., CV, DPV, SWV) • Oxidation and reduction processes can be measured • Not affected by color or turbidity of samples	**Naked-eye detection** ***Transmittance/Reflectance or Fluorescence*** • In situ detection; the detector (eye) is intrinsically worn • Very simple measurement, equipment-free for transmittance/reflectance modes • Low-cost analysis
Disadvantages	
Electrical/Electrochemical	*Optical*
Electrical • Not extremely sensitive and selective • Complicate multidetection **Electrochemical** ***Potentiometry*** • Measurements in conductive media • Not extremely sensitive • Stable reference electrode required ***Amperometry*** • Measuring at a fixed potential can compromise the selectivity • Passivation of surface electrode in reusable electrodes ***Voltammetry*** • Measurements require conductive medium in most of the cases • More complicate instrumentation for generation of the excitation signal	**Photoplethysmography** ***Transmittance or Reflectance*** • Low operational durability under repetitive mechanical deformation • High power consumption for long term and portable applications **Colorimetry** ***Absorbance/Transmittance or Reflectance*** • Reflectance provides nonlinear calibration curves • Interferences from turbid or colored samples • Interferences from light scattering **Fluorescence** • Not many species are fluorescent • Emission-based detection, therefore an additional excitation light source is required **Naked-eye detection** ***Transmittance/Reflectance or Fluorescence*** • More appropriate for qualitative detection • Dependent on illumination conditions and substrate color • Subject to person-to-person variabilities • Difficult to discriminate color • Non-instrumental, and therefore, not very sensitive

(*continued*)

TABLE 4.2 (Cont'd).

Challenges

Electrical/Electrochemical	*Optical*
Electrical • Application to more biochemical parameters **Electrochemical** *Potentiometry* • Incorporation of new selective agents • Improvement of integrated sampling cells (and disposability) • Decrease sampling time for continuous measurement • Inclusion of energy storage modules for long term measurements *Amperometry* • New electrode materials and fabrication technologies • Improvement of the integration with microfluidics/electrofluidics • Measurement in low conductive media (favored with miniaturized electrodes) • Parallelization of assays *Voltammetry* • New electrode materials • Integration with biochemical assays • Development of compact devices with all the required components (potentiostat…) • Decreasing required power to increase autonomy	**Photoplethysmography** *Transmittance or Reflectance* • Improvement of conformal adhesion • Decrease of skin irritation for long measurements • Removal of motion artifacts **Colorimetry** *Absorbance/Transmittance or Reflectance* • Better integration to smartphones • Combined storage of reagents for color development and biochemical analysis **Fluorescence** • Combination of other principles such as magnetism (fluorescent magnetic particles) **Naked-eye detection** *Transmittance/Reflectance or Fluorescence* • Multianalyte detection • Search for stable dyes or selective agents for (bio)chemical sensing • Dual detection to confirm dubious results • Sensitivity increase

Opportunities

Electrical/Electrochemical	*Optical*
Electrical • Self-sustaining devices **Electrochemical** *Potentiometry* • Selective membrane development • Self-sustaining devices *Amperometry* • Improvement miniaturization and integration • Self-sustaining devices • Integration of different electrochemical modes (e.g., potentiometric and amperometric)	**Photoplethysmography** *Transmittance or Reflectance* • Use of arrays and algorithms for evaluation of body conditions • Measurement at different wavelengths for detection of hemoglobin derivatives (early notice of exposure to specific drugs or toxins) **Colorimetry** *Absorbance/Transmittance or Reflectance* • Use of transmittance mode on porous substrates

Opportunities	
Electrical/Electrochemical	*Optical*
• Easy combination with smartphones • Integration of several sensors for smart clothes ***Voltammetry*** • Specific applications: e.g., in vivo measurements • Spatial resolution employing a high number of electrodes (e.g., thousand) • Incorporation of nanomaterials in devices beyond academic research • Self-sustaining devices	• Extending the use on new materials • Innovative integration with microfluidics (e.g., threads, fabrics…) **Fluorescence** • Integration of synthetic biology for noninvasive monitoring including isothermal amplification and CRISPR-based tools **Naked-eye detection** ***Transmittance/Reflectance or Fluorescence*** • Application to colorless and toxic compounds monitoring by chemosensing (gas) • Smart food packaging • Development of color on innovative materials

and opportunities of the most common detection techniques are compared. Electrical, electrochemical and optical techniques (with naked-eye detection considered separately by its relevance in all the modes) are contemplated. The increasingly close relationship between disciplines will help to deliver promising devices, maintaining the interest on this hot topic, already converted in a very active research area.

List of acronyms

μPAD	Microfluidic paper-based analytical device
2-FMA	2-fluoro-methamphetamine
AN	Ammonium nitrate
ASV	Anodic stripping voltammetry
BG	Blood glucose
CAS	CRISPR-associated
CCD	Charge-coupled device
CD	Carbon dot
CMOS	Complementary metal-oxide semiconductors
CMYK	Cyan, magenta, yellow and black
$CoCl_2$	Cobalt(II) chloride
CRISPR	Clustered regularly interspaced short palindromic repeats
CV	Cyclic voltammetry
DIC	Digital image colorimetry
DPV	Differential pulse voltammetry
FET	Field-effect transistor
EuMOF	Eu metal organic framework
$HgCl_2$	Mercury(II) chloride

HSB	Hue, saturation and brightness
HIS	Hue, intensity and saturation
HSL	Hue, saturation and luminance
HSV	Hue, saturation and value
In_2O_3	Indium(III) oxide
ISF	Interstitial fluid
NFC	Near field communication
NIR	Near infrared radiation
NM	Nitromethane
LED	Light-emitting diode
LSV	Linear sweep voltammetry
OLED	Organic LED
OP	Organophosphorus pesticide
OPD	Organic photodetectors
PANI	Polyaniline
PC	Photonic crystal
PEDOT	Poly(3,4-ethylenedioxythiophene)
PEI	Polyethylene imine
PET	Polyethylene terephthalate
PPG	Photoplethysmography
PSS	Polystyrene sulfonate
PVB	Polyvinyl butyral
PVC	Polyvinyl chloride
PyrC	1-Pyrenecarboxaldehyde
QD	Quantum dot
RGB	Red, green and blue
RFID	Radiofrequency identification
ROS	Reactive oxygen species
RPA	Recombinase polymerase amplification
SEM	Scanning electron microscope
SERS	Surface-enhanced Raman scattering
SWV	Square wave voltammetry
THC	Tetrahydrocannabinol

Acknowledgments

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Chapter 5

Signal enhancement strategies

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5.1 Introduction

As the name suggests, the multidisciplinary field of microfluidics focuses on the precise manipulation of minute amounts of liquids within networks of channels with dimensions within the micrometer scale (tens to hundreds).[1–3] These manipulations can include many processes such as movement of fluids, sorting of cells and particles, aerosolization of drugs, among many others. So, when this technology is coupled with other detection/conventional transduction methods, such as electrochemical or optical methods, portable point-of-care (POC) platforms can be created.[4–6]

Besides, playing an important role in advancing POC devices, the application of microfluidics offers several advantages. First, as microfluidic channel networks are easy to fabricate and (can be) simple in design, the ease of adaptation toward miniaturization is highly feasible. Second, due to capillary forces and micron scale effects that arise in the microchannels, only small sample amounts are required for analysis and the need for external and bulky equipment can be neglected as analytical and various benchtop processes, such as sampling, mixing, etc., can still be achieved.[7,8]

Despite these advantages, measuring low analyte concentrations (ultra-low detection limits) and low detection signals are still key issues that need to be addressed. Over the years, many different strategies have been developed to amplify the signal, including methods to concentrate or accumulate the analyte within the microfluidic network, or by means of pretreatments, functionalization, and signal amplification using nanomaterials. While these approaches have yet to meet the clinical requirements to be commercially available and

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standardized, given the trajectory and progress of research, it is fathomable that the future of wearable technology, and its impact on personalized healthcare, is not that far off.

5.2 Part A—Sample collection via microfluidics

The most fundamental, and obvious, feature of a wearable device is its ability to collect samples for processing and analysis. Moreover, when considering diagnostic processes and aiming for *true* lab-on-a-chip applications, sample preparation, such as pretreatment, filtering, mixing, etc., are often also required for analysis. Fortuitously, microfluidics is highly suited and offers many promising attributes for flexible and wearable devices.

Microfluidics has seen great development and progress since its first uses in microanalytics and microelectronics.[1] Typically for wearables, microfluidic networks are designed for the purpose and functions of: (1) sampling of body fluids with the intention to be as noninvasive as possible, (2) facilitating the right conditions for detection by means of storage or pretreatment steps, and (3) directing and transporting the collected sample to the detection site or sensor.[9,10]

Over the years, the fabrication processes of microfluidic structures have undergone a lot of changes where several methods and techniques have been implemented for various materials and architectures. However, the most commonly used, still, are the processes of soft lithography, which were first introduced by Whitesides in the late 1990s.[11,12]

Soft lithography encompasses a set of techniques for the fabrication of micro/nanoscale structures. As the name suggests, soft lithography is centered round the use and processing of mechanically soft elastomeric materials as molds, stamps, and masks to produce microstructures and patterns onto substrates.[13,14] Of the elastomeric materials, polydimethylsiloxane (PDMS) is the most commonly used polymer in soft lithography as it possesses many attractive properties, such as low costing, ease of preparation, nontoxicity, optically transparent, has moderate stiffness when cured and can easily conform to various surfaces curvatures to achieve total surface contact—a quality that is important to forming and sealing microfluidic systems.[14]

Seen as a complementary extension to photolithography, which uses light and specifically designed photomasks to achieve the intended layout, soft lithography extends the photolithography process and is a cheaper and faster approach, offering for more flexibility and versatility in fabrication. In fact, the fabrication of microfluidic structures can typically feature several methods of both these techniques. However, in comparison, soft lithography can be applied for curved surfaces; a limitation in photolithography as it affects the distribution of light through the photomask, and has the capability to construct (quasi) 3-D microstructures; while photolithography typically results in 2-D microstructures. Moreover, soft lithography is able to achieve higher resolutions than that of photolithography, and lateral features as small as 30 nm – 500 μm [12] have been reported.

5.3 Fabrication techniques of microfluidic structures

5.3.1 Soft lithography

One of the main advantages of using elastomeric materials for microfluidics is the versatility of design due to the nature of the prepolymer material.[15] Typically, the prepolymer is a prepared solution, containing the polymer and a cross-linking agent, which can then be easily poured into, or casted onto, a microfluidic master mold and hardened by curing at various temperatures and times. Typically, the master mold is fabricated using photo or e-beam lithography and can then be reused over and over. Fig. 5.1 shows the various methods for creating pattered or microfluidic structures using PDMS and soft lithography.

1. Replica molding

Replica molding (Fig. 5.1A) is used to duplicate 3-D designs and patterns using a master mold. The prepared PDMS polymer can be poured directly onto the master, cured, and then easily peeled off, resulting in an embossed PDMS structure with the microfluidic design. Moreover, the embossed PDMS device can also act as the master mold if a device with complementary features is desired. Thus, this method not only allows for hundreds of devices to be made using the same mold, but also facilitates for patterning using a wider range of materials, such as biocompatible polymers such as polyethylene glycol, epoxies, and agar.[16,17]

2. Micromolding in capillaries

In particular to using the embossed PDMS device as a mold, micromolding within the capillaries is also a common technique used to form networks of microchannels (Fig. 5.1B). Here, the embossed device is firmly placed in contact with a solid substrate, such as glass or silicon wafer, with the embossed features meeting the substrate and ensuring the interface between the PDMS and substrate is uniformly sealed. Prepolymer solution is then placed along the edge of the PDMS features and is drawn into the features by capillary action. Once cured, the PDMS can be easily peeled away, leaving micropatterned features on the substrate.[12,15]

3. Microcontact printing

Embossed PDMS devices can also be used for stamping applications and processes—called microcontact printing (Fig. 5.1C) —as the elastomeric properties (namely the stiffness) and surface inertness of PDMS can provide uniform contact between the features of the stamp and the surface of the substrate. In this technique, the embossed side can be coated with various inks to be transferred onto a surface or substrate. The possibilities of the inks are endless and can range from traditional printing inks, to conducting inks containing nanomaterials or even biomolecule-based inks made with proteins or suspensions of cells.[18,19]

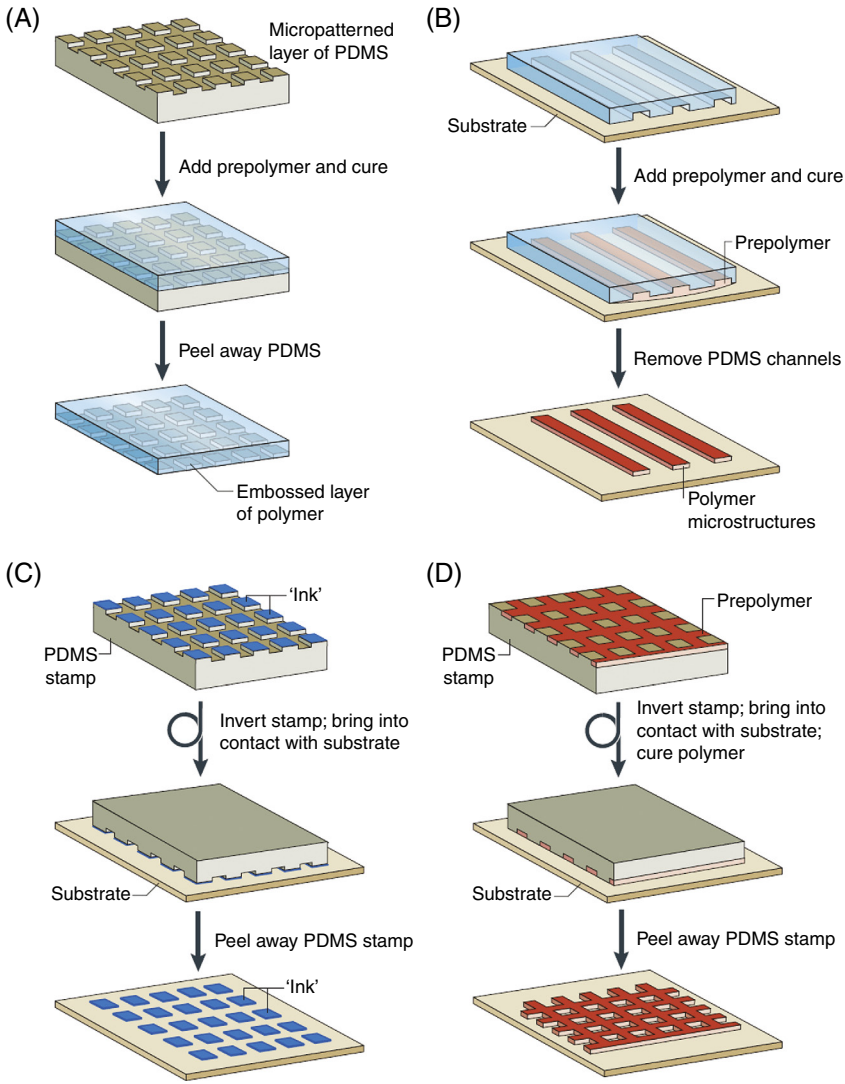

FIG. 5.1 Key microfluidic patterning techniques used in soft lithography. (A) Replica molding, (B) micromolding in capillaries, (C) microcontact printing, and (D) microtransfer molding *(reproduced with permission from ref,*[15] *copyright 2007, Springer Nature Publishing).*

4. Microtransfer molding

Alternatively, to microcontact printing, microtransfer molding (Fig. 5.1D) uses the "negative" features of the embossed PDMS device to mold structures onto a substrate. In this technique, prepolymer solution is placed onto the embossed PDMS side to fill the "negative" space. The excess prepolymer is then removed, by scraping the surface or by blowing with nitrogen (N_2), and

then placed onto a substrate, again ensuring uniform contact. After curing the prepolymer, the PDMS layer can be peeled away, leaving the patterned microstructures on the substrate.[15]

In particular for wearable devices, another use of feature embossed PDMS is as the housing unit for the device. As PDMS offers flexibility for curved surfaces, PDMS can be used as a microfluidic device itself where the network of microchannels and microstructures is patterned onto the surface at the desired depths to maintain capillary forces and laminar flow effects. Furthermore, functionalization of PDMS with biomolecules and receptors can be achieved.[20] Using various techniques, such as thiol-ene chemistry, plasma treating, etc., the hydrophobic nature of PDMS can be reduced while also adding selectivity and specificity to the device.[21,22]

Interestingly, over the years, many researchers have developed and designed specific microstructures and architectures that can act as valves, pumps, directional flow guides, mixers, etc. to obtain an innovative and comprehensive wearable device.[23,24] Geometries such as microneedle arrays are shown to be effective and efficient approaches to not only sample fluids found on the skin, but also as drug delivery vessels. Reservoirs and channel geometries, such as bends, spirals, and zigzags, can be integrated to dictate and control flow rates, slowing down or delaying the flow of fluids from reaching sensor electrodes or to enable time for functionalization steps. In particular, reservoirs prefilled with receptors or fluorescent labels can also act as functionalization or reaction chambers that interact with targets in sweat, for example, and can provide for better quantitative analysis.[25] Moreover, due to the inertness of PDMS, electronic components can also be integrated into the PDMS matrix to add an element of complexity and to obtain a complete lab-on-a-chip device.[26,27]

5.3.2 Wax printing on cellulose-based materials

Aside from polymer-based microfluidics, porous materials, such as cellulose (being paper the most popular choice), also possess intrinsic microfluidic capabilities via the use of capillary forces. In comparison to PDMS-based microfluidics, these porous material–based devices are of lower costs, widely available, and are simpler to fabricate and adaptable to many designs and purposes. Moreover, paper-based microfluidic devices are particularly popular in resource-limited environments, such as developing countries, due to its portability, and ease of use.[28]

In particular, paper-based microfluidics has been extensively researched and adapted for many diagnostic applications,[29,30] where the most commercially available example can be seen in the at-home pregnancy test. Aside from cost effectiveness and portability, conventional paper has numerous advantages as analytical devices: (1) compatibility and ease of functionalization with biological samples and biomolecules, (2) ease of disposal (i.e., disposal by incineration to minimize and eliminate risks in contamination), (3) potential for simple

storage and transporting conditions that will depend more on the biological material embedded, (4) white paper is highly contrasting with colored agents and is suitable for naked-eye readout platforms, and (5) flexible so to be easily adapted to many printing technologies.

In fact, a common and cost-effective method for directing the flow of fluid through porous substrates is via wax printing. The hydrophobic nature of wax acts as a barrier to guide the flow through the device. Depending on the various geometries of the design, such as widths, lengths, and shapes of the channels, flow parameters, such as speed of flow, and analytical processes, such as functionalization, filtering, and mixing, can be controlled.[31]

The process of wax printing is very straightforward: using a wax printer (solid-ink printer), the microfluidic design is printed onto the paper/porous substrate (similar to a typical office printer) and then gently heated at low temperatures to melt and seep the wax into the substrate to create the hydrophobic barrier. A key limitation of wax printing is the low resolution that is obtained after the printing and heating steps. First, compared to the resolutions obtained using lithographic methods, the dimensions of the microfluidic design to be printed will be at the mercy of the printing resolution of the printer itself. And second, the spreading and movement of the wax upon heating is difficult to control as the redistribution occurs both laterally and vertically in the paper substrate. However, submillimeter patterns can be achieved by combining wax printing with photolithography and/or laser cutting.[32–34]

However, despite its advantages for microfluidics on absorbent media, such as paper and plastic membranes, solid wax printers have recently been discontinued. While the instruments are readily available, research groups that are currently using these printers are relying on old and dated equipment that are refurbished, or adapted, for the group´s needs. For this reason, an alternative technology with similar advantages is highly sought after. As such, toner laser printers represent as a possible alternative, despite the additional requirements of heating the ink at much higher temperatures than for solid wax ink, and washing steps to prevent interference from redox compounds formed in the process.[35]

5.3.3 3-D printing/additive approaches

Besides soft lithography, another strategy for the fabrication of 3-D structures is by using additive methods or more commonly known as 3-D printing, which approaches the fabrication process by using point-by-point or layer-by-layer means. Here, by using 3-D digital models, designed with Computer Aided Design (CAD) software, microfluidic devices can be easily printed using a 3-D printer. As the models are designed digitally, there is great freedom to the overall layout and can facilitate for many innovative designs, where minor adjustments and customization can be made at each iteration for rapid prototyping. Moreover, the printing aspect allows for selective placement of material, thus negating waste and increasing production efficiency. In this regard, and in

particular for mass production, the main advantage is the potential for automation and large-scale production with great accuracy and reproducibility,[36–38] and without the need for clean room facilities.

The use of additive methods for *complete* microfluidic device fabrication, in particular for wearables, is limited due to the low resolutions achieved and restrictions to geometric versatility.[10,36] However, the use of 3-D printing to fabricate molds offers the advantages of reusable molds; thus saving time and printing costs; and the compatibility of with conventional microfluidic fabrication materials such as PDMS.[10,11,22] Throughout the years, researchers have developed many microscale 3-D printing techniques that have proven advantageous for lab-on-a-chip or POC systems. The main additive approaches are briefly discussed next:

1. Stereolithography

One of the earliest forms of 3-D printing was stereolithography; a laser-based technique that involves curing prepolymeric resin in a layer-by-layer manner. In each layer, the area that is cured is designed as 2-D cross-sectional shape of the final device, while the excess or uncured resin is simply washed away. In this way, successive layers can be built to form the 3-D device. Stereolithography offers very high resolutions and the convenience of automation, but is limited to only a select list of biocompatible materials and is challenging to adapt for multimaterial printing.[39]

2. Extrusion-based 3-D printing

Extrusion-based additive approaches can be known by a few other names: fused deposition modeling or fused filament fabrication. Generally, in this approach, extruded layers of polymer filaments are repeatedly overlaid and fused or solidified together upon rapid cooling to form the 3-D structure. This process is enabled by a motor-driven nozzle head, capable of heating and moving in 3-D planes, that continuously extrudes, or feeds, a thermoplastic polymer onto the build platform—akin to the widely available and commercial 3-D printers.[40,41]

The advantages here are low cost, simplicity, and compatibility with inexpensive biocompatible materials such as polylactic acid and polyglycolic acid. However, full use of extrusion-based methods for complete microfluidic fabrication has been greatly hindered by the considerably low resolutions obtained and the processing times. Among drawbacks, the common, and more detrimental, issues that arise are leakages due the filament bonding and weak mechanical properties of the final product. The main cause of the weakness can be attributed to interlayer distortion resulting from the printing method. Moreover, while support materials are generally not required during the printing of the larger device itself, internal supports for complex microfluidic designs are often difficult to remove and can affect the function of the device. On the other hand, these techniques can be used to place sacrificial materials, for example as support structures or as larger mold features, which can be subsequently removed. Similarly,

extrusion-based methods can also be used to fabricate other components that are typically required for integrated systems, such as battery encasings, external antennas, and light-emitting diodes, among others.[10]

3. Polyjet printing

Using similar photopolymers and resins like in stereolithography, polyjet printing employs inkjet-style printing technology to create 3-D structures layer-by-layer. After printing each layer, the ink is cured by UV radiation before subsequent layers are added to from the complete device. In comparison to the other additive approaches, the main advantages of polyjet printing are the relatively high resolutions that can be achieved, the wide variety of materials that can be used, and the capacity to print with multiple materials on the same device. However, there are limitations to the dimensions of the microstructures that are to be considered. Polyjet printing requires the use of support materials for void spaces and removal of these supports is often difficult; especially when the channel features are less than 200 μm or have complex design features such as corners or serpentines. Moreover, to extend the latter drawback, various design aspects are also limited. Without proper removal of these supports, the entire flow of the microfluidic device can be disrupted or render the device as nonfunctional.[10,41]

5.4 Membranes

The combination of membranes in microfluidic systems is a widely researched and popular approach to add complexity and functionality to the wearable device.[42] In itself, membrane science and technology is a broad and interdisciplinary field that uses elements from process engineering and materials science and chemistry, and has already found many uses for a diverse range of applications.[43,44]

Membranes are characterized as a semipermeable barrier or interface, and are generally used to *control the transportation* of liquid bodies and its contents within a system—thus filtering or separation particulates from liquids. In the case of microfluidics and wearable devices, transport through membranes is driven by a difference in chemical potential on both sides of the membrane. The difference can be due to a gradient in (partial) pressure, electrical potential, or concentration. Moreover, the morphology of the membrane also has great influence on the mechanism of transport and affects its purpose in the microfluidic device. Important membrane characteristics to consider include pore size, shape and distribution, permeability, molecular weight cut off, membrane material, etc.

There are a few approaches used to integrate membranes into microfluidic devices. In regards to wearable technology, the most compatible method for flexible devices may include: (1) direct incorporation by clamping or gluing directly into the microfluidic device,[45] (2) *in-situ* preparation of membranes into the flexible material during casting and molding,[46] and (3) use of membrane

as the substrate.[43] Integration of membranes using approaches (1) or (2) also allows for modification and functionalization of the membrane with biomolecules, such as bovine serum albumin or extraction fluids, and enables the membrane to facilitate more functionality.

Despite its most common uses for filtration and separation purposes, membrane technology has great versatility and can also be employed as supports for cell culture scaffolds and offers large surface area for effective adsorption, catalytic reactions,[43] or as substrates for functionalization with bioreceptors. In regard to wearables, the usage of membranes has many practical applications that enable various lab-on-a-chip functionalities and processes.

Aside from the capillary forces of microchannels, osmotic pressure can also be employed to aid in effective sample collection. Generally, in this approach, a saline or glycerol-soaked hydrogel disk interfaced with a membrane is integrated into the microfluidic network to create the osmotic pressure to drive the sample uptake. The use of membranes to create osmotic pressure can also facilitate for sample concentration and cleaning *via* microdialysis.[47] By careful selection of the membrane material and pore size, particulates can be collected or filtered by the membrane as water is transported through the membrane.

5.5 Sampling for wearable sensing

Aside from the physical versatility and cost effectiveness of microfluidic technology, operational complexity and various functions, such as sampling, mixing, filtering, etc., also can be achieved while enabling miniaturization of many conventional laboratory techniques. In principle, and particularly to skin/epidermal-based wearable devices, microfluidic structures can facilitate the efficient uptake of fluids due to a combination of capillary forces and natural pressure that is caused by perspiration.[48–51] In addition, as aforementioned, the use of osmotic pressure, with the integration of membranes, can also aid in sampling. Key benefits to either of these sampling methods, by capillary or osmotic property, are that it can be applied to any biofluid found on the skin, such as tears and saliva, and is noninvasive and nonirritating to the skin.[52]

There are many inherent advantages of using microfluidics for wearable technologies. For example, consider the sampling and analysis of sweat using a skin-based wearable integrated with microfluidics. Due to the influence and effect of fluids on the micron scale, as previously described, sweat on the surface of the skin can be continuously sampled as it travels along the microchannels to fill up reservoirs or transported toward the sensor electrodes (Fig. 5.2). In addition to sampling, the microchannels also house the sweat and prevent evaporation and/or reabsorption back into the skin.[53] Specifically designed reservoirs and architectures can also enable other functions, such as storage for later use, and delayed or controlled release in the case of functionalization and pretreatment steps.

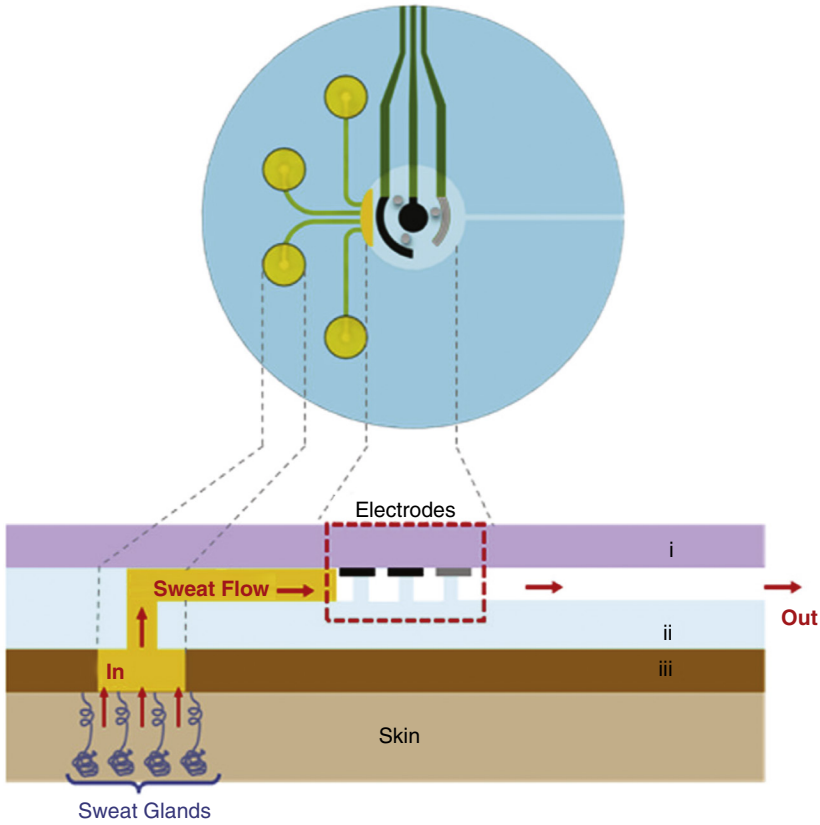

FIG. 5.2 **Cross-sectional schematic of microfluidics in a wearable device** *(reprinted with permission from ref,[52] copyright 2017, American Chemical Society)*.

Although the sensor material and type also influence the performance parameters, there can be significant improvements of the sensing accuracy and reliability as precise and small amounts of liquids are analyzed on the electrode or by the sensor. Moreover, as some body fluids are generally secreted in low amounts, lower sampling volumes prove to be sufficient for the sensor and can also ease the burden on patients, that is strenuous exercise to induce sweating.[49,54]

To this regard, often conventional approaches for the collection of body fluids are invasive, such as puncturing of the skin, or application of an external stress like heat or electrical pulse[3,55], and are sometimes required to be completed multiple times (particularly for monitoring purposes) and at multiple locations, and extract large sample volumes. Thus, a key element of wearable technology, enabled by the use of microfluidics, is the ability to collect and process samples in a noninvasive, efficient and safe manner.[56]

Although blood is a common and widely researched body fluid for clinical purposes, its sampling and collection is invasive. Moreover, blood does not always provide sufficient information about the health status of an individual, especially in the case of health monitoring and evaluation of metabolite levels. Thus, it is necessary to collect and examine other bodily fluids. Fortunately, bodily fluids such as sweat, tears, and saliva, can be easily collect in a noninvasive manner and is well suited for long-term monitoring with wearable devices. Here we discuss the different matrixes that are sampled by microfluidic wearable technology for healthcare.

1. Sweat

As mentioned above, sweat is an obvious and straightforward sample that can be collected in a continuous and noninvasive manner. Sweat samples can reflect the overall health status of an individual and can be characterized by various parameters, including salinity, pH, and contains a variety of components, such as electrolytes, hormones, enzymes, proteins, etc., that are ideal natural biomarkers for patient monitoring and healthcare.[57,58] Biologically, the function of sweat is to regulate body temperature in response to environmental factors and physiological conditions. Thus, sweat rate and sweat loss are also indicators for the health status of an individual.[13,59,60] Moreover, the concentrations of the components within sweat can also reveal vital information for disease diagnosis. For example, excessive loss of sodium and potassium in sweat can be signs of hyponatremia, hypokalemia, muscle cramps, or dehydration.[61] In fact, monitoring these components within sweat is a common method used to screen for cystic fibrosis.[3]

There are two key challenges for wearable technologies when dealing with sweat: the first, as mentioned above, is the requirement for minimally invasive or noninvasive sampling methods in a variety of situations such as aquatic or dry environments.[54,62] This issue is relatively simple to address as the implementation of microfluidic systems answers the requirement of noninvasive sampling. Furthermore, as the technology is based on flexible materials, the usage of such systems can be placed on many uneven and curved surfaces, such as the surface of the skin. There are many studies that have developed a microfluidic device for sweat analysis that also aimed to highlight the compatibility of elastomers and similar flexible materials for wearables.[22,49,54] These studies demonstrated the excellent mechanical properties of elastomers under various strain tests, including stretching, bending, and twisting, and was even shown to be fully functional in underwater for many hours.

Second, and perhaps more challenging, is the capability to provide quantitative and rapid analysis of multiple parameters in real time. Again, microfluidic technology holds several advantages over conventional methods. By coupling microfluidic technology with various aspects of microelectronics, numerous wearable devices have been developed, for single and multi-analyte sensing, achieving impressive performance parameters, such as great sensitivity. For

example, the Rogers group has introduced a flexible and soft skin–compatible microfluidic device that was capable of digitally monitoring sweat in real time.[59] The device was able to quantify the sweat rate and conductivity, and to transmit the collected data wirelessly to any electronic device with near-field communications technology.

2. Interstitial fluid

Skin is made up of many layers and the depth in which the samples are taken is another important aspect to consider. Usually located under the skin, interstitial fluids are a great source of proteins and unique biomarkers[63] and can be readily accessed from the skin surface by iontophoresis or sonophoresis (ultrasound).[64] In fact, with many similarities to blood, analysis of interstitial fluid for important biomarkers, such salts, proteins, sugars, etc., and parameters, such as pH, can reveal the physiological status of the blood contents and the health of the patient.[65–67] For example, the status of diabetic patients can be observed by monitoring the glucose levels in interstitial fluids, which in turn are closely related to blood glucose concentrations.[68]

To obtain more comprehensive information, dual sampling and analysis of interstitial fluids and sweat can be conducted. The key challenge to this, however, lies in the separation and simultaneous collection of the biofluids, as they both share the same sampling site—the surface of the skin—and mixing appears to be inevitable. Kim et al. developed a single wearable device that simultaneously and noninvasively collected and analyzed both sweat and interstitial fluids for alcohol levels.[57] The device works by performing, in parallel, reverse iontophoretic extraction of interstitial fluid and iontophoretic delivery of sweat at separate locations of the same platform. At each separate location, an electrochemical biosensor was embedded for monitoring of the corresponding biomarkers.

3. Tears, saliva, and breath

Other bodily fluids that are also promising for diagnostics, and even *more* accessible, are tears and saliva. Similar to that of sweat, the components of tears and saliva hold multiple physiologically relevant biomarkers and chemicals.[3,67] For instance, tears are abundant in proteins and lipids, and can be used for glucose detection. In fact, the analysis of tear samples has shown strong correlation to the progression and detection of diabetes, as it is widely known that diabetes can have great effect on the production and composition of tears, and the environment around the eyes.[69] For the sampling of tears, typically swabs and capillary micropipettes are used. However, unlike saliva, sampling and continuous monitoring of tears can be uncomfortable and can cause irritation; which in turn can influence the quality of the sample and affect the analysis.

Saliva, on the other hand, contains important biomarkers from several diseases, including cardiovascular disease, cancer, and HIV,[70–72] and the overall status of oral and throat health.[73] Typically, research based on saliva samples primarily aim for the sensing of bacteria, hormones, and other biochemical,

such as phosphates and lactates, whose concentration levels are an important indicator for clinical diagnostics.[74] While saliva is the most accessible bodily fluid, the components and make-up of saliva are highly influenced and easily altered by the foods we eat, and thus often provides inadequate physiological insight.[10]

Although seemingly obscure toward microfluidics, another interesting and biologically important matrix for diagnostics is breath. In comparison to other matrices, such as blood and sweat, the advantages of using breath for diagnostics are that it is highly accessible, with minimum to no discomfort to the patient, and has rapid sampling and analysis times (within minutes). Moreover, exhaled breath is abundant in biomarkers, such as volatile organic compounds, and can reveal the health status or disease progression within a patient. For example, the presence of acetone and ethanol is found in the breath of diabetics, and high levels of benzene and methane are indictors of patients with lung and colon cancer, respectively,[75,76] while hydrogen peroxide in the case of lung disease is an important biomarker associated with asthma, chronic obstructive disease, and lung cancer. Therefore, its real-time detection with wearable sensors is attracting the attention of the scientific community.[77]

Unlike liquid matrices, the transport of gas samples within the microfluidic network is not largely reliant of capillary forces. However, the coating of the microchannels is more essential for microfluidic gas-sensing devices. They are typically coated with metallic or polymeric layers that will affect the transfer rate, or flow rate, of the gas molecules as it travels toward a sensor (typically a general purpose Metal Oxide Semiconductor (MOS) sensor positioned at the terminal of the channel network. Each different type of gas, or gas mixture, will have a distinctive voltage-time response, or "smell print," depending on its diffusion, adsorption, and desorption rates as it travels along the coated microchannel.[78] Then, with the unique smell-print, identification and quantification of the gas molecules can be obtained using different classification and regression models.[10,78]

5.6 Challenges and future perspectives

Particularly for lab-on-a-chip platforms, using both flexible and solid substrates, microfluidics facilitates many standard processes and has become an essential element for miniaturization. However, despite great advancements over the years, there are still many challenges and limitations that need to be addressed. Technical aspects such as low sample volumes and sample contamination are key issues that commonly arise. Although only small sample volumes are required for analysis with microfluidics, the presence of target molecules in patient samples is often very low; thus, there is a need for preconcentration of the analyte. Although the above-mentioned methods aim to achieve accumulation of analyte, by means of filtering or pretreatments, concentration amounts may *still* be too little or well below required for clinical use. The solution

to simply "collect more samples" can also be an ineffective, and perhaps an uncomfortable way, in the case of sweat, to increase analyte concentrations; as higher sample volumes can also require more work to separate the analyte from other components. To this regard, the complexity of bodily fluids should also be considered when sampling as contamination from other components also poses a key issue. Whether the source of contamination is from the surface of the skin or from other similar proteins and analytes within the sample matrix, contamination greatly, and very easily, affects the accuracy of results and is very detrimental in diagnostics.

Although many researchers have strived to provide solutions to these issues by configuring or designing specific internal microfluidic networks, Peng et al. have approached these issues in a different and creative way.[60] Their method proposes the use of a cosmetic-grade oil as an interface between the skin and the microporous membrane of their wearable device to collect samples in the nanoliter scale, while also reducing the changes of contamination from the surface of the skin. The authors found that the oil facilitated the accumulation and isolation of sweat directly under the device above the skin which could then be rapidly sampled via the membrane. Furthermore, the hydrophobic nature of the oil was able to block out, or separate, the hydrophilic contaminants (due to their low oil solubility) on the skin from interacting with the membrane.

In particular for wider availability and commercialization, another important issue to be addressed is that analytical performance parameters within the clinical ranges, as well as the standard requirements, should be met. Another major issue worth highlighting is the capability of the devices for continuous and real-time sampling; especially for long-term health monitoring. Although microfluidics can facilitate continuous and real-time sampling, analysis of the sample is largely influenced by the functionalities of the sensor and the sensing material (see Chapter 4); which are not discussed in this chapter. Improvements of performance parameters, such as limit of detection (LOD) values, repeatability, selectivity, etc., are on-going motivations within research and academia, where many approaches have been developed and sought after. A common approach in adding sensitivity and selectivity to the device and in enhancing the detection signals is by using novel nanomaterials, which will be discussed in the next part.

It is evident that the progress of wearable technology has been greatly influenced and enabled by the use of microfluidics for sampling and sample pretreatment and processing steps. Despite the tremendous advancements, there are still various areas in need of improvement and specific issues required to be addressed. As technology and research advances, it is only fathomable that microfluidics, in terms of design and methods of integration, will find many innovative uses and be included in numerous creative approaches and strategies to realize and excel the field of wearable devices for personalized healthcare and monitoring.

5.7 Part B—Nanomaterial-based signal amplification strategies

Traditional sensor systems based on rigid and solid materials still present with limitations in terms of flexibility and consistency, and hinder the progress of high performing wearable sensors. Wearable sensors include essential sensing elements, such as receptor/recognizer, transducer, conductive path, and flexible substrate (Fig. 5.3).[79] Due to the requirements of flexibility, nanomaterials are widely applied as transducers, conductive path, and recognizer in wearable sensors. In addition to the superior mechanical properties, nanomaterials can also be used for signal enhancements strategies in sensing applications owing to their physiochemical properties in the nanoscale. In this section, general sensing principles and nanomaterial-powered devices for signal enhancement in wearable sensors are discussed.

5.8 Definition

Nanomaterials are defined as materials with an external dimension or internal structure in nanoscale of less than 100 nm that present distinctive properties of the original material at bulk scale. Due to the decrease in size, the surface-to-volume ratio is enhanced as more atoms are exposed to the surface. Therefore, the surface properties of these materials are more apparent, expressing different

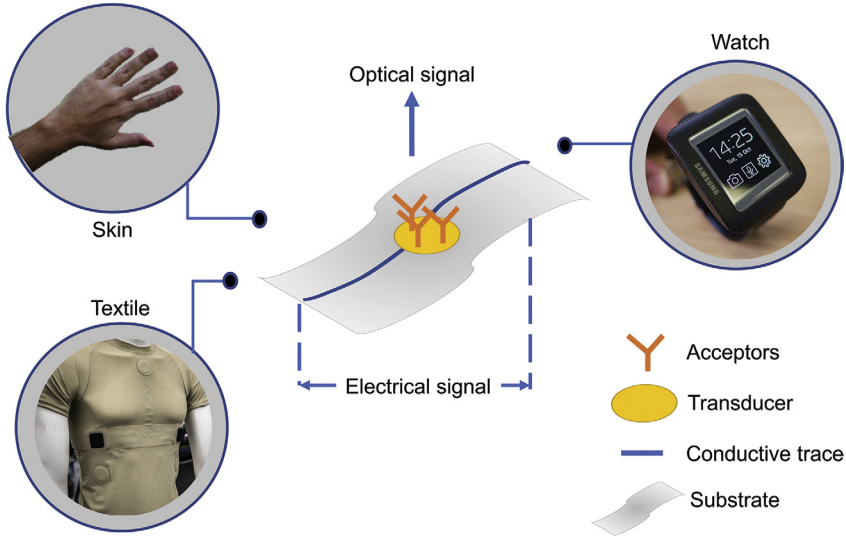

FIG. 5.3 Wearable sensors *(images: body sourced from airforcemedicine.af.mil,[81] others: Wikipedia).*

and unique properties when compared to its bulk counterpart. Besides, at the nanoscale, quantum confinement of the charge carriers induces changes in the electronic structure of the nanomaterials.[80]

5.9 History

The term "nano" was derived from the Greek word "nannos," meaning "very short man." Unbeknownst then, the application of nanotechnology has had a long history, where in AD 300 and AD 1700, Damascus and Romans used nanoparticles (NPs) to fabricate steel swords to enhance its performance. Maya Blue, an NP of corrosion resistant azure pigment, was discovered to be used in AD 800, while silver (Ag) and copper (Cu) NPs were found to be used in pottery from the Middle Ages and Renaissance era.

In more recent history, the first scientific reports of the synthesis of a colloidal solution of AuNPs, called "activated gold," was by Michael Faraday in 1857. To which was presented, by Faraday at the Royal Society of London, with a purple color slide stating that it contained "gold reduced in exceedingly fine particles."

On December 29, 1959, at an American Physical Society meeting at the California Institute of Technology (Caltech), physicist Richard Feynman gave a lecture called "There's Plenty of Room at the Bottom" long before the term "nanotechnology" was used. In his talk, Feynman described a process in which scientists would be able to manipulate and control individual atoms and molecules. It was not till over a decade later, in his explorations of ultraprecision machining, that Professor Norio Taniguchi coined the term nanotechnology. And it was not until 1981, with the development of the scanning tunneling microscope, that researchers could "see" individual atoms; and, thus, sparked the exploration of modern nanotechnology.[82]

5.10 Features for sensing

As mentioned above, the properties of nanomaterials greatly differ from with the bulk materials due to their nanoscale dimension. These properties, including mechanical, physiochemical, optical, etc., offer many advantages for their use in sensing applications. In this section, the most important physical and chemical properties of nanomaterials are highlighted, and introduce common methods and strategies for their integration into wearable sensing platforms.

1. Surface-to-volume ratio

Most evident, the decrease in the size of nanomaterials leads to an increase in the surface-to-volume ratio which exposes more atoms to the surface and renders the surface more reactive on itself and to the surrounding environment.[83] Moreover, the increase in the surface area also allows for a higher specific area for conjugation with more receptors and provides more active sites. This effect

greatly enhances the efficiency of chemical/biological recognition and reaction[84,85]. In this scenario, the plasmonic nanopapers developed by the research group of Morales-Narváez stand out[86–88]. Barajas-Carmona et al. explored the plasmonic properties of silver NPs (AgNPs) grafted onto nanocellulose paper as a wearable sensor on skin to detect the exposition level to UV sunlight. In this way, the authors took advantage of the growth effect of the AgNPs in the presence of the UV light that induces changes in the surface-to-volume ratio and the quantum confinement of the electrons in the NPs, that is translated into a change of the NPs' color that is easily visualized [88]. Besides, a similar feature was observed in the cellulose nanopaper based on a mixture of AgNPs with gold NPs (AuNPs).[87] On the other hand, the nanosize can also prove to be potentially toxic. In particular to wearable sensors where these devices are in direct contact with the skin surface, effects of toxicity cannot be ignored. Much progress has been made so far in the study of the biocompatibility, cytotoxicity, and biodegradability of the nanomaterials; however, these materials are still under a careful evaluation.[89–92]

2. Agglomeration/aggregation state

Aggregation occurs when the balance between surface charge repulsion and particle attraction (e.g., Van der Waals force) is broken. AuNPs are highly sensitive to the surrounding chemical solution, for example pH, ion concentration, ion species and temperature,[93] any changes in environment can trigger the particles to agglomerate or cluster together. In fact, aggregation causes a change of physical features such as size and morphology, which in turn can affect the properties of nanomaterials such as light adsorption, plasmonic resonance, fluorescence, etc.[94] Due to these changing features, NPs are widely used in the optical sensing platforms for detecting pH, ion concentration, and clinically relevant biomolecules.

3. Electronic characteristics

The electrical conductivity of bulk metals is influenced by their electronic band structures, and the mobility of electrons within the lattice. In nanomaterials, however, the phenomenon is different as the electronic energy levels are not continuous but are discrete (finite density of states). As such, the effects of quantum confinement are more apparent and dictate the electronic behaviors in the metallic and semiconductor nanomaterials, and give rise to unique electronic properties not observed in the bulk.[95] For example, fluorescence as the transducing signal can be generated by carbon quantum dots—a phenomenon that is not observed in bulk carbon materials.

Another advantage is the high electrical mobility of nanomaterials, especially in low-dimensional nanomaterials (1-D and 2-D) due to its confined size limit.[96,97] This is an important characteristic, especially for field effect transistor (FET) based sensing devices as it affects the carriers' mobility rates and increases the conductivity and switching speeds. For example, due to the distinct band

structure and physical structure of the graphene and carbon nanotubes (CNTs), the mean free path of their charge carriers is high, making possible the charge carriers to move by microns (0.3 μm for graphene) in the surface of these materials before a scattering process occurs.[98] This contributes to the high mobility values of the charge carriers in these nanomaterials (15,000 and 79,000 cm^2/Vs at room temperature for graphene and semiconducting CNTs, respectively),[98,99] improving the electrical transport and the performance of the FET devices based on these nanomaterials, turning these devices ideal for the development of wearable devices such as electronic skins (e-skins) to monitor physical parameters. Besides, the high electrical conductivity of nanomaterials with metallic behavior, such as AuNPs, silver, and gold nanowires (NWs), metallic CNTs, and even graphene (a semiconductor with a zero band gap) highly improves the electrical sensitivity of the interactions of the target molecules in the surface of these nanomaterials, leading the development of (bio)chemical wearable sensors able to achieve lower LODs.[100,101]

It is common in wearable sensors to incorporate conducting fillers in flexible polymer matrices aiming to develop conductive polymers that act as sensors for monitoring physical parameters. In this way, the use 1-D nanomaterials (1-D), including NWs, CNTs and nanofibers, as a nanofiller in an insulating polymer matrix shows many advantages mainly due the high aspect ratio of 1-D nanomaterials which allows to use smaller amount of materials for building a high-effciency percolation conductive network, with a lower percolation threshold.[102]

4. Magnetic properties

Due to the small dimension, the increased surface area promotes the magnetic coupling with adjacent atoms, which manifests the diverse magnetic properties of several nanomaterials. The magnetic properties are used in a variety of applications such as ferrofluids, drug delivery, catalysis, and magnetic memory storage devices.[103] However, in particular to biosensing, their small size and large surface area are typically harnessed, and it is utilized as a transporting tool to carry and accumulate receptors and targets. In this sense, the work conducted by Zamora-Galvez et al.[104] explored very well these features of the magnetic nanomaterials. The authors developed a nanocomposite based on molecularly imprinted polymer (MIP)–decorated magnetite NPs to separate, preconcentrate, and manipulate the sulfonamides (the analyte) which is selectively captured by the MIP onto the surface of the composite, in screen-printed electrochemical sensors. Combining electrochemical impedance spectroscopy-based detection, the high surface area of the magnetic nanocomposite, and its extraordinary ability to preconcentrate the analytes, the MIP sensor was able to detect impressive levels of sulfonamides, showing a LOD of 1×10^{-12} mol/L (2.8×10^{-4} parts per billion). Moreover, magnetic NPs can also be used as labels in electrochemical sensing for its electrocatalysis of redox process.[105]

5. Mechanical properties

The essential characteristics of wearable sensors are stretchability and flexibility, which can be challenging for conventional rigid bulk materials. However, on the nanoscale, nanomaterials show superior mechanical properties in terms of hardness, elastic modulus, and fatigue strength. For example, graphene presents with a record strength (130 GPa) and Young's modulus (1 TPa).[106] Besides, due to the unique physical structures, the 1-D and 2-D materials can be stretchable and bendable, but without drastically altering their electrical conductivity, preventing the delamination, and/or cracking process of the activity material under large mechanical strain in the wearable sensors, which is a key requirement in the design of materials for e-skin devices.[107,108] As such, nanomaterials are promising candidates for wearable sensors and can be integrated as conductive paths and transducers. For example, some 1-D materials, such as CNTs and silver NWs, are very popular to be used in wearable sensors.[109]

6. Optical properties

Optical platforms, in particular naked-eye detection methods, are very popular in POC testing. The optical properties of nanomaterials are very well suited for such optical platforms and can be finely tuned as the properties are strongly influenced by the size of the nanomaterials. As mentioned previously, similar to the expression of electronic properties, the band structure also affects the optical properties, such as fluorescence, of the nanomaterial. Changes to the band structure, for example by binding events with biological targets, can cause shifts or intensity changes in the spectrum. This highly sensitive characteristic can then be harnessed and used for optical biosensing platforms.[110] Another optical feature that may be affected is the change in the localized surface plasmon resonance, which occurs at the surface of plasmonic nanomaterials.[111] The electromagnetic wave stimulates the resonant movement of electrons into the conductive band when the size of the nanomaterials is smaller than the mean electron free path. Different sizes of metal NPs correspond to different peaks in terms of absorbance and scattering, respectively, thus this phenomenon offers visually observable signals by means of plasmonic color changes. Hence, both these optical features are widely utilized as colorimetric, fluorescent, and spectrometric platforms for sensing chemical and biological targets.[112,113]

Another interesting optical property of some nanomaterials, especially 1-D and 2-D, is their transparency. So these nanomaterials, such as NWs, CNTs, graphene, and transition metal dichalcogenides (TMDs), have very low light absorption; for example, in the case of a graphene monolayer, it is just 2.3% of the light.[98] In this way, these nanomaterials are ideal candidates for the design of flexible transparent conductors, that is an appealing field in the development of e-skin,[114,115] smart contact lenses,[116] among others.

7. Catalysis

Catalysis plays an important role in selectivity and efficiently propels reactions to obtain the desired product and reactants. Because of the large fraction

of atoms exposed on the surface, nanomaterials have more active sites and, thus, can be well suited as highly efficient catalysts. Materials such as metallic NPs, metal oxides, zeolites and organized carbon nanomaterials are commonly used for catalytic applications. In terms of biosensing, the purpose of such nanomaterial catalysts is to substitute for the function of enzymes in enzyme-based sensors, as they can be expensive to purchase and require very delicate handling as they are highly affected by surrounding conditions. The most common approach is to integrate these catalysts working as a label to trigger the reaction with the substrate by monitoring the electron transportation.[117] In some cases, the catalytic event or reaction causes a change in color, for example, using 3,3′,5,5′-tetramethylbenzidine, which can be used as an optical platform as well. Moreover, catalytic nanomaterials, such as noble metallic particles, can directly catalyze some gas oxidation and production, such as hydrogen, methane, etc., which can also be monitored via electron transport to the transducer. This could be used for building conductive sensing platform in gas sensing.[118] On the other hand, the catalytic nanomaterials can be employed in the development of electrochemical biosensors, decreasing the overpotential necessary for an electrochemical reaction to occur and increasing the output signals.

5.11 Classification and examples (0-D/1-D/2-D/3-D nanomaterials)

0Due to the complexity of nanomaterials, we organized and classify the nanomaterials as presented in Barhoum et al.'s book as: (i) 0-D nanomaterials (0DNMs), (ii) 1-D nanomaterials (1DNMs), (iii) 2-D nanomaterials (2DNMs) and (iv) 3-D nanomaterials (3DNMs).[119] Some popular examples are shown in Fig. 5.4.

5.11.1 0-D nanomaterials (0DNMs)

0DNMs are defined with all dimensions less than 100 nm and can include morphologies such as metallic NPs/nanoclusters (like noble NPs), metal oxide particles (such as transition oxide NPs), magnetic NPs, carbon dots, fullerene and quantum dots (Fig. 5.4). These materials possess features such as photoactive, high efficiency for catalysis (owing to their high curvature of the NP surfaces), more surface defects, and quantum electronic properties. Thus, they can be applied to optical and electrochemical sensing platforms to enhance their sensitivity.

A widely researched and used 0DNM are gold NPs, which have several advantages for chemical and biological sensing, in particular for signal enhancement functions. AuNPs can be synthesized by a simple method, and are typically stable in aqueous environments. Due to the plasmonic effect, AuNPs are ideal for optical sensing platforms. The high surface-to-volume ratio provides

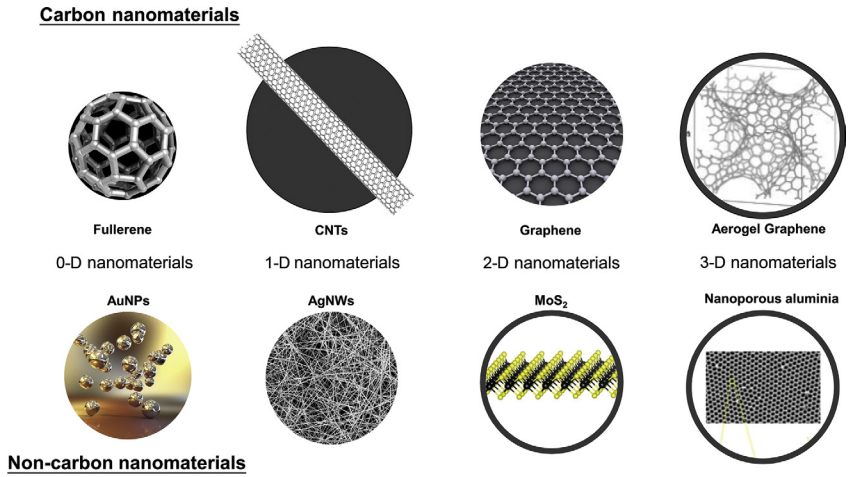

FIG. 5.4 Dimensional classification of nanomaterials *(images: graphene reproduced with permission from ref,[120] copyright 2018 Elsevier, AuNP sourced from azonano.com,[121] AgNWs reproduced with permission from ref,[122] copyright 2019, Nature, nanoporous alumina reproduced with permission from ref,[123] copyright 2018 Elsevier, others: Wikipedia).*

a large number of sites to be conjugated with a wide range of biomolecules, such as ligands, proteins, nucleic acids, etc., for single or multi-analyte detection. By harnessing the ease of functionalization nature of AuNP, enhancement of the sensing signal can be achieved through and efficient binding of analyte to receptors on the AuNP. This enhancement strategy is widely used in surface plasmon resonance, enzyme-linked immunosorbent assay, and lateral flow assay devices.[124] AuNPs also play an important role in electrochemical sensing platforms as labels due to their superior electrocatalytic properties. By monitoring and detecting the drastic change in electron transport during a catalysis event, the sensing signal can be enhanced in the electrochemical platforms.

5.11.2 1-D nanomaterials (1DNMs)

1DNMs are considered as nanomaterials that possess dimensions where one dimension is significantly larger than the other two in the nanoscale. Based on this definition, 1DNMs are typically NWs, nanotubes, and nanofibers. 1DNMs are applied in wearable sensors due to its unique structure and high surface-to-volume ratios, which have been shown to be beneficial for signal-enhancing purposes.[125,126] The wire-like structure can easily form a percolation network that is beneficial for stretchability and flexibility. Also, as the electrons are confined to the 1-D structure, the conductive nature of the nanomaterial remains. Moreover, in comparison to other nanomaterials, 1DNMs are also superior in

transparency without much trade-off in the other properties[107] and, thus, it is a promising candidate in wearable sensing and compatible with FETs to achieve higher sensitivity.[127]

CNTs, as an example of 1DNMs, are well-ordered, internally hollow, long cylindrical structures composed of sp^2-hybridized carbon atoms (a rolled-up graphene sheet). CNTs are typically found in two types: single-walled CNTs (SWCNTs) and multi-walled nanocarbon tubes (MWCNTs). The CNTs can show either a semiconductor or metallic behavior that is related to their diameter and chirality. The chirality of the CNTs depends on how the graphene sheet is oriented on rolling, which is specified by a vector (called a chiral vector), so the CNTs can be armchair, zig-zag, and/or chiral. In this way, the armchair CNTs share electrical properties similar to metals, which include the MWCNTs; and the zigzag and chiral CNTs possess electrical properties similar to semiconductors, which include the SWCNTs.[128] Depending on their electrical properties, a specific type of CNTs can be chosen for the design of the wearable sensors. For example, MWCNTs due to their metallic properties are good candidates for the development of wearable electrochemical sweat sensors, acting as a working electrode, and to be used as a nanofiller in flexible polymeric substrates, in its turn, the semiconductor SWCNTs are indicated for the development of tactile sensors, based on FETs for e-skin applications. Considering the general high surface area that CNTs can provide for conjugation with receptors and targets, CNTs can also provide high efficiency for mass transport of analytes to enhance the sensing signal and are highly compatible with wearable technologies.

5.11.3 2-D nanomaterials (2DNMs)

Nanomaterials have one external dimension in the nanoscale and the others significantly larger. 2DNMs include nanosheets and nanofilms. In this system, electrons are confined within one dimension, indicating electrons cannot move freely within the associated dimension. Similar to 0-D and 1-D nanostructures, 2-D can also be (1) amorphous or crystalline, and (2) composed of metallic, ceramic, or polymeric matrixes. 2-D nanostructures are promising for applications, including sensors, electronics/optoelectronics, and biomedicine. The atomic thickness offers them a high mechanical flexibility and optical transparency, which makes them a promising material for the fabrication of electronic and optoelectronic sensors. In addition to graphene nanosheets, other graphene-like 2-D nanosheets, such as graphitic carbon nitride ($g\text{-}C_3N_4$), boron nitride, TMDs, and transition metal oxides, have received significant consideration in the past few years due to their features such as large surface area, excellent thermal conductivity and electric conductivity, and ease of functionalizing the surfaces.[129]

In recent years, graphene-based nanomaterials become an excellent sensing platform for carrying active probes and molecule of interest, which is favorable

for the construction of the novel biointerfaces for biosensing applications. Since its discovery in 2004,[130] graphene has attracted considerable attention owing to its remarkable electrical, optical, mechanical, thermal, and biocompatibility properties. The idealized structure of graphene is completely two dimensional. It comprises a single layer of sp^2-hybridized carbon atoms joined by covalent bonds to form a flat hexagonal lattice. Graphene has outstanding physical properties including high carrier mobility and capacity, an ultrathin form factor, an ambipolar field effect, and highly tunable conductance; it is therefore very useful in science and technology. Graphene comprises a 2-D, single atom-thick honeycomb lattice of carbon atoms; it has exceptional mechanical strength and flexibility, which makes it very useful for flexible electronic devices. Particularly, graphene has been extensively explored in the development of high sensitivity biosensors based on FETs (gFETs),[131–133] by using the modulation of the conductivity in the gFETs as a function of the interaction between the target molecule and the bioreceptor, immobilized on the graphene surface. In this way, the gFETs are very appealing devices for the design of very sensitive wearable sensors for the detection of nonelectroactive biomarkers (such as proteins) in sweat samples.

As an alternative for graphene, a vibrant research area on TMDs has emerged during past decade, which represent 2-D layered materials with ultrathin structure. The properties of TMDs highly depend on the degree of crystallinity, number of layers, and stacking sequences in their crystals and thin films. The molybdenum disulfide (MoS_2) is the most popular member of layered TMDs and has withdrawn immense attention due to its extraordinary crystal, electronic and optical properties. Featuring unique structure, layers of Mo atoms are arranged in a hexagonal array sandwiched between sulfur (S) layers in which Mo–S is held by strong covalent bond while Van der Waals interactions exist between S layers. MoS_2 semiconductors have recently attracted attention because of their outstanding mechanical and optical transmittance, high gauge factor, and tunable band gap in function of the number of layers, which can exhibit high photoluminescence when found in a monolayer (direct band gap)[134]. MoS_2 nanosheets own piezoelectric properties and have been explored as a material-based piezoresistive sensors, improving the sensitivity of these sensors and offering high operation stability.[135,136]

5.11.4 3-D nanomaterials (3DNMs)

3DNMs include nano-sized grains or nano-sized internal pores without the confinement in all external dimensions and provide different shapes such as foams, sponges, hydrogels, and aerogels. As such, 3DNMs have huge surface area and improved mechanical deformation behavior, making it promising in wearable sensors. To fully take advantage of the large surface area of 3DNMs for signal enhancement, the porous surface can be modified with receptors and catalysts.

In another approach, 3DNMs can be used as the transducer themselves, which provide numerous reactive sites directly without any surface modification, and thus, the sensor signal can be enhanced. For example, porous silica, zeolites, metal oxides, and carbon are always used as transducers and/or supporters for the immobilization of bioreceptors, such as enzymes and other nanomaterials (like metal NPs) improving the loading density of these species[137–139].

In addition, due to the high surface of 3DNMs, they become ideal candidates for the development of wearable devices for gas sensing. The high electrical conductivity, lightness, and high surface area of graphene aerogels,[140] can greatly improve the sensitivity in the detection of target molecules in the gas phase, allowing the development of wearable sensors to be very useful in the search for toxic gases in workplaces, promoting the safety of local workers.

5.12 Nanomaterials enhanced strategy

In physical sensors, the key use of nanomaterials is to achieve high flexibility, while not addressing issues concerning signal enhancement. Thus, in the physical sensors part, we only show the applications of wearable sensors pertaining to personal healthcare and list some remarkable or novel examples. While in (bio)chemical sensors, the purpose of the nanomaterials is to enhance the sensitivity. Thus, in the (bio)chemical sensors part, we will further discuss the signal amplification strategies with reported examples.

5.12.1 Physical sensors

Physical signals such as motion (e.g., activity, tremor), cardiac signals (such as heartbeat, pulse shape), blood pressures, and respiration conditions are very important parameters to health, and wearable sensors provide a conformal tool to monitor them in real time. Nanomaterials, as previously described, have superior mechanical and electrical properties and are highly suitable for flexible sensors as these properties remain mostly unchanged upon stretching or bending, also preventing the delamination and/or cracking process of the activity material under large mechanical strain.[107,108] The principle of sensing mechanical changes is simple: when a mechanical force is applied to the nanomaterials' conductive network, deformation occurs. Based on this deformation, changes to the resistance or capacitance of the nanomaterials occur. Hence, the conductivity or capacity can be the electrical signal to present the deformation of the network. Moreover, another interesting property of nanomaterials is the ability to transfer physical energy such as touching, pressing, and strain into electrical signals. Thus, it is widely applied in wearable physical sensors, especially in mechanical force detection. Next are several examples of physical sensors based on nanomaterials. Electrophysiological sensors, temperature sensors, and photodetector sensors are also included as important compensation in wearable physical sensors.

1. Strain sensors

Strain sensors are mainly based on resistive and capacitive measurements. The structure of resistive-based platform typically consists of two parts: an electrically conductive sensing network and a flexible substrate. When applying the strain on the sensor, the microstructural deformation leads to the change of electrical resistance. After releasing the strain, the sensing network recovers back to its original state and "restoring" the original resistance. On the other hand, capacitive strain sensors are composed of a dielectric layer sandwiched between a pair of electrodes. Tensile strain brings the two electrodes closer, causing an increase in capacitance; while release of the strain decreases the capacitance as the electrodes move away from each other. Thus, based on the requirement for stretchability and flexibility, strain sensors are normally fabricated with low-dimensional materials (1DNMs and 2DNMs) for their good conductivity and transparency such as Ag NWs, CNTs, grapheme, and related composites.

Amjadi et al.[141] developed resistive strain sensors with high sensitivity, stretchability, and stability based on the sandwich-structured silver NWs (AgNWs) and PDMS nanocomposite, as shown in Fig. 5.5A. By using AgNWs, the gauge factor and stretchability were found to be enhanced. The strain sensors were integrated to a glove on every finger with the interest for monitoring the movement of the fingers. Besides, the fabrication process was considered simple and cost efficient.

Another interesting application of the mechanical properties of the nanomaterials in strain sensors is related with the employment of 3-D structures in the amplification of the response signal in wearable sensors. This is the case of graphene aerogels for the monitoring of physical parameters. An et al.[142] reported the fabrication of a neat graphene aerogel with microextrusion printing for the development of electronic sensor devices with a 3-D nanostructure. The printed graphene aerogel exhibits excellent electrical conductivity and reversible mechanical deformation properties. The electrical resistive response of the aerogel to different strains can be clearly discriminated, in this way the authors showed that the graphene aerogel flexible sensors can monitor in detail the movement of joints, that with a rational design, a wearable graphene aerogel sensor can achieve the remarkable gesture language analysis for a deaf–mute communication auxiliary device or gesture manipulation apparatuses.

Besides the conventional resistive platform, there is a novel strain sensing sensor based on the piezoelectric properties of 2DNMs. Piezoelectric materials can accumulate an electric charge in response to applied mechanical tension, facilitating the conversion from mechanical energy to electrical energy and vice versa.[143] The piezoelectricity causes charge accumulation when applying mechanical force. The advantage of this is that the sensor can be self-powered device without additional power source, which is very interesting and promising to help the wearable sensor reduce weight and have a simpler design. Thus, these materials are ideal for the development of e-skins and wearable sensors. This sensing principle is very well demonstrated in the work of Wu et al.[144]

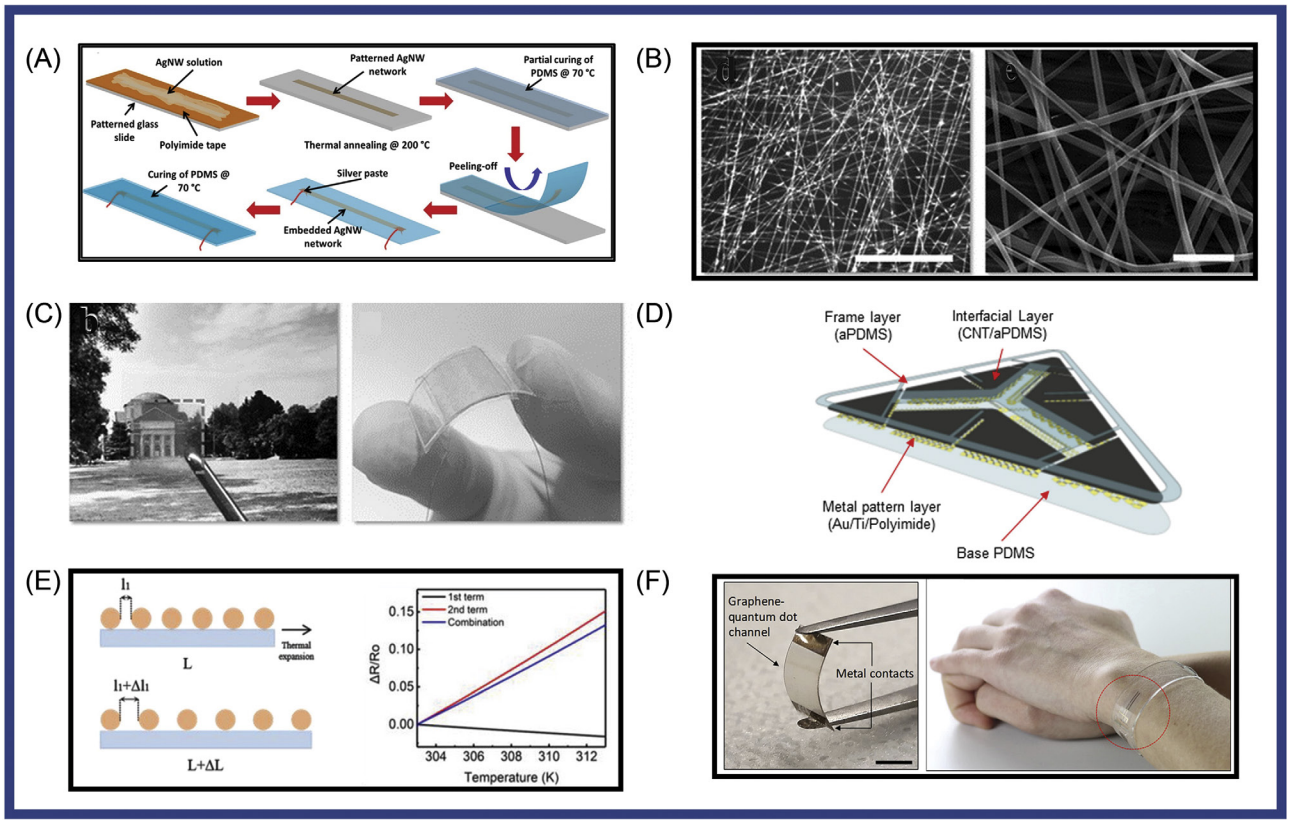

FIG. 5.5 **Physical wearable sensors based on nanomaterials.** (A) Strain sensor by AgNWs and PDMS composites *(reproduced with permission from ref,*[141] *copyright 2014, American Chemical Society)*, (B) morphology of silk nanofibers, and (C) flexible and transparent pressure sensor out of these silk nanofibers *(reproduced with permission from ref,*[147] *copyright 2017, Wiley)*, (D) EGC sensor based on CNTs for long-term monitoring *(reproduced with permission from ref,*[149] *copyright 2015, IEEE Publishing)*, (E) novel temperature sensing platform using Ag nanocrystals *(reproduced with permission from ref,*[150] *copyright 2019, Wiley)*, and (F) resistive photodetector by GQDs *(reproduced with permission from ref,*[155] *copyright 2019, AAAS publishing)*.

Here, the authors took advantage of the flexibility and piezoelectric properties of MoS_2 and demonstrated the sensing array integration of single-layer MoS_2 nanosheets, which enhanced the sensitivity by boosting the piezoelectric output for energy conversion. High-quality single-layer MoS_2 crystals were grown by seed-free chemical vapor deposition on a Si/SiO_2 substrate, and then transferred from the growth substrate to flexible polyethylene terephthalate. Monolayer MoS_2 boosted the piezoelectricity energy transfer which is beneficial for strain sensing. Besides, monolayer MoS_2 presents a high gauge factor (i.e., the ratio of relative change in electrical resistance to the mechanical strain), high mechanical strength, and flexibility, making this material an appealing candidate for e-skin applications.[145,146]

2. Pressure sensors

Pressure sensors and touch sensors share similar transduction principle with strain sensors, as mentioned above. In regard to wearable sensors, it is important for pressure sensors to have high sensitivities in response to small biosignals, such as a pulse, and accommodate for movements and deformation of the skin while also maintaining comfort. As such, flexible substrates, or even textiles, have been explored for the fabrication of wearable physical sensors.

Wang et al. demonstrated this concept by developing a pressure sensor based on a novel substrate: a silk nanofiber membrane.[147] The flexible and ultrathin substrate was obtained from silkworm silk through electrospinning and a heat treatment process on a large scale. N-doped carbon nanofiber (Fig. 5.5B) was then synthesized by carbonization of silk substrate and used as the resistive transducer. The nanostructure of the silk substrate and the carbon nanofibers formed a conductive network, which contributed to the high sensing performance. Moreover, the sensor also had good transparency, as shown in Fig. 5.5C, and was applied for real-time and *in-situ* monitoring of several human physiological signals, such as radial artery pulse, respiration, jugular venous pulses, and vocal cords vibrations. In future, this pressure sensor could be integrated into artificial limbs, which may aid people suffering disabilities and have lost the sense of touch.

3. Electrophysiological sensors

Electrophysiological sensors are used to record the bioelectric signals in biological tissues. Common applications and instruments based on these sensors for healthcare and diagnostics include the electrocardiogram (ECG) to measure the electrical activity of the heart; the electromyogram that measures the electrical activity of muscles; and the electroencephalogram that observes the electrical activity of the brain.[148] However, a key setback of these instruments is that the pregelled (wet) electrodes typically employed cannot sustain long-term use due to the gel losing moisture over time. Thus, due to the outstanding electrical and mechanical properties of nanomaterials, the integration of these materials as a sensor element in electrophysiological sensors emerges as an excellent strategy for real-time monitoring with high sensitivity.

To overcome this problem, Lee et al.[149] developed continuous and inconspicuous health monitoring electronics by using CNTs and PDMS composites (Fig. 5.5D). The nanocomposite functioned as the resistive transducer to translate the cardiac beats (mechanical force) into a voltage signal. In this way, a gel is not necessary for the detection. Besides, this nanocomposite is stretchable and flexible for conformal attachment to the skin. Even under various environmental conditions, such as when taking shower, the sensor had strong adhesion to the skin. This work can be considered as a potential approach that satisfies the POC requirements of ECG sensors for personal healthcare and monitoring of heart rate.

4. Temperature sensors

Body temperature is one of the vital signals, which is closely related to various types of diseases such as heat stroke, infection, fever, physiological status, and cognitive status of body.[148] Hence, body temperature needs to be monitored in real time and with high precision. Most of the presented temperature sensors are based on resistive sensing platforms, where by using metallic and semiconductive materials as the transducers, the temperature influences the carriers scattering and causes changes in conductivity.

In a study by Bang et al., a temperature sensor was designed in a novel way by depositing Ag nanocrystals modified with ligands onto flexible PDMS substrates (Fig. 5.5E).[150] The temperature change was measured by monitoring changes in the resistance, which in turn is largely influenced by interparticle distance that was affected by thermal expansion. In this way, the enhanced signal was achieved by harnessing the electronic characteristics of the nanomaterials. Moreover, the flexibility and stretchability of the Ag nanocrystals within the PDMS substrate was good. However, the ligands of the nanocrystals were not stable at high temperatures, and the sensing range should be considered for specific applications.

Nanomaterials such as graphene present desirable properties for the development of wearable temperature sensors. Graphene shows high flexibility, as commented before, can be easily integrated into various substrates for use on the surface of the skin, and, more importantly, graphene is one of the best conductors of heat achieving thermal conductivity values of up to 5,000 W/mK at room temperature.[151] These outstanding properties of graphene were used by Sahatiya et al. in the development of a graphene-based wearable temperature sensor and infrared photodetector on a flexible polyimide substrate.[152] The authors demonstrated the fabrication of an ultrasensitive wearable human body temperature sensor that works in the temperature range of 35–45 °C. The graphene sheets and the temperature sensor based on graphene exhibited impressive negative temperature coefficient values of $-41.30 \times 10^{-4}\ °C^{-1}$ and $-74.29 \times 10^{-4}\ °C^{-1}$, respectively, which are greater than those exhibited by some commercial sensors. The temperature sensor based on graphene and polyimide, developed by the authors, represents a cost-effective solution to the next generation of miniaturized and low-power wearable sensors.

5. Photodetectors

Photodetectors are found in various applications for personal healthcare including heart rate monitoring, evaluating saturated oxygen levels, and stress via smartphones,[153] and other wearables. The optical properties of suitable materials for photodetectors must be able to absorb the (specific) wavelength of light to excite the electrons within the bandgap structure; which leads to an electrical signal or output. In addition to having good mechanical properties and high transparency, 1DNMs and 2DNMs are ideal candidates for wearable devices due to their optical properties.[154]

For example, Polat et al. fabricated a photodetector for health monitoring purposes in the form of a sensing bracelet.[155] This sensing system was based on graphene quantum dots (GQD) as the optical transducer. When illuminated, absorbed photons created electron-hole pairs in the GQD layer, which are then separated by the built-in electric field and caused an increase in conductivity. By coupling the device with wireless communication, this photodetector was able to perform real-time and quantitative detection with the aid of a smartphone. The sensing bracelet also demonstrated low-power consumption and could sustain long-term use (Fig. 5.5F).

To highlight the advantages of using nanomaterials in wearables, Table 5.1 shows a few examples to compare the devices fabricated with and without nanomaterials. In all the cases, the sensitivity was enhanced with the presence of the nanomaterials. Moreover, the stretchability was also found to be improved by integrating 1DNMs, which can be attributed to its superior mechanical properties.

5.12.2 (Bio)chemical sensors

The goal of wearable (bio)chemical sensors is to monitor various healthcare indicators, such as ions, metabolites, targets contained in the exhaled breath and pathogenetic bacteria, etc., to reveal the health status of a patient. As such, nanomaterials offer many advantages and opportunities to improve and miniaturize these sensors. Here, enhancement strategies are discussed by specific examples based on the type of nanomaterials, due the diversity of (bio)chemical sensors.

1. 0DNM for signal amplification

Sensing platforms based on 0DNMs are mainly adopted for optical and electrochemical approaches. Bujes-Garrido et al. reported a simple electrochemical wearable sensor to detect Cl ions, an important biological indicator to monitor electrolyte in human body, with AgNPs and screen printed voltammetric sensors.[168] By harnessing the chemical reaction between Cl ions and the AgNPs, the electrons generated from the reaction (electrical output) could be monitored, as displayed in Fig. 5.6A. This disposable and wearable sensor was then applied for the detection of Cl ions in sweat. As the 0DNMs have larger surface-to-volume area than their bulk, more active sites are accessible to drive the reaction.

TABLE 5.1 Few examples of wearable devices and the comparison between nanomaterial- and non-nanomaterial-based sensors.

	Sensor type	Examples of wearable devices			
		With nanomaterials	**Reference**	**Without nanomaterials**	**Reference**
0DNMs	Pressure sensor	Addition of Ag Nanocrystals showed improved sensitivity of 2.72 × 104 K/Pa	156	The pressure sensor of the same material with micro-only structure had the sensitivity of 34.4 K/Pa	156
1DNMs	Lactate sensor	The combination of silver nanowires with molecularly imprinted polymers for the detection of lactate in sweat observed improved detection range of 10^{-6}–0.1 M and a limit of detection of 0.22 μM	157	Enzyme-free molecularly imprinted polymer-based lactate sensor reported detection range of 3–100 mM and a detection limit of 1.5 mM	158
	Strain sensor	Integration of acid interface–engineered CNTs on Ecoflex substrate showed improvements in stretchability (more than 100%) and a gauge factor (with 732.8 under 10% strain, 2131.8 from 10% to 30% strain and 234.9 from 30% to 40%)	159	The strain sensor fabricated by embedded conductive carbon black in Ecoflex substrate showed the gauge factor of 3.8 ± 0.6	160
2DNMs	Strain sensor	Graphene was woven into the fabric network with gauge factor of 50	161	Carbon ink–coated yarn network showed the gauge factor of 6.1	162
	Cortisol sensor	Flexible membranes functionalized with MoS_2 nanosheets for detection of cortisol in sweat with improved dynamic range of 1–500 ng/mL and a limit of detection of 1 ng/mL	163	Similar sensor based on zinc oxide reported a dynamic range of 10–200 ng/mL with a comparable limit of detection	164
3DNMs	Pressure sensor	Sensor based on 3-D porous conductive nanocomposites displayed high sensitivity of 0.062 k/Pa and an extremely low-pressure detection limit of ∼3 Pa	165	Similar pressure sensor with carbon black/silicone rubber as the sensing element achieved a sensitivity of 2.53×10^{-4} K/Pa	166
	Sweat sensor	Ion selective electrode based on gold nanodendrite array for detection of Na^+ in sweat, resulting in improved performance stability and a limit of detections of 0.8×10^{-6} M	167	Conventional gold electrodes recorded a limit of detection of 2.5×10^{-6} M and similar selectivity against other ions in sweat	167

Furthermore, it was shown that the AgNPs were able to enhance the signal by taking advantages of their surface properties.

The same enhancement strategy, for wearable sensors, can also be applied to gas phase samples. Many semiconductive nanomaterials are used as transducers and have shown selectivity and sensitive to specific gases. Again, by taking advantage of the high surface areas, the gas analytes react with the adsorbed oxygen on the surface, and extract or release the electrons to the nanomaterials causing changes in conductivity. Song et al. used lead(II) sulfide (PbS) quantum dots to fabricate humidity-resistive sensors to detect NO_2 at room temperature.[169] Besides the enhancement strategy, a novel mechanical fabrication strategy was also addressed in this study (Fig. 5.6B). To achieve better mechanical robustness on the skin, the substrate was prestretched first, and then the electrode and transducers were deposited. After releasing the stretching force, the structure crumples, making it robust to the movement. At last, a fully stretchable and wearable gas sensor was developed, providing the application for monitoring the gaseous environment or exhaled breath.

2. 1DNM for signal amplification

Due to the unique confinement on two dimensions, 1DNMs present with good mechanical properties, good conductivity, and large surface area. Moreover, the surface of 1DNMs also offers opportunities for functionalization, which can be used to tune their properties as well as enhance selectivity. This approach can be applied to other nanomaterials also, thus further highlighting these advantages. Bandodkar et al. constructed a CNTs-based electrochemical sensor and biofuel cell.[170] Thanks to the superior mechanical resistance of CNTs, the sensor could sustain strains as high as 500% without influencing the sensing performance. For linking the receptor to the surface, the CNTs were functionalized with selective ionophores and enzymes with the interest to detect a wide range of analytes. This wearable sensor was tested to detect ammonium, as a model, by potentiometry. Taking advantages of the biofuel concept, where glucose was both the analyte and the biofuel, the enzymatic reaction generated changes in the current change and was monitored by amperometry. Moreover, the sensor could also operate on a self-powered mode without an external power source (Fig. 5.6C).

3. 2DNM for signal amplification

2DNMs possess high flexibility, transparency, and carry mobility, and are well suited for optical and electronic wearable sensing devices. In terms of chemical sensing, the large basal plane is very attractive for supporting a large number of receptors compared with bulky materials. In an interesting study, Mannoor et al. presented a sensor that is wearable on tooth enamel and was capable of wireless data transmission.[171] In this sensor, the transducer was selected as graphene printed onto silk in an interdigitated configuration. The transducer itself was then functionalized with antimicrobial peptides as receptors for selective binding to bacteria (*Helicobacter pylori*) in the saliva. Due

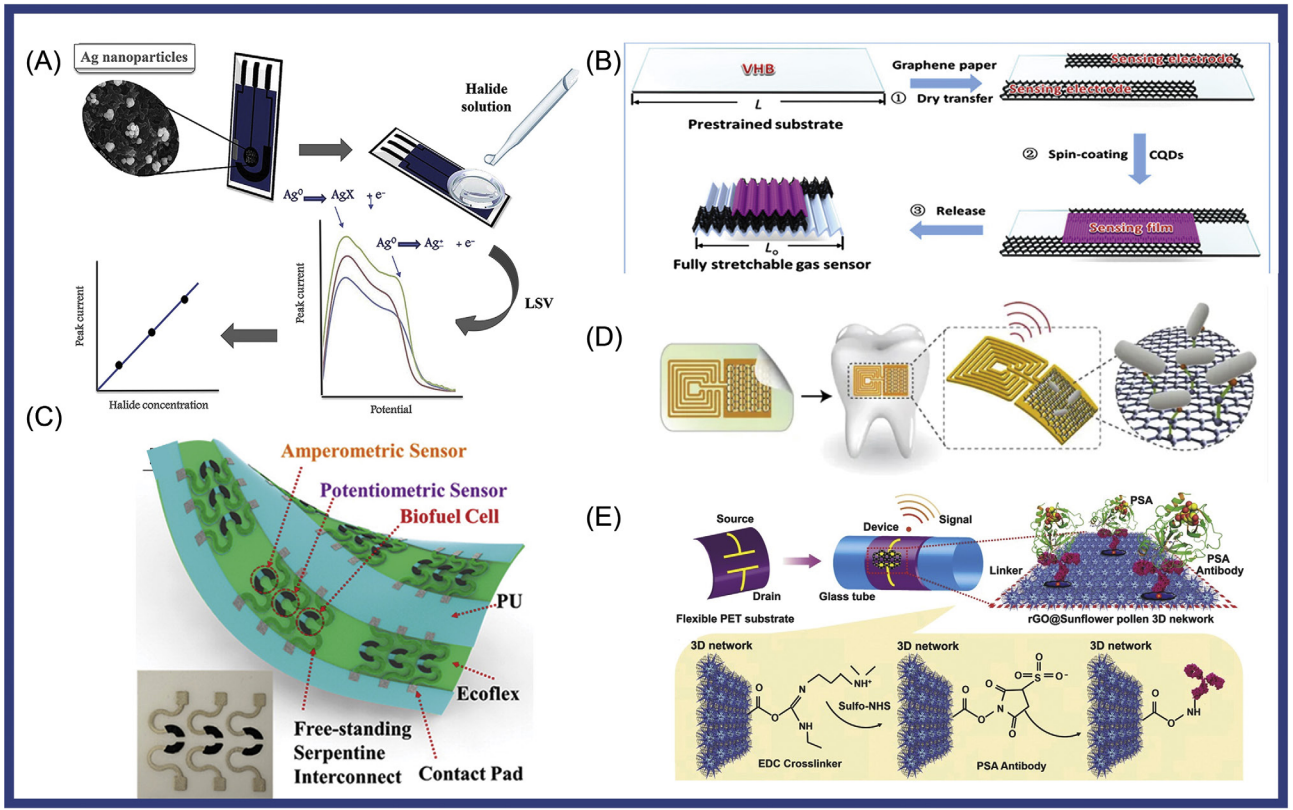

FIG. 5.6 **Chemical and biological wearable sensors.** (A) Flexible sensor employing an AgNPs-modified electrode for Cl ion sensing *(reproduced with permission from ref,*[168] *copyright 2017, Elsevier)*. (B) Fully stretchable gas sensor using quantum dots *(reproduced with permission from ref,*[169] *copyright 2018, American Chemical Society)*. (C) Self-powered biofuel glucose sensor based on CNTs as transducer *(reproduced with permission from ref,*[170] *copyright 2016, American Chemical Society)*. (D) Graphene biosensor for wireless bacteria detection *(reproduced with permission from ref,*[171] *copyright 2012, Nature Research)*. (E) Graphene-encapsulated nanocomposites for sensing PSA biomarkers *(reproduced with permission from ref,*[172] *copyright 2016, Wiley)*.

to the large surface area of graphene, the signal was enhanced and the sensor achieved an excellent detection limit of ~100 cells. The wireless communication module enabled the sensing system to communicate with smartphones for quantitative analysis, as shown in Fig. 5.6D.

4. 3DNM for signal amplification

3DNMs have two exceptional advances in chemical sensing: the large reactive surface providing more sites for chemical reaction and free-standing 3-D structure that is beneficial for introducing fluid or gas for a contact with the surface. In some cases, such as heavy metal sensors, the 3-D structure can accumulate and capture more ions and enhance the obtained signal. A novel example by combining the advantages of large basal plane of 2DNMs and 3-D free-standing structure can be seen in the work of Wang et al.[172] Here, the authors reported a novel flexible FET biosensor employing a transducer out of reduced graphene oxide (rGO) encapsulated 3-D natural pollen for the selective and sensitive detection of prostate-specific antigen (PSA) biomarkers (Fig. 5.6E). Harnessing the large surface of the graphene-based 3-D structure, the sensitivity of the sensor was significantly improved, allowing the PSA detection down to 1.7×10^{-18} mol/mL.

5.13 Conclusions and future perspectives

In conclusion, due their interesting chemical and physical properties, including (1) high electrical conductivity, (2) plasmonic effect, (3) high surface area and aspect ratio, (4) flexibility, and (5) stretchability, nanomaterials can offer many advantages and opportunities for the development of wearable (bio)sensors over the traditional bulk materials. Based on different platforms, the enhancement strategies have been developed to improve the performance of the wearable (bio)sensors by using nanomaterials. The improvement of electrical percolation on polymer nanocomposites, the superior stretchability on strain sensors, the ultra-high sensitivity on biochemical detection, and other features of the low-dimensional materials appears as appealing advantages in the use of the nanomaterials in wearable (bio)sensors. Besides, nanomaterials can offer new opportunities to the implementation of electrical/optical wearable (bio)sensors based on inkjet printing technologies, allowing to design a whole (hybrid) printable sensor in different types of flexible substrates.

However, it is evident that most of the presented enhancement strategies still face various challenges that have hindered its translation and adaptation into wearable sensors for real applications. Obstacles such as trade-off in material properties and the high demand for simplicity, robustness and design of sensing systems still need to be addressed. For example, in physical wearable sensors, nanomaterials, normally 1DNMs and 2DNMs, are applied due to their supreme mechanical and electronic properties. However, the nanomaterials can only provide the ability to meet the mechanical requirements. Nearly no research has been found to use nanomaterials to specifically enhance the sensitivity.

In chemical and biological sensors, the enhancement strategies are mainly to take advantage of large surface area provided by nanomaterials to support more receptors. In fact, we found there to be a huge mismatch between the presented excellent sensing platforms, corresponding enhancement strategies, and the poor immobilization in wearable sensors. Due to this mismatch, many wearable sensors are mainly limited to physical and gas sensors. Nevertheless, there are few wearable sensing studies that describe immunosensors or DNA sensors. However, due to their complexity, these sensors still face many challenges that warrant further investigation before their use in real wearable applications.

One solution and approach worth exploring is to develop microfluidics integrated with nanomaterials on the skin to control biofluids and mimic laboratory conditions. In this way, the enhancement strategies previously discussed could be harnessed for future wearable sensors. Moreover, another approach is to develop other strategies to exploit the full potential of nanomaterials. A strategy could include developing new nanocomposites that combine different materials of different composition, morphologies, and dimensional order. By doing so, the combination of nanomaterials could uncover unique or synergistic effects of the materials' properties; thus further amplifying the detection signal or broadening its use in wearable sensors. These approaches only further demonstrate and highlight the relevance and importance of nanomaterials for wearable technologies.

Furthermore, we also found there is an increasing trend of wearable sensing studies focusing not on the sole sensor itself but the whole sensing system, including substrate material and comfortability, wireless communication module, and power management. The ability of wireless communication especially with smartphone will become increasingly important in wearable sensors (see Chapter 12). Besides, power consumption still remains as a key issue. Self-powered, such as piezo- and biofuel-based, wearable platforms will be more popular in the future. Instead of batteries, more different forms of energy will be involved in wearable sensors such as Radio-Frequency IDentification (RFID), wireless charging, solar cells, and fuel cell (see Chapter 6). Hence, we think the development of wearable sensors is still in the early stage and needs a lot of efforts from cross-disciplinary fields in sensing, materials, chemistry, biology, and electronic engineering.

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Abbreviations

0DNMs	0-D nanomaterials
1-D	One dimensional
1DNMs	1-D nanomaterials
2-D	Two dimensional
2DNMs	2-D nanomaterials
3-D	Three dimensional
3DNMs	3-D nanomaterials
Ag	Silver
AgNPs	Silver nanoparticles
AgNWs	Silver nanowires
AuNPs	Gold nanoparticles
CAD	Computer-aided design
Cl	Chloride
CNTs	Carbon nanotubes
ECG	Electrocardiogram
e-skins	Electronic skins
FET	Field effect transistor
g-C_3N_4	Graphitic carbon nitride
gFET	Graphene-based field effect transistor
GQD	Graphene quantum dots
HIV	Human immunodeficiency virus
LOD	Limit of detection
MIP	Molecularly imprinted polymer
MOS	Metal oxide semiconductor
MoS_2	Molybdenum disulfide
MWCNTs	Multi-walled carbon nanotubes
N_2	Nitrogen
NO_2	Nitrogen dioxide
PbS	Lead(II) sulfide
PDMS	Polydimethylsiloxane
PLA	Polylactic acid
POC	Point-of-care
PSA	Prostate-specific antigen
RFID	Radio-frequency identification
rGO	Reduced graphene oxide
Si	Silicon
SiO_2	Silicon dioxide
SWCNTs	Single-walled carbon nanotubes
TMDs	Transition metal dichalcogenides

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Chapter 6

Healthcare data analytics for wearable sensors

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6.1 Introduction

The increasing popularity of wearable devices in recent years has resulted in the production of a diverse range of physiological and functional data that can now be captured continuously for applications in sports, wellbeing, and healthcare.[1] This myriad of information requires efficient methods of classification and analysis, where deep learning is a promising technique for large-scale data analytics.[2] Traditional computing architecture relies on cloud computing to provide the computational power. However, the cost of data transportation sometimes can be unacceptable, especially for latency-sensitive applications.

6.2 Machine learning at the edge

In recent years, the emergence of edge computing in various fields has shown great potential in reducing latency, saving cost and power.[3] Different from the cloud computing architecture, edge computing enables data processing at the edge of the network. On one hand, data computing is put closer to the data source, which greatly facilitates the development of delay-sensitive applications. On the other hand, the network traffic is largely reduced as the local processing avoids a large percentage of data transmission, which remarkably saves the cost. Running computation on a device itself, instead of in a remote server, also offers large benefits to privacy.

Wearable health devices such as smartphones or smartwatches are now very popular and affordable.[4] They are equipped with multiple sensors that continuously produce a collection of physiological data. Typically, these devices have modest computing resources for data processing and transfer. However, in most cases they only provide relatively simple metrics, such as step counts or cadence. To produce a deeper insight from the data, it needs to be transferred to the cloud or to another more powerful device. It would be advantageous if more complex analysis could be done on these devices. The emergence of deep

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learning methodologies, which can extract discriminating features of the data, and increased processing capabilities in wearable technologies has increased the possibility of performing more complex data analysis on-site in real time without transferring the data.

To solve these problems, the direct use of raw electrical impedance data without a significant amount of preprocessing can be used for health informatics with the help of on-device artificial intelligence (AI) or Edge AI. In this sense, the wearable device is the "edge" to a mobile phone or other central station, which would traditionally perform more complex analysis.[5] The microcontrollers used in modern wearable devices have greatly increased in computational power in recent years, and recent developments have been made into porting advanced analysis tools, such as artificial neural networks onto them for classification and prediction. One such method recently developed is the Tensorflow Lite (TF Lite) for microcontrollers,[6] which allows for neural network (NN) models to be run on supported microcontrollers for classification, forecasting, and feature detection.

A low-power and slimmer version of a machine learning (ML) model through local communication was developed, as shown in Fig. 6.1. The proposed framework was implemented along with traditional model of the TF Lite platform, which can be used for many ML tasks, such as image and text classification, generative adversarial networks, and time-series forecasting.[7] One of the most useful high-level AI frameworks for using the TF platform is Keras, which allows for the deployment of NN models by specifying layer dimensions, weights, and automatically performing fitting and evaluation of the models.[8] This greatly streamlines the NN design and training processes, allowing for rapid testing, modification, and tuning. Another primary benefit of edge AI is its speed. Any task or action can happen faster if the data do not have to be transmitted back and forth for processing. Also, the AI's ability to detect issues by integrating smart wearables and analytics functionality to deploy intelligence at the edge for rapid insights is considered as a large advantage.

Edge AI system is capable of performing data processing at the hardware level, which improves the response time of the overall system to achieve a real-time solution.[9] A major obstacle to the small profile wireless sensor nodes is the power consumption of the overall platform. This is especially true for small profile platforms, as batteries for small units are often under 50 mAh.[10] An ultra-low power control and monitoring system must be developed to give the platform a long enough runtime to be a feasible source of streaming data. Offloading computation onto the wearable device will decrease the rate, and amount of data that need to be sent over wirelessly to the central device, as the raw data may not be sent at a high data rate. By only sending decisions when polled or when one is needed, the relatively high power required by the wireless radio will only be necessary for short, one packet data transfers, and the duty cycle of transmission will be greatly decreased.

This is a main motivation with a small wearable, as the operational lifespan of the device is limited by the size and capacity of its battery which can fit

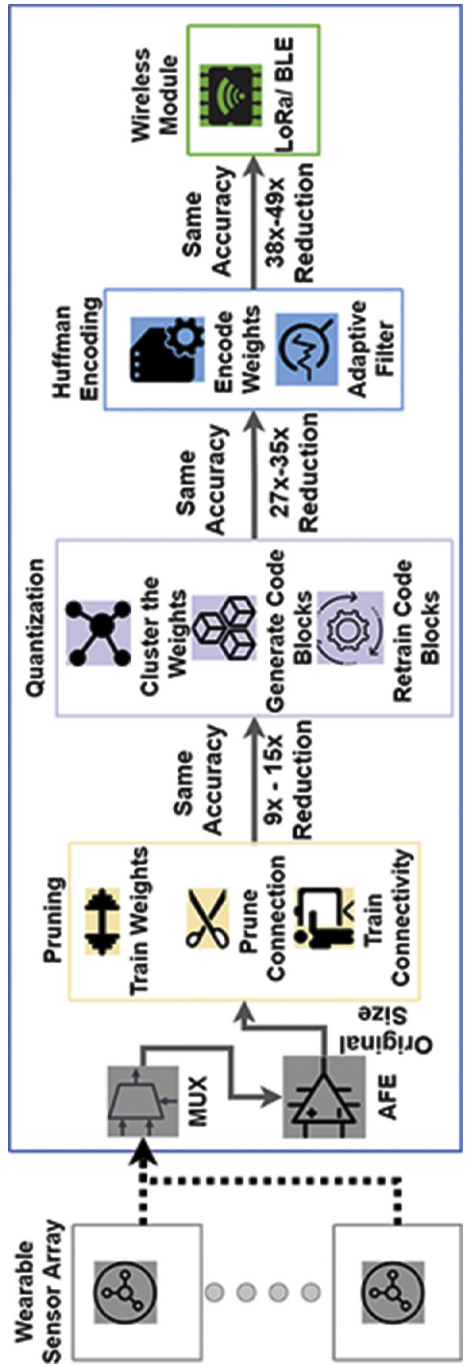

FIG. 6.1 Edge AI–based data compression technique.

within a ring on a human index finger. When the microcontroller is not performing a wireless transmission, current draw is significantly lower, therefore the trade between additional computation on the device and less use of wireless transmissions is clear. Decreasing the duty cycle of wireless transmissions is paramount to extending the functional time of the device. Another disadvantage to the larger, highly accurate networks is their size, as they cannot be easily stored and loaded onto embedded devices, due to memory limitations. This can be mitigated by fusing operations in a network together, at the cost of accuracy. This is how the TF Lite converter utility functions and can be used to turn Keras models into microcontroller compatible TF Lite models.

The advantage of using the Edge AI methods is the possibility of rapid learning of generalizable predictive patterns in combining variables in a nonlinear fashion, possibly increasing the predictive performance when compared to simpler models. In addition, this can be used to perform the automatic feature extraction, useful when there is a plethora of variables (e.g., different immittance parameters over many frequencies) present and the important ones are not yet known. Additionally, *in-situ* performance analysis on data collected from low-power wearable devices can greatly improve power efficiency by decreasing the amount of data being sent over wirelessly to just significant features, rather than real-time data. Traditional multiclass methods for pattern recognition such as extended support vector machines and k-nearest neighbors will also be compared with the proposed method. As one size model does not fit all, researchers should find a suitable microprocessor by using multiple architectures (such as ARM, AMD64, ASIC and FPGA).[10] These microcontrollers support cutting-edge applications and are designed to run a slimmer version of TensorFlow, called TF Lite.

6.3 Uncertainties in healthcare data

In the modern world, data are generated and collected through the web and by sensors (such as wearables) due the increased usage and advancements in electronic devices. The International Data Corporation (IDC) reported that in 2011, the overall data volume generated in the world was 1.8 Zeta Byte, and within 5 years it increased by nearly nine times.[11] Due to this availability and usage of data, the term Big Data has emerged, and a variant of its definition is as such high volume, velocity, and variety of data that demand cost-effective, innovative forms of processing for enhanced insight and decision making.[12] Compared with traditional datasets, Big Data typically include masses of unstructured data that need more real-time analysis.[13] The value chain of Big Data can be roughly broken down into several phases, that is, data generation, data acquisition, data storage, data analysis and development of models that aid in decision making through the analyzing of such data.[14]

To obtain critical information regarding large datasets, data analysis techniques are employed to transform big data into smart data. For example, in the

field of healthcare, better schedule of insulin deliveries can improve glucose management, but on the other hand, a dose that is too large can harm or kill the patient.[15] In the context of agriculture, avoiding the use of a pesticide improves the quality of a crop and increase profits, but waiting too long after the pest is detected can lead to a crop failure.[16] With the improvement of data availability in such complex domains, there is a growing focus to improve decision making using ML. ML is a branch of AI which is based on the idea that computer systems can learn from data by identifying patterns and then carry out classifications or predictions with the purpose of aiding humans in decision making.[17] At its core, ML consists of computational methods or techniques which can be used to solve analytical problems. For instance, historical patient data could be used to train such models to detect a disease and apply the optimal treatment.[18]

While ML holds a lot of promise, the results from such models become unreliable due to the challenges that are introduced by uncertainty. Uncertainty refers to situations involving unknown or imperfect knowledge and is inherent in stochastic and partially observable environments.[19] Furthermore, uncertainty can be embedded in the entire analytic process (e.g., collecting, organizing, and analyzing Big Data). Dealing with incomplete and imprecise information is a critical challenge for most ML techniques focused on how uncertainty impacts the performance of learning from Big Data,[16] whereas a separate concern lies in mitigating uncertainty inherent within a massive dataset. When scaling these issues up to the Big Data level, even small errors accumulate through positive feedback loops and effectively compound any errors in the entire analytic procedure.[20] Therefore, an ML model could generate an optimal solution based on its training data; however, if the uncertainty in the data and the model parameters are not taken into consideration then such optimal solutions have a high risk of failure. Bad decisions can cause large losses, injury, or death. Therefore, having confidence in the predicted solution's quality is essential. For the predicted solutions from such models to be reliable, datasets of appropriate size and accuracy is required. Often, despite the availability of data, the required volume and accuracy cannot be met and sometimes the data themselves are subject to change due to future environmental variability. Therefore, the incorporation of data and model parameter uncertainty should be at the forefront during the development of such ML models.

Merging data from several sources using multisensor data fusion algorithms exploits the data redundancy to reduce the uncertainty.[21] However, if these sources provide inconsistent data, catastrophic fusion may occur where the effectiveness of the multisensory data fusion is dramatically lower than the performance of each of the individual sensors. Different algorithms have been proposed to quantify sensor uncertainty with different characteristics, capabilities, and limitations. For example, probabilistic fusion, evidential belief reasoning, random set theoretic fusion, simplified Bayesian approach, and hybrid fusion approaches.[22] Providing sensor uncertainty information may yield deeper insights into how a model produces its result and the confidence of that result.

Given these issues we anticipate sensor uncertainty quantification will play major role in healthcare data analytics as the diversity of data and information available continues to increase.

6.4 Data analysis in healthcare using Big Data

Data processing algorithms in healthcare greatly benefit from regularly sampled and reliable data. Therefore, there is need of a data acritude to solve two key problems in large-scale datasets: (1) high dimensionality and (2) uncertainty quantification. The architecture shown in Fig. 6.2 starts with a data preparation phase where the data cleaning, formatting, normalization, and randomization will take place. This phase will ensure that the data are structured and filtered before it goes through a data decomposition process. Data cleaning and formatting play a fundamental role as one the first steps of most data processing workflows. However, traditional methods assume that clean signals are a linear combination under a sparsity constraint of the atoms in a learned overcomplete

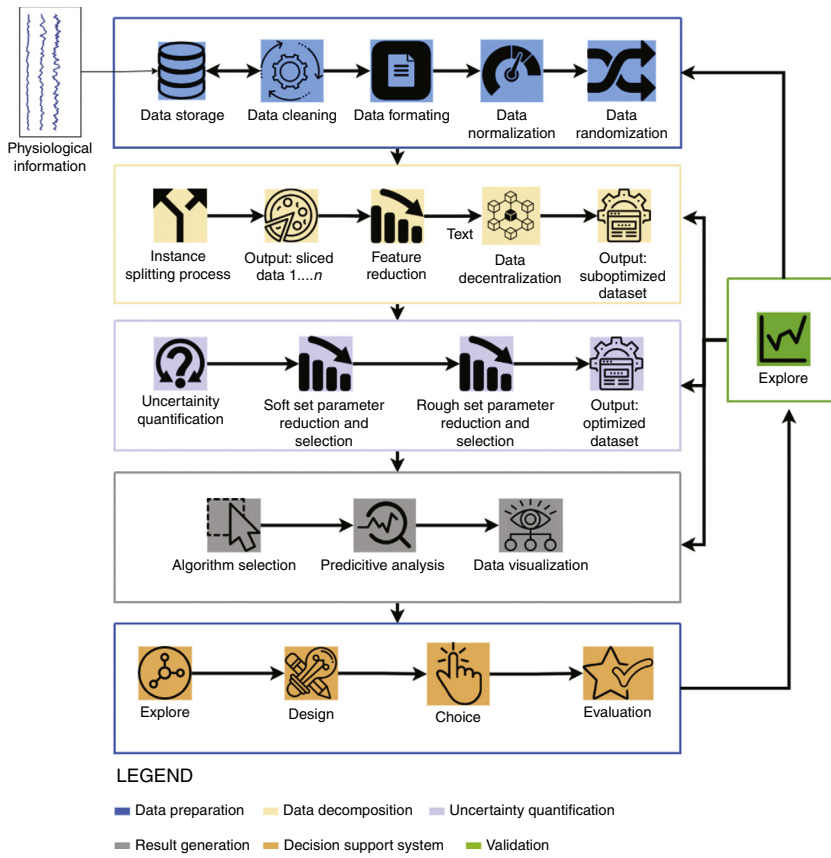

FIG. 6.2 Big Data architecture for health informatics.

dictionary (i.e., a frame created by a set of m functions with $m > n$, n being the signal dimension).[23] The architecture leverages convolutional autoencoders to clean (i.e., interpolate and denoise) unstructured health information data in the shot-gather domain. As the health information's have a long sequence of preprocessing functions, GPU tensors should be performed for these operations.

The output of Phase 1 is fed to the Phase 2 where data decomposition will take place. A major task of data decomposition is to extract features from raw datasets by creating new features from the existing ones (and then discarding the original features). These new reduced set of features should then be able to summarize most of the information contained in the original set of features. Principal component analysis (PCA) is a common feature extraction method in data science.[24] This method selects variables according to the magnitude (from largest to smallest in absolute values) of their coefficients (loadings). However, PCA suffers from linearity which can be solved using Kernel PCA[25] or deep convolutional autoencoder (DCAE).[26] These models should be explored, especially DCAE on hierarchy model time series data in an unsupervised manner, it is a powerful method for learning high-level and mid-level abstraction from low-level raw data. Evaluation and validation can be performed by comparing the results from the proposed architecture with traditional dimensional reduction methods (PCA, t-SNE (t-distributed stochastic neighbor embedding), or UMAP (Uniform Manifold Approximation and Projection)).[27] This method will identify the most important attribute to be set as the suboptimized attribute set.

In Phase 3, the suboptimized dataset will go through another parameterization process. The importance of uncertainty quantifications of the dataset is described in the aforementioned section. Especially for data analytics in healthcare where we are dealing with large datasets, we require an additional soft and rough selection process to generate fully optimized data. In Phase 4, the data go through a detailed analysis, such as regression, inversion, and prediction processes which have been discussed in the next section. The optimized data must be transformed into high-resolution maps to provide an image of the underlying subsurface, referred to as the "inverse problem." Once the data flow is represented graphically, decision making becomes much easier. This incorporates an interactive analysis of Big Data, where we suggest generating plots, tables, identify quirks, outliers, missing data patterns, and problems with the datasets. In the last phase, which requires human interaction, analytical outcomes, algorithms, and recommendations should be evaluated.

6.5 Algorithmic approach for data storage and access

Storing large volumes of data is one of the primary challenges for data analysis in healthcare, but many organizations are comfortable with data storage on their own premises. It has several advantages such as control over security, access, and up-time. However, loading this significant amount of data into memory of even the most powerful of computing nodes is not an effective method to work with Big Data. The best approach for analyzing large amounts of complex

data such as in healthcare is to distribute and process it in parallel on multiple nodes. One important challenge in parallelizing the computations is distribution of the tasks and handling failures to process those tasks. Several methods can be used to optimize this problem, particularly open-source distributed application platforms including Hadoop, NoSQL Apache Spark, etc.[28,29] The problem of failure of these platforms are handled by the filling systems (for instance, HDFS (Hadoop Distributed File System), IPFS (InterPlanetary File System), etc.) and the problem of combining data is handled by a MapReduce programming paradigm.[30] MapReduce basically reduces the problem of disk reads and writes by providing a programming model dealing in computation with keys and values. The main issues with these algorithms are increasing their data locality rate and decreasing their response and completion time. There are many MapReduce scheduling algorithms that focus on these issues, for example, a matchmaking algorithm uses a locality ID to increase its data locality rate, while HybS[31] uses a dynamic job priority.

6.6 Signal conditioning, wireless communication, and regulatory landscape

Wireless body area networks (WBAN) are a subset of wireless sensor network (WSN) that consists of multiple tiny sensors implanted inside the body or attached to the body to usually measure physiological signs containing valuable health information (such as heart rate, galvanic skin resistance, skin temperature, etc.).[32] The WBAN architecture is developed in such a way that these on-body or implanted sensors can crosstalk between each other as well as a central remote station for further analysis. One of the major challenges of these tiny sensors is that they are constrained by the minimum energy requirement due to their limited battery lifetime and miniature size of the battery to be easily wearable. Additionally, the data management of such a heterogeneous architecture of WSN adds multiple layers of dimensions to the design (including channel capacity, high traffic, authentication).[33] However, with recent advances in miniaturized electronics and the development of short-range and ultra-low power wireless communication (e.g., long-range (LoRa), Bluetooth Low Energy), interest in WBAN is exponentially increasing.[34] In the following, we will discuss three aspects of WBAN: (1) sensing with Analog Front End (AFE), (2) wireless transmission protocols, and (3) the regulatory landscape.

Due to the continuous monitoring of sensors in WBAN, the power consumption of signal acquisition, AFEs play an important role in the overall power consumption of the sensing devices as well as the quality of the sensor readings. For example, low noise operation of the AFE is one of the primary specifications of an electrocardiogram (ECG) front-end, and signal acquisition systems often compromise the power consumption of the system to achieve lower input-referred noise specifications or vice versa.[35] Therefore, special care for low power and high input impedance sensors should be taken into consideration for the signal

conditioning circuit, which is also referred to as an AFE. The AFE comprises multiple stages of buffer, differential amplifiers, and filters. The purpose of the AFE is to extract, amplify, and filter small biopotential signals in the presence of different noise sources. The AFE circuit generally starts with a buffer amplifier that helps to improve the input impedance and bootstraps the biasing network.[36] The high impedance of the sensor requires the use of high-impedance voltage buffers in front of the differential amplifier to ensure an accurate open circuit voltage measurement. The output signal will be connected to an ultra-high input impedance instrumental amplifier.[37] This provides the differential gain and drives the common line. The multiorder (such as fourth, eighth) band pass filter also used to reduce the low- and high-frequency components.[37] The hardware AFE platform is designed such that the system acquires optimal performance with very low power consumption. The signal then will be converted to a digital signal by a built-in analog to digital converter of the microprocessor, then data will transmit wirelessly to the host (like PC, notebook, smartphone) through wireless transition protocols (such as LoRa, Wi-Fi, Bluetooth 4.0).

Most popular *wireless protocols* in WBAN are Bluetooth low energy (BLE), Wi-Fi, ZigBee, LoRa, and most recently narrow band Internet of things (NB-IoT). Bluetooth is an inexpensive module for short-range communication protocol between portables and fixed devices requiring extreme low-power (2–60 μA) consumption.[38] It is an ideal candidate for mobile-to-device communication and widely accepted by commercial vendors (Apple Watch, Fitbit, etc.). Lower layers of the Wi-Fi protocol were also adopted for WBAN, allowing higher data rate and throughput for low-power sensor networks. Wi-Fi modules are not as low as BLE in terms of power consumption but have a longer distance range than BLE (∼100 m).[39] ZigBee is another wireless communication protocol, less popular recently, generally used for low power and low data rate communication protected by the use of the Advanced Encryption Standard.[4] LoRa has become an integral part of the WBAN application in the last decade and is a commonly used protocol inside the LPWAN (low-power wide-area network) family.

Lots of industries are adopting IoT data collecting methods to predict future outcomes.[40] Remote health monitoring, precision farming, smart in-home appliances, and wearable technology are just a few examples of industries that have adopted the modern data collection methods often used in IoT applications. These industries combine the forces of mass data collection and modern ML algorithms to train models to predict the future outcomes for very specific parameters. This has resulted in major investments in the industry, and an increase in demand for more efficient and cheaper devices to use in these applications.

The LoRa protocol can be applied perfectly in LoRa settings, as most devices do not need to send large amounts of data, but also need to be energy-efficient enough to last more than a year unmanaged. LoRa provides an efficient way to send relatively small amounts of data relatively far, up to 2000 m in some

cases, as a relatively low energy-cost.[41] In the last few years, the evolution of 3rd Generation Partnership Project (3GPP) standards related to IoT has attracted a lot interest due to the high demand of cellular stakeholders who require a standard solution to go one step further to provide a real cellular and standard solution for LPWAN, which worked as a driving force for the development of NB-IoT.[42] The NB-IoT is a massive LPWAN technology proposed by 3GPP for data perception and acquisition intended for intelligent low-data-rate applications. The NB-IoT allows massive connections of nodes with ultra-low power, bidirectional triggering features, and data plane. Additionally, NB-IoT provides effective indoor coverage with massive low-throughput and low-cost devices. Additional advantages worth noting are its low power consumption and optimized network architecture.[40] Undoubtedly, NB-IoT is a promising candidate for WBAN and soon will be evolved into large-scale deployments around the world.

Healthcare technology is facing a wide range of challenges from data security, trust issues, and incentivization to regulatory and ethical hurdles. Regulations related to noninvasive wearables are in flux, as few agencies view them as low-risk devices and avoid the tedious regulatory process of commercialization. However, some of these devices are clearly ignorant of potential security issues associated with data breaching and personal information, hence making wearables more liable for the protection of public data. In the United States, smartwatches and fitness bands are usually falling under low-risk wearable systems and do not require Food and Drug Administration (FDA) approvals. However, recent developed systems such as QardioCore and AliveCor for a wearable ECG monitoring are required to have FDA approvals before reaching to the consumer market[43]. This is indication that FDA is increasing their bar for noninvasive wearables to provide standardized guidance.

6.7 Conclusion and outlook

Despite the current challenges of wearable systems, designers will always be analyzing their best options for optimum solutions. The type, size, accuracy, and location of the wearable sensors also play a fundamental role in the system design. For example, with new materials evolving (such as graphene) the battery life and power consumption of the wearables can be optimized including how the device is communicating and working with other devices. Also, these materials can also be used for energy-harvesting technology, which converts energy from the surrounding through solar, kinetic, and temperature deviation. These could introduce a self-powered (i.e., battery less) wearable system using energy-harvesting module, which will decrease total weight. Reliability and accuracy of the sensor data are another challenge and researchers should pay careful attention to design resilient data analytics. Lastly, one of the major properties of the wearables is user acceptance. One direction of the future research should be focused on aesthetic design, portability, accessibility, simple, smart, and easy to use.

Heterogeneous healthcare data analytics are a recent reality in healthcare and still under development with the aim to be integrated in medical health systems. There are few systems that are capable of providing instantaneous single-parameter assessment and transmission. But the major potential of healthcare systems can be explored by integrating several physical, chemical, and/or biological sensors, intelligent processing, seamless transmission, and data privacy. Therefore, in the upcoming years a set of new interesting challenges to overcome them in healthcare systems should be taken.

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Abbreviations

AFE	Analog front end
AI	Artificial intelligence
BLE	Bluetooth low energy
DCAE	Deep convolutional autoencoder
ECG	Electrocardiogram
FDA	Food and Drug Administration
LoRa	Long range
ML	Machine learning
NB-IoT	Narrow-band internet of things
NN	Neural network
PCA	Principal component analysis
TF	Tensor flow
WBAN	Wireless body area networks
WSN	Wireless sensor Network
3GPP	3rd Generation Partnership Project

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Chapter 7

Wearable physical sensors

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7.1 Introduction

Wearable physical sensors are devices worn on a person to continuously monitor and track human conditions such as steps, metabolism, heart rate, calories, and so on. Smart watches are a common example of wearable physical sensors. The ongoing development of wearable physical sensors has enabled wireless measurements for both physical and physiological platforms. In recent years, the rapid expansion of wearable physical sensors has established their importance and potential future utility during the era of the Internet of Things (IoTs). The compelling evidence can be traced to the increase of scientific reports in this field.[1]

A significant amount of time and effort has been invested in studying wearable physical sensor platforms. In this chapter, we will introduce six sensing platforms based on their electrical parameters. We will first introduce the recent advancements of nanogenerators that are self-powered and operable without external power supplies such as a battery. As seen in Fig. 7.1, this chapter will cover two main types of self-powered nanogenerators: triboelectric nanogenerators (TENGs) and piezoelectric nanogenerators (PENGs). Next, we will introduce the four different modalities of non-self-powered wearable physical sensors: capacitive, electret, field-effect transistor (FET), and resistive. Each modality has a different working mechanism, which will be explained in detail in each section.

Recently, research has been focused on developing wearable physical sensors with compelling features that are deemed user-friendly, including integration capabilities and being cost-effective, lightweight, flexible, diverse in material choice, physically dynamic, and structurally simple. Over the last few years, the applications of these sensors have emerged in the fields of healthcare monitoring, soft robotics, portable electronics, and environmental detection.[1] This chapter will also provide example applications of important wearable physical sensors.

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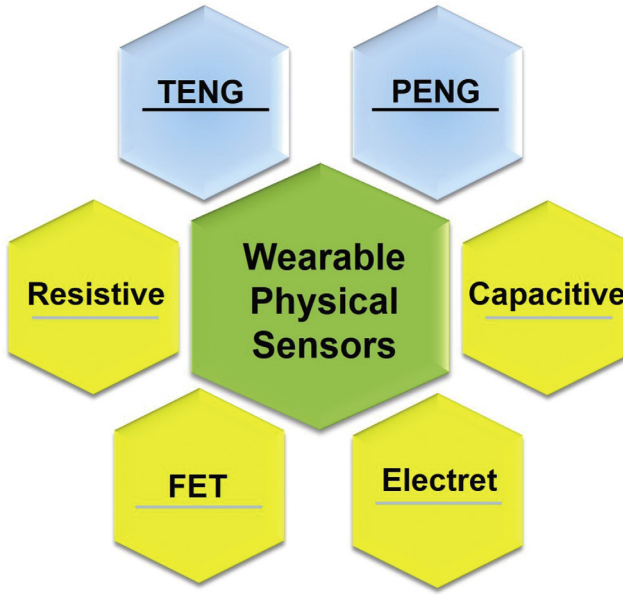

FIG. 7.1 The wearable physical sensors. In general, we have two categories: one is self-powered wearable physical sensors based on TENGs and PENGs and another is non-self-powered wearable physical sensors based on FET, resistive, electret, and capacitive effects.

7.2 Self-powered wearable physical sensors

Self-powered wearable physical sensors are promising due to their capability to harvest the inexhaustible source of biomechanical energy from human motion, ranging from slight movements, such as pulse and respiration, to larger movements such as muscle contractions.[2] Zhong Ling Wang's lab proposed the novel concept of nanogenerators that could convert mechanical energy into electrical signals, which could be further utilized for self-powered physical sensors. The two types of self-powered nanogenerators discussed in this section are TENGs and PENGs, which differ in their electricity-generation mechanism.

7.2.1 Triboelectric nanogenerators

TENGs have emerged favorably within recent years as the next-generation of sensing and therapeutic devices, driven by their innate self-powering, micro/nano-scale, and morphologically versatile nature.[3–5] The working mechanism of TENGs involves the coupling of the triboelectric effect and electrostatic induction between two materials in contact.[6,7] The triboelectric effect occurs when two materials come into frictional contact with one another, which results in the charge transfer from one material to the other due to their difference in electron affinity as listed in the triboelectric series. Consequently, one material becomes positively charged and the other negatively charged. When the

materials are separated, a potential difference is induced due to the development of these opposing charges, which drives the flow of electrons further between the electrodes to reach equilibrium and therefore, generates an alternating current (AC) output.[8] Overall, TENGs can be divided into four main working modes: vertical contact-separation, lateral sliding, single-electrode, and free-standing triboelectric-layer mode.

7.2.1.1 Vertical contact-separation mode

The operational principle behind vertical contact-separation mode (Fig. 7.2A) can be described as two electrodes that are each connected to different triboelectric materials, with each triboelectric layer periodically coming into contact with one another via vertical movement and resulting in surface charge transfer. When the two materials are not connected, the potential drops. Consequently, free electrons from one electrode flow toward the other electrode to balance out the potential difference. When coming into frictional contact again, a flow of electrons in the reverse direction is generated. This cycle of contact and separation between the materials induces an AC output.[9]

7.2.1.2 Lateral sliding mode

The lateral sliding mode in Fig. 7.2B induces electricity via the sliding movement of the top triboelectric layer over the bottom one. In the triboelectric series, the top layer is positive, while the bottom layer is negative. In the starting position, the two layers fully overlap each other. At this point, the two layers have equal and opposite charge density, due to their shared interface. As the

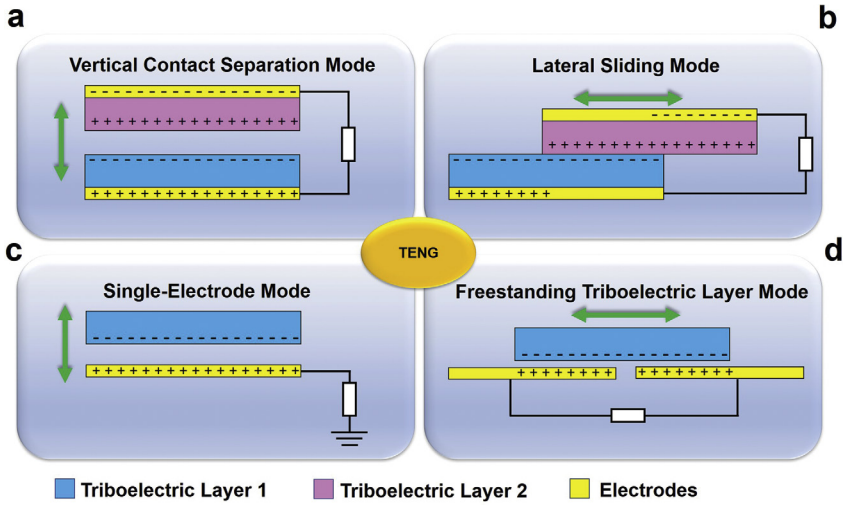

FIG. 7.2 Four working modes of TENG. (A) Vertical contact separation mode. (B) Lateral sliding mode. (C) Single-electrode mode. (D) Free-standing triboelectric layer mode.

top positive layer slides outward, the contact surface area decreases, creating a separation of charge. This potential difference drives the flow of electrons from the bottom electrode to the top electrode until the top layer completely slides outward, thereby producing the first half of the AC output cycle. When the top layer slides inward, the flow of electrons will reverse, producing the second half of the AC output cycle. [8,10,11]

7.2.1.3 Single-electrode mode

The vertical contact-separation mode and the lateral sliding mode, discussed in subsections 7.2.1.1 and 7.2.1.2, require two electrodes. However, in real-life scenarios, such as human walking or vehicle movement, an interconnected lead between the two entities does not exist. To address this problem, the single-electrode mode, as shown in Fig. 7.2C, was introduced, which features ground as one of the electrodes. Similary, the top layer is negatively charged and the bottom layer positively charged when in contact. When the two materials separate, in an open circuit, a potential difference is established between the bottom electrode and ground which drives electron flow from the ground to the electrode. This mode can accommodate both the vertical contact-separation and lateral sliding movement.[12]

7.2.1.4 Free-standing triboelectric layer mode

Free-standing triboelectric layer mode is another design method that does not require two electrodes (Fig. 7.2D). In this mode, the moving material becomes charged after coming into contact with the air or another object. The material retains its charge density for a long period even without consistent frictional contact. The electrode is symmetrically connected to two bottom dielectric layers, with a small gap separating the two. The freestanding top layer can come into contact and slide back and forth along the two bottom dielectric layers. This movement drives an asymmetric charge distribution, which generates an AC current between the two electrodes.[13]

7.2.2 TENG-based physiological sensors

Due to the demand for early diagnosis and healthcare monitoring, physiological sensing has become increasingly relevant in recent years. With an interest growing around wearable physical sensors, researchers have been working to make them lightweight, durable, comfortable, flexible, and washable. The optimization of these sensors has called for unconventional monitoring systems that do not require batteries. In particular, one monitoring system is the self-powered TENG, which can adequately address the aforementioned demands.

7.2.2.1 Respiratory monitoring

Monitoring human respiratory movement can provide early and valuable insights for diagnosis and treatment of pulmonary diseases. Developing noninvasive and

self-powered solutions by means of TENGs can pave a path towards smarter health monitoring systems. Additionally, movement associated with breathing provides an excellent source of biomechanical energy for electrical energy generation. The development of respiratory monitoring sensors is becoming more intelligently adaptive to the user's daily life by meeting the current demands of IoT and advancing facile textiles.

In the early stages of respiratory monitoring, Zhong Lin Wang's group constructed a membrane-based wearable sensor that is not only capable of respiratory applications, but can also measure heartbeat and provide security surveillance. As seen in Fig. 7.3A, the device in question comprised two active triboelectric layers: fluorinated ethylene propylene (FEP) and a latex membrane. It was secured to the abdomen and acted as an active air pressure sensor. The sensor detected breathing at a rate of 32 breaths per minute. As a side note, the device measured a heart rate of 72 beats per minute. Zhong Lin Wang's work displayed the multipurpose applications of TENGs, therefore, establishing an early foundation for developing other low-cost and easily-fabricated wearable TENG-based sensors.[14]

Building from this foundation, Yi et al. devised a stretchable rubber–based TENG (SR-TENG) that provided multi-sensing capabilities ranging from monitoring respiration to movements of limbs. The coupling effects of triboelectrification and electrostatic induction occurred between stretchable rubber and aluminum (Al) film layers. The SR-TENG served as an active sensor for diaphragmatic breathing and was capable of recognizing exhalation, inhalation, and breathing rate. Furthermore, it could characterize the bending angles of the knees.[15]

Zhao et al. revolutionized respiratory monitoring via the development of an interwoven metallic yarn, textile-based wearable TENG sensor. Copper (Cu)-coated polyethylene terephthalate (PET) warp yarns interwoven with polyimide-coated Cu-PET weft yarns produced a highly deformable and sensitive chest strap as shown in Fig. 7.3B. When attached to the chest, the device demonstrated an accurate respiratory depth and rate detection in real time and could distinguish deep, shallow, rapid, and slow breathing state. Moreover, the as-made TENG showed incredible washability in a standard washing machine with no damage after 20 tests. With its woven structures, the wearable textile-based TENG was remarkably lightweight and flexible compared to cotton fabrics while simultaneously displaying superior respiratory monitoring.[16]

By adapting an intelligent wireless respiratory monitoring and alert system, Wang et al. developed medical mask with an embedded TENG that was driven by airflow. Air was harnessed and converted into electrical energy by passing through an acrylic tube to agitate the polytetrafluoroethylene (PTFE) film, allowing for a constant contact and separation with the fixed Cu film. With this structure, normal exhalation can serve as airflow. The device characterized slow, rapid, shallow, and deep breathing based on different electrical outputs. Moreover, it could quantify the volume of air by the number of accumulated charges. Access to this data is crucial for patients with asthma or emphysema.[17]

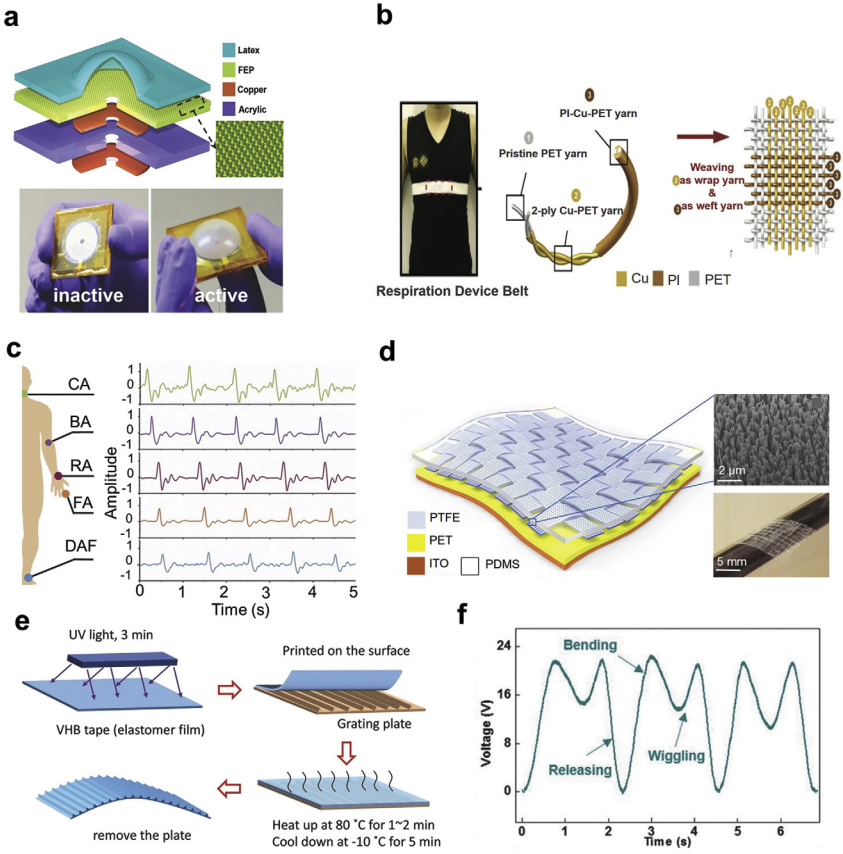

FIG. 7.3 TENG-based wearable physical sensors. (A) Schematic of the membrane-based triboelectric sensor for respiratory sensing. Reproduced with permission.[14] Copyright 2014, John Wiley and Sons. (B) Deformable respiration device belt made out of warp and weft yarns and the structure of the woven device. Reproduced with permission.[16] Copyright 2016, John Wiley and Sons. (C) Amplitudes of signal outputs of self-powered ultrasensitive pulse sensor on different arteries. Reproduced with permission.[20] Copyright 2017, John Wiley and Sons. (D) Schematic illustration of the weaving structure of self-powered pressure sensor for pulse waves. A scanning electron microscope image and the actual product are shown on the side. Reproduced with permission.[21] Copyright 2018, John Wiley and Sons. (E) Treatment of the top surface of the on-skin TENG. Reproduced with permission.[22] Copyright 2017, John Wiley and Sons. (F) Graph of voltage for measuring the arm muscle motion by the active motion sensor. Reproduced with permission.[24] Copyright 2018, John Wiley and Sons.

Advancing in the direction of wearability, Yun-Ze Long's group constructed a TENG-based fabric using polyvinylidene fluoride (PVDF) and polyamide 6 as the active materials. The device could characterize normal, deep, and rapid breathing in real time. Moreover, it could function as a self-powered tapping alert mechanism in critical health scenarios and notify designated people when the user's breathing stops.[18] The device's ability to become as an active fabric that could be directly sewn to become clothing makes it unique and special.

Above are some examples of innovative wearable physical sensors at the forefront of respiratory monitoring based on TENG. Due to TENG's advantages in being self-powered, stretchable, lightweight, durable, and much more, TENG-based devices have allowed for more long-term and high-performance sensors in this field.

7.2.2.2 Cardiovascular monitoring

Currently, pulses monitoring generally uses photoplethysmography and piezoelectric pulse transducers. These approaches can be expensive, complex, short-lasting, and unsuitable for wearable environments. Researchers have been exploring TENG-based wearable physical sensors for cardiovascular monitoring to detect a human pulse and address related issues.

Yang et al. developed the first bionic membrane sensor (BMS) that also served as the first wearable TENG cardiovascular sensor. The human eardrum inspired the design of the BMS. The two triboelectric layers for the single-electrode mode were a PTFE membrane and nylon. The pulse was determined by electrical outputs, induced by a dynamic pressure change when attaching the BMS to the skin. Even inearly development, the BMS could distinguish results from young and elderly patients by using an augmentation and reflection index. The researchers claimed that their device could potentially be utilized as a non-invasive wearable medical sensor to estimate the risk of cardiovascular diseases (CVDs).[19]

Ouyang et al. worked toward more intuitive wearability rather than skin-attached devices by incorporating wearable TENG on clothing with a wireless feedback system. The self-powered ultrasensitive pulse sensor (SUPS) for cardiac monitoring utilized Kapton and Cu films as the active triboelectric layers. The researchers integrated the SUPS, analog-digital conversion, 8M-bit data storage, and a Bluetooth chip to construct a wireless system. Indeed, the SUPS demonstrated superior capability to successfully detect differences in healthy subjects and patients based on their pulse wave velocity (PWV), a measure of arterial stiffness used in the diagnosis of arteriosclerosis. As seen in Fig. 7.3C, the device could measure at different arterial locations. These highly indicative data could be helpful in assessing CVDs.[20]

Active triboelectric layers can be organized within a fabric modality to further advance the wearability of TENG-based devices. Meng et al. developed a flexible woven self-power pressure sensor (WCSPS) for CVD diagnosis as shown in Fig. 7.3D. PTFE and PET were interwoven as the triboelectric layers, with indium tin oxide acting as an electrode. Similar to the previous device, the WCSPS was integrated into a wireless transmission system for use on a mobile phone. The system could continuously measure blood pressure and PWV. The graph of the data could be used to characterize cardiovascular conditions.[21]

Wearable TENG-based cardiovascular sensing has become one of the most researched concentrations in its field because of the feasibility of detecting pulses and the availability of past research. Although these are only a few

examples in this field's extensive research, cardiovascular sensing still remains as one of the most flourishing research topics. TENGs can provide cutting-edge technology to keep track of cardiovascular issues. Moreover, the versatility of TENG's wearability, ranging from patches on the skin to active textile sensors and its incorporation within the IoT, has innovatively helped to bring about the possibility of rapid cardiovascular diagnosis.[3]

7.2.2.3 Motion monitoring

TENG-based wearable sensors focus mostly on motion monitoring because energy generated from human motion goes hand-in-hand with the sensing capabilities of the device that can spontaneously provide motion monitoring. This section will delve into different types of wearable physical motion sensors ranging from small-scale motion, such as eye blinking and finger bending, to large-scale and full body motion detection, such as joint movement. Different material compositions and fabrication schemes will also be investigated to fully understand the dynamics of TENG-based sensors in this field.

To effectively serve as physical motion sensors, wearable physical sensors ideally need to be highly flexible, lightweight, and ultrathin. Indeed, Chen et al.'s elastic TENG met these demands by creating a sensor that operated as a second layer of skin on the human body. The sensor was fabricated by utilizing the single-electrode mode, as shown in Fig. 7.3E, by smearing carbon/silicon grease, that acted as an electrode, onto the surface of very high bond (VHB) films, that acted as dielectric elastomers. This device can be attractive to the youth as it can be applied as a body paint or temporary tattoo. The elastic TENG could fully be incorporated with the motion of finger bending and function properly during gripping, squeezing, and clapping motions while also feeling no resistance from the device. Due to its superior ultrathin thickness and stretchability that smoothly integrate with the skin, this TENG device could serve as an active sensory system or an external energy supply for electronic skins—soft conformable electronics that mimic functionalities of human or animal skin, artificial muscles, and soft robotics.[22]

Another wearable on-the-skin conformal TENG was constructed by Chu et al. to aid in communication. This ultrathin device consisted of polydimethylsiloxane (PDMS) and graphene with poly(methyl methacrylate) on a PET substrate. The researchers demonstrated its capability in assistive communication by wirelessly transforming analogous human motions to digital Morse signals and displaying the results on a mobile phone. This procedure has the potential to help individuals with speech impairments.[23]

Building off of stretchable wearable TENGs, Xuhui Sun's group utilized stretchable and transparent wrinkled poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) TENG (WP-TENG) for active motion detection. To fabricate the WP-TENG, the researchers blade-coated a conductive PEDOT:PSS film on a stretchable PDMS. The PEDOT:PSS film was grooved to make it wrinkled. The contact and separation with the human skin produced

an electrical output. The device could sense human joint bending and stretching by characterizing the output voltage's peak value (Fig. 7.3F) and the number of peaks. Besides acting as an active sensor, the superior energy-harvesting efficiency and active sensing ability of the WP-TENG could be integrated in future applications in electronic skins, soft robotics, and human-machine interactions.[24]

Another example of stretchable and transparent sensors is Wang et al.'s device that could detect and spatially map trajectory profiles. To achieve the goal of stretchability and transparency for their wearable tactile sensor, the researchers utilized stretchable and transparent patterned silver (Ag) nanofibers electrodes on elastomeric layers of PDMS. This device was unique in its integration with the game *Pac-Man*, in which the user commanded left, right, up, and down while wearing the device on their skin. This paper hypothesized future applications in tactile sensing in the form of touch pads, robotics, and wearable electronics.[25]

The bionic stretchable nanogenerator (BSNG), bioinspired by the electric eel, is a wearable TENG-based sensor with a unique application in underwater sensing. This device is capable of monitoring human movement in liquid environments and integration with a wireless transmission system. The BSNG was composed of two layers: a PDMS-silicone double layer and a deionized-water-filled chamber. The BSNG was fixed as a band to wear on the elbow and knee, of a volunteer while swimming breaststroke, freestyle, and backstroke styles and tread water. However, one limitation of this device was its large size. The researchers proposed improvements centered around smaller, thinner, and softer sensors.[26]

Later advancements in wearable motion monitoring TENGs involved textile-based large-scale body devices. Nowadays, many TENGs that have adapted the idea of stretchability as body movements involve bending which cause changes in the device shape. Yin et al. produced a stretchable and tailorable TENG from a nanofibrous membrane. Nanofibrous PVDF and thermoplastic polyurethane nanomembrane with an Ag substrate were the active triboelectric materials. The tailorable TENG detected different motions such as knee and wrist bending in slight, moderate, and sharp modes by examining the output voltage strength and frequency. Finally, this device offered superior air permeability compared to that of commercially available blue jeans, signifying long-term wearability.[27]

Lin et al. developed a pressure-sensitive, large-scale, and washable smart textile for sleep monitoring to explore full-body motion detection. Wavy-structured PET films were sandwiched between top and bottom fabrics, which laminated the arrays of conductive fibers. This device had the ability to record real-time sleep behavior of the user by collecting voltage generated from the body movement. The researchers mapped out the pressure distribution from the values of the voltage signal to identify sleep postures. Due to its simple device fabrication, smart textiles could be mass-produced.[28]

These examples of TENG-based motion sensors provide the basic backbones of current innovative research in the field. The dynamic design approaches, ranging from small-scale to large-scale body motions, supply users with various applications such as fitness,[26] healthcare,[28,29] language assistance,[23,30] and more. In the meantime, motion sensing is the most approachable field of TENG-based devices because of its intuitive nature of simultaneously harnessing biomechanical energy and converting those data to diagnose or detect physical changes.

The aforementioned TENG-based devices and their applications are only a few of the many innovations for wearable physical sensors. In addition, many of the studies only had expressed the potential applications of their devices without delving deeper in studying the applications themselves. However, it is still useful to summarize prospective insights on what can be available and hope that novel innovations can be established based on these current studies in wearable physical TENG-based sensors.

7.2.3 Piezoelectric nanogenerators

PENGs convert energy by utilizing piezoelectric materials to generate a voltage potential. Zhong Lin Wang's group first designed the PENG in 2006. The fundamental mechanism of PENGs will be detailed more specifically next. Multiple research studies have been conducted to examine the principle of PENGs and to develop a wide variety of flexible PENG devices. The following section will summarize the three working modes of PENG: AC PENG, direct current (DC) PENG, and noncontact AC PENG. Furthermore, several applications of wearable physical PENG sensors will be explored.

7.2.3.1 Introduction to piezoelectricity

The name "piezo" was derived from the Greek word *piezein (πιέζειν)*, which means press or squeeze. The piezoelectric effect was first proven by the French physicist brothers Pierre and Jacques Curie. Piezoelectricity is defined as a change in electric polarization when subjected to applied stress or strain. When this mechanical force is applied to a crystal, the anions and cations are displaced to produce an electric dipole moment, therefore, generating an electrical voltage. The direct piezoelectric effect is a linear relationship between the stress, σ, applied to a piezoelectric material and the resulting charge density, D.

$$D = d\sigma \tag{7.1}$$

where d (CN^{-1}) is the piezoelectric coefficient.

Piezoelectric materials include 20 classes[31] that are broken down into pyroelectric and nonpyroelectric materials. Pyroelectricity is described as the ability for materials to generate temporary voltage when heated or cooled. The positions of atoms in the crystal structure are slightly modified, leading to a change

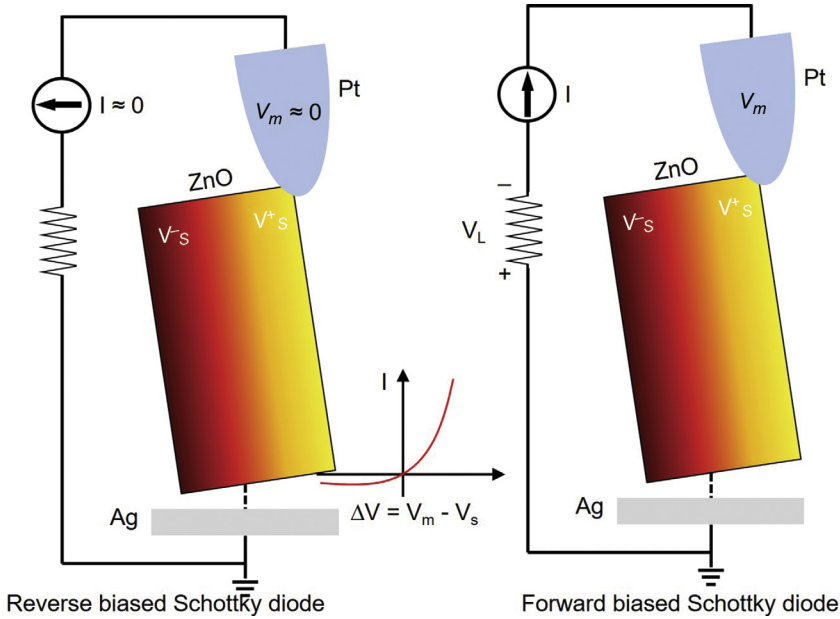

FIG. 7.4 Working principle of PENG. The AFM conductive tip comes into contact with the semiconductor ZnO NW at two reversed local contact potentials. The inset shows the Schottky rectifying behavior of the reverse- and forward-biased Schottky diode.[32]

in the polarization of the material. Pyroelectricity is broken down into ferroelectricity and nonferroelectricity. Ferroelectricity describes materials that have a spontaneous electric polarization which can be reversed by an external electric field.

Zinc oxide (ZnO) is deemed as a widely used and well-studied piezoelectric material. It falls in the category of pyroelectricity and nonferroelectricity. Zn^{2+} and O^{2-} form tetrahedral coordination. As a nanowire (NW), one side is connected to a fixed electrode and the other is settled. According to Fig. 7.4, when the driving electrode deforms the free end of ZnO NW, one side of the NW is compressed while the other side stretched, yielding a piezoelectric potential.[32] The Schottky barrier at both tips of the ZnO leads to electrical current generation by temporarily storing electrical energy in the ZnO NW. The external circuit connecting the ZnO NW will drive the electrons through the external load to reach a balanced state by based on the piezoelectric potential. Constant changes in the external force on the ZnO will produce a continuous current pulse in the external circuit.[33] Materials from the same piezoelectric category as ZnO also have a similar mechanism as previously described. Researchers have investigated ZnO's synthesis, composition, growth mechanism, and possible applications in many fields such as optoelectronics, sensors, transducers, and biomedical sciences.[34]

7.2.3.2 AC PENGs

Most conventional PENGs are based on the generation of an AC. Essentially, by looking at the mechanism of ZnO, one can understand the mechanism of AC PENG. Moreover, even PENGs fabricated on a flexible substrate that bends and stretches the NW, which is fixed on both sides by the electrodes, still generate an AC.[35]

To improve the performance of an AC PENG, the contacts at the two ends of the NW must be robust enough for the mechanical deformation to transfer from the electrodes to the NWs. The crystallographic orientation of the NWs should also be the same to ensure the alignment of the polarities of the piezoelectric potential. In addition, the NWs must be stretched and released synchronously. Finally, the Schottky contact between the NW and the electrode can be adjusted to help accumulate charges.[36]

7.2.3.3 DC PENGs

As most conventional PENGs are based on AC signal generation, external sources such as a battery or an increase in the PENG size are required to convert to DC. This limitation can also lead to reduced power efficiency. To address this issue, 2-D ZnO nanosheets, also known as ZnO NW arrays, have been developed to generate DC electricity and improve mechanical durability. A continuous layer of ZnO on the substrate serves as a large electrode connecting the NWs with a metal electrode. The conductive atomic force microscope (AFM) tip deforms the NWs and scans across the ZnO arrays in a contact mode. Fig. 7.4 demonstrates the process of DC generation. The platinum (Pt) tip has a potential (V_m) of nearly zero, making the metal tip-ZnO interface negatively biased or a reverse-biased Schottky diode. Current flows across the interface. When the AFM tip contacts the compressed side of the NW, the interface is a forward-biased Schottky diode and produces an increase in the output current and electrons can flow freely across the interface.[32,37]

To improve the performance of DC PENGs, some proposals have been discussed. First, the elimination of AFMs for making mechanical deformation will make the device more adaptable, mobile, and cost-effective. Second, having all the NWs work simultaneously and continuously generate electricity will enhance the electrical output. Lastly, harvesting mechanical energy in the form of a wave vibration from the environment will yield independent and wireless operations.

7.2.3.4 Noncontact AC PENGs

One example of a noncontact AC PENG is based on composite matrix conical NWs. The driving force for the flow of electrons in the external load is the induced electric potential difference across the plate electrodes. The advantages of noncontact AC PENG include its ability to better preserve electrons at the NW or electrode interface. It can also uniformly distribute the stress onto all

NWs. Lastly, with noncontact AC PENG, there is more freedom for the selection of the metal electrode. Unlike the contact-based PENG, this type of PENG does not need to form a Schottky barrier.[38]

7.2.4 PENG-based physiological sensors

Similar to TENG-based technology for physiological sensing, PENG-based sensors are well established due to their unique features in their self-powered mechanism, simple structural design, and ease of implementation. With the abundance of piezoelectric materials, it is not a surprise that PENG-based sensing is one of the most widely researched topics in the field of self-powered devices, with the industry goal of producing comfortable, flexible, and sustainable active wearable physical sensors. The following sections will go over PENG-based wearable physical sensors in cardiovascular and motion monitoring, voice recognition, and dermal and gastrointestinal sensing.

7.2.4.1 Cardiovascular monitoring

Besides triboelectric sensors, piezoelectric sensors for cardiovascular monitoring attract exciting research for their flexibility, durability, robustness, conformability, wearability, and more. Indeed, PENG-based sensors are essential to the burgeoning field of wearable physical sensors. In addition to being a self-powered device, PENG-based sensors are also advantageous in their integration with wireless transmission capabilities, which will contribute productively to the era of the IoT.

The inorganic PENG sensor based on lead zirconate titanate (PZT) thin film on an ultrathin plastic developed by Park et al. provides comfortable cardiovascular monitoring to the user. The complete attachment of the device on rugged skin allows for sensitive responsiveness to minuscule pulse changes from the surface of the epidermis. It was able to detect radial/carotid pulse signals in the near-surface arteries. Then, the pulse signals were processed and wirelessly transmitted to a smartphone in real time as systematically demonstrated in Fig. 7.5A.[39]

Unlike the aforementioned device, the flexible PENG-based sensor by Mandal's lab utilized bio-inspired piezoelectric materials, specifically fish skin. The material comprised self-assembled collagen nanofibrils, possessing a stable crystalline structure and nonlinear electrostriction effect. The fish skin–based nanogenerator (FSKNG) precisely measured real-time arterial pulses.[40]

Mandal's lab also developed another PENG sensor that, instead, used highly aligned Pt nanoparticles interfaced with 1-D PVDF nanofibers. By attaching the device to the wrist, arterial blood pressure and heart rate were determined. The researchers could use the readout data to quantify age-related heart conditions. The device's flexibility, biocompatibility, light weight, large-scale production, and cost effectiveness make it promising.[41]

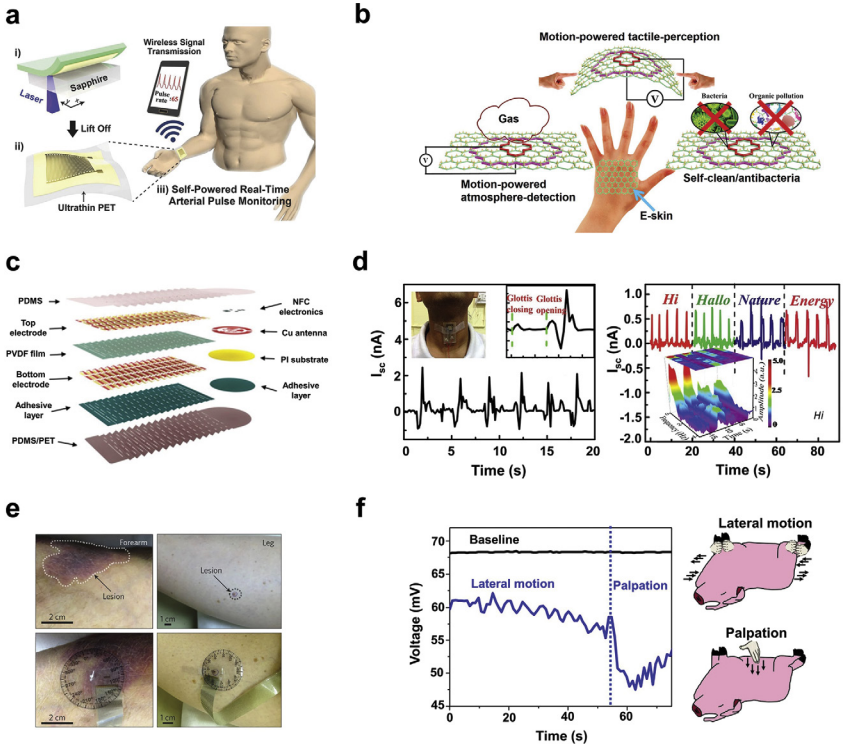

FIG. 7.5 **PENG-based wearable physical sensors.** (A) Fabrication process of the self-powered pressure sensor and its integration with mobile application for pulse rate measurement. *Reproduced with permission.*[39] *Copyright 2017, John Wiley and Sons.* (B) Structure of the flexible self-powered electronic skin with multiple functions. *Reproduced with permission.*[44] *Copyright 2017, Elsevier.* (C) Schematic illustration of the multilayered structures of the stretchable sensor. *Reproduced with permission.*[45] *Copyright 2019, John Wiley and Sons.* (D) Graphs of swallowing motion detection and speaking of different words.[40] *Copyright 2017, American Chemistry Society*. (E) Photograph of forearm/leg with/without an attached device. *Reproduced with permission.*[55] *Copyright 2015, Springer Nature.* (F) Graph of voltage obtained from lateral motion and palpation cycle in pig. *Reproduced with permission.*[56] *Copyright 2017, Springer Nature*.

Wu et al.'s PENG sensor that used selenium (Se) NWs instead of ZnO wires demonstrated great potential for self-powered biomedical devices by its exploration of a new piezoelectric nanomaterial. By successfully integrating Se NWs into a wearable physical piezoelectric device for PENG sensing, the radial artery pulse was successfully measured in real time on the wrist of healthy human subjects without an external power source. With the ability to detect small-scale biomechanical signals such as pulses, this device was unsurprisingly implemented into a multi-sensing application and will be further discussed in the subsection 7.2.4.3.[42]

Researchers have experimented with different materials besides ZnO NWs to improve PENG-based sensors. Usually, the sensors are often directly attached

to human skin to measure pulse rather than being incorporated into or as textiles. Nonetheless, some sensors could perform multifunctionally, sensing different physiological conditions at the same time.

7.2.4.2 Motion monitoring

Similar to their TENG-based counterpart, PENG-based wearable sensors also concentrate on motion monitoring. Due to their advantage of flexibility, these devices are commonly and popularly used in this field. Most motion sensors target small-scale movements such as from the digits, limbs, and the control of robotic arms using a human-machine interface. Moreover, researchers have begun incorporating these devices into passive and active textiles.

Early in 2013, Persano et al. aligned PVDF nanofibers as a piezoelectric sensor. The researchers developed a human motion monitoring device with light weight, low cost, and large-scale feasibility. The device was tested to measure vibration/acceleration and orientation by attaching the device to the arm or around the finger. Even at the nascent progress, the PENG sensor exhibited excellent output performance, inspiring future perspectives for upcoming PENG studies.[43]

A fascinating material system and device architecture established by He et al. was the PENG-based electronic skin made out of tetrapod ZnO and PVDF on a flexible fabric substrate as shown in Fig. 7.5B. As a hybrid composed of piezoelectric, gas sensing, and photocatalytic properties, this tetrapod ZnO sensor not only can deliver motion sensing but also can self-clean. By attaching the electronic skin on the elbow, bending and releasing motions could be recorded distinctively.[44]

Sun et al. addressed the limitation of stretchability in conventional piezoelectric sensors by applying a kirigami approach. Fig. 7.5C shows the layers of the sensor. By introducing a network of cut patterns onto a piezoelectric film, the team was able to induce anisotropic and local bending. While implementing stretchability, the electrical performance of the film was still retained. The kirigami-induced 3-D buckling also permitted air permeability while allowing for secured attachment onto many points of the human body. Ultimately, the purpose of this device was to function as a wearable sensor by measuring knee flexion. The authors claimed that it could also perform *in vivo*.[45]

Chenyang Xue's lab designed a high-performance stretchable PENG (SPENG). To achieve this, they implemented dispersed high-weighted PZT particles and Ag-coated glass microsphere fillers into silicone rubber matrices, in which all were solidified into an all-in-one structure. The SPENG acted as an active tension and gesture sensor for monitoring joint movements. As such, users such as athletes and convalescents can use the device as a smart wristband. Therefore, the SPENG was encapsulated in a fabric wristband and was designed to communicate wirelessly with a smartphone. Besides playing a role in personalized medicine, the authors claimed that the device could have potential values in cloud computing and Big Data Technology.[46]

Wu et al. integrated trigonal-structured Se NWs, instead of the commonly used ZnO NWs, into their wearable piezoelectric devices for self-power motion sensing. The ultrathin device was conformably and comfortably worn to successfully distinguish electrical signals in finger movement and vocal activities such as coughing, gargling, and swallowing. As a new class of piezoelectric nanomaterial, Se-NWs-based PENG sensors require more research to show their vast applications in the future, not only as sensors but also in energy and electronic applications.[42]

Bo Sheng Wang's lab implemented the unique fabrication technique of near-field electrospinning to develop a paper-based PENG sensor, featuring 3-D architectures of PVDF nanofibers. A piece of printing paper acted as a grounded conductive plate and a fiber collector. To demonstrate its application, the sensor was placed on the underarm of clothing and on the elbow to distinguish bending angles. As this device was only in its pilot stage, there was no integration of it to enhance the wearability despite its current paper-based design being uncomfortable on human skin and textiles. Regardless, paper-based sensors were a novel idea.[47]

Following the ultrathin concept, the 16-μm PENG-based active sensor by Lee et al. monitored tiny local skin deformations. By being ultrathin, the device was extremely flexible. The electrons flowed between the ZnO NW arrays and the Al electrode on an Al foil by anodization, on which the anodic Al oxide served as an insulating layer. The sensor was attached on the surface of an eyelid to track eye movement and monitor sleeping patterns, tiredness, and brain activity. It could be twisted around in loops without hindering the ability to efficiently generate energy output and function on any surface and shape of a biological entity.[48]

Tae Hyung Sung's lab took a unique approach to address transparency in piezoelectric sensors. To make the sensor transparent and flexible, they utilized boron nitride nanosheets as a piezoelectric active component and PDMS as a flexible element. Direct attachment on the skin at the elbow, neck, wrist, and knee allowed the sensor to sense motion and record different output voltages in real time. The differences in signal forms allowed for the characterization of which body part is moving.[49]

Another example of a transparent and SPENG sensor is Lim et al.'s graphene-heterostructured mechanical sensor. The lab claimed that because of the ultrathin, lightweight, and stretchable features of the device, it resulted in a high degree of comfort, superior adhesion, and aesthetically pleasing appearance. Integrating the sensor with a stimulator yielded a closed-loop interactive human-machine interface system to control a robotic arm and transfer feedback signals. When wearing the sensor on the lateral side of the forearm and the top side of the wrist, motions such as bending, pressing, and relaxing generate different electrical signals and cause the robotic arm to exhibit the same motion. The current system showed superior performance for robotic control.[50]

Flexible sensors are a popular trend in PENG research. Consequently, many studies have covered this topic with various designs. Linlin Li's lab developed

a flexible PENG sensor with the compelling features of dual-mode detection (pressure and curvature), by using polyacrylonitrile-C/ barium titanate (BTO) nanofiber film. Consequently, their design stood out from other types of flexible PENG sensors. The BTO nanoparticles enhanced the sensor's sensitivity for pressure sensing by compiling both piezoelectric and triboelectric effects. It measured swallowing, walking, and finger movements such as flexure and tapping as a multifunctional motion sensor. The authors believed that their device could be broadly used for medical diagnostics in the future.[51]

Despite using standard PVDF/ZnO nanofiber materials for their PENG sensor, Deng et al. devised a unique device featuring a novel cowpea structure. Instead of developing into medical diagnostic technology, this device primarily sensed motion for human-machine interaction. The user could control a robotic hand by wearing several of these sensors on their fingers.[52]

The FSKNG by Mandal's lab mentioned previously in subsection 7.2.4.1 could also sense motions of the wrist and produce a measurable output current. Fish skin could mimic the stretching and shrinking of human skin, therefore, making the detection of bending possible. Another possible motion-sensing application was laryngeal prominence, which could be measured by placing the sensor on a subject's throat. Consequently, this biopiezoelectric sensor is useful for breathing, such as for the early diagnosis of sudden infant death syndrome.[40]

Another example of a PENG sensor that could detect movements near the throat area is from Mandal's lab, which was previously mentioned in subsection 7.2.4.1. In their study, the Pt PENG was attached to the front of the neck and sensed downward movements of the thyroid cartilage that connects to the Adam's apple. This gave the sensor the ability to detect swallowing conditions such as oropharyngeal dysphagia.[41]

Maksim Skorobogatiy's lab developed an active textile PENG sensor to advance wearability. The sensor featured micro/nanostructured fibers with a soft, hollow polycarbonate core, surrounded by alternating layers of piezoelectric nanocomposites (carbon nanotubes (CNT) or BTO) and a conductive polymer (PVDF). The researchers wrapped the smart textile around a human subject's elbow to measure folding and relaxing states. The device was portable, wearable, and efficient, owing to the low-cost, textile materials.[53]

PENG-sensors have been adapted to different materials and motion applications such as sensing the motions of the limbs and throat and performing as human-machine interfaces. Moreover, many studies have prioritized low cost and large-scale production. As such, the future of PENG-based sensors toward industry and commercialization is inevitable.

7.2.4.3 Voice recognition

Acoustic sensors are a core technology for artificial intelligence and human-machine interactions. Current commercialized acoustic sensors are condensed microelectromechanical systems (MEMS). The disadvantages of MEMS are its low resonance and the need for an external power source. Bioinspired by the

basilar membrane, the self-powered flexible piezoelectric acoustic (f-PAS) sensor by Han et al. provided an accurate voice recognition ranging from 100 to 4000 Hz. To fabricate this device, the researchers used inorganic-based laser lift to fabricate a flexible PZT membrane, which mimicked the structure of the basilar membrane. The application of f-PAS includes voice and speaker recognition.[54] To build on this topic, the aforementioned FSKNG is suitable for developing a speech pattern/voice recognition system involving the detection of movements around the throat. Fig. 7.5D illustrates the ability of the sensor to detect swallowing motion and distinguish different words from the obtained signals.[40] Being reasonably new, there are still innovations for researchers to establish unique perspectives. In the future, acoustic sensors can likely be adapted to the fields of augmented reality and virtual reality.

7.2.4.4 Dermal sensing

One compelling application of PENG sensor targets *in-vivo* measurements of soft tissue viscoelasticity. Assessing soft tissues and organs can provide useful information for clinical diagnostics and treatments. However, currently existing methods are invasive. To address this, the PENG-based sensors can also be attached *ex vivo*. The nanoribbons of PZT provided soft and reversible lamination onto the skin for quantitative assessment and spatial mapping. The researchers also accounted for the pharmacological and cosmetic agents on the skin and different bodily locations such as the heart and the lung. For the proof-of-concept, a conformal modulus sensor (CMS) was fabricated, consisting of seven actuators and six sensors. Then, it was attached to two different skin regions (Fig. 7.5E): normal and lesion sites. Based on different moduli, the CMS was proven to reveal localized changes in skin properties.[55]

7.2.4.5 Gastrointestinal sensing

Ingestible electronics, especially self-powered ones, have not been focused on in the mainstream. Current applications are nonflexible and solid. Dagdeviren et al. addressed this limitation by incorporating a flexible PZT piezoelectric sensor that sensed mechanical deformation within the gastric cavity. Moreover, the device could be folded into a capsule for delivery and unfolded to settle on the stomach lining in immediate juxtaposition with the mucosa. It has the ability to sense fluids and food even during ambulation and ingestion in harsh *in-vivo* environments, as shown in Fig. 7.5F. This study in gastrointestinal sensing could aid diagnosis and treatments for gastrointestinal motility disorders and even for the assessment of obesity. This field still needs further investigation to transform the device into a wireless system with more bioresorbable materials.[56]

The above studies are only a few examples of the vast PENG research that currently exists. Due to the tradeoff in both TENG and PENG technologies, many current systems hybridize the two together to give more durable, robust, and highly efficient sensors.[57–61]

7.3 Non-self-powered wearable physical sensors

Beyond TENGs and PENGs, several other wearable physical sensors exist, which include capacitive, electret, FET, and resistive, all of which are non-self-powered. However, their presence in this field still provides different types of mechanisms and usefulness for certain applications in wearability.

7.3.1 Capacitive

The modality of capacitive sensing has been used in many areas such as for the measurement of liquid levels, humidity, and material compositions (touchscreen devices). This type of sensor has recently been adopted into wearable and ambient technologies as it can be altered in different materials and forms of wearability. Consequently, wearable physical capacitive sensors can be integrated into complex daily activities to monitor pulse, respiration, and electrocardiogram. Due to its small size and low price, the most used application is motion sensing.

7.3.1.1 Working principle

Capacitive sensors consist of a dielectric sandwiched between two parallel metal plates as shown in Fig. 7.6A. Capacitive sensors rely on the variation of the capacitance when the measured variable is applied to it (Fig. 7.6B, C). The capacitance, C, is given by

$$C = \frac{\varepsilon_r \varepsilon_0 A}{d} \tag{7.2}$$

where A is overlapping area of the plates, d is the distance between the two plates, εr is the permittivity of air or free space, and ε_0 is the dielectric constant.

7.3.1.2 Applications

The capacitive mechanisms provide promising applications in wearable physical sensing, especially due to their flexible and/or stretchable properties. Lipomi et al. reported skin-like capacitive sensors based on transparent elastic films of

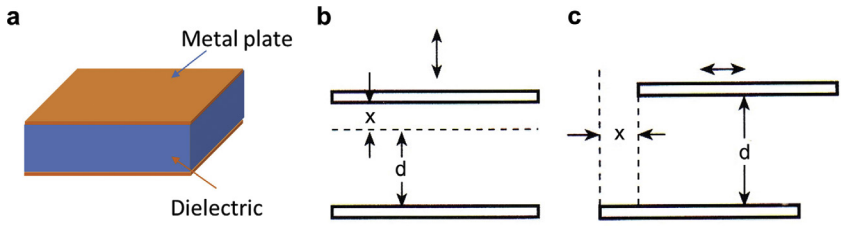

FIG. 7.6 Working principle of wearable physical sensors based on capacitive effect. (A) Setup and materials of a capacitive sensor. (B) Mechanism of a vertical movement. (C) Mechanism of a lateral movement.

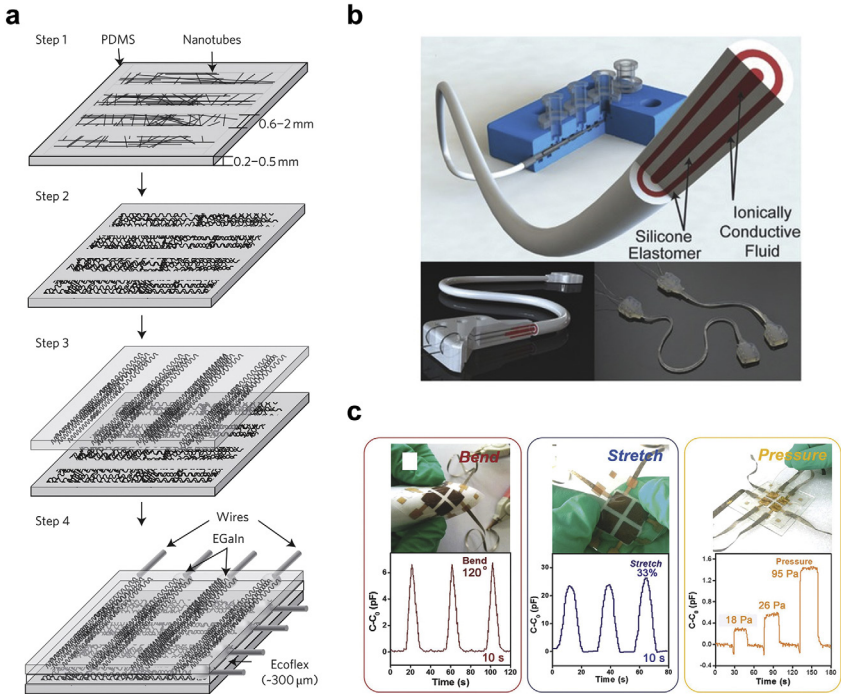

FIG. 7.7 Applications of sensors based on capacitive effect. (A) Steps of fabricating arrays of transparent and compressible capacitive sensors. At step 1, waves are produced from applying strain and releasing. At step 2, a second pattern substrate is positioned over the first. At step 3, two substrates are bonded to produce a dielectric layer. At step 4, liquid metal–coated electrodes are embedded within the device. *Reproduced with permission.*[62] *Copyright 2011, Springer Nature*. (B) Schematic illustration of multicore-shell and actual images of the capacitive soft strain sensor. *Reproduced with permission.*[63] *Copyright 2015, John Wiley and Sons.* (C) Application of flexible capacitive tactile sensor on bending, stretching, and pressuring by a hair. *Reproduced with permission.*[64] *Copyright 2016, Willey-Blackwell*.

carbon nanotubes. Although the device was less sensitive than others, it was the first transparent and stretchable device to detect pressure and strain in 2011. Fig. 7.7A shows the fabrication steps to make the device transparent and stretchable. The advantage of the skin-like properties included stretch reverse, ease of bending into hairpin turns, dynamic integrations with displays and solar cells, and conformation to biological surfaces such as skin and organs without wrinkling.[62]

Later on, Frutiger et al. proposed a new method for fabricating textile capacitive soft strain sensors (Fig. 7.7B) via multicore-shell fiber printing. The researchers claimed the wearable sensors could provide accurate and hysteresis-free strain measurements. The sensor was integrated into the textiles via sewing and weaving to detect walking gait and wrist bending.[63] Finally, Li et al. developed a flexible capacitive tactile sensor based on microstructured PDMS/Au

electrodes and a polystyrene microsphere dielectric layer. The resemblance to bionic microstructure from lotus leaves, which enhanced the sensor with high sensitivity and reproducibility, was a compelling feature of the device. It was characterized by distinct outputs for bending force, stretching force, and touching pressure as demonstrated by the graphs in Fig. 7.7C.[64]

Within the wearable applications, there can be dynamic variations in skin sites and clothing properties that interfere with the signal amplitude, dynamic range, and output. These variations would require further research in this field.

7.3.2 Electret

Recent advances in electret technology offer medical prosthesis applications, sensors, actuators, filters, and MEMS.[65] Electret-based materials have been implemented mostly as microphones. Electret-based devices consume low energy and are inexpensive. This section overviews the basic mechanisms of forming electrets and highlights some early and recently conducted research in the field of electrets as wearable physical sensors.

7.3.2.1 Working principle

An electret is a piece of electricized (polarized) dielectric material with quasi-permanent real charges. Over a hundred years ago, the term electret was coined as the counterpart of a magnet. In modern times, thermoelectrets and photoelectrets are important, especially for optoelectronic devices.[65]

An electret-forming material needs continuity and two flat surfaces, usually in the form of a sheet, ribbon, film-coated electrode, and much more. More specifically, an electret is a permanently charged material, formed from polarization in a high electric field by the process of space charge polarization in proximity to the electrodes such as shown in Fig. 7.8A, trapping of bulk charges inside the material, and dipolar polarization due to polar molecules. Another method of forming an electret is by applying corona or electron beam ejection with heat or light on high melting point materials. Depending on the material and application, certain techniques to form an electret are preferred.

7.3.2.2 Applications

In 1966, Sessler of Bell Laboratories was the first to introduce an electret condenser microphone (Fig. 7.8B).[66] This application of electret paved the way for tape recorders, stereos, telephones, and hearing aids. Advancements in this technology have led to miniature electret microphones on silicon chips, also known as microelectron-mechanical systems. Over time, researchers devised wearable sensing systems based on electret. One such application is the electret-based silicon sensor to detect sound and pressure as seen in Fig. 7.8C. This device was incorporated in hearing aids.[67] More recently, electret materials were hybridized with other materials to create hybrids such as piezoelectrets. The combination of materials as piezoelectrets provides flexibility, light weight, large, and stable

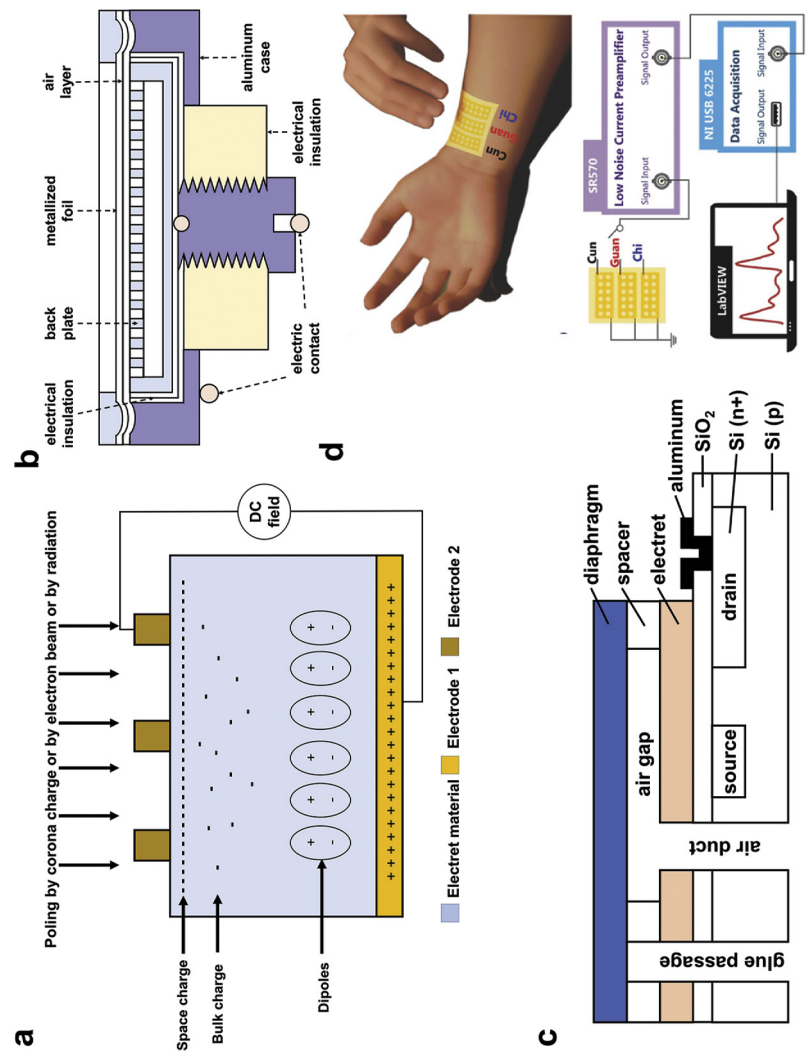

FIG. 7.8 **Electret material and electret-based sensors.** (A) Different mechanism of charge trapping in an electret material.[65] (B) A cross-sectional view of the original electret condenser microphone.[66] (C) Schematic drawing of the integrated electret pressure sensor.[67] (D) A system of signal processing in which data from the traditional Chinese medicine pulse palpation are transmitted, visualized, and analyzed. *Reproduced with permission.*[68] *Copyright 2018, John Wiley and Sons.*

piezoelectric coefficient for high sensitivity, and most notably, self-powered functionality.

Piezoelectrets are polymer foam–based space-charge electrets that possess a strong piezoelectric effect. Chu et al. produced one example using the piezoelectret system. The researchers developed a sensor capable of real-time and continuous monitoring of physiological signals. The piezoelectret system consisted of an FEP/Ecoflex/FEP sandwich structure and functioned on the working principle of pressing and releasing to induce electrical currents flowing in opposite directions. Like the previously mentioned study, as displayed in Fig. 7.8D, this one also focused on detecting human pulse with an add-on mobile application that received immediate updates of the results. A unique feature of the device's design was its inspiration from traditional Chinese medicine by mimicking the three-finger pulse palpation at the Cun, Guan, and Chi positions.[68]

In conclusion, besides applications in microphones or acoustic sensing, current electret and hybridized electret-based sensors are carried out in other platforms such as biomedical sensing as mentioned above, with a future goal of miniaturization and integration into other devices.

7.3.3 Field-effect transistor (FET)

In recent studies, FETs have progressed to be responsive to physical, chemical, and biological stimuli.[69] Conventional applications of FETs include logic circuits as signal amplifiers and sensors in (in)organic semiconductor materials. FETs display several compelling features such as light weight, portability, flexibility, and easy adaptation to sensors for data detection and collection, contributing greatly to the field of wearable sensors.[70]

7.3.3.1 Working principle

FET, also known as a voltage operated device, comprises a thin piece of a single type of semiconductor sandwiched between two slices of another type and are able to control the flow of current between the emitter and the collector using electric fields as seen in Fig. 7.9A, B. A FET is composed of three parts: the base, collector, and emitter. There are two basic types of FET: junction-gate device and insulated-gate device. The latter is commonly known as metal oxide semiconductor field effector transistor (MOSFET), which is the most widely used type. In Fig. 7.9C even more subtypes of FETs are illustrated.[71]

7.3.3.2 FET applications

FET applications, when focusing on wearable physical sensing platforms, are often used for wearable physiological monitoring as an amplifier when coupled with the other elements of a device. Devised by Nae-Eung Lee's group, as shown in Fig. 7.9D, the flexible reduced graphene oxide (rGO) FET for physical movements offered compelling features such as high sensitivity, stability, and

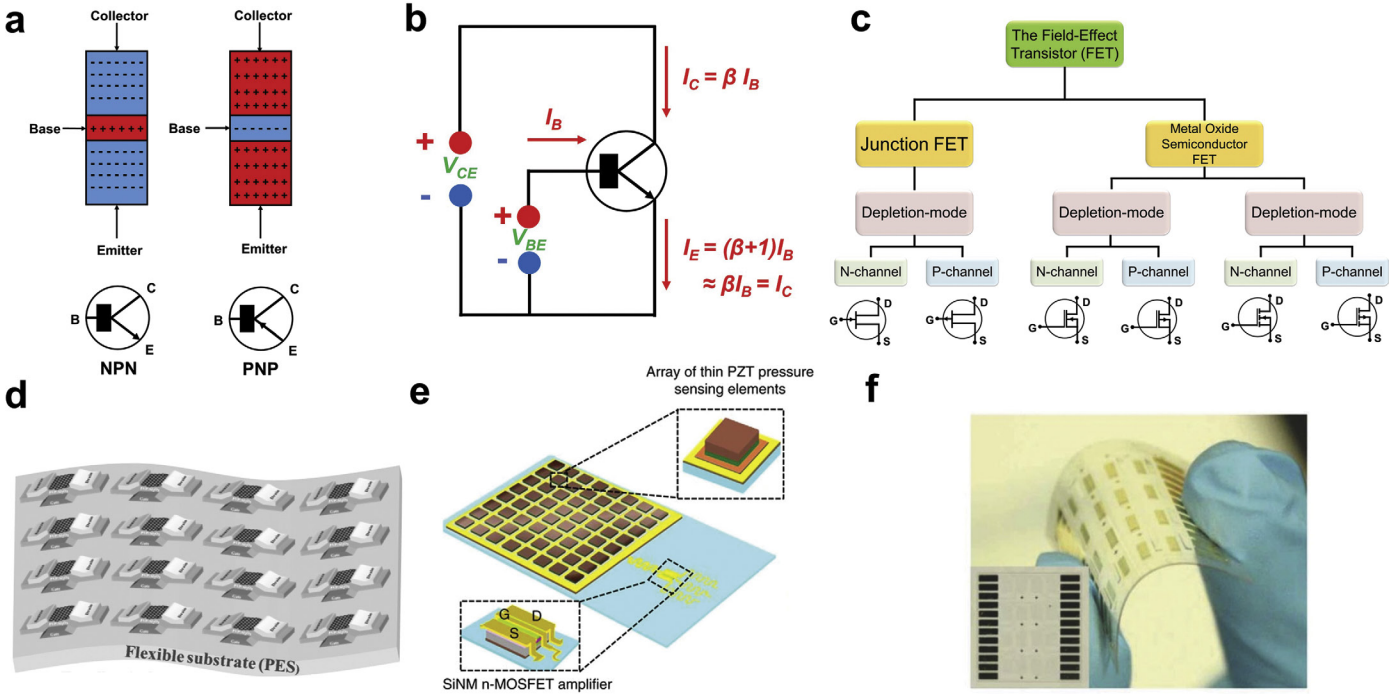

FIG. 7.9 The mechanism of FET and FET-related sensing applications. (A) Basic structure of a FET. (B) Conventional view of NPN bipolar transistor. (C) Breakdown chart of different types of FETs.[71] (D) rGO FET on flexible polyethersulfone substrate. *Reproduced with permission.*[72] *Copyright 2014, John Wiley and Sons.* (E) Device that includes a square array of piezoelectric thin-film transfer on PZT films. *Reproduced with permission.*[73] *Copyright 2014, Springer Nature.* (F) Photographic image of the active-matrix strain sensor array and inset of the optical microscopy image. *Reproduced with permission.*[74] *Copyright 2015, John Wiley and Sons.*

repeatability to detect tensile and compressive strains. The novelty of this sensor came from the incorporation of the rGO channel as the sensing layer, offering the ability to modify electrical resistance in case of a low-level strain.[72]

In another study, the Rogers' group manipulated the signals of the FET, and exploited the films of PZT in capacitor structures. These structures were connected to the silicon MOSFET (Fig. 7.9E), amplifying the piezoelectric voltage response of PZT and converted it to a current output. The sensors were utilized as an early detection of cardiovascular disease and provided continuous health assessments. By attaching it on the near-surface arteries, the device could measure the radial arterial augmentation index and the pulse pressure velocity.[73]

Cho's group provided another example of FET by coupling a piezopotential-powered active-matrix strain sensor array as displayed in Fig. 7.9F. The piezoelectric polymer, poly(vinylidene fluoride-co-trifluoroethylene), was easily patterned onto coplanar-gate graphene transistors. The resulting sensor was mounted onto a human finger to continuously monitor finger movements such as bending, holding, and releasing. This design concept also incorporated transparency and stretchability to conform to the human skin.[74] Indeed, these are only a few examples of the available FET-based sensors in this field.

7.3.4 Resistive

Developing highly sensitive and stretchable resistive sensors is an important goal for researchers in this field because most of the sensors are wearable and act as electronic skin. Human skin exhibits high flexibility and stretchability and allows us to sense surrounding pressure, temperature, humidity, pain, and so on. Through bioinspiration from such a versatile organ, researchers designed models that mimic the skin, called electronic skins, which are utilized in several fields such as wearable electronics and robotics. One of the proposed platforms is a resistive sensor that supplies the needs for flexibility and stretchability.

7.3.4.1 Working principle

Resistive sensors convert mechanical change such as displacement into an electrical output. They rely on the variation of the resistance of the material when applied by the measured variable. The resistance of a material, as shown in Fig. 7.10A, B, depends on the cross-sectional area or thickness, length, temperature, and conductivity. Additionally, the resistance changes according to the applied stress. Many resistors and conductors have a uniform cross-section and their resistance, R, is given by

$$R = \rho \frac{l}{S} \tag{7.3}$$

where ρ is the resistivity of the element's material, l is its length, and S is its cross-sectional area.

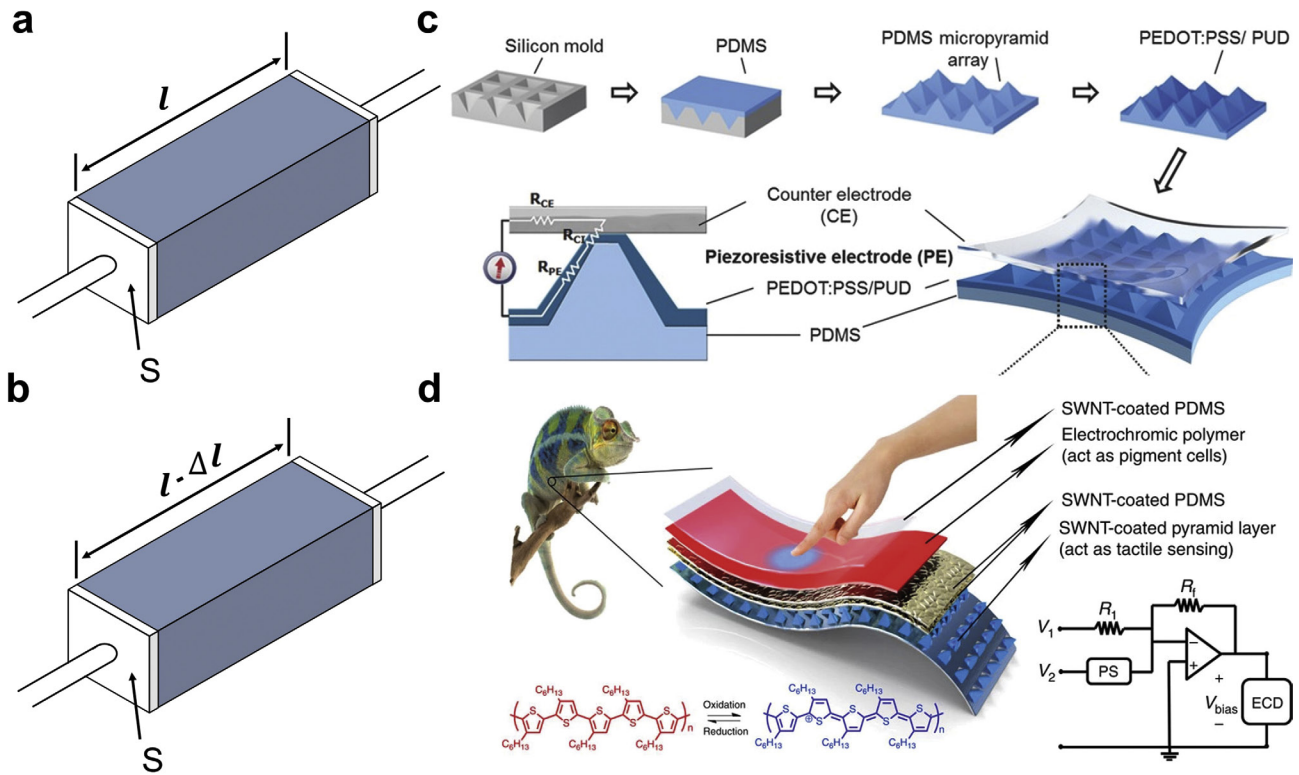

FIG. 7.10 **Working principle and example of a wearable physical sensor based on resistive effect**. A piece of resistive material with electrical contacts on both ends in (A) original state and (B) stretched state. (C) Fabrication process of PEDOT:PSS/polyurethane dispersion thin film coating the pyramid surface and circuit model for the sensing principle, relying on the change of the pyramid's geometry in response to pressure. *Reproduced with permission.*[75] *Copyright 2014, John Wiley and Sons.* (D) Structure of neutral and oxidized electrochromic polymer in poly(3-hexylthiophene-2,5-diyl, P3HT) and the schematic of the circuit layout and layers of the sensor. *Reproduced with permission.*[76] *Copyright 2015, Springer Nature.*

7.3.4.2 Applications

The development of highly stretchable and sensitive resistive sensors is one of the rising research topics in the field of electronic skins and wearable electronics. For this reason, many researchers concentrate on finding appropriate materials and fabrication methods to achieve a high degree of sensitivity and stretchability while simultaneously employing the resistive sensors in practical applications. In the following, certain applications which have been implemented are discussed in detail.

In this regard, Choong et al. demonstrated a highly stretchable resistive pressure sensor based on a conductive elastomeric composite. A layer of PEDOT:PSS was deposited on PDMS with micropyramid arrays. Fig. 7.10C details the fabrication process of the formation of the micropyramid array. The sensor was capable of detecting an increase in pressure caused by a leaf. To demonstrate its ability in biomedical sensing, the pressure sensor was integrated onto a bandage to be worn on a human wrist, positioned above the radial artery to monitor blood pressure. Furthermore, the sensor could mimic the ability of a bare human fingertip to sense texture via touch when it was wrapped around a human index fingertip. With these potential applications and as the first resistive sensor for noninvasive measurement of human pulse waveforms, this sensor was expected to be incorporated into wearable applications and could be powered by energy-harvesting devices such as TENGs.[75]

Similar to other types of sensors, reflective sensors also rely on bioinspiration. Chou et al. employed the remarkable ability of skin color change in chameleons and cephalopods to fabricate a stretchable electronic skin with interactive color changing controlled by tactile sensing. The tunable resistive pressure sensor detected, in real time, the applied pressure during visible color change. To make the resistive pressure sensor have adjustable and sufficient resistance values and range switching, the researchers utilized an elastic pyramidal-microstructure PDMS coated with a layer of single-wall carbon nanotubes. This sensor was then integrated with stretchable organic electrochromic devices (ECD). Fig. 7.10D provides a systematic overview of the color-changing resistive sensor and its layout. The interactive wearable device combined with the sensor and the ECD provided color change based on applied pressure and could be worn on the wrist. The color of ECD turned from red to green when a handshake was performed. No other applications were reported in this publication, but the authors expected the system to be implemented in military applications and smart robots.[76]

Chan's group developed another example of a pressure sensor. The piezoresistive sensor comprised PDMS microhump patterns of various sizes. On top of the PDMS layer acted as the active layer, made up of spin-coated PEDOT:PSS. By being flexible and highly sensitive, the device could measure the pressure and pulse of a normal and a pregnant woman when wrapped around the wrist. Additionally, the device could sense human body motion such as finger gesture, eye winking, and smiling. This new design of irregular PDMS microhumps

achieved several sensing applications while being reasonably sensitive, quick, and inexpensive.[77]

Another version of flexible electronic skin was produced by Park et al. with improvements in sensitivity, response time, and stability during temperature change. The design was based on CNT-composite elastomer films, comprising of interlocked microdome arrays, leading to giant tunneling piezoresistance. The sensor had the ability to sense human breathing patterns and voice vibrations. The gas would flow past the surface and deform the interlocked microdome arrays, causing a decrease in resistance. As the interlocked geometry was not ideal, the researchers hoped to optimize the alignment and position of the microdome arrays in the future. By integrating this platform to other sensors, they predicted that it could improve electronic skin applications in medical diagnoses and wearable sensing.[78]

Pan et al. designed a different platform of pressure sensors for electronic skin based on an elastic, microstructured conducting polymer (EMCP) film. The key innovation was found within the materials that were comprised of EMCP made out of interconnected hollow-sphered structures of polypyrene (PPy). PPy can elastically deform and recover and therefore, provide contact stability. Notably, the device only exhibited a slight change within the temperature range of –10 to 100 °C, which made it a potential candidate for usage in harsh environments. The authors did not delve into researching potential wearable applications of the sensor. However, they predicted that due to its temperature-withstanding ability, ultrahigh sensitivity, and quick response time, this device could be used in human-machine interface, robotics, and industrial monitoring applications.[79]

In summary, the design of (piezo)resistive sensors are capable of providing high sensitivity and stretchability. The various wearable applications can be helpful in the fields of biomedical sensing, prosthetic arms, human-machine interfacing, robotics, and much more. Many researchers also took into account the commercialization of their devices by considering factors such as low cost and large-scale fabrication. Moreover, the integration of these resistive sensors with other self-powered platforms, such as TENGs and PENGs, could be possible.

7.4 Conclusions and future perspectives

Wearable physical sensors are gaining momentum and moving forward quickly to match the pace of technological trends, with their future expected to address a few key challenges. First, power output enhancement is required for these devices to function for an extended period of time to meet the demands of continuous monitoring, particularly for self-powered sensors. To optimize the power output, innovative approaches in material selection, operation mechanisms, device structure, etc., can be explored. To be used on the human body, these devices also have to be highly flexible, sensitive, durable, and comfortable on the skin. For example, researchers should account for humidity due to

sweat by utilizing waterproof and water-resistant concepts and careful packaging techniques.

Additionally, commercialization is a critical challenge that needs to be addressed currently. With 266 companies, 431 devices, and an average price of $326,[80] the development for a class of next-generation powered wearable physical sensors is warranted by a compound annual growth rate of 24.7%[81] and $2.86 billion by 2025.[82] However, the aforementioned devices are limited to experimental lab-scale use. The need for a large-scale fabrication environment outside of a lab is necessary for supplying a large quantity of these devices. This capability is hindered by some devices needing manual assembly due to their complexity. To achieve mass production and reduce time and effort in device fabrication, researchers should investigate machine-fabricated approaches such as textile technologies. Leading to commercialization, creative designs are essential parameters to attract users in a competitive market of wearable physical bioelectronics.

The development of wearable physical sensors can significantly advance both healthcare and non-healthcare industries. In particular, the use of self-powered nanogenerators can provide an alternative power source to the traditionally bulky and environmentally unfriendly battery-powered devices in wearable bioelectronics. With the power of the IoT embedded in 5G wireless networks, wearable physical sensors are expected to become smarter, improve user interaction, advance endpoint security, and revolutionize the future of electronics.

This chapter introduced two types of self-powered wearable physical sensors (TENGs and PENGs) and four types of non-self-powered sensors (capacitive, electret, FET, and resistive). The fundamental mechanisms, structural designs, and examples of applications of these technologies have been demonstrated. This work is expected to provide some basic insights for readers and inspiration for future research in wearable physical sensors.

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Abbreviations

AC	Alternating current
AFM	Atomic force microscope
Al	Aluminum
Ag	Silver
BMS	Bionic membrane sensor
BSNG	Bionic stretchable nanogenerator
BTO	Barium titanate

CMS	Conformal modulus sensor
CNT	Carbon nanotubes
Cu	Copper
CVDs	Cardiovascular diseases
DC	Direct current
ECD	Electrochromic devices
EMCP	Elastic, microstructured conducting polymer
f-PAS	Flexible piezoelectric acoustic
FEP	Fluorinated ethylene propylene
FET	Field-effect transistor
FSKNG	Fish skin–based nanogenerator
IoTs	Internet of Things
MEMS	Microelectromechanical systems
MOSFET	Metal oxide semiconductor field effector transistor
NW	Nanowire
PDMS	Polydimethylsiloxane
PEDOT:PSS	Poly(3,4-ethylenedioxythiophene) polystyrene sulfonate
PENGs	Piezoelectric nanogenerators
PET	Polyethylene terephthalate
PPy	Polypyrene
Pt	Platinum
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
PWV	Pulse wave velocity
PZT	Lead zirconate titanate
rGO	Reduced graphene oxide
Se	Selenium
SPENG	Stretchable PENG
SR-TENG	Stretchable rubber–based TENG
SUPS	Self-powered ultrasensitive pulse sensor
TENGs	Triboelectric nanogenerators
WCSPS	Weaving self-power pressure sensor
WP-TENG	Wrinkled PEDOT:PSS TENG
ZnO	Zinc oxide

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Chapter 8

Wearable chemosensors

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8.1 Introduction

Chemosensors are defined by the International Union of Pure and Applied Chemistry (IUPAC) as "a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal".[1,2] Therefore, wearable chemical sensors or chemosensors are devices used to monitor the wearer's biochemical information by measuring the levels of metabolites (e.g., glucose, lactate), electrolytes (e.g., Na^+, K^+, Cl^-), and substances (e.g., drugs, heavy metals, alcohol). Compared with methodologies employed to access the body's physiological information, such as laboratorial blood analysis, and point-of-care devices, the greatest advantage of wearing a chemosensor is the ability to perform continuous monitoring of target analytes and capture their dynamic fast changes in real time, which enables efficient decision making and early diagnostic of diseases.[3] Devices used by diabetes patients for continuous glucose monitoring are one the most successful examples of wearable chemosensors.[4]

The basic requirements of wearable chemosensors include comfort of wear, reliability, and noninvasiveness. Comfort of wearing and user-friendly interface ensure the wearer's acceptance and compliance for the device. This feature is directly related with the properties of the materials used during fabrication, such as stretchable, flexible, and mechanically resilient materials integrated with a friendly interface.[5] Reliability is related with the analytical performance of the biosensors, including accuracy, precision, stability, and reproducibility. For medical applications, the analytical performance is utterly important and must be comparable with standard laboratory analysis once medication intake is directly entwined with the sensor's performance. Noninvasiveness is also related with comfort regarding pain relief, a noninvasive approach comprises the replacement of blood collection/analysis by alternative biofluids to acquire the body's instantaneous chemical composition, for this, biofluids such as saliva, sweat, tears, and interstitial fluid have been extensively explored.[3,6]

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Chemosensors can be classified into categories such as electrochemical, piezoelectric, calorimetric, pressure sensitive, or optical sensors. For wearable applications, optical and electrochemical sensors are the most convenient approaches once their signal transduction is simple and of easy integration with smart mobile devices.[7] Great efforts from several research groups have been driven toward the development of such wearable sensors, however, despite the important advancements in the field, challenges related with inherent properties of wearable sensors persist, such as uncontrollable conditions related to the biofluid, pH, temperature, drug-drug interaction, diet, and influence of external parameters such as humidity, temperature, and body motion. In addition, the concentrations of biomarkers are usually extremally low and their correlation with blood analyte levels varies for each person.

In this chapter, the criteria for selecting a biomarker, the analytical requirements, and current challenges will be presented. The discussion will focus on electrochemical and colorimetric sensors applied to sweat, saliva, ISF, and tears biofluids.

8.2 Chemical biomarkers

Biomarker discovery is a rapidly growing field in wearable technology and involves interdisciplinary collaboration between wearable developers and medical personnel to correlate chemical levels of molecules with specific diseases or conditions. Selecting the biomarker of interest is one of the most important steps in developing a wearable chemical sensor. There are important criteria related to the analyte choice that will further impose the device fabrication and application. First, to qualify as a potential biomarker, the biomolecule concentration in the body needs to correlate with health, sports, nutrition, or other physiological states. Thus, biomarkers can be divided into different categories, such as diagnostics, disease monitoring, sports, nutrition, drug compliance, drug screening, and safety. Secondly, the concentration of target molecules in alternative biofluids must be detectable and the time lag between the changes observed in blood and biofluid should not hinder the real-time interpretation of the acquired signal. In addition, the appropriated biofluid needs to be selected based on the molecule metabolism and partitioning.[8] Finally, once demonstrated that the biomarker is relevant and possible to detect in the specific body fluid, a comprehensive validation must be performed in order to correlate the concentrations measured in the alternative biofluid to blood concentrations. For this, parallel analysis must be performed in laboratory settings using standard techniques applied to the collected human samples (sweat, saliva, tears, ISF). Validation is one of the most challenging steps as sampling locations and timing windows can differ greatly from the human interfaced device, leading to deviations when comparing data obtained on-body and in vitro. Due to the complexity of the biofluids and their close correlation of composition with the wearer's lifestyle, universal correlation is extremely hard to achieve,

thus, individual blood calibrations are usually employed to ensure the sensor performance. Extensive study of real-time calibration using internal analytes standard is urgently needed.

8.3 Analytical parameters

Measuring the concentration of a single analyte from a complex matrix is challenging even in laboratory settings. Some samples need to be pretreated, the analyte measured several times, and the signal compared against a calibration curve. Wearable chemosensors have the difficult task of performing at the same level as laboratory-controlled analysis in an uncontrolled environment. The analytical signal acquired on-body can be classified as qualitative, semiquantitative, or quantitative. The first group comprises sensors whose response is yes or no, such as pathogens and pregnancy tests. Semiquantitative analysis includes sensors able to differentiate trends: high, medium, and low concentrations. In contrast, quantitative wearable sensors must report the concentration of analytes with statistical and analytical values; for this, parameters such as selectivity, accuracy (precision and trueness), stability, matrix variation, linear range, limit of detection (LOD), and limit of quantitation (LOQ) must be extensively studied.[9,10]

For measurements performed directly on the body, sample pretreatment is not an option, the selectivity of the sensor needs to be intrinsic to the recognition layer, such selectivity is achieved by using enzymes, bioaffinity receptors, and ion-selective membranes (Fig. 8.1). To ensure satisfactory selectivity, in vitro tests are performed by testing the sensor's response to major constituent substances of the biofluid and molecules with similar structure and activity as the target biomarker. Precision is related to sensor reproducibility; therefore, fabrication steps are major sources of deviations in sensor precision. Accuracy is related to how close the measured concentration is to the real value. Several parameters contribute to deviations in sensor accuracy including sensor biofouling, which can underestimate the values; and variations in pH and temperature which can change the recognition layer activity (e.g., gain/loss of enzyme activity). Low accuracy is also expected for analytes with poor correlation to blood. High accuracy is especially desired for medical devices, thus, to ensure accuracy, human samples must be collected in order to validate the sensor against gold standard methods such as liquid chromatography–mass spectrometry. Sensor accuracy is also related to other parameters such as stability once the signal measured might vary within time due drifting of the signal. Sensor stability is related to intrinsic and external factors, for example, intrinsic stability issues might be related to the biorecognition layer's own stability and immobilization. The use of biological elements in the recognition layer decreases the overall operational lifetime of the sensor once these biomolecules start to degrade. In addition, poor immobilization of the sensing layer can cause leaching of the same, hence, signal fluctuation. Even if a wearable sensor fulfills

FIG. 8.1 Wearable chemosensors used to continuously monitor the body's real-time chemical information. An electrochemical transducer (working electrode) is modified with a target selective (bio)recognition layer to translate the chemical interaction into a readable electrical signal. A colorimetric or optical transducer relies on the visual color or intensity changes of optically active molecules for qualitative, semi-quantitative or quantitative analysis.

all of the above requirements, it will still not be reliable if the linear range and limit of detection do not englobe the analyte concentration. In most cases, the concentrations of biomarkers in sweat, saliva, teras, ISF are in the range of nano to micro molar, thus, highly sensitive sensors need to be developed to differentiate and resolve very low concentrations of analytes. In order to increase sensor sensitivity, nanomaterials such as gold nanoparticles and carbon nanotubes are employed, however, the use of such catalysts and signal enhancers could raise concerns related to their biocompatibility and toxicity for the human body.[11]

8.4 Intrinsic challenges of wearable chemosensors

Concurrently with the requirements for reliable analytical performance, there are intrinsic challenges inherent to wearables that need to be addressed.[3,12] Mechanical deformation is an issue present in all wearable platforms. Wearable chemosensors are usually in close contact with the skin, clothes, or accessories, therefore, they must be conformal to the body surface and resilient to deformation, besides, the signal acquisition should be robust enough to filter or disregard motion artifacts that could lead to misleading readings. Variations in temperature are another important fact that wearables need to account for. As previously discussed, the biorecognition layer (e.g., enzymes) can display different activities under different temperatures, pHs, and salt concentrations. Thus, wearable

devices need to include auxiliary temperature, pH, and electrolyte sensors for real-time correction of the signal obtained. External factors play an important role for the sensor performance, if exposed to high temperatures, humidity, or light conditions, the recorded response might be negatively affected. External factors can also include different habits and lifestyles regarding diets and medications which can alter the biofluid composition with possible drug interaction and interference. Another common challenge for all wearable platforms is the safety of the materials used during fabrication. Complex mediators and nanoparticles are generally used to enhance sensor performance, however, when the sensor is on the body, the biocompatibility of such materials must be studied carefully.

8.5 Wearable platforms

There are several partitioning pathways in the human body responsible for transferring analytes from the bloodstream to the peripheral fluids.[6,8] This partitioning depends on the analyte properties and body physiology. The monitoring of a specific analyte should be matched with the correct biofluid where the analyte can be found, thus, the target biomarker will dictate the biofluid and wearable platform to be used.[6] In the next sections, the main challenges related to each biofluid will be discussed.

8.5.1 Sweat sensors

Sweat contains rich analytical information and can be readily accessed from different body locations.[13] Moreover, sweat can be generated on-demand via exercising or chemically stimulated through iontophoresis. Epidermal microfluidics is most appropriate for sweat analysis.[14] Sweat glands are responsible for pumping sweat through the inlets and channels of the microfluid layer ensuring a constant sweat flow over the detector to avoid the mixture of old and new biofluid, and at the same time, the fluidic system helps to minimize contamination and sweat evaporation (Fig. 8.2A).[15–17] Sweat from exercising has great advantages related with the production of large volumes of fluid and intense flow rate. This translates into a very small-time lag between sweat generation and analyte measurement once the detector chamber can be rapidly filled. Important considerations need to be taken when analyzing sweat biomarkers during exercising. First, sweat production is ceased once the activity is completed, this limits the monitoring to the time window of exercising and to health wearers capable of such activities. Thus, this approach is mainly applied to the study of athletic performance during sports or physical activities. During exercising the body temperature elevates increasing the probability of signal fluctuations due to changes in enzyme activity (for enzymatic sensors). Signal fluctuation can also arise due to pH changes. Sweat pH is very dynamic, it can fluctuate from 7 to 4 during intense activity causing possible interference in the analyte

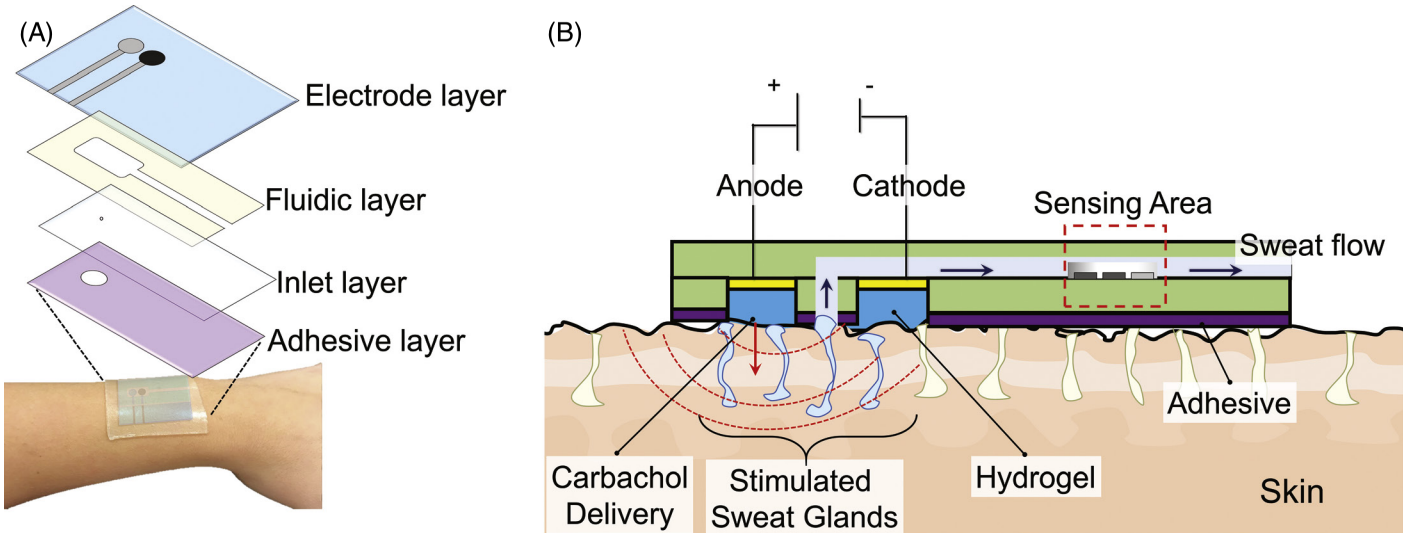

FIG. 8.2 Epidermal microfluidic devices for sweat sampling and analysis. (A) Example of a layered assembly of a microfluidic sensor patch. The first layer, in contact with the skin, is comprised of a skin adhesive layer with an inlet opening for sweat collection. This inlet can sample secreted sweat from sweat glands. Once the inlet is filled, it is guided to the reservoir of the fluidic layer where the detector is located. The outlet in the fluidic layer ensures constant flow over the sensor and biofluid replenishment. (B) Sweat stimulation via iontophoresis. A microfluidic layer containing a cathode and anode electrode used for simultaneous sweat stimulation, sampling, and analysis.

recognition reaction.[10] Mechanical deformation and motion artifacts are more prone to occur in wearable sensors used during exercise.[3] In spite of all these issues involved in sweat analysis during exercise, wearable devices properly designed to address temperature, pH, and flow variations can successfully monitor the target analyte with minimum deviation from the real value.[18]

For medical applications, chemically stimulated sweat is used for biomarker monitoring. Sweat can be readily stimulated by using cholinergic drugs, such as carbachol, delivery to the skin via iontophoresis. For an iontophoretic sweat induction, a cathode and an anode electrode are employed, and the sweat stimulating drug is loaded in the hydrogel used under the anode electrode placed in direct contact with the skin (Fig. 8.2B). Next, a mild current is applied between cathode and anode to deliver the positively charged sweat drug into the skin by electrostatic repulsion.[19] An epidermal microfluidic module can be integrated into the system to collect the stimulated sweat which enables the continuous monitoring of sweat analytes (Fig. 8.2B). Variations in temperature and composition of stimulated sweat are not so prominent as the ones occurring during exercising, however, it is important to notice that stimulated sweat can have different compositions from sweat produced during exercising. Motion artifacts are decreased for sweat obtained during resting. There are different challenges related to the monitoring of stimulated sweat. After consecutive iontophoresis steps, and several hours of sweat production, the stimulating drug can be depleted from the hydrogel ceasing sweat production, at this point, the device must be replaced in order to resume the monitoring. Concurrently, skin irritation and drug resistance can build up following multiple sweat stimulation. In addition, the delivery system consumes considerable power, requiring reliable batteries or energy sources to be integrated into the design. There are common challenges for sweat produced during exercising and resting. Sweat composition can vary depending on the location where the device is placed, and the composition can be altered by food and medication/drug intake. Overall, despite the great advantages and intense research toward wearable sweat sensors, the successful implementation is still limited by the unclear correlation of sweat analytes with blood.

8.5.2 Saliva sensors

Human saliva represents an attractive alternative for noninvasive monitoring of biomarkers once saliva collection is relatively easy, offering large volumes for chemical analysis. Saliva composition is rich in metabolites and electrolytes molecules with good blood correlation.[20] However, monitoring saliva biomarkers is one of the most difficult tasks. Saliva is a very viscous fluid containing several contaminants ranging from large proteins and bacteria to remaining food debris. Electrochemical detection of saliva biomarkers usually requires a pretreatment step involving either filtration, dilution, or both. Therefore, designing a wearable salivary sensor is extremely challenging. Mouthguards[21,22] and tooth

enamel[23] have been demonstrated as promising saliva-based wearable devices (Fig. 8.3). Common challenges for these platforms are the strong biofouling effect, the integration with electronics, and the use of alternative nontoxic components in the recognition layer. Moreover, the correlation of saliva analytes with blood can be compromised in the presence of high saliva flow (analyte dilution) or internal bleeding in the mouth (overestimation of the analyte). The combination of these challenges has hindered the development of wearable salivary sensors, even though saliva represents a biomarker-rich accessible biofluid and offers new sensing opportunities.

8.5.3 Interstitial fluid sensors

Interstitial fluid (ISF) is the fluid surrounding the cells in the extracellular medium. It is originated from small molecules that diffuse from blood capillaries to the cells. Thereat, there is an elevated correlation between ISF analytes and blood composition, making ISF an attractive biofluid for biomarker monitoring. ISF is currently one of the most reliable biofluids for medical applications. Nevertheless, ISF is not readily available, the most immediate accessible ISF is underneath the epidermis, the most external skin layer. Wearable ISF monitoring devices rely mainly on two approaches to access ISF, either by applying reverse iontophoresis (RI)[24,25] or by epidermal microneedles.[26,27] RI is used to extract ISF molecules to the skin surface, it consists in employing a hydrogel-based cathode and an anode electrode to apply a mild current through the skin to induce ion migration. Positively charged molecules migrate toward the cathode, while negatively charged molecules migrate to the anode. Because the skin is naturally negatively charged, the flux of positively charged molecules induces an intra skin electro-osmotic flow net to the cathode, provoking the movement of neutral molecules, such as glucose, toward the same electrode (Fig. 8.4A). Then, the molecules are accumulated and measured in the hydrogel. Skin irritation due to the electrical current and the lack of flow on the sensor (leading to accumulation of analytes) are the major drawbacks of this methodology. Microneedles are small enough to penetrate just the epidermis to sample or measure analytes in ISF (Fig. 8.4B). Hollow microneedles integrated into pumps can be used to sample ISF, while electrochemical biosensors can be placed on solid microneedles for continuous in situ detection.[26] Because of their small sizes, these needles do not reach any nerve system, thus, the process is painless and minimally invasive. Biofouling is the major challenge regarding ISF-based sensors, the body's response to foreign objects can hinder the performance of wearable microneedles rapidly, therefore, great efforts are driven toward antifouling strategies for these implantable devices. Considerable advances have been made in the field of wearable ISF devices, especially regarding the continuous glucose monitoring for diabetes patients, where minimally invasive devices are already commercialized to monitor glucose in ISF for weeks upon implanting the sensor under the skin.

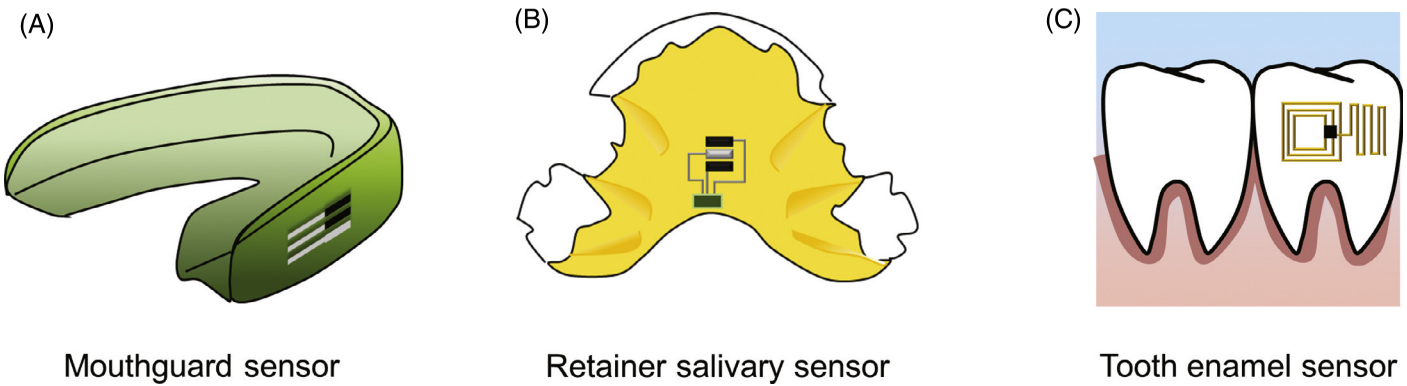

FIG. 8.3 Examples of platforms for saliva-based wearable sensors. (A) Chemosensors can be integrated into mouthguards for monitoring saliva biomarkers during sports or sleep. Electronics can be embedded in the mouthguard structure and the collected sensor signal can be wirelessly sent to a smart device. (B) Retainers and (C) tooth enamels can be used to monitor saliva biomarkers during daily activities, food debris, and internal mouth bleeding are major interferents for these saliva sensors.

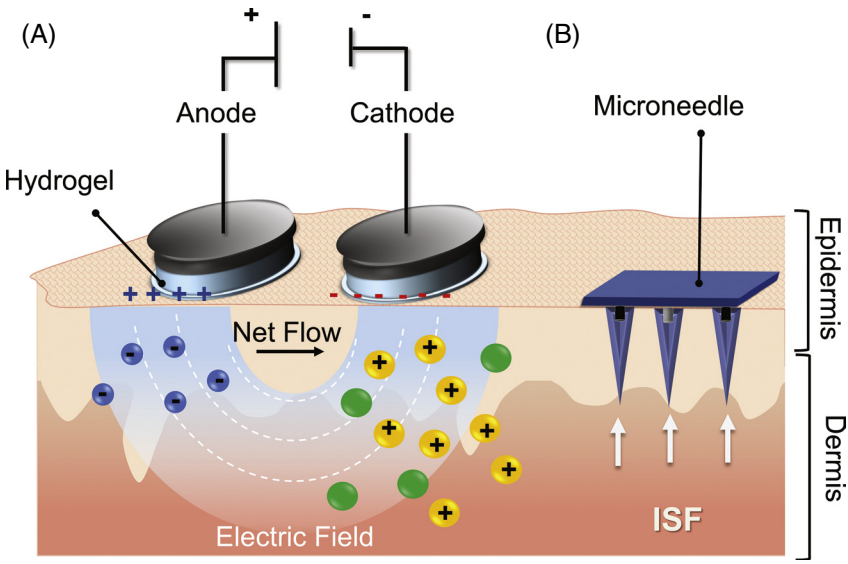

FIG. 8.4 Common methodologies for accessing ISF. (A) Reverse iontophoresis employs hydrogel-based cathode and anode electrodes. A mild current is applied between these electrodes to induce ion migration, positively charged molecules migrate to the cathode and negatively charged ones migrate to the anode. Because the skin is naturally negatively charged, there is a higher density of negative charge on the cathode, provoking a net flow of ISF to this electrode that carries neutral molecules (green spheres) with the positive ones. (B) Microneedles can access ISF by piercing the skin epidermis. ISF can then be sampled or measured in situ.

8.5.4 Tear sensors

Tears are essential to lubricate and protect the eyes, they are secreted by lachrymal glands upon physical, chemical, or emotional stimuli. Analytes present in lacrimal fluid have a close correlation with blood, therefore, wearable tears sensors are a very promising platform.[28] Nonetheless, the great challenge in accessing tears has hindered the development of tear-based biosensors. There are mainly three types of tears; reflex, emotional, and basal. Biomarker concentration varies within the different types of tears, mainly due to dilution effects. For example, reflex tears are produced to wash away any harmful particles from the eyes, therefore, they are generated in large volumes, thus, causing severe analyte dilution and loss of blood correlation. Basal tear (fluid layer always present in the eyes) is the most promising for biomarker monitoring once its composition correlates very well with blood. However, the low volume of this type of tear and its sensitive location limits the development of such wearable platforms (Fig. 8.5A). Contact lenses and spring-based sensors have been demonstrated for basal tears analysis.[29–31] In general, any tear collection or sampling protocol can cause eye irritation. Wearing contact lens modified with chemicals and embedded electronics in direct contact with the eyes can facilitate infections

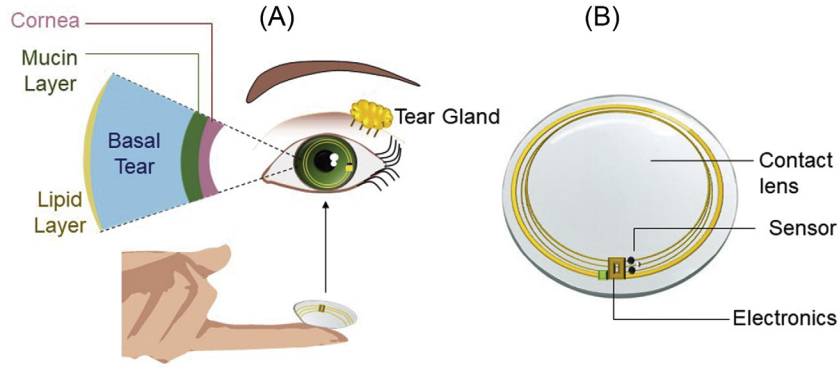

FIG. 8.5 Contact lens as a tear-based wearable platform. (A) Contact lens measures tear analytes from the basal tear, permanent fluid present in the eye. (B) The chemosensor and electronics can be enclosure inside the contact lens structure. The signal can be acquired electrochemically and sent via the wireless system, or optically via a smartphone application-based image analysis.

apart from decreasing the field of view due to the embedded electrodes, athenea, and battery. Furthermore, the use of contact lens can limit the access of oxygen to the basal tear fluid under the contact lenses, causing poor sensor performance and harm to the eye (Fig. 8.5B).

8.6 System integration

Several techniques, such as thermal, electrochemical, and optical transductions can be used to translate the response from the sensors into a readable signal.[6,9] Electrochemical and optical transduction modes are the most used for wearable chemosensors, while thermal and mass transduction are mostly implemented for monitoring physical parameters, such as motion and temperature.[5,6,32] Wearable electrochemical devices consist of the measurement of the electrical signal generated directly from the chemical reactions on the electrodes or interaction between the target biomarker with the sensing electrodes. Electrochemical sensors can offer a fast response, requires low power, besides enabling wireless signal transmission and system miniaturization (Fig. 8.6A).[33] Although electrochemical sensors present considerable advantages for wearable devices, they may be subject to surface fouling effects and requires a sustainable power supply. Great efforts have been driven toward alternative power sources for wearable devices including biofuel cells powered by fuel present in the biofluid of interest.[34,35] On another note, optical wearable devices monitor molecules with significant absorbance or colorimetric properties. Such colorimetric sensors usually do not rely on an external power source for generating their signal, instead, they rely on changes in color or intensity to indicate the presence, absence, or different concentrations of the analyte. For this, pH-dependent molecules are often used as a primary or secondary probe to monitor

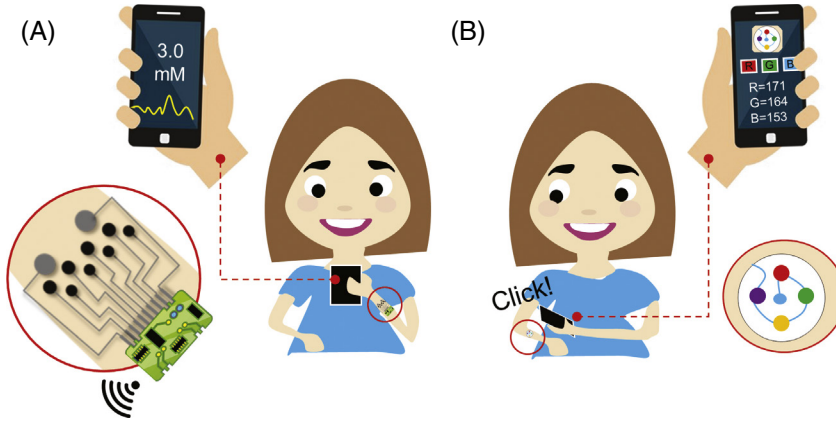

FIG. 8.6 Integrated electrochemical and optical sensors. (A) Example of epidermal electrochemical wearable sensors and wireless signal acquisition. The signal is continuously sent to the smartphone without any action from the user. (B) Example of an epidermal colorimetric wearable sensor and signal acquisition by image analysis. Signal recording is not continuous once the user needs to act (take a photo) in order to perform a reading. The smartphone calculates the intensity of the color and translates it into a concentration.

color changes of reactions or byproducts.[15] One of the main drawbacks of colorimetric techniques is the resolution, small variations in tonality can be hardly discriminated by the naked eye. However, the use of images captured and processed by smart phones have been used to overcome such challenges in order to develop more sensitive colorimetric sensors. In addition, specialized chambers or readers can be coupled to the phone to minimize the influence of the ambient light while acquiring an image and to ensure consistent and trustful readings in any light condition. The integration of colorimetric sensors and smart devices has enabled the development of more complex colorimetric systems based on absorbance, luminescence, or fluorescent emissions by adapting smartphones to function as a spectroscope.[36] Despite the large availability of molecules with optical properties, and the battery-free and low-cost features of optical devices, the multiple steps for signal acquisition and relatively high detection limits of these devices are still a critical bottleneck (Fig. 8.6B).

8.7 Conclusions

The development of wearable chemosensors is fast evolving and wearable glucose sensor is already commercially available offering continuous and accurate glucose monitoring via ISF.[37–39] Increasing investments are currently driven toward the development of reliable sweat sensors, and to the discovery of new sweat biomarkers related with health, nutrition, or sports fields. Sensor stability and analytical performance are the main issues responsible for delaying the launch of these sensors. Existing sweat platforms are well developed and at the

verge of commercialization, these include sweat epidermal fluidic devices for monitoring sweat loss and semi-quantitative readings of electrolytes. Efforts should be direct toward enzymatic sensors to improve their stability and operational lifetime. With the prospects of a great outcome, new applications for wearable chemosensors are frequently studied. For example, machine learning[40,41] has been adopted to reinforce chemosensors toward real-time feedback systems applied to nutrition,[42–44] stress management,[45] medication compliance,[46,47] and drug delivery.[48]

Personal safety has also been explored by means of wearable chemosensors. Safety wearables can identify threats (explosives, nerve agents) and hazard substances (secondhand smoking, pollution) in the wearer's immediate environment to send an early warning of exposure. Furthermore, the wearable concept can be extended beyond the human application, wearable sensors can be applied on food, animals, plant protection and water reserves for quality control. Additionally, the integration of wearable chemosensor and robotic limbs can drastically improve the patient's quality of life by offering sensory experiences such as temperature, texture, and humidity. More efficient solutions for the intrinsic challenges inherent to wearable chemical devices have been studied with a great rate of success. In the very near future, knowing the body's instantaneous chemical, biological and physical parameters will be as easy as looking at an ingredients label on a can of food.

Acknowledgments

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List of acronyms

IUPAC	International Union of Pure and Applied Chemistry
ISF	Interstitial luid
LOD	Limit of detection
LOQ	Limit of quantitation
RI	Reverse iontophoresis

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Chapter 9

Wearable Biosensors

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9.1 Introduction

A biosensor is a device that measures a physical or chemical interaction with an analyte by generating signals that correspond to the amount of target analyte (ions, pH, proteins, nucleic acids, etc.) in the sample. There is a plethora of uses for biosensors, including diagnostics and disease monitoring, drug monitoring, and biomarker detection, and they are generally used with a body fluid such as blood, urine, sweat, saliva, or interstitial fluid (ISF) which contains the analyte of interest.

Wearable biosensors are now emerging in the laboratory, with promise to build on the historical success seen for conventional optical and electrical measures such as heart rate monitors, and chemical-specific measures such as glucose meters. There have been numerous attempts to extend the utility of conventional optical and electrical measures to biochemical measures beyond blood oxygenation (pulse-oximeters). Unfortunately, there are no other optical probes naturally in the body such as hemoglobin, and the road to use optical measures for analytes such as lactate and glucose has only experienced repeated failure to meet clinically expected measurement standards.[1,2] It is clear at this point, that if more things are to be measured from the body, additional biochemical access and biosensors are needed for those biomarkers. This chapter focuses on the current status of the future of wearable technology, which will likely primarily involve biochemical sensing with wearable-accessible biofluids such as ISF and sweat. The chapter reviews each biofluid briefly and provides a summary of the latest technology advances for each. ISF and sweat are chosen as the fluids of interest because they are more easily accessible in continuous form than saliva, tears, or urine.[3] As will be seen in the review, other than continuous glucose monitoring in ISF, the field is generally unexplored with most technologies limited to research and development demonstrations.

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9.2 Noninvasive biosensing: eccrine sweat

9.2.1 Sweat as a biofluid source of analytes

Sweat comes in two forms: eccrine and apocrine sweat that are produced by eccrine and apocrine glands, respectively. Apocrine glands secrete oily sweat through a hair follicle and are limited to the axillae (armpit) and groin. While apocrine sweat may contain interesting analytes as it gains its characteristic odor from bacterial decomposition, the difficulty of access to these regions of the body limits its use cases.[4] Eccrine sweat is easier to collect and is fit for wearable, continuous devices so we will further limit our discussion to it. A diagram of the eccrine sweat gland is shown in Fig. 9.1.

Eccrine sweat glands cover the majority of the body's surface. The base of the gland, termed the secretory coil, is in the 5–40 μm diameter range and

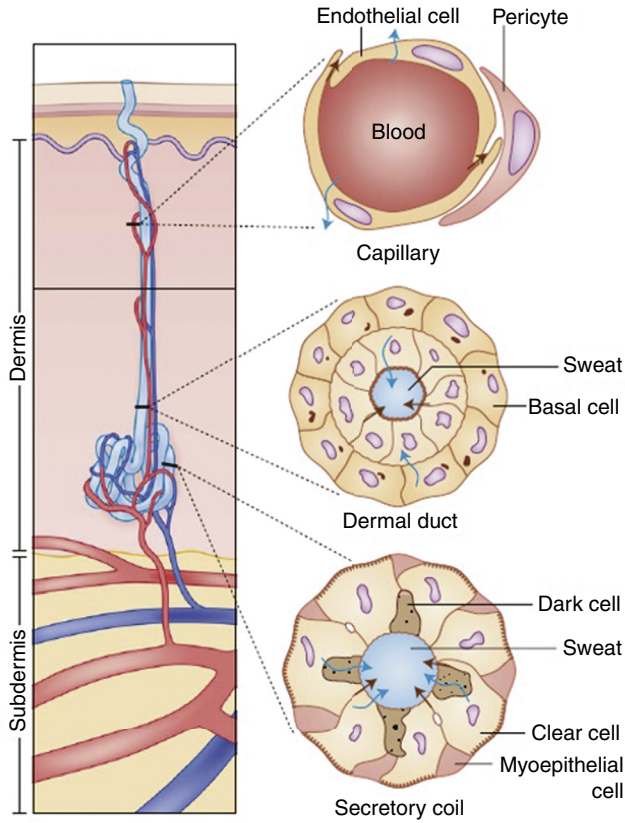

FIG. 9.1 A diagram of the eccrine sweat gland in the dermis as well as diagrams of the endothelial membranes around the capillary, dermal duct, and secretory coil. Note the thickness of the membranes and their ability to transfer analytes to sweat. *Adapted with permission from reference,[3] Copyright 2019, Springer Nature.*

is located in the dermis, the second and thickest layer of the skin. The coil is 2–5 mm in length and has a cell wall, or epithelium, 1–3 cells thick.[5] The coil is highly vascularized and surrounded by ISF. Eccrine sweat glands have a dermal duct that is continuous with the secretory coil. The dermal duct travels through the dermis and epidermis, or outermost layer of skin, to the skin's external surface. This duct is ~2 mm long, with a 10–20 μm inner diameter and double layer of stratified cuboidal epithelium—a special type of epithelium designed for secretion and excretion.

The main function of sweat glands is thermoregulation. Sweat is produced and excreted to the skin's surface where it evaporates and lowers body temperature. Sweating also facilitates excretion of water and electrolytes as well as protection of the skin from bacterial colonization by preserving the acid mantle. It is these functions in combination with the structure of the sweat gland that give rise to sweat's chemical composition from which we derive its importance in biosensing and device creation.

To produce sweat, receptors on the secretory coil are activated leading to chloride secretion inside the coil. The negatively charged chloride ions draw in mainly Na^+ and some additional positively charged ions. Na^+ ions travel along the cell membrane due to transmembrane proteins that facilitate a net negative potential along the membrane surface.[3] The flow of positive charge across the membrane creates electro-osmotic flow into the secretory lumen. Furthermore, water from ISF travels through aquaporins, water-specific channels in the endothelium, as well as paracellularly, or between cells, following the negative osmotic pressure of the secretory coil created by the elevated Na^+ and Cl^- concentrations. This entire process is pulsatory rather than a continuous flux.

Sweat secretion rates can vary from 0.1 to >10 nL/min per gland, with gland densities between tens and hundreds of glands/cm^2 dependent on the location on the body.[5] This allows for rates ranging from 1 nL/min/cm^2 to thousands; however, these numbers vary greatly based on activity, body temperature, the individual being tested, and hydration. Heikenfeld et al noted that the pressure "P" needed to penetrate a hydrophobic pore of radius "r" follows the equation $P = 2\gamma/r$, where "γ" is the surface tension and $\gamma \approx 70$ mN/m.[3] Sweat glands are able to generate pressures reaching 70,000 N/m^2, and are thus able to penetrate a pore up to 2 μm.[5] While higher sweat generation rates are ideal for fluid collection, they may lead to dilution of important biomarkers that increases detection difficulty. As a result, the most promising analytes to measure in sweat are hydrophobic small-molecules such as drugs and hormones, because such analytes easily diffuse through tissue, and therefore from ISF and blood into the inner lumen of the sweat gland with little or no dilution.[3] A list of some common analytes and their concentration in sweat can be seen in Table 9.1. This concept will be explored more thoroughly in the following section where specific technology demonstrations have exploited hydrophobic small-molecule detection in sweat.

TABLE 9.1 Comparison of relevant biomarkers in sweat and plasma. For sweat concentrations (a) indicates active channels or actively locally generated concentrations, (p) indicates passive partitioning into the fluid, and (fd) indicates possible high flow rate dependency. Adapted with permission from reference,[3] Copyright 2019, Springer Nature.

	Na^+	K^+	Lactate	Glucose	Cortisol	Drugs	Cytokines	Antibodies
Molecular weight (Da)	23	39	90	180	362	Mostly hundreds of Da	More than five to tens of kDa	Hundreds of kDa
Lipophilicity	Very low (charged)	Very low (charged)	Very low (charged)	Low (hydroxyls)	High	Often high	Very low	Very low
Blood plasma	135–145 mM	3.5–5 mM	0.5–10 mM (resting to nonresting)	4.1–6.9 mM (venous, resting)	Hundreds of nanomolar total; tens of nanomolar unbound fraction	Mostly equivalent to unbound in plasma	pM to nM	Varies; total ~0.4–16 mg/mL
Sweat	Tens of millimolar (a)	~5–15 mM (under debate)	~5–10's mM (a,p,fd)	~1% of plasma (p, fd)	Unbound similar to plasma (p)	Many equivalent to unbound in plasma (p)	<0.1% of plasma (mainly p, some a)	Local or very highly diluted (a,p)

9.2.2 Sweat biosensing devices

Sweat biosensing has been underdeveloped until recently because it was unknown that sweat can be a valid source of many analytes. As a result, an integrated sweat stimulation method for a prolonged access to sweat was only recently developed. Progress for sweat biosensing requires both understanding of the biofluid itself and also the technology to gain reliable access to eccrine sweat and sense analytes.

Artificial sweat stimulation is needed for dependable access to sweat for most applications outside of active perspiring. Hours to days of localized sweat stimulation can be achieved by delivering an electrically charged cholinergic agent, such as pilocarpine or carbachol, using iontophoresis.[5,6] For sweat sampling technique, there are two general categories: (1) flow into collectors or devices driven by positive pressure; and (2) flow into hydrophilic channels or wicking materials driven by negative pressure. The common challenge for sweat sampling is the volume size. Under the condition of 1 nL/min sweat volume per gland and 100 active glands per cm^2, a 100-μm-thick sweat layer would require over 1.5 h to fill. For a positive pressure–driven system, oil is commonly used to move dead volume and reduce analyte contamination;[7] as for a negative pressure–driven system, a method of utilizing an open microfluidic wicking requires only a few minutes for transferring time from sweat secretion to sensing with only 1 μm thickness.[8]

With over 24 h of sweat stimulation now possible, and an effective sampling method now demonstrated, the biggest remaining technological challenge is sensing itself. One of the challenges for continuous sweat biosensing is that there is no sufficient sweat–blood plasma correlation data to confirm its potential impact. Different types of optical and electrical sensing have been applied to the sensor for different applications in fully integrated devices in the shape of tattoos to band-aid size patches, wristbands, or straps with sweat stimulation integrated.[9] However, a continuous blood-correlated sweat biosensing device had not yet been demonstrated until a recent article about a wearable sweat biosensing device that has been developed to stimulate sweat and measure sweat ethanol concentration with 1:1 blood plasma correlation (Fig. 9.2). As mentioned in the previous section, ethanol, like hormones and drugs, is small and lipophilic and therefore offers the possibility for blood-sweat correlation. As a result, this device provides a strong blood-sweat correlation, as seen in the data of Fig. 9.3.

The patch shown in Fig. 9.2C operates as follows: when the device is applied, iontophoretic sweat stimulation occurs, and the device iontophoretically delivers carbachol from the simulant gel. Stimulated sweat is generated evenly not just beneath the gel but in areas surrounding the gel as well. After sweat is generated, the hex-wick wicks up the sweat and transports it to the sensors and then into the waste pump.[8] The operation is also shown in the diagram in Fig. 9.2B.

The detection range for all demonstrations to date of continuous sweat biosensing devices has been within μM concentration using ion-selective electrodes

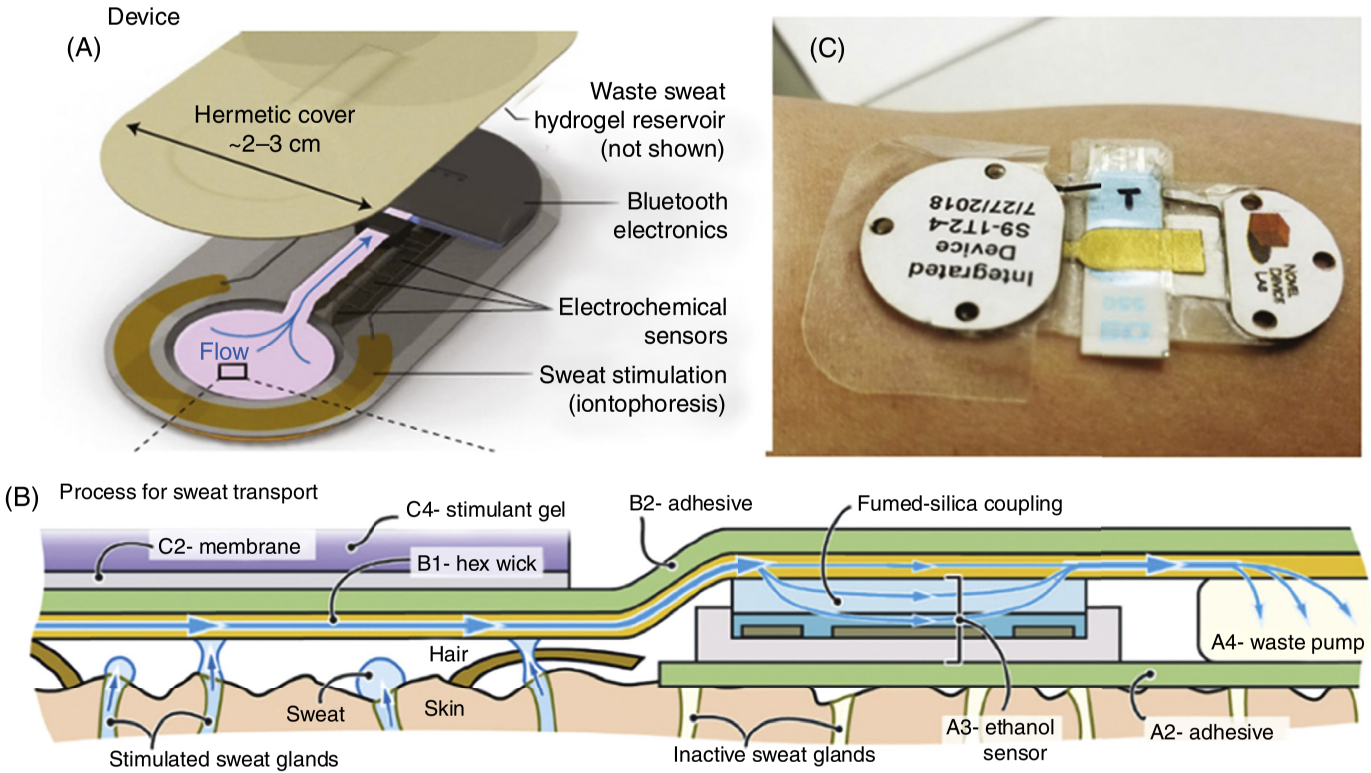

FIG. 9.2 (A) Diagram of a proposed wearable sweat biosensing device. *Adapted with permission from reference,*[3] *Copyright 2019, Springer Nature.* (B) Diagram of the process of sweat transport. *Adapted with permission from reference,*[10] *Copyright 2018, RSC.* (C) Photo of an integrated device with all components, except the wireless electronics and battery for *in-vivo* test. *Adapted with permission from reference,*[10] *Copyright 2018, RSC.*

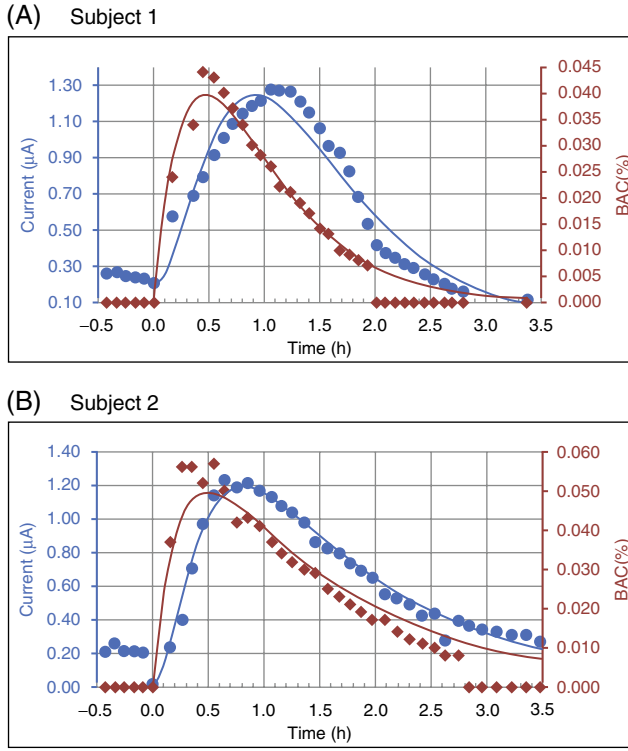

FIG. 9.3 *In-vivo* test data and pharmacokinetic model curves fit to the data for (A and B) subjects 1 and 2 from a fully integrated sweat ethanol biosensing device. *Adapted with permission from reference,*[10] *Copyright 2018, RSC.*

for analytes or using enzymatic sensors for metabolites (such as the ethanol data in Fig. 9.3). This is not relevant for most applications because most drugs and hormones exist in very low nM level concentrations in sweat. Only one fully validated class of sensors for the detection range from nM to μM has been demonstrated: electrochemical aptamer-based sensors.[11] No sweat demonstration with these sensors have been performed yet, primarily because aptamers are highly sensitive to pH and salinity, which varies widely in sweat during secretion.[12] Integrated sweat biosensing devices with electrochemical aptamer-based sensors are therefore arguably the next major needed advancement for sweat biosensing.

9.3 Minimally invasive biosensing: dermal ISF

9.3.1 ISF as a biofluid source of analytes

ISF is available in all layers of skin but the density of cells makes it less abundant in the epidermis. Furthermore, ISF is derived from the capillaries so the further from them the less ISF is to be expected. Dermal ISF is often used as

it balances the ability for minimally invasive collection (shown by the dermis' nearness to the skin surface in Fig. 9.1) as well as having a large analyte profile. Its close proximity and similar composition to plasma enables ISF to be a strong candidate for a large variety of analytes. This is especially true for low molecular weight hydrophilic species—such as sodium, potassium, glucose, and lactate—as they easily and rapidly diffuse paracellularly from the blood through capillary walls without filtration effects.[3] As a result, the concentration of these species in ISF closely matches that in the plasma. This relationship has been well documented in both the laboratory and commercial settings. In one study involving 20 subjects, the total concentration of sodium ions in plasma was directly measured at 141.2 mM, just over the measured ISF concentration at 135.7 mM. Similarly, the total potassium was found to be 4.37 mM compared to 3.9 mM in the ISF.[13] Commercially available glucose monitoring devices show concentrations of blood glucose to be virtually identical to those measured in ISF.[14] It should be noted that these glucose concentrations are equilibrium values implicating that a lag time exists (usually 5–10 min) between plasma glucose concentrations and the associated ISF concentrations. This is largely due to its larger molecular size and dynamic nature in the blood. Smaller hydrophilic molecules, such as lactate, diffuse more rapidly than glucose and display near-identical plasma-to-ISF values.

In the case of small hydrophobic species, the process is less straightforward. Typically, the more hydrophobic a molecule is, the greater its interaction with proteins in the blood. This results in two physical molecular states: protein-bound and unbound (free) fractions. The outcome is a discrepancy in total plasma concentration of a species in the blood and its concentration in ISF. For cortisol (362 Da), you will have a total plasma concentration ranging from 80 to 500 nM, while ISF concentrations are approximately 10 times less at 5–50 nM. The cortisol concentration in the ISF corresponds directly to the free fraction of cortisol in plasma. This makes sense as small lipophilic molecules readily diffuse transcellularly to the ISF. The cortisol fraction that remains bound to proteins, such as transcortin, is hindered by the sheer bulk of the complex and cannot easily diffuse through the capillary wall. Fortunately, in most cases the primary interest is in the free cortisol fraction as it is also the active fraction. The same is true for drugs, and therefore their utility for measurement in ISF is also high.[3]

Proteins, lipids, and other higher molecular weight compounds no longer display simple blood plasma-to-ISF concentration ratios. In fact, there exists an inverse logarithmic relationship between this ratio and a species' molecular weight. For example, ISF-to-blood plasma concentration for insulin (6600 Da) is 0.90, while albumin (68,500 Da) is 0.29, and alpha-2 macroglobulin (775,500 Da) is 0.14.[3] The partition coefficient for these proteins ranges from 2 to 15×10^{-7} cm^2/s and are directly related to its diffusion coefficient. Lipids follow a similar trend where high-density lipoproteins (~250,000 Da) and low-density lipoproteins (~750,000 Da) show roughly a 0.25 and 0.20 concentration ratio, respectively, in ISF compared to blood plasma concentrations.[3] Establishing a

conversion factor for higher molecular weight compounds is essential before useful concentration data can be extracted from ISF concentration measurements. This phenomenon is largely due to the filtration effects of paracellular movement of compounds through tight junctions. The properties of proteins surrounding these tight junctions determine the degree of selectivity and filtration. As a result, the passing species is diluted from the blood to the ISF, making lower concentration measurements more difficult. To summarize, see Table 9.2 for the analyte concentrations in ISF, as an extension of Table 9.1.

Before examining cases for minimally invasive devices it is important to understand the lag-time partitioning of analytes. Consider glucose, which was previously mentioned to suffer from ISF lag. ISF lag contains two steps, either of which can be rate limiting. The first is the inherent lag time as glucose diffuses from plasma to ISF, typically ranging from 5 to 10 min.[3] Then, glucose must diffuse through the membrane of an in-dwelling sensor or through the lumen of a microneedle, adding an additional 1–5 min.[15] Therefore, total ISF lag is often 5–15 min without enhanced data manipulation. Based on our understanding of diffusion, we know these times will increase for larger analytes and could be quicker for smaller analytes. Considering the analyte kinetics when designing a sensor will be paramount as researchers continue to design devices where, ideally, the rate-limiting step of the sensor will always be physiological.

9.3.2 ISF biosensing devices

ISF is the primary biofluid of choice for use in minimally invasive diagnostics, due to its relatively easy and low- or zero-pain access near the surface of the skin. The most prevalent approach for gaining access to this fluid is through the use of indwelling sensors.

Indwelling sensors placed on the tips of needles are commercially utilized as a valuable diagnostic tool for glucose monitoring (Fig. 9.4). These sensors are typically electrochemical sensors that are placed through the dermis into the subcutaneous fat layer. Because these sensors do not require extraction, more accurate lag times for analytes seen in the local ISF can be observed. In the case of continuous sensors, lag times can be minimized even further with clever device design. For example, the FreeStyle Libre Flash Glucose Monitoring System (from Abbott Diabetes Care), an indwelling ISF glucose sensor, reports lag times of only 4.5–4.8 min, and does not require external calibration (Fig. 9.4).[15] To use this device, the spring-loaded inserter is first mated with the sensor pack that contains the sensor itself and the insertion needle. The needle is then impaled into the skin, and the sensor dwells in ISF about 5 mm below the surface while the electronics remain adhered outside on the skin's surface. The user can then read their glucose levels by bringing a near-field communication-enabled meter or phone near the electronics. A study was conducted in which 72 participants wore the device for 2 weeks; the results seen with the ISF glucose sensor device were compared to those seen using standard blood glucose test

TABLE 9.2 Table of ISF concentrations relative to blood plasma. For ISF concentrations (a) indicates active channels or actively locally generated concentrations, (p) indicates passive partitioning into the fluid. Adapted with permission from reference,[3] Copyright 2019, Springer Nature.

	Na^+	K^+	Lactate	Glucose	Cortisol	Drugs	Cytokines	Antibodies
Molecular weight (Da)	23	39	90	180	362	Mostly hundreds of Da	More than five to tens of kDa	Hundreds of kDa
Lipophilicity	Very low (charged)	Very low (charged)	Very low (charged)	Low (hydroxyls)	High	Often high	Very low	Very low
Blood plasma	135–145 mM	3.5–5 mM	0.5–10 mM (resting to nonresting)	4.1–6.9 mM (venous, resting)	Hundreds of nanomolar total; tens of nanomolar unbound fraction	Mostly equivalent to unbound in plasma	Picomolar to nanomolar	Varies; total ~0.4–16 mg/mL
ISF	Similar to plasma	Similar to plasma	Similar to plasma	Similar to plasma	Unbound similar to plasma (p)	Many equivalent to unbound in plasma (p)	80% of plasma (a,p)	15%–25% of plasma

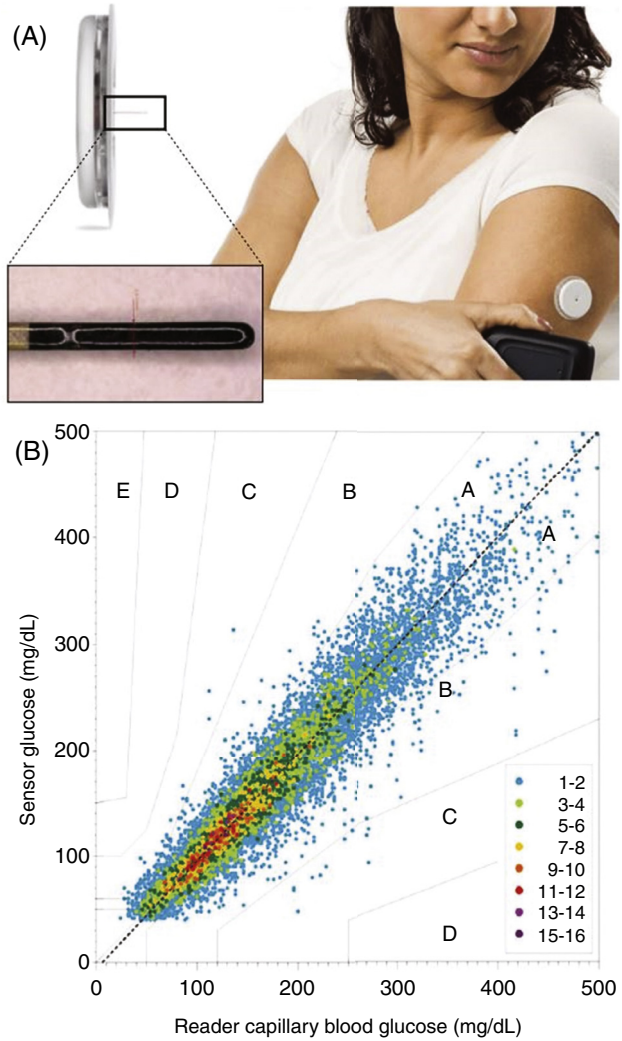

FIG. 9.4 (A) Photo of the Abbott FreeStyle Libre Flash Glucose Monitoring System. *Adapted with permission from reference,*[3] *Copyright 2019, Springer Nature.* (B) Consensus error grid analysis of data collected using the FreeStyle Libre Flash device from (A). The colors correspond to the number of data points from the sensor that overlaps with blood glucose readings. *Adapted with permission from reference,*[15] *Copyright 2015, Mary Ann Liebert, Inc.*

strips.[15] From the total 13,195 paired points obtained, 86.7% were located in the clinically accurate consensus error grid zone A (Fig. 9.4B). This implies that 86.7% of the readings would have prompted the device user to take correct action in regard to insulin or food intake. The increasing accuracy and simplicity of devices that use indwelling ISF electrochemical sensors such as this one is causing increasing market approval and usage of these devices.

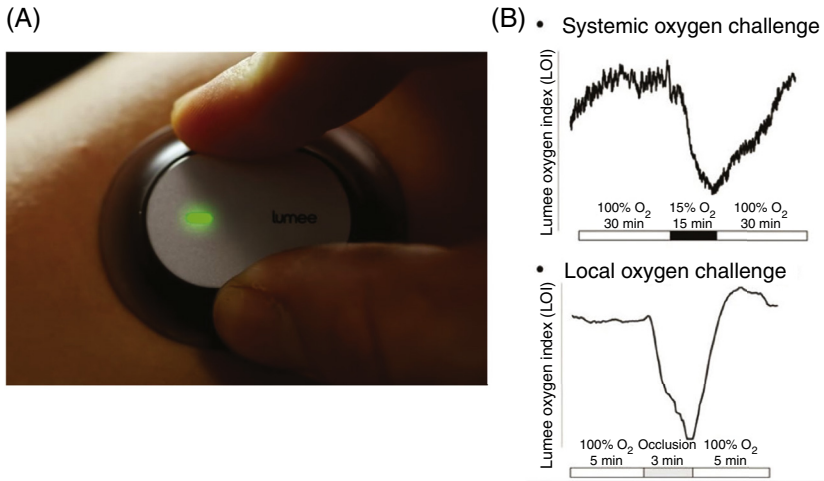

FIG. 9.5 (A) Photo of electronics portion of Lumee Oxygen Platform device, which remains adhered to the surface of the skin, while the hydrogel portion is implanted 2–4 mm into the dermis. Photo credit to Profusa, Inc., creator of Lumee. (B) Plots of both systemic (altered by changing fraction of inspired oxygen) and local (altered by applying tourniquet or pressure cuff to limb) oxygen measurements over time taken by Lumee Device seen in (A). Lumee oxygen index is the micromolar concentration of oxygen calculated from the phosphorescent lifetime of the hydrogel as well as the temperature. *Adapted with permission from reference,*[16] *Copyright 2018, Springer, Cham.*

In addition to indwelling sensors placed on microneedle tips, fully implanted devices are beginning to see growing market acceptance. The Lumee Oxygen Platform device (by Profusa) is a fully implantable hydrogel optical sensor that can provide continuous oxygen readings to the user (Fig. 9.5).[16] The flexible tube-shaped device, which is 5 mm long with a 500 μm diameter, is inserted about 2–4 mm below the skin's surface. When in contact with dissolved oxygen, the phosphorescent hydrogel sends a signal to a near infrared optical reader, which resides on the outside surface of the skin. The Lumee device also has a substance in the hydrogel which keeps the body from recognizing the device as a foreign object, suppressing the immunological response. This novel aspect, which keeps the body from forming scar tissue that would impede the optical readings, allows the device to work for over 9 months without replacement. In addition to the Lumee Oxygen Platform device, Profusa is also working on devices that can measure other analytes that monitor overall health status, such as lactate, carbon dioxide, and glucose.

Another, completely pain-free approach for ISF biosensing is microneedle arrays (Fig. 9.6A). There are two primary methods with which these arrays can be used in a minimally invasive manner to monitor analytes in ISF: (1) analyte diffusion through the fluid to an external sensor, and (2) fluid extraction to an external sensor.

The first method, analyte diffusion, is currently being investigated for glucose concentration monitoring. In this approach (Fig. 9.6),[17] microneedles in an

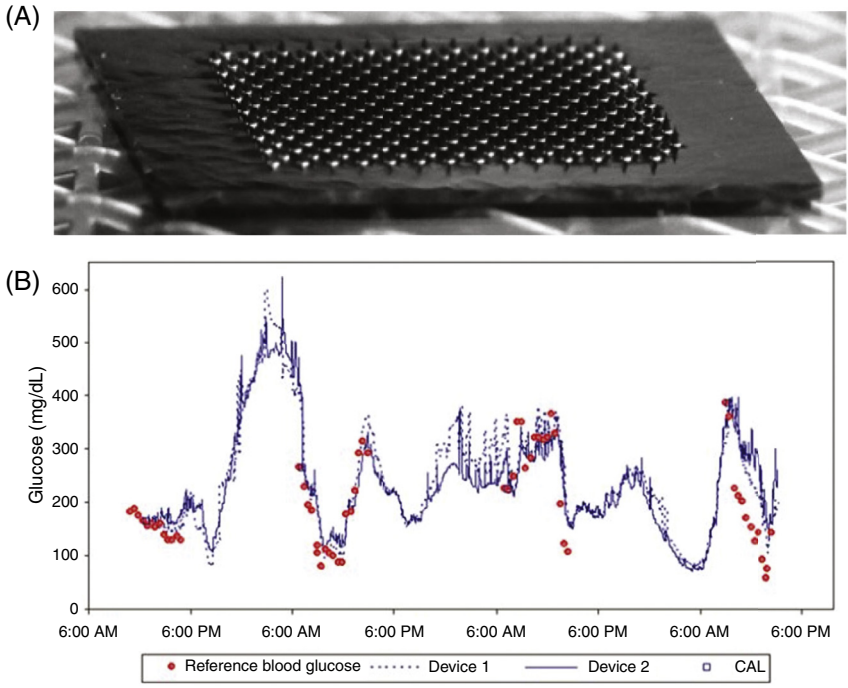

FIG. 9.6 (A) Photo of ArKal Medical microneedle array. *Adapted with permission from reference,*[17] *Copyright 2014, SAGE.* (B) Data generated using the ArKal Medical microneedle array device. This plot displays blood glucose measurements as well as data from two devices which were worn simultaneously by one subject to demonstrate device accuracy and precision. *Adapted with permission from reference,*[17] *Copyright 2014, SAGE.*

array puncture the skin to the depth of the dermis (~500 μm), allowing access to the ISF. The glucose molecules then diffuse from the ISF to an *ex-vivo* sensor located at the skin surface. Using this technique, a study has shown that continuous glucose measurements can be collected for up to 72 h using an ArKal Medical microneedle patch (Fig. 9.6).[17] The data is fairly accurate, with an increase from 10% to 15% in the mean absolute relative difference from the best available commercial devices to the investigated method, respectively. It should be noted that lag times of 17 min were seen for glucose; however, for larger molecular analytes that have blood concentrations that change very slowly, these lag times will be slower yet but also may be viewed as insignificant. Although this approach has seen some success in preliminary studies, it struggles to meet the accuracy and robustness seen with indwelling sensors. Also, due to the large number of needle wounds, swelling and irritation may occur, leading to noncompliance or product rejection.[18]

The second method, extraction of the ISF itself to an external sensor, is currently much less explored. However, there have been studies that have investigated and tested various ISF extraction methods.[19,20] Unfortunately, the general

conclusion is that extraction is unlikely to become a viable method, due to several drawbacks. Depending on the method of extraction, the necessary mechanical hardware (a vacuum pump, for example) can be large and cumbersome. In addition, the time required for withdrawal of the sample fluid directly increases ISF lag. Lastly, it is unclear whether analyte concentrations remain constant when the dermis is compressed/stretched by the withdrawal device or strong suction.[21] This is because dermal compaction or stretch has the potential to alter the pressure balance between the blood capillaries, ISF, and lymphatic capillaries. In light of all these drawbacks, there are currently no devices on market using this strategy, although studies attempting to improve such extraction methods continue to be conducted.

Another notable minimally invasive method of ISF analyte analysis is microdialysis, in which a small catheter is inserted into the skin. In this technique, a semipermeable membrane allows the exchange of small analytes, such as molecules and ions, with fluid in the probe. After the exchange is complete, this fluid can be extracted and sensed. The Glucoday CGM from Menarini utilized this technology for glucose monitoring (Fig. 9.7). It could be worn up to 48 h by the subject and had a delay in response time of less than 2 min.[22] Overall,

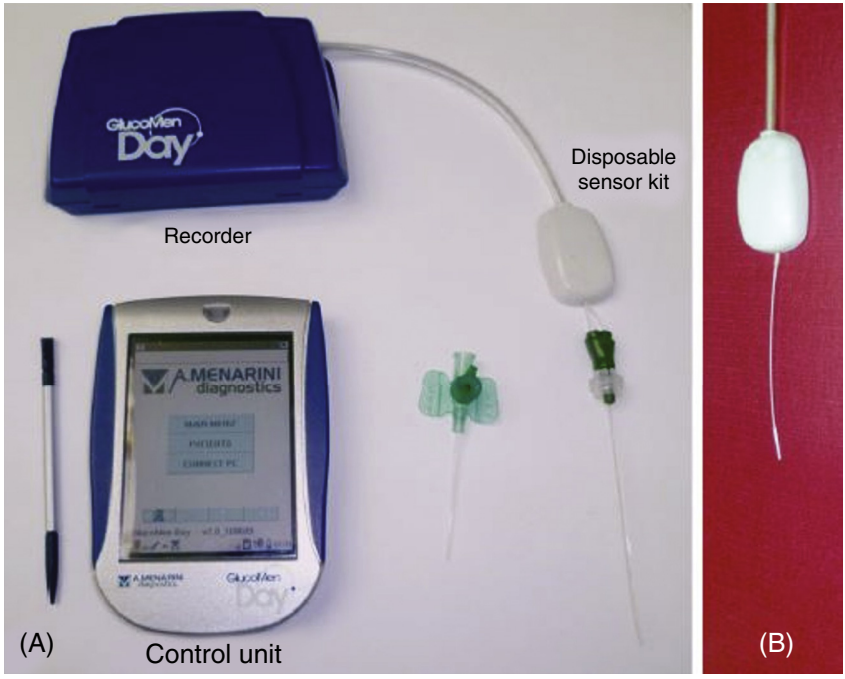

FIG. 9.7 (A) Device components that make up the GlucoMen Day continuous glucose monitoring system. *Adapted with permission from reference,[22] Copyright 2012, SAGE.* (B) Disposable sensor kit for interstitial fluid. *Adapted with permission from reference,[22] Copyright 2012, SAGE.*

microdialysis is being used increasingly to monitor free, unbound analyte concentrations as well as ISF concentrations of regulatory cytokines and other molecules that monitor changes reflecting food intake and exercise.[23]

9.4 Noninvasive biosensing: other body fluids and sources

9.4.1 Saliva, exhaled breath, and tears

Saliva, exhaled breath, and tears, like sweat, are noninvasively acquired; however, these analyte sources will only be mentioned briefly, as they are not well suited for continuous monitoring. They are not likely to be used for wearable biosensors and are better suited for one-time use diagnostic testing devices.

Saliva is a dilute biofluid that is secreted into the mouth primarily by three glands (the parotid, submandibular, and sublingual glands), as well as several minor glands. Molecules enter saliva through active or passive means depending on their size, charge, and hydrophilicity. Although saliva is a relatively convenient, noninvasive biofluid (and therefore ideal for patient self-collection), it is extremely variable in composition.[24] Stimulated saliva, which accounts of ~90% of daily saliva secretion, is much more dilute than unstimulated saliva secretion, and therefore unpredictably alters analyte concentrations. In addition, saliva composition can vary in different portions of the mouth, due to the different secretions from each secretory gland. To help prevent contamination, patients must perform a water rinse and fast for a period of 30–60 min before saliva collection. In conclusion, saliva is a much more convenient biofluid than blood, and is ideal for many at-home testing applications. However, sample heterogeneity, sample preparation, and variance in flow rate (and therefore analyte concentration) are hurdles to saliva becoming a more ubiquitous fluid for diagnostic testing.[3]

The use of exhaled breath as a diagnostic tool has also been explored.[25–28] There are several biomarkers contained in exhaled breath which have been linked to lung cancer, oxidative stress, and diabetes.[25] For example, acetone in the breath has been found to have a positive correlation with high levels of glucose in the blood, and therefore can be used for diabetes monitoring.[26] However, overall, use of breath is hindered by a lack of standardized testing techniques, as well as low sensitivity and accuracy of volatile organic compound biosensors.[27] Amplification is needed to reliably detect target analytes, and the processes required for amplification using exhaled breath are generally more complicated than processes used for biofluids.[28] In addition, it is much harder to determine the necessary conditions and durations of storage for these samples, and contamination from the respiratory tract is extremely likely; it is also suspected that this contamination affects each biomarker differently. Because of these reasons, exhaled breath has yet to become a highly useful diagnostic tool. Nevertheless, researchers are pushing forward these frontiers by means of paper-based electrochemical approaches,

which can be integrated into a commercial airway filter or a facemask, thereby could enable continuous and real-time sampling and monitoring of biomarkers (such as hydrogen peroxide) from exhaled breath.[29]

Tears, overall, have no major advantages over other biofluids that have already been discussed. Gaining convenient access to tears is difficult, for both one-time and continuous measurements. Only very small quantities of tears can be obtained at one time, and, in addition, it is extremely difficult to control tear secretion rate.[3]

9.5 Current challenges and outlook

Although they all have diagnostic potential, saliva, exhaled breath, and tears are not likely to be used for wearable sensors as they are more difficult to obtain for continuous monitoring. Sweat and ISF are biofluids that hold the most interest due to the fact that they are wearable-accessible and contain a plethora of molecules that can be analyzed. However, each biofluid faces its own unique challenges. For example, sweat must be artificially stimulated for continuous monitoring, and sensing is more difficult due to the extremely low sample size (nanoliters). Sweat is also much more dilute than blood, due to an increased filtering effect as analytes pass from the capillaries to ISF, and eventually into the sweat ducts.

When using ISF, one must consider lag times which will be introduced for analyte transfer from blood plasma, as well as the protein bound versus unbound (free) fraction of analyte. There is also a possibility for irritation and infection of the skin where the needles have been inserted into the interstitial space. Lastly, extraction of ISF has been shown to be extremely difficult, and continuous sensing of ISF will therefore likely focus on devices that use indwelling sensors rather than *ex-vivo* sensors.

Self-powered biosensors have also gained increasing popularity lately in the field of wearables research.[30–34] Scientists are attempting to overcome issues such as battery charging and lifetime with devices that can use the body itself as a power source. Overall, it seems that enzymatic reactions (biofuel cells) are the most widely used tool for powering these devices;[30–33] however, mechanical powering mechanisms such as piezoelectric and triboelectric nanogenerators are also being increasingly used.[32] These nanogenerators have a number of benefits, such as high output voltage, low cost, and stability. However, there are still numerous factors impeding successful long-term operation of self-powered devices. For example, as these devices are often wearable or implantable and need to conform to complex structures such as skin and organs, increased flexibility is vital. New hybrid materials must be developed to meet these needs.[34] Also, electrode biofouling and biorecognition element stability are factors that must be considered which may significantly shorten device lifetime.[32]

In conclusion, the future of wearable biosensors depends on the ability of researchers to tackle key issues such as biofluid extraction, sensor limit of

detection, and biofluid blood-plasma correlation for noninvasive biofluids such as sweat and ISF. The newer concept of self-powered biosensing is interesting; however, many key issues such as device flexibility and lifetime still need to be addressed to make these a viable option for the future.

Abbreviation

ISF Interstitial fluid

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Chapter 10

Wearable hybrid sensors

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10.1 Introduction

Natural physiological phenomena offer a wide range of possibilities to assess health status via biophysical (temperature, breath, motion, heart beat) and biochemical (pH, electrolytes, metabolites) processes, which can be measured and quantified with the aid of bio-integrated sensors.[1] Particularly, the combined detection of biochemical and biophysical signals in a wearable device gives rise to hybrid systems through multimodal and multiplexed detection. Thus, we define a wearable hybrid sensor as stacking of three major components, namely substrates, interconnects, and sensing elements. This device can be coupled to the human skin and is able to perform different types of measurements in a single run, such as the acquisition of biophysical, biochemical, and biological information at once, instead of having multiple devices for each purpose. Such hybrid approach may be achieved through multiplexed devices, where multiple analytes/quantities are determined, or by means of multimodal sensors, which operate with multiple detection techniques. These bio-integrated devices have paved the way for noninvasive monitoring systems, allowing for continuous analyses and real-time data acquisition on body conditions through wearable sensing technology.[2] A landmark in the history of biomedical wearable sensors was the instrumentation developed by NASA in the 60s to obtain accurate information about the health of astronauts, securing their comfort during the space mission while performing real-time monitoring of their heartbeat, temperature, blood pressure, and breath.[3] The latest advances in microelectronic engineering and material science fields have prompted the development of on-body fully integrated wearable sensors employed for point-of-care testing and continuous health monitoring.[1,4,5]

The monitoring of biomarkers in the human body, either physical or biochemical, shows remarkable benefits and can lead to a better understanding of day-by-day human physiology. In terms of biophysical monitoring, heart rate and arterial blood pressure are the most prevalent signals to be investigated.

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Differently from the initial era of the soon-to-become wearable systems, which mostly relied on the invasive use of blood samples, noninvasive biological matrices, such as saliva, sweat, tears, hair, and breath are now largely employed in wearable analytical systems.[6–10] Nonetheless, the use of invasive methods still holds great importance as diagnostic tools.[11] In these systems, the biological fluid is incorporated into the wearable system from invasive sites, such as capillary blood and interstitial fluid. Fluid capillarity can also be explored with noninvasive biofluids, such as sweat and tears, for the fabrication of lateral flow assays.[7,8]

The advances seen in the tuning of major properties of materials and the instrumentation employed for the building of wearable sensors are of fundamental importance.[12] Among the most outstanding properties exhibited by advanced polymeric materials employed for wearable systems are flexibility, elasticity, hybridity, and electrical conductivity (see Chapter 2). Portable smart electronic systems can incorporate these polymeric materials to achieve wearable hybrid detectors, which in turn can employ electrochemical, mechanical, and optical transducing methods. With the advent of the IoT (see Chapters 6 and 12), the signals generated by such wearable sensors can, then, be processed either in on-body or off-body fashion, which may be further stored in cloud storage platforms through wireless communication, or directly transmitted to medical staff for further data evaluation.[12–14] Thus, the advantages offered by polymeric materials combined with hybrid detectors integration are the key features to secure operational simplicity, portability, and to reach instrumental success of wearable hybrid sensors.[12–17] Fig. 10.1 provides general information about wearable system as on-body incorporated devices, as well as some major applications and features.

Wearable hybrid sensors are adaptable to the human routine, allowing for the monitoring of simple events, such as the natural daily body movements. In this sense, the major body parts explored for the placement of wearable sensors are the skin, the eyes, and the mouth; being the skin the most popular region due to its wearability and allowing for a noninvasive approach.[8,18,19] More specifically, the skin offers a great slew of possibilities in terms of sensing, such as information from blood vessels, the dermis/epidermis, the muscles, and the mechanical straining.[19,20] Thus, wearable systems can be incorporated on mouthguards, bands, eyeglasses, patches, watches, tattoos, bandages, wound dressings, textiles, facemasks, and contact lenses.[6–8,21–31] Such body-sensor configurations enable the monitoring of important biomarkers, such as zinc, iron, potassium, and sodium,[23,32,33] as well as important biomolecules, such as glucose, proteins, uric acid, lactic acid, dopamine, ascorbic acid, ketone bodies, cholesterol, cortisol, bile acids, and adrenaline.[8,12,17,26] It also possible to monitor the pH, O_2 saturation, pressure, respiration, and heart rate.[4,17,26]

Considering the miscellaneous types of targets to be monitored by a wearable sensor, it becomes necessary to provide the reader with some commentaries on the strategies employed for the assembly of wearable hybrid platforms.

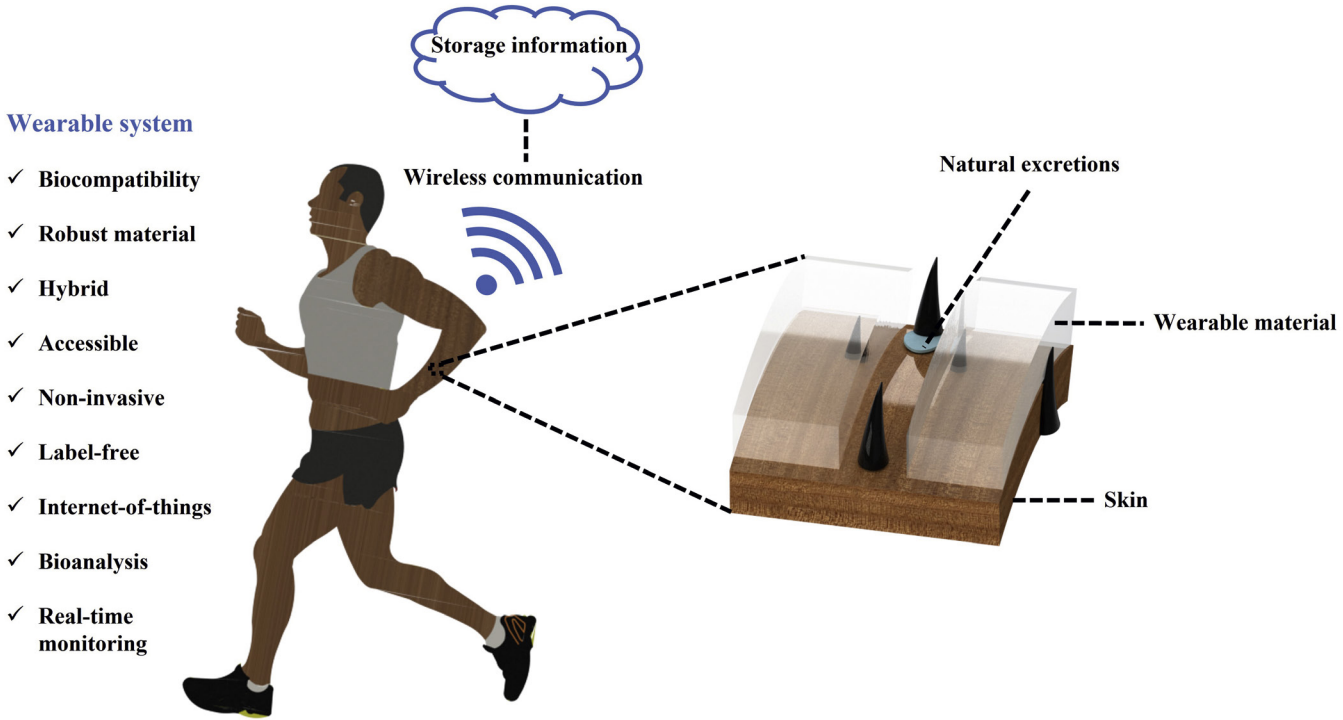

FIG. 10.1 Schematic representation of a wearable sensor employed in on-body fashion, under natural body straining during physical activity, collecting health information, and performing real-time data transmission.

First, it is important to bear in mind that a hybrid sensor may be fabricated through different approaches. For instance, one device may be classified as a hybrid system if it provides the user with a technology able to perform a multiplexed detection, that is, a single device will carry out measurements for several analytes in a single assay. A good example of this class of multiplexed hybrid systems are sensors that detect and quantify glucose, lactate, and sodium, all in a single run (this example is covered in Fig. 10.4, on the Applications section). Another possibility lies in the use of multimodal wearable sensors, which operate through different detection techniques. One important class that resorts to this strategy is the biophysical integrative sensors, in which more than one detection mode is employed to acquire and process biophysical signal, such as body movements and vital signs (more examples are further elaborated in Fig. 10.3, on the Applications section). Also, a wearable hybrid platform may be fabricated by the combination of different types of targets, such as when a sensor can provide the wearer with readings of vital signs, environmental assessment, and biochemical monitoring. More challenging yet, these categories of hybrid systems may be further enhanced with the integration of energy-harvesting modules, which enables devices to operate in an autonomous fashion.

Hence, in this chapter, we introduce the latest contributions on wearable hybrid systems employed for human body monitoring. We carefully demonstrate some outstanding properties of flexible materials and the strategies through which they can be integrated with advanced electronics and bioassays methods. In the sequence, we put in some comments about the advances of the manufacturing processes employed for the fabrication of wearable devices. Also, some major difficulties and particularities of the integration of wearable hybrid sensors with the natural human body movements are further discussed. Lastly, we conclude with some brief considerations on the future perspectives of wearable hybrid sensors for the continuous online monitoring of biophysical and biochemical biomarkers.

10.2 Flexible and stretchable materials

Wearable devices need to be mounted on body segments to form a comfortable system.[17,26] In this way, the biocompatibility, mechanical properties, and physicochemical aspect of materials must be considered to achieve an ideal structure and an effective combination with the skin. According to these approaches, polymeric materials are most usual due to their biocompatibility with the skin in addition to mechanical resilience. These properties provide the flexibility and stretchability crucial to conformal contour suitable on skin. Moreover, polymeric materials exhibit relevant physicochemical aspects such as gas/vapor permeability, water repellency, good adhesion, and translucency. Furthermore, surface chemical composed by silanol and hydroxyl groups enable chemical functionalization. All the previously mentioned properties allow out-of-plane deformation and consequently comfortable accommodation on the skin.

TABLE 10.1 Wearable substrate materials and their main advantages and disadvantages.

Wearable material	Cellulose fiber	Plastic polymer	Silicon rubber	Hydrogel
Advantage	Low-cost Accessible Porous Flexible Capillarity Easy modification	Accessible Highly flexible Highly patternable Wide variety	Large scale Highly flexible Stretchable Excellent adhesion	Highly dissipative Highly stretchable Piezoelectric Tunable properties
Disadvantages	Quality variation Low thermal stability Moisture absorption	Synthesis dependence Microplastic residues Low adhesion	High cost Temporary loss of hydrophobicity	High cost Complex production Gelation rate control

However, the chosen material must be accessible to promote the fabrication process in large scale.[34] Some common substrates along with their advantages and drawbacks are summarized in Table 10.1.

Polymeric structures usually employed on wearable system are cellulose fibers, hydrogels, silicon, polyethylene glycol, and polydimethylsiloxane (PDMS).[4,17,26] The most common substrate employed in wearable sensor is cellulose highlighted nitrocellulose membrane, textiles and fibers incorporated with polymetric structures due to their low cost. Other reasons comprise large pore size that allows diffusion in lateral flow and coupling with optical and electrochemical detectors. These advantages combined with the flexibility can simplify their use as hybrid structures spontaneously connected to skin, to overcome the disadvantages of single-materials systems.[4,26]

The challenges found in wearable hybrid systems encompass achieving an optimal fit between the flexible material and the skin, so that the sampling process can be undertaken in a spontaneous manner without causing harm to the skin environment. As a result, a harmonious integration of skin and sensor allows for a more representative monitoring of the target species.

10.3 Electrically conducting materials

In terms of conducting materials, many substances, as well as their 3D assembly, have been vastly investigated. Carbon materials, for instance, have been widely explored for the fabrication of electrochemical sensors, as they offer

low cost, a wide experimental potential window and are mostly inert under several applications.[35] This wide variety of structures allow for a diverse set of properties, such as high electron mobility, ultrahigh strength, low contact resistance, high optical transparency, and strong thermal stability.[36] Nonetheless, carbon materials commonly present with fracturing when undergoing low strain. Some alternatives to this issue have been devised, such as the fabrication of graphene nanoscrolls in-between stacked graphene layers, resulting in transparent stretchable electrodes with high conductivity under a wide varying strain[37] (see Fig. 10.2A).

Due to their great manufacturing flexibility, allowing a great tuning of their properties, conductive polymers have attracted attention for their integration into wearable sensing platforms There are many types of polymers, such as polyacetylene, polythiophene, polypyrrole, polyaniline, poly(p-phenylene) and poly[3,4-(ethylenedioxy)thiophene]:poly(styrenesulfonate) (PEDOT:PSS), although most flexible and wearable applications have employed either polypyrrole or PEDOT:PSS.[38] Although many studies rely on the use of single polymers, in some instances, the conductive polymer might not show appreciable mechanical deformation when required, which has motivated the addition of plasticizers, such as nonionic surfactants and ionic liquids;[1] while the former may reduce the electrical conductivity,[39] the latter has been shown to yield highly stretchable and conductive sensors[40] (see Fig. 10.2B).

Aside from carbon and conductive polymers, metal nanostructures have also been employed for the fabrication of wearable hybrid sensors. Some candidates that have been extensively explored are copper and silver. For instance, Ag nanowires (NWs) have been achieved with high transparency, flexibility, and electrical conductivity.[42,43] On the other hand, Cu NWs can be achieved with an associated low cost while exhibiting high electrical performance. Metal nanoparticles (NPs), coined as 0-D materials, offer a vast repertoire of synthesis strategies, enabling the tuning of particle size and shape.[20] Another attractive approach has been the use of AgNPs as a conductive material deposited on flexible substrates results in a percolation network, which is responsible for mechanical strain absorption while maintaining the electrical conductivity.[44] AgNPs can also be prepared as colloidal inks to fabricate inkjet-printed electrodes of organic field-effect transistors[41] (see Fig. 10.2C).

10.4 Strategies to manufacture wearable systems

The development of wearable device consists of transferring the materials based on polymeric membranes or electrodes to the body.[12,34,45] These off-body systems are posteriorly incorporated into the body segment via elastic band, textile, adhesive, or chemical interactions of Van der Waals.[4,12,17,45] Protocols based on screen-printed, xurography, pyrolyze, solution casting, dip coating, soft lithography, pressure, spinning and 3-D printing are the most usual ones.[12,45] The

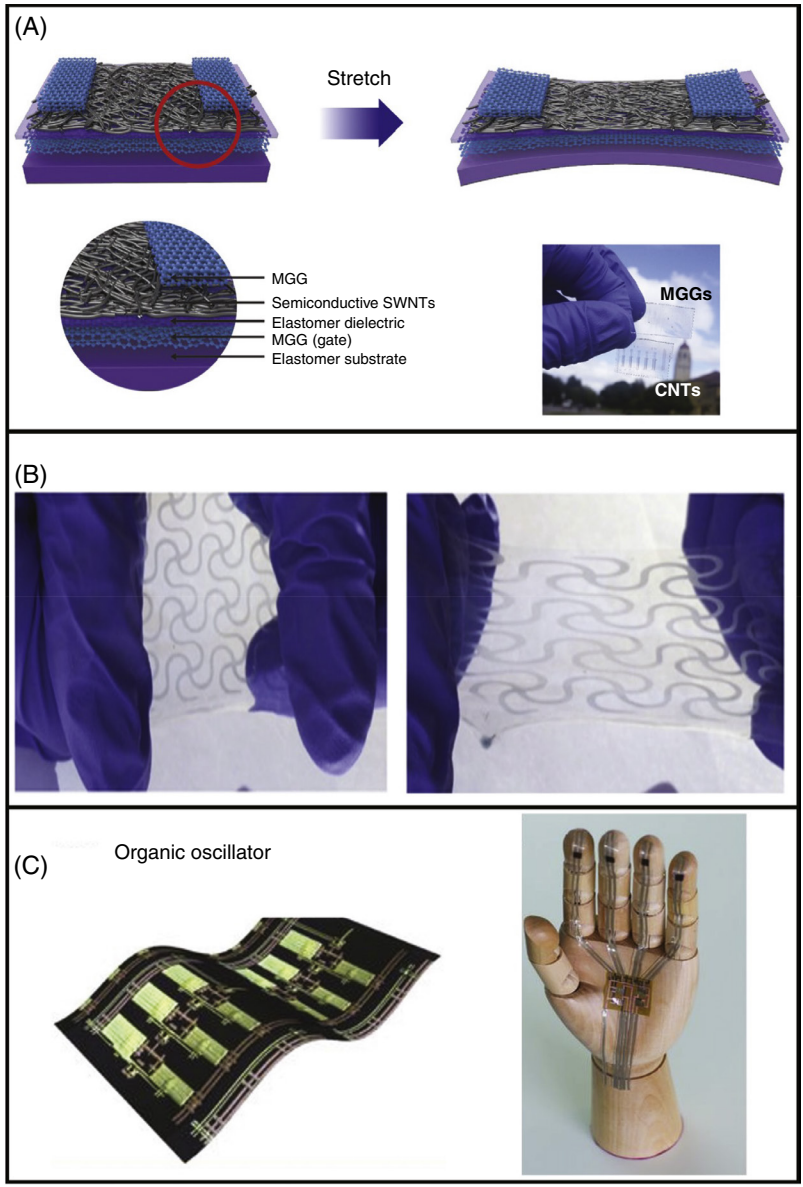

FIG. 10.2 (A) Fully transparent and stretchable all-carbon transistor based on multilayer graphene-graphene scrolls and single-walled carbon nanotubes. *Adapted with permission from reference 37. Copyright 2017 American Association for the Advancement of Science.* (B) PEDOT:PSS film-based highly stretchable and electrically conductive sensor building piece enhanced with the incorporation of ionic liquids. *Adapted with permission from reference 40. Copyright 2017 American Association for the Advancement of Science.* (C) AgNPs-based organic oscillator employed for the fabrication of a skin-inspired organic digital mechanoreceptor for neural-integrated touch feedback sensor. *Adapted with permission from reference 41. Copyright 2015 American Association for the Advancement of Science.*

choice of detector, data acquisition, and signal processing are also relevant to the manufacture a robust wearable hybrid system.

The detectors systems are selected considering the corresponding portability, low-cost, user-friendly operating, selectivity, and fast measure. The signal response can be performed via mechanical, chemical, optical, and/or electrochemical properties.[12,26] Electronic devices based on smartphones are the most popular in wearable systems.[4,26] This system can be easily integrated into different detectors and wireless connection. However, there is a demand for an energy source based on batteries composed of toxic metals such as lithium, lead, mercury, and cadmium. In this way, one of the main challenges of portable detector technology is to develop an energy source using solar energy as the sun offers an environmentally friendly energy.[46]

10.5 Applications

The advent of personalized or, interchangeably, precision medicine has opened unique paths for advanced monitoring and treatment of uncountable diseases and health conditions. As such, wearable devices can be employed as medical tools exhibiting great potential for biomonitoring applications through hybrid detection.[47] It is important to recall the different types of strategies employed for the fabrication of hybrid wearable platforms, such as presented in the introductory section of this chapter. Thus, a hybrid sensor may be built on the premise of a multiplexed detection, where several analytes and signals are simultaneously evaluated, or it can be achieved through multimodal detection, where more than one type of detection technique is employed. Also, a hybrid sensor may be fabricated with the combination and integration of detection modules for different types of analytes/quantities, such as physical, biological, and chemical signals. At last, one promising integrative strategy to assemble a wearable platform is through the addition of energy-harvesting systems, allowing the wearable device to operate in autonomous fashion. Thus, the following sections are dedicated to exploring some fundamentals of these applications of major interest to the analytical field.

10.5.1 Biophysical integrative applications

One major interest when it comes to developing a hybrid wearable sensor is the monitoring of biophysical signals, such as heartbeat, brain activity, peripheral nervous system function, muscle strain, body dynamic motion, and vascular conditions, while allowing the device to operate in an autonomous fashion, that is, to present with self-powering strategies. The combination of biophysical and energy harvesting, then, can be classified as biophysical integrative systems. This approach requires an optimal adherence and conformation of the sensing platform to the body region to be studied.[1] The main reason for this imperative condition lies in the fact that the great majority of biophysical wearable sensors

employ electrodes for mechanical-to-electrical signal transduction. Thus, to provide applications with long-term stability and electrical readout reliability, while allowing the integration of energy-harvesting modules, it is highly desirable that the sensor operates under a low skin-electrode interface impedance. In this sense, a lower impedance can be obtained by enhancing the electrical conductivity of the electrode materials as well as by increasing the size of electrodes (at the expense of a reduced spatial resolution when working with multichannel platforms).[1,48]

Among biophysical signal-aimed wearable hybrid sensors, two major classes are vastly employed, namely resistive and capacitive-type. These two types are commonly employed as strain sensors, the mechanism of action of the former being based on the variation of the electrically conductive material resistance upon stretching and the mechanism of the latter being based on the geometrical changes in the capacitive area following electrode stretching.[49] Both resistive and capacitive wearable sensors share similar advantages and drawbacks, as their applications usually offer simple designs, low cost, high sensitivity, and low noise at the expense of high-power consumption and short lifespan of the conductive materials.[50,51] Differently from these two classes, piezoelectric and triboelectric sensors avoid the need of external power to operate by proving electrical signal generation mechanisms by themselves, which has been a prominent strategy to achieving the integration of energy-harvesting modules to wearable sensors.[20]

While traditional resistive and capacitive approaches have been vastly employed for the fabrication of wearable sensors (for further reference on these applications, check Chapter 7 and the excellent work recently published by Souri and collaborators[49]), the next-generation area of hybrid built-in generator/self-powered wearable devices has gained momentum over the last decade. The fabrication of these body-worn sensors for the surveillance of biophysical signals can be achieved through a myriad of approaches, such as piezoelectricity[52,53] and triboelectricity.[54,55] To avoid inconveniences related to the optimal operation of self-powered devices, while maintaining a comfortable experience for the wearer, creative solutions have been devised, such as the fabrication of wrist-wearable energy-harvesting devices[56] (see Fig. 10.3A), garment-integrated self-cleaning sensors[57] (see Fig. 10.3B), and ambient-harvesting electronics.[58]

Aside from electrically conductive sensors, optical[59] and biometric conformable imaging devices[60] also exhibit promising results for the development of hybrid wearable platforms employed for biophysical monitoring, using both spectroscopical and electrical signal readings.

10.5.2 Biochemical integrative applications

Differently from biophysical sensors, devices that aim at the monitoring of biochemical signals (such as those derived from metabolites, electrolytes,

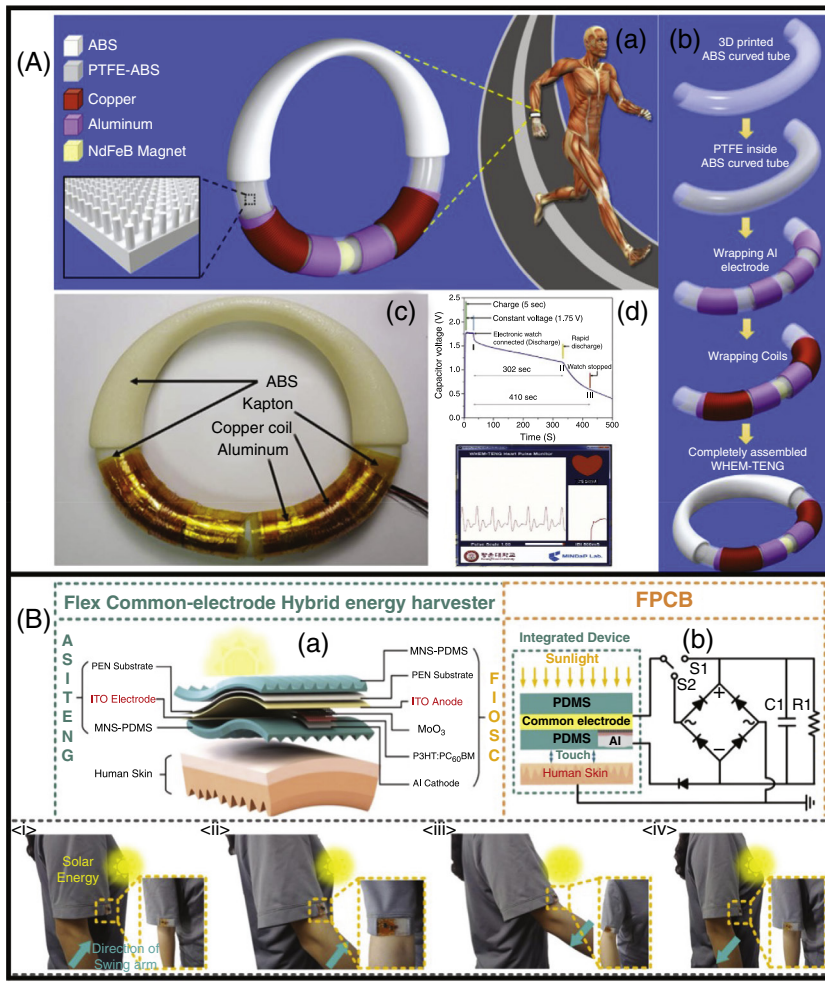

FIG. 10.3 (A) Wearable hybrid electromagnetic-triboelectric nanogenerator. (a) Acrylonitrile butadiene styrene printed nanogenerator. (b) Device construction. (c) Real device assembly. (d) Charging profile and real-time heart rate monitoring. *Adapted with permission from reference 56. Copyright 2018 Elsevier.* (B) Wearable and self-cleaning hybrid energy harvesting system. (a) Device assembly on skin, based on polyethylene naphthalate-indium tin oxide electrode and PDMS substrate. (b) Integrated circuit employed for energy harvesting and motion detection. (i–iv) Arm swing–based energy harvesting mechanism with sensor embedded on garment, while also harvesting energy from sunlight exposure. *Adapted with permission from reference 57. Copyright 2020 Elsevier.*

drugs, and contaminants) do not majorly rely on signal reading variation due to tiny mechanical deformations. Also, biochemical integrative sensors may not necessarily require harvesting modules but might more readily benefit from multimodal and/or multiplexed detection. Thus, biochemical-aimed wearable devices are usually rather concerned with fluid sampling and the reading of a

physicochemical output that can be transduced into either an optical or electrical signal proportional to the concentration of the investigated analyte. Over the last decade, there has been an increasing number of works that propose different kinds of strategies to attain such a goal.

Traditionally, portable devices that aspired to provide the user with a fast and reliable biochemical screening employed invasive methods, such as blood collection.[61,62] However, these invasive strategies pose several inconveniences for the wearer, such as fear, pain, and even infection risks.[63] Consequently, alternative methods started to being sought after, among which the exploring of other biofluids (such as saliva, sweat and tears) began to draw considerable attention. Up to date, two great categories have thriven in the field of biochemical signals-aimed wearable sensors, namely electrochemical and colorimetric (or optical) devices.

Colorimetric wearable sensors offer the advantages of requiring a simple approach to signal transduction, lower weight of device, and can enable low-cost applications. As drawbacks, some colorimetric assays yield irreversible color changes (precluding continuous monitoring), while the color-changing process might not provide a homogeneous pattern for optical detection.[1] Some inspiring works have employed hybrid biochemical approaches, providing the user with both the reading of physiological signals (such as sweat volume rate and body temperature) and biochemical essays (such as the determination of sweat glucose, lactate, chloride, pH, and UV exposure) (see Fig. 10.4A,B)[14,64–66] Such strategies mostly benefit from the employment of multimodal or/and multiplexed detection, especially when colorimetric assays are used. As shown in Fig. 10.4A, a multiplexed wearable platform can be miniaturized to provide the user with a small device that can perform several assays at once. In addition to multianalyte detection, such hybrid sensors can be further augmented by the integration of physiological sensing elements, such as the addition of near-field communication (NFC) modules to the wearable system, allowing for the monitoring of vital signs, such as body temperature (Fig. 10.4B).

Electrochemical wearables started their journey with the first-generation enzymatic sensing, classically carried out by measuring oxygen concentration decrease or the production of hydrogen peroxide.[1] Now, electrochemical devices rely mostly on the second-generation (where artificial mediators carry electrons from catalytic sites to the electrode surface); some ground still needs to be covered in terms of the third-generation biosensors (the communication of the catalytic site to the electrode surface proceeds without the aid of mediators).[67] Despite providing a more flexible alternative for continuous monitoring biochemical information compared to colorimetric sensors, electrochemical/optical wearable devices might suffer from the influence of environmental changes to biorecognition elements (enzymes, antibodies, etc.) employed. Moreover, the need for a constant reaction process in the biofluid (such as in sweat) is another drawback that most biorecognition-based sensors need to confront. To tackle such obstacles, synthetic materials have been employed as enzyme substitute,

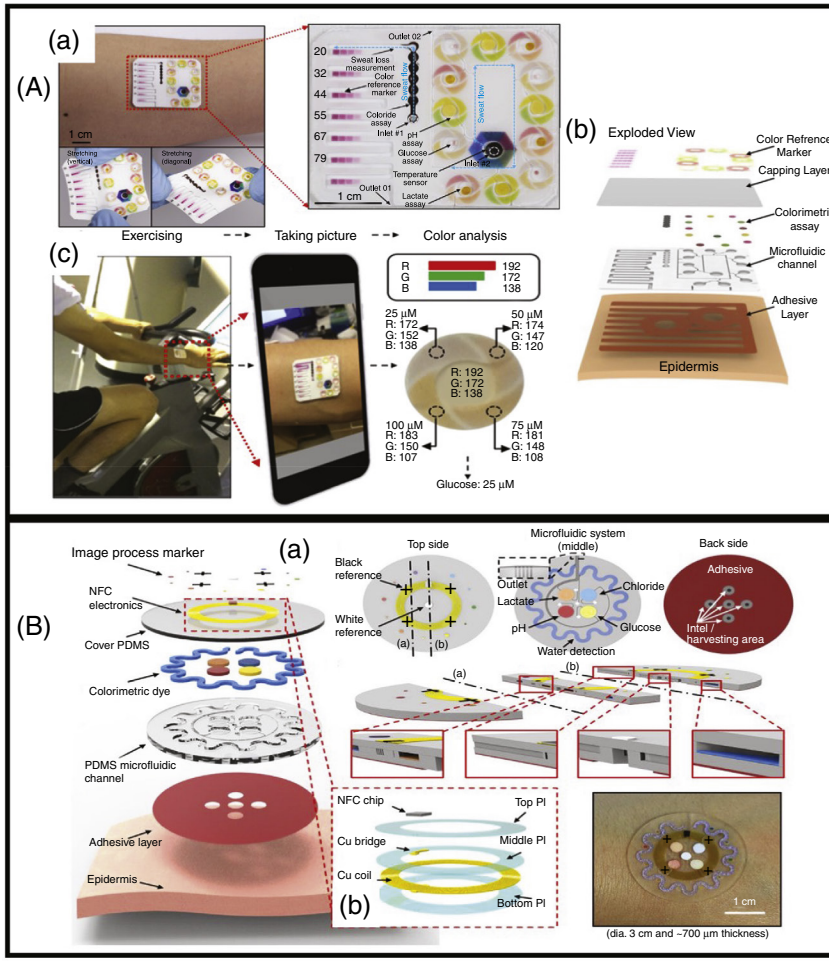

FIG. 10.4 (A) Soft, skin-integrated multifunctional microfluidic system for colorimetric analysis. (a) Wearable sensing platform on skin under mechanical deformation (stretching). (b) Device fabrication. (c) Real-time smartphone-based colorimetric detection of chloride, glucose, lactate, pH, and temperature monitoring. *Adapted with permission from reference 65. Copyright 2019 American Chemical Society.* (B) PDMS-based wearable hybrid sensor for sweat detection of bio-analytes. (a) Schematics of the assembly of the wearable, soft, microfluidic device employed for the colorimetric monitoring of lactate, glucose, sodium, pH, sweat volume rate, and body temperature (near-field communication (NFC) assisted). (b) Schematics showing the construction of the NFC module integrated onto the wearable device for the wireless monitoring of body temperature. *Adapted with permission from Reference 14. Copyright 2016 American Association for the Advancement of Science.*

allowing the nonenzymatic electrochemical detection of glucose in sweat.[68] Also, localized sweat stimulation attained with the employment of transcutaneous delivery of sweat-inducing drugs through iontophoresis has been attempted to continuously measure ethanol in sweat.[69]

10.5.3 Exploring further applications

As wearable hybrid sensors are on the rise both on the academic/experimental and commercial level, there have been several contributions to this topic over the last few years. Considering it to be a growing research area, there can be found a very diverse assortment of strategies employed for the fabrication of hybrid on-skin platforms. While some authors have geared their major interest toward the building of multiplexed detection platforms, aiming at a single device capable of performing a whole health panel screening, some other research groups have chosen to advance the field through creating multimodal, self-powered sensors. Thus, at this point it is still too soon to generalize hybrid sensors as a single category. Rather, hybrid strategies have been shown to become increasingly plural when it comes to how a wearable device may be built and how it operates optimizing the comfort experienced by the wearer.

In terms of commercial applications, wearable sensors have majorly advanced through the introduction of several wearable electronics that usually employ the multimodal and/or multiplexed detection strategy for biophysical signal. Some well-known examples of this class of devices are the smart watches,[70] such as the Mi Band (produced by Xiaomi) and the Apple Watch (produced by Apple). While both provide the user with beat-by-beat blood pressure screening, along with heartbeat rate and some hemodynamic scanning, the latter has recently launched an augment version capable of performing real-time electrocardiograms on the wearer without any external device.[71,72] Beyond the on-skin advances, there has been some progress on wearable devices that are surgically implanted in the wearer. One tremendous advance seen in this field is the introduction of automated low-flow pumps (Alfa Pump)[73] employed for the therapeutic control of refractory ascites in cirrhotic and cancer patients. The sensing activity of the device is given by the constant monitoring of the abdominal pressure built up by the accumulation of the ascitic fluid in the peritoneal cavity. This example is especially important considering it has offered individuals with a new and less invasive alternative to deal with a life-threatening condition that crushes the life quality of these patients.

Additionally, Table 10.2 shows some noteworthy works that have been developed in the aims of building new hybrid wearable sensors. As previously considered, it displays a diverse set of strategies, including multimodal, multiplexed, energy harvesting, and other types of approaches.

TABLE 10.2 Some important features of wearable sensors employing hybrid detection mechanisms.

Targets	Hybrid strategy	Signal detection	Flexible materials	Body placement	Reference
pH, biomarkers, electrolytes, sweat rate, and body temperature	Multimodal/ multiplexed	Colorimetric	PDMS	Volar forearm and lower back	14
Strain and temperature sensing	Multimodal	Resistive	Conductive hydrogel/ thermochromic elastomer hybrid fibers	Along wrist-finger segment	19
Heart rate, deep breathing, cough, and blood oxygen saturation	Multiplexed	Light emission detection	PDMS-based stretchable waveguide, AgNWs matrix and organic photodetector	Fingertip	74
Temperature and humidity sensing	Multiplexed/ self-powered	Capacitive	Rigid sensor	Shoes	75
Electrocardiogram, photoplethysmogram, blood pressure, electromyogram, body fat, pulse wave, respiration and skin temperature	Multimodal/ multiplexed	Piezo-resistive, pyro-resistive, electrometric, opto-metric, and hybrids	Flexible printed circuit board	Wrist and over face	76
Sweat lactic acid and urea, and strain sensing	Multimodal/ multiplexed	Fluorescence sensing and resistive approach	Office paper	Body joints	77
Temperature and humidity	Multiplexed	Resistive	Cotton fabric	Garment	78

Electrocardiogram and body temperature	Multimodal/ multiplexed	Thermistor and voltage reading	Kapton polyimide substrate	Lower left rib cage	79
Sweat lactate and electrocardiogram	Multimodal/ multiplexed	Amperometric and voltage reading	Highly flexible polyester substrate	Fourth intercostal space of the chest	80
Sweat glucose and urea	Multiplexed	Colorimetric	Cotton thread	Tested on artificial sweat only	81
Touch, temperature, pressure, and electromyogram	Multimodal/ multiplexed	Impedimetric and resistive approach	Substrate-free conductive nanomeshes laminated directly on skin	Forefinger	82
Optical reflection and temperature related to compromised blood circulation	Multimodal	Temperature sensor and optical reflection sensor	PDMS	Induced compromised circulation in rat models	83
Storage of electrochemical energy from sweat lactate oxidation for further use	Biochemical integrative/energy harvesting	Lactate is enzymatically oxidized, and the generated electrical energy is harvested by textile-based hybrid supercapacitor-biofuel cell	Lycra shiny milliskin nylon spandex fabric	Wrist	84
Sweat temperature, pH, and concentrations of chloride, glucose and lactate	Multiplexed	Colorimetric	Soft silicon elastomer	Forearm, forehead, chest, and armpit	65

10.6 Conclusions and outlook

So far, much has been done in terms of advances in wearable hybrid sensors, encompassing a multitude of new possibilities. As shown in this chapter, on-body devices can integrate multiple analytical and signal processing strategies, which can be engineered to obtain sensors capable of carrying out the determination of multiple analytes and body signals. Also, these wearable hybrid sensors can perform continuous monitoring, and even the conjugation of all the retrieved information with powerful cutting-edge in-built energy harvesting and storage intelligent systems coupled with the latest Internet-of-things trends. In this sense, there is a promising future for body- and garment-worn hybrid platforms.

However, some obstacles need to be attended in this near future to augment the robustness and reliability of sensors. Such challenges include the unsettling relationship between sensor stretchability and sensitivity, which has been shown to operate in mismatched ranges (while the stretchability expects an intact morphology of the electrically conducting element, sensitivity usually relies on morphological changes under small mechanical stress). Another obstacle is related to the simplicity and the seamless integration of flexible substrates and electronic circuitry. While there is a great progress in this area, much must be done to provide the wearer with a compact, simple, and thoroughly comfortable wearable device.

Abbreviations

IoT	Internet-of-Things
NFC	Near-field communication
NP	Nanoparticles
NW	Nanowires
PDMS	Polydimethylsiloxane
PEDOT:PSS	Poly[3,4-(ethylenedioxy)thiophene]:poly(styrenesulfonate)
POC	Point-of-care test

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Chapter 11

Smart-agriculture: wearable devices for plant protection

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11.1 Introduction

Taking advantage of modern agriculture, the expanding global population has been provided with sufficient, diverse, and high-quality foods, especially in those less developed countries and regions where people's daily diet has been much improved, helping people free of famine and malnutrition issues while boosting local economy.[1] However, the appealing bonus of modern agriculture, such as high crop yield and high quality, largely relies on the intensive input of agrochemicals, for instance chemical fertilizers and synthetic pesticides, which has generated alarming environmental issues including biodiversity decline, soil deterioration, and contamination of water resources.[2–4] In recent decades, the rising public concerns on food and environmental safety that emerged from modern agriculture intensification have been translated into more rigorous standards in agricultural products and environments,[5–7] which stands in the urgent need for highly efficient, versatile, and eco-friendly strategies to monitor and manage the overall process of agricultural production.

Growing crops is never easy. In particular, due to the long-term intensive and mono-cultivar cultivation, the frequent occurrence of various pests (including arthropods, vertebrates, pathogens, and weeds) has presented a huge threat to the high-quality production of grains, vegetables, fruits, and other crops. To maintain high-quality and sustainable production of crops, a myriad of practices on the basis of plant protection science has long been critical and practical to prevent unbearable economic losses and related social consequences from agricultural pests that damage or interfere with plant growth, including the use of pesticides, the adoption of biological controlling approaches, and even genetically modified strategies.[8–10] Instead of the sole use of agrochemicals to control pests, the scope of modern plant protection

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has shifted to adopt more ecosystem-based ways, for instance the global implementation of integrated pest management (IPM), in which the biological control using pests' predators and parasites is highly recommended to adopt with reduced agrochemical input.[11–12] Over the past 40 years, strategies such as IPM have provided valuable paradigms to boost crop yield while minimize survival hazard and risks toward nontarget organisms.[13–14] Despite these agroecosystem-based approaches being practiced widely, the continued high consumption of agrochemicals still likely leads residual issues to affect food quality and environmental security, challenging the long-term stability and sustainability of agroecosystems.[15–16] As a result, how to monitor the relationship between ecological well-being and the efficacy of pest management has long been a tough task.

On the basis of biological, ecological, and meteorological factors, various techniques have been discovered capable of monitoring plant stress to predict the likelihood of pest occurrence, which helps save valuable time for effective practices to refrain economic losses. Besides, chromatographic instrumental analyses have been taken as the golden rules to provide the most reliable and precise qualification and quantification of pesticide residues for safeguarding food and environmental safety.[17–19] However, routine approaches usually demand high economic capability and well-trained professionals to operate, which seems insufficient for the on-site large-scale applications. Recently, inspired by the impressive achievements in material science, increasing attention has been paid to employ multiple materials (i.e., hybrid systems) and recognition elements-based sensing strategies to develop accurate, rapid, versatile, integrated, and user-friendly platforms for modern plant protection, aiming to monitor crops' status and stress (including plant growth, infection and the possible risk from residual agrochemicals). Among those, wearable devices, which generally refer to a group of sensors that are flexible, stretchable and portable to be worn directly on the point of interest (e.g., on a user or a plant surface),[20–21] have offered a revolutionary technological alternative for a wide range of applications from personal healthcare to biomedical monitoring.[22–24] Lately, taking advantage of tremendous advances in microfabrication, mobile and telemetric devices, material science, flexible electronics, and their integration with the sensing modalities, we have witnessed the exciting progress in the design and fabrication of wearable devices,[25–27] which inspires researchers to introduce them for agricultural aims. Due to their promising properties such as high accuracy, availability, and feasibility in direct real-time detection with simultaneous feedback, wearable devices have gained raising interest for altering the routine methods in plant protection with less money, time, and labor. In this chapter, we focus on the key advances of how to enable wearable devices in monitoring plants during the last 5 years, highlighting their abilities, challenges, and prospects for field applications, and their potential in balancing agricultural disturbance and ecosystem sustainability (Fig. 11.1).

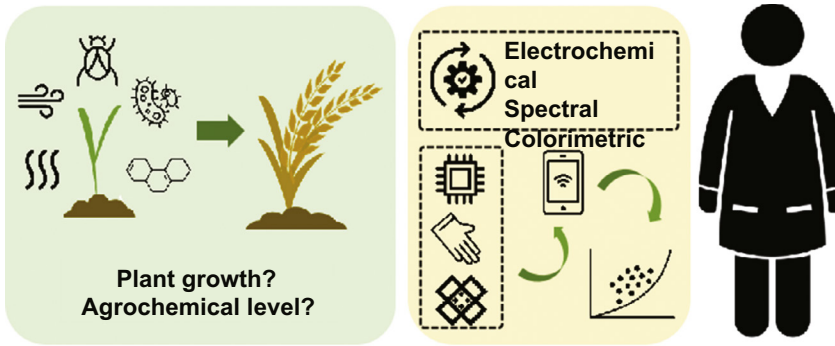

FIG. 11.1 **The generic demonstration of wearable sensing devices used for plant protection.**

11.2 Wearable devices for monitoring plant status under stress

The growth of crops suffers from various ambient stress including heat, frost, drought, and salinity, which are blamed as the major causes for yield loss. Meanwhile, the intensification of agriculture increases the frequency and intensity of fungal/bacterial pathogen-, virus-, and nematode-related invasive plant diseases, which dramatically impair crop productivity that may fail to meet the growing demand of food without effective protection.[28] More importantly, agricultural production is also faced with the inevitable challenge of global climate change that would accelerate and magnify all the mentioned stress for crop plants.[29–30] According to the guidance of plant protection, the most effective approach to control plant diseases is not the application of pesticides after infection, but the timely prevention by integrated practices based on early symptoms such as visible changes in color and shape on the host surfaces (leaves, stems and fruits) and the appearance of small spots to lower the possibility of pathogen infection. As the invasion activity and virulence capacity of most plant pathogens are easily affected by environmental conditions, the rapid detection of temperature and humidity changes as well as the sensitive diagnose of pathogen identities play a critical role in effective prevention.

For a long time, the conventional approaches for plant monitoring depend on active imaging systems and molecular high-throughput identification by adopting the polymerase chain reaction technique.[31] As mentioned, though being standard and highly accurate, these methods require large investments, limiting their possibilities to proceed outdoor large-scale tasks. Inspired by the recent achievements of nano-biotechnology, increasing chemo/biosensors capable of diverse applications have emerged thanks to the use of novel and sensitive biorecognition elements, which were reviewed in details by Kwak *et al.,*[32] Giraldo *et al.,*[33] and Dincer *et al.*[34] Notably, as a current trend of sensors, wearable devices seem to be appealing candidates to construct the new generation platform for sensing plant stresses stemming from complex external factors for their

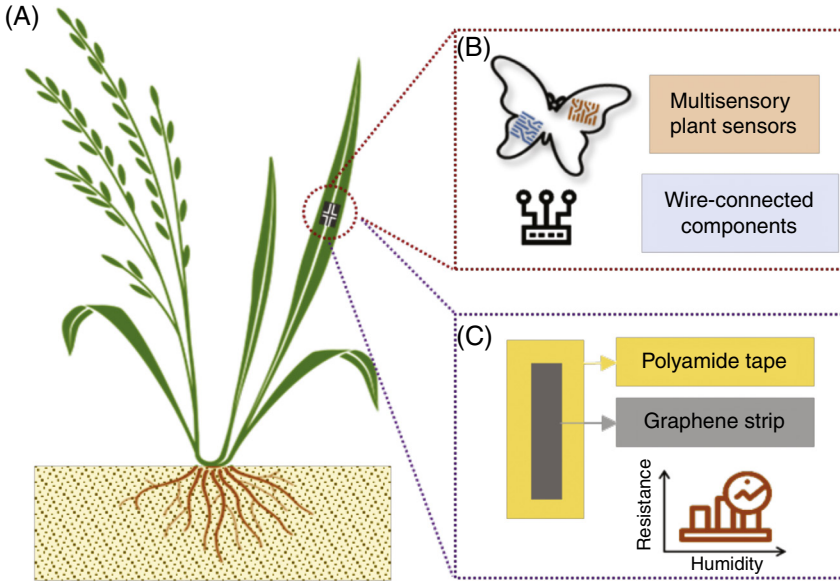

FIG. 11.2 Wearable devices for monitoring plant status under stress. (A) The schematic of placing sensors on the surface of plant leaf. (B) The flexible, thin, ultra-lightweight and stretchable butterfly-shaped sensors for the real-time monitoring of temperature and humidity levels via the electrical wires–connected system components (including a miniaturized programmable-system-on-chip and rechargeable battery);[35] and (C) the on-tape RH graphene sensors for estimating water movement within a plant.[37]

excellent sensitivity, flexibility, and portability, underlying the need for noninvasive, miniature and biocompatible plant sensors (Fig. 11.2).

Similar to those wearable devices for personal health, one of the most important aspects for designing wearable devices for plants is to select lightweight, stretchable, flexible, and biocompatible materials to avoid mechanical injury on leaf or stem surface while seamless sensing. Consequently, those flexible, low-cost, and easy-to-modify materials are widely applied as substrates for wearables. To record plant growth, a strain-sensing wearable device was fabricated by depositing a thin gold metal film on polydimethylsiloxane (PDMS) membrane, which was ultra-lightweight, highly robust, stretchable, and biocompatible to monitor the elongation of barley stems.[35] Meanwhile, a multisensory platform for microclimate detection using flexible and light butterfly shaped polyimide/PDMS membrane has also been demonstrated. This electronic sensor was easily anchored to plant leaf surface, exhibiting long-term stability, high sensitivity to temperature, and humidity and low costs.

Besides, the large family of carbon nanomaterials are promising candidates as substrates not only for their intensively studied potential for multiple sensing, but also for their flexibility, diversity, and ultra-lightweight that are expected to miniaturize the devices.[36] For instance, a graphene-patterned PDMS tape was

fabricated as relative humidity (RH) sensors to track the time required for water movement within a plant from the roots to the leaves. By installing these RH sensors on leaf surface, the variation in electrical resistance of graphene caused by the changing local humidity due to leaf stomata opening was recorded to estimate the time point of water loss.[37] Unlike the microclimate monitoring, this graphene@PDMS-based tape sensor developed a simple, effective, and noninvasive approach to monitor the physiological status of crop plants, offering accurate data during plant growth. Moreover, plants have evolved complex signaling mechanisms to trigger systemic defense against stressful conditions and hazardous organisms in response to survival challenges. During these processes, the concentration fluctuations of phytohormones, glucose, sucrose, cytosolic Ca^{2+}, and other small molecules are intricately linked to defense mechanisms in plants, which are commonly targeted for decoding the adaptive responses of plants against stress. Based on the uncovered H_2O_2-related postwounding signaling pathway, single-walled nanotubes (SWNTs) were specifically tailored according to corona phase molecular recognition (CoPhMoRe) framework as nondestructive optical probes that allowed real-time, high spatial and temporal resolution for monitoring H_2O_2 *in vivo* via fluorescence signals in the near-infrared range where living tissues were relatively transparent, which exhibited general adaptability for several plant species.[38] This smart SWNT probes-integrated optical monitoring design was different from the widely applied electronic sensing approaches, offering novel, low power, and biocompatible wearables for plants.

Aside from ambient stress, the frequent incidence of plant diseases challenges agricultural productivity globally, and even leads to devastating crop losses in less developed countries and regions. Instead of classic molecular detection methods, the pathogenic DNA-, antibody-, aptamer-based biosensors exhibit strong potential for rapid, highly specific and sensitive, and reproducible detection of plant diseases.[39–40] However, the genetic analysis of pathogens requires multistep extraction and purification, and thus, sensors are usually constrained to realize *in-situ* noninvasive detection of plant disease. Alternatively, the volatile organic compounds from plant foliage could be used as target analytes to establish specific platforms capable of identifying pathogen species. Li *et al.*[41] developed a portable paper-based colorimetric sensor device that employed cysteine-functionalized gold nanomaterials and organic dyes for noninvasive and precise detection of characteristic leaf volatiles (at the ppm level) emitted by *Phytophthora infestans* that causes late blight in tomatoes. By integrating plasmonic nanostructures as sensing elements and a portable smartphone reader, the foliage volatiles-marked device has facilitated smart, flexible, cost-effective diagnosis of plant disease in field. Although this design was not achieved by wearable seamless sensing, it has encouraged the usage of a large range of key diagnostic markers of infectious plant diseases, which could motivate a novel direction for developing noninvasive plant wearables.

To date, compared to the extensive study of wearables for human healthcare, wearables in plants have just started their journey. Those aforementioned proof-of-concept designs may clarify the basic rules for plant wearables including (1) characteristic markers for specific detection, (2) high sensitivity, (3) noninvasive sampling, and (4) user-friendly signal readout. Incorporating with recent progress in artificial intelligence and Big Data technologies (see Chapter 12), the next-generation wearable devices are expected to enable more precise, automatic, remote, and labor-saving on-site monitoring of plant status, which would largely contribute to a large-scale cooperative network allowing in-time plant protection.

11.3 Wearable devices for detecting pesticides from agricultural products and environment

Besides the maintenance of plant growth, the core aim of plant protection is to prevent yield loss from phytophagous insects and competitive weeds. As a group of the most widely used agrochemicals, synthetic pesticides have substantially enhanced agricultural productivity by the effective control of pests. In fact, less than 30% of applied pesticides can be successfully absorbed by plant blades and perform their pest-killing/repelling and weed-controlling functions. As a consequence, a large portion of applied pesticides transfers and accumulates in the edible crops and environmental matrices by rainfall and vaporization, and eventually causes ubiquitous pesticide residual contamination and potential risks of exposure.[42–43] More concernedly, the unprecedented biodiversity decline in the atmospheric and terrestrial ecosystems has emerged as a major consequence of the long-term extensive input of pesticides.[4,44] In response to the rising public concern over pesticide residues in food, water, air, and nontarget ecosystems, the coercive ban of highly toxic pesticides for agricultural uses has been globally authorized and gradually implemented under the guidance of the Rotterdam Convention on prior informed consent.[45] To better avoid healthy risks from residual pesticides; however, the effective, economic, and easy-to-operate approaches are still needed for rapid and accurate pesticide detection, which has become one essential task of sustainable development of modern plant protection.

Pesticide detection has long relied on chromatographic analysis, which performs with excellent accuracy and precision but requires well-equipped labs with expensive instruments and trained professionals. By harnessing recent progress of sensing techniques, a myriad of rapid, versatile, and miniature methods have emerged, aiming to provide competent alternatives to tackle the lack of applicability of chromatographic analyses for developing reliable field-deployable detection platforms. In the process of (bio)sensing, the specific recognition of pesticide compounds by abiotic or biotic elements plays a vital role that enables accurate extraction and identification of target pesticides from real samples against potential interferences. Different from those complicated

instrumental analysis, the ability of *in-situ* precise and rapid qualification of compounds has been of the greatest importance, facilitating a wide range of (bio) sensing platforms as a new generation technique for pesticide detection. More importantly, numerous materials with dimensional and functional advantages have been employed not only as the scaffold carrying pesticide-recognizing elements but also as the key signal transferring and magnifying component to establish miniature and portable devices for on-field applications. The existing literature elaborates many different materials to construct feasible (bio)sensing platforms for tracing pesticides from environmental matrices and agricultural products.[46–49] Inspired by these concepts, we have witnessed the recent booming emergence of pesticide-sensing approaches coupling with varied recognition mechanisms and advantageous materials, which lays a critical foundation for the advanced construction of wearable devices for pesticide detection.

Due to the lack of simplicity and applicability in real applications, most proof-of-concept (bio)sensing platforms worked under laboratorial conditions but failed to meet the ultimate need for *in-situ* pesticide monitoring. Benefited vastly from the ingenious sensing strategies with versatile material assembly, this bottleneck flaw is substantially improved by one of the most powerful strengths of wearable devices, the portability.[50] Regarding the pesticide recognition methods in wearables, the selective capture of pesticide compounds can be realized by abiotic recognition thanks to structural affinity (e.g., nanoparticles, molecularly imprinted polymers and metal-organic frameworks), or by biorecognition elements (e.g., antigen-antibody, DNA/RNA, aptamer, protein, etc.). Moreover, a bunch of functional skeleton materials endow wearable devices with remarkable sensibility in on-field applications, which efficiently transduces the pesticide-recognizing event into an easy signal readout, such as colorimetric changes to simplify the testing procedure. In terms of its portability, the adoption of disposable gloves, tattoos, and tapes provides various miniature sensing forms to minimize operational difficulties for *in-situ* application. To date, based on the methods to read out the pesticide-recognizing reactions, wearable devices can be divided into three major categories: electrochemical, spectroscopy-based, and colorimetric devices (Fig. 11.3, Table 11.1).

11.3.1 Wearable electrochemical devices

Thanks to their remarkable properties such as high sensitivity, fast response, and instrumental simplicity, electrochemical sensors have long been a powerful tool to measure changes in current, potential, conductance, or impedance occurring at redox reactions by pesticide recognition on modified electrodes.[51] Taking advantage of material science, flexible electronics, and their integration with various sensing modalities, electrochemical techniques have driven the tremendous progress of the design and fabrication of wearable devices. In a well-designed configuration of a wearable sensor, it contains three essential components, which are the substrate (to support the sensing architecture), the

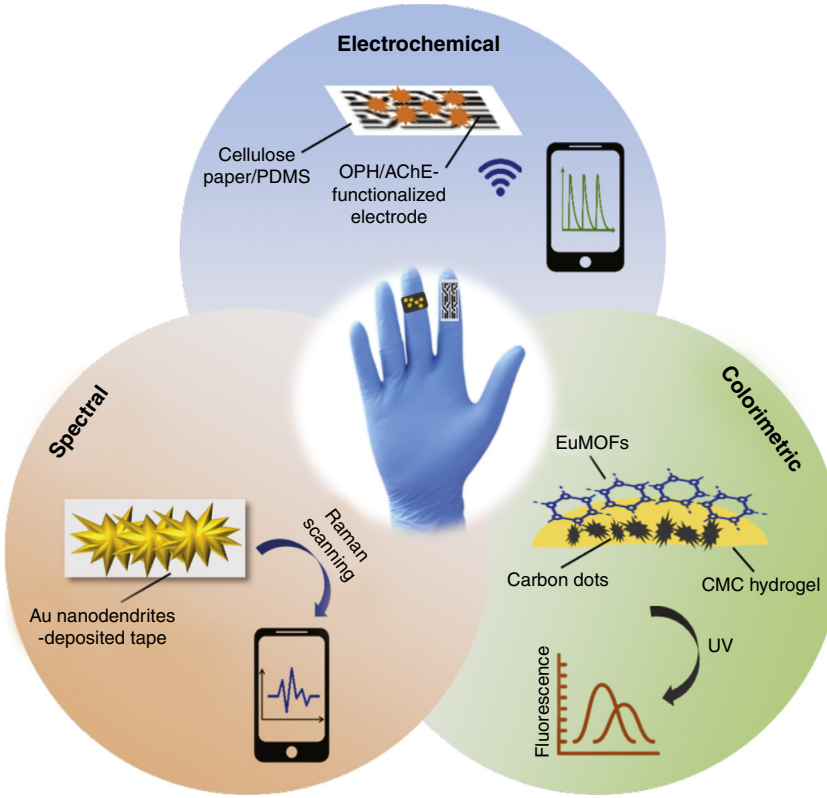

FIG. 11.3 Wearable devices for detecting pesticides from agricultural products and environment. Based on the lab-on-a-glove platform, the noninvasive sampling and rapid detection of OP pesticides is realized by several representative strategies. The enzyme OPH/AChE-functionalized electrodes enable the electrochemical detection of OPs.[55–56] Using Au nanodendrites-deposited conductive tape, spectroscopy-based detection of pesticides can be realized by a portable SERS method.[66] Carboxymethyl cellulose (CMC) hydrogel integrating with EuMOFs and carbon dots (CDs) is capable for the fluorescent detection of chlorpyrifos.[74]

active layer (including pesticide-recognition materials or electrical circuits), and the interface (that works as an adhesive layer to keep the active layer on the substrate). Previously, typical methods and common materials to design and fabricate such flexible electrochemical devices have been comprehensively reviewed.[25,52]

More specifically, the materials as qualified substrates should be flexible and stretchable to adjust the strain movement on skin surface. As some pesticides could be toxic and highly bioavailable, the substrates need to be stable and chemically inert as a shelter to prevent possible epidermal contact with toxic pesticide compounds, which commonly are polymers (polyethylenimine), cellulose fiber (paper, textile), and PDMS. In the active layer, structure-modified or biorecognition element–decorated electrodes are capable

TABLE 11.1 Representative designs and features of wearable devices for on-site pesticide detection.

Transduction method	Recognition element	Substrate	Signal readout	Sensitivity	Features	Reference
Electrochemical	Organophosphate hydrolase (OPH) and pH-sensitive polyaniline (PANi)	Tattoo paper	Potentiometric	10 mM	Miniaturized device, epidermal compatibility, and wireless data transmission	Mishra *et al.*[54]
	OPH enzyme	Nitrile glove	Voltammetric	200 μM	Lab-on-a-glove device, swipe sampling, stratchability, real-time wireless data transmission	Mishra *et al.*[55]
	AChE-functionalized electrodes	Nanoporous gold leaf tape	Amperometric	0.53 pM	Peel-and-stick detection	Hondred *et al.*[56]
Spectroscopy-based	Gold nanoislands	Plasmonic tattoo paper	SERS	0.1 μM	Green fabrication, *in situ*, *ex situ*, and multiplexed detection	Wang *et al.*[65]
	Au nanodendrites-modified microwell	Patterned tape	SERS	10^{-5} M	Lab-on-a-glove device, facile operation module, and accessible signal readout	He *et al.*[66]
Colorimetric	Fluorescent EuMOFs and nanosized carbon dots	Glove with flexible aerogel	Colorimetric	89 nM	Flexibility, noninvasive swiping collection and rapid response	Xu *et al.*[74]
Multimodal	OPH enzyme	Epidermal tattoo/ textile	Voltammetric and colorimetric	12 mg/L	On-body sensing, wireless data transmission	Mishra *et al.*[81]

of designating pesticide molecules with high sensitivity and selectivity, and the signal of pesticide-binding is transduced by integrated external electronic circuits for a fast signal readout. For example, the stretchable organophosphorus hydrolase (OPH) enzyme electrodes were ink printed upon an elastomeric gelatin gel substrate to build up a flexible and resilient electrochemical sensor that was able to stick directly on epidermal skin like a tattoo.[53] When the vaporized organophosphorus (OP) agent (i.e., insecticide methyl paraoxon) reacted with OPH-decorated working electrode, an anodic peak current proportional was yielded and transduced wirelessly to a mobile device to offer rapid and selective square-wave voltammetric detection of OPs. The tattoo sensor performed with good selectivity against matrix interferences and a sufficient limit-of-detection (LOD) in terms of OP air density. Moreover, this study demonstrated the fabrication of textile-based OPH electrodes, which performed as sensitively as the skin wearables, showing considerable promise to produce pesticide-designated wearable electrochemical devices for better protection against toxic contact. According to the similar principle, an OPH-immobilized pH-sensitive skin-worn tattoo sensor was fabricated by monitoring local pH change due to the proton release during the enzymatic hydrolysis of OPs,[54] and the resulted potentiometric response was rapidly transmitted to a mobile device via Bluetooth. Further, the same research group presented a disposable "lab-on-a-glove" device integrating a printable OPH-based sensing system with surface swiping for collection and a compact electronic interface for real-time wireless data transmission which offers elevated flexibility, robustness, applicability, and simplicity for on-field detection.[55]

To further broaden the detection range, the adoption of nanostructured metallic materials and microfluidics significantly improves the sensitivity of enzyme-based electrochemical wearable sensors. In a previous study, the acetylcholinesterase (AChE)-functionalized electrodes were created by patterning the nanoporous gold leaf (NPGL) via electrochemical etching on a flexible adhesive polyimide substrate.[56] Integrated with the attractive advantages of NPGL such as high and tunable surface area, electrical conductivity, biocompatibility, and rich surface chemistry, the prepared device can be used as disposable peel-and-stick tape sensors or on-body sticker sensors for the rapid detection of paraoxon with high sensitivity, which offered great promise for alerting pesticide exposure in field settings.

Recently, some studies demonstrated a novel and facile approach coupling with 3-D origami paper–based electrodes to prepare electrochemical pesticide-sensing devices.[57] In this regard, cellulose paper is used as an integrated platform to load printed electrodes and active regents (i.e., enzymes). Through paper folding/unfolding, pesticides in samples are contacted with preloaded reagents on electrodes to produce signals that can be read and quantified by mobile devices. More importantly, the origami design allows the loading of multiple recognition elements, which realizes more selective analysis with

improved sensitivity (down to ppm level for even real environmental samples) or simultaneous analysis for several pesticides.[57] For on-field applications, these miniaturized portable origami-like sensing devices can be carried on arms like bandages,[58–59] which demonstrate the great potential for the *in-situ* rapid pesticide detection by even unskilled operators with simplified procedures.

11.3.2 Wearable spectroscopy-based devices

Unlike electrochemical detection that transmits pesticide-recognizing signals through integrated flexible electronic board, spectral analysis distinguishes target pesticides based on the spectrum differences due to the unique physical properties of each compound (such as atomic structures, absorbance and composition), which realizes simultaneous qualification and quantification of target pesticides by one scan with portable devices. In fact, common spectral analyses are intensively employed for chemical detection with high accuracy including spectrophotometry and infrared (IR) spectroscopy.[60–61] Similar to the laboratory-based chromatographic techniques, conventional spectroscopy-based methods show limited applicability to meet the rising needs of rapid, easy, and sensitive on-site detection of interested chemicals. However, the current advances in portable miniaturized devices enable the fast and reliable readout of spectrum signals, such as handheld Raman spectrometers. Combining with the tremendous progress in (bio)sensing strategies and flexible materials, wearable spectroscopy-based devices are promising candidates to be expanded as an important class for on-site detection of pesticides with high sensitivity, feasibility, and simplicity.

Among currently available portable spectroscopy devices, the handheld Raman spectroscopy is one of the most widely adopted miniature equipment for point-of-need applications. Particularly, the surface-enhanced Raman scattering (SERS) strategies are intensively exploited, applying multiple materials (such as noble metal nanoparticles, carbon materials, molecular-imprinted polymers) to enhance the sensitivity and selectivity of sensing systems as well as to magnify the Raman spectral response to pesticide-capturing event.[62–63] For instance, a silver nanoparticle–decorated nanocellulose film demonstrated good sensitivity and reproducibly as a flexible jellylike SERS substrate to realize noninvasive sampling and rapid analysis of pesticide thiram and thiabendazole.[64] Further, another sensing platform was fabricated using the gold patterned-paper as a SERS tattoo that allowed the *in-situ* detection of pesticide thiabendazole from fruit surface,[65] highlighting the considerable potential of SERS methods for the on-site pesticide measurement. Therefore, a new trend of wearable devices depending on SERS platforms is currently emerging, and their advantages include the robustness, feasibility, and simplicity for a sensitive quantification of pesticide(s) due to the spectral identities. For example, an Au nanodendrites-modified microwell carbon tape was fabricated to anchor target pesticides via microdroplets as well as to improve SERS activity, which

exhibited a lab-on-a-glove tape sensor with a facile operation module and accessible signal readout that was capable for on-site detection of multiple pesticides.[66]

Besides, more advanced functional materials are employed to improve the sensitivity and selectivity of SERS platforms. In this case, the authors proposed the integration of the surface plasmon-polariton supported gold grating surface with the metal-organic framework (MOF-5) as a perfect SERS probe for sensitive, selective, and reproducible SERS detection of OPs with a sensitivity down to fM-range.[67] Due to the portability of SERS instrument, the Au/MOF-5 grating complex holds considerable potential to be expanded to environmental conditions such as the soil matrix, which endows the SERS-based devices with broad applicability for on-field applications.

Due to the unique physicochemical properties of each chemical species, the qualification and quantification of pesticides according to their adsorption/emission/scattering/IR spectral differences have an inherent strength in terms of selective measurement. Besides, the tremendous development of portable Raman scanners has vastly facilitated more SERS-related spectral detection of pesticides, which may bring more impressive devices in the close future.

11.3.3 Wearable colorimetric devices

Compared to the electrochemical and spectroscopy-based methods requiring an external device for signal readout, colorimetric approaches have drawn massive interests due to their direct visualization of target-capturing reaction to realize on-site rapid tests by the naked eye.[68–69] Based on the AChE-induced enzymatic colorimetric reaction, the first generation of pesticide colorimetric tests has been fabricated and commercialized for decades, in which the cellulose paper featured high stability and adsorption capacity has been employed as a flexible and easy-to-functionalization substrate to immobilize AChE enzymes and color-alterable dyes. However, the practical application of the first-generation paper-based detection was hindered as the AChE enzymes are only available for recognizing OPs and carbamates, leading to the lack of selectivity and availability for most pesticides as well as the disability for quantification. Thanks to the remarkable progress in material science and novel (bio)recognition elements (such as aptamers, DNA, full cells, MIPs, luminescent MOFs, etc.), the next generation of colorimetric detection has been largely improved to have versatile (bio)sensing properties, such as high selectivity, sensitivity, broad availability, simple fabrication, and most importantly, the capability to enable analyte quantification via optical changes. Currently, to further enhance the practical applicability and efficiency of visual detection, the design of wearable colorimetric devices with marked simplicity in device configuration and operational procedure are emerging with considerable potential to offer feasible platforms for *in-situ* pesticide analysis.

Among these devices, the cellulose (paper)-based platforms are dominant in the colorimetric sensors due to their abundance, low cost, high stability, and

adsorption, which seem to be one of the most attractive candidates for the large-scale fabrication and on-site applications.[70–71] Interestingly, as the changes in colorimetric properties could be caused by various factors (such as thermal, structural and electrochemical changes), numerous wearable colorimetric devices are designed coupling with other advantageous methods to improve their sensitivity and applicability, aiming to give rapid and visual information readable by the naked eye. In particular, the newly developed origami paper designs help to vastly enhance the selectivity and sensitivity of paper-based devices for on-site sensing. For instance, as their flower-like structures allow the separate loading of multiple enzymes (including AChE, choline oxidase, and horseradish peroxidase) and functional materials, the origami paper devices enable the fabrication of all-in-one enzyme-inorganic hybrid nanoflowers for the dual optical and electrochemical (i.e., multimodal) sensing, and reach an LOD down to the femtogram/mL level for paraoxon.[72]

Alternatively, the "lab-on-a-glove" devices have appealed growing interests in wearable sensing for several reasons: (1) flexibility, stretchability, and robustness of substrates; (2) noninvasive and rapid swiping collection of samples; and (3) epidermal protection to minimize exposure to toxic pesticides. These glove-based platforms have readily demonstrated their promising advantages in creating wearable electrochemical devices.[73] In the design of colorimetric wearables, the application of novel materials could enhance selectivity and sensitivity of the system without compromising simplicity and thus, has been intensively exploited. For instance, a one-off "lab-on-a-glove" device that integrated CMC aerogel as a flexible host with europium metal-organic frameworks (EuMOFs) for red emission and nanosized carbon dots for blue emission as two fluorescent centers was demonstrated.[74] The luminescent EuMOFs (as a working center) can be quenched due to the competitive absorption effect by target chlorpyrifos while the blue emission of carbon dots (as a reference center) had no response to chlorpyrifos. Based on the changes in fluorescent color and density, the multiple elements–decorated nitrile glove performed a naked-eye ratiometric double-signal detection of chlorpyrifos by noninvasive swiping with rapid response (30 s) and a high sensitivity (nM-range).

On the other hand, recent advances demonstrate certain materials that can reversibly change their colors or optical properties through redox reactions, which have brought out a novel class of substrates to fabricate more flexible and functional wearable devices, offering a great opportunity to further miniaturize the devices with more simplified operational procedure and clearer signal reading.[75] In this case, by integrating iridium oxide nanoparticle-deposited electrochromic material with pesticide chlorpyrifos-recognizing molecularly imprinted polypyrrole, the electrochromic chemosensor was able to identify and quantify chlorpyrifos by direct visual inspection and smartphone imaging with a superior LOD (100-fM range).[76] These sensitive, selective, flexible, and miniaturized electrochromic architectures offered good repeatability and reproducibility for a novel sensing method for portable and visible detection of interested pesticides.

11.4 Current challenges and conclusion

The implementation of proper plant protection practices is aimed to prevent crops against stress from environmental factors and pest species, and to safeguard the quality security of agricultural products in a sustainable manner. As an excellent alternative for instrumental analyses, the use of (bio)sensors has demonstrated powerful strengths to provide versatile, reliable, and cost-effective monitoring platforms, which would greatly help to facilitate the progress of intelligent and efficient crop protection in the modern agriculture. Particularly, we are witnessing the inspirational advances in wearable devices integrating the (bio)sensing techniques, flexible and portable platforms, and smart data transmission, which bring novel insights and possibilities to further improve their performance and feasibility for on-site applications. However, constant efforts are still highly required to realize the ultimate large-scale implementation of wearable devices in agriculture, which seems to be currently constrained mainly due to the big challenge of how to optimize those "proof-of-concept" platforms for industrial production while maintaining their advantageous features such as high sensitivity, efficiency, simplicity, and stability against environmental interferences. To be more specific, the lack of standardized fabrication of (bio) sensing elements as well as the lack of flexible readout electronics for device configuration would detain the reliability and repeatability of monitoring and the efficiency and accuracy of signal transmission.

It is noteworthy that the emerging trend in agricultural mechanization and intellectualization with data-oriented management has broadened general interests toward automatic, intelligent, and sustainable development for plant protection. That would encourage more academic efforts and industrial capital to be invested to overcome the current difficulties of wearable sensing devices, showing their tremendous potential to create a new era of smart agricultural production. For instance, novel facile platforms such as paper/polymer-based microfluidic devices capable of multiplexed sampling and synchronous sensing are widely attractive due to their improved detection efficiency.[77–78] Also, a new class of artificial intelligence technologies integrating machine deep learning network has contributed to the more precise prediction of agricultural conditions.[79–80] Most importantly, lessons must be learned from the precedent agricultural intensification at the cost of environmental compromise, so the sustainability of all expected measures should be adequately considered and evaluated. In this regard, the usage of biocompatible and sustainable materials without potential risk would be a core edge for wearables sensors in the future smart agriculture.

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Abbreviations

AChE	Acetylcholinesterase
Au	Gold
CD	Carbon dots
CMC	Carboxymethyl cellulose
EuMOFs	Europium metal-organic frameworks
IPM	Integrated pest management
IR	Infrared
LOD	Limit of detection
MIP	Molecularly imprinted polymer
NPGL	Nanoporous gold leaf
OPH	Organophosphorus hydrolase
OP	Organophosphorus
PDMS	Polydimethylsiloxane
RH	Relative humidity
SERS	Surface-enhanced Raman scattering
SWNTs	Single-walled nanotubes

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Chapter 12

Internet of wearable things

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12.1 Wearables and Internet of Things

We have witnessed a significant progress in the design and fabrication of wearable sensors and their applications in different sectors such as healthcare and fitness, medicine, sport, lifestyle, communication, safety, security, and business in recent years.[1–6] However, achieving the ideal wearable sensors that can meet our growing expectations and needs in different areas requires parallel developments in various fields such as electronics, (bio)chemistry, information technology (IT), business, computer science, etc.

An advanced (i.e., smart) wearable device (combining sensing with theragnostic capabilities) should be sensitive, specific, self-powered and remotely monitorable, reportable, programmable, and controllable. For example, a smart wearable device, while being self-powered, can analyze and monitor the body's glucose correctly and accurately, warn us if there is any increase or decrease in the glucose level, send the data if needed to users, medical centers, doctors, and even predetermined people. Moreover, at the same time, this device might inject the appropriate dose of insulin according to the smart data resulted/analyzed via smart algorithms/patterns tailored to the background and diet of the patients. Such smart analysis will lead to precision medicine and personalized healthcare, which encourages smarter decisions and a more decentralized form of care and eventually empowers users.

To achieve such smart wearable devices, they should have this capacity to collect, transmit, and receive the data via a smartphone (or an alternative smart readout device such as a laptop or tablet) for further data analysis via new digital technologies such as big data analytics (BDA), machine learning (ML), deep learning (DL), and artificial intelligence (AI), which requires an inter/intraconnectivity and data exchanging ecosystem between such devices, other systems, and finally their end-users. In this regard, Internet, due to its unique and fascinating features, can be the most ideal channel of communication and candidate for such connectivity.[7] Since its advent, Internet has immensely changed our life, so that nowadays it has become an integral part of our daily life. Besides, such universal connectivity opens up new doors and provides a unique infrastructure for implementing new solutions, that is, smart solutions.[8]

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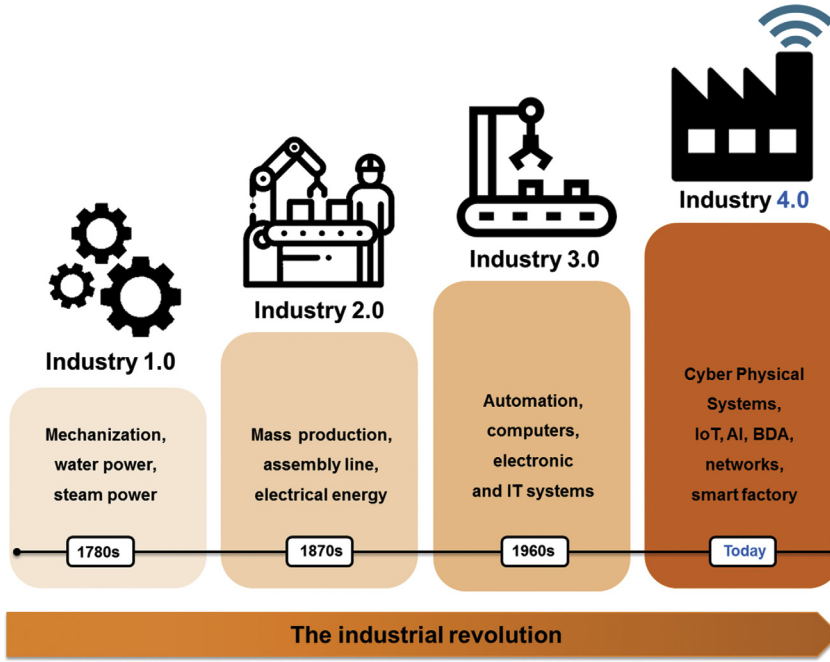

FIG. 12.1 **Evolution of industrial revolution.**

Keeping such Internet influence in mind, billions of users and edge devices/things have been connected to each other via Internet.[9] Such novel paradigm for connecting "things" or "objects" to Internet is known as the "Internet of Things (IoT)".[8] IoT is a digital technology for connecting things and exchanging the data with other devices and smart systems via Internet; consequently, those "things" can be sensible, reportable, controllable, and manageable.[10] Given the wide range of IoT applications in healthcare, industry, education, agriculture, smart homes, and smart cities, the number of Internet-connected devices is projected to reach over 50 billion by 2020 with a $3.04 trillion market.[11] IoT proved to be the next big thing not only in supply chain management, IT, and network market but also in the healthcare, building, energy, life science, consumer, home, industry, transportation, retail, security, and public safety sectors in Industry 4.0 era.[12]

Industry 4.0, the fourth industrial revolution is a term that is used for the next industrial revolution and closely connected to IoT, cyber-physical system (CPS),[13] information and communications technology, enterprise architecture, and enterprise integration.[14–17] This industrial revolution has been preceded by three others in the history of mankind. After mechanization (Industry 1.0), mass production (Industry 2.0), and automation (Industry 3.0), the idea of IoT influenced the approach of industry 4.0. Fig. 12.1 shows the evolution of the industrial revolution.[14–17]

It is noteworthy that IoT in Industry 4.0 era also personalizes products with the accurate engineering of user-specific devices, which generates exceptional results with the aid of physical, chemical, and biologicals sensors.[18,19] Innovative

services, patient data analysis, sensors devoted to disease diagnosis, waste recycling management, precise surgery, medical imaging, accurate information, medical researches, and digitally service management are some of the important capabilities of Industry 4.0 or better called Healthcare 4.0 in the medical field.[18] Wearables in Healthcare 4.0 era provide innovative and smart services to users by analyzing the data through sensors and IoT. IoT is in the heart of Industry/Healthcare/Analytics 4.0.[20,21] Without such a revolution, we may not be able to witness its advancements in different fields. In fact, IoT is the backbone of cyber-physical evolution and smart manufacturing in Industry 4.0 era.[22]

Derived from IoT, one of the evolving areas in Healthcare 4.0[21] is Internet of Wearable Things (IoWT).[23] IoWT, as its name suggests, connects wearable devices to Internet and as an emerging technology derived from IoT has revolutionized the healthcare industry and attracted huge attention with its special characteristics in recent years. The number of internet connected wearable devices worldwide is forecasted to account for over one billion, with a total of more than $90 billion market in 2022.[24]

Wearables in the form of smart devices, including but not limited to contact lenses eyeglasses,[25–30] patches bands,[31–36] tattoos,[37–39] bandages and wound dressings,[40–44] have become popular in recent years. What makes all of these wearables unique, is their connectability to Internet. Based on such capability via IoT technology and smartphone gateways such as Wireless Fidelity (Wi-Fi), Bluetooth, near-field communication (NFC), and other communication technologies, data can be sent to cloud servers or smartphone for real-time monitoring, storage, and analysis to generate the smart data:[45] On-device or cloud-based analysis.[46]

12.2 Toward IoWT

IoT is empowering a more tailored and personalized form of care where users are "self-managing" and "self-monitoring" their own well-being and suppliers can make such experience much more improved and precise at the point-of-use.[47] High costs of centralized healthcare, delay in providing services, not being tailored and personalized to users' needs and high-probability of different kinds of errors are some of the main reasons for the transition from centralized to decentralized healthcare and that is the philosophy behind wearables' popularity and their collaboration with IoT. Such deduction can be attributed to other types of wearables as well.[19] Fig. 12.2 shows two different timelines: the above timeline is related to IoT and the below one to wearable technology. In parallel with the progress made in both technologies over the past decades, in 2013, as highlighted in Fig. 12.2, IoT and wearables have reached an intersection and consequently, IoWT has emerged. It is noteworthy that such a viewpoint about the emergence of IoWT is based on our above-mentioned definition of ideal wearables.

IoWT-based devices, due to their capability of "sensing, computing, and communicating"[48] are the ideal starting point for the above-mentioned transition from centralized to decentralized healthcare systems. Real-time connectivity, low latency, availability, small sizes, user-friendly designs, Internet-connected gateways, cloud

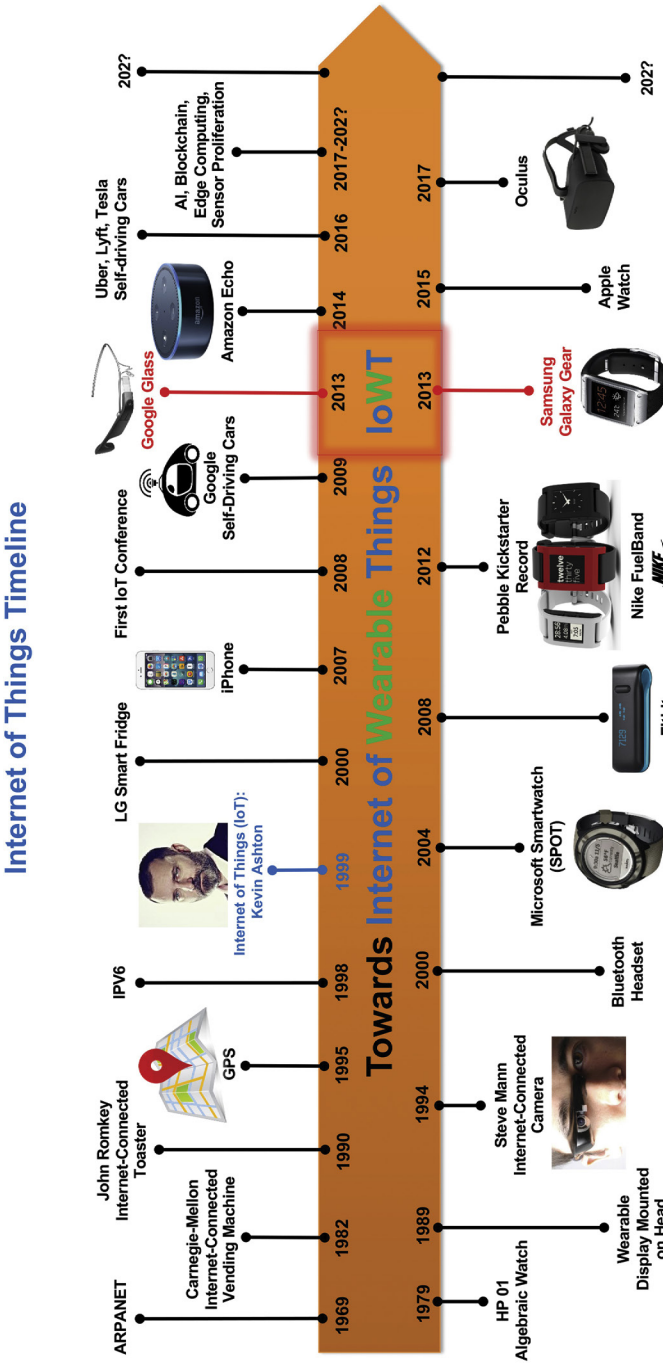

FIG. 12.2 Historical timelines of IoT and wearable technology toward Internet of Wearable Things.

and big data support, personalization, patient-physician interaction, telemedicine/telehealth, and the ability to couple with smartphones are some of the characteristics and philosophy behind such exciting collaboration between wearables and IoT, which outweigh the disadvantages such as security and privacy concerns.[48–50]

It is worth mentioning that reaching real-time connectivity is only possible via smartphones (or alternative devices) and fog computing via Internet. Smartphones with a lot of fascinating characteristics such as being user-friendly, fast processors, high-resolution camera, large-capacity, embedded systems (i.e., Bluetooth, Wi-Fi, NFC) are the best interoperable and mediators for connecting all these wearables in an ecosystem via Internet to reach a higher level of smartness for a smarter living/health: A 24/7 lab in our pocket.[51,52] On the other hand, compared to the cloud, fog computing offers low latency, geographical and large-scale distribution, mobility and location awareness, flexibility and heterogeneity, and scalability.[53] That is what we need to establish a decentralized ecosystem capable of handling our growing expectations and needs in Industry 4.0 era. In fact, smartphones and fog computing provide a high level of interoperability and lowest latency, respectively.[53]

Connecting a wearable sensor to a smartphone and end-user, transmitting the data to the fog and cloud servers, and a decision-maker, optimizing the results via new digital technologies such as ML, DL and Al—for precision medicine and personalized healthcare—are only possible with Industry 4.0 technologies and their infrastructure. Such a process can be translated as a classical foundation for IoT: an edge device (physical layer) via smartphone (perception layer) with the presupposition of connectivity to Internet collects via Wi-Fi or mobile data (network layer), transfers, and present the results (application layer). Wearables' coupling with smartphones not only provides real-time connectivity but also with the proliferation of mobile apps, they can be more personalized to users' needs and reach smart connectivity via new digital technologies.

Successful implementation of IoWT requires some modifications on the hardware side, a smart architectural framework, cloud and fog analysis, and BDA to observe and record human health status and provide smarter solutions based on such data. Therefore, apart from hardware developments, software improvements such as an architecture/roadmap tailored to users' needs based on IoT concept is highly demanded as well.[36,54,55] Moreover, such fast growth of wearables mentioned above will lead to a large accumulation of data, which is called "Big Data."[56] Different types of analytical techniques for better applicability of wearables based on such big data are needed. New digital technologies such as BDA,[56] blockchain,[57] data mining,[58] neural network,[59] ML,[60] DL,[61] and AI[62] are some of them. Integrating these new digital technologies for better interoperability and application of IoT devices is of paramount importance and demanding job. In this regard, we have already recommended a four-layer (either between or mediating) conceptual model for better interoperability and functionality of our developed wearable sweat patch.[36] Such a model can be a roadmap for similar works in the field of wearables as well. Certain protocols corresponding to each layer have also been proposed (see Fig. 12.3).

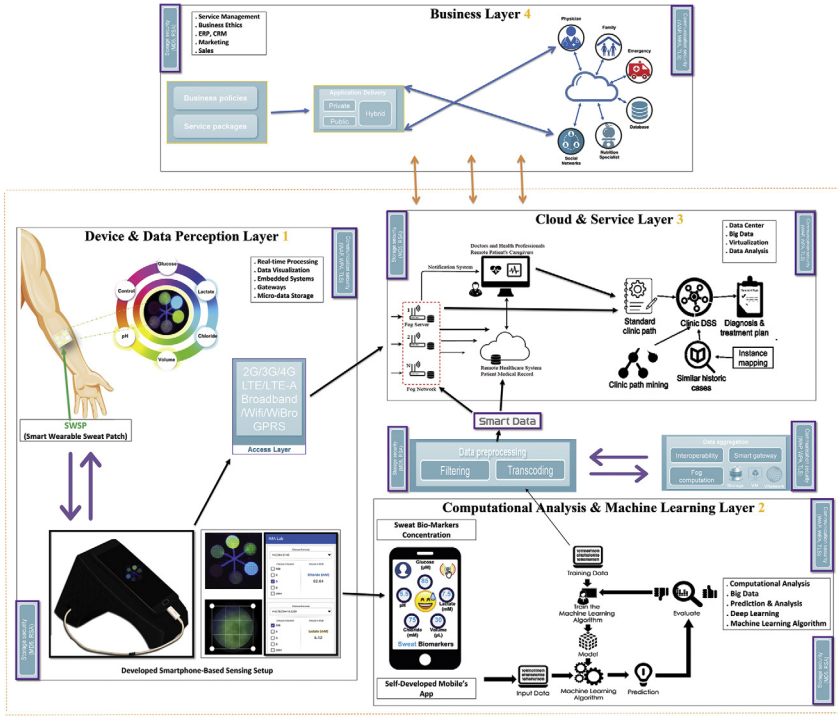

FIG. 12.3 An exemplary IoWT model recommended for the developed smart wearable sweat patch. Reprinted with permission.[36] *Copyright 2020, Elsevier.*

This model is based on the notion and combination of the Edge-Fog-Cloud approach to optimize the data resulted from the developed sweat patch with the help of ML and cloud computing with mediating the role of fog approach to improve and enhance real-time and computational analysis, data storage, and service management for end-users. ML, cloud computing, BDA, data processing, security, smart data, computational analysis, business service management are inseparable parts of the proposed model. The focus of the recommended model is on the smartphone. The use of smartphones made such collaboration between different layers possible. We took smartphones as IoT gateways to reach interoperability and created our own tailored ecosystem.[63] Prior to transmitting the data to the cloud, data will be analyzed and purified via an ML algorithm for generating smart data with the mediating role of fog computing. Generating smart data will lead to smarter applications and services such as mHealth,[64] e-Diagnostics,[65] and telemedicine/telehealth.[66]

For a general view about the recent studies in the field of IoWT, some of the developed/developing IoWT-based devices, which have been used for physical, biological, and chemical sensing applications, are provided in Table 12.1 along with their applications, wearability, connectivity, and interoperability.

TABLE 12.1 Overview of some of the developed IoWT-based devices used for physical, biological, and chemical sensing applications.

Wearable sensor	Application	Wearability	Connectivity	Interoperability	Reference
Apple watch	GR and HC	Wrist-worn	Bluetooth	Smartphone	67
Samsung watch	GR and HC	Wrist-worn	Bluetooth	Smartphone	68
Smartwatch	HC/identify atrial fibrillation	Wrist-worn	Bluetooth	Smartphone	69
Google smart glass	HC/rapid diagnostic test reader	Face-worn	Bluetooth	Smartphone	70
Google smart lens	HC/tear glucose monitoring	Eye-worn	Wireless	Smartphone	25
Smart eyeglasses	HC/monitoring of lactate and K^+ in sweat	Face-worn	Bluetooth	Smartwatch, Smartphone/laptop	26
Smart contact sensor	HC/glucose monitoring	Eye-worn	Wireless	Smartphone	27
Smart contact lens	HC/tear glucose and intraocular pressure monitoring	Eye-worn	Wireless	Smart reader	28
Smart contact lens	HC/tear glucose monitoring	Eye-worn	Wireless	Smartphone	29
Smart contact lens	HC/tear glucose monitoring	Eye-worn	Wireless	Smart reader	30
Smart sensor arrays	HC/monitoring of glucose, lactate, Na^+, and K^+ in sweat and measurement of skin temperature	On-body	Wireless	Smartphone	31
Cardiac sensor patch	HC/remote and ambulatory monitoring of cardiac and heart rate	Chest-worn	NFC	Smartphone	32
Multifunctional wearable patch	HC/diagnosis and therapy of movement disorders	On-skin	Wireless	NR	33
Fully integrated electrochemical sensor	HC/simultaneous monitoring of Ca^{2+} and pH in sweat, urine, and tears	On-body	Wireless	Smartphone	34

(*continued*)

TABLE 12.1 (Cont'd)

Wearable sensor	Application	Wearability	Connectivity	Interoperability	Reference
Chemical–physical hybrid patch	HC/real-time monitoring of sweat lactate and electrocardiogram	On-skin	Bluetooth	Laptop/smartphone/tablet	35
Smart microfluidic sensor patch	HC/monitoring of sweat biomarkers (glucose, lactate, pH, chloride, and volume)	On-body	Wireless	Smartphone	36
Tattoo sensor	HC/sweat alcohol monitoring	Skin-worn	Bluetooth	Smartphone	37
Tattoo sensor	HC/sweat alcohol and ISF glucose monitoring and sampling	Skin-worn	Wireless	Laptop/smartphone/tablet	38
Tattoo sensor	HC/sweat Na^+ monitoring	Skin-worn	Bluetooth	NR	39
Smart bandage	HC/wound uric acid monitoring	On-body	Wireless/RFID/NFC	Laptop/smartphone/tablet	40
Smart bandage-microneedle sensor	HC/skin melanoma screening	On-body	Wireless	Laptop/smartphone/tablet	41
Smart bandage	HC/chronic wounds monitoring	On-body	Wireless	Smartphone	42
Smart dressing	HC/wound pH monitoring	On-body	Wireless	Smartphone	43
Multifunctional wound dressing	HC/wound pH monitoring and drug delivery	On-body	Wireless	Smartphone	44
Fully perspiration-powered smart electronic skin	HC/multiplexed monitoring of metabolic biomarkers (pH, NH_4^+, urea, and glucose) and physical parameters (strain, temperature, and pressure)	On-skin	Bluetooth	Laptop/smartphone/tablet	71
Human motion–powered smart sensor patch	HC/sweat Na^+ and pH monitoring	On-body	Bluetooth	Smartphone	72

GR, general; HC, healthcare; ISF, interstitial fluid; RFID, Radio-frequency identification; NR, not reported.

12.3 Concluding remarks and future perspectives

In this chapter, we highlighted the features of smart wearable sensors, the importance and necessity of their development, and how to approach them via IoWT. Here, the role of Internet as the most ideal candidate for inter/intraconnectivity of wearables, IoT, new digital technologies such as BDA, ML, DL, and AI, smartphones as IoT gateways, and fog computing in the development of smart IoWT devices in Industry 4.0 era have been discussed along with the philosophy and timeline of IoWT. An exemplary IoT-based model, which is designed based on smart analysis facilitated with the assist of new digital technologies such as ML and subsequently smart data generation, has also been highlighted for better functionality and interoperability of wearables toward IoWT. Without such smart data analysis/generation, wearables seem useless in the future, especially in smart cities.[73,74] Smart cities are based on IoT and it is the paradigm shift that empowers citizens in different areas such as healthcare and transportation.[75] The philosophy behind such smartness is to make their lives easier via smart services/solutions. Therefore, without smart data analysis behind future products, they are useless and, in this regard, wearables are no exception.

Internet of Medical Things (IoMT), e-diagnostics, and telehealth/telemedicine are some good examples of such transformation that endorse such a claim. Besides, some of the developed/developing IoWT-based devices utilized for various physical, biological, and chemical sensing applications along with their applications, wearability, connectivity, and interoperability have been overviewed.

In the following, there are some challenges ahead that should be met for the widespread applications of IoWT technology in the future. The standardization and interoperability are among these issues that should be considered in the development of future IoWT sensors as there is a variety of wearable devices, which are using different platforms (such as iOS, Android, Linux, etc.). In this regard, Standards Developing Organizations such as ITU-T, ISO/IEC JTC 1, W3C, and OIC have started working in this area.[76] As its availability and unique nature of smartphones, by coupling all our wearable devices with smartphones, we can reach a high level of interoperability and standardization. Besides, with 5G, and probably 6G in the near future, all latency issues can be solved and subsequently all forthcoming efforts focused on standardization, security, and privacy of the digital data generated via wearables.

Furthermore, IoWT has brought a new challenge for the research community. Most of the wearables are battery/NFC-powered, therefore their limited battery-life is a bottleneck that needs to be tackled. Apart from ethical and security challenges, energy-efficient solutions are other active research issues for wearable sensors.[6] Future IoWT sensors should wirelessly be operated and self-powered. In this regard, more recently, Wei Gao's research group have developed a flexible and self-powered electronic skin (e-skin) that can be utilized for continuous and real-time multiplexed monitoring of key biomarkers of sweat (e.g., urea, glucose, NH_4^+, and pH) and physical parameters (e.g., temperature, pressure, and strain) and wirelessly transmitting the personalized information

data via Bluetooth communication to a mobile user interface. Interestingly, the implemented e-skin can efficiently harvest its energy through lactate biofuel cells from human perspiration with a long-term stability.[71] They have also developed a battery-free wearable sweat patch/sensor that can reliably and efficiently extract its power from human body motion and wirelessly send data to the user.[72]

Last but not least, IoWT will pave the way for a more decentralized form of healthcare and effectively reduce turnaround time,[77] society cost,[78] and carbon footprints.[79] As a piece of a larger puzzle, they will help us to reach an ideal destination proposed by the social thinker, Jeremy Rifkin: "Zero Marginal Cost Society."[80] He believes that Big Data will make us happy via the digitized global network called IoT.[80] He theorizes how every "thing" will be linked via sensors and software to the IoT platform, frequently feeding big data to every node from homes, vehicles, businesses, etc. "Rifkin sees IoT as allowing economic exchange through a collaborative commons that will eclipse the capitalist marketplace and save the planet."[80] That is what ideal future smart cities are trying to reach and build.

Given the fascinating and unrivaled features of IoWT sensors and their ever-increasing development, they will have a significant role in the progress of future smart cities. Moreover, by learning from the current coronavirus disease 2019 (COVID-19) pandemic situation, whose rapid and unbelievable mortality/morbidity rate has shocked the whole world, and by considering the potential capability of IoWT sensors for real-time, continuous, and widespread monitoring of respiratory infections especially at early and even presymptomatic stages, we believe these smart wearables can play a pivotal role in control, surveillance, management, and more importantly prediction and prevention of the next possible epidemics/pandemics.[81–83]

Abbreviations

AI	Artificial intelligence
BDA	Big data analytics
DL	Deep learning
E-skin	Electronic skin
IoMT	Internet of medical things
IoT	Internet of things
IoWT	Internet of wearable things
IT	Information technology
ML	Machine learning
NFC	Near-field communication
Wi-Fi	Wireless fidelity

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