Review

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Non-invasive wearable electrochemical sensors: a review

Amay J. Bandodkar and Joseph Wang

Department of NanoEngineering, University of California, San Diego La Jolla, CA 92093, USA

Wearable sensors have garnered considerable recent interest owing to their tremendous promise for a plethora of applications. Yet the absence of reliable non-invasive chemical sensors has greatly hindered progress in the area of on-body sensing. Electrochemical sensors offer considerable promise as wearable chemical sensors that are suitable for diverse applications owing to their high performance, inherent miniaturization, and low cost. A wide range of wearable electrochemical sensors and biosensors has been developed for real-time non-invasive monitoring of electrolytes and metabolites in sweat, tears, or saliva as indicators of a wearer's health status. With continued innovation and attention to key challenges, such non-invasive electrochemical sensors and biosensors are expected to open up new exciting avenues in the field of wearable wireless sensing devices and body-sensor networks, and thus find considerable use in a wide range of personal health-care monitoring applications, as well as in sport and military applications.

Why continuous non-invasive chemical sensing?

Chemical sensors and biosensors have been widely used as attractive alternatives to the bulky, expensive, and complex analytical instruments used in the health-care sector [1] (Box 1). Over decades, several of these devices have been developed for detecting vital analytes using optical, piezoelectric, and electrochemical transducers. Of these, electrochemical sensors have gained a dominating role in clinical diagnostics owing to their high performance, portability, simplicity, and low cost [2]. Substantial progress in electrochemical sensing has led to the development of commercial hand-held analyzers, such as the ACCU-CHEK (Roche Diagnostics, Inc.), iSTAT (Abbott, Inc.), or Lactate Scout (Sports Resource Group, Inc.), for detecting metabolites and electrolytes. However, most of these sensors rely on blood samples. The intrusive nature of these sensors thus poses a major hurdle to the patient and impedes the temporal information acquisition that is desired for diverse biomedical applications. This is especially true in the case of neonatal, elderly, and hemophobic patients, for whom blood sampling is challenging. Continuous analyte monitoring is of particular

Corresponding author: Wang, J. (josephwang@ucsd.edu).

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Glossary

Amperometric sensors: devices that measure the current produced during the oxidation or reduction of an electroactive species at a constant applied potential. This current is proportional to the concentration of the electroactive product.
Biocompatibility: is a condition of being harmless to living tissue or a living system by not being toxic or injurious and not causing immunological rejection.
Biofouling: the accumulation and growth of undesired biomaterials on a surface.
Biofluid: a biological fluid. Biofluids can be excreted (such as urine or sweat), secreted (such as breast milk or bile), obtained with a needle (such as blood or cerebrospinal fluid), or develop as a result of a pathological process (such as blister or cyst fluid).
Biofuel cell: is a specific type of fuel cell that uses enzymes as a catalyst to oxidize its fuel and generate electricity.
Cariogenic potential: the ability of a food to cause tooth decay. It is evaluated by measuring plaque-pH during and for 30 minutes after consumption of the food product.
Conjuntiva: a thin membrane that covers the inner surface of the eyelid and the white part of the eyeball.
Electrochemical transducers: devices that convert chemical information into measureable electrical signal (such as current, voltage, charge, and impedance). Electrochemical transducers are utilized in fabricating electrochemical sensors in which the analyte concentration is proportional the recorded electrical signal.
GOx: glucose oxidase enzyme is an oxido-reductase that catalyses the oxidation of glucose to hydrogen peroxide and D-gluconic acid.
Hypotonic solution: a solution that has lower solute concentration as compared to its surrounding solution.
Keratoconjunctivitis sicca: is also known as dry eye syndrome. It is an eye disease caused by eye dryness due to either decreased tear production or increased tear film evaporation.
Non-invasive sensors: devices that do not require biofluids obtained by penetrating the body, as by incision or injection.
Optical transducers: devices that transform non-optical signal into an optical signal. They are widely used for developing optical chemical sensors. Such sensors convert chemical information into optical signal. The analyte concentration is proportional to the optical signal.
Paracellular transport: transfer of substances across an epithelium by passing through the intercellular space between the cells.
Polyethylene terephthalate (PET): a thermoplastic polymer resin. It is produced from ethylene glycol and dimethyl terephthalate or terephthalic acid.
Potentiometric sensors: devices that measure the electromotive force generated between two electrodes. The measured electromotive force has a direct dependence on the analyte concentration.
Plaque acidogenicity: the ability of a bacteria present in the dental plaque to form acids from fermentable sugars.
Reverse iontophoresis-based electrochemical sensing: is a technique that involves passing a mild current across two electrodes applied to the skin. This causes electro-osmotic flow of the metabolites from the subcutaneous layer to surface of the skin. The extracted ISF is then electrochemically analyzed and the analyte concentration is quantified.
Selectivity: is the ability of a sensor to identify the target chemical species present in a sample medium containing several other interfering chemicals.
Sensitivity: is the measure of the signal generated by a sensor upon exposure to unit analyte concentration.
Sialochemistry: a branch of chemistry that focuses on analysis of salivary composition.
Transcellular transport: transfer of substances through the cell, passing through both the apical membrane and basolateral membrane.

Box 1. Chemical Sensors/biosensors

The International Union of Pure and Applied Chemistry defines a chemical sensor 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.'' A typical chemical sensor contains two basic functional units: a receptor and a physico-chemical transducer. If the receptor consists of a biological component (e.g., enzyme, antibody, DNA etc), the device is known as a biosensor (Figure I). The receptor transforms the analyte concentration into a chemical or physical output signal with a defined sensitivity. The main role of the receptor is to provide high selectivity towards the desired analyte in the presence of potentially interfering chemical species. The receptors thus help in obviating false-positive results. The transducer is another crucial component of the sensor that serves to convert the signal generated by the receptor–analyte interaction to a readable value. Biosensors can be distinguished based on their receptors, as either catalytic or affinity-based. Similarly, they can be classified according to the type of transducer used as electrochemical, optical, piezoelectric, and calorimetric sensors.

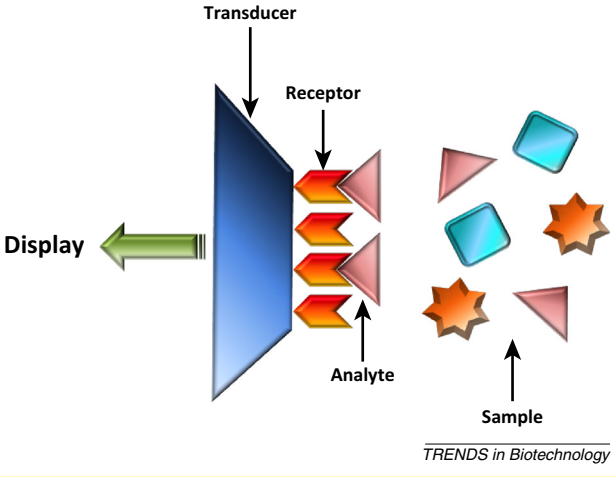

Figure I. Schematic showing important components of a typical sensor.

importance in different areas. For example, optimum diabetes management mandates regular glucose monitoring. Similarly, athletes require continuous assessment of their fitness level during training. Real-time detection of pathogens in biofluids (see Glossary) can alert the person about the plausible onset of disease. Monitoring drug efficacy is another scenario in which continuous measurements are of great importance. In the above-mentioned cases, invasive sensors have obvious limitations because continuous availability of the required sampling media (blood, urine, serum, and so on) is impractical.

Wearable sensors have received tremendous attention over the past decade [3–5]. These non-invasive devices offer considerable promise for continuous monitoring of a wearer's health, tracking exercise activity, and assessing soldier performance. By providing valuable real-time information, such wearable sensors allow individuals to change their lifestyle for maintaining optimal health status. The growing interest in wearable sensors reflects major shifts from centralized hospital-based patient care to home-based personal management, as the latter aims at lowering health-care costs.

Major endeavors towards on-body monitoring of wearer's health or fitness have resulted in the demonstration of a plethora of physical sensor devices [4,5]. Unlike wearable physical sensors for monitoring vital-signs, non-invasive chemical sensors and biosensors, which are based on the transduction of chemical information, are still in their infancy [3]. The limited availability of wearable chemical sensors has hindered further progress towards continuous personal health monitoring. This is due to several key challenges that have yet to be successfully addressed, such as obtaining sensor response using low analyte concentrations and small sampling volumes of the biofluid and mechanical resiliency, biofouling, and biocompatibility of the sensors. The recent introduction of non-invasive wearable electrochemical sensors attempts to address these key challenges and fill major gaps in the wearable sensor technology.

Wearable non-invasive electrochemical biosensors

Similar to their *in vitro* counterparts, wearable non-invasive electrochemical sensors can detect target analytes in tears, saliva, sweat, and skin interstitial fluid. Researchers have recently made considerable efforts to develop wearable chemical sensors that can conveniently monitor these biofluids (Table 1).

Saliva-based sensors

Saliva is a complex biofluid comprising numerous constituents permeating from blood via transcellular or paracellular paths. Hence, sialochemistry offers an excellent non-invasive alternative to blood analysis for monitoring emotional, hormonal, nutritional, and metabolic state of the human body [6]. Saliva is also readily available compared to blood and requires fewer pretreatment steps. These virtues of saliva have attracted the attention of several researchers to develop portable *in vitro* salivary diagnostic tools [7].

The field of wearable salivary sensing has experienced considerable progress, aimed primarily towards the incorporation of sensors within partial dentures. The first examples of such wearable sensors were demonstrated already in the 1960s for monitoring mastication. Plaque pH is a useful parameter for studying plaque acidogenicity [8], whereas monitoring fluoride activity informs an individual about the fluoride dentifrice efficacy. Denture-based devices were thus modified to continuously monitor pH [9] and fluoride activity [10] in saliva and dental plaque (Figure 1A). These potentiometric sensors were fabricated by incorporating liquid junction-based electrodes, miniature transmitters, and a power supply. Although these sensors provide continuous real-time detection, they face several limitations, particularly the replacement of several teeth by the sensors and the possibility of leakage of the internal solution. Additionally, the pre-calibration step adds extra work-load for the user. Temperature variations affect the response of potentiometric sensors and hence require the incorporation of temperature sensor for compensation. Minamitani *et al*. [11] addressed some of these issues by integrating a temperature sensor and liquid junction-free iridium oxide pH electrode on a denture base. Such a device can be miniaturized and easily worn by an individual without the need for replacing teeth.

An ideal salivary sensor must conform well to the complex anatomy of the mouth with minimal inconvenience to

Table 1. Selected wearable salivary electrochemical sensors

Platform[a]	Biofluid	Recognition element	Technique	Analyte	Refs
Denture	Saliva	Glass membrane	Potentiometry	pH	[9]
Partial chrome-cobalt denture	Saliva	Lanthanum fluoride	Potentiometry	Fluoride	[10]
Mouthguard	Saliva	Lactate oxidase	Amperometry	Lactate	[12]
Graphene on silk	Saliva	Peptides	Resistometry	*Staphylococcus aureus*	[13]
Polytetrafluoroethylene	Tears	Bare gold	Conductometry	Electrolytes	[18]
Gas-permeable membrane	Tears	Bare platinum	Amperometry	Oxygen	[19]
Polypropylene	Tears	GOx	Amperometry	Glucose	[21]
Polyimide	Tears	GOx	Amperometry	Norepinephrine and glucose	[23]
PET contact lens	Tears	GOx	Amperometry	Glucose	[24–26]
PET contact lens	Tears	Lactate oxidase	Amperometry	Lactate	[28]
Cotton (underwear)	Sweat	Bare carbon	Amperometry	β-nicotinamide adenine dinucleotide and hydrogen peroxide	[41]
Polyimide/Lycra blend	Sweat	Sodium ionophore	Potentiometry	Sodium	[43]
Cotton yarn	Sweat	Hydrogen, ammonia, and potassium ionophore	Potentiometry	pH, ammonium, and potassium	[45]
Polyester	Sweat	Ag/AgCl	Potentiometry	Chloride	[46]
Gas-permeable membrane	Sweat	Platinum	Amperometry	Oxygen	[47]
Elastomeric stamps	Sweat	Bare carbon	Voltammetry	Uric acid	[49]
Temporary tattoo	Sweat	Lactate oxidase	Amperometry	Lactate	[50]
Temporary tattoo	Sweat	Polyaniline	Potentiometry	pH	[51]
Temporary tattoo	Sweat	Ammonium ionophore	Potentiometry	Ammonium	[52]
Temporary tattoo	Sweat	Sodium ionophore	Potentiometry	Sodium	[53]
Parylene skin patch	Sweat	Lactate oxidase	Conductometry	Lactate	[54]

[a]Abbreviations: GOx, glucose oxidase enzyme; PET, polyethylene terephthalate.

the wearer. The sensor must also integrate wireless data transmission capability to transmit data over long distances. Keeping this in mind, our group developed a wearable non-invasive mouthguard amperometric biosensor for detecting lactate [12] (Figure 1B). This represents the first example of a wearable electrochemical salivary sensor for continuous metabolite sensing. The sensor was fabricated on polyethylene terephthalate (PET) substrate and subsequently affixed to a mouthguard for continuous salivary lactate detection in undiluted human saliva samples. Future studies will focus on continuous non-invasive monitoring of salivary lactate with integrated electronic backbone and wireless transmitter within the mouthguard. Mannoor *et al*. recently demonstrated a novel dental tattoo for continuous wireless monitoring of bacteria by bio-functionalizing antimicrobial peptides on graphene-modified silk tattoo substrates [13] (Figure 1C). The sensor displayed excellent specificity, response time, and single-molecule detection ability. However, real-time on-body applications have not been described.

Tear-based sensors

Tears are a complex extracellular fluid containing proteins/peptides, electrolytes, lipids, and metabolites from lacrimal glands, ocular surface epithelial cells, Meibiomian glands, goblet cells, and blood. Because blood is one of the sources of these constituents, tears can be used as an attractive fluid for non-invasive monitoring. This is especially true for continuous diabetes management due to a correlation between glucose levels in tears and blood [14]. Conventional bench-top instruments have been traditionally used for detecting amino acids [15], antioxidants [16], and metabolites [17] in human tears. However *in vitro* tear analysis has several limitations. Evaporation of collected tears (commonly 5–10 μL) during transport to laboratories represents a major factor affecting the accuracy of such centralized tear analyses. Considering the delicate nature of the human eye, utmost care must be taken during the sample collection. Additionally, the measured analyte concentration often depends on the collection method utilized [16,17].

Wearable sensors that detect analytes directly on the human retina may circumvent the aforementioned limitations. The earliest forms of ocular sensors were fabricated on strip-based flexible substrates. These devices are developed by first fabricating bare electrodes onto flexible or stretchable substrates using standard lithographic techniques [18–22] (Figure 2A). Low-cost thick film printing technology has also been used to develop high-fidelity ocular sensors [23] (Figure 2B). Several techniques, such as drop casting and polymer entrapment [20], and direct mixing of bio-molecules within inks [23], have been utilized to functionalize the electrode transducers with receptors. Strip-based ocular sensors have been developed for monitoring *keratoconjunctivitis sicca* [18], transcutaneous oxygen [19], and glucose [20–23]. These fast and selective devices were evaluated with bench-top analyzers. No efforts were made to integrate the electronics directly on the sensor platform for data processing and readout, making these sensors less attractive for on-body operations. Furthermore, most of the sensors are fabricated on partially flexible yet partly hard plastic substrates that may cause eye irritation. Such eye irritation stimulates tear glands and leads to formation of reflex tears, and may thus alter the analyte concentration and lead to false readings.

The challenges faced by the strip-based ocular sensors can be addressed by developing a soft contact lens-based sensor with integrated wireless electronics. For example,

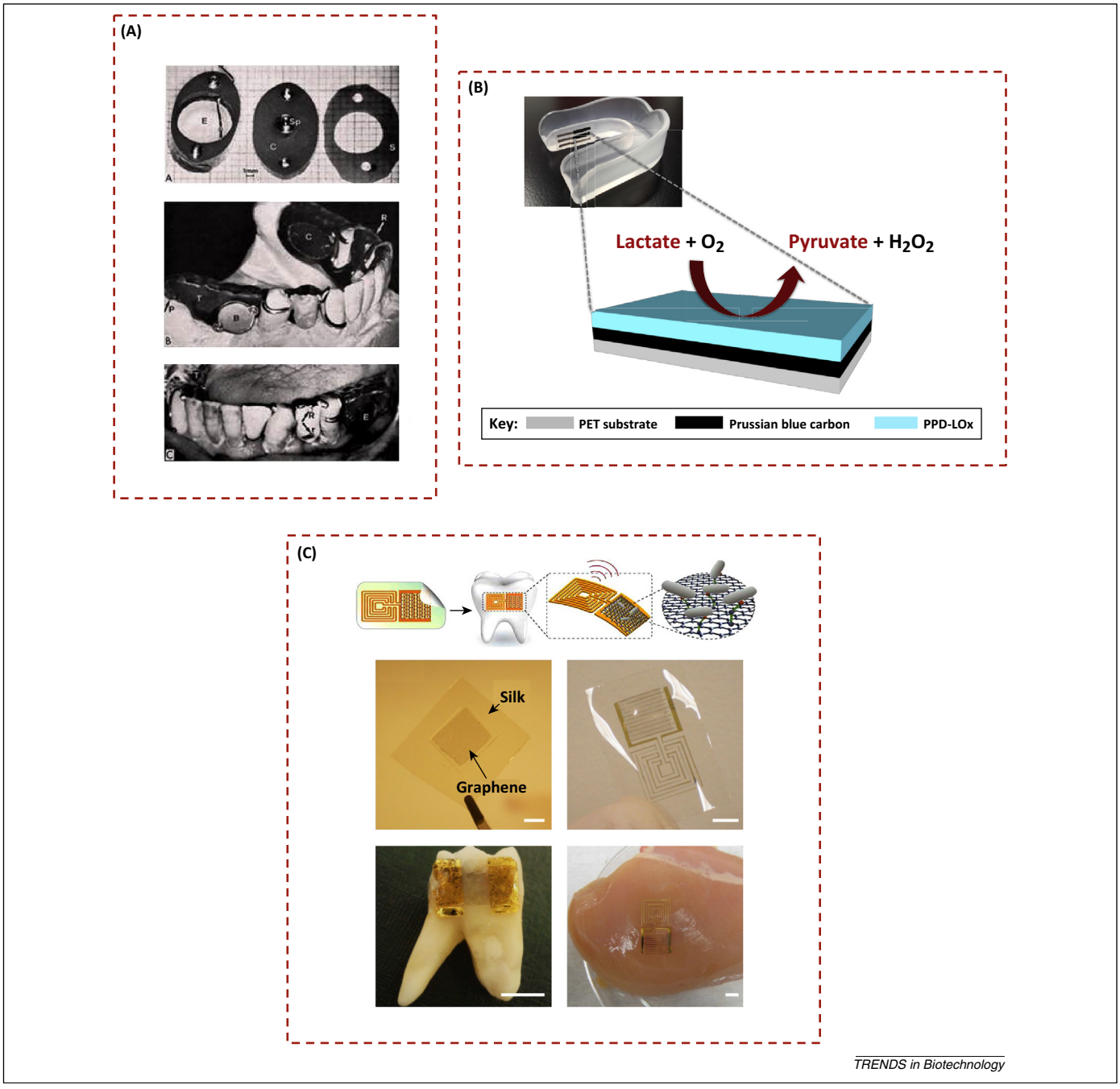

Figure 1. Salivary electrochemical sensors. **(A)** A potentiometric partial denture-based fluoride sensor [10]. **(B)** A mouthguard biosensor and its various components for continuous salivary lactate monitoring [12]. **(C)** A schematic and real image of a wireless tattoo-based resistive sensor for *Staphylococcus aureus* [13].

Parviz's team developed contact lens amperometric glucose sensors with in-built wireless electronics for continuous data transmission [24–26]. The device is now being currently developed by Google. The group first demonstrated the biofunctionalization of a PET-based contact-lens with glucose oxidase enzyme (GOx) within a Titania sol–gel matrix [24]. In this early work the sensor was hardwired, but the group subsequently demonstrated a contact-lens sensor with integrated wireless electronics for data recording and charging [25]. The authors later modified their wireless sensor to incorporate a dual sensor consisting of activated and deactivated GOx for minimizing interference effect [26] (Figure 2C). The authors studied the effects of ageing, temperature, and biofouling on the sensor response and demonstrated excellent sensitivity, detection limit, and linear range using a polymer eye model. However, real-life applications of the wireless electrochemical ocular glucose sensor, analogous to optical monitoring, have yet to be demonstrated. Diurnal variation in tear glucose level is affected by several conditions, including prolonged eye closure, mild mechanical stimulation, exposure to irritating vapors, and responses to osmotic imbalance [27]. Proper attention must be given to study the effect of such conditions on the sensor response. NovioSense glucose sensor (NovioSense BV) is another potential commercial product being developed in the Netherlands. It consists of a number of parallel coiled wires forming a micro-electrochemical cell with

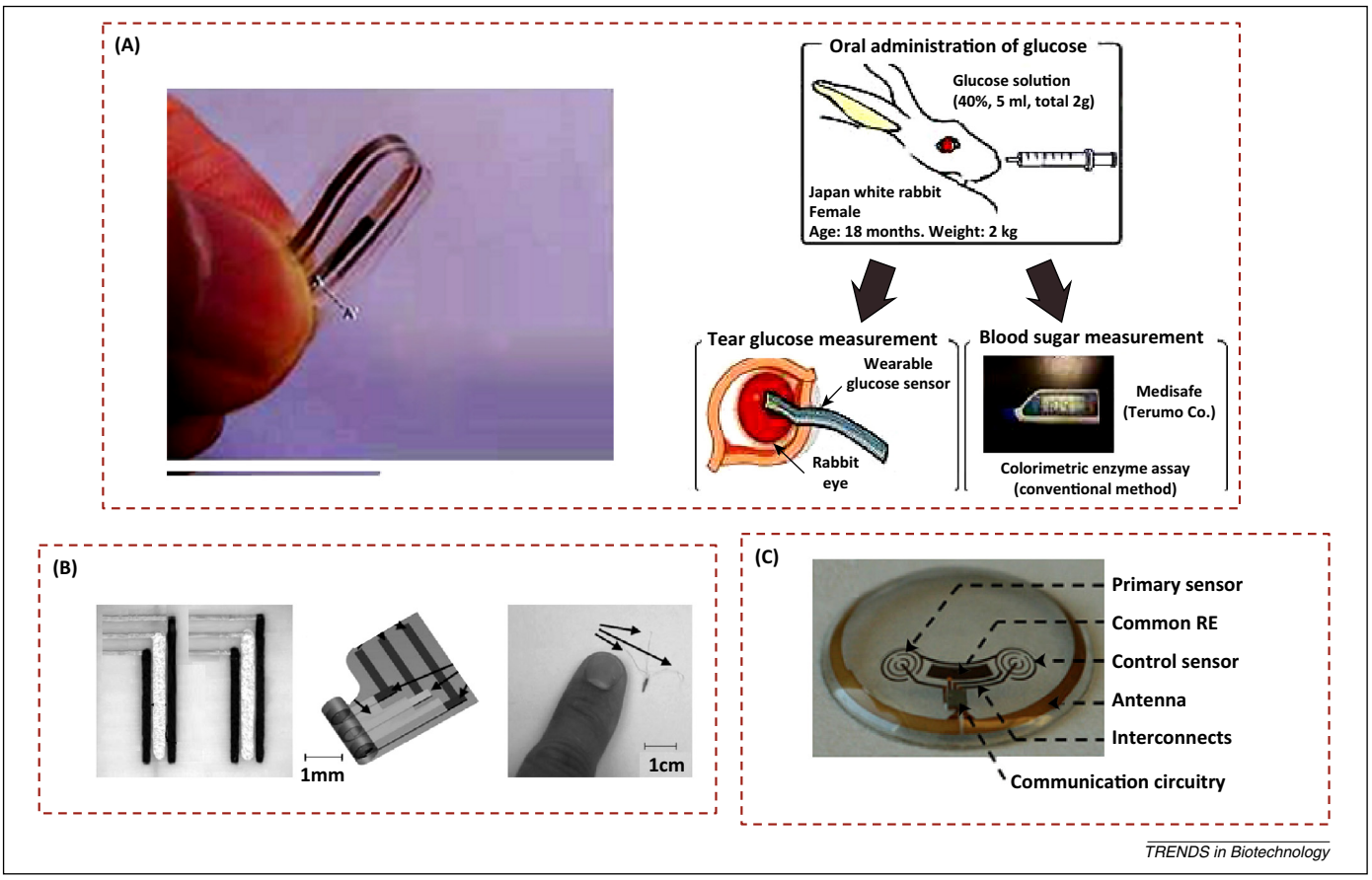

Figure 2. Tear-based electrochemical sensors. **(A)** A flexible strip-based glucose sensor and the method for applying the sensor for tear glucose measurement [21]. **(B)** A screen-printed electrochemical sensor for continuous glucose and neurotransmitters sensing [23]. **(C)** A soft contact lens-based wireless glucose sensor [26].

immobilized GOx. The coiled device can be easily placed within the eyelid for continuous wireless glucose sensing. The first human trials of this device are expected in 2014. Efforts have also been made in developing tear-based sensors for detecting lactate as an indicator of hypoxic conditions [28].

A major challenge in wearable ocular sensoring is obtaining a suitable power source. The lachrymal fluid contains several metabolites that can be used as potential biofuels for powering the ocular sensors. Recently Falk *et al.* have demonstrated biofuel cells that are capable of generating usable energy from lycramal glucose [29] and ascorbate [30].

Sweat-based sensors

Human sweat contains abundant information about a person's health status and thus is an excellent biofluid for non-invasive chemo-sensing [31]. For example, sodium, lactate, ammonium, and calcium levels in sweat are indicators of electrolyte imbalance [32] and cystic fibrosis (CF) [33], physical stress [34], osteoporosis [35], and bone mineral loss [36], respectively. Continuous detection of the above mentioned analytes is highly desired for optimal physiological balance. Sweat has also been used for monitoring a person's intoxication level [37] and signs of drug abuse [38], among other applications. Wearable, non-invasive sensors are therefore needed for such sweat monitoring. Non-invasive electrochemical sensors for monitoring sweat can mainly be divided into two types: fabric/flexible plastic-based devices [3] and the newly emerging epidermal-based sensors [39].

Fabric/flexible plastic-based sensors

Fabrics represent an excellent class of substrates for developing wearable sensors because they are in constant contact with the skin. Furthermore, the large surface area of textiles provides ample space for integrating the accompanying electronics. From the chemistry stand point, various fabrics such as wool, cotton, and nylon offer a rich variety of physical and chemical properties that can be utilized for incorporating chemical sensors within the fabric. Realizing these attributes, our group developed low-cost textile-based electrochemical sensors that were screen-printed onto various fabrics [3,40]. An optimal textile must possess inert properties, should not affect the electrochemical behavior of the analyte, and be a suitable platform for integrating multiple sensors. The sensors should also adhere well to the textile and operate desirably under normal and heavy wear. Keeping cognizance of these requirements, we compared the effect of various textile substrates on the print quality and analytical response of such printed sensors [40]. These textile-based sensors were tested under various conditions of repeated mechanical stress and washing. Accurate sensor response mandates continuous intimate contact of the textile sensor with the skin. We satisfied this condition by demonstrating the

first example of a sensor screen-printed directly on the waistband of undergarments [41]. The printed textile sensor is robust and endures repeated bending and stretching stress. Recently we demonstrated a bandage-based printed pH sensor for wound monitoring [42]. Diamond's group has been active in the field of textile-based sensors and has successfully demonstrated a wearable potentiometric sodium sensor [43] for CF monitoring (Figure 3A) and a fabric-based conductometric sensor for measuring the extent of dehydration [44]. Other groups have also developed wearable potentiometric sensors for pH, NH_4^+, and K^+ [45] and Cl^- [46] (Figure 3B). These have been fabricated on carbon nanotube-modified yarns [45] and by screen-printing technology [46]. Efforts have also been directed towards developing wearable sensors on flexible plastics, and elastomers. Over the past few years, several sensors have been reported that can monitor a range of variables, including transcutaneous oxygen [47] and humidity [48].

Epidermal-based sensors

Efficient functioning of a wearable sensor mandates conformal contact between the electrode surface and the biofluid. This prerequisite is often challenging in case of fabric-based sensors because intimate contact with the skin is restricted to limited regions. Chemical sensing directly on the skin can overcome this hurdle. Recent efforts to realize such sensors have resulted in epidermal electrochemical sensors for continuously monitoring analytes presiding over the skin. Our group was among the first to develop such electrochemical sensors. We first proposed the use of elastomeric stamps to print electrodes directly on human epidermis [49]. The method involves wetting customized stamps with conductive inks followed by contact printing of the electrode designs on the skin. Thereafter, we proposed a more robust, scalable system based on temporary tattoos. The earliest work illustrated the detailed fabrication protocol for realizing such temporary tattoo-based electrochemical sensors [39]. The fabrication process involves screen printing of

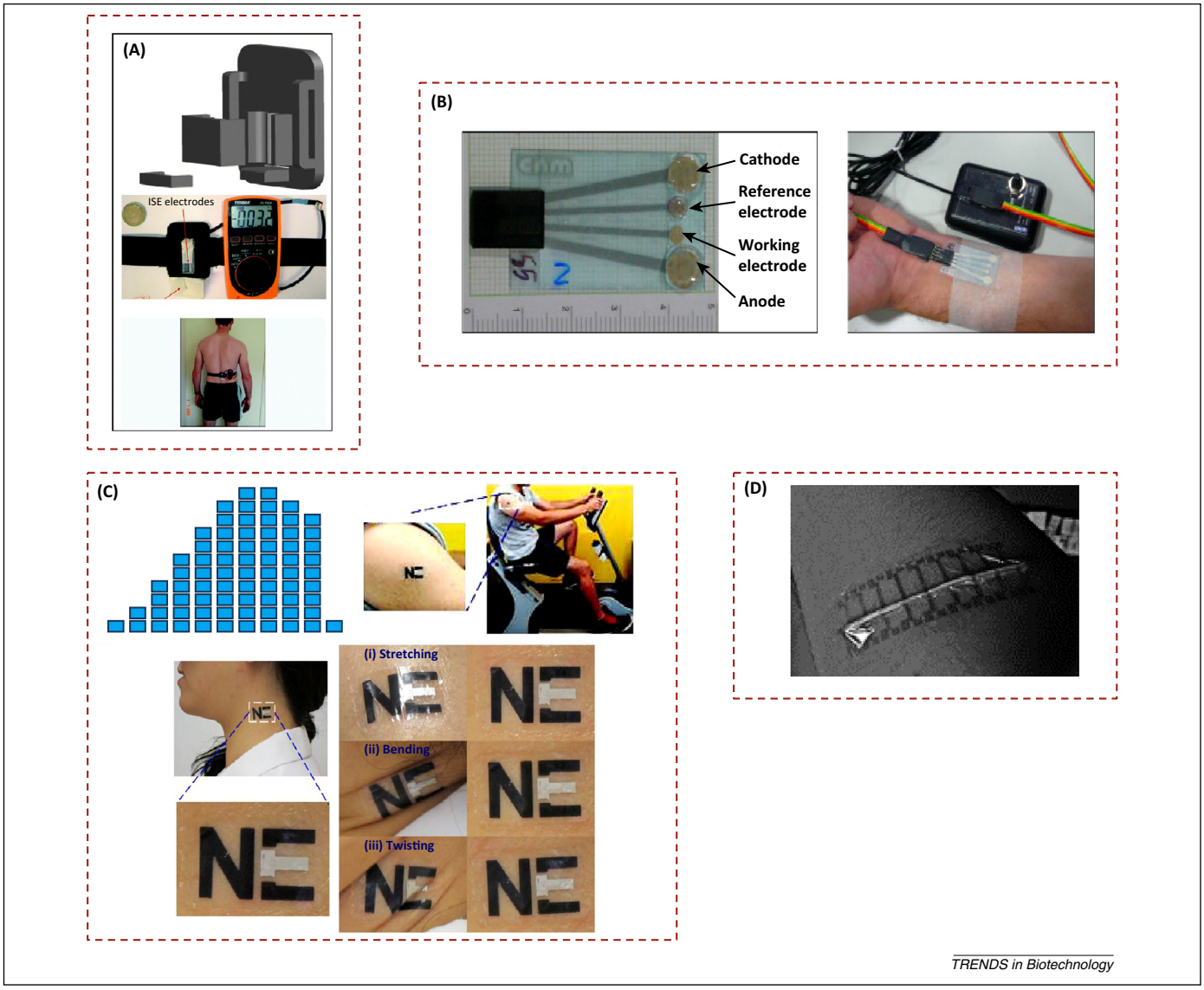

Figure 3. Sweat-based electrochemical sensors. **(A)** A wearable potentiometric sodium sensor worn by a subject [43]. **(B)** A flexible plastic-based sweat chloride sensor system consisting of the ion-selective electrodes for chloride sensing and iontophoretic electrodes for initiating chemically induced sweating [45]. **(C)** A participant on the stationary cycle wearing a lactate tattoo biosensor and the exercise intensity mode followed during continuous on-body lactate monitoring study. The tattoo sensor is resilient against repeated strains when applied to the neck of a subject [50]. **(D)** A skin patch-based electrochemical organic transistor for continuous lactate monitoring in human sweat [54].

conductive and insulating inks on commercial temporary tattoo-base paper to form the sensor. The skin experiences regular mechanical stress due to bodily movements. The new tattoo sensors are made resilient to such deformations by incorporating finely dispersed carbon fibers. Subsequent modification of the tattoo electrode transducers with the corresponding receptor and reagent layer imparts the desired selectivity for detecting a wide range of analytes.

For example, we introduced an enzymatic tattoo amperometric biosensor involving immobilized lactate oxidase for continuously monitoring lactate levels in the perspiration as a biomarker of physical stress [50] (Figure 3C). By combining solid-state potentiometry and tattoo sensor technology we also developed epidermal sensors for monitoring acidity [51] and ammonium [52] in sweat. Our most recent work delineates the fabrication of a potentiometric tattoo sensor, coupled with wearable transceiver, for continuous wireless monitoring of sodium levels in human perspiration [53]. The autonomous nature of this system makes the device highly ergonomic. Separate efforts by other groups have led to skin patch-based sensors for sweat lactate [54] (Figure 3D) or alcohol [55]. Finding a suitable energy source to power wearable sensors is another challenge. We recently demonstrated a tattoo-based epidermal biofuel cell that can non-invasively harness usable electrical energy from lactate present in the human perspiration [56]. The energy generated can then be used to power wearable devices.

Skin interstitial fluid-based sensors

A rich variety of vital information can be obtained from skin interstitial fluid (ISF) in a completely non-invasive and continuous fashion. Over the past three decades, researchers have used the ISF for non-invasive detection of inherited metabolic diseases [57], organ failure [58], and drug efficacy [59]. However, most of the activity in this field has focused on non-invasive glucose sensors in connection to efficient diabetes management [60]. The correlation between ISF and blood glucose has prompted several industrial and academic researchers to develop optical-, ultrasound-, heat-, and electrochemical-based devices for continuous, non-invasive glucose monitoring [60]. Of these, reverse iontophoresis-based electrochemical glucose sensing is the most widely recognized technique [61]. This technique led to the development of the GlucoWatch® Automatic Glucose Biographer Manufacturer (Cygnus, Inc.), a commercial wearable non-invasive electrochemical glucose monitoring device (Figure 4). However, the primary concern of patients reporting skin irritation led to subsequent retrieval of the device from the market [60]. Other wearable non-invasive glucose sensors based on impedance spectroscopy (Pendra, Pendragon Medical Ltd.) or optical (C8 MediSensors, C8 MediSensors, Inc.) transducers have met a similar fate or have not yet been successfully commercialized. Such developments underscore the technical challenges associated with continuous non-invasive glucose sensors and the need to find viable solutions to these critical problems.

Challenges in implementing wearable sensors

There are still several challenges that need to be addressed before the realization of wearable non-invasive chemical

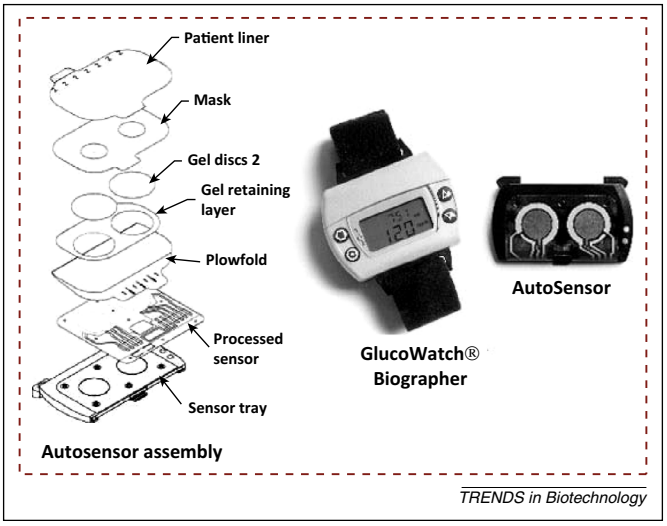

Figure 4. Skin interstitial fluid-based electrochemical sensor. An exploded schematic revealing various components of the GlucoWatch [61].

sensors. Particular attention should be given to technological issues such as the resiliency of these devices, their long-term stability, and their biocompatibility. For example, epidermal sensors face complex mechanical deformations during normal bodily movements. The extent of such deformations increases when the wearer is performing intense physical activity. Additional deformation and challenges occur with textile-based sensors, where washing of the textiles exerts immense mechanical, chemical, and heat degradation. Extensive efforts need to be taken in developing sensors that can withstand such severe stresses over extended periods or rigorous use. The past decade has seen significant advances in stretchable electronics [62]. Researchers working in the field of wearable electrochemical sensors can look up to such developments to address the issue of mechanical resiliency while keeping the cost of devices low.

Some of the target analytes (such as pathogens and proteins) may require bioaffinity protocols. Continuous monitoring of such analytes mandates regeneration of the receptors. This is currently achieved *in vitro* by subjecting the sensor to harsh conditions (extreme pH solutions) and washing steps that are incompatible with on-body operations. Another grave issue that mares the introduction of a suitable wearable bio-affinity sensor is the ability to detect extremely low biomarker levels. Current *in vitro* portable devices rely on multi-step procedures, such as sandwich immunoassays, that are not readily amenable to wearable non-invasive sensing platform. Powering the wearable sensors represents another major challenge. Wearable biofuel cells [56], piezoelectric energy harvesting [63], and thin-film batteries [64] may hold the answer to this problem. However, there are still several issues that need to be addressed in the case of such power sources [65,66]. Shrinking of the sensors and the associated electronics to increase the functionality and portability of the wearable systems is another front that requires attention. Recent innovations in the field of nano-electronics can accomplish these requirements. Chemical sensors require direct contact of the reagent layer with biofluids, whereas the associated passive electronic components must be

sealed from the aqueous environment. Satisfying this demand, while maintaining the aesthetics of the device, becomes a daunting task when a miniaturized sensor is desired.

Attention should also be given to the development of calibration-free and user-independent wearable potentiometric sensors and to related storage and stability issues. Plaques develop within minutes over teeth, and this biofilm can hinder the performance of wearable salivary sensors. Coverage of the sensors with antimicrobial or protective coating may minimize this issue. Efforts should also be devoted towards enhancing the sensitivity of wearable sensors. This is often accomplished via nanomaterial-based signal amplification. However, the potential toxicity of nanomaterials should be considered prior to their on-body application.

Concluding remarks and future perspectives

It is expected that with attention to key challenges, such as those discussed above, wearable electrochemical sensors will bring many exciting opportunities for continuously monitoring the human body across a broad range of biomedical and fitness applications. With the entry of big multinational companies, such as Google, and several smaller companies, such as NovioSense, OrSense, and Electrozyme, the nascent field of wearable, non-invasive electrochemical sensors is expected to grow rapidly, with new innovative devices entering the consumer market in the coming years.

The prospects of such wearable chemical sensors are immense in diverse fields. For example, new non-invasive electrochemical sensors for continuous personalized health monitoring are expected to provide low-cost solutions for remote monitoring of elderly people at home or in nursing homes and for the self-management of chronic diseases. Such remote health-monitoring devices would thus lead to major improvements in patient monitoring and care while greatly reducing costs. New wearable sensors for additional important analytes are highly desired. A wide variety of new non-invasive sensing devices are thus expected to be introduced in the near future. These may include devices for non-invasive monitoring of catecholamines [67] and antioxidants [16] in tears; cortisol [7] and pathogens [68] in saliva; or amino acids [69], calcium [35], and pathogens [70] in sweat/ISF. The fusion of several wearable chemical sensors should lead to non-invasive multi-analyte sensing. Furthermore, integration of radiofrequency identification or Bluetooth devices with wearable chemical and physical sensors will enable users to wirelessly transmit data to their cellphone/computer in a more user-friendly fashion. Such real-time monitoring devices will enable a more comprehensive assessment of the wearer's health-care status, including his or her stress and performance levels.

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