

Review

Advances in Wearable Chemosensors

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Abstract: In this review, the latest research on wearable chemosensors is presented. In focus are the results from open literature, mainly from the last three years. The progress in wearable chemosensors is presented with attention drawn to the measuring technologies, their ability to provide robust data, the manufacturing techniques, as well their autonomy and ability to produce power. However, from statistical studies, the issue of patients' trust in these technologies has arisen. People do not trust their personal data be transferred, stored, and processed through the vastness of the internet, which allows for timely diagnosis and treatment. The issue of power consumption and autonomy of chemosensor-integrated devices is also studied and the most recent solutions to this problem thoroughly presented.

Keywords: wearable chemosensors; flexible electronics; electrochemistry; biomarkers; biological fluids

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1. Introduction

The term “Chemosensors” was most probably introduced in 1928 by De Castro as mentioned by Butler and Osborne [1], referring to the function of free nerves in biological systems. An explosion, however, has been happening lately since numerous papers on this topic are published every year. Moreover, the tremendous technological revolution in low-priced microelectronics under Android and other open-source operating systems (OS) for micro-devices has opened a new wide field in the market for the so-called “wearables”. Already we possess, or it is very affordable to obtain, wearable smart-micro-devices, sometimes incorporating cell-phone features, which also have special sensors installed allowing for our blood pressure, blood glucose, saturated oxygen SpO₂, cardiac rhythm, and of course, body temperature [2]. It is needless to mention that whole new pathways have opened into the detection of biochemical substances [3] and indices such as the pH of human sweat [4], or the epidermis [5], as well as the pH values of other body fluids, critical for the health of female organism [6]. Details in the progress made in recent optical, electrochemical, and transistor-based sensors provide an overview of the status of the scientific efforts towards pH sensing, especially as candidate sensors for wearable devices [7]. Optical sensors are especially projected to have a bright future ahead of them due to their intrinsic noninvasive character [8].

It is anticipated that wearable biometric monitoring devices (BMDs) and artificial intelligence (AI) will enable automatic diagnosis and patient biometric data collection and cloud storage in the next decade. Unfortunately, the biomedical community has not yet reached the point where a patient fully trusts a wearable device for diagnosis and health-monitoring. In a recent study performed on adult patients with chronic conditions in France [9], a mere 20% considered that the benefits of wearables technologies (e.g., improving the reactivity in care and reducing the burden of treatment) greatly outweighed the dangers. Only 3% of participants answered that possible negative aspects such as improper use of human intelligence, risks of data server's hacking, and private patient

information misuse greatly outweighed potential benefits. It was established that as much as 35% of the patients would refuse to endorse at least one existing or soon-to-be-available application using BMDs and AI-based tools to benefit their healthcare. Accounting for patients' perspectives will allow for exploiting BMDs with AI without impairing the human aspects of care, generating a burden or intruding on patients' lives.

Another interesting issue in wearables is the electrical power, as most of them are supported by one-use or rechargeable batteries. However, studies point out that it is feasible to harvest thermoelectric energy from the human body heat via the Seebeck effect [10]. This methodology seems to be an effective route to develop flexible and miniature thermoelectric generators, enabling an uninterrupted power supply for the wearable devices or corroborating the charging of internal batteries.

This review study aims at presenting the latest progress achieved mainly in the last three years in wearable chemosensors with a focus on healthcare monitoring, due to the intense scientific work invested worldwide, the developments in most sensor types as part of integrated wearable systems will be presented. Evidently, a particular paragraph is dedicated in this work to fully developed wearable sensors or devices. However, one can discover proposals and studies devoted to the concept of "artificial nose", i.e., sensor systems, providing sensory effects for vapor [11] or aromatic oils [12], and those in the most modern trend of "wearables" [13,14]. Still, the concepts mentioned above exist as differentiated ones, to a certain extent.

Marching into the second decade of the 21st century, we already have a possible pathway above the biocompatibility of chemosensors in healthcare to follow at least: we must design and produce chemosensor wearables for unified, unique, ubiquitous, and unobtrusive (U4) for customized quantified output as stated by Haghi et al. in 2020 [15].

2. Technical and Science Background

2.1. Model Structure of a Typical Chemosensor

According to the International Union of Pure and Applied Chemistry, a chemosensor is defined 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" [14]. As shown in Figure 1, a typical chemosensor consists of two main functional units: a receptor that selectively recognizes the analytes of interest with high sensitivity and transforms their concentration into a physical or chemical output signal, and a transducer that alters this output signal to a readable value. Moreover, there is a signal amplifier circuit, a microcontroller, and wireless communication modules for the signal transmission to different displays, such as a mobile phone or smart watch.

Wearable chemosensors can be categorized based on their receptors as affinity or catalytic-based, as well as on sensing principles as electrochemical, capacitive, calorimetric, piezoelectric, optical, and piezoresistive sensors [16–18]. Over the past decade, due to the evolving of new technologies, many types of wearable sensors have been rapidly developed since they can provide noninvasive monitoring and real-time information of a wearer's health status in daily life. Apart from health monitoring, they can be used to improve athlete's fitness, the optimization of soldier's performance [18–20], and a wide range of purposes like security, communications, and business [19–21]. More specifically, wearable electrochemical sensors have received great attention because of their flexibility, portability, and biocompatibility, offering in situ personal health monitoring. Furthermore, the growing interest in those types of wearable sensors stems from the effort of decreasing health care costs transferring the centralized diagnosis and clinical monitoring of a patient at hospitals to personalized care at home [14,16,22,23]. Point-of-care-testing exhibit several advantages in patient's continuous health monitoring, such as convenient application for unskilled users, following of specific biochemical biomarkers, and a significant decrease of testing duration; however, it will never replace laboratory tests.

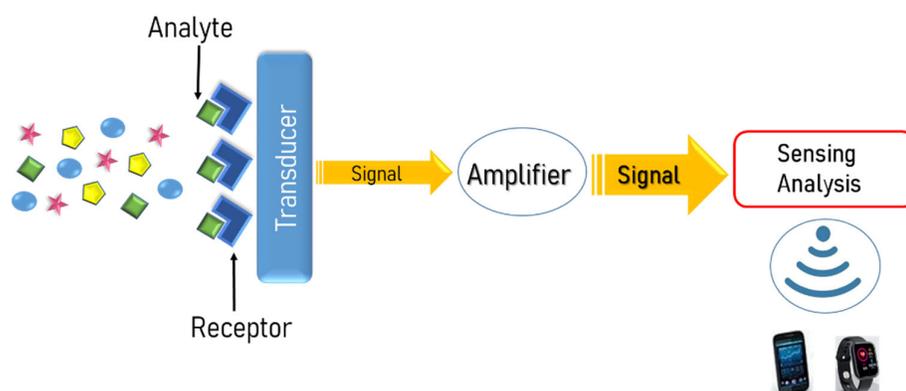


Figure 1. Schematic illustration of the basic functional units of a typical chemosensor.

2.2. Chemosensor Realization Technologies

Generally, wearable chemosensor platforms enabling remote detection and monitoring of analytes comprise three functional elements: (1) the sensing system for physiological signal's detection and collection, (2) the communication system for data transferring to a remote receptor, and (3) the data analysis system where the collected information from the sensing system will be extracted and evaluated [24]. The great requirement for highly sensitive, portable, and easy-to-use sensing devices that can provide important physiological information forced researchers to develop various detection platforms. Lately, advances in wearable chemosensors have been achieved due to the miniaturization of sensor's electronics, the progress in material science and engineering, the growth of wireless communication systems, and the advances in energy harvesting systems. Such an advanced system is presented on the example of pollutants detection in Figure 2.

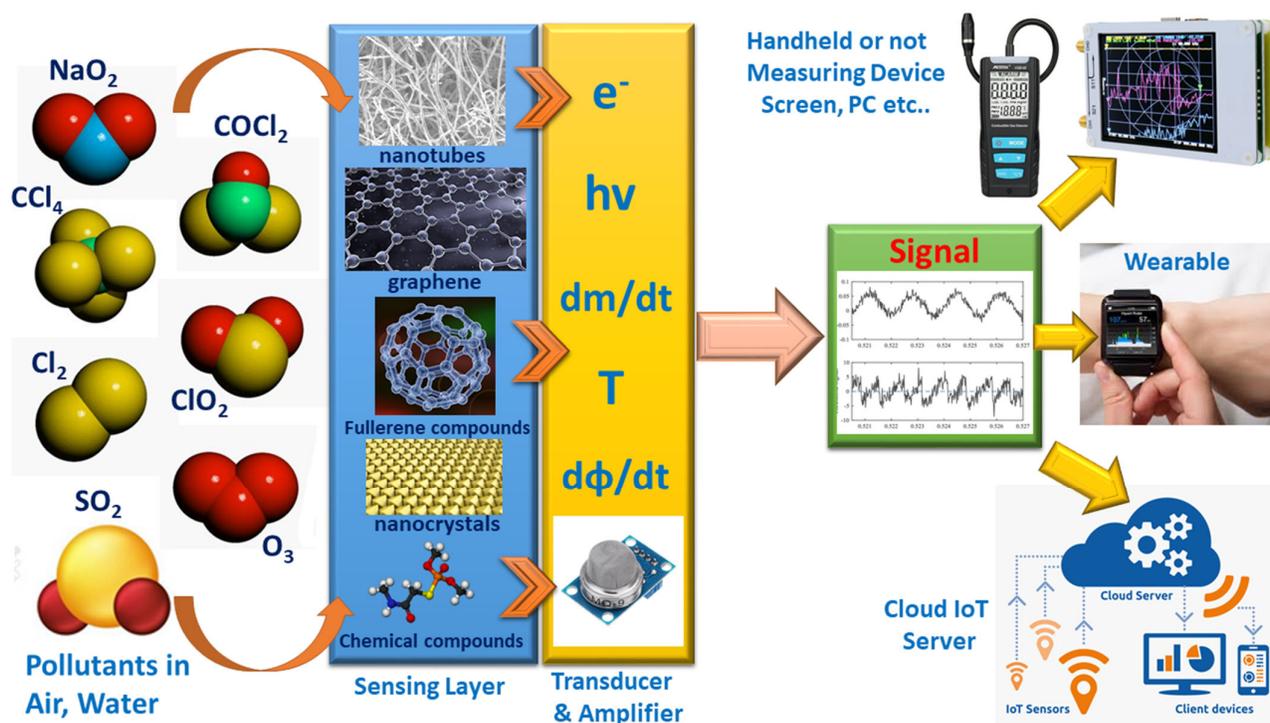


Figure 2. Schematic function-diagram of the functions of a modern chemosensor with its variants (wearable, device, and cloud-based).

The miniaturization of electronic circuits and devices has contributed significantly to wearable chemosensor's evolution since one of the major obstacles to further employment of sensing technology into wearable applications was the sensor's size. Recent advances in the field of microelectronics enable the development of miniature electronic circuits preserving sensing capability, microcontroller operations, and data transmission. Figure 3 illustrates the configuration of a typical example of a sensor employing this technology. The electronic microcircuit system is integrated onto a flexible substrate, detecting the targeted analyte's signals, and transmitting the corresponding data wirelessly via Bluetooth. Nowadays, miniaturized devices are widely used in many applications, taking advantage of design versatility, high analytical efficacy, and low cost due to the minimization of fabrication materials.

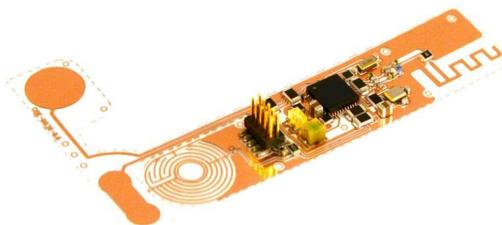


Figure 3. Bluetooth sensor circuit mounted on a flexible substrate. Source: <https://www.edn.com/product-how-to-build-your-own-designs-on-flexible-circuit-boards> (accessed on 20 March 2021).

Another essential component for the construction of wearable chemosensors is the sensing electrodes which are mostly metal-based films. Simultaneously, great efforts have been made for the development of new materials that could be used for the fabrication of wearable biochemical biosensors to ameliorate the sensor's functionality, such as carbon and polymeric materials, nanocomposites, and nanoparticles [25–27]. Furthermore, the flexibility and stretchability of biointegrated electrodes play a key role in developing wearable electronics since it is a crucial design parameter for the uninterrupted operation of the sensor's microcircuits. The term “electrode's stretchability” is defined as the electrode's ability to maintain its conductivity under mechanical deformation and can be quantified as the strain at which the electrode losses its conductivity and being nonconductive [28]. Since it is reported that even a minimum stretch of 1% could provoke a detachment of the electrode from the substrate [29,30], it is well understood that there is a high demand for high stretchability to preserve the seamless performance of the electrodes in the sensor device. Although there is difficulty finding materials that combine high conductivity and stretchability, composites of stretchable polymers with a conductive metal or carbon are used to obtain the desired properties [28,31].

Moreover, an emerging area for researchers in the field of chemistry is microfluidics [32,33]. Recently, microfluidics technology has gained attention because of the reduction in samples and solvent quantities required, resulting in lesser amounts of residue. This technology seems to have great prominence in wearable chemosensor platforms since it can be applied in portable sensor devices of various configurations and composition of the detector [33–35], whilst a local anesthetic (dibucaine) was detected with success at arrays of liquid/liquid micro interfaces [36]. Additionally, 2D and 3D printing technologies are used to develop new systems or upgrade existing ones, such as inkjet printing of wireless chemosensors [37]. Herein, further development and combination of the above-mentioned technologies with electrochemical techniques for the fabrication of miniaturized devices could guide a revolution in wearable chemosensors. Moreover, the combination of microfluidics with optics could guide applications for microfluidic drug delivery and drug screening [38], avoiding toxicity effects [39], as well as for tumor-treating [40] (Figure 4).

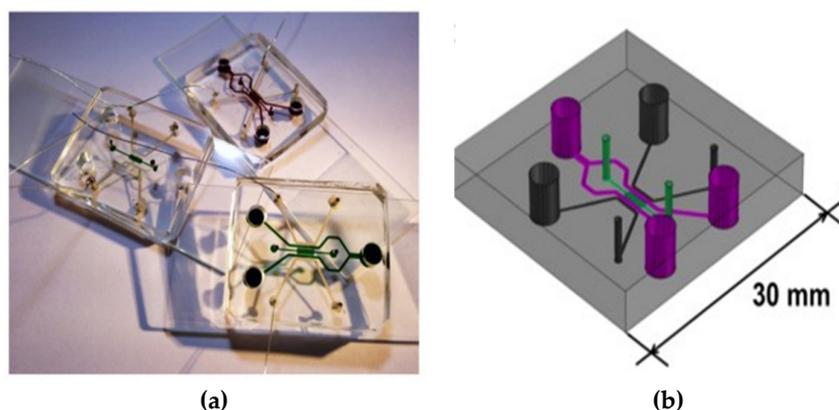


Figure 4. Microfluidic device with embedded contactless electrodes for the investigation of the effects of tumor-treating fields on cancer cells in a 3D extracellular-matrix-like hydrogel (a) and the 3D CAD overview(b) [40]. (Copyright: Creative Commons CC BY. 2016, Pavese et. al)

2.3. Micro & Nano-Fabrication Techniques

While many chemosensors are designed in the microscale, in our age nanofabrication techniques are gaining acceptance since materials in the nanoscale demonstrate remarkable properties (physical, chemical, thermoelectrical, mechanical, as well as biological) that makes them attractive candidates for applications in wearable chemosensors offering amended performances. Depending on the sensor's type, the most suitable nanomaterials, fabrication methods, and transduction principles are selected in order to develop a sensing system with satisfying functionality and compatible wearability. The nanomaterials that will be used to prepare the sensing layer play a key role in selecting the proper fabrication method, whilst several different techniques and processes may be applied for the fabrication of a wearable chemosensor. Researchers use several common fabrication technologies, including printing [41–44], lithography [45,46], and coating for fabricating sensors in the microscale. As a recent example of micro-fabrication via coating, in their latest paper Koralli et al. [47] presented the fabrication of a p-type Cu_xO and $\text{Cu}_x\text{O}:\text{Au}$ compound thin films synthesized by Pulsed Laser Deposition in order to act as a CO gas detector.

In this work, pure CuO and compound CuO:Au thermoelectric thin film sensors have been fabricated via PLD technique on the surface of a Pyrex glass tube as a substrate to detect CO gas in ambient air. A new type of cylindrical ceramic heater has been developed, characterized by a low heating power consumption to elevate operating temperatures necessary for efficient CO detection. The film's elemental composition was investigated by large-area EDS mapping and have proven the existence of Au nanoparticles of the CuO:Au compound, homogeneously distributed on the film surface, as shown in Figure 5. CO gas sensing revealed good repeatability and stability of the CuO and CuO:Au sensors for many months. Sensor sensitivity was ~ 60 ppm/air or better, while the CuO:Au compound film has shown a slightly better sensitivity by a factor of $\times 1.5$ [47]. Another example of a gas sensor was proposed by Zuliani et al. who fabricated a monolithically integrated gas sensors array in combination with a flow sensor to provide acetone quantification in breath [48], since the concentration levels of acetone in human breath are a crucial biomarker for well-being and an indicator for early stages of lung cancer.

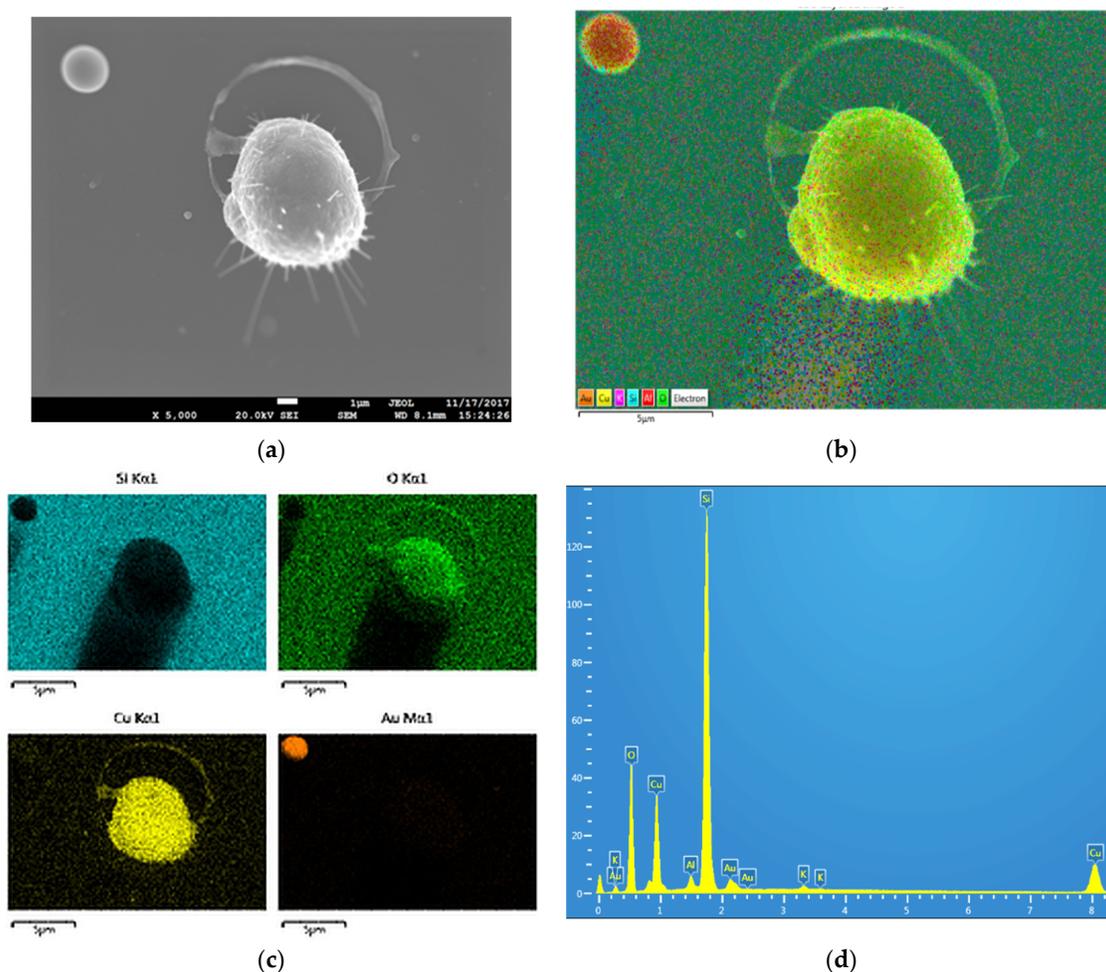


Figure 5. (a) SEM picture of a CuO/Au particle of the chemosensor surface for the detection of CO gas, (b) SEM/EDS elemental analysis composite image, (c) SEM/EDS image maps of the Cu/Au particle, and (d) SEM/EDS counts/element analysis spectrum. [Koralli, P.; Petropoulou, G.; Mouzakis, D.E.; Mousdis, G.K.M. Efficient CO sensing by a CuO: Au nanocomposite thin film deposited by PLD on a Pyrex tube. *Sens. Actuators A. Phys.* 2021, submitted for publication].

Extremely powerful tools of fabrication are also in use for manufacturing sensors in the nanoscale. A direct measurement of electron transport was made possible between DNA molecules by means of carbon nanotube (CNT) as a nanoelectrode. The CNT electrodes were fabricated by focused ion beam bombardment (FIBB)[49]. Similarly, focused ion beam (FIB) systems employ a finely focused beam of ions (typically gallium ions) that, when operated at high beam currents, can be used to locally sputter or mill the sample surface that is exposed to the ion beam[50]. FIB systems have been produced and used commercially for many years, primarily in the semiconductor industry, and thus they have matured and are widely available although with a relative high cost [51].

In general, surface patterning in the micro and nanoscales, has become increasingly important as it enables manufacturing of NEMS-MEMS and sensors allowing for systematic investigation of cell-biomaterial interaction. Additionally, by these technologies it is possible to manufacture rapid, high-throughput tests for disease diagnosis and drug screening [52]. Recent advances in three-dimensional patterning allow for recapitulation of the cellular microenvironment, providing valuable insights into the interplay between biomolecules, cells, and biomaterials and facilitating the generation of personalized tissues for regenerative medicine applications [53].

It must be here reported, that, the whole armory of almost all types of micro- and nanoenabled chemo/bio sensors was made available to public health systems to detect

COVID-19 virus symptoms [54] and presence in human breath, fluids etc.[55]. Criticism on which sensor–development pathways are best in such pandemics, has also been recently published [56].

2.4. 3D Printing

Two-dimensional printing is applying for the preparation of conductive thin films integrated onto inert substrate materials such as ceramics, glass or polymers, as well as for the fabrication of screen-printed electrodes [57,58], whilst 3D printing facilitates the production of analytical devices and custom labware showing applications in many fields (biomedical engineering, medical science, etc.) [59–61]. Moreover, 3D printing is a cost-effective process that exhibits several sustainability benefits, such as materials savings, free design, complex structure’s manufacturing, and extension of the product life [62], while due to significant progress in the additive manufacturing process, the fabrication of electronic components and circuits is possible. Several commonly used 3D printing techniques are inkjet printing, fused deposition modelling (FDM), selective laser sintering (SLS), powder bed fusion, stereolithography (SLA), and laminated object manufacturing (LOM), whilst the direct energy deposition (DED) is mostly used for the fabrication of large and less complex components [63].

In the past few years, several studies have presented the development of novel 3D-printed microfluidic devices with applications in chemistry and biology [31,64]. Gowers et al. presented a 3D-printed microfluidic analysis device that acts as a biosensor for the continuous monitoring of glucose and lactate levels in human tissue, comprising an FDA-approved clinical microdialysis probe [65]. Under this strategy, Katseli and co-workers designed a ring-shaped wearable sensor device for noninvasive perspiration glucose monitoring, which was fabricated using commercially available filaments and a dual extruder 3D printer through a single-step printing process. The ring sensor was smartphone-addressable enabling self-testing nonenzymatic measurement of glucose levels in sweat [66]. A highly innovative glucose sensor was fabricated by printing a photonic microstructure with a periodicity of 1.6 μm , on a glucose-selective hydrogel film functionalized with phenylboronic acid [67] for wearable contact lenses. Yeh et al. reported the fabrication of a novel low-cost rotation chip for the real-time determination of the antibiotic-resistant bacteria profile. More specifically, the 3D printed device successfully made a rapid antibiotic-resistant screening test of *E. coli* by analyzing the RGB color values via a smartphone pixel analysis app [68]. Another group presented a portable 3D printed plastic optical fiber sensor compatible with use in IoT sensor applications for respiratory monitoring. The sensor was able to detect and discriminate between normal breathing, deep breathing, and breath-holding through the signal’s amplitude change [69]. Gevaerd et al. reported the development of a low-cost, portable, and microfluidic electrochemical sensor device fabricated via 3D printing for the determination of cortisol levels in saliva samples. The lab-made point-of-care sensor device had the ability to detect cortisol in a range of 0.25 to 25.0 $\mu\text{mol/L}$ with exceptional analytical performance [70]. In further development of 3D printed biosensing, a new type of flexible piezoresistive tactile sensor was fabricated via a 3D printing method that mimics the texture and sensitivity of human skin. In this design, researchers used a new type of elastomeric 3D printing ink that contains carbon nanotubes distributed on the surfaces of interconnected polydimethylsiloxane microspheres in order to fabricate an electronic skin that simulates touch behavior of human skin, exhibiting high sensitivity, large durability and short time response [71].

Three-dimensional printing of a resin-based on the composite between a poly(ethylene glycol) diacrylate (PEGDA) host matrix and a poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) filler, and the related cumulative volatile organic compounds’ (VOCs) adsorbent properties was recently reported [72]. In the context of an interesting approach for volatile organic compounds (VOCs) sensing, an environmentally sustainable route to produce graphene ink designed explicitly for 3D extrusion-printing technology was shown [73]. The fabricated sensor devices under this strategy and the new

ink displayed high-resolution patterning (average height/thickness of $\sim 12 \mu\text{m}$) and a 10-fold improvement in surface area/volume (SA/V) ratio compared to a conventional method of drop-casting.

3. Body Fluids Used for Analysis

In modern medicine, wearable devices for health care should be characterized by preventive, predictive, personalized, and participatory medicine, according to the 4P medical model [74]. Wearable chemosensors that can be directly worn on the human body can provide meaningful information by perceiving, recording, and real-time analyzing a patient's pathological and physiological signs with high accuracy. Among the diversified types of biosensors, the electrochemical-based sensing systems are widely used since they demonstrate remarkable advantages such as an easy and low-cost manufacturing process, high sensitivity, quick response, and low energy consumption [75]. Thus far, blood is considered the best diagnostic medium for evaluating human physiology that has been extensively studied; nevertheless, it is unsuitable for continuous monitoring via a wearable device due to the invasive nature of sampling [76]. However, other easily accessible non-invasive body fluids that contain a plethora of physiologically relevant chemical biomarkers (Figure 6) representative of human's health can be examined by wearable chemosensors such as breath, saliva, tears, sweat, intercellular fluids (ICF), and urine. Among the body fluids mentioned above, saliva, tears, and sweat are biofluids easily obtained, providing continuous access by a wearable device for real-time health status monitoring, whilst sweat is the most approachable sample within a garment structure.

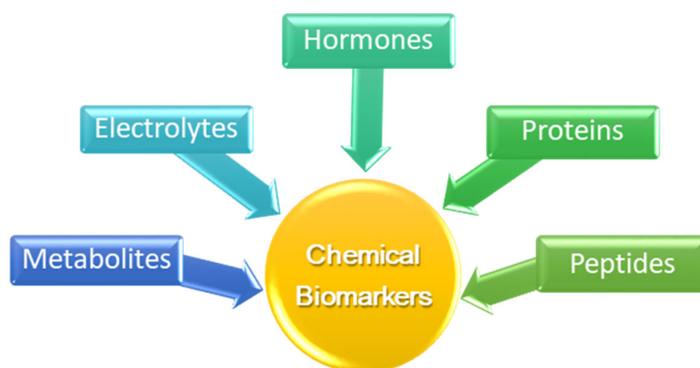


Figure 6. Chemical biomarkers that can be detected via wearable chemosensors.

3.1. Saliva

Saliva is a mixture of secretions by the salivary glands rich in chemical information due to various disease-signaling biomarkers that correspond to the health status [77]. It represents a complex watery biofluid consisting of proteins, antibodies, electrolytes, hormones, enzymes, cytokines, white blood cells, epithelial cells, and mucus [14,77] offering a beneficial sample compared to blood. The wealth of biological markers contained in the saliva is attributed to the diffusion from the bloodstream via transcellular/paracellular paths [78]. Consequently, saliva has been characterized as a “mirror of the body” that can be used for diagnostic testing [79,80] and supervise human health status. Many studies have been reported according to wearable salivary sensors, and recently, this field exhibited rapid development since wearable orally mounted biosensing platforms can be an appealing way to acquire dynamic chemical information without pain. Additionally, saliva has been used with success to detect caries risk, periodontitis, oral cancer, breast cancer, salivary gland diseases, and serious viruses such as hepatitis, HIV, and HCV [81].

Electrochemical sensors seem to be more engaging among different sensor types because of their facile fabrication and integration methods. The progress in the miniaturization of electrochemical sensing devices and their incorporation in dental accessories has led to the development of various wearable salivary sensors. Manoor et al. developed a novel graphene wireless nanosensor for passive monitoring of pathogenic bacteria from saliva. The graphene monolayers were printed on water-soluble silk that integrated onto the tooth enamel providing noninvasive, real-time wireless bacteria detection via graphene functionalization nanotransducer with antimicrobial peptides [82]. Kim's group reported for the first time the development of a new noninvasive metabolite biosensor for the monitor of salivary lactate mounted on a mouthguard that is commonly used by athletes for protection against dental injuries. This specific wearable biosensing system demonstrates high sensitivity, selectivity, and stability in salivary lactate detection by integrating wireless electronics and flexible screen-printed lactate oxidase (LOx) enzymatic electrodes [83]. The same researcher's group, based on the idea of the mouthguard biosensor, developed a noninvasive platform for salivary uric acid monitoring by embodying a miniaturized electronic system consisting of a potentiostat, a microcontroller, and a Bluetooth Low Energy (BLE) transceiver into a mouthguard [84].

Since it is established that salivary glycose is correlated with glucose level in blood [85], it would be useful to construct a biosensor for the noninvasive monitoring of saliva glucose concentrations for the administration of diabetes patients. In such an attempt, Arawaka et al. developed a detachable "cavitas sensor" with a telemetry system [86]. The mouthguard sensor platform comprised a Pt and Ag/AgCl electrode with an enzyme membrane. Nevertheless, the aforementioned mouthguard saliva glucose sensor was found to be suffering from the contamination of saliva when tested in the human oral cavity. Thereafter, they reported the development of an improved mouthguard glucose sensor for the measurement of salivary glucose using cellulose acetate film as an interference rejection membrane, which ameliorated the reaction of ascorbic acid and uric acid in saliva on electrodes of the mouthguard [87]. Gevaerd et al. introduced a portable and microfluidic electrochemical sensor to detect cortisol levels in saliva acquired via 3D printing [70], whilst another group fabricated an enzyme-based biosensor to detect low cholesterol concentrations in saliva by using Pt nanoclusters [88].

Another significant application of salivary biosensors is in wearables for infant's safety since they are incapable of providing any feedback about their health status. In contrast, neonates' existing wearable sensors cannot provide information about chemical biomarkers, and they are limited only to recording physical parameters. Moreover, most existing monitoring systems are bulky and require hard-wired connections [89]. Recently, García-Carmona et al. reported the development of the first chemical wearable sensor for neonates monitoring saliva glucose [90]. The enzymatic biosensor's platform is incorporated into a regular pacifier, and a modified nipple fluidic system is utilized for saliva collection and glucose concentration's levels simultaneously.

Consequently, oral salivary wearable chemosensors exhibit great potential for monitoring important biomarkers of both infants' and adults' health status. Notwithstanding further development, oral salivary wearable chemosensors should overcome several challenges according to the protracted operation of those biosensing platforms, such as maintaining a foreign device in the oral cavity for a long time, the possibility of toxicity issues, and contamination risks derived from bleeding gums or food. In any case, a critical evaluation of the developed system is required to reserve the reliability and safety of the biosensing device [13,91].

3.2. Tears

Human tears constitute a complex biofluid with a variety of important chemical components such as proteins, lipids, electrolytes, enzymes, metabolites, and water in an amount of more than 98% [92]. In comparison to other biological fluids like saliva or sweat, the tear is considered a relatively simple fluid as it contains fewer proteins due to

the blood–tear barrier filtering process. This characteristic makes tears an attractive candidate for prolonged noninvasive monitoring of human health via specific analytes since surface biofouling is restricted because of the low protein density [91]. Traditional tear sensors used extracted human tear samples for *in vitro* analysis. Nevertheless, *in vitro* techniques encountered several problems like the sample's evaporation during the sensing process [93]. Hence, wearable tear sensor devices were developed based on contact lenses that could work directly on the retina, collecting basal tears.

The development of tear-based biosensors is mainly focused on glucose monitoring, supervision of lactic acid levels, as well as on the detection of cancer biomarkers. Taking into consideration that the percentage of diabetes globally is estimated at 9%, thus demonstrating an increasing trend within the next decades [94], an alternative glucose assessment has been proposed via tear-based biosensors instead of the commonly used method for glucose levels recording in blood samples by an invasive finger-prick test [95]. Moreover, the detection of glucose concentration in tears can be used to ascertain various eye diseases (e.g., xerophthalmia, glaucoma, macular oedema, keratitis, corneal diseases, and diabetic retinopathy) [94,96,97]. Thus, the efficient monitoring of glucose concentration in tears for early medical intervention is of great importance, considering the correlation between tear and blood glucose level [96]. First, wearable tear sensors prepared onto contact lens were developed for glucose detection based on optical characterization [98], while in the sequel, several groups prepared strip-based tear sensors on flexible substrates, which probably irritate the eye [96,99]. To summarize these limitations, soft contact lenses were used for the fabrication of chemosensors, whilst different designs have been proposed to monitor glucose levels in tear fluid *in vivo*.

A concept patented by Google and developed in collaboration with Parviz's group refers to designing a glucose sensor implanted in contact lens based on wireless electronics to transmit the results to an external device (e.g., smartphone) [100–102]. This biosensor includes a miniaturized amperometric glucose sensor, a wireless microchip, and a tiny battery embedded on a common lens hydrogel material for noninvasive continuous glucose analysis. Recently, Elsherif et al. developed a wearable soft contact lens optical sensor for glucose monitoring [67]. In particular, a photonic microstructure-based sensor was printed on the surface of glucose-sensitive hydrogel networks functionalized with phenylboronic acid. The biosensor was integrated to the surface of a commercial contact lens, while a smartphone application was created to record the lens's reflective power corresponding to the change of glucose concentration in tear. Under this strategy, Park's group reported the development of a fabrication method of a smart contact lens that can provide real-time monitoring of glucose levels in tear fluid via a wireless operated display [103]. This biosensor platform consists of a glucose sensor, an LED pixel, a rectifier circuit, and a transparent, stretchable antenna, which were fully embedded onto a mechanical stress-tunable hybrid substrate visualizing real-time sensing signals according to glucose levels. Moreover, the same group also reported the development of a multifunctional wearable soft contact lens sensor, which on the one hand could monitor the glucose concentration in tears, and on the other could measure the intraocular pressure simultaneously, combining the detection of disease-related biomarkers with the evaluation of the ocular's cavity condition [104].

Furthermore, the development of a nanoparticle embedded contact lens which comprises cerium oxide (III) and glucose oxidase is reported [105]. This biocompatible biosensor is based on spectroscopy since it can perceive changes in the reflectance spectrum of the contact lens and correlates them with glucose levels through the development of a correlation curve. The evaluation of this sensor platform came out via the diabetic mouse model comparing blood glucose concentration to the assessed tear glucose concentration.

Another approach refers to the fabrication of a wearable tear-based biosensor without eye contact for monitoring alcohol, glucose, and vitamin nutrients [106]. In this design, a wearable eyeglasses-based platform comprises a hydrophilic fluidic channel mounted onto the eyeglasses' nose-bridge pad to collect and measure tears biomarkers with

wireless electronics. Such an eyeglass platform addresses drawbacks involving contact lenses platforms that directly contact the eye, whilst they can be improved by incorporating smart glasses and energy harvesting systems.

In conclusion, significant efforts have been made in the development of the tear-based biosensor targeting glucose detection; however, there is a significant potential for the detection of other biomarkers containing in human tears, which could indicate the general health status of individuals. Indicatively, tears also contain lacryglobin, a protein that has been reported to be associated with patients with breast, lung, colon, prostate, or ovarian cancer [107]. On the other side, the power supply of these devices remains a challenge. Researchers make great efforts to prepare contact lenses biosensors that will be self-powering using solar power or biofuel cell [108,109].

3.3. Sweat

Perspiration is a natural process of the human body, which helps prevent a dangerous increase in body temperature through secretions from sweat glands allocated across the human body at densities of >100 glands/cm² [110]. Furthermore, sweat is an easily accessible body fluid related to human's metabolic rate, and its composition provides important insights into an individual's health status and electrolyte balance [111]. Since sweat filtrates blood plasma, it is a biofluid containing a variety of electrolytes (Na⁺, K⁺, Ca²⁺, Cl⁻, and NH⁴⁺), metabolites, small molecules (cortisol, ethanol, lactate, and urea), hormones, small proteins (cytokines), peptides (neuropeptides), as well as environmental contaminants from the skin [5,110,112]. The measurement and evaluation of those components via wearable sensors could be helpful for noninvasive periodic or real-time health monitoring and diagnosing of diseases, for sports applications, as well as for safety and security [113]. Studies suggest that increased sweat chloride levels are an indicator of cystic fibrosis [112,114], sweat lactate correlates to physical stress and could be applicable in the identification of aerobic to anaerobic states transitions [35,115], whilst excessive sweat electrolyte loss could cause dehydration, hyponatremia, and hypokalemia [116]. Additionally, the sodium ion has been characterized as a crucial perspiration biomarker; hence, many Na⁺ sensors have been developed [117,118].

In order to achieve continuous sweat sampling, wearable chemosensors or biosensors attached to the skin have been developed, which are generally categorized into two main groups: the tattoo sensors and the patch and electrode sensors [99,113]. Epidermal-based platforms provide better skin contact, although they demonstrate a shorter lifespan than textile or watch-type biosensors. Moreover, different electrochemical methods have been used for the fabrication of diagnostic devices due to the exhibition of several advantages, such as low cost, easy construction, and good integration [111,119]. Among them, the potentiometric is the analytical method widely applied for perspiration measurements since it is based on correlations between ion concentration and electrochemical potential of the electrode [16,113,120].

The first epidermal tattoo-based sensor was reported by Kim and co-workers in 2011 [121]. After that, Jia et al. developed a noninvasive tattoo electrochemical sensor for continuous real-time monitoring of lactate in human sweat under the wearer's intense exercise [115]. This specific enzymatic biosensor had the ability to identify lactate in human perspiration up to 20mM selectively. Bandodkar et al. reported the fabrication of novel tattoo-based potentiometric ion-selective electrodes (ISEs) to measure epidermal pH [5]. In this design, a combination of solid-contact polymer ISE procedure with a screen-printing technique was applied to develop a temporary transfer tattoo paper acting as a sensor with high sensitivity and rapid response to pH changes in human sweat. Another researcher's group introduced a potentiometric tattoo-based biosensor for selectively real-time on-body detection of a model G-type nerve agent simulant [122]. In particular, this epidermal sensor exhibits excellent sensitivity and fast response in detecting diisopropyl fluorophosphates (DFP), a fluorine-containing organophosphate that demonstrates a similar structure to the chemical warfare agent's Soman and Sarin.

Latest advances in material science, energy harvesting, and wireless communication have improved the fabrication of wearable sweat-analyzing chemosensors [123]. Recently, Sempionatto and co-workers demonstrated the fabrication of a vitamin C epidermal tattoo-based biosensor for vitamin C concentration tracking in sweat after swallowing fruit juices or vitamin C pills [124]. Specifically, an enzymatic biosensor based on ascorbate oxidase's immobilization is mounted on a flexible polyurethane substrate and via screen-printed electrodes enables the amperometric determination of vitamin C physiology in perspiration. Pal et al. presented low-cost waterproof electronic decals (WPEDs), which can easily be mounted onto skin to monitor human's sweat pH with a sensitivity of $0.407 \log(\Omega)/\text{pH}$, whilst it can be placed on the surface of a paper-based sample container for the detection of bacterial vaginosis via the measurement of changes in the vaginal pH [6]. WPEDs, combined with a wireless impedance analyzer, offer real-time monitoring of perspiration's pH, providing accurate point-of-care diagnostics. Furthermore, Yu et al. reported a flexible and fully perspiration-powered electronic skin (PPES) for multiple real-time metabolic sensing [125]. In this approach, a soft e-skin comprises of multimodal sensors for the detection and monitoring of different key metabolic analytes containing in human sweat, such as pH, NH_4^+ , glucose, and urea, as well as the skin temperature, whilst the detected signals are wirelessly transmitted via Bluetooth low energy (BLE). The whole multisensory platform is battery-free and self-powered since it harvests energy from human perspiration via highly efficient lactate biofuel cells (BFCs).

Roy et al. reported the development of carbon nanotube-based (CNT) wearable sensor for sweat sensing, taking advantage of the good mechanical flexibility and strength that CNT-polymer composites exhibit [126], whilst Martin's group presented the fabrication of a flexible epidermal sensor device for perspiration sampling and real-time monitoring of sweat metabolites (lactate and glucose) via the combination of soft microfluidic platforms with wearable epidermal electrochemical sensor's array [35]. Xiao and co-workers reported the fabrication of a microfluidic-based wearable sensor device for sweat sampling and the colorimetric detection of perspiration glucose via the enzymatic oxidation of o-dianisidine [127]. Wiorek et al. fabricated and studied an epidermal patch glucose biosensor, with pH and temperature correction for more accurate measurements [128]. Bhandodkar et al. also proposed the colorimetric and electrochemical analysis of perspiration electrolytes and metabolites, respectively, as well as the volumetric analysis of sweat by applying a battery-free hybrid skin patch [129]. Herein, the suggested wearable device combines biofuel cells sensors that harvest energy from lactate and glucose fuels, with near-field communication technology and soft microfluidics resulting in a sensor platform that is light-weight, cheap, and small-sized. Zhang et al. reported a flexible electrochemical sensor for monitoring lactate levels in perspiration based on Ag nanowires (AgNWs) and molecularly imprinted polymers (MIPs) implemented by the screen-printing technique. The resulting epidermal biosensor fulfils the 3S criteria for sensitivity, selectivity, and stability in the monitoring of sweat lactate [130]. Indeed, screen-printed sensors are widely developed and adopted for sweat lactate monitoring [131] but also other critical hormonal secretions of the human body, such as the multi-role serotonin [132]. Further, Yu and co-workers developed a flexible chip with gold nanopine needles deposited on gold electrode array acting as a signal amplifier for the real-time monitoring of perspiration lactate and glucose levels. The produced electrochemical biosensor demonstrated high selectivity, stability, and reproducibility, whilst was able to detect lactate concentration down to $54 \mu\text{mol/L}$ and glucose concentration down to $7 \mu\text{mol/L}$ [133].

Nevertheless, many efforts have been made to fabricate electrochemical sensors for human perspiration monitor and analysis embedded into wearable accessories. Gao and co-workers demonstrate a flexible, fully integrated sensor system for multiplexed and simultaneous sweat analysis [134]. This sensor design includes a flexible PET substrate onto which the sensor array is mounted, a Bluetooth for the wireless transmission of recorded signals, and a lithium battery integrated into a wristband or headband, enabling the measurement of a variety of electrolytes and metabolites containing in human sweat,

as well as skin temperature. Various perspiration-sensing watch-type wearable sensors have also been developed [135–138]. Zhao et al. reported the fabrication of a disposable freestanding electrochemical system (FESS) enabled smartwatch, which promotes sensing measurements of different sweat biomarkers and simultaneously provides out-of-plane signal interconnection via double-side adhesion [137]. Sim and co-workers proposed a watch-type sweat rate sensor device for human thermal status monitoring [135], whilst another group developed a smartwatch for noninvasive monitoring of sweat glucose levels, which is fully integrated and self-powered by photovoltaic solar cells [136]. In this design, the smartwatch comprises flexible photovoltaic cells for solar energy conversion and harvesting, flexible Zn-MnO₂ photocharging batteries for energy storage, an enzymatic sensor for perspiration glucose monitoring, a PCB controlling module, and an electronic ink screen for real-time and in situ data display. Moreover, Sempionatto et al. reported the first example of a biofluid sensor embodied on eyeglasses since millions of people widely wear them and represent stylish fashion accessories compared to tattoos, wristbands, or headbands, which are also used for wearable sensor platforms [139]. More specifically, an amperometric lactate biosensor and a potentiometric potassium ISE are integrated into the nose-bridge pads of eyeglasses and interface them with a wireless electronic backbone mounted onto the glasses' arms providing real-time monitoring of the aforementioned sweat electrolytes and metabolites. Recently, the development of a wearable smart textile sweat lactate biosensor was reported by Wang et al. Under this strategy, stretchable, highly conductive, and insensitive to strain gold fibers were produced by applying the dry-spinning method to fabricate a standard three-electrode lactate sensing system into textiles with a planar layout [140]. The resulting textile biosensor for the estimation of perspiration lactate levels exhibits a high sensitivity of 19.13 $\mu\text{A}/\text{mM cm}^2$ in phosphate-buffered solution (PBS) and 14.6 $\mu\text{A}/\text{mM cm}^2$ in artificial sweat, respectively.

Thus far, despite the development of wearable chemosensors for in situ monitoring of perspiration at the epidermis layer, further studies are required to verify the utility of sweat as a reliable diagnostic biofluid and to address remaining challenges as the contamination, evaporation and degradation of samples during the multistep processes of collection, storage, transport, and analysis [13,112,129,141].

4. Energy Harvesting for Wearables

Power management of wearable sensor devices remains a major challenge for researchers. Different energy harvesting approaches have been developed for wearables energy supply taking into consideration specific requirements of sensor platforms such as size, measurement technique, and sampling frequency. Additional factors regarding wireless communications for data transmission to a display (via Bluetooth, NFC, or passive RFID) also significantly affect energy consumption depending on the operation ranges and bandwidths, as well as location tracking and operation distances.

Catching up from the introductory reference to thermoelectric power generation via the Seebeck effect, some more effects come into play in this area. The thermoelectric effect is the direct conversion of temperature difference to electric voltage and vice versa via a thermocouple. A thermoelectric device creates a voltage when there is a temperature gradient between the sides of the device.

However, promising thermoelectrics are capable of supplying power by converting body heat, but wearable thermoelectrics have not been as yet, capable of producing electrical power stable or high enough for supporting the uninterrupted operation of commercial types of health monitoring sensors. For this purpose, synergistic integration of a wearable thermoelectric generator (WTEG) and a new type of marketed Li-S battery on the basis of a commercial glucose sensor was proposed [2]. The WTEG has delivered power in a stable and continuous mode, showing a path to overcome one of the biggest hurdles in fully applying thermoelectrics for wearable electronics in practice. As exhibited, the major disadvantage of low thermoelectric output voltage, hampering batteries' charging, has been greatly alleviated by using the high-performance Li-S battery. The

charging voltage of this battery is only half of the standard Li-ion batteries. The WTEG hybrid system was able to continuously produce power as much as 378 μW , operating a commercial glucose sensor (power consumption: 64 μW) and storing the surplus in the Li-S batteries for providing a stable continuous voltage of 2 V even under large fluctuations in power supply and consumption.

Although batteries still remain the most versatile option for wearable platforms continuous power supply [142], their main drawbacks are the weight and the inflexibility of the bulky construction that provoke anatomical inconvenience to the body and impede the sensor's performance [143,144]. Consequently, flexible, and stretchable energy collectors have been developed and integrated into wearable electrochemical sensors in order to provide self-powering by exploiting energy from biofluids. This very innovative strategy is based on flexible and fully perspiration-powered integrated electronic skin (PPES) for multiplexed metabolic sensing in situ, utilizing biofuel already mentioned above [125] or a tattoo-based wireless fuel cell, using lactate from sweat as fuel [145]. Energy harvesting mechanism seems to be the customary fuel cells, which uses a pair of electrodes: a cathode and an anode. Generally, in wearable biofuel cells, the biofuels' electro-oxidation in the biofluid of interest is caused by the anode's functionalization with enzymes generating electrons flow to the cathode, creating an electrical current that can be utilized for the power supply of an external circuit [91]. The cathode for the oxygen in the biofluid can be amended either by using oxidase enzymes such as bilirubin oxidase or laccase or by utilizing inorganic metal materials like Pt and Pd. Several studies have reported the use of efficacious biofuel cells [146]. Chen et al. presented the fabrication of a flexible and stretchable wearable enzymatic biofuel cell that harvests energy from sweat, where lactate oxidase was used for the anode and bilirubin oxidase for the cathode, respectively [147]. This specific biofuel cell achieved a maximum power of 450 μW when the device was placed on a volunteer's arm under exercise conditions, while it could power supply a commercial LED (Figure 7). Another exciting approach recently proposed was a thin, soft, skin-integrated foam-based triboelectric nanogenerator for tactile sensing and energy harvesting [148]. Lately, even ZnO nanorods have been proposed as fillers in a polymeric composite film for sustainable energy harvesting in chemosensors [149], while an alveolus-inspired membrane sensor (AIMS) for self-powered wearable nitrogen dioxide detection and personal physiological assessment was also reported [41].

Additionally, wearable devices for both energy harvesting and storage have been presented. Lv et al. developed a flexible and stretchable textile-based hybrid device with both internal and external functionalized surfaces. In this design, the internal surface that was contacted to the body utilized energy harvesting from perspiration's lactate oxidation, whilst the external surface comprises supercapacitors for energy storage. The biofuel also had the ability to act as a self-powered sensor where the sensor signal was proportional to the lactate concentration and to the output power [150].

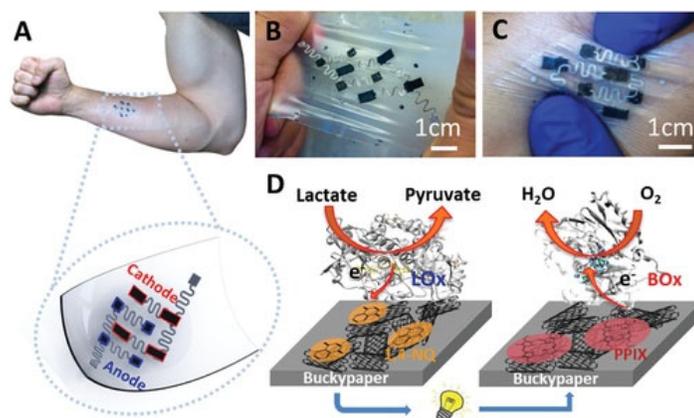


Figure 7. A stretchable biofuel cell sensor device mounted on a human arm (**top**) and the redox energy generation from the sweat lactate oxidation at the anode and oxygen reduction at the cathode (**bottom**) Reprinted with permission from [147]. 2019, Xiaohong Chen, Lu Yin, Jian Lv, et al.

5. Conclusions and Future Perspectives

An effort was undertaken to present the latest progress in the last three years in chemosensors, emphasizing wearables, which is a hot research topic. The authors have tried to incorporate the latest results and proposals for chemosensors for biological fluids in the international literature. In this sense, one can stipulate the idea that the thin border between biosensors and chemosensors is easy to cross. The only criterion is the analyte, possibly in order to be able to distinguish between the two large groups. Certainly, as can be deduced from the works presented in the current study, the wearables are the perfect common ground or integrated application for both these types. It is easy to conclude that significant steps are already taken in making the wearable chemo- and biosensors energy-autonomous. Additionally, their ability to sense more substances is increased. Optical chemosensors are foreseen to have a bright future ahead. Inkjet, screen, and 3D printing procedures will allow for the cheap, easy, and reliable manufacturing of these types of sensors.

Although there has been significant progress in the last few years, there are still significant requirements such as power management, real-time communication, and biocompatibility that have to be addressed for the next generation of wearable chemosensors. The continuous demand for comprising multiple modalities in a sensor platform in combination with wireless communication services and data analytics increases the devices' power requirements. Several strategies are applied to address the power management challenge, such as the implementation of energy harvesting techniques, the development of supercapacitors, and the fabrication of flexible and light-weight batteries; however, the device's energy consumption remains one of the major problems facing existing wearable sensors.

Additionally, the real-time, continuous, and uninterrupted transmission of information to a wearer or a computer device is a significant aspect of wearable technology. Up to now, wearable sensor platforms exhibit data transmission capability via Bluetooth, NFC, and high-frequency passive RFID communication protocols. Nevertheless, these communication technologies demonstrate several drawbacks, mainly the compatibility with low-rate data. Researchers should investigate other types of wireless communication technologies that will be used in wearable applications, like optical wireless technologies, as well as develop advanced algorithms for the information's transmission.

Furthermore, the sensor's resistance to mechanical damages or the capability to be self-healing is another issue that must be improved during subsequent years. The employed techniques are not sufficient to protect the sensor device from ordinary wear and tear, unanticipated damage, or unintended stain. Consequently, many efforts have been made for the development of devices that have the ability of self-healing (partially or

completely) mimicking natural systems. The advancements of the field of nanomaterials gives the researchers the opportunity to fabricate such devices in order to improve their reliability and promote durability and lifespan.

Since wearable biosensor devices are highly desired for the real-time determination of a human's health condition, as well as for elderly care and they are promising in terms of personalized medicine, it is crucial to amend their stability, reliability, safety, and biocompatibility in order to pass from test devices to their commercialization. The nanomaterials' biocompatibility that comes into direct contact with the epidermis without causing toxicity effects is essential to be considered in the design and development of wearable biosensors. Various factors such as the size, the shape, and the roughness of the materials placed on the epidermis, as well as their chemistry and degradation, could affect the biocompatibility of the sensor, although it is difficult to predict how exactly a material will behave when interacts with an individual. Regarding this matter, our knowledge, so far, is limited, and there must be further investigation for the development of biocompatible nanomaterials towards safe usage in wearables. According to flexible biosensor platforms, apart from the reliability of the noninvasive sampling of biofluids, another challenge that must be addressed is the interference that provokes several physiological factors, such as temperature, as well as the adhesion of the sensor to the epidermis. Additionally, the sampling frequency is one more factor that has to be investigated in detail since there must be a balance taking into consideration, on the one hand, the sampling rate and on the other hand, the energy consumption of the device. Hence, there must be an optimization between power management and sampling frequency. Additionally, a major issue arose from population research because the common person or patients still do not place their trust in these sensors for medical monitoring and timely treatment. Handling and security of (their) big data and personalized information is a significant issue that should be considered and confronted as early as possible.

However, we are optimistic about the high potential of wearable chemosensors technologies along with the advances in the Industry 4.0, IoT and all advances to come it can be foreseen that the lifestyle and quality of life and health shall improve in the coming years. Our speed to counteract pandemics and detect pathogens will improve and likewise personalized medicine and being alert to dangerous conditions of our health will considerably increase our abilities to the protection of human life.

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