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Wearable electrochemical biosensors in North America

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ABSTRACT

Tremendous research and commercialization efforts around the world are focused on developing novel wearable electrochemical biosensors that can noninvasively and continuously screen for biochemical markers in body fluids for the prognosis, diagnosis and management of diseases, as well as the monitoring of fitness. Researchers in North America are leading the development of innovative wearable platforms that can comfortably comply to the human body and efficiently sample fluids such as sweat, interstitial fluids, tear and saliva for the electrochemical detection of biomarkers through various sensing approaches such as potentiometric ion selective electrodes and amperometric enzymatic sensors. We start this review with a historical timeline overviewing the major milestones in the development of wearable electrochemical sensors by North American institutions. We then describe how such research efforts have led to pioneering developments and are driving the advancement and commercialization of wearable electrochemical sensors: from minimally invasive continuous glucose monitors for chronic disease management to non-invasive sweat electrolyte sensors for dehydration monitoring in fitness applications. While many countries across the globe have contributed significantly to this rapidly emerging field, their contributions are beyond the scope of this review. Furthermore, we share our perspective on the promising future of wearable electrochemical sensors in applications spanning from remote and personalized healthcare to wellness.

1. Introduction

Wearable sensors are integrated with the human body to help monitor remotely and continuously the wearer's health and performance. While wearable sensors enabling physiological data collection have widely been applied in medical and consumer products, their potential role in managing the current COVID-19 pandemic has gained tremendous recent attention (Adans-Dester et al., 2020). With many studies supporting the relevance of COVID-19 to multiple physiologic metrics, such as resting heart rate, respiration rate, blood oxygen saturation, core and skin temperature, wearable sensors could also aid early detection of presymptomatic viral infections/transmissions and thus, allowing timely interventions to prevent imminent outbreaks (Seshadri et al., 2020). Besides the commercially available wearable sensors and activity monitors (Apple Watch, Fitbit, or WHOOP Strap) that track vital signs and physical metrics, the new generation of wearable chemical and biochemical sensors can offer a comprehensive molecular information toward diverse applications in major fields, ranging from personalized medicine, athletes or soldier performance, nutrition and wellness, safety and security (Yang and Gao, 2019). Such wearable biosensors enable noninvasive measurements of the dynamically fluctuating biochemical markers in peripheral biofluids, such as sweat, interstitial fluid (ISF), tears, and saliva (Kim et al., 2019; Yang and Gao, 2019).

While the rapid recent progress in the field of wearable chemical sensors has been made through major contributions from many influential researchers from across the globe, this review focuses exclusively on the developments of wearable chemical sensors in the North American region. In particular, the United States (US) has played a pivotal role in the majority of the cutting-edge wearable chemical sensor research, with pioneering contributions from several leading groups. Fig. 1 presents the current main academic players in the area of wearable biosensors within North America. Unfortunately, our analysis did not identify major active research groups focusing on wearable chemical sensors in Canada and Mexico, although we noticed several new Canadian start-ups which are active in this area. Thanks to major investments and highly skilled human capital, the US is known as home for many

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technological innovations, with its Silicon Valley serving as the worldwide technology center and home to giant high-tech corporations, such as Apple, Intel, and Google. Coupling such a dynamic private sector with leading universities attracting many creative talents, and major US government funding (from agencies such as DOD and NIH), has made this country the leading force in technological areas, such as the Internet of Things (IoT) or digital medicine. In addition, owing to rapidly growing healthcare demands, the US has led the development of commercial continuous glucose monitoring (CGM) systems that have inspired the introduction of wearable chemical sensors for other target analytes.

When the first wearable CGM device was introduced by Minimed iPro in the late 1990s, many people doubted its ability to replace the self-monitoring blood glucose (SMBG) strips (Garg and Kaan Akturk, 2018). Later in 2005, Medtronic (USA) commercialized the first CGM device (marketed as Guardian TM), and this was followed in 2006 by the STS system from Dexcom (USA). Major improvements in the design, functionality, and cost of CGM devices over the past decade have now made CGM devices the new standard of care for many patients with diabetes (Teymourian et al., 2020a). By offering remote monitoring of diabetic patients, such wearable CGMs have recently played a pivotal role during the current coronavirus pandemic, circumventing major risks of blood testing by healthcare providers.

Early efforts toward wearable non-invasive sensor technology have faced some skepticism regarding their ability to offer reliable monitoring of chemical markers. This may in part be due to the challenges experienced by the first commercial real-time, non-invasive CGM, the GlucoWatch (Cygnus Inc., CA). This first non-invasive glucose sensor platform received FDA approval in 1999 but was later retracted from the market due to reported skin irritations and reproducibility issues (Kim et al., 2018a). Nevertheless, the pioneering idea of wristwatch-based chemical monitoring has inspired researchers to pursue innovative ideas toward the development of a wide range of powerful wearable chemical sensing platforms. Yet, expanding the commercial success of market driven CGM to other clinically important analytes, and to different biofluids has experienced key challenges. However, due to innovative technological and scientific advances in diverse areas, ranging from nano/micro-fabrication methods, materials chemistry, flexible electronics, to bioelectronics, along with the advent of digital communication technology and wireless sensor networks, the field of wearable chemical sensors has experienced a major boom over the past decade (Choi et al., 2019; Kim et al., 2019; Yu et al., 2020a).

In this review article, we will provide a historical overview of substantial achievements in the field of wearable platforms made in North America over the past decade, starting from the early stage (2008–2014), followed by the middle stage (2015–2017) and ending with the present state-of-the-art (2018–2020). We will also discuss the prospects and challenges for the next decade (2020–2030) in order to stimulate further activity and advances in this paradigm-shifting technology. Subsequently, we will highlight different wearable platforms along with various electrochemical and recognition approaches utilized in wearable systems. This section will be followed by a discussion of the sampling methods available to access different biofluids. We will conclude with a brief overview of ongoing commercialization efforts, while staying geographically focused on North America throughout this article.

2. Historical perspective of wearable electrochemical sensors

Fig. 2 shows a timeline depicting key advances in wearable chemical sensors by North American researchers over the past two decades, starting with the introduction of the first commercial CGM devices including GlucoWatch (Fig. 2a) and Medtronic's Minimed (Fig. 2b) in early 2000s. In this section, we review the evolution timeline of these landmark developments in the wearable chemical sensors field.

2.1. The early stage (2008–2014)

During the early stage, the first devices with potential wearability were described by combining traditional sensing chemistries and versatile electrode fabrication techniques involving flexible body-compliant substrates. These early studies laid the foundation for the current on-body wearable platforms. A pioneering report in 2008 described a miniaturized flexible thick-film rolled glucose biosensor, suitable for insertion into the tear drainage canal, fabricated by screen printing onto a polyimide substrate (Kagie et al., 2008). In a follow up

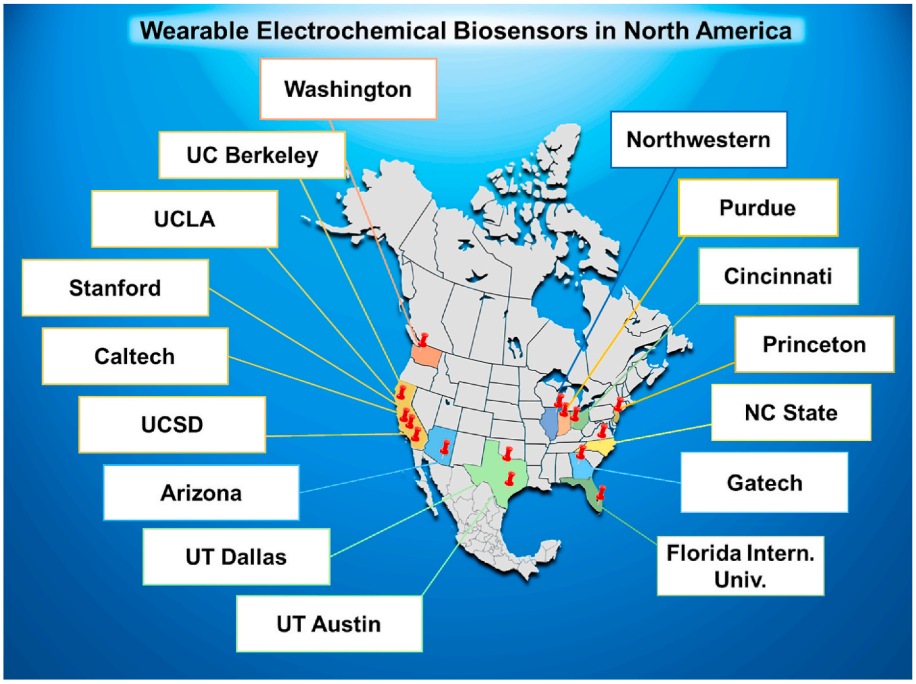


Fig. 1. Research activity of wearable electrochemical biosensors in North American universities over the past decade.

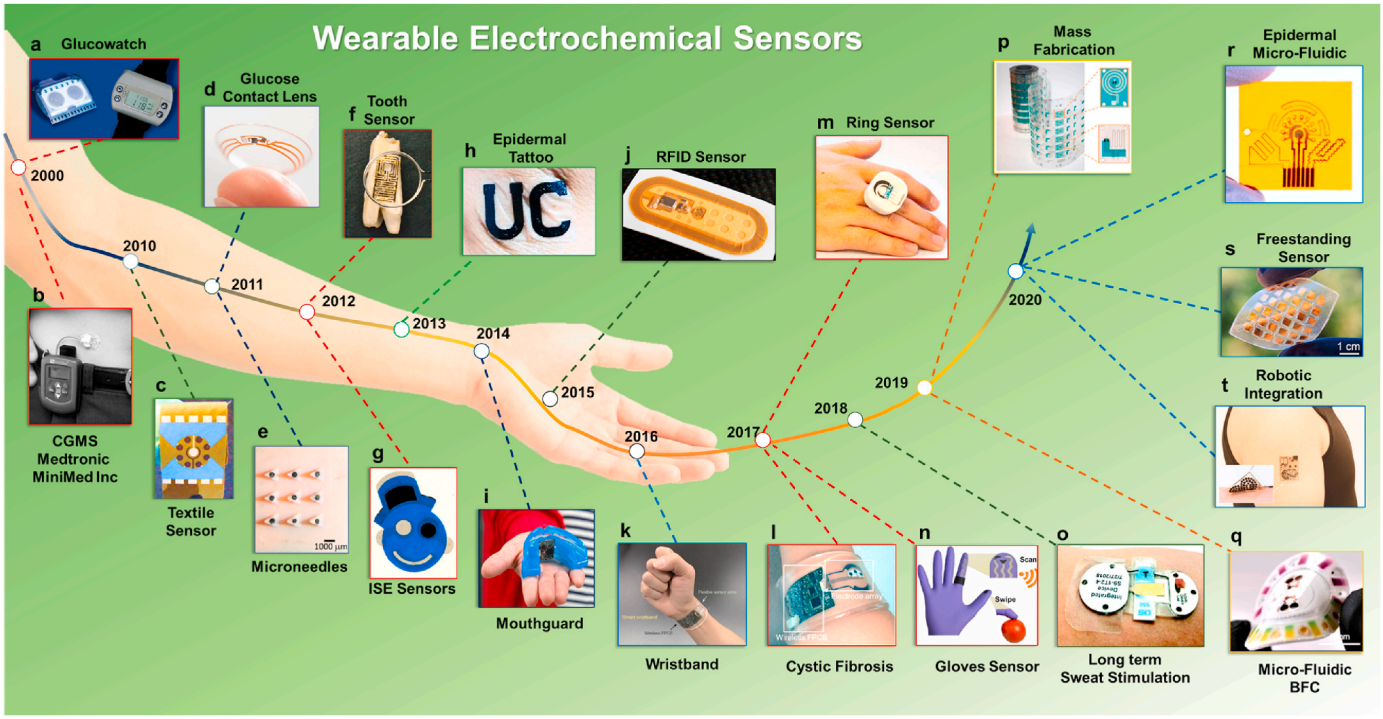


Fig. 2. Evolution timeline of wearable chemical sensors in North America. a, First commercial CGM devices including GlucoWatch (Tierney et al., 2000) and b, Medtronic's Minimed (Gross et al., 2000). c, First textile-based wearable sensor realized through screen printing on the elastic waist of underwear (Yang et al., 2010). d, First report on a contact lens with embedded sensor for potential application in tear glucose monitoring (Yao et al., 2011). e, Use of microneedle arrays toward minimally invasive detection of biomarkers on the tip of microneedles (Windmiller et al., 2011). f, First salivary sensor on tooth enamel for bacteria detection (Mannoor et al., 2012). g, h, Epidermal sensors and biofuel cells based on transfer tattoos (Bandodkar et al., 2013a; Jia et al., 2013). i, Wearable mouthguard biosensor for amperometric lactate biosensing in human saliva samples (Valdés-Ramírez et al., 2014a). j, First integrated wearable sensors using wireless transmission based on radio frequency identification (RFID) (Rose et al., 2015). k, First example of fully integrated, multiplexed wearable sensor for metabolites and electrolytes detection in sweat (Gao et al., 2016a). l, Iontophoretic-based sweat stimulation to sample the biofluid under sedentary condition (Emaminejad et al., 2017). m, Wearable sensors for defense and safety including ring and n, glove-based sensors for detecting vapor explosives and nerve-agents (Mishra et al., 2017; Sempionatto et al., 2017a). o, Stimulated sweat collection using 'hex-wick' material to reduce the required sweat sampling volume (Hauke et al., 2018). p, Mass fabrication of microfluidic sensing patches via roll-to-roll processes for reproducible sweat analysis(Nyein et al., 2019). q, Epidermal BFC-powered sweat biosensor integrated with colorimetric sensors (Bandodkar et al., 2019). r, Laser-engraved graphene-based wearable sweat sensors for detection of low analytes concentration (Yang et al., 2020). s, Freestanding sensor system-enabled smartwatch featuring sweat sampling, electrochemical sensing, and data display/transmission in sedentary and high-intensity exercise settings (Zhao et al., 2020). t, Fully sweat-powered integrated electronic skin toward multiplexed metabolic sensing (Yu et al., 2020b).

study in 2010, the same group challenged a flexible biosensor printed on the PET substrate against severe bending-induced mechanical stress and demonstrated that such a platform can tolerate repeated bending cycles (Chuang et al., 2010b). In the same year, we witnessed the first textile-based wearable sensor realized through screen printing on the elastic waist of underwear (Fig. 2c) (Yang et al., 2010). Such textile sensors with the electrodes in direct contact with the skin displayed an attractive electrochemical performance toward in-vitro detection of chemical markers. This study was followed by another report on textile sensors in 2010, describing the same principle but with the electrodes printed on the outside surface of garments toward detection of explosive threats present in the surrounding environment (Chuang et al., 2010a). The next year, 2011, we saw the first report on a contact lens with embedded sensor for potential application in tear glucose monitoring (Fig. 2d) (Yao et al., 2011). In the same year, the use of microneedle arrays toward minimally invasive detection of biomarkers on the tip of microneedles was reported (Fig. 2e) (Windmiller et al., 2011). In 2012, the first salivary sensor was reported, relying on the printing of graphene on bioresorbable silk that was transferred onto a tooth enamel to warn against bacteria in saliva, while also achieving wireless powering and readout (Fig. 2f) (Mannoor et al., 2012). Epidermal sensors and biofuel cells based on transfer tattoos were introduced by Wang's group in 2012 (Fig. 2g and h) (Bandodkar et al., 2013a , Jia et al., 2013). The same group described the first glove-based sensor for voltammetric detection of security threats (Bandodkar et al., 2013b). Finally in 2014, a wearable mouthguard biosensor was developed by Wang's group for amperometric lactate biosensing in human saliva samples (Fig. 2i) (Valdés-Ramírez et al., 2014a).

2.2. The rapid growth stage (2015–2017)

During this medium stage, major advances were made for translating the early wearable designs closer to their ultimate aim of on-body application. The first reports of fully-integrated wearable sensors toward wireless transmission of sensed information to the user interface were published in 2015, based on radio frequency identification (RFID) adhesive patch for hydration monitoring in sweat (Fig. 2j) (Rose et al., 2015) and on Bluetooth low energy (BLE) transceiver integrated with a mouthguard platform for salivary uric acid monitoring (Kim et al., 2015b). In a landmark development, in 2016, Javey's group in UC Berkeley demonstrated the first example of a fully-integrated, multiplexed wearable sensor which could be integrated in a wristband or a headband enabling the detection of a number of metabolites and electrolytes in sweat samples (Fig. 2k) (Gao et al., 2016a). During the same year (2016), Rogers' group integrated a soft, flexible and stretchable microfluidic system into a multiplexed sweat patch sensor with wireless electronics, enabling spontaneous sweat routing into the fluidic network and a set of reservoirs towards simultaneous colorimetric detection of pH, chloride, glucose and lactate (Koh et al., 2016). The sweat fluidic sampling principle was further expanded by Wang's group in 2017

towards the integration of the electrochemical biosensors inside the reservoir of microfluidic device (Martín et al., 2017). While sweat sampling in these studies were based on fitness cycling, two different studies in 2016 and 2017 (Fig. 2l) demonstrated iontophoretic-based sweat stimulation to sample the biofluid under sedentary condition (Emaminejad et al., 2017; Kim et al., 2016). Another key advance was the introduction of a hybrid chemical-electrophysiological sensor that offered simultaneous monitoring of both biochemical and electric signals toward attaining more comprehensive information on health status of individuals (Imani et al., 2016). With growing needs for on-body security monitoring applications, year 2017 witnessed the development of wearable sensors for defense and safety (Fig. 2m and n), including ring- and glove-based sensors for detecting vapor explosives and nerve-agents for the safety of wearers and first responders (Mishra et al., 2017; Sempionatto et al., 2017a).

2.3. The present state-of-the-art (2018–2020)

Over the past three years, the major research activity and trends in wearable chemical sensors have focused on expanding the scope of detectable analytes, from the common metabolites or electrolytes to more challenging biomarkers, and toward improving the design and fabrication of the wearable systems. In this regard, an innovated design for sweat stimulation based alcohol monitoring was reported in 2018, relying on the use of 'hex-wick' material to reduce the required sweat sampling volume and hence, to reduce the sweat-blood lag time (Fig. 2o) (Hauke et al., 2018). A report in 2019 described mass fabrication of microfluidic sensing patches via roll-to-roll processes for reproducible sweat analysis (Fig. 2p) (Nyein et al., 2019). Innovative fabrication was also demonstrated in the integration of an epidermal microfluidic BFC sweat biosensor with colorimetric sensors (Fig. 2q) (Bandodkar et al., 2019). Continued fabrication innovations in 2020 involved the large scale fabrication of laser-engraved graphene-based wearable sweat sensors for low concentration analytes including uric acid and tyrosine (Fig. 2r) (Yang et al., 2020). Another 2020 report illustrated a free-standing sensor system-enabled smartwatch featuring sweat sampling, electrochemical sensing, and data display/transmission in sedentary and high-intensity exercise settings (Fig. 2s) (Zhao et al., 2020). Major advances have also been achieved toward self-powered wearable devices including the first demonstration of a complementary metal-oxide-semiconductor (CMOS) biofuel cell (BFC)-based low power chemical biosensor with digital wireless readout (Yeknami et al., 2018), a solar cell-powered fully-integrated smartwatch for sweat glucose monitoring (Zhao et al., 2019), and a flexible, fully sweat-powered integrated electronic skin toward multiplexed metabolic sensing (Fig. 2t) (Yu et al., 2020b). Efforts aimed at expanding the scope of detectable analytes beyond common metabolites and electrolytes, have led to the detection of stress hormone cortisol in sweat relying on various recognition elements of bioaffinity-based (Torrente-Rodríguez et al., 2020a) and molecularly imprinted polymer (MIP)-based (Parlak et al., 2018) sensors. Additionally, several studies have reported the detection of various drugs, either therapeutic or illicit, in sweat and ISF samples (Goud et al., 2019; Mishra et al., 2020a; Tai et al, 2018, 2019; Yang et al., 2020). Add to these, the studies on utilizing the great potential of electrochemical aptamer-based sensors toward in-vivo detection of drug targets in blood samples of anesthetized animals (Arroyo-Currás et al., 2018; Dauphin-Ducharme et al., 2019). Although the catheter-based blood monitoring used in such aptamer-based sensors was invasive, such bioelectronic detection route holds considerable promise in real-time, continuous minimally invasive or non-invasive monitoring of a wide range of endogenous and exogeneous target analytes, including drugs, proteins and hormones.

2.4. The transitional stage into commercial devices (2020–2030)

With the continuing advances and innovations from North America and around the globe during the next decade, we expect to see rapid translation of the technology into the medical devices toward health monitoring in real-life applications. Such transitional step should involve improving the sensor characteristics toward addressing key challenges faced with real scenarios of on-body monitoring (e.g., biofouling) along with the extensive preclinical and clinical trials, and validation of the data against gold standard measuring techniques to ascertain the required standard level of precision and accuracy.

While the field of diabetes care remains to be the major focus, seeking for innovations mainly toward developing miniaturized CGM wearables with longer life span, self-powered and multiplexed sensing ability, major efforts will be directed to translate the wearable chemical sensing technology to other important fields with huge potential markets. Therapeutic drug monitoring (TDM) using wearables has already attracted lots of interest (Teymourian et al., 2020c), owing to the aging population and the high prevalence of drugs, and we expect to see first commercial TDM wearables during the forecast period. Fitness monitoring, personalized nutrition, and security monitoring are other fields expected to take some share in the growing market of wearable chemical sensors. The current coronavirus pandemic has further ignited the interests in remote monitoring capability for the people who are in need of receiving constant medical care. The next wave of wearable sensors is anticipated to expand the application areas of wearable devices from healthcare to sports, law enforcement, defense, security and even to space missions.

With most of the current activity inside the US is taking place in a few leading universities from west coast area, we anticipate increasing contributions from institutions in the Midwest and east coast. Also, growing contributions from our Canadian and Mexican neighbors will be foreseen during the present decade.

3. Wearable platforms

3.1. Epidermal sensors

Unlike traditional rigid and freestanding electrochemical sensors, skin-interfaced epidermal electrochemical sensors need to comply with the soft and curvilinear surface of the human skin. Thus, epidermal sensors are engineered to be flexible or stretchable, while retaining desirable electrochemical and mechanical stabilities. Furthermore, for commercialization and widespread use of epidermal electrochemical sensors, production costs must be reduced through low-cost and scalable mass manufacturing procedures (Matzeu et al., 2020). To meet such requirements, it is necessary to meticulously choose substrate materials, electrode materials, and electrode fabrication techniques. Researchers in North America have explored various scalable fabrication procedures such as screen printing, gravure printing, inkjet printing, and laser engraving to pattern electrochemical electrodes on substrates such as plastics, textiles, and paper for the development of epidermal electrochemical sensors.

Screen printing is a standard sensor fabrication technique widely adopted in point of care blood glucose sensor strips. Silver/silver chloride and carbon electrodes have been screen printed on temporary transfer tattoo paper to form flexible and highly conformal tattoo biosensors (Fig. 3a) for the real time analysis of sweat biomarkers such as pH and lactate (Bandodkar et al., 2013a; Jia et al., 2013). In addition, stress-enduring inks have been engineered to screen print a biofuel cell-supercapacitor system on a textile to demonstrate energy harvesting from sweat and energy storage during exercise (Fig. 3b) (Lv et al., 2018). A similar printing approach can be adopted for textile-based self-powered sweat sensors (Jeerapan et al., 2016). On another account, roll-to-roll gravure printing was used to mass produce electrochemical electrodes on a 150 m flexible PET roll, and the resulting sensors were used to monitor sweat pH during exercise (Bariya et al., 2018). An attractive alternative to printing electrodes is to laser engrave graphene electrodes on PI substrates using a CO_2 laser-cutting machine. A single

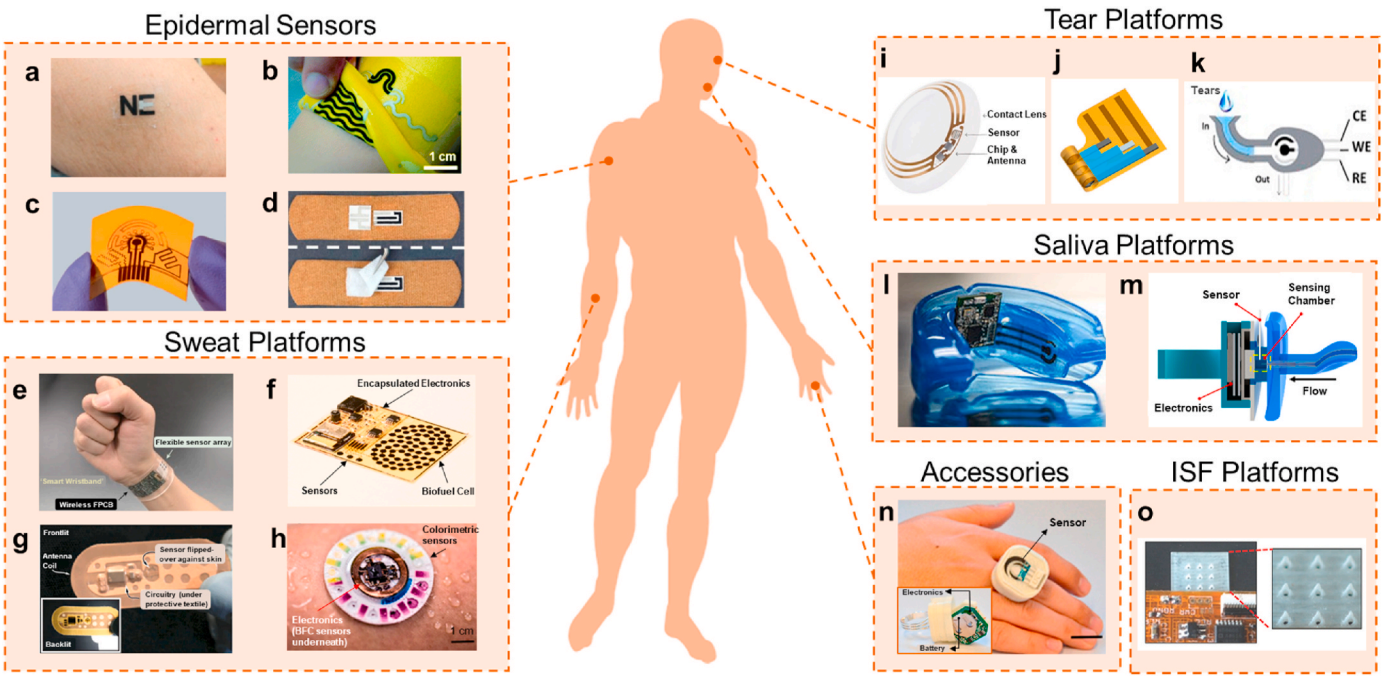


Fig. 3. Wearable sensors and platforms. Epidermal sensors are fabricated by patterning electrodes on a flexible and/or stretchable substrate. a, An electrochemical tattoo biosensor for real-time and noninvasive lactate monitoring in sweat (Jia et al., 2013). b, Textile-based electrochemical armband for energy harvesting and storage (Lv et al., 2018). c, Laser-engraved graphene epidermal sensors for monitoring uric acid and tyrosine in sweat (Yang et al., 2020). d, Omniphobic paper-based smart bandages for monitoring uric acid and pH levels in open wounds. Wearable sweat platforms integrate epidermal sensors into a device that acquires, processes, and transmits the electrochemical sweat sensor data to a user interface (Pal et al., 2018). e, A battery powered smart wristband for the multiplexed analysis of glucose, lactate, sodium and potassium in sweat (Gao et al., 2016a). f, A biofuel cell powered battery-free electronic skin for the multiplexed analysis of sweat biomarkers such as urea, ammonia, glucose and pH (Yu et al., 2020b). g, Battery-free RFID sensor bandage for monitoring sweat sodium (Rose et al., 2014). h, Battery-free hybrid NFC sensor patch for the simultaneous colorimetric analysis pH and chloride, and electrochemical analysis of glucose and lactate (Bandodkar et al., 2019). Tear Platforms. Wearable platforms used for tear monitoring. i, Google's soft contact lens for monitoring glucose in tears with embedded electronics and antenna. j, Flexible rolled thick-film flow-cell for glucose detection in the lachrymal channel (Kagie et al., 2008). k, Eyeglasses mounted super hydrophilic microchannel for tear collection and analysis (Sempionatto et al., 2019a). Saliva Platforms. Salivary wearable sensors are developed for continuous saliva monitoring. l, mouth guard saliva platform integrated with screen printed sensor and electronic circuit for monitoring lactate levels during exercise (Kim et al., 2015b). m, Pacifier biosensor platform containing microchannel modified nipple for saliva collection and detection outside of the mouth in the integrated detection chamber (García-Carmona et al., 2019). Accessories. Commonly used accessories with added sensing capabilities. n, Ring sensor platform with integrated detector exposed on the cap and embedded miniaturized electronics for monitoring dangerous vapors such as explosives and nerve agents. ISF platforms, Wearable devices developed to monitor ISF biomarkers in situ (Sempionatto et al., 2017a). o, Hollow microneedles filled with enzyme rich carbon paste for monitoring tyrosinase toward cancer skin screening (Ciui et al., 2018).

laser-cutting machine was used to fabricate all key components of a disposable epidermal microfluidic sensor patch, including highly sensitive laser engraved electrochemical and physical sensors as well as a microfluidic module (Fig. 3c) (Yang et al., 2020).

Bandage based epidermal sensors have also been developed for the monitoring of key biomarkers in open wounds such as pH and uric acid (Kassal et al., 2015). Screen printing was used to directly screen print electrodes on the cellulose pad of commercial bandages; Stencil printing was used to print electrodes on a layer of omniphobic paper that is sandwiched between the bandage and an absorbent pad (Fig. 3d) (Guinovart et al., 2014; Pal et al., 2018).

3.2. Sweat sensing platforms

For wearable use, epidermal electrochemical sweat sensors are integrated into a wearable platform that can comfortably adhere to the skin while acquiring and distributing real-time electrochemical sensor data. Advances in wearable sweat sensing platforms are driven by miniaturization of sensors, advances in material science, power and size reduction of flexible electronics, and innovations in energy harvesting. Researchers in North America have implemented batteries and various energy harvesting approaches in powering wearable electronics to acquire frequent electrochemical measurement data and conveniently transmit the data to a smart phone via Bluetooth, high-frequency passive RFID, and NFC protocols. When determining an appropriate power source and data transmission technology for the platform, it is crucial to consider factors such as the sweat sensor's intended application, electrochemical measurement technique, and location of wear.

The first demonstration of a fully integrated multiplexed wearable sweat sensing platform consisted of an absorbent pad interfaced flexible sensor array, a Bluetooth enabled wireless FPCB, and a lithium battery all fixed into place by a transparent wristband or headband (Fig. 3e) (Gao et al., 2016a). Sweat-sensing smart watches with integrated display modules have also been demonstrated (Zhao et al., 2019, 2020). In one account, the sweat-sensing smart watch integrates a flexible solar cell and a flexible rechargeable battery as a watch band to self-power the platform.

If paired with low-powered electronics and adequate power management strategies, wearable energy harvesting modules such as solar cells, biofuel cells, and triboelectric nanogenerators can steadily scavenge ambient energies to continuously power battery-free wearable sweat sensing platforms. A flexible and fully perspiration-powered integrated electronic skin platform demonstrates that highly efficient lactate biofuel cells can scavenge energy from our sweat metabolites to power the continuous data acquisition and Bluetooth transmission of multiplexed sweat sensors without a battery (Fig. 3f) (Yu et al., 2020b). A flexible PCB based triboelectric nanogenerator was also integrated in a battery-free wearable platform to harvest energy from exercise induced

human motion for the dynamic monitoring of sweat electrolytes (Song et al., 2020). Factors such as the availability of light, sweat, and body motion may steer the usage of these battery-free sweat sensing platforms toward different application scenarios.

Passive RFID and NFC based battery free wearable electrochemical sweat sensors can harvest radio frequency energy to acquire and transmit measurement data to a mobile phone over a short distance. An adhesive RFID sensor bandage with minimal electronic components was developed for the potentiometric measurement of sweat electrolytes (Fig. 3g) (Rose et al., 2014). In passive RFID or NFC enabled sensors, an electrochemical measurement can be performed every instance the phone is brought near the antenna. While a potentiometric electrolyte measurement can occur nearly instantaneously, many sweat metabolite sensors are based on chronoamperometric and voltammetric measurements that need to actively bias the sensors for at least tens of seconds. Therefore, short distance radio frequency energy harvesting devices are generally desirable for passive and instantaneous electrochemical measurements such as potentiometry, or in scenarios where the user can bring the smart phone into proximity of the wearable device for some duration. A hybrid skin patch that implements the colorimetric analysis of sweat electrolytes and the electrochemical analysis of sweat metabolites tackles this limitation of NFC-based devices by using BFCs as sensors (Fig. 3h) (Bandodkar et al., 2019). Instead of using the glucose or lactate BFC to power the electronics, the BFC generated voltage signal indicates the sweat metabolite concentration that can be instantaneously acquired at an NFC activation event.

3.3. Tear sensing platforms

Tears composition includes a variety of medical relevant biomarkers such as glucose, uric acid and different electrolytes. Yet, when compared with other noninvasive biofluids (e.g., saliva, sweat), tear is a relatively simple biofluid having less proteins in its composition due to the blood-tear barrier filtering process that decreases the tear protein content. This feature is attractive for continuous monitoring of analytes, using wearable platforms, as the low protein density minimizes their nonspecific adsorption and, therefore, the surface biofouling. Hence, a variety of wearable tear biosensing platforms has been developed over the past decade by North America researchers.

The Google contact lens, developed in collaboration with Parviz's lab, is a great example of the efforts toward wearable tear sensors (Senior, 2014; Yao et al, 2011, 2012). It involved integration of an amperometric glucose sensor and wireless electronics on a contact lens for continuous glucose monitoring (Fig. 3i). Powering these devices constitutes a major challenge. Thus, additional efforts were directed toward the integration of an energy harvesting biofuel cell onto the contact lenses for a battery-free self-sustainable contact lens biosensor (Reid et al., 2015).

Alternative platforms based on fluidic devices were also introduced for the "on the flow" detection of tears analytes, increasing further the operational time of the sensor by minimizing the contact of the sensor with the biofluid. A small rolled flexible thick-film electrochemical biosensor was presented for monitoring dynamic changes in norepinephrine and glucose levels in tears (Kagie et al., 2008). This involved screen-printing of an enzyme modified ink on a flexible Kapton substrate which was laterally rolled to create the fluidic channel for insertion in the tear canal (Fig. 3j). A less invasive approach, with no contact with the eyes, was presented by combining a fluidic sensor with an eyeglass for the monitoring of several tears' analytes (Sempionatto et al., 2019a). A super hydrophilic fluidic channel was integrated on the nose pad of the eyeglasses for simultaneous tears collection and analysis (Fig. 3k). The system was applied successfully for electrochemical monitoring of tears glucose, vitamins and alcohol. Such eyeglass platform offers integration with smart glasses devices and incorporation of the electronics and batteries onto the eyeglasses' frame.

Choosing an appropriate platform for tears analysis is crucial for the successful application of the wearable sensor. Continuous or time discrete analyses demand different platforms and are related to different types of analytes and tears (e.g. basal or reflex). Several reviews have discussed the criterion for the selection as well the advantage and disadvantages of each platform (Kim et al., 2019; Tseng et al., 2018; Yu et al., 2019).

3.4. Saliva sensing platforms

Saliva is an easily accessible non-invasive biofluid which is rich in chemical information. Accordingly, wearable salivary sensors have been extensively studied. However, prolonged operation of such oral salivary wearables is subject to major challenges involving: i) keeping a foreign device in the mouth over extended period; ii) toxicity and biocompatibility issues; iii) risk of contamination from food or bleeding gums; iv) surface biofouling from salivary macromolecules.

Despite these challenges, researchers in North America have demonstrated salivary sensing in dental accessories (Mannoor et al., 2012), mouthguards (Kim et al., 2015b), and even in foodstuff (García-Carmona et al., 2019). Mouthguards are oral devices, commonly used for protection against sports-related dental injuries, are convenient platforms for the short-term monitoring of activity associated biomarkers such as lactate and electrolytes (). A lactate mouthguard sensor was developed by integrating flexible screen-printed lactate-oxidase modified electrodes and wireless electronics into the mouthguard structure (Fig. 3l). The same concept of a mouthguard metabolite biosensor was demonstrated for the amperometric monitoring of uric acid for monitoring the treatment efficacy of gout disease (Kim et al., 2015b). For other circumstances, implantable tooth and dental adhesives have been demonstrated (Mannoor et al., 2012).

Salivary sensors are especially important for the safe development of wearables for babies. Most of the existing wearables for infants are bulky, rigid and cannot perform biochemical detection. A pacifier-based biosensor for the monitoring of saliva glucose in infants was recently developed (García-Carmona et al., 2019). A regular pacifier with a modified nipple fluidic system was thus used for simultaneous saliva collection and detection (Fig. 3m). The pacifier fluidic sensor uses the natural mouth movement of the baby for pumping saliva through the fluidic channel towards the biosensor detection chamber located outside the mouth.

Wearable saliva biosensors can be readily expanded towards the monitoring of several other clinically relevant biomarkers, offering useful and timely insights into the adult and babies' health.

3.5. Accessories sensing platforms

As the wearable sensor technology evolved rapidly in North America, reliable and low-cost sensors are on the verge of commercialization by several successful startups. Instead of introducing additional sensor-carrying wearable platform, such commercial efforts would benefit from adding the sensing functionality directly onto existing devices or accessories. The use of common accessories, such as contact lens (Yao et al., 2011), eyeglasses (Sempionatto et al., 2019a), gloves (Barfidokht et al., 2019), pacifiers (García-Carmona et al., 2019), and watches (Zhao et al., 2020), has been largely explored in parallel with textile-based sensors for functional sensing and/or energy harvesting.

New platforms and applications have been recently explored by North American researchers toward the development of wearable chemical sensors. A versatile ring sensor platform has been demonstrated for safety and security applications involving rapid detection of vapors of explosives and nerve agents (Sempionatto et al., 2017a). For this, a screen-printed solid electrolyte sensor was designed to fit in the cap of a 3D printed ring case, where the customized miniatured electronics was enclosed (Fig. 3n). A similar ring-based platform was used for on-site detection saliva THC and alcohol (Mishra et al., 2020b). Variety of other devices contacting our body are expected to integrate

sensing or energy harvesting capabilities.

3.6. ISF sensing platform

The interstitial fluid (ISF) is extremely attractive for biomedical applications of wearable devices, since its composition is closely related to the blood (Heikenfeld et al., 2019). ISF is the fluid surrounding the cells and it is in constant equilibrium with blood capillaries through diffusion. There are basically two approaches to access this biofluid: i) Reverse iontophoresis (RI) or ii) epidermal microneedles devices.

RI consists in applying a mild electric current through the skin using two electrodes, the cathode and the anode. The current then induces ions to migrate from the inside of the skin to the surface carrying small non charged molecules, such as glucose, within the electro-osmotic flow. A tattoo-like epidermal sensor, coupling RI extraction and amperometric detection, was used successfully for tracking ISF glucose levels (Bandodkar et al., 2015). In addition, RI ISF extraction was combined with direct iontophoretic sweat stimulation for the simultaneous monitoring of glucose in ISF and alcohol in sweat (Kim et al., 2018b). Microneedle sensing devices, used to puncture the outer skin layer to access ISF with no pain or damage, providing an attractive minimally invasive wearable platform for monitoring ISF biomarkers with the possibility of integrating different sensors on a single microneedle array. Hollow microneedles were used for electrochemical detection of alcohol (Mohan et al., 2017), L-dopa (Goud et al., 2019), tyrosinase (Ciui et al., 2018) and as self-powered glucose sensors (Valdés-Ramírez et al., 2014cb) (Fig. 3o).

Owing to the significant medical relevance, ISF sensing platforms offer great promise for future development of closed loop systems, where the correct concentration of analyte must be detected in order to adjust the drug concentration to be delivered. Such 'Sense-Act' applications would require extremely reliable (accurate and stable) ISF sensors.

4. Chemical approaches

North America is well known for the highly developed electronics sector. This fast-evolving semiconductor industry has amplified research efforts toward wearable bioelectronic sensors. This sensor category relies on the measurement of an electrical signal, originated from the interaction of the analyte and a recognition element immobilized on the sensing surface, with the signal intensity being proportional to the analyte concentration. The wearable chemical sensing area has largely benefited from the advances in electronics where different electrochemical approaches have been integrated with miniaturized electronics for fast and autonomous on-body operations. There are three operational modes commonly used for wearable bioelectronics: amperometry, voltammetry and potentiometry techniques (Fig. 4), although other modes - such as impedance or field effect transistors (FET) - have been reported in a few cases. Selecting the electrochemical detection technique depends mostly on the target analyte, where potentiometry is commonly used for monitoring electrolytes (e.g. Na^+ and Cl^-) while amperometry is the method of choice for detecting key metabolites (e.g. glucose and lactate). An appropriate (bio)recognition layer is included in the sensor design to impart the selectivity, based on which the wearable sensors are classified into enzyme-, ionophore-, and affinity-based platforms. In this section, we briefly discuss the various electrochemical approaches and the recognition chemistries used in wearable devices.

4.1. Amperometric sensors

Amperometric sensors rely on the monitoring of current at a fixed applied potential, with the temporal current variations reflecting the dynamically-changing analyte concentration (Wang, 2006) (Fig. 4a). There are several criteria to be considered when choosing the appropriate electrode material, the applied potential, and the surface modification. Most commonly, wearable amperometric biosensors rely on carbon or platinum electrodes modified with redox enzymes. Enzymatic sensors offer great selectivity for the target analyte in the complex biofluids (sweat, saliva, tears or ISF) due to the selective enzyme recognition. An amperometric dual enzyme sensor was developed for the simultaneous monitoring of alcohol in sweat and glucose in ISF with great selectivity (Kim et al., 2018b) (Fig. 4ai). In addition, a multiplexed freestanding (motion independent) wearable sensor system based on enzyme recognition, mounted on a smartwatch, was able to successfully monitor different analytes (lactate, glucose) in sweat during physical activity and in the resting state (Zhao et al., 2020) (Fig. 4aii). The oxidase family of enzymes has contributed to a considerable number of wearable enzymatic sensors, reported for detecting important analytes, such as alcohol (Campbell et al., 2018; Hauke et al., 2018; Kim et al., 2016), lactate (Currano et al., 2018; Gao et al., 2016a; Sempionatto et al., 2017b), vitamin C (Sempionatto et al., 2020), and glucose (Bandodkar et al., 2015). Such oxidase enzyme-based wearable platforms commonly rely on detecting the oxidation of the hydrogen peroxide enzymatic product (Fig. 4a). Second generation oxidase biosensors rely on the use of mediators as electron acceptors instead of oxygen, in which mediators shuttle electrons from the enzyme to the electrode surface, reducing the overpotential and minimizing the redox reaction of interferents. Glucose biosensor is one of the most studied systems due to the tremendous interest in the management of diabetes (Kim et al., 2018a; Wang, 2008; Zhao et al., 2019). Additionally, other enzyme classes have been also reported for wearable sensors, including tyrosinase for levodopa (Goud et al., 2019; Tai et al., 2019), 3-hydroxybutyrate dehydrogenase for ketone bodies (Teymourian et al., 2020b), and uricase for uric acid monitoring (Kassal et al., 2015; Kim et al., 2015b).

Amperometric wearable biosensors are widely used since they can provide fast and continuous response using simple data collection (current monitoring), minimizing the lag time between the non-invasive wearable measurements and blood analyte concentration, and offer facile integration with low power electric circuits. The main drawback is the limited choice of redox enzymes available and hence the limited scope of metabolites that can be easily detected using this approach.

4.2. Voltammetric sensors

Similar to amperometric sensors, voltammetric sensors rely on measurements of the current response but in connection to a potential scanning operation. Such operation leads to an electrochemical (current vs potential) signature, known as a voltammogram, consisting of one or more peak currents (Fig. 4b). Depending on the specific applied potential-time waveform, there are several voltammetric techniques, including cyclic voltammetry (CV), differential pulse voltammetry (DPV), and square wave voltammetry (SWV). A comprehensive discussion on these different voltammetric techniques is presented in the literature (Wang, 2006). Voltammetry can offer high sensitivity down to the 10 nM level. Further improvements in the sensitivity are achieved by coupling it with a preconcentration step, as in anodic stripping voltammetry (ASV) used for detecting trace metals (Gao et al., 2016b; Kim et al., 2015a). For wearable sensing voltammetric applications, SWV is commonly used as it couples fast response with high sensitivity. DPV also offers high sensitivity. Wearable DPV-based non-enzymatic sensors were described for the sweat monitoring of methylxanthine drugs (such as caffeine) (Fig. 4bi) (Tai et al., 2018) and analgesic drugs (acetaminophen) (Lin et al., 2020). Further, a forensic glove was developed for SWV detection of the opioid drug fentanyl (Barfidokht et al., 2019) (Fig. 4bii). Voltammetric techniques have also been demonstrated for the sensitive detection of opioids and nerve agents (Mishra et al., 2020a), and explosives (Sempionatto et al., 2017a). While offering additional information regarding the redox behavior of the target, voltammetric techniques generally have slower response times compared to amperometric detection.

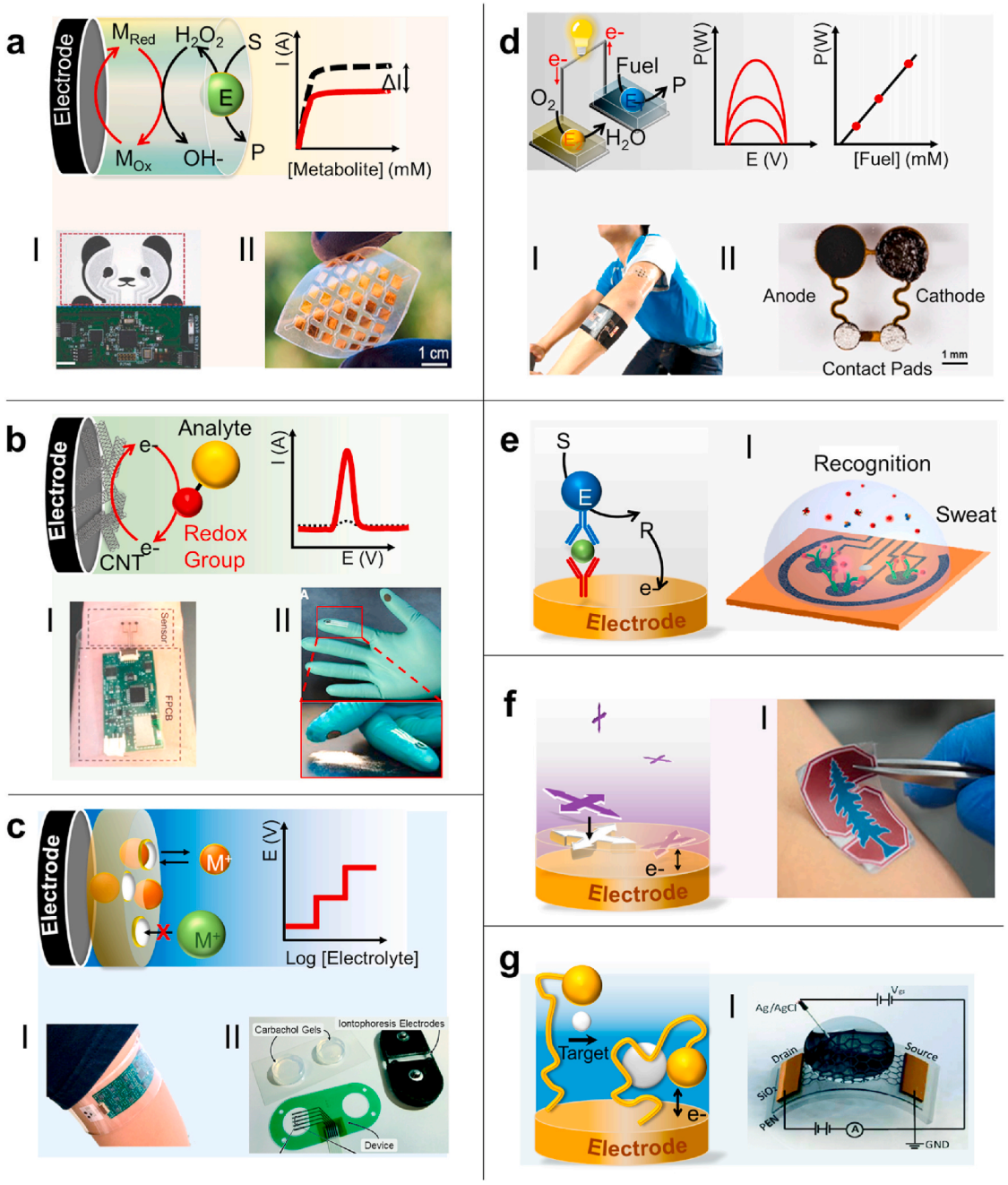


Fig. 4. Chemical approaches for wearable electrochemical sensor detection of analytes. a, Amperometric sensors using oxidase enzymes and mediators for electron shuttle. The characteristic signal is the chronoamperogram generated by monitoring the electrical current while applying constant potential. Examples of amperometric sensor include the wearable tattoo for the simultaneous monitoring of sweat alcohol and ISF glucose (I) (Kim et al., 2018b) and the freestanding sensor system-enabled smartwatch for monitoring sweat lactate and glucose during exercising (II) (Zhao et al., 2020). b, Voltammetric sensors based on the detection of electroactive molecular groups; square wave voltammetry (shown on the right) is one of the common techniques used. Examples of voltammetric sensors include the methylxanthine drug monitoring sweat patch (I) (Tai et al., 2018) and the fentanyl detecting gloves (II) (Barfidokht et al., 2019). c, Potentiometric sensors based on the ion selective electrodes (ISE). A selective membrane is used for specific ion recognition, leading to a potential difference across the membrane and to a potential signal between the ISE and the reference electrode. Examples of wearable potentiometric sensors include the platform for noninvasive simultaneous monitoring of Ca^{2+} and pH (I) (Nyein et al., 2016) and the integrated sudomotor axon reflex sweat stimulation for continuous sodium monitoring (II) (Sonner et al., 2017). d, Energy Harvester Sensors based on the use of biofuel cells. Enzymatic fuel oxidation takes place in the anode electrode generating electrons to the cathode for the enzymatic reduction reaction of oxygen. The electron flux can be used to power electronic devices or as an indicator of the fuel concentration for self-powered sensors. Examples of self-powered sensors include the sweat lactate BFC based on flexible buck paper (I) (Chen et al., 2019) and the epidermal BFC-powered lactate sweat biosensor integrated with colorimetric sensors (II) (Bandodkar et al., 2019). e, Affinity sensor based on the use of antibody receptor and enzyme tag for electrochemical detection. Example of electrochemical immunosensor sensor include the sweat cortisol detection patch (I) (Torrente-Rodríguez et al., 2020a). f, Affinity sensor based on the use of molecular imprinting polymer, where the analyte is polymerized with the conductive polymer creating the recognition sites. Example include the wearable organic electrochemical device for noninvasive sweat cortisol sensing (I) (Parlak et al., 2018). g, Affinity sensor based on the use of aptamers, a synthetic molecule capable of changing shape and fold in the presence of the target molecule; example include the wearable sweat patch for the measurement of cytokine biomarkers (i) (Hao et al., 2018).

4.3. Potentiometric sensors

Potentiometric sensors rely on the concentration-dependent potential difference across a selective membrane to generate an analytically useful potential difference between the reference and working electrodes, in which the latter is referred to as the ion selective electrode (ISE). Specifically, the potential difference between the membrane and the reference electrode is proportional to the logarithm of the ion activity. The specificity of ISEs relies on the use of ionophore receptors, mainly in connection to a polyvinyl chloride (PVC) polymeric membrane (Wang, 2006). The pH sensor is a well-known example of potentiometric sensors and it has been translated to a variety of wearable platforms, such as epidermal tattoo (Bandodkar et al., 2013a) and bandage for wound healing (Guinovart et al., 2014). A wearable platform for pH and Ca^{2+} based on PANI and PEDOT:PSS polymer deposition, respectively, was developed for measuring these parameters in body fluids such as sweat, urine, and tears (Nyein et al., 2016). The sensor was validated using inductively coupled plasma-mass spectrometry (ICP/MS) and a commercial pH meter toward the diagnosis of primary hyperparathyroidism and kidney stones (Fig. 4ci). Solid contact ISE-based wearable sensor has also been developed for monitoring electrolytes such as Na^{+} (Sonner et al., 2017). An iontophoretic sensor was developed for continuous sweat generation (over 5 h) and sodium monitoring (Fig. 4cii). Solid contact potentiometric sensors can readily be used for the continuous, real-time tracking of the electrolytes. They are low cost, and highly selective and can simply be integrated with low power consumption electronics (Wang et al., 2018). However, potentiometric sensors have intrinsic low sensitivity and may be subject to drifts or interferences from other ions competing for the receptor recognition.

4.4. Energy harvester sensors

The major drawback of wearable electrochemical sensors is the need for constant power supply. Current batteries are rigid, bulky and not anatomically compliant to the body which hinders the performance of the electrochemical wearable sensors (Chen et al, 2016, 2020; Kumar et al., 2017; Liu et al., 2017; Yin et al., 2018; Zhang et al., 2020). In order to address this challenge, flexible and stretchable wearable energy harvesters have been developed to collect useable energy present in biofluids to either power the electrochemical sensors or to act as a self-powered electrochemical sensor themselves. The mechanism for harvesting energy is similar to the conventional fuel cells which employs a pair of anode and cathode electrodes. For wearable biofuel cells (BFC), the anode is usually functionalized with enzymes for the electro oxidation of the biofuels present in the target biofluid, which generates electrons that flow toward the cathode to the oxidant molecule (oxygen), generating a net electrical current that can be used in an external circuit (Fig. 4d). The cathode compartment can be modified either with non-biological materials such Ru, Pd and Pt, or by utilizing laccase or bilirubin oxidase enzymes for the reduction of oxygen present in the biofluid. Efficient BFC have been reported with the use of lactate oxidase and bilirubin oxidase for the oxidation of sweat lactate and reduction of oxygen, respectively (Chen et al., 2019). An absolute power of 450 μW was achieved when the device was applied to the arm of a volunteer during exercise (Fig. 4di) and when connected to a voltage booster, this power was enough to power an LED under both pulse discharge and continuous discharge modes. A BFC system was integrated in a microfluidic device system for sampling sweat during exercising (Bandodkar et al., 2019). The BFC was able to successfully harvest energy from lactate and glucose fuels (Fig. 4dii). Harvesting energy from biofluids is not trivial, as our body retains the maximum energy possible, excreting only few molecules with some energetic value. To this, hybrid devices combining energy harvesting and storage were demonstrated (Lv et al., 2018). The textile-based hybrid device was functionalized in the internal and external surfaces. The surface in contact with the body was used for harvesting energy from sweat which was stored in the supercapacitors located in the external face. The BFC could also act as a self-powered sensor by providing the power source and sensor signal simultaneously, with the power output proportional to the fuel/analyte concentration.

4.5. Affinity sensors

The vast majority of reported wearable platforms have been developed for monitoring common metabolites (e.g. glucose and lactate) or electrolytes (e.g. Na^{+} and Cl^{-}), reflecting the availability and easy adaptation of corresponding enzyme- or ionophore-based recognition elements, respectively, for continuous on-body operation. While these bioassays are reversible and can be used for the continuous operation of wearable devices, their corresponding bioaffinity assays are commonly not reversible and hence not reusable. Antibodies are natural biorecognition elements which have been well established for in-vitro biosensing applications due to their high specificity and large commercial availability for a broad range of target analytes. Antibody-based sensors or 'immunosensors' rely on the specific binding of antibody-antigen with high affinity, typically in the nanomolar or picomolar concentration range, to produce a measurable analytical signal (Fig. 4e). Enzyme labeling immunoassay strategies, either in sandwich or competitive format, have been the most widely used immunosensing protocols in portable point-of-care devices. While such labeling strategy was recently integrated with on-body platforms toward measuring sweat cortisol levels (Torrente-Rodríguez et al., 2020a) (Fig. 4ei), the methodology itself cannot be applied for continuous, real-time analyte monitoring due to the inherent problems of antibodies as bioaffinity tools such as slow recognition, limited stability, difficult regeneration and their need for additional washing or detection steps (Tu et al., 2020). Label-free, non-faradaic impedimetric analyses are wash-free and do not require additional reagents and hence, offer more feasibility for implementing on-body measurements although still facing the challenge of regenerating the free antibody (Kinnamon et al., 2017). Hence, the potential of such devices for continuous wearable protein biomarker monitoring applications remains unclear.

The limitations of antibody-based natural receptors have stimulated interest in employing synthetic receptors with higher stability, cost-effectiveness and scalability. Molecularly-imprinted polymers (MIPs) have been investigated as potential candidates to natural antibodies. MIP-based sensors rely on creating molecular imprinted cavities which are complementary in size, shape and chemical functionality with the imprinted (template) molecule (Fig. 4f). Regarding the wearable electrochemical monitoring applications, the integration of an MIP membrane and organic field effect transistor-based transduction was described for sweat cortisol measurement (Parlak et al., 2018) (Fig. 4fi). MIPs can also be paired with voltammetric techniques to add an additional layer of selectivity for the sensitive voltammetric detection of electroactive molecules. Future development of MIP-based wearable sensors should address the problems related to their limited sensitivity (especially for large analytes) and to on-body receptor regeneration.

Aptamers are another class of artificial receptors which have recently shown immense potential in continuous, in-vivo monitoring of target analytes. Aptamers functionalized by a redox reporter molecule (e.g. methylene blue) can specifically and reversibly bind to the analyte of interest, leading to a conformational change (folding) and electrical signal (Arroyo-Currás et al., 2020) (Fig. 4g). Such a binding-induced response reflects changes of electron transfer characteristics of the redox reporter associated with such folding and is proportional to concentration of the target biomarker. The reversible binding nature of the target molecules thus offers great promise for real-time, continuous operation in connection to rapid SWV transduction (Arroyo-Currás et al., 2018). Aptamers can also offer high sensitivities owing to their small size and thus, the capability to be packed densely on the sensor surface (Tu et al., 2020). In this sense, ultrasensitive (pM) detection of

cytokine biomarkers (e.g. tumor necrosis factor-α (TNF-α)) was demonstrated using aptamer functionalized graphene channels of a FET device on a flexible substrate (Hao et al., 2018) (Fig. 4gi). The limited commercial availability of the aptamer probes is the main disadvantage of aptamer sensors as there are only a few aptamer screening companies (Arroyo-Currás et al., 2020).

5. Fluid sampling

Biofluid extraction is a critical component of non-invasive wearable biomarker sensing (Choi et al., 2018). While fluids such as sweat and tears are secreted naturally, medical applications of biofluid monitoring often require on demand and controlled stimulation of adequate sample volumes. Also, the extracted biofluid must be collected efficiently and sampled in real-time to minimize sample contamination, degradation, leakage and evaporation. Lastly, the physical dimensions and characteristics of the extraction and collection segments must be compatible to enable smooth and facile integration into a wearable device.

5.1. Sweat stimulation and collection

Sweat can be stimulated both physically through heat and chemically through drugs. In early endeavors, sweat was typically induced physically by controlling environmental temperatures, or by generating internal heat through exercise. While exercise induced sweat is a great candidate for fitness monitoring, health monitoring and disease

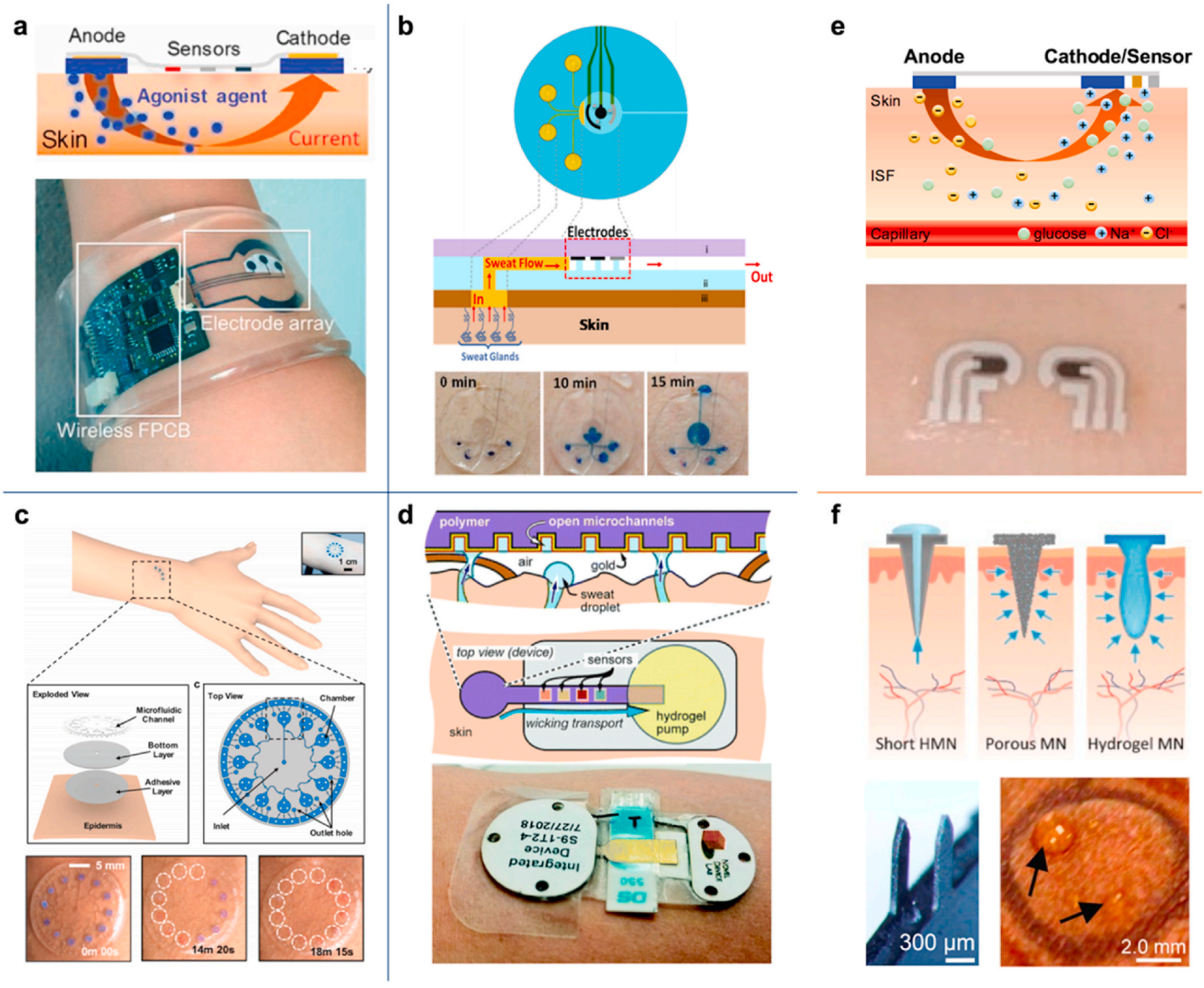


Fig. 5. Methods for sampling biofluids. Sweat can be stimulated physically (heat) or chemically (iontophoresis), then efficiently collected by micro/nanofluidic systems. a, (top) Schematic illustrating iontophoretic drug delivery and (bottom) an integrated wristband for iontophoretic sweat extraction and electrochemical monitoring of cystic fibrosis and glucose in sweat (Emaminejad et al., 2017). b, An epidermal microfluidic microchip device for enhanced sweat sampling and electrochemical detection of sweat glucose and lactate (Martín et al., 2017). c, Skin-mounted microfluidic networks with capillary bursting valves that guide the flow of sweat for time dependent colorimetric detection of sweat lactate, sodium and potassium (Choi et al., 2017). d, (top) Schematic depicting nanoliter regime sweat sampling via open nanofluidic films (hex-wick) (Twine et al., 2018), and (bottom) its implementation in an integrated iontophoretic sweat stimulation and sweat ethanol biosensing patch (Hauke et al., 2018). ISF can also be extracted chemically (reverse-iontophoresis) and physically (microneedles). e, (top) Schematic showing the operation mechanism for the reverse-iontophoretic extraction of ISF and subsequent analysis of ISF glucose, and (bottom) its implementation as a tattoo-based electrochemical system (Bandodkar et al., 2015). f, (top) Diagrams of hollow, porous and hydrogel microneedles for the minimally invasive extraction of ISF (Liu et al., 2020). (bottom) The left shows two stainless steel microneedles for puncturing skin micropores, and the right shows ISF extracted from skin micropores via suction (Samant and Prausnitz, 2018).

diagnostic applications require sweat stimulation in sedentary scenarios as well. Fortunately, sweat can also be chemically stimulated through iontophoresis, a well-established stimulation method where cholinergic agonists such as pilocarpine and acetylcholine are delivered to sweat glands by an electrical current. Traditionally, sweat was collected by using whole body washdown techniques, absorbent pads, or arm bags for subsequent benchtop analysis (Baker et al., 2009; van Heyningen and Weiner, 1952).

The opportunity of sweat based non-invasive diagnosis of cystic fibrosis (CF) in infants spurred the development of commercial Macroduct Sweat Collection Systems that include a pilocarpine iontophoresis stimulation module, and a fluidic sweat collector wristband module (Hammond et al., 1994). While the system's simplicity and improved sweat collection capacity in terms of sample preservation and sample volume was a breakthrough, the system still required three rather bulky and separate components for sweat stimulation, sweat collection, and sweat analysis. For more convenient and accurate iontophoretic sweat analysis, researchers developed miniaturized iontophoretic interfaces and integrated them into wireless wearable sweat sensing platforms to stimulate sweat secretion and measure sweat analytes in real time and in situ. Iontophoresis electrodes and electrochemical sensors were integrated into a flexible wristband, where the chemically induced sweat is collected by a rayon absorbent pad for the immediate analysis of sweat analytes such as sodium, chloride and glucose (Emaminejad et al., 2017) (Fig. 5a). Iontophoresis electrodes and an amperometric ethanol sensor were also integrated on a screen-printed wearable tattoo platform for non-invasive alcohol monitoring (Kim et al., 2016).

Epidermal microfluidic devices can enhance sweat collection by minimizing sample leakage, evaporation and contamination, while improving sample transport for better temporal resolution and accuracy in sweat analyte measurements. A flexible epidermal microfluidic device consisting of a top PDMS sensor layer, a middle PDMS microfluidic layer, and a bottom double-sided adhesive inlet layer was constructed with the aid of theoretical simulations for the optimization of the sampling process (Martín et al., 2017) (Fig. 5 b). Mounted conformally on the epidermis, the microfluidic sensor patch was paired with flexible wireless electronics to analyze exercise induced sweat glucose and lactate levels. A family of soft, skin-compatible microfluidic devices for the colorimetric sensing of sweat have been developed (Choi et al., 2017; Koh et al., 2016). In one of the examples, an epidermal microfluidic network was developed with capillary bursting valves to guide sweat into sequentially filling a series of micro-reservoirs for the time dependent chrono-sampling of sweat (Choi et al., 2017) (Fig. 5c). While colorimetric sweat sensing is beyond the scope of this review, the microfluidic device concepts incorporated in these devices may be adopted for electrochemical sensors.

In some cases, prolonged iontophoretic stimulation or natural sweat may yield ultra-low sample volumes in the nanoliter level. Such low sample volumes would take long to fill microfluidic reservoirs and analyte exchange with transport medium such as absorbent pads would foul the sample. To overcome these challenges, open nanofluidic polymer wicking films (hex wick) coated with gold were developed for the rapid collection and transport of ultra-low sample volumes (Twine et al., 2018) (Fig. 5d). A wearable device integrating this hex wick with an iontophoresis module, an amperometric ethanol sensor, and a waste pump was developed to measure continuous and blood-correlated sweat ethanol levels (Hauke et al., 2018).

5.2. ISF extraction

While ISF contains a wide array of significant biomarkers well correlated with blood concentrations, a lack of effective sampling methods has hindered its use in clinical applications. Although ISF is not secreted through skin naturally, reverse iontophoresis and microneedles can be used to access the fluids while causing minimal discomfort. Reverse iontophoresis is a variant of direct iontophoresis where the current flowing from the anode to the cathode is primarily driven by the migration of positively charged sodium ions towards the cathode, rather than by the migration of negatively charged drug molecules away from the anode. In reverse iontophoresis, the current increases the permeability of the skin, and the convective flow of cations leads to the accumulation of small volumes of ISF at the cathode (Bandodkar et al., 2015). A flexible tattoo-based wearable platform combining the reverse iontophoretic extraction and amperometric detection of interstitial glucose was developed for a proof-of-concept study (Bandodkar et al., 2015) (Fig. 5e). A mild current was used for ISF extraction and the subjects did not report any perceptible discomfort. Taking advantage of the congruence between iontophoretic sweat extraction and reverse iontophoretic ISF extraction platforms, a dual-iontophoretic tattoo--based biosensor platform capable of simultaneously stimulating sweat (via pilocarpine delivery at the anode) and extracting ISF (at the cathode) was developed. The platform was validated through the parallel detection of sweat alcohol levels and ISF glucose levels in subjects (Kim et al., 2018b).

Microneedles are minimally invasive because they do not penetrate deep enough to reach the nerve endings in the dermis. While microneedle patches have been thoroughly investigated for epidermal drug delivery, their application for ISF sensing has yet to be explored in depth. One approach is to use microneedle patches to extract ISF from the skin (Liu et al., 2020). A proteomic study demonstrated that the protein content in microneedle extracted ISF matches that in serum and plasma samples in terms of diversity (Tran et al., 2018). To realize real-time and wearable electrochemical analysis of microneedle extracted ISF, maximizing sample volume is a key challenge. A study conducted to systematically compare the ISF collection efficacies of several different types of microneedles, found that porous and hollow microneedles that extracted ISF via capillary action could extract more ISF than hydrogel microneedles that relied on diffusion (Samant and Prausnitz, 2018) (Fig. 5f). Furthermore, the study found that using solid microneedles to puncture micropores in the skin, and subsequently collecting the ISF via suction induced negative pressure yields the most sample volume (2.3 ± 2.1 μL per person in 20 min). Applying negative pressure on capillary force driven hollow microneedles is another interesting approach to increase ISF flow rate. Integrating these microneedle ISF-sampling patches into an epidermal wearable sensor device is a challenge to look forward to in the future. Microneedles can also be used for direct ISF analysis based on immobilizing the bioreceptor (commonly enzyme) onto electrode transducer present at the microneedle tip (Goud et al., 2019; Mohan et al., 2017). Microneedle sensor arrays can be used also for multiplexed electrochemical detection of multiple biomarkers, such as key diabetes biomarkers, in connection to individually addressable microneedle electrodes (Teymourian et al., 2020b).

6. Diabetes-driven commercialization efforts

While first attempts of glucose quantitation date back to the mid-1800s based on colorimetric, semi-quantitative urine glucose measurements, the modern diabetes care started with the advent of electrochemical home glucose meters during 1980s. Such self-monitoring blood glucose (SMBG) strips have seen many advances over the past 3 decades, with improved accuracy and faster response, and have played a pivotal role in daily diabetes management. Major limitations of point-of-care SMBG strips, such as the painful finger pricking procedure and limited temporal information regarding dynamic glucose fluctuations, have created an enormous desire among the diabetes care community for a less painful device that can be worn by the patient and provide continuous monitoring of glucose levels (Teymourian et al., 2020a). To realize such a vision, two products of Minimed iPro and GlucoWatch Biographer (Cygnus, Redwood, CA) were the first platforms appeared in the market. The GlucoWatch was a pioneering device that was approved by FDA in 1999 to provide non-invasive ISF glucose readings on a

wristwatch. This ambitious product failed to live up to the hype and was retracted from the market in 2007. However, the introduction of these wearable commercial products sparked an ongoing competition within the medical device industry to develop reliable CGM platforms that appeal to the ever-increasing diabetes community.

Major efforts have been directed over the past two decades at overcoming the drawbacks of initial CGM products, including limited accuracy and lifetime, need for blood glucose calibrations and sensor-pump integration. This activity has led to many breakthrough developments into the field, leading to the current generation of CGM platforms as the new standard of care for people with diabetes, especially type 1 diabetes patients. The latest versions of personal CGMs of Abbott's FreeStyle Libre 2 (Abbott, Alameda, CA) (FDA, 2020) and Dexcom's G6 (Dexcom, San Diego, CA) (Dexcom Continuous Glucose Monitoring Systems, 2018) offer calibration-free, continuous glucose monitoring data and trends, have alarms to notify the wearer of high (hyperglycemia) and low (hypoglycemia) glucose levels and can be worn for up to 14 and 10 days, respectively. As another key development, Medtronic (Northridge, CA) gained FDA approval in 2017 for its Guardian Sensor 3 with 7 days wear time, which in connection to Medtronic MiniMed 670G insulin pump was the first hybrid closed-loop system capable of automatically adjusting basal insulin delivery based on glucose readings (MiniMed 670G Insulin Pump System, 2017M). Such CGM devices, relying on a thin needle-mounted enzymatic biocatalytic sensing technology, are now offering competing accuracies to SMBG strips, as they have mean absolute relative difference (MARD) of $\leq$10%.

With growing accumulative evidence supporting the benefits of CGM devices, such systems have gained increasing acceptance and popularity, although immense efforts are currently going on to tackle their limited lifetime and high costs, and to provide further miniaturization and enhanced data security. Implantable glucose monitoring sensors have also emerged with extended wear time. Fluorescence transduction-based Eversense from Senseonics (Germantown, MD) has been FDA approved in 2020 with 90 days wear time (Eversense, 2020). Glysens (San Diego, CA) is another company working on developing an implantable CGM system, Eclipse 3 ICGM, which can be potentially worn for up to two years (Eclipse 3 ICGM System, 2020).

Microneedles have also attracted tremendous recent interests. Unlike their needle based CGM counterparts which sample the subcutaneous fat tissue at 5–11 mm depth, microneedles reach the ISF at $\approx$500 μm and thus, provide painless glucose monitoring. One promising company, Biolinq (San Diego, CA), is currently working on developing such microneedle based CGM patches (Biolinq CGM System, 2019). Microneedles offer additional advantages of multiplexed monitoring of other diabetes biomarkers, along with glucose, toward tighter glycemic control and also, the possibility of integrating the sensing and delivery modules on a single patch toward a miniaturized fully closed loop patch.

Developing wearable, non-invasive platforms for glucose measurements constitutes another active area of commercialization in diabetes care. For example, researchers in University of California San Diego are running clinical trials to evaluate the potential of RI-based tattoo sensors for ISF glucose monitoring (Chao et al., 2020). Sweat and tears are other potential biofluids which have been investigated for glucose sensing, although a strong correlation between the glucose level in these biofluids and blood glucose has not been fully established yet. The unsuccessful example of the Google contact lens highlights the extreme importance and challenges of such correlation studies.

7. Ongoing commercialization and future opportunities

Current ongoing commercialization efforts focus not only on improving microneedle-based minimally invasive wearable ISF glucose sensors, but also on pioneering wearable sweat sensor-based dehydration monitoring systems for fitness, military, and industrial workforce applications. With a vast market and a set of well validated biomarkers (sweat electrolytes) at hand, companies such as General Electric Global Research have been working on a wearable sweat sensor for several years for the electrochemical detection of sweat sodium and potassium levels (Alizadeh et al., 2018). In 2018, their first generation sweat sensors underwent a valuable field test at the U.S. Air Force Academy bootcamp, and the device design has since been honed (Kloberdanz, 2019). Epicore Biosystems is a startup, commercializing the Gatorade Gx Sweat Patch, which roots from the epidermal microfluidic colorimetric sweat sensor technology developed at Northwestern University. Other key players developing sweat sensors for dehydration monitoring include: Nix Biosensors, a Harvard Launch Lab-based company, and Kenzen, a startup with Headquarters in New York. Large corporations, such as Google, are also showing growing interest in wearable sensing devices, displayed by their recent efforts in acquiring Fitbit. Further clinical validation of various sweat biomarkers and advances in sensor technologies are on the way to propel the commercialization of wearable sweat sensors into the domains of disease monitoring, diagnostics and prognostics. The sweat sensor research at the University of Cincinnati, for example, has led to the founding of Eccrine Systems that focuses on the development of aptamer-based electrochemical sweat sensing technologies for therapeutic drug monitoring (Arroyo-Currás et al., 2020).

In the future, wearable electrochemical sensors are in line to play a critical role in disease management. Firstly, therapeutic drug monitoring (TDM) is a clinical practice by which drug dosage regimens are optimized through the periodic sampling of plasma or serum drug levels. While tedious, conventional TDM is crucial for safely administering drugs that have a narrow therapeutic range or highly intervariable pharmacokinetics, such as lithium, L-Dopa, and phenytoin. Drug concentrations in sweat and ISF often correlate well with that of plasma or serum, and there is a major opportunity in applying wearable electrochemical sensors to make TDM cheaper, less invasive, and more accessible (Kovacs et al., 1998; Tai et al., 2018; Teymourian et al., 2020c). As an example, a wearable electrochemical microneedle sensor has been developed for the continuous monitoring of L-Dopa toward the effective management of Parkinson's disease (Goud et al., 2019). Next, just as the continuous monitoring of glucose has revolutionized the management of diabetes, continuous monitoring of other major disease biomarkers can significantly impact patients suffering from alternate diseases. For instance, while gout is not as common as diabetes, it still affects roughly 4% of the US population. Clinically, uric acid levels in blood are often used for the management of gout. In a recent study, a highly sensitive sweat uric acid assay was developed and tested in human trials, demonstrating considerable potential of using wearable sweat sensors for gout management (Yang et al., 2020).

For wearable sensors to be used in reliable selective detection of molecules in complex biofluids with high sensitivity, accuracy, and precision, they need to demonstrate analytical performance similar to established laboratory-based analytical methods (Sempionatto et al., 2019). This can be challenging since wearable sensors are constantly exposed to uncontrolled conditions during on-body operations, including varying pH, temperature, pressure, ionic strength, humidity, and biofouling and foreign body response (in case of transdermal sensors). Additionally, the natural variations in the body fluid compositions together with different medication and nutrition habits can influence the sensor performance. Gaining further understanding of these changing conditions and natural variations will guide efforts for further improving the sensor accuracy. To achieve accurate wearable chemical sensors, extensive large-scale human trials need to be accomplished to establish strong validations of the sensor response with the gold-standard, laboratory-based analytical instruments (Hauke et al., 2018; Yang et al., 2020). Further advances in biosensing transduction methods through joint multidisciplinary efforts are expected to exploit the full potential of wearable sensors for many applications in our daily lives.

During the time of the COVID-19 pandemic, access to laboratory based molecular diagnostic kits has been lagging behind the enormous

demands for widespread population level testing, prompting the employment of auxiliary wearable sensor devices that can continuously monitor physiological and molecular parameters to predict subtle early symptoms of infection and disease progression (Jeong et al., 2020). State of the art wearable physiological sensors can be utilized to monitor symptoms such as fever, cough and shortness of breath, while developments in wearable electrochemical sensor technologies have the potential to continuously monitor molecular markers of virus infection as well as symptoms such as inflammation. Many biomarkers have been associated with the relevance of COVID-19 by recent studies. For example, bidirectional relationship has been shown between COVID-19 and diabetes in which not only diabetes is associated with an increased risk of severe COVID-19, but new-onset diabetes or complication of the preexisting diabetes, e.g. diabetic ketoacidosis and hyperosmolarity, has been observed in COVID-19 patients (Chee et al., 2020; Li et al., 2020; Ren et al., 2020; Gao et al., 2020). The overreaction of the immune system or the so-called cytokine storm, in which the cytokines accumulation results in local inflammation or hyperinflammation, has been seen during viral infections such as COVID-19 (Tang et al., 2020). The levels of lactate dehydrogenase have also been correlated with the relevance of COVID-19 cases (Henry et al., 2020). Recent studies suggest that current cutting-edge wearable biochemical sensors are capable of monitoring metabolic and proteomic profiles to help in preventing severe complications caused by the current infectious disease or to in monitoring the health of vulnerable populations. For example, to aid COVID-19 patients, the sweat patches developed by Epicore Biosystems can be used to monitor electrolyte levels and fatigue or to track the cytokines in the sweat (Smart Patch, 2020). Although not wearable, a recent point-of-care wireless electrochemical platform, named SARS-CoV-2 RapidPlex, developed by Gao's group has shown promise for the low cost and rapid detection of COVID-19 related biochemical markers in serum and saliva samples (Torrente-Rodríguez et al., 2020b). In a pilot study, the multiplexed immunosensors were able to detect nucleocapsid protein, anti-spike protein IgG and IgM, and C-reactive protein in serum and saliva samples to categorize patients into infectious, vulnerable, and/or immune groups. Development of advanced microfluidics for automated sample handling or electrochemical sensors with alternate sensing mechanisms are crucial to enable the wearable monitoring of the aforementioned COVID related biomarkers.

Healthy individuals can also benefit greatly from wearable electrochemical sensors in terms of managing their health, wellness and nutrition. Recently, a flexible tattoo epidermal sensor was developed to track the dynamic changes in sweat vitamin C levels (Sempionatto et al., 2020). Trace levels of vitamins, minerals and amino acids in our fluids can thus be continuously analyzed to provide personalized nutrition guidance. Furthermore, non-invasive and continuous analysis of stress hormones, such as cortisol, can provide a better understanding of our mental state and equip us to better cope with stress before it takes a significant toll on our health. A recently developed sweat cortisol sensing platform has shown a strong empirical correlation between sweat and serum cortisol concentrations (Torrente-Rodríguez et al., 2020a). Widespread public adoption of such wearable molecular-level health monitors can elevate public health consciousness towards improved quality of life.

8. Conclusion, prospects and challenges

In this review, we have presented the contributions of North American researchers to the development of wearable electrochemical sensors. Many pioneering studies have been developed in the USA as a result of active collaborations between academic and industrial entities fueled by a steep rise in demands for more advanced healthcare and increasing investment by private and government bodies. We have discussed the importance of the first concept of wearable biosensors, with the rise and mishap of GlucoWatch, which inspired and challenged other venues and researches to improve and modify on-body worn bioelectronics. Thus, innovative wearable devices were engineered and became seeds to innumerable startups with the great vision of the complete lab on the body.

Our discussion indicates that the wearable biosensors field is a hot research topic mainly in the US coastal universities, with less activity from the US central (mid-Western) region. In addition, while researchers from Canada and Mexico are more active in developing wearable physical sensors toward detection and monitoring of vital signs (e.g. heart rate, blood pressure, etc.), they are less engaged in the development of wearable electrochemical sensors for detecting chemical markers.

We were able to realize that, at least in North America, the main driving force for wearable biosensors is still related to glucose monitoring. Continuous glucose monitoring is, as of today, lively explored by many successful industrial entities and it has motivated and inspired dynamic research in the continuous monitoring of several other analytes, such as drugs or nutrients.

This review also discussed the platforms and detection principles used for wearable sensors, together with their advantages and disadvantages. For example, we presented several opportunities and challenges in developing wearable affinity sensors. Nowadays, the washing and incubation steps associated with such sensors present major challenges for continuous on-body operation. An elegant and sophisticated solution to overcome such challenges would be the development of wearable fluidic systems with actuator elements capable of storing and delivering the necessary mixtures autonomously and reversibly, which demands tremendous research efforts for realization.

The integration of electrochemical systems with wireless electronics is a strong research topic in North America. The fast-growing advancement in the field is boosted by main US players including Silicon Valley enthusiasts, companies such as Google, Apple, Fitbit and several venture capitalists, along with major engineering efforts in leading US universities, towards the development of flexible, stretchable and skin conformal electronic circuits. We will soon witness automized soft robots capable of detecting and monitoring biochemical molecules in the immediate surroundings and environment. For this future, smart biogloves and textiles will play vital role on giving mechanical robotic protheses the ability to mimic the human skin. These new sensing capabilities must follow the desired features for wearables which comprise the use of the appropriate matrix, sampling and methodology for a continuous, non-invasive and comprehensive monitoring (Fig. 6).

We expect that reviewing these exciting and innovative devices developed in North America will encourage more researchers,

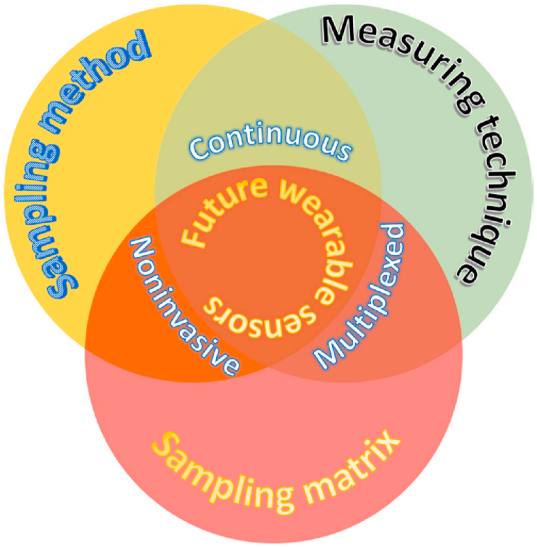


Fig. 6. Desirable features for future wearable sensing platforms.

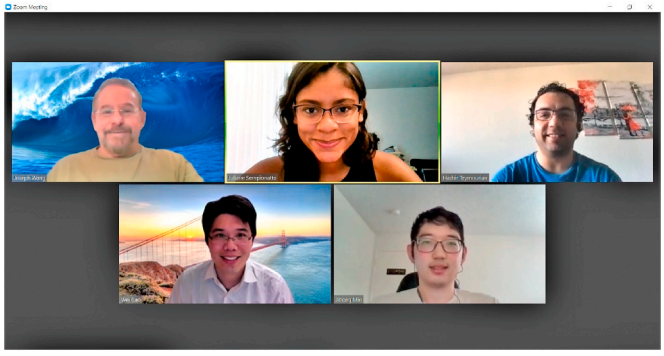
companies and entrepreneurs around the world to join this incredible journey toward decoding the biological language of our body, translating every sweat, saliva and tear droplet into relevant diagnostic information capable of saving and improving our lives. Indeed, researchers from Asia and Europe have already made major contributions to this exciting field, which are beyond the scope of this article. Being able to understand the chemical signals that our body is transmitting is extremally important, especially in these difficult times imposed by the current COVID-19 pandemic. In North America, wearable devices are becoming great allies to the prevention and reduction of the disease spreading, especially regarding testing and screening of patients (Adans-Dester et al., 2020). The COVID-19 pandemic represents a major new driving force that shapes the development of modern wearable medical devices. Greater attention is thus currently being directed toward wearables able to monitor temperature, heart rate, sleep quality, and blood oxygenation which are features associated with the symptoms for the early detection of COVID-19. These capabilities will soon be combined with wearable chemical sensors to enable patients and medical personnel to be aware of the symptoms on its early stages. The importance of wearables during such pandemic episodes goes further than helping in the prevention and monitoring of COVID-19 patients. During these difficult times, wearables are lifeboats for chronic diseases patients who need regular medical care and would otherwise be exposed to contamination or risks by visiting the hospital. Telemedicine coupled with wearables is extremely valuable for decreasing the number of physical visits while keeping close medical monitoring. Self-monitoring is the key for health, telemedicine, prevention, and wellness, and wearable electrochemical sensors are the key keepers in these directions.

Author contributions

J.M., J.R.S., and H.T. contributed equally. All the authors co-wrote the paper.

Declaration of competing interest

The authors declare that they have no known financial or personal competing interests that could have influence the work reported in this paper.



Authors from the UCSD and Caltech (top and bottom, respectively).

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