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Perspective—Challenges in Developing Wearable Electrochemical Sensors for Longitudinal Health Monitoring

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Wearable electrochemical sensors have the potential to overcome the problem of infrequent clinical visits that leads to transient events of potential diagnostic importance being unduly overlooked. The promise of real-time, personalized health care has driven multidisciplinary work on fabricating various forms of wearable sensors. Although remarkable advances in device form factor and integrated circuit design have been achieved, notable hurdles, such as shelf life, reusability, flex and sweat resistance, and longitudinal performance, remain unaddressed. This perspective seeks to summarize major advances in current wearable electrochemical sensors and to highlight the most pressing challenges that will benefit from collective research endeavors.

Table I) enable a variety of chemical sensing possibilities. Although conventional approaches to obtain sweat samples involve intense exercise or high-temperature environments that induce sweating, drugs like pilocarpine, methacholine, acetylcholine, can also be used to chemically stimulate eccrine sweat glands and comfortably collect the necessary sweat samples under natural settings. Physical stimuli, for example, exposing skin to aqueous ethanol, can also help to collect sweat.

Device categories.—To make a sensor for real-time and on-body sweat analysis, besides the fundamental requirements of sensitivity and selectivity, comfortability and portability are also critical. Nowadays, many studies focus on creating wearable sensors containing electrochemical transducers due to their instrumental simplicity and ready miniaturization capability. Moreover, electrochemical techniques are powerful tools owing to their high performance, low cost and compatibility with near-field communication, which enables final readouts on ubiquitous mobile phones.

In terms of the electrochemical sensor, the input (a physical or chemical event) occurs at the sensor’s surface and is translated into an electrical signal by transducer components (target-specific receptors or recognition elements on the working electrode). Typically, these signals are also calibrated using either an external standard or an internal reference electrode. Depending on the nature of their final output, electrochemical sensors are divided into three major types as listed in Table II.

Current Status of Wearable Sensing Systems

To date, mostly skin-mounted electrochemical sensors (tattoos) have been developed, which display notable sensitivity and selectivity. Human skin is very anisotropic and viscoelastic, with a Young’s modulus ranging from 57 to 140 MPa and a 25%–80% breaking elongation. Generally speaking, materials that are compatible with the unique mechanical strength of human skin can be divided into natural and synthetic classes. Common natural materials are cellulose-based (cotton) or protein-based (wool or silk), while synthetic materials are polymers exhibiting elastic properties, including PET, poly(amide)s, poly(acrylonitrile), and poly(propylene) (PP).

The working electrode is a key component in all known iterations of smart tattoos. The broadly defined structure of the working electrode in a wearable sensor consists of a flexible substrate, a conducting material, a recognition agent, and a biocompatible protective layer. Flexible substrates, such as poly(vinyl alcohol) (PVA) based temporary tattoos, silicones (e.g. PDMS), Ecoflex,
Solaris) and inert plastics (e.g. PET, PEN), exhibit elastic properties similar to human skin and have therefore been used as substrates for skin-mounted biosensors.16

Two basic steps are needed to realize functional sensors on these flexible substrates. First, finding a proper conductive base and recognition agent to ensure good chemical response. Then the second step is to develop a method to load these materials onto the flexible substrate that ensures the active layer will not be delaminated with varying skin tension. Although forming films of conventional conductive materials, such as metals or conductive carbon, on flexible substrates can be challenging due to their hardness or brittle nature, new materials and processing methods have been developed to address this problem in recent years. In terms of metals, designing serpentine conducting lines with periodicities guided by theoretical simulations can increase their stretchability and bendability.31 Another way is to leverage solution-processible inks of nanostructured conductors, such as metal nanoparticles and graphene.17 These inks can be easily printed onto flexible substrates via methods like screen-printing, inkjet printing, gravure printing, and doctor blading.32 Also, due to their tunable conductivity and highly ordered 3D structures, conductive polymers are another powerful alternative. Electrolysisynthesis, in situ solution-based polymerization and reactive vapor deposition have all been applied to create conducting polymer films on flexible substrates.33

Recognition agents, namely bio-receptors, vary depending on the target analyte. In terms of potentiometric and impedimetric sensors where no current flows in the system, binding and recognition sites are provided by commercial ionophores,23 hydrogel templates, self-assembled monolayers,9 or antibodies (for ion, charged gas and biological factors, such as temperature, pH and humidity (too much or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and fouled or compromised when diluted with inappropriate solutions or too little humidity), and 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recognition elements, particularly in wearable systems. Metal-organic frameworks and nanomaterials have also been proposed. In particular, MIPs are gaining recognition as a versatile tool for preparing synthetic polymers with tailor-made recognition sites and/or suitable ligand environments for specific analytes. Alberto et al. introduced a tailor-made polymeric membrane that facilitated the stable and selective molecular recognition of cortisol, a human stress hormone. Although these artificial receptors can be cheaper and more resistant to aging-induced degradation as compared to natural enzyme analogs, some limitations still need to be considered. Because their catalytic activity and analyte affinities are not as good as their enzymatic counterparts, electrodes functionalized with artificial receptors require more time to read out the data in real-time. Also, globally weaker selectivities may lead to false positives originating from nonspecific binding events.

Another problem of enzymatic recognition elements is the efficiency of signal transduction. Three common methods to transduce an enzymatic reaction into an electrical signal are used. The first is to sense a product or byproduct of the reaction. Famously, for example, oxygen serves as the final electron acceptor during glucose sensing and is reduced to peroxide by glucose oxidase (GOx). In this case, many working electrodes are built to sense the peroxide final product of the glucose sensing reaction and thus contain a combination of GOx along with horseradish peroxidase (HRP) or a Prussian Blue (PB) electrocatalyst, both of which sense peroxide. However, this method of signal transduction requires complicated active layer formulations that may complicate the electrode fabrication process. Another method is to measure electrons shuttled to redox mediators. In this case, electrons from the target analyte are first transferred to the enzyme binding partner and then quickly transferred to the mediator, which leads to a change in the observed current that is proportional to the concentration of the target analyte. Since reactive sites can be buried deep within an enzyme, mediators can increase the total contact surface area and enhance electron transfer rates. Similar to the first instance, molecular electrocatalysts and metal/carbon nanomaterials are often employed as mediators but these compounds frequently lead to electrode decay by freely diffusing into the recognition layer instead of the conductive base. Moreover, many common mediators are highly cytotoxic and, therefore, can only be incorporated into wearable systems if thick encapsulation layers are used. The most efficient but the most difficult third method is to directly detect electron transfer from the enzyme active site to the electrode surface upon analyte binding. Highly-structured "template" layers can be used to immobilize enzymes close to the electrode surface and, thus, facilitate electron transfer. In Wang’s research, a mesoporous silicate foam (MCF) with pore diameters of 20 nm was designed and synthesized to immobilize Hb and GOx, realizing direct electron transfer from these enzymes to the underlying working electrode surface upon analyte binding. However, this strategy cannot be easily translated to flexible and wearable systems. Bioengineering strategies to realize artificial enzyme derivatives with exposed active sites have also been explored to create optimal recognition elements for electrochemical sensors.

In summary, enzymes are weak candidates for reusable sensors, even though they provide enviable chemo-specificity. Finding artificial substitutes that are cheaper and produced in bulk is desired, particularly for long-term health monitoring. Since skin provides the perfect large-area platform for distributed sensing networks, one possible strategy is to sacrifice chemo-specificity and use multiplexed sensors along with pattern recognition algorithms to achieve signal accuracy in wearable systems.

Signal accuracy: false positives and false negatives.—Signal accuracy is compromised by surface fouling effects, which represent a major challenge to the continuous operation of wearable biosensors. Wearable biosensors can also be exposed to fluctuating conditions during prolonged outdoor activity that may affect the stability or activity of fragile bio-receptors. Achieving wearable biosensors with long-term operational stability and signal accuracy requires a combination of proper receptor immobilization, protective (or target-selective) membranes, and storage conditions.

To ensure the reliability of the response during prolonged operation, robust antifouling surface protection is needed, along with active calibration mechanisms (multimodal, multianalyte sensing and drift correction). Biofouling is driven by the accumulation of interferent analytes on the sensor surface through nonspecific binding. Such rapid adsorption impedes diffusion and/or binding of the target analyte, leading to a gradual decrease of the sensing signal over time and eventual evolution of false negatives.

These issues can be partially addressed using microfluidic sampling systems and optimizing surface coating techniques. Microfluidic systems, featuring multiple reaction chambers separated by using various valving techniques, can track time-dependent changes in analyte concentration in sweat. Also, calibrated analytes in different channels can collaboratively reveal sweat dynamics, as defined by instantaneous sweat rate and total sweat loss.

Accuracy on-body measurements also require active removal of old fluids. Washing away analytes after each sensing event will significantly enhance the longterm performance of wearable electrochemical sensors and reduce the occurrence of false positives due to incomplete target clearance after a singular recognition event. In this case, hydrogel coatings or shells are promising due to their viscoelastic properties, which respond to various external stimuli like electrical field and pH, and tunable affinities for different biological components. For example, an ionic hydrogel can reversibly swell and de-swell relative to an aqueous condition and therefore enable excess analytes to flow away. Hydrogels with a high dielectric constant can undergo voltage-induced, reversible deformations that can mechanically effect interferent unbinding.

Wear resistance and reusability.—Temporary tattoo sensors, tiny and adhesive, can be easily fixed on human skin and have presented excellent efficiency to date. However, with respect to long-term usage, some limitations should be carefully considered. Tattoo sensors, or other tight-fitting sensors, usually require skin preparation in advance, such as hair shaving and alcohol cleaning of the contact area, which largely excludes them from widespread use and everyday wear. The surface chemistry/biochemistry of the wearer’s skin may also influence sensing performance. For example, the adhesive glue used to affix the sensor to skin may dry out and cause the device to shift or fall-off. Dissolution of the active layers may also occur when the sensor is exposed to large quantities of sweat, which will lead to signal degradation and evolution of false negatives, in addition to skin irritation if any of the active layer components are not biocompatible. Lastly, considering the metastable adhesive interaction between the tattoo and the wearer’s skin, the ability of such skin-mounted devices to withstand continuous body stretching, fracturing and slipping is not assured.

Fabric-based and/or garment-integrated sensors.—Conceptually, textiles and garments, which we wear in daily life, provide a pervasive platform for distributed sensing networks while also exhibiting excellent mechanical properties and longevity. With the aid of efficient knitting and weaving methodologies, functional fibers can be easily integrated into textiles and garments. Moreover, the ordered structure of textiles is naturally suitable for an electrochemical sensor composed of three adjacent electrodes.

Although various iterations of fiber- and fabric-based colorimetric sensors are known, fibers and fabrics have not been widely investigated as platforms for electrochemical sensors. A long-standing challenge is creating a high-performing working electrode directly on the surface of textiles that also displays stability against the harsh mechanical and chemical stresses to which textiles and
garments are regularly subject. Existing fabrication methods (mentioned previously) work best with a flat, uniform substrate, thus largely excluding fibers and off-the-shelf textiles. Furthermore, the loose structure of textiles can easily deform printed conductive layers and lead to delamination.

Recently, selected researchers have demonstrated the use of specialized conductive fibers, such as carbon fibers,\textsuperscript{24} stainless steel yarns,\textsuperscript{24} metallic fibers,\textsuperscript{25} and silver-coated nylon threads\textsuperscript{26} as both platforms for fiber-based working electrodes and as interconnects for distributed sensing systems. Wang et al. created fiber-based working electrodes by electrodeposition active materials onto carbon fibers and integrating these fibers into a sensing array.\textsuperscript{27} In Zhao’s work, a thin gold fiber made by dry-spinning gold nanowires was used for glucose sensing.\textsuperscript{28}

Depositing conductive polymers on commercially-available garments and textiles is an alternative way. However, caution should be exercised when using solution-based deposition processes to make polymer coatings (for example, electrochemical deposition, in situ solution polymerization and dip-coating) because many off-the-shelf fibers and fabrics may get impregnated with the evolving polymer and/or mechanically deformed by the solvents used during the synthesis process.\textsuperscript{29} Thanks to nascent, creative polymer synthesis approaches, these problems can be overcome—conductive polymers can be deposited on arbitrary textiles via reactive vapor deposition, which curtails solvent use and enables rugged and conformal polymer coatings that are remarkably launderable-stable and resistant against fouling with continued wear. Andrew et al.\textsuperscript{30} used reactive vapor deposition to create garment-embedded fabric sensors to detect various body motions.

Summary

The promise of real-time, personalized health care has driven exciting and multidisciplinary work on fabricating various forms of wearable and/or skin-mounted electronic sensors. In this short review, we highlight major advances in creating wearable electrochemical sensors for longitudinal health monitoring. Although rapid progress has been made in the past few years to realize wearable electrochemical sensors with high sensitivity and chemo-selectivity, limitations in longterm performance, shelf life and reusability are waiting to be overcome. Here, four attractive “targets of opportunity” are proposed, ranging from active layer development to novel device platforms and systems-level approaches, to address these challenges. We expect that collaborative endeavors from researchers with diverse expertise will contribute significantly to driving this area forward.

References