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The role of sampling in wearable sweat sensors

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ABSTRACT

Wearable sweat sensors demonstrate outstanding performance in non-invasive, real-time monitoring of vital biomarkers in sweat, which offer an opportunity for individuals to achieve dynamic monitoring their own physiology in molecular-level. As a key step in sweat analysis that impact the accuracy of results, frequently-used sweat sampling methods are introduced in this review, and the emphasis is sweat sampling in wearable sensors including absorbent materials, superhydrophobic/superhydrophilic surface, sweat guidance and epidermal microfluidic systems. In the end, we also propose the remaining challenges in the practical, large-scale application of wearable sweat sensors and provide personal prospects on the future development.

1. Introduction

Human sweat, a very important biofluid, consists of water (99%), ions (Na^+, K^+, Ca^{2+}, etc.), metabolites (glucose, lactate, ethanol, etc.), hormones, small proteins and peptides, providing a wealth of chemical information about physiological and metabolic status [1–3]. Generally, most accessible sweat is secreted from eccrine sweat glands, which are almost located all over the body surface at densities of > 100 glands/cm^2 and especially concentrate in the skin of the palms, soles, axillae and forehead to control body temperature, enabling numerous accessible sampling sites [4]. The rich composition, non-invasive availability and certain relation to blood chemistry make sweat analysis attractive in non-invasive medical monitoring and diagnostics [5,6]. For example, chloride concentration in sweat is the gold standard for cystic fibrosis diagnosis [7,8], sweat sodium and chloride loss are important for athletes to guide the fluid intake strategies and maintain the proper balance between hydration and electrolyte levels [9,10], while excessive loss of sodium in sweat will increase the risk of hyponatremia [11]. Uric acid and creatinine levels in sweat can provide early warning for kidney disease [12,13], and sweat glucose analysis can be used to evaluate glucose concentration in blood for diabetes screening in clinical applications [14].

Sweat analysis involves several stages including sweat collection, extraction, storage and detection. It has been reported that sweat composition depends heavily on its generated position and type [15], therefore, the sampling method has a significant impact on the accuracy and reliability of sweat analysis results. Traditional sweat sampling is separate from subsequent steps, which cannot meet the needs of dynamic, in situ, real-time monitoring and may cause several problems such as sample evaporation, degradation or contamination. Emerging wearable sensors, classes of skin-compatible devices, enable autonomously and continuously monitor a range of body indicators in wearable formats like patches, tattoos, clothing, wristbands or headbands [2,16,17]. Such devices act as a “lab on the skin” capable of sample collection, storage and detection, especially suitable for non-invasive, real-time monitoring of biomarkers in sweat without disrupting the stratum corneum of the body's skin [5]. Further integration of wearable sensors with big-data analytics can realize continuously monitoring of individualized fitness, early detection of dynamic health conditions, and better management of chronic diseases [1].

In this review, we introduce the traditional sampling methods and modified sampling approaches applied in wearable devices for sweat analysis in detail (Fig. 1), and discuss their advantages and disadvantages. In the end, a prospect section about remaining challenges in practical applications of wearable sweat sensors, the potential improvements and the future research directions will be given.

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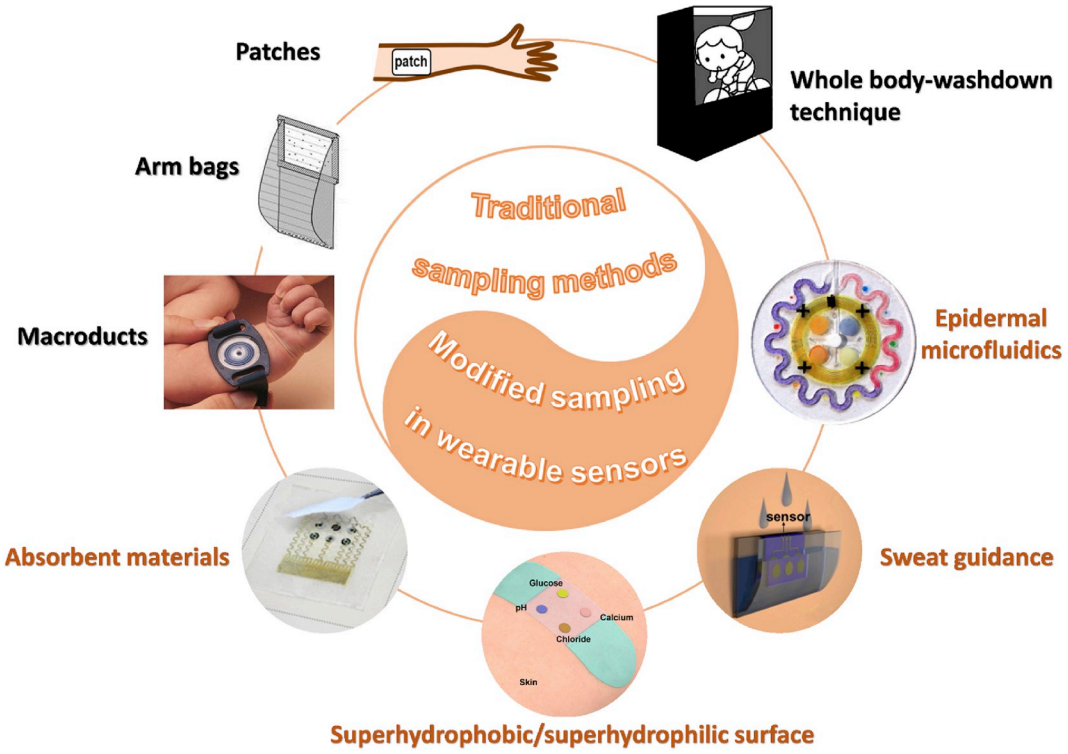

Fig. 1. Schematic diagram of sweat sampling methods, mainly including whole body-washdown technique, patches, arm bags, Macroducts, absorbent materials, superhydrophobic/superhydrophilic surface, sweat guidance and epidermal microfluidic systems. Arm bags image: Reproduced with permission [18]. Copyright 2007, Elsevier. Absorbent materials image: Reproduced with permission [19]. Copyright 2017, The American Association for the Advancement of Science. Superhydrophobic/superhydrophilic surface image: Reproduced with permission [20]. Copyright 2019, American Chemical Society. Sweat guidance image: Reproduced with permission [21]. Copyright 2019, American Chemical Society. Epidermal microfluidics image: Reproduced with permission [22]. Copyright 2017, American Association for the Advancement of Science.

2. Sweat sampling methods

From an analytical point of view, sampling step has by far the greatest impact on the accuracy of the electrolytes and metabolites concentration in sweat [23,24]. To overcome several problems in sampling step, researchers never stop to develop new sampling methods and improve the existing methods, which will be introduced in this chapter in details.

2.1. Traditional sweat sampling methods

Whole body-washdown technique. The whole body-washdown technique is considered as the gold standard to determine whole body sweat electrolyte loss since all sweat runoff is collected and the normal evaporative sweating process is undisturbed [25]. All equipment and the subject are carefully rinsed with deionized water before exercise. Subjects wearing minimal clothes ride a cycle ergometer in a plastic isolation box [26]. Following exercise, subjects, the box, equipment, clothes, and all the touched objects are rinsed with deionized water thoroughly again to collect all electrolytes produced on the body for further analysis. The whole body sweat loss is the change in nude-body mass before and after exercise.

This whole body-washdown technique is one of the early sampling methods to research the composition and mechanism of sweat, which avoids the extraneous contamination with electrolytes and has no interference with the normal sweating process. to allow studies of sweat composition and electrolyte loss under physiological conditions [26]. However, this method is limited by a controlled laboratory setting, complex steps, and single mode of exercise testing, thus is not practical for field studies and treadmill protocols.

Patches. Patches possessing hydrophilic and porous structure are usually sandwiched between the skin and an outer membrane in sweat collection devices with obvious advantages of natural abundance, light weight, flexible structure, low cost and facile surface-modification. It is highly flexible to apply patches in one or multiple specific sites like forearm, thigh, back, and calf for sweat accumulation over hours [27]. Then the collected sweat is carefully weighed, extracted and diluted for further analysis [28].

Comparing with whole body-washdown technique, the regional sweat collection by patches generally overestimates the analyte concentration like [Na^+] and [K^+], but there are significant correlations between the results of the two methods [25]. Careful skin preparation before the sweat collection is necessary to reduce the contamination from cosmetics or bacterial on skin. Despite the simplicity of this method, during the tedious collecting and processing steps, volume losses can be as high as 2% per minute [29], and the results are also significantly affected by different sweating regions, individual health level, environmental conditions and exercise intensity. In addition, patches are time-consuming to apply, easy to detach, and may have an hydromeiosis effect on sweat rates due to sweat pools formation on skin surfaces, suppressed sweat evaporation, and increased local skin temperatures [30,31].

Polymer bags/films. Arm bags have a long history as simple and disposable sweat collectors. During the early experiment, a dry oilskin irrigation envelope was completely and loosely encased the whole arm and hand of the subject and fitted firmly around the top of the arm just below the axilia, and the sweat was collected in the bags and drained through an outlet at the bottom of the bag [32,33]. Appenzeller et al. presented an improved commercial sweat collection system to obtain native (not evaporated) sweat [18]. The system consisted of an adhesive rubber to cover the skin on the lower back and a polypropylene

copolymer bag to accumulate sweat. All components of the system had no effect on sweat composition for the period of use. Boysen et al. used a sheet of polyethylene film placed over a thin layer of vaseline and paraffin oil on the skin to develop an anaerobic sweat collector, by which enabled large volumes of sweat collection with less contamination and evaporative water loss [34]. However, the inhibited sweat evaporation from the skin surface will not only lead to the changed sweat composition, but also cause blocked sweat gland ducts and progressively falling sweating rates [35].

Macroducts. The Macroduct is another common commercial sweat collector for sweat rate and content analysis, which is initially used for cystic fibrosis diagnosis combining with pilocarpine iontophoresis stimulation. A typical Macroduct collector consists of a circular plastic capsule affixed to the skin and a spiral plastic tube to collect sweat [36]. Comparing with patches, sampling by Macroducts can avoid sweat leakage, contamination, and potential hydromeiosis because sweat is almost immediately removed from the skin [31]. Macroducts can also be conveniently applied in many other environments besides laboratory conditions, and enable dynamically track parameters over time rather than a single measurement during the entire experiment [37].

However, most of these above mentioned ex situ sweat sampling methods not only involve tedious procedures, large equipment and trained professionals, but also limited by insufficient sample volumes, non-negligible sample evaporation from the skin surface, possible analyte degradation between sampling and testing, and uncontrollable sweating rate and region, which may strongly affect the reliability and sensitivity of the testing results [1]. Additionally, the separation of sampling from analysis is failed to provide a real-time profile of sweat content secretion. Therefore, by functionalizing the materials and miniaturizing the devices based on traditional sampling methods, in situ real-time and continues sweat sensing devices integrating sampling and analysis have been developed as the present tendency that will be discussed in next chapter.

2.2. Sweat sampling in wearable sensors

Sweat can be on-demand generated through exercise or local iontophoresis stimulation, and restricted to the designated location placed wearable epidermal sensors. Through in situ sampling techniques to control sweat flow, sensors can perform the real-time measurements in the fresh generated sweat rather than the mixture of new and old sweat, realizing autonomous and continuous sweat sensing.

2.2.1. Functional absorbent materials

Currently, variety of modified absorbent materials, such as paper, nonwoven fabrics, cellulosic materials, hydrogels and rayon pad, have been widely used as sweat sampling zone in wearable sensors [38–40].

Introduction of porous substrates between the sensing component and the skin in wearable sensors can eliminate direct contact, minimize abrasion and avoid blocked glands or measurement artifacts when sweat and its contents are trapped between the sensor and the skin. As shown in Fig. 2A, the pores in the cellular substrate facilitated sweat flow and accumulated sweat underneath the sensor, which enhanced breathability for sweat glands and minimized sweat artifacts [41]. Kim et al. designed a “panda-like” tattoo platform using different hydrogels covered on the electrodes for efficient biofluid sampling and storage (Fig. 2B) [42]. Besides as dual biofluid (sweat and interstitial fluid) sampling platform and a storage reservoir for electrochemical sensing, the porous hydrogels formed by buffered solution were used to protect skin from the potential pH changes due to ionic build-up at the sampling site during repeated sensing and avoid skin burning during iontophoresis operation. Such hydrogels integrated the fluid stimulation, sampling, and measurement into a single shared platform.

Functional porous substrates can also be introduced as sensing components while sampling. Rogers' group reported a stretchable and wireless sensor for sensing of sweat from the surface of the skin, which included an inductive coil and a planar capacitor formed with interdigitated electrodes mounted onto hydrophilic porous substrates (Fig. 2C) [43]. The functional substrates not only allowed spontaneous sweat sampling through capillary forces without complex microfluidic handling systems, but also were used to detect specific components like OH^-, H^+, Cu^+, and Fe^{2+} in sweat by introducing indicator compounds into the depths of the substrates. Gu's group fabricated a wearable sensor based on a reduced oxide graphene film onto a porous inverse opal acetylcellulose (IOAC) film for simultaneous, in situ monitoring of human motions and ion concentrations in sweat [45]. The porous IOAC

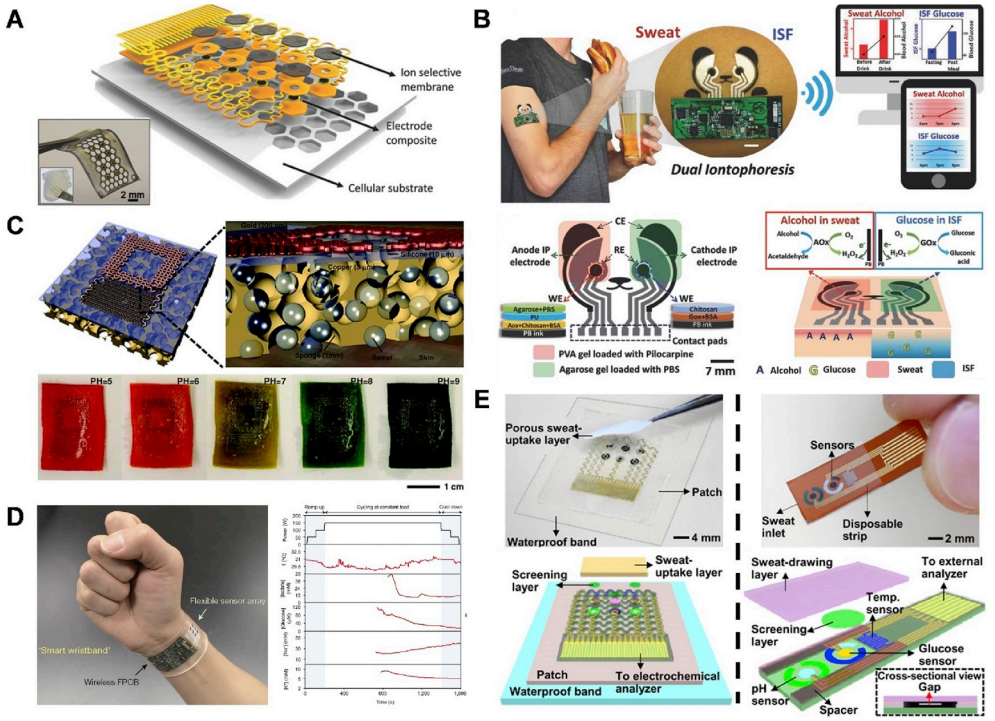

Fig. 2. Functional absorbent materials for sweat sampling in wearable sensors. (A) An ion selective sensor on a cellular substrate. Reproduced with permission [41]. Copyright 2017, John Wiley and Sons. (B) Wearable glucose and alcohol biosensors on a printed tattoo platform with hydrogels for efficient sample collection. Reproduced with permission [42]. Copyright 2018, John Wiley and Sons. (C) Passive wireless capacitive sensors that the coil structure mounted onto hydrophilic porous substrates for pH sensing. Reproduced with permission [43]. Copyright 2014, John Wiley and Sons. (D) Wearable multiplexed sweat sensing array with an absorbent thin rayon pad placed between the skin and the sensor array for sampling. Reproduced with permission [44]. Copyright 2016, Springer Nature. (E) Wearable sweat monitoring patch (left) and a disposable sweat monitoring strip (right). Reproduced with permission [19]. Copyright 2017, American Association for the Advancement of Science.

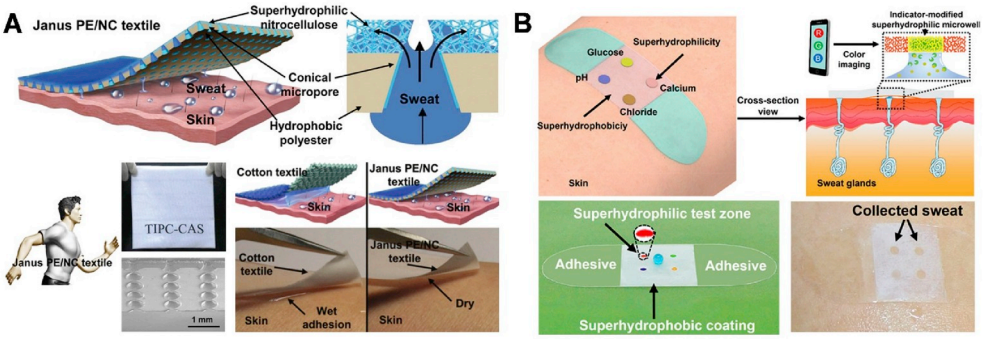

Fig. 3. Superhydrophobic/superhydrophilic surface for sweat sampling in wearable sensors. (A) Janus PE/NC textile with conical micropores for directional sweat transport. Reproduce with permission [49]. Copyright 2019, John Wiley and Sons (B) A superwettable band for sweat sampling and multiplex targets analysis. Reproduce with permission [20]. Copyright 2019, American Chemical Society.

film as multifunctional microstructured substrate was used for highly sensitive motion sensing, sweat collection and ion concentrations analysis. When placed on the surface of skin, the porous IOAC substrate spontaneously absorbed the sweat as the skin perspires, leading to the change of refractive index of the IOAC. Therefore, the ion concentrations in sweat could be simply detected through colorimetry or reflection peak shift.

Incorporation of absorbent materials into wearable sensors placed near the sensing site can obtain the real-time data by removing old sweat accumulation [8,19,44]. Gao et al. placed a thin rayon pad between the skin and the sensor array in a fully integrated device to absorb sweat, prevent the direct mechanical contact between the sensors and skin, and minimize abrasion (Fig. 2D) [44]. During on-body experiments, the newly generated sweat would rinse away the old and refill the pad about 10 μl of sweat, which was sufficient for stable and reliable sensor readings. This platform enabled advance large-scale and real-time physiological and clinical monitoring through sweat sensing. Lee et al. modified the absorbent patch with careful multilayer design to optimize the sweat control and increase the sweat collection efficiency for noninvasive sweat glucose monitoring [19]. As shown in the left of Fig. 2E, the ultrathin and stretchable patch-based wearable device was conformal contact with the skin, and integrated with a hydrophilic sweat-uptake layer and a water-proof layer for efficient sweat collection. During the on-body testing, sweat was accumulated in the porous sweat-uptake layer which was made of wood pulp, rayon and half sponge sheet, and then delivered to the sensors through the Nafion layer. The waterproof band behind the silicone patch aided the sweat collection by separating the sweat from external humidity, suppressing sweat evaporation and preventing delamination of the patch from the skin. The same sensors were further miniaturized as a disposable strip as shown in the right of Fig. 2E. The strip-type sensor absorbed sweat by the capillary force formed in the gap between the sweat-drawing layer and substrate, and only needed 1 μl of sweat to stably operate, enabling faster sweat sampling and sensing for reliable measurement. By inserted to a separate smart band, the strip-type disposable sensor performed independently analysis of glucose concentration in the strip with minimized artifacts and abrasion due to the separated sweat collection and sensing.

Similar to absorbent patches, fabrics with inherent moisture wicking properties can bring sweat to a storage area through capillary action [46–48]. Diamond's group reported a sweat sensor belt that integrated a sodium selective electrode and a fluid handling system into a platform for real-time measurement of sodium concentration in sweat [24]. The sweat pump fabric, a patch of polyimide/lycra, formed a seal against the skin through the rim to prevent sweat evaporation and the mixing of sweat on the back, and enabled efficiently capture sweat and continually wicked fresh sweat into a terminal reservoir up to 3 h.

2.2.2. Superhydrophobic/superhydrophilic surface

The surface wettability of traditional fabric can be modified to achieve superhydrophobic/superhydrophilic states capable of good microdroplet anchoring ability, enrichment ability, low droplet usage, holding great potential in fabrication of multifunctional wearable devices [50]. Li et al. reported a novel superhydrophobic coating that could endow various substrates like cloth or plastic with superhydrophobic properties, which could be used as sensitive wearable sensing electronics for human heal care even under wet and corrosive conditions [51]. Dai et al. fabricated a hydrophobic/superhydrophilic textile by modifying a commercial Janus polyester/nitrocellulose (PE/NC) membrane with asymmetric and regularly hydrophilic conical micropore array for directional sweat transport (Fig. 3A) [49]. This Janus textile enabled unidirectionally pump the excessive sweat from the hydrophobic layer to the superhydrophilic layer through asymmetric hydrophilic conical micropores, thereby effectively managing excess sweat and avoiding undesired sticky from sweat. Xu's group demonstrated a superwettable sweat band by combining superhydrophobic/superhydrophilic microarrays with nanodendritic colorimetric biosensors for efficient in situ sweat sampling and analysis [20]. Treated with roll-to-roll coating of the nanoparticle suspension and the shadow-masked oxygen plasma etching techniques, this superwettable band achieved improved interface controllability and enhanced sampling efficiency in well-defined sites. On the superwettable band, the secreted sweat droplets were repelled by the superhydrophobic silica coating and precisely collected onto superhydrophilic microwells driven by the extreme wettability gradient with negligible lateral spreading (Fig. 3B). Notably, contamination from skin or environment and memory may have impacts on the sweat concentration.

2.2.3. Sweat guidance

Some researchers fabricated sweat guiding channels for efficient sweat collection. Liu et al. designed a sweat-based conductivity sensor device with a polydimethylsiloxane (PDMS) sweat collector for real-time, non-invasive physiological condition monitoring (Fig. 4A) [52]. The PDMS sweat collector prepared by 3D printed plastic molds was punched at the center and inserted by a tube to collect sweat from skin. When subject wore the device in the exercise, the sweat was pumped from sweat glands by hydraulic pressure and guided to the sensing zone through the tube, while the increasing pressure in the tube had no significant effect on sweating mechanisms. It was important to keep the sealed contact of the PDMS on the skin because the skin uncovered with PDMS would lose the pressure and lead to the sweat leakage on the opposite side of the sweat flow. Wang et al. proposed a wearable “sweatband” sensor platform for efficient sweat collection and real-time analysis of sweat sodium during an indoor exercise [21]. As shown in Fig. 4B, the channel on the commercially available sweatband (made from silicone) could efficiently guide the flow of the sweat on the forehead and transport it to the chip surface of sensors driven by the gravity and the oscillation of the movement.

2.2.4. Epidermal microfluidic systems

With the development of materials and device manufacture, lab-on-a-chip type microfluidics can be designed in thin, soft, “skin-like”

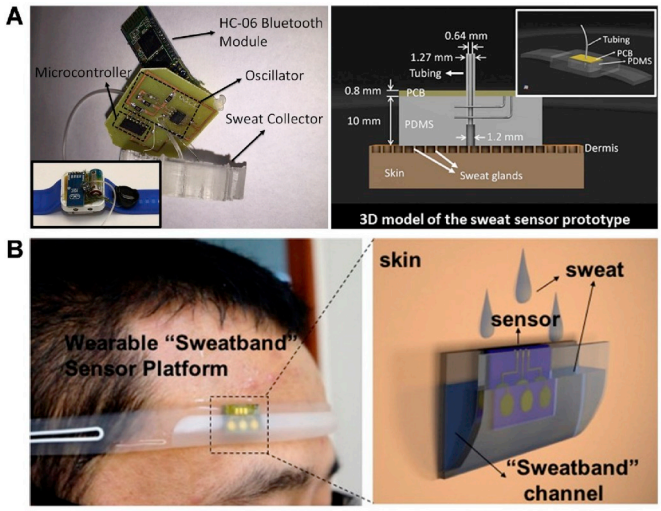

Fig. 4. Sweat guidance for sweat sampling in wearable sensors. (A) Wearable conductivity sensors with PDMS sweat collector for wireless real-time sweat monitoring. Reproduced with permission [52]. Copyright 2019, Elsevier. (B) Wearable sweatband sensor platform containing sweat guidance channels for real-time analysis of sweat sodium. Reproduced with permission [21]. Copyright 2019, American Chemical Society.

formats for wearable applications. Mounted on nearly any part of the body, such wearable epidermal microfluidic devices utilize sweat secretion pressure and capillary action to guide sweat flow from secretion sites to controlled channels for continuous sampling with sufficient spatiotemporal resolution, and enhance sensing in a well-defined encapsulated chamber by eliminating external contamination and preventing sweat evaporation. Thus, wearable epidermal microfluidic devices can not only characterize the local sweat chemistry in freshly secreted sweat, but also measure the average and instantaneous sweat loss or rate for real-time analysis or subsequent studies [6,39,53].

Integration of electrochemical sweat sensors and microfluidics is an attractive platform for efficient sweat sampling and artifact minimization. Such devices contact the skin surface by adhesives, utilize flexible printed circuit boards as the supporter of packaged electrodes and associated electronic components, and measure currents, potentials or impedances at functionalized electrodes to transduce analyte concentrations, allowing natural contact to the soft human body and real-time in situ molecular monitoring with unique advantages including high sensitivity, high selectivity, light weight, great conformability and low cost [1,5,6]. Fig. 5A presented a flexible microfluidic sweat sensing patch merging sensors interfaced with a printed circuit board inside a microfluidic channel for real-time electrochemical sensing and sweat rate analysis [54]. Since the sweat was spontaneously pumped from secretion sites to the microfluidic channel via sweat secretion pressure and capillary action, the sensing patch possessed efficient sweat sampling and autonomous analysis of dynamic changes in sweat compositions.

In addition, colorimetric signal transduction has been exploited in epidermal microfluidic systems to utilize the colorimetric response of reagents to the target analytes like electrolytes or metabolites in sweat, and digital equipment capable of capturing high-quality images such as smartphones for simple quantitative assays [6,57,58], which obviates the need of electrochemical measurements, power supplies and data communication hardware in electrochemical sensors, and facilitate miniaturized wearable devices [2]. Rogers' group demonstrated a typical epidermal microfluidic device for sophisticated sweat sampling, colorimetric detection of virous sweat biomarkers like chloride and hydronium ions, glucose, and lactate through multiple channels, and sweat loss quantification [22]. As shown in Fig. 5B, sweat entered inlet regions of the overlying soft microfluidic system and was guided through a network of microchannels and reservoirs filled with color-responsive materials drove by the combination of natural pressure associated with perspiration and capillary effects in the microchannels. The adhesive film ensured the device to stably, strongly, and seamlessly contact to the skin for efficient sweat sampling. A smartphone recorded the color changes and converted them into quantitative information by NFC, then digitized the RGB color information about the concentration of the marker and showed on the screen by the mobile application. For simple semiquantitative analysis, observation by naked eye or comparison against color calibration markings was feasible [59,60].

Recent advances in sweat collection and sensing technologies expanded the functions of microfluidic devices and the range of analytes for people with special needs in some situations. Reeder et al. proposed skin-integrated microfluidic systems that enabled capture, storage, and analysis of sweat during aquatic exercise even underwater [55]. As shown in Fig. 5C, the device consisted of microchannels for sweat sampling, a chamber containing colorimetric chemical reagent, electronics for wireless communication and temperature sensing, a set of reference color markers, and a skin-safe adhesive. The microfluidic platform made of elastomeric, moldable polymer could efficiently prevent the penetration of water, water vapor, and water-borne chemistries from the surroundings. In addition, the inlets, outlets, and channels of microfluidic platform were designed to prevent interference or contamination from aquatic environments without impeding the inflow of sweat. Therefore, the device enabled robust bonding to the skin, reliable sweat collection, and quantitative in situ measurements of local sweat chloride concentration, local sweat loss (and sweat rate) and skin temperature in aquatic environments. Gao's group reported a mass-produced, all-laser-engraved microfluidic device for first sensitive detection of low-concentration uric acid (UA) and tyrosine (Tyr) in sweat which were associated with diseases such as gout and metabolic disorders (Fig. 5D) [56]. As sweat secretion began, the multi-inlet microfluidic module enabled dynamic sweat sampling by constantly supplying newly secreted sweat to sensor scribed on the polyimide substrate and obtained multiplexed sensing with high temporal resolution. In addition, circular patterns of microfluidic channels could be used for measuring sweat loss and sweat rate. Such multimodal sensor successfully realized efficient microfluidic sweat sampling, multiplexed vital-sign sensing of skin temperature and respiration rate, and sensitive molecular sensing of UA and Try in human sweat in situ following a similar trend as in serum, suggesting an enormous potential for non-invasive, continuous gout monitoring.

3. Prospects and challenges

Herein, we have summarized and highlighted the traditional and modified sweat sampling methods in this review. Traditional sweat analysis relies on extraction using whole body-washdown technique, patches, polymer bags/films or Macroducts and subsequent detection by professional equipment, involving several problems such as uncontrollable sweating rate and region, non-real-time monitoring, inevitable sample evaporation and contamination. Recent progress in wearable sweat devices realize the integration of sweat sampling, storage and analysis into a multifunctional platform. By utilizing modified absorbent materials, sweat guidance, superhydrophobic/-superhydrophilic surface or epidermal microfluidic channels as efficient sampling methods, the wearable sweat devices enable autonomous and continuous sensing of vital electrolytes and metabolites in sweat with high sensitivity and reliability. Table 1 detailedly summarized the advantages and remaining challenges of different sweat sampling methods discussed in this review.

Although these new sampling methods greatly enhance the sensing performance of wearable devices, the real-time, non-invasive sweat monitoring remain several challenges in future applications. First, sampling with enhanced sweat rates is crucial. Currently, intense exercise or iontophoresis are main approaches to stimulate sweat

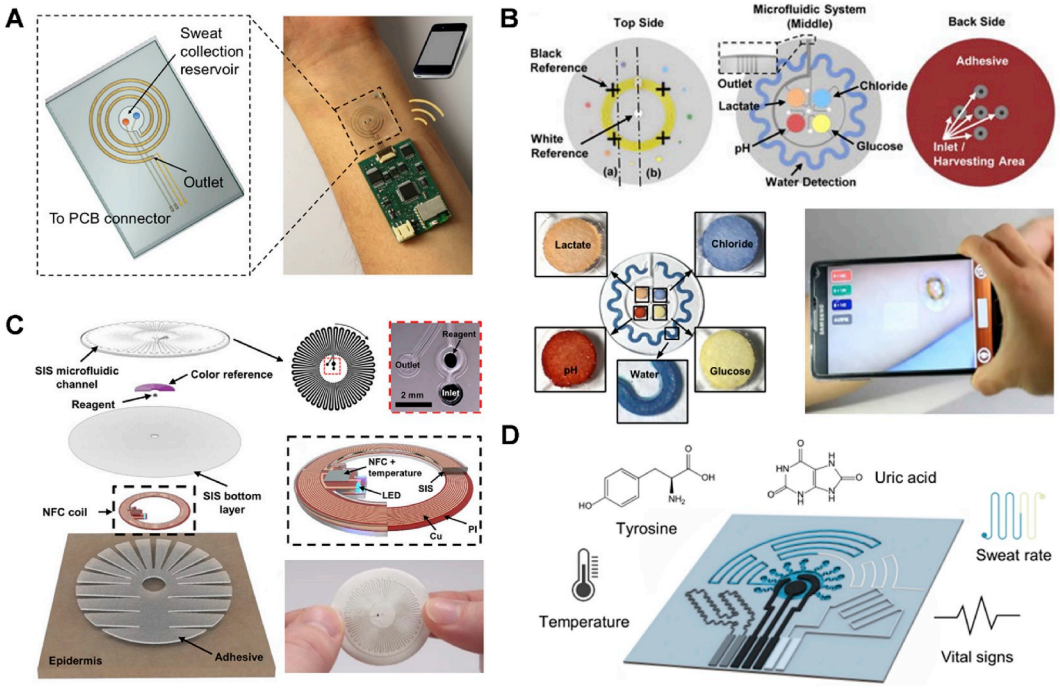

Fig. 5. Epidermal microfluidic systems for sweat sampling. (A) Wearable sweat sensing patches for dynamic sweat secretion analysis. Reproduced with permission [54]. Copyright 2018, American Chemical Society. (B) Colorimetric microfluidic device with smartphone-based imaging equipment for sweat analysis. Reproduced with permission [22]. Copyright 2017, American Association for the Advancement of Science. (C) Waterproof microfluidic devices for sweat collection and analysis in aquatic settings. Reproduced with permission [55]. Copyright 2019, American Association for the Advancement of Science. (D) Laser-engraved microfluidic wearable sensors for sensitive detection of uric acid and tyrosine in sweat. Reproduced with permission [56]. Copyright 2019, Springer Nature.

generation. However, sweat secretion rates will not exceed 20 nL/min/gland even in exertive exercise [3]. Locally stimulate sweating via iontophoresis is better suited for invalids, the old men or babies to acquire enough sweat in sedentary situations comparing with exercise, but the current density of the device must be carefully controlled because repeated application of iontophoretic current at the same location may harm the skin [61]. For better sensing performance, developing ultrasensitive sensors that can work at low level of sweat or exploring

Table 1
Summary of sweat sampling methods.

Method	Advantages	Remaining challenges	Refs
Whole body-washdown technique	• Estimation of whole body electrolyte losses during passive exposure • No interference with the normal sweating process	• Controlled laboratory setting • Complex steps • Single mode of exercise testing	[26]
Patches	• Low cost • Flexible to apply at specific sites	• Contamination from skin • Hydromeiosis effect • High volume loss • Time-consuming to apply and easy to detach	[27,28,30,31]
Polymer bags/films	• Less contamination and evaporative water loss	• Changed sweat composition • Blocked sweat gland ducts • Gradually decreasing sweating rates	[18,32–35]
Macroducts	• No leakage and sample contamination • No hydromeiosis effect • Unrestricted work environment • Dynamical track of parameters	• Possible analyte degradation between sampling and testing • Uncontrollable sweating rate and region	[36]
Functional absorbent materials	• Numerous varieties • Low cost • Multiple functions • Real-time and continuous sampling • Enhanced breathability of sweat glands	• Reusability and durability	[19,24,41–44]
Superhydrophobic/superhydrophilic surface	• Good microdroplet anchoring ability • Sample enrichment ability • Low droplet usage • Enhanced sampling efficiency at specific sites	• Contamination from skin or environment • Memory effect	[20,50]
Sweat guidance	• No significant effect on sweating	• Possible sweat leakage due to unsealed contact to skin	[21,52]
Epidermal microfluidic systems	• Continuous sampling • Real-time analysis • Convenient to mount on any part of the body • No contamination • No sweat evaporation	• Reusability and durability	[54–56,64]

highly efficient techniques for biomarker extraction will be promising.

Contamination from the skin surface or from surrounding environment is difficult to completely eliminate once the sweat is secreted from the gland and contact with skin, which have a large impact on the accuracy of sensor readings. Simple washing of skin surface cannot mitigate contamination such as bacteria, which are estimated as high as $10^{10}/cm^2$ on the skin and may cause considerable errors in the concentrations by consuming glucose, proteins or cellular metabolites in sweat [62,63]. One possible solution is to isolate sweat from the skin surface by coating an occluding layer of petroleum jelly or oil on the skin surface.

To realize the commercial-scale manufacturing of wearable sweat sensors, there are a number of considerations, including: (1) Sensor fabrication at large scale. Commercial-scale manufacture require not only a highly feasible fabrication process, but also relatively low costs. (2) Reusability and durability. Actually, adhesives used in many wearable devices can only last for several days due to many factors such as updateable stratum corneum, skin oils, bath and irritation, and some chemical probes in sensors are consumed or slowly degrade over time. Therefore, sensors with long-term reusability and durability in complex biological fluid system are urgently needed, which are dependent on the advanced materials and manufacturing processes. (3) Sensitivity and Specificity. Considering the concentrations of analytes in sweat are often diluted to a very low level in some cases, ultrasensitive sensors with preconcentration techniques are required. In addition, contaminant and non-specific binding may cause signal change so sensor specificity is crucial. (4) Extensions in variety of sweat analytes. Current sensors can monitor limited kinds of electrolytes and metabolites in sweat. Thus, it is the future trend to fabricate wearable sensors capable of simultaneous monitor of multiple analytes in sweat. (5) Calibration ability. Self-calibration schemes based on large-scale tests should be employed in wearable devices since the results of sensors are easily influenced by environmental humidity or temperature, and/or individual difference in diets and sweat collection regions.

These challenges suggest that there is still broad space and much potential to be tapped in the practical application of wearable sensors, encouraging more researchers to devote more efforts to accelerate the commercialization of such wearable sensors. We envision that the non-invasive wearable sweat devices will be revolutionize biomedical detection for better personalized and predictive healthcare after overcoming these challenges.

CRediT authorship contribution statement

Conghui Liu: Writing - original draft. **Tailin Xu:** Conceptualization, Writing - review & editing, Funding acquisition. **Dongdong Wang:** Writing - original draft. **Xueji Zhang:** Supervision, Funding acquisition.

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