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Diving into Sweat: Advances, Challenges, and Future Directions in Wearable Sweat Sensing

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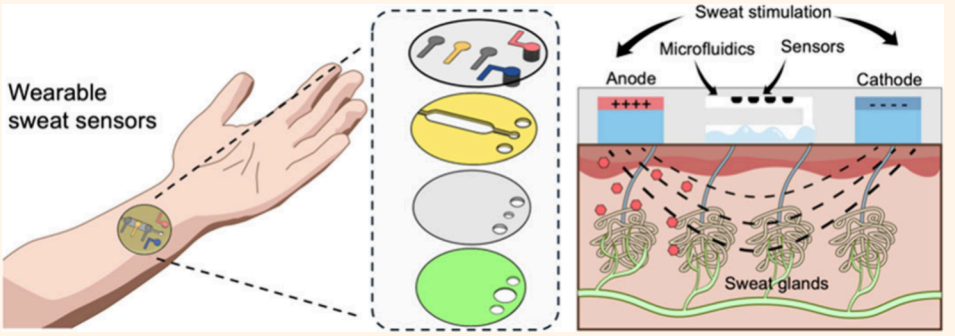

ABSTRACT: **Sweat analysis has advanced from diagnosing cystic fibrosis and testing for illicit drugs to noninvasive monitoring of health biomarkers. This article introduces the rapid development of wearable and flexible sweat sensors, highlighting key milestones and various sensing strategies for real-time monitoring of analytes. We discuss challenges such as developing high-performance nanomaterial-based biosensors, ensuring continuous sweat production and sampling, achieving high sweat/blood correlation, and biocompatibility. The potential of machine learning to enhance these sensors for personalized healthcare is presented, enabling real-time tracking and prediction of physiological changes and disease onset. Leveraging advancements in flexible electronics, nanomaterials, biosensing, and data analytics, wearable sweat biosensors promise to revolutionize disease management, prevention, and prediction, promoting healthier lifestyles and transforming medical practices globally.**

1. INTRODUCTION

Sweat analysis for clinical applications dates back to the 1940s and 1950s.[1−3] Initially, sweat was primarily used for diagnosing cystic fibrosis[4] and testing for illicit drugs.[5,6] Over time, the diverse array of chemicals present in sweat has attracted substantial attention from researchers for the noninvasive monitoring of health-related biomarkers. The advancements in nanotechnology, particularly through the development of high performance nanobiosensors and mechanically resilient nanocomposite-based flexible electronics, have substantially boosted the development of wearable chemical sensors which now enable continuous, real-time tracking of target molecule concentrations.[3,7,8]

Sweat is an ideal biofluid for wearable platforms due to its availability on almost all parts of the human body. There are three main types of sweat glands: eccrine, apocrine, and sebaceous glands (Figure 1a,b).[9,10] Eccrine glands, the most common type, number between 2 to 4 million and are spread throughout the body, though they are most densely concentrated on the palms of the hands and soles of the feet. We are born with a total number of sweat glands, and as we grow, the skin expands, and the sweat gland density decreases. These glands produce a mixture of chemical molecules derived from interstitial fluid and the gland itself, making eccrine sweat the most commonly used for noninvasive biomarker monitoring.

Apocrine glands are located mainly in the axilla, face, scalp, and chest. These glands are larger than eccrine glands and open into hair follicles instead of the skin. The sweat they secrete is rich in lipids, proteins, ammonia, and pheromones, contributing to body odor. The third type, sebaceous glands, also associated with hair follicles, secrete lipid-rich fluid composed of cholesterol, triglycerides, and wax. The number and size of the sebaceous glands dictate the rate of sebum

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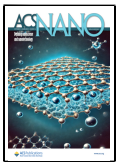

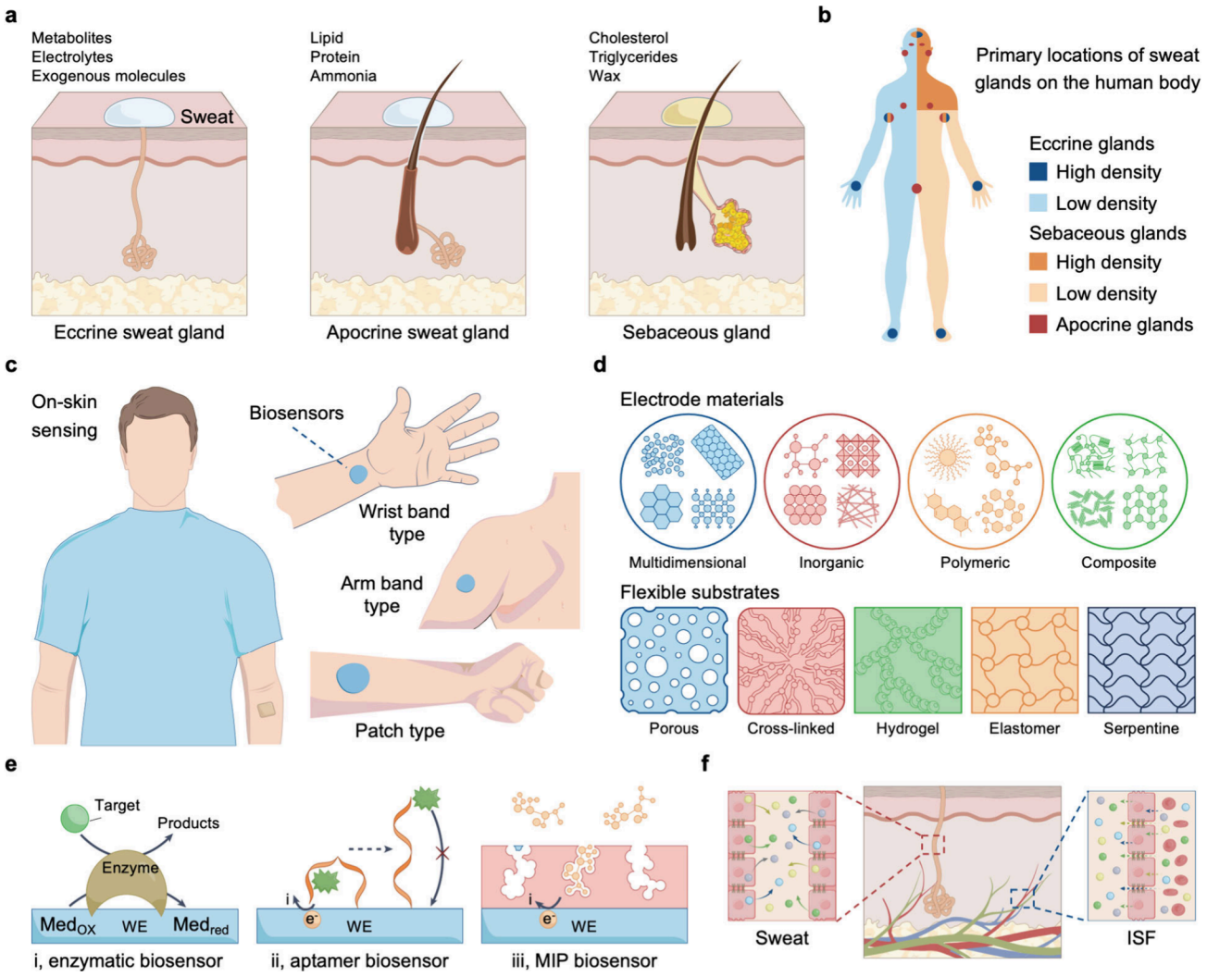

Figure 1. Wearable sweat sensors. (a) Types of sweat glands. Eccrine glands produce sweat rich in metabolites, electrolytes, and exogenous molecules. Apocrine glands, opening to hair follicles, secrete sweat rich in lipids, proteins, and ammonia. Sebaceous glands excrete cholesterol, triglycerides, and wax. (b) Location of sweat glands. Eccrine glands are distributed throughout the body with higher density on palms and soles. Sebaceous glands are mainly on the chest and back. Apocrine glands are concentrated in the armpits and groin. (c) Sensor placement. Common locations include areas rich in sweat glands with minimal stress and movement deformation. (d) Examples of electrode and substrate materials used to fabricate sensitive, flexible, and stretchable sensors. Strategies include the use of nanomaterials such as graphene, CNTs, metallic nanoparticles, composites, etc. to increase electron transport and the use of elastomers, porous, and patterned materials for the fabrication of stretchable substrates. (e) Examples of wearable electrochemical sensing mechanisms. (i) Redox enzymatic reaction: The analyte in sweat interacts with the enzyme, producing hydrogen peroxide, which is detected by the electrochemical sensor; (ii) aptamers-based sensing: Binding with target changes the aptamer's conformation, altering the distance between the redox probe at one end of the aptamer and the working electrode, thus provoking changes in the electrochemical signal. (iii) MIP-based biosensing: MIP/target binding affects the access of the redox probe or electrode to sweat electrolytes, resulting in changes to the electrochemical signal. (f) Molecule partitioning. Molecules partition from blood vessels to interstitial fluid and sweat glands passively between cells, through cells, and via active transport.

production. In general, these different types of sweat glands influence the overall sweat composition.[11,12] This variety of sweat glands affects the optimal placement of the biosensor. Different sweat glands are located in various regions of the body and secrete distinct compositions of sweat. Additionally, sweat gland density and flow rate vary across different body parts. Therefore, the sensor must be strategically placed in locations with high sweat density and minimal mechanical deformation, considering the most probable location for detecting the target analyte (Figure 1c).

Over the past decade, with the aid of advances in nanotechnology and flexible electronics, the development of wearable sweat sensors has accelerated rapidly.[8] During this time, several proof-of-concept demonstrations have emerged in the research field. For example, sweat sensors were reported for monitoring of individual analytes such as lactate, pH, Na^+, and NH_4^+ using epidermal tattoo platforms[13,14] or skin-conformal sensor bandages.[15]

The year 2016 marked a pivotal moment for wearable sweat sensors, as several landmark studies greatly stimulated research and innovation in the field. A fully integrated mechanically flexible wearable sweat sensor system was demonstrated, capable of simultaneous and multiplexed monitoring of metabolites (e.g., glucose and lactate) and electrolytes (e.g., Na^+ and K^+), along with signal processing and wireless data communication.[16] In the same year, an epidermal microfluidic

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system was introduced for the simultaneous sweat collection and in-flow analysis of glucose, lactate, chloride, and pH using a colorimetric approach.[9] Additionally, the concept of closed-loop noninvasive diabetes management was demonstrated using a wearable graphene-based electrochemical sensor which could analyze sweat glucose levels and potentially deliver drugs through a microneedle platform.[17] Since then, numerous progress in wearable sweat sensors have been reported, focusing on the detection of various biomarkers,[18−21] microfluidic sampling and analysis,[22−25] and diverse biomedical applications.[26−29]

Currently most wearable sweat sensors are based on electrochemical methods, while the remainder typically use optical methods.[7,30,31] Electrochemical biosensors on the skin allow for a "hands-free" configuration, allowing the wearer to experience minimal hassle during measurement. However, these sensors face challenges related to electronic noise and motion artifacts due to their electronic systems. On the other side, optical sensors, primarily colorimetric sensors, do not require integrated electronics in the sensor patch but necessitate the user to take a picture of the sensor to monitor in color changes. These color variations can be difficult to detect with the naked eye, and the ambient light can influence the color intensity, leading to over- or underestimation of concentrations.[2] Despite these challenges, both electrochemical and colorimetric wearable sweat sensors are noninvasive, eliminating the need to break the skin for blood collection.

During the rapid development of wearable sweat sensors, the introduction of a system for sweat stimulation was crucial for the widespread application of the wearable sweat sensors in daily activities. For early wearable platforms, sweat was primarily obtained during vigorous exercise, limiting their applications to sports and individuals capable of enduring such physical exertion.[26,30,32,33] The incorporation of iontophoresis, using agonist agents such as pilocarpine and carbachol, into the wearable skin sensors enabled autonomous sweat production without the need for physical exercise or excessive heat stress.[34−36] It should be noted that, with the application of nanotechnology in the form of nanostructures, and nanopatterns, efficient and miniaturized microfluidics have been studied for collecting passive sweat, such as sweat generated continuously on our fingertips.[37−41]

Despite the advancements in sweat analysis, many challenges remain before wearable sweat sensors can achieve their full potential and reach commercial viability. This article will explore current approaches addressing some of the most critical bottlenecks in sweat analysis, including the material development, high-sensitivity analyte detection, and path toward device commercialization.

2. CHALLENGES AND OPPORTUNITIES FOR SWEAT ANALYSIS

2.1. Wearable Sensor Development for in Situ Detection of Sweat Analytes. Skin-interfaced wearable biosensors are the most commonly used platform for sweat analysis, offering real-time and continuous monitoring to capture dynamic physiological changes. However, the necessity for close skin contact imposes stringent requirements on the materials used in fabrication, especially nanomaterials, with a focus on minimizing toxicity and preventing interference with analytes. Substrate materials and biorecognition layers must be biocompatible, and the materials in direct contact with skin should also be nonreactive. Additionally, the chemical methods used for electrode modification and fabrication must be rigorously tested to prevent the leakage of potentially toxic substances. This is especially important for materials gathering sweat integrated with biofuel cells or energy harvesters, which utilize various nanoscale catalysts and mediators.[38,42,43] Recently, flexible quasi-two-dimensional perovskite solar cells have also been employed to power wearable sweat sensors.[44] Due to the biocompatibility concerns related to the Pb composition in the perovskite solar cells, reliable encapsulation agents against sweat exposure are thus required to ensure no heavy metal leakage from the solar cells occurs due to mechanical deformation.[44]

Given the skin's flexibility, the wearable devices must emulate such characteristics. Various flexible and stretchable sweat biosensors (Figure 1d) have been developed using elastomers such as polydimethylsiloxane (PDMS), polystyrene (PS), styrene-ethylene-butylene-styrene (SEBS), and other silicon-based polymers, which provide the necessary mechanical resilience.[45,46] Nanotechnology has played a crucial role in enhancing the mechanical resilience and electrical performance of elastic substrates. The incorporation of highly conductive nanowire fillers, which promote the percolation effect, has enabled the development of wearable sweat sensors with high stretchability, allowing them to conform to body movements and deformations.[43,47] Moreover, nanofiber materials or materials with engineered wettability gradients (e.g., superhydrophobic/superhydrophilic Janus membranes) have been utilized in the wearable patch design to realize high breathability, conformal contact with skin, sweat permeability, and/or exceptional sweat collection efficiency.[48−52] Many other recent studies related to the use of nanomaterials for flexible substrates can also be found in the literature.[53−59]

Once the substrate is established, the fabrication of high-performance electrochemical sensors should be taken into consideration. To enhance the performance of sweat sensors, increasing the surface-to-volume ratio and overall surface area can significantly boost detection signals. Nanoengineered stretchable electrodes have been created using various conductive nanomaterials such as metallic nanoparticles and nanowires, carbon nanotubes (CNTs), poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS), etc.[58,60,61] For example, silver flakes and SEBS have been used to fabricate conductive and stretchable electrodes to convey the silver traces for the electrochemical sensor on SEBS based substrates.[62] In this case, silver flakes were utilized as conductive fillers in the SEBS matrix, ensuring compatibility between electrode and substrate and preventing peeling and delamination upon mechanical deformation. Additionally, Prussian Blue (PB) nanoparticles and carbon ink were combined with SEBS substrate to fabricate the active part of the working electrode. It has been demonstrated that nanotextured electrodes, which increase in the sensor's surface area, can also extend sensor longevity.[63] Additionally, device surfaces have also been developed with nanocomposite antifouling agents, including proteins such as bovine serum albumin (BSA), to further improve the performance of wearable sweat devices.[64]

Many of the reported wearable electrochemical sweat biosensors utilize enzymes as the biorecognition layer on the working electrode (Figure 1e). These enzymes are proteins capable of catalyzing a biochemical reaction specifically for a target analyte. During the enzymatic reaction, the substrates are converted into products as the enzyme undergoes a change

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in shape, which decreases the activation energy of the reaction. Next, the products are released into the solution, and the enzyme recovers to its initial state regenerating themselves for the next bioreaction.[65] This rapid and spontaneous regeneration gives enzymes a significant advantage in wearable sweat sensors, as new concentrations can be measured continuously without carryover. Despite their great promise, there are a limited number of enzymes available for a finite number of target analytes. Among these, redox enzymes are the most commonly used in electrochemical wearable sensors because they generate or consume electrons that can be easily detected by the electrode.

In order to broaden the spectrum of target analytes, new approaches like aptamers have been explored (Figure 1e). Aptamers are short single stranded nucleic acids that fold into a highly specific order. They bind to proteins or other biomolecular targets by affinity, similar to the antibody's interactions. Additionally, aptamers can be chemically engineered giving control over the selectivity and affinity of the target analyte. A common strategy used for aptamer designing is the sequential evolution of ligands by exponential enrichment (SELEX). This consists of an iterative process, where a library of aptamers is passed through a column and nonbinding aptamers are discarded and binding aptamers to the proposed target are copied and amplified. Aptamers can be spontaneously regenerated, or regenerated on demand by applying heat, solvent, or an electrical potential, making them great candidates for continuous monitoring of analytes.[66]

Aptamer-based wearable sweat sensors have been developed toward the detection of cortisol, a hormone related to stress, present in sweat at low nanomolar concentrations.[67] For this, a field-effect transistor (FET) biosensor array was modified with a cortisol-specific aptamer and coupled to a In_2O_3 nanometer-thin-film FETs. The signal and cortisol concentrations were determined by transducing cortisol-aptamers binding to electrical signals on FETs. The sweat cortisol aptamer-based sensor was able to track the physiological levels of cortisol in sweat. A similar approach, using different aptamers as the recognition receptor, has been employed to monitor cortisol levels in sweat.[68,69] It should be noted that most reported wearable aptamer sensors still face challenges in continuous monitoring. There is a high demand for developing aptamers with suitable binding and dissociation affinities to address these issues.

On another note, the use of nanotechnology has enabled the development of molecularly imprinted polymers (MIP), which have garnered great attention as a powerful tool for detecting several classes of molecules (Figure 1e). In this approach, an electroactive monomer is polymerized on the electrode surface in the presence of the target molecule. Once the molecule is removed, it leaves an imprint in the polymer matrix, allowing for the detection of the same molecule based on the shape of the imprint on the electrode. MIP sensors have shown promise for detecting various substances, including vitamins and amino acids.[36] A versatile MIP approach has been demonstrated for the detection of trace levels of metabolites in sweat. For instance, a wearable sweat sensor was developed using graphene functionalized with MIP and redox-active reporter nanoparticles.[36] This strategy was used to create wearable sweat sensors to detect trace levels of multiple metabolites and nutrients, including all essential amino acids and vitamins in sweat.[23] The use of MIP biosensors have also been demonstrated for the electrochemical monitoring of sweat cortisol.[70] For this, an MIP network was integrated with a PB redox probe, offering label-free amperometric detection. The redox probe was polymerized with the template molecule, creating a responsive polymeric matrix. This cortisol MIP sensor was further enhanced with a highly permeable, sweat-wicking porous hydrogel to efficiently capture sweat from the fingertips.

Despite significant advances of nanotechnology in broadening the detection of sweat analytes, there are still intrinsic challenges related to the type of molecules that can be found in sweat. There are various mechanisms for the partitioning of chemical molecules to sweat, many still unknown for certain molecules.[3,11] In general, molecules migrate from the blood vessels to the interstitial fluid and finally to the sweat duct (Figure 1). The paths for this migration include diffusion in between the cells, through the cells, and active transport.[3,11] This "filtering" of blood limits the molecular weight of the biomarkers in sweat, and their concentration in the biofluid. Consequently, molecules in sweat are usually present in much lower concentrations than in blood, posing a significant challenge for wearable sweat sensing (Figure 1f). However, recent advances in nanotechnology, nanomaterials, and flexible electronics have paved the way for the development of next-generation high-performance wearable sweat biosensors.[8,45,71] Thanks to their high surface-to-volume ratio and unique optical and electrochemical properties, various nanomaterials are playing a crucial role in addressing these challenges and enhancing the detection of ultralow-level analytes in sweat.

For instance, the use of nanomaterials for signal enhancement has been demonstrated for highly sensitive detection of C-reactive protein (CRP) in sweat.[72] CRP levels increase during systemic chronic inflammation and can be used to assess a patient's physiological inflammatory state. CRP levels in sweat are relatively small, in the pM concentration range. For the successful detection and monitoring of CRP levels in sweat, gold nanoparticles (AuNPs)-decorated mesoporous laser-engraved graphene was used as the substrate electrode, which was further functionalized with anti-CRP capture antibodies (cAbs). Detector antibodies (dAbs)-loaded AuNPs bind to the mesoporous graphene electrode upon CRP recognition. Owing to the signal ON detection approach and the integration of various nanomaterials in the sensor design, the resulting sensor was able to detect few pM level CRP in sweat and successfully identified elevated CRP levels in patients with chronic and acute inflammations associated with heart failure, and active and past infections such as COVID-19.

Recently, nanomaterials coupled with aptamers as the target recognition element have been used to detect pM levels of the female hormone estradiol in sweat.[73] An epidermal microfluidic device was integrated with inkjet-printed AuNPs electrodes that were modified and $Ti_3C_2T_x$ MXene—a 2D transition metal carbide. The detection of estradiol was realized in the microfluidic chamber, containing a top biorecognition interface modified with estradiol aptamers conjugated with a methylene blue (MB) modified single-stranded DNA (ssDNA). In the presence of sweat containing estradiol molecules, the MB-ssDNA was displaced and captured by the nearby working electrode, which was formed by the AuNPs/MXene working electrode modified with sulfhydryl single-stranded DNA (SH-ssDNA). When in contact with the working electrode surface, the MB-ssDNA probe generates a signal due to the MB's redox reaction. The sensor was able to track the fertility window in female

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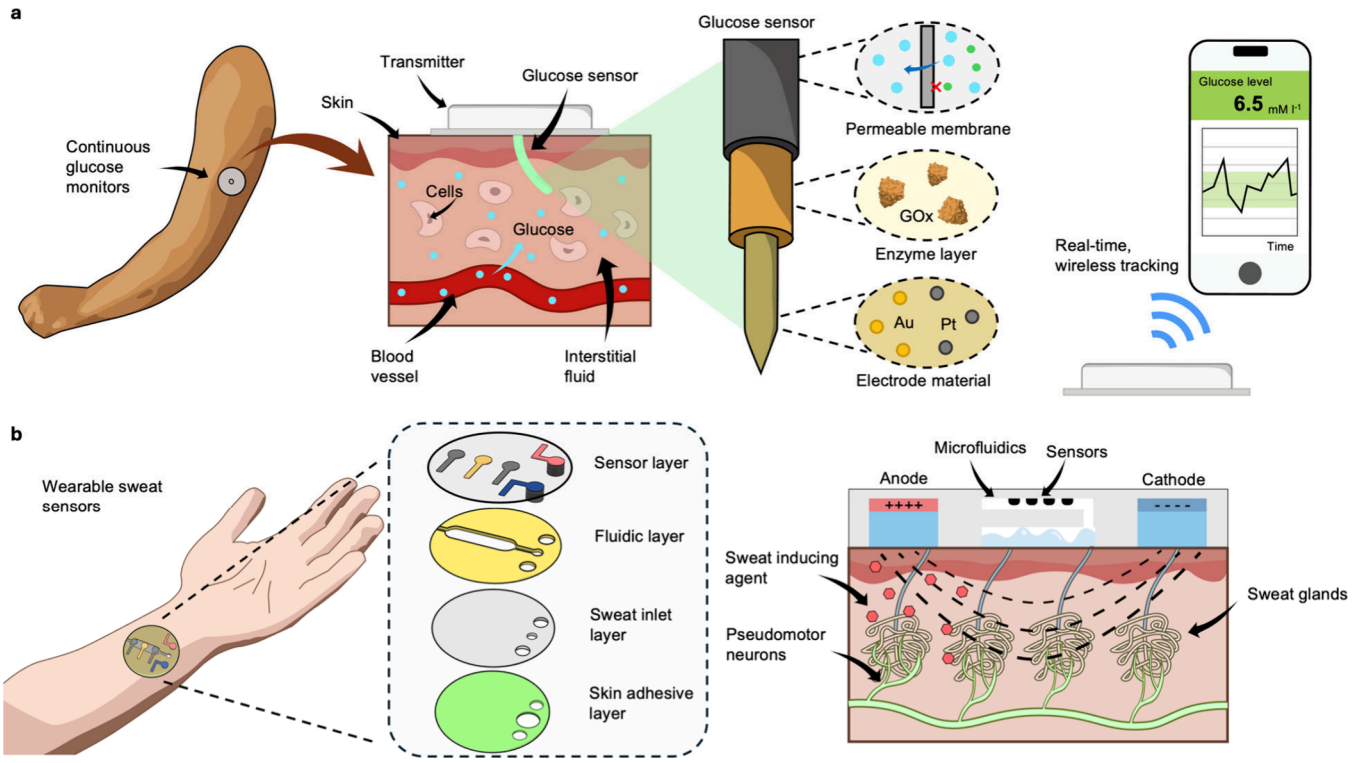

Figure 2. Minimally invasive ISF analysis vs noninvasive microfluidic wearable sweat analysis. (a) Schematic showing the working principle of a continuous glucose monitoring device. The sensor is composed of a microneedle placed under the skin in contact with the interstitial fluid. The needle is modified with a permeable membrane to prevent biofouling, an enzymatic layer with the enzyme glucose oxidase, and the actual working electrode that can be composed of several conductive materials. (b) Schematic showing the layered assembling of a wearable microfluidic sweat sensing device. The left side illustrates the layers from bottom to top include skin adhesive layer with the opening for sweat collection, sweat inlet layer made of soft and flexible material, fluidic layer containing the microchannels, electrode reservoir, and sweat outlet, electrode layer where the electrochemical (or optical) sensor is located. The right side shows a schematic of the iontophoresis process for sweat stimulation and microfluidics-based sweat sampling, transport, and sensing.

volunteers during their menstrual cycles by analyzing their estradiol levels in sweat.

Although size separated nanomaterials will further require testing and optimization, they may be able to reduce stress/strain on flexible sensors. However, challenges such as material uniformity and scalability must still be addressed for consistency across devices. Ongoing research is focused on improving nanomaterial reproducibility, which could significantly reduce sensor inconsistencies, such as false positives and poor signal-to-noise ratios. These advancements, along with scalable and cost-effective manufacturing, are essential for enabling the mass deployment of this technology.

2.2. The Correlation of Sweat and Blood Analyte Levels. Despite the fast advances in nanotechnology for wearable sensor development, sweat analysis is still limited by the lack of rigorous studies regarding correlation of the sweat and blood composition. As previously mentioned, interstitial fluid is the precursor to sweat, and there is a limitation in the size of molecules that can partition to the sweat duct. Additionally, some molecules, such as lactate, can originate from the sweat gland itself, decreasing the overall correlation.[3,74] Other factors that might affect the correlation is related to the sweat collection strategies. Collecting sweat direct from the skin by scratching the surface might contaminate the sweat sample with molecules deposited on the skin such as residual contents of the sweat duct, sebum secretions, epidermal cells, and other skin surface contaminants.

Even the different types of sweat and their various locations can lead to deviations in the accuracy. For example, sweat from physical exercise usually presents low pH, variable electrolyte concentrations, and regional variations, and is prone to dilution effects. Stimulated sweat using cholinergic drugs such as pilocarpine or carbachol can have different compositions (e.g., altered pH levels). Natural perspiration comes out at very low sweat rates, and the analyzed biomarker levels may be more strongly affected by evaporation or skin contamination. Thus, controlling sweat collection is critical to ensure accurate measurements of the target analyte.[3]

Successful strategies to correct or prevent variables originating from sweat collection include the integration of auxiliary pH, temperature, and electrolytes sensors.[72,73] Real time calibration is crucial when working with amperometric or voltammetric sensors since pH and temperature can affect the rate of chemical reactions, resulting in varying current signal output. Another important factor to consider is the sweat rate which could potentially influence the sweat analyte levels. Sweat flow rate can be developed and integrated in the sweat sampling microfluidics[44,75,76] for potential sensor calibration applications. It should be noted that the sweat rate itself serves as an important biomarker for monitoring hydration, stress, and withdrawal from substance-use disorders.[77,78] The use of epidermal microfluidic devices also decreased evaporation and skin contamination (Figure 2b). Adhesion to the skin is another challenge faced by sweat sensors. Sweat itself tends to weaken the adhesion of the device. A perfect sealing is needed

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Table 1. Sensing Strategies and Correlation for Sweat Analytes

(bio)recognition element	analyte	material	signal transduction	correlation coefficient	reference
Aptamer	Estradiol	AuNPs, Ti_3C_2Tx MXene	SWV	0.837 (n = 51)	73
	Cortisol	In_2O_3	FET	0.73 (n = 17) (sweat vs saliva)	67
Enzyme	Cholesterol	Agarose/WPU/PEDOT:PSS hydrogels + carbon microparticles	Amperometry	0.95 and 0.92 (n = 21) before and after food intake	39
	Ethanol	Chitosan/fumed silica/gelatin	Amperometry	Three subjects: 0.9789, 0.9779, 0.9474	100
		PtNPs	Amperometry	Two subjects: 0.87 and 0.79[a]	119
	Glucose	γ-aminopropyltriethoxysilane gel	Amperometry	0.75 (n = 25)	120
		Au+AgNPs-CQDs@PSi	Fluorescence	0.92 (n = 23)[a]	121
		Au nanodendrites/Prussian Blue layer	Amperometry	0.797 (n = 3)	44
	Lactate	Agarose/WPU/PEDOT:PSS hydrogels + carbon microparticles	Amperometry	0.89 (n = 21)	39
	Urea	CNTs-COOH - PVC/nonactin/DOS membrane - Nafion	Potentiometry	0.974 (n = 8)	95
	Uric acid	AgNWs@PB aerogel	Amperometry	0.891 (n = 8)	122
	Vitamin C	Au nanodendrites + PEDOT:$LiClO_4$ polymer	Amperometry	Two subjects: 0.81 and 0.72	123
Antibody	Cortisol	Graphene/PPA film	Amperometry	0.87 (n = 4)	124
	CRP	Graphene/AuNPs	SWV	0.841 (n = 80)	72
	Cytokines	ZnO	EIS	0.95 (n = 10)[a]	125
MIP	BCAA	Graphene/PB/APBA-pyrrole MIP	LSV	0.69 (n = 65)	36
	Phenylalanine	PANI/Au	DPV	Two subjects: 0.947 and 0.878	126
No (bio)receptor	Acetaminophen	Nafion	DPV	Two subjects: 0.95 and 0.93[a] (sweat vs saliva)	119
	Glucose	XSBR-PEDOT:PSS-AMWCNTs/AuNPs	Amperometry	0.94 (n = 2)[a]	127
	Uric acid	PyTS@Ti_3C_2Tx MXene	DPV	0.98 (n = 4)[a]	128
		Graphene	DPV	0.864 (n = 46)	26

[a]Calculated from data. WPU: waterborne polyurethane, PtNPs: platinum nanoparticles, AgNPs: silver nanoparticles, BCAA: branch chain amino acids, PSI: luminescent porous silicon particles, CQDs: carbon quantum dots, CNTs-COOH: carboxylated multi−walled carbon nanotubes, PVC: polyvinyl chloride, DOS: bis(2-ethylhexyl) sebacate, PB: Prussian blue, PEDOT: poly(3,4-ethylenedioxythiophene), PPA: pyrrole propionic acid, EIS: electrochemical impedance spectroscopy, LSV: linear sweep voltammetry, o-NPOE: o-nitrophenyl octyl ether, TDDMACl: tridodecyl-(methyl)ammonium chloride, EMF: electromotive force, XSBR: carboxylated styrene butadiene rubber, AMWCNTs: aminated multiwalled carbon nanotubes, MOF: metal−organic framework, PyTS: 1,3,6,8-pyrenetetrasulfonic acid sodium salt, PANI: polyaniline, PPy: polypyrrole, APBA: 3-aminophenylboronic acid.

to ensure enough pressure from the sweat glands and continuous flow on the microfluidics. Strategies and materials for proper adhesion have been studied.[79−82] Commercial products, such as medical adhesive and double-sided tapes have been successfully employed. Other engineered adhesives have been developed for hydrogel/skin interface and for direct contact with the skin.[80,83,84]

Several analytes have been well correlated with blood by using the above-mentioned strategies including glucose.[85−87] The correlation between sweat and blood analytes have been reported along with biorecognition elements as shown in Table 1.[2,88,89]

2.3. Commercial Barriers and Recent Advances toward Personalized Healthcare. The fast development of wearable technology has led to a proliferation of smart devices capable of tracking various physiological parameters continuously and in real time. Smart watches, rings, wrist bands, and other gadgets can measure our heart rate, blood pressure, temperature, physical status, and many other signals. The first generation of such smart wearables was launched a decade ago, gaining popularity among users concerned about their health and fitness.[90,91] Wearable sweat biosensors represent the next generation of smart wearables, capable of tracking chemical information in real time and overcoming the delay, hassle, and costs of laboratory blood tests.

The synergy of nanotechnology, flexible electronics, system miniaturization, and machine learning allows for the development of such wearables and the continuous monitoring of the body's biochemical status, leading to better disease management, such as diabetes, and early prevention of illnesses, including cardiometabolic disorders. Despite the vast potential of this technology, wearable sweat biosensors are not yet commercially available. Although there has been significant attention and effort in developing these devices, none are currently on the market.

The most successful wearable biosensors today are the continuous glucose monitoring (CGM) devices for interstitial fluid (ISF). Companies like Dexcom and Abbott have pioneered the development and commercialization of wearable glucose sensors. These sensors consisting of a small needle modified with the biorecognition layer, that is in contact with ISF to monitor glucose levels continuous and in real time (Figure 2a).[92−94] These subcutaneous sensors can remain in the body for weeks, alleviating some of the hassle for type I diabetes patients who would otherwise need to perform finger pricks multiple times a day. While sweat glucose sensors are not yet commercially available, a few startup companies are dedicated to developing sweat sensors for fitness applications.

There are important technology barriers preventing sweat sensors from being available for over the counter or online purchase, one of which includes the continuous generation of sweat.[3] Dynamic sweat biosensing requires a continuous flow of sweat, which is not a problem while exercising but poses a challenge for daily continuous monitoring. Sweat stimulation can be achieved using cholinergic agents such as pilocarpine and carbachol, with pilocarpine stimulation lasting around 1−2

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h, and carbachol lasting over 24 h.[34] An integrated microfluidic iontophoresis module can readily sample simulated sweat for dynamic biomarker analysis (Figure 2b).

Other methodologies have been explored for sweat sampling, such as use of hydrogels,[38,95−99] which can accumulate a certain volume of sweat over time, concentrating the analyte for posterior measurements. However, the drawback of hydrogels is the loss of temporal resolution due to sweat accumulation. Other strategies for sampling low-volume sweat include the use of nano- and microstructures in wicking microfluidics, which are designed to actively guide sweat through the channels using capillary forces driven by the wettability gradients, rather than relying on pressure. This approach shows promise for maintaining a continuous flow, though challenges in fluidic and electrode fabrication may arise.[40,49,100−103]

Another potential risk associated with iontophoresis stimulation for sweat production is skin allergies and irritation. It is important to note that sweat stimulation differs from the reverse iontophoresis used in GlucoWatch, a commercial wearable glucose sensor discontinued due to rashes and irritation caused by frequent current or voltage application for ISF glucose extraction.[104] Skin irritation risks have been minimized by using lower currents and significantly reducing the frequency of iontophoresis. A single short-term iontophoresis session can result in continuous prolonged sweat production, especially when using carbachol as the simulation agent.

As we discussed earlier, one of the most important technology barriers for sweat biosensors is the correlation of sweat analytes and blood. While individual correlations have been demonstrated for glucose, cortisol, uric acid, and other analytes, these correlations often diminish when data from multiple individuals are combined, resulting in a low global correlation. This lack of global correlation hampers the wearability of sweat sensors, requiring users to frequently perform single-point calibrations with blood values. This is not ideal, as the primary goal of sweat sensors is to eliminate the need for blood collection. The lack of global correlation causes skepticism in the medical community. To overcome such barriers, more studies regarding sweat production and understanding of partitioning of molecules are required.

Correlation issues can potentially be addressed by using data-driven technological approaches such as machine learning (ML). For example, to overcome calibration barriers, data collected through IoT devices via Bluetooth and RFID technology, along with health informatics, can be combined with supervised machine learning algorithms integrated with sweat sensor databases. Advances in machine learning, combined with continuous measurement of sweat composition, have enabled applications that eliminate the need for direct correlation with blood to assess health conditions. A study has demonstrated the use of variations in the concentrations of six sweat analytes, coupled with other physical sensors (i.e., pulse waveforms, galvanic skin response, temperature), to classify the type of stressors the user was experiencing or the user's state anxiety levels.[105] The multimodal wearable sensor was able to distinguish between mental and physical stress by analyzing the sensor output and creating a "signature biomarker" for each stressor.[65] This approach can be a powerful tool for biomarker discovery, allowing large amount of data sets to be correlated to the disease onset, treatment efficacy, and chronic condition prevention. Once the data are trained for a specific user and task, the need to correlate sweat concentrations with blood becomes unnecessary.

These approaches will be pivotal for the inclusion into smart applications for global and personal health monitoring. To date, there are health disparities in research due to computational analysts requiring much more clinical data. The lack of clinical data from a broad sample of populations, including minorities, can lead to machine learning algorithms that do not work well for certain members of these populations due to algorithmic bias from models trained on mostly homogeneous data sets.[106]

Models lacking diversity will not generalize well with broader populations. Such models could overfit certain majority groups due to missed variations of underrepresented training data causing a lack of trust and slow adoption of such sensors. The overfitting of models will also cause regulatory challenges with legal standards regarding discrimination of nonrepresentative models.

Hospitals should have their own partitioned relational databases as different environmental factors and patient populations play a large role when developing supervised ML algorithms, such as decision trees. These healthcare statistics will allow for hospitals to assess, improve, and communicate the quality of patient care, developing better policies creating a proactive rather than a reactive environment. Sensors such as these will also support the implementation of evidence-based medicine approaches.

The main advantage of widespread adoption of sweat sensors by all stakeholders is the ability to perform continuous monitoring of analytes. However, reliable outputs from wearable sweat sensors depend on the stability performance of the biosensor. A stable reading ensures the absence of artifacts in the signal related to movement or chemical interference that might lead to misleading concentrations. A recent study demonstrated remarkable 100-h stability for biosensors operating continuously in sweat.[105] The wearable sensors were tested in volunteers during normal routines, including sleep, eating, and working activities. Such stability was achieved by judicious optimization of the electrode fabrication and use of analogous composite materials (e.g., nickel hexacyanoferrate in enzymatic sensors and hydrophobic SEBS in ion-selective sensors) for stabilizing and conserving sweat biosensor interfaces.[105]

A critical aspect of this approach is the scalable fabrication technology, leading to accessible devices. Costs and scalability are one of the main concerns for the widespread acceptance of wearable sweat sensors. Approaches such as screen printing,[107] inkjet printing,[73,108] roll-to-roll printing,[109] laser engraving,[26,110] and 3D printing[111,112] have been used to realize high quality stable sweat sensors. These techniques are more accessible when compared to photolithography and thin film evaporations, which require highly trained personnel and exclusive dedicated facilities.[16,113]

Aesthetics can also affect the compliance of sweat devices. To address this, sweat biosensors have been integrated into already accepted gadgets such as glasses, watches, rings, earbuds, clothes, and other accessories.[114]

3. FUTURE OF WEARABLE SWEAT BIOSENSORS

Wearable sweat biosensors hold great promise for noninvasive monitoring of analytes enabling continuous tracking of target biomarkers. This capability is particularly beneficial for

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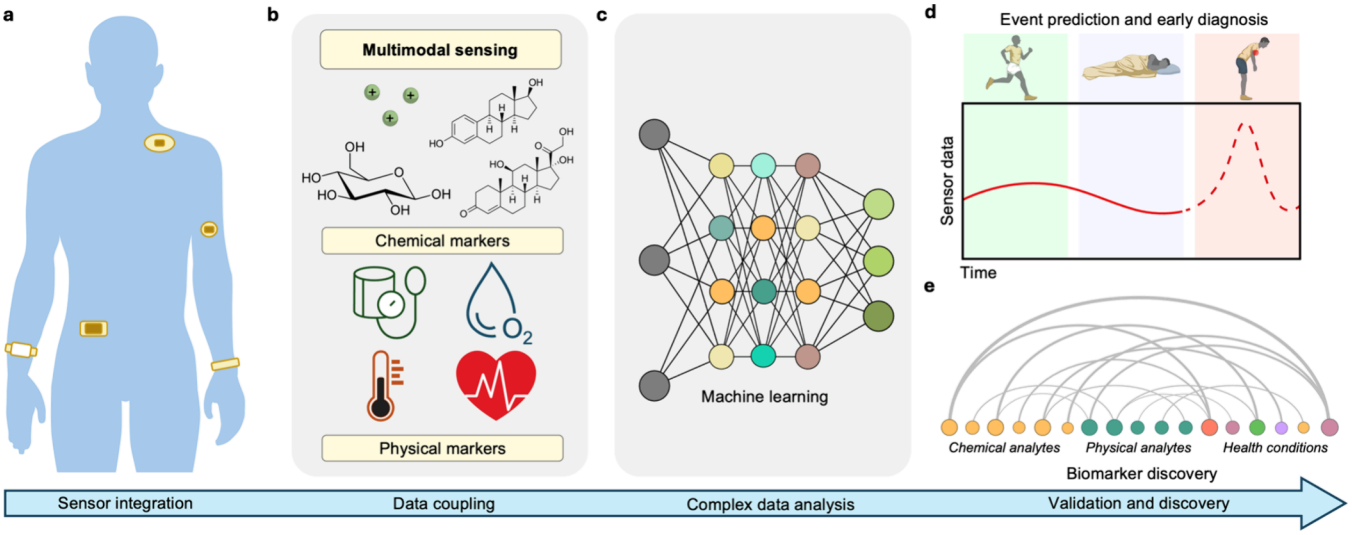

Figure 3. Machine learning-augmented multimodal wearable physiochemical sensors. (a, b) Various sensors placed on the body (a) collect biological information such as analyte concentrations, heart rate, temperature, blood pressure, blood oxygenation (b). (c) The data from these wearable devices are collected simultaneously in real time and transmitted to a processing device, such as a cell phone. (d) The data can be trained to predict events by correlating with historical data. (e) A signature biomarker is then established for the trained profile.

studying dynamic events such as glucose fluctuations, cortisol bursts, and pharmacokinetics profiles. Real-time updates on the body's physiological composition can be used in various applications, from monitoring chronic diseases to prevention and even prediction. The integration of nanoparticles and nanocomposites into these wearable sweat sensors substantially boosts their performance by enhancing signal transduction, increasing sensitivity, and enabling more accurate and rapid detection of biological markers.

The application of wearables to monitor diseases such as diabetes and diagnose conditions such as gout[26] and cystic fibrosis[35] has been already demonstrated. Recently, the new concept of biomarker signatures has emerged involving monitoring, diagnosing diseases and other conditions that lack a single specific biomarker by tracking multiple signals concurrently.[65] For example, measuring lactate levels alongside blood pressure and heart parameters can aid in the early and precise diagnosis of sepsis. The monitoring of glucose, lactate, uric acid, sodium, potassium, ammonium, galvanic skin resistance (GSR), temperature, and pulse has shown the ability to classify different types of stress, being able to classify anxiety levels.[105]

Combining multimodal and multisensing technology with machine learning can validate biomarker signatures by correlating multiple parameters to specific body conditions (Figure 3). Continuous monitoring of chemical and physical parameters, enhanced by machine learning, can make clinical predictions.[115] With sufficient data, it is possible to detect the onset of sudden acute events such as strokes, heart attacks, and epilepsy, giving patients time to act and potentially saving millions of lives.

Even before reaching this stage, knowledge of our body's biological status can lead to lifestyle changes for preventive care. Cardiometabolic disorders, which manifest through type II diabetes, hypertension, and high lipidic levels, take years to develop. They are strongly correlated to obesity, and approximately 25% of adults in Westernized countries have obesity.[116,117] Continuous monitoring of glucose, lipids, and blood pressure can prompt individuals to change diets and include physical exercise in the daily life.

The embodiment of personalized healthcare using wearable sweat biosensors is only possible with the successful commercialization. Scalable and low-cost fabrication of nanomaterial-engineered sensors is a cornerstone for creating these advanced biosensors. This approach enables the precise construction of nanostructured components, which are essential for their functionality, delivering highly consistent and reproducible results that ensure reliability and performance in real-world applications. The medical community's adoption of the wearable sweat sensing technologies, and their wider applications, will depend on the collective efforts of various communities to conduct large scale human studies, as well as thorough investigations into the clinical relevance of data collected through wearable sweat sensors.[118]

Wearable noninvasive sweat biosensors are poised to become an integral part of our daily lives, paving the way for a new era in health monitoring. By combining sweat biosensors with advanced algorithms, individuals will have instant access to their health status, influencing health insurance calculations and medical care practices. Recording personalized activity and diet choices will become the norm, with this technology playing a crucial role in promoting longer, healthier lifestyles. This shift will mark the beginning of an era focused on health awareness, prompting new city policies based on population health and leading to a transformation in global paradigms.

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Notes

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